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Exposure to Ambient Air Pollution and Onset of Parkinson's Disease in a Large Cohort Study

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ABSTRACT

The emerging literature studying the association between exposure to ambient air pollution and Parkinson's Disease (PD) so far draws mixed conclusions. This study provides new evidence on this issue using data from a large and nationally representative cohort tracked over an extended period. We tracked a 28% representative sample of the Northern Ireland population between 2009 and 2016, with complete address records matched to annual average data on fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) concentrations at the 1km grid-square level, together with comprehensive information on PD medications dispensed over this period. We used these data to estimate associations between pollution exposure and PD onset as proxied by first receipt of PD medication, controlling extensively for potentially confounding factors at the neighbourhood, household and individual levels. Additionally, we estimated associations for sub-samples split by age and sex. There was no evidence of an association between medium-term $PM_{2.5}$ or NO_2 exposure and the risk of onset of PD in the overall cohort, nor among over-50s or samples split by sex. However, we found a positive association between early onset of PD (aged under 50 years as of 2011) and $PM_{2.5}$ exposure, with more tentative evidence of an association with NO_2 exposure. We discuss potential biological and non-biological explanations for this age-related contrast.

HIGHLIGHTS

- We investigated associations between air pollution exposure and Parkinson's (PD).
- $PM_{2.5}$ and NO_2 exposures were not associated with risk of PD onset in the overall cohort.
- This was also the case for samples split by sex and a sample restricted to over-50s.
- But pollution exposure, particularly $PM_{2.5,}$ was associated with onset of PD for <50s.

INTRODUCTION

According to the Global Burden of Disease (GBD) study, approximately 8.5 million people worldwide were affected by Parkinson's Disease (PD) in 2019. Rapid global growth of new PD cases is partly due to population ageing, with a 145% increase estimated by GBD from 1990 to 2016.[1] In the United Kingdom (UK), the estimated prevalence of PD for people aged over 20 in 2018 was 145,519. Moreover, it has been estimated that 1 in every 37 people will be diagnosed with PD at some point in their life, equivalent to a 2.7% lifetime risk of diagnosis. Both the prevalence and incidence of PD are expected to rise in the UK, with a predicted 18% rise in prevalence between 2018 and 2025, and yearly incidence expected to rise to over 21,000.[2] In the United States the estimated figures for age- and sex-adjusted Parkinson's disease incidence range from 108 to 212 per 100,000 for individuals aged 65 and above, and from 47 to 77 per 100,000 for those aged 45 and above.[3] Thus, research that improves our understanding of modifiable determinants of PD has potential to help inform interventions to alleviate what is predicted to be a growing health, wellbeing, and economic burden on society, both globally and within the UK.

Much about PD's etiology remains unknown, but both environmental and genetic factors, as well as their interaction, are thought to explain its onset. An emerging literature has begun to examine the role of exposure to ambient air pollutants (e.g., particulate matter (PM_{10}, $PM_{2.5}$) and nitrogen oxides (NOx, and NO_2)) as potential contributors to the development and progression of PD.[4] Ambient air pollution is one important factor in neuro-inflammation and oxidative stress, conditions which can lead to the loss of dopamine-generating cells in the substantia nigra and cause PD.[5] It can also increase the risk of neurodegenerative diseases, including PD, indirectly through cardiovascular health[6–10] or cerebrovascular disease.[11] Other suggested risk factors for PD are thought to include dairy products, pesticides, high body-mass index, diabetes, cancer, and brain injury.[12]

So far there is no clear consensus in the literature on ambient air pollution and PD. Several studies have considered the role of exposure to particulate matter ($PM_{2.5}$ and/or PM_{10}).[4,13–29] The effects of exposure to pollutants such as SO_2, NO_2, NOx, CO and Ozone have also been studied[4,17,19,30–32] as well as the effect of exposure to airborne metals such as lead, copper and manganese.[15,33,34] These studies have produced a range of findings that taken together appear inconclusive, even within pollutant types: some have demonstrated strong statistical associations between ambient air pollution and PD,[4,21,30,33,34] while others have found weak or no associations.[14,19,29,32,35] This mixed picture is also reflected in the few studies that have estimated multipollutant models.[4,28,36] Further, where statistically significant associations are found, they vary considerably in magnitude. Table A1 in the Appendix provides further details.

One potential contributing factor to the mixed nature of research findings across the literature is the extent of variation in study populations and their contexts and in factors such as exposure durations and outcome measures employed.[25,27] For example, some studies have restricted estimation to older age groups[17,24] while others include younger age groups.[4,14] Study contexts have varied widely, including in respect to typical pollution levels experienced. Exposure durations studied have also varied from the short term (which can be as short as 8 days)[21], to the long term (often defined as exposure of 2 years or more)[20], with medium-term exposures falling somewhere in between (e.g., one year exposure durations).[37] Outcome measures studied have included self-reported PD cases, sometimes with verification from neurologists;[14,19,29,35] PD drug prescriptions;[17,31] cases from hospital register or other health administrative databases;[4,21–24,26,30,32,37] and in one recent case PD-related mortality collected from mortality registries.[28] Other factors that vary across the literature include the nature of the study design (cohort versus case-control), sample size, the pollutants studied (most commonly but not exclusively $PM_{2.5}$ and NO_2), how pollutant concentrations are measured, and the degree to which studies adjust associations for potentially confounding variables. Having said that, research findings have been mixed even within similar study types and contexts.

Additional research on the extent to which ambient air pollution is a risk factor for PD is clearly warranted. In this paper, we studied this question using new data from a large and nationally representative cohort tracked over an extended period. Specifically, we tracked a 28% representative sample of the Northern Ireland population between 2009 and 2016, with complete address records matched to annual average data on fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) concentrations at the 1km grid-square level, with PD onset proxied by receipt of first prescription for PD-related medication. It is the first such study for Northern Ireland.

We also contribute to the literature by exploring the associations between exposures to $PM_{2.5}$ and NO_2 and the probability of the onset of PD separately by age and sex. Few existing studies have attempted to do so, and where they have, findings have been inconclusive.[35,37]But recent studies have investigated sex-related differences in PD pathophysiology, with a focus on the role of oestrogen (hormone responsible for the development of the female reproductive system).[38] There is also some evidence suggesting etiologic differences in early versus late onset of PD.[39] Non-biological factors might also lead to variation in estimated associations between pollution exposure and PD onset by age and sex. For example, diagnosis latency (the time interval between the onset of symptoms and confirmed diagnosis of a disease) may differ along these dimensions.[40] Few studies in the existing ambient air pollution and PD literature explicitly address the potential implications of such delays for estimated associations.

MATERIALS AND METHODS

Data

The study used data from a new linkage between the Northern Ireland Longitudinal Study (NILS), matched to pollution data at the 1km grid-square level, and the Enhanced Prescribing Database (EPD). The NILS is a longitudinal study that tracks a 28% representative sample of the Northern Ireland population drawn from the NI Health Card Registration System, which contains address histories updated biannually. The NILS is linked to several other administrative datasets including Census records for 2011, which provided rich information on socioeconomic and demographic characteristics and contexts for sample members.[41] The pollution data, matched at the residential property level to NILS participants, provided annual 1km grid-square modelled pollution data from 2009-2016 for both $PM_{2.5}$ and NO_2. These data were produced by Ricardo Energy & Environment for the UK Government's air quality assessments.[42] These data were then linked to the EPD, which contains detailed information relating to all primary care prescriptions dispensed in Northern Ireland[43], made available to us at six-monthly frequency from January 2010 onwards. From this we extracted data on prescriptions in each six-month period (January-June (hereafter semester 1) and July-December (hereafter semester 2) of each year, from a defined list of items covering drugs that, according to the British National Formulary (BNF) classification system, were prescribed for PD at the time. The data were anonymized and analysed in a trusted research environment under strict confidentiality and security protocols by ONS-accredited researchers.

Analysis sample

Our analysis sample included all NILS members present in the 2011 Census who were aged 28 years or older at the time, had full address records, could be linked to the EPD, and were not in receipt of PD medication prior to the semester January-June 2012, which we treated as the first at-risk period for the purposes of modelling PD onset. This gave a total of 292,925 individuals, from which 3,089 started receiving medication for PD during our analysis period, i.e., at some point between 2012 semester 1 and 2016 semester 2, inclusive, or until such time as they attrited from the NILS sample through death or emigration. Compared to the full NILS sample returned in the 2011 Census and aged 28+ years at that time (but similarly excluding those with PD prescriptions prior to 2012 semester 1),

our analysis sample was slightly (around 3.5%) smaller, mainly due to missing information on exposure to pollution at some point during the analysis period due to incomplete address records. In terms of measured characteristics, however, the two samples were very similar (see Table 1).

