Associations between long-term exposure to ambient air pollution and Parkinson's disease: a cross-sectional study

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Abstract

Background: Epidemiological studies have reported contradictory results regarding the effects of ambient air pollution on Parkinson's disease (PD). This study investigated the associations between long-term exposure to particulate matter < 2.5 μm in diameter ($PM_{2.5}$) and nitrogen