Outcome variable

The outcome variable was drawn from the EPD and set equal to 1 from the point at which the individual had received any prescription for PD in the relevant semester, and 0 otherwise. The following categories of prescriptions were included: Dopaminergic (dopamine) drugs used to treat Parkinsonism; Antimuscarinic Drugs Used in Parkinsonism; and prescription for Essential Tremor, Chorea, Tics & Related disorders. Prescription data have been used in numerous existing studies on the health effects of ambient air pollution in relation to various health conditions,[44–46] but rarely in the pollution and PD literature.[17,31] Such prescription-based measures have advantages and disadvantages as proxies for the onset of PD. On the one hand, they are objective and a prescription first requires a PD diagnosis. On the other hand, not all individuals diagnosed with PD may receive a prescription, or not immediately, and in some cases a first course of medication may come directly from a hospital setting rather than via a primary care prescription. Together, these suggest some undercounting and/or lag in the measurement of PD onset was possible. If any such undercounted patients were disproportionately exposed to high (low) levels of pollution, our estimates may have underestimated (overestimated) the true effect of exposure to pollution on PD onset. We mitigated concerns related to delays in diagnosis and/or receiving a first primary care prescription following diagnosis by conducting sensitivity analysis varying the lag length for exposure. This was also important for the sub-sample analysis given recent evidence that such delays may increase with age of PD onset.[40]

Exposure variables

Exposure variables were derived from annual average $PM_{2.5}$ and NO_2 concentrations modelled at the 1km grid-square level across Northern Ireland produced by Ricardo Energy & Environment for the UK Government's air quality assessments. These concentrations were themselves derived from the aggregation of values from a variety of large and small point sources, as well as area and distance sources, using various datasets, including the UK National Atmospheric Emissions Inventory.[42] Modelled concentrations were calibrated with data from the UK national monitoring network and evaluated using data from monitoring sites not used in the calibration process prior to their publication. These data have been used in several existing studies of the health effects of ambient air pollution exposure within the UK,[47,48] including specifically in Northern Ireland.[49] Similar modelled pollution data have also been used extensively in the international literature,[50–53] including in the specific literature on the association between ambient air pollution and PD.[14,30,32] The trade-off for the population coverage that such data offer is the potential for measurement error in pollution concentrations. For an analysis of its potential implications for estimated health effects of exposure see Samoli et al. (2020).[54]

$PM_{2.5}$ and NO_2 are the two pollutants which have attracted most interest in the air pollution-PD literature to date, and our focus on these pollutants reflected this. All individuals in the sample were assigned exposure values for $PM_{2.5}$ and NO_2, via their residential address, for every six-month period from January-June 2009 (2009 semester 1) through to July-December 2016 (2016 semester 2). Addresses are updated every six months in the NILS, in April and October of each year. We used April addresses to determine exposures for semester 1 and October addresses to determine exposures for semester 2 of each year. In other words, six-monthly exposures were assigned according to address at approximately the mid-point of each semester. Note that although the underlying pollution data were annual frequency, there was within-year variation in exposure in our analysis sample where individuals changed residential address between April and October in any given year.

These data are most suited to examining the effects of *medium-term* exposures to these pollutants, initially defined as exposure to pollution over the semester one year previously. This initial choice of a one-year lag for exposures was motivated by recent evidence on the average delay between first

onset of symptoms and PD diagnosis.[40] Note that the duration of exposure typically considered as 'medium-term' in the literature varies from several weeks up to several years.[55,56] In sensitivity analysis we also defined exposures as two-year moving averages and varied the lag length of (both 6-month and 2-year moving average) exposures from zero (i.e. contemporaneous exposures) to a lag of 6 and 18 months.

Covariates

The 2011 Census link allowed adjustment for a rich set of individual and household socio-economic and demographic covariates, each measured in March 2011. These variables are listed in Table 1, along with their (unweighted) sample means, both overall and separately for those in our analysis sample who did and did not experience PD onset.[1] Table 1 also compares the analysis sample to the equivalent full sample of NILS members present in 2011 Census. We supplemented these covariates with neighbourhood deprivation indicators corresponding to 2011 Census residential address. These give the deprivation rank decile of the individual's residential super output area (SOA) according to the 2010 multiple deprivation measure (MDM) index[57]. Note there are 890 SOAs in NI with an average population of 790 households.

Table 1. Characteristics and exposures of the study population by PD onset

	Without PD Onset	With PD Onset	Analysis Sample	Full NILS Sample Aged 28+ in 2011 Census
Number of Individuals	289836	3089	292925	303467
Individual Characteristics (%)				
Age in 2011				
28-30	6.3	1.6	6.3	6.3
31-35	10.3	3.8	10.2	10.1
36-40	11.1	6.1	11.1	11.9
41-45	11.9	7.2	11.8	11.6
46-50	11.8	8.3	11.8	11.5
51-55	10.5	8.8	10.5	10.3
56-60	8.9	9.1	8.9	8.7
61-65	8.5	12.3	8.5	8.4
66-70	7.1	12.5	7.1	7.1
71-75	5.4	12.2	5.4	5.5
76-80	4.0	10.7	4.1	4.3
80+	4.2	7.4	4.3	5.2
Sex				
Male	47.5	40.3	47.4	47.3
Female	52.5	59.7	52.6	52.7
Country of Birth				
Northern Ireland	88.1	91.4	88.1	87.7
Rest of the UK	5.2	4.7	5.2	5.3
Republic of Ireland	2.7	2.7	2.7	2.8
Born Elsewhere	3.9	1.4	3.9	4.2
Educational Attainment				
No Educational Qualifications	32.3	54.1	33.0	33.3
Below Degree or Equivalent	37.7	28.0	37.1	36.9

[1] Approximately 0.1% of the sample had non-response (missing/edited) across multiple covariates, which closely corresponded to individuals residing in communal establishments at the time of the 2011 Census. These individuals were excluded from the sample.

Degree, Equivalent or above	30.0	17.9	29.8	29.8
General Health in 2011				
Very good/Good/Fair	92.1	80.7	92.0	91.5
Very Bad/Bad	7.9	19.3	8.0	8.4
Long term AL Illness in 2011				
No Long-Term AL Illness	71.9	41.6	71.6	70.4
Has a Long-Term AL Illness	28.1	58.4	28.4	29.6
Economic Activity in 2011				
Employed/Self Employed	57.0	28.1	56.7	55.6
Inactive/Unemployed	43.0	71.9	43.4	44.4
Religion				
Catholic	38.5	36.8	38.5	38.3
Protestant/Other	46.7	50.9	46.7	46.8
No Religion or None Stated	14.8	12.3	14.8	15.0
Marital Status in 2011				
Never married	19.6	13.8	19.6	19.9
Married	60.7	57.6	60.6	59.7
Separated/ Divorced/ Widowed	19.5	28.6	19.6	20.2
2011 Household Characteristics (%)				
Dependent Children in HH				
0	64.2	80.8	64.4	63.8
1	14.1	8.9	14.0	13.7
2	13.5	5.9	13.5	13.2
3+	8.2	4.4	8.2	8.0
# of Cars in HH				
0	15.1	22.6	15.2	15.3
1	37.9	44.9	38.0	37.6
2	34.1	23.2	34.1	33.3
3+	12.8	9.1	12.7	12.4
# of persons per room in HH				
Max 1 person	97.9	98.5	97.9	96.6
More than 1 person	2.1	1.5	2.1	2.1
Area Characteristics (%)				
SOA deprivation (MDM) 2011				
1 (Most Deprived)	9.3	11.4	9.3	9.4
2	9.6	10.8	9.6	9.6
3	10.1	11.9	10.1	10.6
4	10.4	11.9	10.4	10.8
5	10.5	11.1	10.6	11.2
6	10.5	9.0	10.4	10.8
7	10.3	9.2	10.3	10.5
8	10.0	9.8	10.0	9.9
9	9.9	8.1	9.8	9.2
10 (Least Deprived)	9.4	7.8	9.4	8.0
Pollution Exposures (µg/m³)				
$PM_{2.5}$ *(Mean*[SD])	7.5 [1.5]	7.6 [1.5]	7.5 [1.5]	
NO_2 (Mean[SD])	9.0 [4.7]	9.1 [4.6]	9.0 [4.7]	

$PM_{2.5}$ Quartiles (%)			
<6.49	25.6	24.6	25.6
6.49 to 7.55	22.9	21.5	22.3
7.55 to 8.83	31.4	31.5	31.4
>8.83	18.0	20.3	18.0
NO_2 Quartiles (%)			
<5.24	24.5	23.4	24.5
5.24 to 8.10	25.0	24.9	25.0
8.10 to 11.92	24.8	25.2	24.8
>11.92	23.6	24.4	23.6

Note. The analysis sample consists of all NILS members present in the 2011 Census who were aged 28 years or older at the time, had full address records, could be linked to the EPD, and were not in receipt of PD medication prior to January 2012, and not living in a communal establishment. The last column reports statistics for the full NILS sample aged 28+, returned at the 2011 Census, but similarly excluding those receiving PD medication prior to January 2012. The table reports the percentage of each sample reporting each characteristic in 2011. All variables are from Census 2011 except pollution exposures which are averaged over the whole exposure period. Pollutant quartiles are constructed using their distributions over the whole exposure period. Statistics are unweighted. MDM refers to the 2010 Multiple Deprivation Measure linked to 2011 Census address.

Model

We used Cox Proportional Hazard (CPH) models to examine the associations between pollution exposures and the onset of PD.[4,17,28,32] We estimated hazard ratios (HRs) for the association between medium-term exposure to ambient $PM_{2.5}$ and NO_2 and receiving a first prescription for PD. Following Jo et al. (2021),[4] exposure to ambient air pollution was modelled both in continuous/linear form and in categorical form (as quartiles). We estimated unadjusted models as well as models adjusted for covariates at individual, household and neighbourhood level. Note that 7.1% of individuals are right censored at some point during the analysis period due to death or emigration.

In our preferred specification, analysis of PD onset starts in the period 2012 semester 1 with exposures measured from the corresponding semester one year previously (2011 semester 1). This ensured that measured exposures did not precede measurement of the covariates. In sensitivity analysis we relaxed this restriction, modelling PD onsets from the first available data point (2010 semester 2) with corresponding exposures prior to the 2011 Census date, in addition to examining sensitivity to the length and lag of the exposure period. Standard errors were clustered at the SOA level. Analysis was performed in the trusted research environment of the Northern Ireland Statistics and Research Agency (NISRA) using STATA 17. The data provided are anonymized, and researchers do not have access to addresses or other sensitive information.

RESULTS

Table 1 shows that between 2012 semester 1 and 2016 semester 2, there were 3,089 individuals who received a first prescription for PD, while 289,836 individuals did not. There were clear differences in measured 2011 characteristics between the two groups. For example, compared to those not experiencing PD onset over this period, those experiencing PD onset were more likely to be older; female; born in Northern Ireland; without educational qualifications; to report poor general health in the 2011 Census; to be inactive or unemployed; to be divorced/separated/widowed or never married; to have no dependent children in the household; to have no cars in the household; and to live in more deprived neighbourhoods. In other words, there was a clear age/sex/disadvantage contrast between the two groups. When comparing exposure to pollutants over the analysis period, those experiencing PD onset were found to be exposed to broadly similar levels of $PM_{2.5}$ and NO_2 on average compared to those not experiencing PD onset, with only slightly higher (lower) percentages in the highest (lowest) quartiles of the relevant exposure distributions.

Table 2 presents our preferred CPH model estimates for the effects of medium-term exposure to $PM_{2.5}$ (Panel A) and NO_2 (Panel B) on the onset of PD for the whole sample (six-month exposures lagged one year). Model 1 estimates are unadjusted with no conditioning on measured characteristics, while Model 2 estimates are adjusted for measured individual, household and area characteristics as listed in Table 1. Full results for Model 2 are presented in Appendix Table A2.

Table 2. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's Disease onset, one year lag, overall sample

	Model 1 (Unadjusted)		Model 2 (Adjusted)	
	(a) linear	(b) quartiles	(a) linear	(b) quartiles
Panel A ($PM_{2.5}$, $\mu g/m^3$)				
Linear model	1.03** (1.01-1.06)		0.99 (0.96-1.02)	
Quartiles model				
1st (reference)				
2nd		1.04 (0.93-1.16)		1.01 (0.90-1.13)
3rd		1.04 (0.92-1.17)		0.98 (0.87-1.11)
4th		1.18* (1.03-1.34)		1.01 (0.88-1.16)
Observations	2688153	2688153	2688153	2688153
Covariates	NO	NO	YES	YES
Panel B (NO_2, $\mu g/m^3$)				
Linear model	1.00 (1.00-1.01)		0.99 (0.98-1.00)	
Quartiles model				
1st (reference)				
2nd		0.95 (0.85-1.06)		0.96 (0.86-1.07)
3rd		1.00 (0.89-1.12)		0.95 (0.84-1.07)
4th		1.07 (0.96-1.19)		0.94 (0.83-1.06)
Observations	2688153	2688153	2688153	2688153
Covariates	NO	NO	YES	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with one year lag. Covariates are at individual, household and neighbourhood levels as listed in Table 1. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.*

Despite some evidence of an association between PD onset and lagged $PM_{2.5}$ exposure in the unadjusted models (Table 2, Model 1, Panel A), there was no such evidence in the adjusted models (Table 2, Model 2), nor for NO_2 exposure in either unadjusted or adjusted models. In the linear adjusted model, the estimated hazard ratios were 0.99 for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ and also 0.99 for a 1 $\mu g/m^3$ increase in NO_2 (95% confidence intervals 0.96-1.02 for $PM_{2.5}$ and 0.98-1.00 for NO_2). Estimated Model 2 hazard ratios for exposure quartiles were also everywhere close to 1 and statistically insignificant for both pollutants, with no suggestion of dose response.

Subsample Analysis by Sex and Age

Tables 3 and 4 present equivalent estimates for the study population split by sex (Table 3), and age (Table 4) respectively. In each case we present estimates for the linear and categorical exposure versions of the models in a single column to save space.

In line with Table 2, Table 3 shows no statistically significant associations between $PM_{2.5}$ or NO_2 exposure and PD onset for either men or women once estimates were adjusted for measured confounders, despite a statistically significant association between $PM_{2.5}$ exposure and PD onset for females (but not males) in unadjusted models. Table 4 presents similar evidence for those aged 50+ years in 2011, with no statistically significant associations between pollution exposure and PD onset either in the adjusted or unadjusted models, bar a statistically significant hazard ratio marginally below 1 in the adjusted continuous model for NO_2 exposure – statistically significant at the 95% level but not the 99% level - which likely reflected Type 1 error. In contrast, positive associations between the estimated hazard rate for PD onset and exposure to $PM_{2.5}$ remained statistically significant at either the 95% or 99% level for the younger age group (under 50 years in 2011), after adjusting for measured confounders, in both the linear and categorical exposure models. The estimated hazard ratios were 1.05 (1.01-1.11) in the adjusted linear exposure model and 1.26 (1.01-1.56), 1.23 (0.97-1.55) and 1.30 (1.01-1.67) for quartiles 2, 3 and 4 respectively, in the adjusted model with categorical exposures. There was also tentative evidence of a positive association with NO_2 exposure, with the estimated hazard ratio for 3rd quartile exposure statistically significant at the 95% level (hazard ratio 1.24, confidence interval 1.00-1.54).

Table 3. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's Disease onset, one year lag, by sex

	Male		Female	
	Model 1	Model 2	Model 1	Model 2
Panel A ($PM_{2.5}$, µg/m³)				
Linear model	1.01	0.99	1.05**	0.99
	(0.97-1.06)	(0.95-1.04)	(1.01-1.08)	(0.95-1.03)
Quartiles model				
1st (reference)				
2nd	1.16	1.16	0.95	0.91
	(0.97-1.39)	(0.97-1.39)	(0.82-1.11)	(0.79-1.05)
3rd	1.16	1.14	0.95	0.88
	(0.96-1.40)	(0.94-1.38)	(0.81-1.12)	(0.75-1.04)
4th	1.17	1.09	1.16	0.95
	(0.95-1.44)	(0.88-1.36)	(0.98-1.37)	(0.80-1.13)
Observations	1265787	1265787	1422366	1422366
Covariates	NO	YES	NO	YES
Panel B (NO_2, µg/m³)				
Linear model	1.00	0.99	1.01	0.99
	(0.99-1.01)	(0.98-1.01)	(1.00-1.02)	(0.98-1.00)
Quartiles model				
1st (reference)				
2nd	0.96	0.98	0.94	0.93
	(0.81-1.14)	(0.82-1.17)	(0.81-1.08)	(0.80-1.07)
3rd	0.97	0.94	1.01	0.95
	(0.82-1.14)	(0.81-1.18)	(0.88-1.16)	(0.82-1.10)
4th	1.01	0.94	1.10	0.93
	(0.86-1.19)	(0.78-1.13)	(0.95-1.26)	(0.80-1.10)
Observations	1265787	1265787	1422366	1422366
Covariates	NO	YES	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 µg/m3 increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with one year lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table 4. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's Disease onset, one year lag, by age

	Age in 2011 < 50 years		Age in 2011 >= 50 years	
	Model 1	Model 2	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)				
Linear model	1.12***	1.05*	1.00	0.97
	(1.07 -1.17)	(1.00 -1.11)	(0.97-1.03)	(0.94-1.01)
Quartiles model				
1st (reference)				
2nd	1.32*	1.26**	0.94	0.93
	(1.06-1.64)	(1.01-1.56)	(0.82-1.07)	(0.82-1.06)
3rd	1.33*	1.23	0.93	0.91
	(1.05-1.68)	(0.97-1.55)	(0.81-1.07)	(0.79-1.05)
4th	1.65***	1.30*	1.02	0.93
	(1.30-2.08)	(1.01-1.67)	(0.87-1.18)	(0.79-1.09)
Observations	1413737	1413737	1274416	1274416
Covariates	NO	YES	NO	YES
Panel B (NO_2, $\mu g/m^3$)				
Linear model	1.02***	1.00	0.99	0.99*
	(1.01-1.04)	(0.99-1.02)	(0.99-1.01)	(0.98-1.00)
Quartiles model				
1st (reference)				
2nd	1.01	1.01	0.93	0.94
	(0.82-1.24)	(0.81-1.24)	(0.82-1.06)	(0.82-1.06)
3rd	1.31**	1.24*	0.89	0.86*
	(1.08-1.60)	(1.00-1.54)	(0.78-1.01)	(0.75-0.98)
4th	1.41***	1.19	0.95	0.86*
	(1.15-1.72)	(0.94-1.51)	(0.83-1.07)	(0.75-1.00)
Observations	1413737	1413737	1274416	1274416
Covariates	NO	YES	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 µg/m3 increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with one year lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Sensitivity Analysis

Our finding of no statistically significant association in the overall sample between either $PM_{2.5}$ or NO_2 exposure and PD onset in models adjusted for measured individual, household and neighbourhood confounders was robust to estimation as dual-pollutant rather than single-pollutant models (Figure A1); to extending the sample by including those with partially missing exposure information by imputing exposure information missing for a given period using the within-individual average exposure in adjacent periods (Table A3); to beginning our analysis window for PD onset from the first

available data point (2010 semester 2) excluding those who were on PD drugs in the prior period (2010 semester 1) rather than restricting exposures to be post-Census (Table A4); to specifying exposure contemporaneously, as well as to varying the exposure lag to 6 and 18 months instead of the one-year lag (Tables A5 to A7). Additionally, medium-term exposure, defined as exposure to pollution over a semester, was replaced with two-year moving average exposures when considering various lagged effects: one year, 18 months, and contemporaneous effects. This substitution attenuated the estimated pollution effects, even in unadjusted models when considering one year lag (Tables A8 to A10).

In addition, to explore whether age-related differences in the delay between symptom onset and receipt of the first prescription might explain the contrast in results between younger and older age groups shown in Table 4, we re-estimated age-group-specific models using six-month exposure periods with various lagged effects: no lag, 6-month lag, and 18-month lag (Tables A11 to A13). Most significant associations disappeared when we shortened the lag from one year to 6 months or no lag (Tables A11 and A12). This aligns with our expectations based on literature[40] suggesting that a one-year lag is potentially the most appropriate model. However, our main findings remained robust to extension of the lag to 18 months (Table A13). Estimates were in line with those for our preferred model presented in Table 4, with null exposure effects on the hazard for PD onset for the older age group and statistically significant and positive effects for the younger age group, with some evidence of dose response for both NO_2 and $PM_{2.5}$ exposure. For the older age group, we did not find evidence for a positive association between pollution exposure and PD onset even at longer lags. Although we cannot rule out that our estimates were affected by delays to diagnosis and/or first prescription, such delays do not appear to explain the contrast in results by age.

Finally, we explored the robustness of age-group specific models to changing the exposure duration from one semester to two years moving average exposure with one year lag (Table A14), and by beginning our analysis window for PD onset from the first available data point (2010 semester 2) excluding those who were on PD drugs in the prior period (2010 semester 1) rather than restricting exposures to be post-Census (Table A15). In both cases, our estimates of $PM_{2.5}$ exposure effects were similar to those reported in Table 4, although estimated NO_2 exposure effects were no longer statistically significant.

DISCUSSION

Like many existing studies we found evidence of a positive unadjusted association between medium-term $PM_{2.5}$ (but not NO_2) exposures and PD onset for the NILS-EPD cohort analysed here.[23,24,25] But there were also marked differences in (pre-onset) characteristics between those who did and did not experience PD onset in our cohort, for example with those going on to experience PD onset being on average older, more socially disadvantaged by a variety of individual, household and neighbourhood measures, and more likely to be female. Once we adjusted for these differences in measured characteristics, we found no evidence of positive associations between PD onset and either $PM_{2.5}$ or NO_2 exposures for the overall cohort. This finding of no association in adjusted models is consistent with the findings of around half of the existing studies listed in Table A1.[13,14,19,29]

Comparing our own findings to those of other studies is complicated by variation in factors such as exposure levels and durations studied, the extent to which exposures are lagged, PD measures employed, population studied, and the extent of statistical adjustment for potentially confounding measurable factors. For example, our study took place in a relatively low pollution context compared to most existing studies reported in Table A1. Exceptions to this include Salimi et al. (2020)[19], which similarly found no statistically significant association between exposure to both NO_2 and $PM_{2.5}$ and

self-reported PD in New South Wales, Australia; Rumrich et al. (2023),[13] which similarly found no association between $PM_{2.5}$ exposures and PD onsets in Finnish data; and Cole-Hunter et al. (2023),[28] which found a positive and statistically significant association between PD mortality and $PM_{2.5}$ exposure across six European countries, in contrast to our own finding. Note, however, that Salimi et al. (2020)[19] and Rumrich et al. (2023)[13] used diagnosis-based outcome measures (closer to our own prescriptions-based measure), whereas Cole-Hunter et al. (2023)[28] used a measure of PD mortality.

Among the few studies in the overall pollution-PD literature that have used prescription-based outcome measures, conclusions appear similarly mixed. For example, Cerza et al. (2018)[17] (who combine drug registry data with other outcome measures) found no statistically significant association between PD and $PM_{2.5}$ exposure. In contrast, Lee at al. (2016)[31] reported a statistically significant positive association, albeit for pollutants other than $PM_{2.5}$ and NO_2 (e.g., CO and NOx).

This study is one of few to have examined evidence for heterogeneity in the effect of exposure to pollution on PD onset. In line with our estimates for the overall cohort, we found no evidence of $PM_{2.5}$ or NO_2 effects on PD onset in subsamples by sex and for those aged 50+ years based on Census 2011. But we found some evidence hinting at positive and statistically significant associations between $PM_{2.5}$ and PD onset among those aged under 50 years at that point, with more tentative indication of an association with NO_2 exposure. Again, existing evidence in these respects is mixed, with Lee et al. (2022)[37] reporting a significant association with $PM_{2.5}$ exposure for males but not females and Liu et al. (2016)[35] reporting no significant association for either males or females (although they report a significant association with PM_{10} exposure for females but not males). These two studies took contrasting approaches in other respects, however, with the former paper using hospital admission records in cohort data and the latter using self-reported measures in case-control data, for example. Lee et al. (2022)[37] also estimated associations by age group (reporting a significant association with $PM_{2.5}$ exposure among study participants over-65 but not among those under-65). Though not directly comparable, the former finding appears at odds with our own finding of a significant association for under-50s but not for over-50s.

Our finding – unique in the literature to date – that exposure to pollution (particularly $PM_{2.5}$ pollution) is associated, albeit tentatively, with the onset of PD among <50s but not with onset of PD among those aged 50+ years in the NILS-EPD cohort might reflect a genuine difference in the etiology of PD across age cohorts. There is some existing evidence for etiologic differences in early versus late onset of PD.[39] However, given that PD has several clinical subtypes, pathogenic genes and putative causative environmental agents[58], reaching a fuller understanding of such differences remains a challenge for the wider literature. There may also be one or more non-biological explanations for this contrast. We conjecture here that one such potential explanation is differences in the delay between onset of symptoms and PD diagnosis and/or first prescription for PD medication, given existing evidence of higher diagnostic delays for PD at older ages. Such delays introduce uncertainty regarding the relevant lag structure for exposures within models of PD onset and, crucially, might also differentially attenuate estimated associations at a given lag length by age group. Most of the PD-pollution literature ignores this potential source of bias, although it is acknowledged by some studies.[23,24] In the absence of data on the onset of symptoms, we have been unable to examine this issue explicitly here. Nevertheless, we have shown that our conclusions, and crucially the contrast between estimated pollution effects for under-50s and over-50s, are robust to extending the lag of exposures beyond 12 months, although less so to shortening the lag below 12 months. The suggestion is that diagnostic delays and/or gaps between diagnosis and first prescription are unlikely to fully explain the contrasting findings for the younger and older age groups, although we cannot rule out some role. Further research on the possible age-specificity of the association between PD and ambient air pollution exposure, and potential mechanisms for this, is clearly warranted.

In addition to the limited extent to which we can test alternative explanations for the age contrast in our estimates, this study has other limitations, some of which are common to some existing studies in this literature, and others which represent trade-offs with alternatives adopted in some other studies. For example, our data only enabled us to consider outdoor air pollution, despite growing evidence of the importance of indoor air pollution in health outcomes.[59–61] To achieve population coverage, we used modelled pollution data in the form of annual averages at 1km grid-square level. Using prescription data to measure PD outcomes rather than alternatives likely reduces scope for some forms of measurement error in the outcome but may introduce others, e.g., if PD-related drugs are dispensed to people without PD but with some other underlying health conditions. Lastly, although our data enabled us to study the effects of exposure durations ranging from six months to two years, we were not able to study the effects of short-term pollution events or of longer-term exposures. The most appropriate exposure duration or durations to study in the case of PD, and with what lags, remains unclear.

It is crucial to emphasize that our overall null finding should not undermine the importance of reducing population exposures to $PM_{2.5}$ or NO_2. There is a substantial body of literature that demonstrates strong conditional associations between exposures and a wide range of health outcomes at the population level, and a growing number of quasi-experimental studies that support a potentially or likely-causal interpretation of the association between ambient air pollution and at least some of these health outcomes.[9,62–69] There are also several studies in the emerging PD-pollution literature which provide convincing evidence that pollution exposure is positively associated with PD onset in at least some contexts. Further, this study has presented evidence for such an association at younger ages, even in the comparatively low pollution context of Northern Ireland.

CONCLUSION

This study contributes to the emerging literature examining the association between exposure to medium-term ambient air pollution and the onset of PD by providing new evidence for a previously unstudied, large and nationally representative cohort for Northern Ireland. These data have several advantages for this purpose, including complete address records which enable linkage to pollutant concentrations at the local level over an extended time frame; linkage to detailed Census data which enables statistical adjustment for a rich set of covariates at individual, household and neighbourhood levels; and linkage to primary care prescriptions register data reducing the scope for the kinds of measurement errors associated with self-reports or hospital-based outcome measures.[70–72] We also examined evidence for heterogeneous PD-pollution associations by conducting subgroup analysis by sex and age.

We found no evidence of associations between $PM_{2.5}$ and NO_2 exposures and PD onset for the overall cohort after adjusting for covariates. Similarly, we found no evidence of associations between exposures and PD onset in male and female subsamples and for those aged 50+ years. However, we found evidence of statistically significant and positive associations between PD onset and $PM_{2.5}$ exposure, and more tentatively NO_2 exposure, among those in our study population aged under 50 years.

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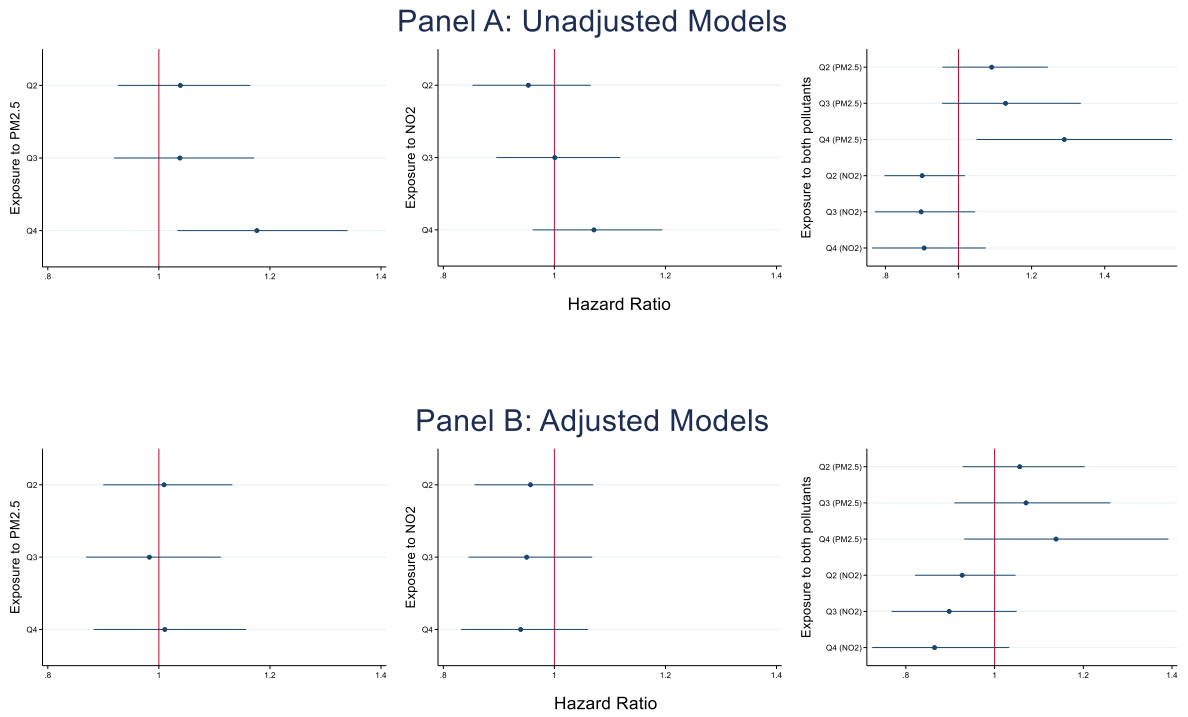
APPENDIX

Figure A1. Hazard ratios for the association between medium-term exposure, with one year lag, to $PM_{2.5}$ and NO_2 and PD onset, overall sample, single and dual-pollutant models



Note. All graphs show hazard ratios with 95% confidence intervals, based on coefficient estimates from a Cox Proportional Hazards (CPH) model with standard errors clustered by SOA. Panel A presents unadjusted model and Panel B presents adjusted model estimates controlling for covariates listed in Table 1. Hazard ratios for a 1 μg/m³ increase in $PM_{2.5}$ and NO_2 are estimated using two separate models (the left-hand chart for $PM_{2.5}$ and the middle chart for NO_2) as well as a combined model including both pollutants (the right-hand chart). Only quartile models are presented.

Table A1. Previous studies on the association between Parkinson Disease and $PM_{2.5}$ or NO_2 air pollution

Author (year of publication)	Country	Study design/Method	HR or OR (95% CI)	Mean exposure level	PD measure
$PM_{2.5}$ (µg /m^3)					
Palacios et al. (2014)	USA	Cohort/CPH[2]	1.10 (0.83-1.45)	N/A	self-reported
Liu et al. (2016)	USA	Case-control/LR[3]	**1.29 (0.94-1.76)**	13.1[4]	Self-reported
Cerza et al. (2018)	Italy	Cohort/CPH	0.96 (0.92–1.01) per 5 µg/m3	17	Several sources Drug Prescriptions + Hospital discharges
Palacios et al. (2017)	USA	Cohort/CPH	0.97 (0.72-1.32)[5]	14.7[6]	Self-reported
Lee et al. (2017)[7]	South Korea	Case-control /LR	**1.61 (1.14-2.29)** per 10 µg/m3	N/A	emergency admission cases with primarily diagnosed PD
Shin et al. (2018)	Canada	Cohort/CPH	**1.04 (1.01-1.08)** for every IQR-increase	9.8	physician claims for PD
Salimi et al. (2020)	Australia	Cohort/LR	1.01 (0.98-1.04)	5.8	Self-reported
Shi et al. (2020)	USA	Cohort	**1.13 (1.12-1.14)** per 5 µg/m3	9.7	Hospital admission
Jo et al. (2021)	South Korea	Cohort/CPH	0.89 (0.60-1.32) HR for highest vs lowest quartile	26.5 (18.0-44.4)[8]	National Health Insurance registered Code
Wijngaarden et al. (2021)	USA	Cohort/Poisson	**1.06 (1.00, 1.12)** per interquartile range (IQR) increase	8.6-11.8 [9]	Hospital admission with relevant ICD codes
Rhew et al. (2021)	USA	Case-control/LR	1.13 (0.92-1.31)	10.27	Hospital admissions

[2] Cox Proportional Hazard Models
[3] Logistic Regression
[4] Median of the 3rd quantile range
[5] Comparing the top to the bottom quintile of PM exposure
[6] Median of the 3rd quantile range
[7] This is an example for short term exposure effect following a unit increase in 8-day moving average.
[8] Median (range)
[9] Range across various sites

Lee et al. (2022)	South Korea	Cohort /CPH	**1.19 (1.01-1.19)** per interquartile range (3.3 µg/m3)	30.4[10]	emergency admission cases with primarily diagnosed PD
Cole-Hunter et al. (2023)	Six European countries	Cohort/CPH	**1.25 (1.01-1.55)** per 5 µg/m3	N/A	PD mortality from mortality registries
Rumrich et al. (2023)	Finland	Case-Control/LR	0.99(0.96, 1.02) per interquartile range (3.9 µg/m3)	7.7	Incident PD diagnosis using Finnish special reimbursement register.
NO_2 (ppm or µg /m^3)					
Ritz et al. (2016)	Denmark	Case-control/LR	**1.21 (1.11-1.31)**	13.71 µg/m^3	National Hospital Register
Liu et al. (2016)	USA	Case-control/LR	1.02 (0.95-1.11)	11.8[11]	Self-reported
Cerza et al. (2016)	Italy	Cohort/CPH	0.97 (0.96–0.99) per 10 µg /m3 increase	42.7	
Lee et al. (2017)	South Korea	Case-control /LR	**2.35 (1.39-3.97)** per 10 ppb	N/A	emergency admission cases with primarily diagnosed PD
Shin et al. (2018)	Canada	Cohort/CPH	**1.03 (1.00-1.06)** for every IQR-increase	14.7 ppb	physician claims for PD
Salimi et al. (2020)	Australia	Cohort/LR	1.03 (0.98-1.08)	11.9 µg/m^3	Self-reported
Jo et al. (2021)	South Korea	Cohort/CPH	**1.41 (1.02-1.95)** HR for highest vs lowest quartile	0.033 (0.026-0.045) ppm[12]	National Health Insurance registered Code
Cole-Hunter et al. (2023)	Six European countries	Cohort/CPH	1.13 (0.95–1.34) per 10 µg /m3 increase	N/A	PD mortality from mortality registries

[10] Median of the 3rd quantile range
[11] Median of the 3rd quantile range in ppb
[12] Median (range)

Table A2. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's Disease onset, one year lag, overall sample, full regression results, Model 2

	$PM_{2.5}$		NO_2	
	Linear Model	Quartiles Model	Linear Model	Quartiles Model
Lagged linear effect	0.99		0.99	
	(0.96 - 1.02)		(0.98 - 1.00)	
Lagged Quartiles effect				
(Ref: 1st Quartile)				
Quartile 2		1.01		0.96
		(0.90 - 1.13)		(0.86 - 1.07)
Quartile 3		0.99		0.95
		(0.87 - 1.11)		(0.84 - 1.07)
Quartile 4		1.01		0.94
		(0.88 - 1.16)		(0.83 - 1.06)
Gender (Ref: Female)				
Male	0.82***	0.82***	0.82***	0.82***
	(0.76 - 0.89)	(0.76 - 0.89)	(0.76 - 0.89)	(0.76 - 0.89)
Age Group (Ref: < =30)				
31-35	1.41*	1.41*	1.41*	1.41*
	(1.02 – 1.97)	(1.02 - 1.97)	(1.02 – 1.97)	(1.02 - 1.97)
36-40	1.90***	1.91***	1.90***	1.90***
	(1.37 - 2.64)	(1.37 - 2.64)	(1.37 - 2.64)	(1.37 - 2.64)
41-45	1.95***	1.95***	1.95***	1.95***
	(1.42 - 2.68)	(1.42 - 2.68)	(1.42 - 2.67)	(1.42 - 2.67)
46-50	2.00***	2.00***	2.00***	2.00***
	(1.46 – 2.73)	(1.46 – 2.73)	(1.46 – 2.74)	(1.46 – 2.74)
51-55	2.17***	2.17***	2.17***	2.17***
	(1.59 - 2.97)	(1.59 - 2.97)	(1.59 - 2.97)	(1.59 - 2.97)
56-60	2.28***	2.28***	2.28***	2.28***
	(1.66 – 3.14)	(1.66 – 3.14)	(1.66 – 3.14)	(1.66 – 3.14)
61-65	2.77***	2.77***	2.77***	2.77***
	(2.00 – 3.82)	(2.00 – 3.82)	(2.00 – 3.82)	(2.00 – 3.82)
66-70	3.13***	3.13***	3.13***	3.13***
	(2.26 – 4.35)	(2.26 – 4.35)	(2.26 – 4.35)	(2.25 – 4.34)
71-75	3.73***	3.73***	3.73***	3.73***
	(2.68 – 5.18)	(2.68 – 5.18)	(2.69 – 5.18)	(2.68 – 5.17)
76-80	4.31***	4.31***	4.31***	4.30***
	(3.10 – 6.00)	(3.10 – 6.00)	(3.10 – 6.00)	(3.10 – 6.00)
80+	2.99***	2.99***	3.00***	2.99***
	(2.11 - 4.24)	(2.11 -4.24)	(2.11 - 4.25)	(2.11 -4.24)
COB (Ref: Northern Ireland)				
Rest of UK	0.99	0.99	0.98	0.99
	(0.84 - 1.16)	(0.84 - 1.16)	(0.83 - 1.16)	(0.84 - 1.16)
Republic of Ireland	0.87	0.87	0.86	0.86
	(0.69 - 1.09)	(0.69 - 1.09)	(0.68 - 1.08)	(0.69 - 1.09)
Born Elsewhere	0.65**	0.65**	0.65**	0.55**
	(0.48 - 0.89)	(0.48 - 0.89)	(0.48 - 0.89)	(0.48 - 0.89)
Education (Ref: No Qualifications)				
Below Degree or Equivalent	0.88*	0.88**	0.89*	0.88*
	(0.80 - 0.97)	(0.80 - 0.97)	(0.81 - 0.97)	(0.81 - 0.97)
Degree, Equivalent or above	0.74***	0.74***	0.75***	0.75***
	(0.66 - 0.83)	(0.66 - 0.83)	(0.67 - 0.83)	(0.67 - 0.83)
Economic Status (Ref: Inactive)				

Empl= Employed/self emp	0.72***	0.72***	0.73***	0.72***
	(0.65 – 0.81)	(0.65 – 0.81)	(0.65 – 0.81)	(0.65 – 0.81)
Marital Status (Ref: Never Married)				
Married	1.13	1.13	1.13	1.13
	(0.99 - 1.28)	(0.99 - 1.28)	(1.00 - 1.28)	(1.00 - 1.28)
Separated/Divorced/Widowed	1.08	1.08	1.08	1.08
	(0.95 - 1.23)	(0.95 - 1.23)	(0.94 - 1.23)	(0.95 - 1.24)
Other	0.61	0.61	0.60	0.60
	(0.19 - 1.89)	(0.19 - 1.89)	(0.19 - 1.89)	(0.19 - 1.89)
Religion (Ref: Catholic)				
Protestant or Other Christian/Religion	1.07	1.07	1.08	1.07
	(0.98 - 1.17)	(0.98 - 1.17)	(0.99 - 1.18)	(0.95 - 1.19)
No Religion or None Stated	1.06	1.06	1.07	1.07
	(0.94 - 1.21)	(0.94 – 1.21)	(0.95 - 1.22)	(0.94 - 1.21)
General Health (Ref: Bad/Very bad Health)				
health = 1, Fair/Good/Very good GH	0.72***	0.72***	0.72***	0.72***
	(0.657 - 0.80)	(0.65 - 0.80)	(0.65 - 0.80)	(0.65 - 0.80)
LTAL Illness (Ref: NO)				
With Long-Term Illness	1.99***	1.99***	1.91***	1.91***
	(1.81 – 2.18)	(1.81 – 2.18)	(1.72 – 2.12)	(1.73– 2.12)
No. of Children in Household (Ref: 0)				
1	0.90	0.95	0.90	0.99
	(0.78 - 1.03)	(0.78 - 1.03)	(0.78 - 1.04)	(0.78 - 1.04)
2	0.74***	0.74***	0.74***	0.74***
	(0.63 - 0.88)	(0.63 - 0.88)	(0.63 - 0.83)	(0.63 - 0.83)
3+	0.90	0.90	0.89	0.89
	(0.73 - 1.10)	(0.73 - 1.10)	(0.72 - 1.10)	(0.72 - 1.10)
No. of Cars in Household (Ref: 0)				
1	0.99	1.00	0.99	0.99
	(0.90 - 1.10)	(0.90- 1.11)	(0.89 - 1.09)	(0.89 - 1.10)
2	0.90	0.91	0.89	0.90
	(0.79 -1.03)	(0.80 – 1.04)	(0.78 - 1.02)	(0.78 - 1.02)
3+	0.96	0.97	0.94	0.95
	(0.82 - 1.14)	(0.82 - 1.15)	(0.80 - 1.11)	(0.80 - 1.13)
People per room (Ref: >1)				
ppr = 1	1.01	1.01	1.01	1.01
	(0.73 - 1.40)	(0.73 - 1.40)	(0.73 - 1.40)	(0.73 - 1.40)
2010 Multiple Deprivation Measure (Ref: 1 (Most deprived))				
2	1.01	1.02	0.98	1.01
	(0.86 - 1.19)	(0.87 - 1.20)	(0.84 - 1.16)	(0.86 - 1.19)
3	1.03	1.04	1.00	1.03
	(0.88 - 1.21)	(0.89 - 1.22)	(0.85 - 1.18)	(0.87 - 1.20)
4	1.08	1.09	1.03	1.06
	(0.91 - 1.27)	(0.93 - 1.28)	(0.87 - 1.21)	(0.90 - 1.25)
5	1.06	1.07	1.01	1.04
	(0.88 - 1.26)	(0.90 - 1.27)	(0.85 - 1.21)	(0.87 - 1.24)
6	0.89	0.90	0.85	0.87
	(0.74 - 1.06)	(0.76 – 1.07)	(0.71 - 1.01)	(0.73 – 1.04)
7	0.96	0.97	0.92	0.95
	(0.80 - 1.15)	(0.81 - 1.16)	(0.76 - 1.11)	(0.79 - 1.14)
8	1.01	1.02	0.97	1.00
	(0.85 - 1.19)	(0.86 - 1.21)	(0.81 - 1.15)	(0.84 - 1.19)

9	0.93	0.93	0.90	0.92
	(0.78 - 1.10)	(0.79 - 1.11)	(0.75 - 1.07)	(0.78 - 1.10)
10 (Least deprived)	0.88	0.89	0.86	0.89
	(0.72 - 1.08)	(0.73 - 1.09)	(0.71 - 1.05)	(0.73 - 1.08)
Observations	2688153	2688153	2688153	2688153

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 μg/m^3 increase in $PM_{2.5}$ and NO_2 along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with one year lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A3. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, one year lag, extended sample

	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)		
Linear model	1.05* (1.01-1.09)	1.00 (0.95-1.04)
Quartiles model 1st (reference)		
2nd	1.03 (0.91-1.15)	0.99 (0.88-1.12)
3rd	1.01 (0.90-1.14)	0.95 (0.84-1.08)
4th	1.16* (1.02-1.32)	0.99 (0.87-1.14)
Observations	2765090	2765090
Covariates	NO	YES
Panel B (NO_2, $\mu g/m^3$)		
Linear model	1.03 (0.99-1.06)	0.98 (0.94-1.02)
Quartiles model		
1st (reference)		
2nd	0.96 (0.92-1.18)	0.96 (0.86-1.07)
3rd	1.00 (0.89-1.11)	0.94 (0.84-1.06)
4th	1.08 (0.97-1.21)	0.94 (0.83-1.06)
Observations	2762062	2762062
Covariates	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The extended sample includes those excluded from the original analysis sample on grounds of missing exposure values, with missing values imputed using exposure information in adjacent periods. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with one year lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.*

Table A4. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample, one year lag, extended at-risk period

	Model 1	Model 2
Panel A ($PM_{2.5}$, µg/m^3)		
Linear model	1.04* (1.01-1.06)	0.99 (0.97-1.02)
Quartiles model 1st (reference)		
2nd	1.06 (0.95-1.18)	1.03 (0.92-1.15)
3rd	1.03 (0.92-1.16)	0.97 (0.86-1.01)
4th	1.17* (1.03-1.32)	1.00 (0.87-1.13)
Observations	3234774	3234774
Covariates	NO	YES
Panel B (NO_2, µg/m^3)		
Linear model	1.01 (1.00-1.01)	0.99 (0.98-1.00)
Quartiles model		
1st (reference)		
2nd	1.00 (0.91-1.11)	1.00 (0.90-1.11)
3rd	1.01 (0.91-1.13)	0.96 (0.86-1.07)
4th	1.07 (0.97-1.19)	0.93 (0.83-1.04)
Observations	3234774	3234774
Covariates	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 µg/m^3 increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The extended at-risk period runs from 2010 S2. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with one year lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A5. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample, contemporaneous exposures

	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)		
Linear model	1.02* (1.00-1.05)	0.98 (0.96-1.01)
Quartiles model 1st (reference)		
2nd	1.10 (0.99-1.22)	1.06 (0.95-1.18)
3rd	1.03 (0.91-1.15)	0.96 (0.86-1.09)
4th	1.15* (1.02-1.29)	0.97 (0.86-1.09)
Observations	2697318	2697318
Covariates	NO	YES
Panel B (NO_2, $\mu g/m^3$)		
Linear model	1.00 (1.00-1.01)	0.99* (0.98-1.00)
Quartiles model		
1st (reference)		
2nd	1.04 (0.93-1.16)	1.04 (0.93-1.16)
3rd	1.04 (0.93-1.16)	0.99 (0.88-1.11)
4th	1.08 (0.97-1.21)	0.95 (0.84-1.08)
Observations	2697318	2697318
Covariates	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with no lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A6. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample, 6 months lag exposures

	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)		
Linear model	1.03* (1.00-1.06)	0.99 (0.96-1.02)
Quartiles model 1st (reference)		
2nd	1.07 (0.96-1.19)	1.03 (0.92-1.15)
3rd	1.01 (0.89-1.13)	0.95 (0.84-1.07)
4th	1.17* (1.03-1.32)	1.00 (0.88-1.14)
Observations	2693667	2693667
Covariates	NO	YES
Panel B (NO_2, $\mu g/m^3$)		
Linear model	1.00 (1.00-1.01)	0.99 (0.98-1.00)
Quartiles model		
1st (reference)		
2nd	0.98 (0.88-1.10)	0.99 (0.89-1.10)
3rd	1.02 (0.92-1.14)	0.97 (0.87-1.09)
4th	1.11 (0.99-1.23)	0.98 (0.87-1.11)
Observations	2693667	2693667
Covariates	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with 6 months lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A7. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample, 18 months lag exposures

	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)		
Linear model	1.03* (1.00-1.06)	0.99 (0.96-1.02)
Quartiles model 1st (reference)		
2nd	1.01 (0.88-1.14)	1.00 (0.88-1.14)
3rd	1.05 (0.92-1.19)	1.01 (0.89-1.15)
4th	1.11 (0.97-1.27)	0.97 (0.84-1.12)
Observations	2681410	2681410
Covariates	NO	YES
Panel B (NO_2, $\mu g/m^3$)		
Linear model	1.00 (1.00-1.01)	0.99 (0.98-1.00)
Quartiles model		
1st (reference)		
2nd	1.02 (0.91-1.14)	1.03 (0.92-1.15)
3rd	1.03 (0.92-1.15)	0.98 (0.87-1.10)
4th	1.07 (0.96-1.19)	0.94 (0.83-1.06)
Observations	2681410	2681410
Covariates	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with 18 months lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A8. Hazard ratios (95% CI) for the association between 2-year moving average exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample with one year lag

	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)		
Linear model	1.03 (1.00-1.05)	0.98 (0.95-1.01)
Quartiles model 1st (reference)		
2nd	0.96 (0.85-1.08)	0.98 (0.86-1.11)
3rd	1.03 (0.91-1.16)	1.01 (0.89-1.14)
4th	1.08 (0.96-1.21)	0.95 (0.84-1.09)
Observations	2639622	2639622
Covariates	NO	YES
Panel B (NO_2, $\mu g/m^3$)		
Linear model	1.00 (1.00-1.01)	0.99 (0.98-1.00)
Quartiles model		
1st (reference)		
2nd	1.00 (0.89-1.12)	1.01 (0.90-1.14)
3rd	0.99 (0.93-1.18)	0.95 (0.84-1.07)
4th	1.09 (0.99-1.27)	0.96 (0.88-1.15)
Observations	2639608	2639608
Covariates	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports 2-year moving average exposure effect lagged one year. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A9. Hazard ratios (95% CI) for the association between 2-year moving average exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample with 18 months lag

	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)		
Linear model	1.02 (0.99-1.05)	0.98 (0.95-1.01)
Quartiles model 1st (reference)		
2nd	0.89* (0.79-0.99)	0.90 (0.94-1.24)
3rd	0.99 (0.89-1.12)	0.97 (0.99-1.30)
4th	1.03 (0.92-1.15)	0.91 (0.81-1.03)
Observations	2632661	2632661
Covariates	NO	YES
Panel B (NO_2, $\mu g/m^3$)		
Linear model	1.00 (1.00-1.01)	0.99 (0.98-1.00)
Quartiles model		
1st (reference)		
2nd	0.99 (0.88-1.11)	1.01 (0.90-1.13)
3rd	1.00 (0.89-1.12)	0.97 (0.86-1.10)
4th	1.11 (0.99-1.24)	0.99 (0.88-1.12)
Observations	2632644	2632644
Covariates	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports 2-year moving average exposure effect lagged 18 months. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A10. Hazard ratios (95% CI) for the association between 2-year moving average exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample, contemporaneous exposure

	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)		
Linear model	1.03* (1.00-1.06)	0.99 (0.96-1.02)
Quartiles model 1st (reference)		
2nd	0.97 (0.87-1.08)	0.98 (0.87-1.09)
3rd	1.14* (0.89-1.11)	1.13 (0.84-1.07)
4th	1.10 (0.98-1.24)	1.03 (0.84-1.09)
Observations	2649917	2167775
Covariates	NO	YES
Panel B (NO_2, $\mu g/m^3$)		
Linear model	1.00 (1.00-1.01)	0.99 (0.98-1.00)
Quartiles model		
1st (reference)		
2nd	1.04 (0.93-1.17)	1.06 (0.95-1.19)
3rd	1.03 (0.92-1.16)	1.00 (0.89-1.13)
4th	1.11 (0.99-1.24)	0.99 (0.88-1.11)
Observations	2649917	2649917
Covariates	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Each cell presents the estimated hazard ratio for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports 2-year moving average exposure effect with no lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.*

Table A11. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample, contemporaneous exposure, by age

	Age in 2011 < 50 years		Age in 2011 >= 50 years	
	Model 1	Model 2	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)				
Linear model	1.10***	1.03	0.99	0.97
	(1.05 -1.14)	(0.98 -1.08)	(0.96-1.02)	(0.94-1.00)
Quartiles model				
1st (reference)				
2nd	1.22*	1.15	1.04	1.02
	(1.01-1.49)	(0.94-1.40)	(0.92-1.18)	(0.90-1.16)
3rd	1.21	1.10	0.94	0.92
	(0.98-1.49)	(0.88-1.37)	(0.82-1.08)	(0.79-1.06)
4th	1.50***	1.16	1.01	0.92
	(1.21-1.85)	(0.92-1.46)	(0.88-1.17)	(0.79-1.07)
Observations	1419326	1419326	1277992	1277992
Covariates	NO	YES	NO	YES
Panel B (NO_2, $\mu g/m^3$)				
Linear model	1.02***	1.00	0.99	0.99*
	(1.01-1.04)	(0.99-1.02)	(0.99-1.01)	(0.98-1.00)
Quartiles model				
1st (reference)				
2nd	0.94	0.94	1.07	1.07
	(0.77-1.15)	(0.76-1.15)	(0.95-1.21)	(0.95-1.22)
3rd	1.32**	1.26*	0.93	0.90
	(1.09-1.61)	(1.02-1.56)	(0.81-1.05)	(0.79-1.03)
4th	1.35***	1.14	0.98	0.89
	(1.10-1.65)	(0.91-1.44)	(0.85-1.11)	(0.77-1.03)
Observations	1419326	1419326	1277992	1277992
Covariates	NO	YES	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Sample splits by age below and above 50, and each cell presents the estimated hazard ratio for a 1 µg/m3 increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with no lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A12. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample with 6 months lag, by age

	Age in 2011 < 50 years		Age in 2011 >= 50 years	
	Model 1	Model 2	Model 1	Model 2
Panel A ($PM_{2.5}$, µg/m³)				
Linear model	1.10***	1.03	1.00	0.98
	(1.05 -1.15)	(0.98 -1.08)	(0.97-1.03)	(0.94-1.01)
Quartiles model				
1st (reference)				
2nd	1.28*	1.20	1.04	1.02
	(1.05-1.56)	(0.98-1.47)	(0.92-1.18)	(0.90-1.16)
3rd	1.17	1.05	0.94	0.92
	(0.93-1.45)	(0.84-1.33)	(0.82-1.08)	(0.79-1.06)
4th	1.50***	1.15	1.01	0.92
	(1.20-1.87)	(0.91-1.47)	(0.88-1.17)	(0.79-1.07)
Observations	1416956	1416956	1276711	1276711
Covariates	NO	YES	NO	YES
Panel B (NO_2, µg/m³)				
Linear model	1.02***	1.00	1.00	0.99*
	(1.01-1.04)	(0.99-1.02)	(0.99-1.01)	(0.98-1.00)
Quartiles model				
1st (reference)				
2nd	0.95	0.95	0.99	1.00
	(0.77-1.16)	(0.77-1.17)	(0.88-1.13)	(0.88-1.13)
3rd	1.32**	1.26*	0.90	0.88
	(1.08-1.61)	(1.02-1.56)	(0.80-1.02)	(0.77-1.00)
4th	1.43***	1.23	0.98	0.91
	(1.17-1.75)	(0.98-1.55)	(0.87-1.12)	(0.79-1.05)
Observations	1416956	1416956	1276711	1276711
Controls	NO	YES	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Sample splits by age below and above 50, and each cell presents the estimated hazard ratio for a 1 µg/m3 increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with 6 months lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A13. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample, 18 months lag exposures, by age

	Age in 2011 < 50 years		Age in 2011 >= 50 years	
	Model 1	Model 2	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)				
Linear model	1.11***	1.05*	1.00	0.97
	(1.07 -1.16)	(1.00 -1.10)	(0.96-1.03)	(0.93-1.00)
Quartiles model				
1st (reference)				
2nd	1.18	1.16	0.94	0.93
	(0.98-1.89)	(0.91-1.48)	(0.81-1.09)	(0.82-1.09)
3rd	1.36*	1.31*	0.94	0.92
	(1.07-1.73)	(1.03-1.67)	(0.81-1.09)	(0.79-1.07)
4th	1.54***	1.27	0.96	0.88
	(1.21-1.97)	(1.01-1.67)	(0.82-1.12)	(0.74-1.04)
Observations	1409732	1409732	1271678	1271678
Covariates	NO	YES	NO	YES
Panel B (NO_2, $\mu g/m^3$)				
Linear model	1.02***	1.01	0.99	0.99*
	(1.01-1.04)	(0.99-1.02)	(0.99-1.00)	(0.98-1.00)
Quartiles model				
1st (reference)				
2nd	1.06	1.06	1.01	1.01
	(0.82-1.24)	(0.81-1.24)	(0.89-1.14)	(0.89-1.15)
3rd	1.31**	1.24*	0.92	0.90
	(1.08-1.60)	(1.00-1.54)	(0.81-1.04)	(0.78-1.02)
4th	1.41***	1.20	0.95	0.86*
	(1.15-1.72)	(0.94-1.51)	(0.83-1.07)	(0.75-1.00)
Observations	1409732	1409732	1271678	1271678
Covariates	NO	YES	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Sample splits by age below and above 50, and each cell presents the estimated hazard ratio for a 1 µg/m3 increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with 18 months lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A14. Hazard ratios (95% CI) for the association between 2-year moving average exposure to $PM_{2.5}$ and NO_2 and Parkinson's Disease onset, one year lag, by age

	Age in 2011 < 50 years		Age in 2011 >= 50 years	
	Model 1	Model 2	Model 1	Model 2
Panel A ($PM_{2.5}$, µg/m³)				
Linear model	1.12***	1.06*	0.99	0.96*
	(1.07 -1.17)	(1.01 -1.11)	(0.95-1.02)	(0.92-0.99)
Quartiles model				
1st (reference)				
2nd	0.96	0.99	0.94	0.97
	(0.77-1.19)	(0.78-1.24)	(0.82-1.09)	(0.84-1.12)
3rd	1.14	1.13	0.97	0.96
	(0.92-1.41)	(0.90-1.42)	(0.85-1.12)	(0.83-1.12)
4th	1.49***	1.28*	0.93	0.86*
	(1.22-1.82)	(1.02-1.61)	(0.81-1.07)	(0.74-0.99)
Observations	1386259	1386259	1253363	1253363
Covariates	NO	YES	NO	YES
Panel B (NO_2, µg/m³)				
Linear model	1.03***	1.00	0.99	0.99*
	(1.01-1.04)	(0.99-1.02)	(0.99-1.00)	(0.97-1.00)
Quartiles model				
1st (reference)				
2nd	0.98	0.98	1.01	1.02
	(0.79-1.22)	(0.78-1.22)	(0.82-1.06)	(0.89-1.16)
3rd	1.18	1.12	0.91	0.90
	(0.95-1.45)	(0.89-1. 04)	(0.78-1.01)	(0.78-1.02)
4th	1.45***	1.24	0.95	0.88
	(1.19-1.18)	(0.99-1.56)	(0.84-1.09)	(0.76-1.01)
Observations	1386247	1386247	1253361	1253361
Controls	NO	YES	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Sample splits by age below and above 50, and each cell presents the estimated hazard ratio for a 1 µg/m3 increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports 2 years moving average exposure effect with one year lag. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table A15. Hazard ratios (95% CI) for the association between medium-term exposure to $PM_{2.5}$ and NO_2 and Parkinson's disease, overall sample, with one year lag, extended at-risk period, by age

	Age in 2011 < 50 years		Age in 2011 >= 50 years	
	Model 1	Model 2	Model 1	Model 2
Panel A ($PM_{2.5}$, $\mu g/m^3$)				
Linear model	1.12***	1.05*	1.00	0.97
	(1.07 -1.16)	(1.00 -1.10)	(0.97-1.03)	(0.94-1.01)
Quartiles model				
1st (reference)				
2nd	1.31*	1.24*	0.97	0.96
	(1.06-1.60)	(1.01-1.53)	(0.86-1.10)	(0.85-1.09)
3rd	1.28*	1.19	0.94	0.91
	(1.03-1.60)	(0.95-1.49)	(0.82-1.07)	(0.79-1.04)
4th	1.60***	1.27*	1.01	0.92
	(1.29-1.99)	(1.00-1.60)	(0.88-1.17)	(0.79-1.07)
Observations	1693748	1693748	1541026	1541026
Covariates	NO	YES	NO	YES
Panel B (NO_2, $\mu g/m^3$)				
Linear model	1.02***	1.00	0.99	0.99*
	(1.01-1.04)	(0.99-1.02)	(0.99-1.01)	(0.98-1.00)
Quartiles model				
1st (reference)				
2nd	1.05	1.04	0.99	0.98
	(0.86-1.27)	(0.86-1.27)	(0.88-1.11)	(0.87-1.10)
3rd	1.28*	1.20	0.92	0.88*
	(1.06-1.54)	(0.98-1.47)	(0.81-1.03)	(0.78-1.00)
4th	1.39***	1.16	0.98	0.86*
	(1.14-1.68)	(0.93-1.44)	(0.85-1.11)	(0.76-0.98)
Observations	1693748	1693748	1541026	1541026
Covariates	NO	YES	NO	YES

*Notes. Each model is a Cox Proportional Hazard (CPH) model with standard error clustered by SOA. Sample splits by age below and above 50, and each cell presents the estimated hazard ratio for a 1 µg/m3 increase in $PM_{2.5}$ (Panel A) and NO_2 (Panel B) along with the 95% confidence interval in parentheses. The table reports a medium-term exposure effect defined as exposure to pollution over the semester with one year lag. Extended at-risk sample refers to extending at risk period to 2010 S2. Covariates are at individual, household and neighbourhood levels listed in Table 1. * p < 0.05, ** p < 0.01, *** p <0.001.*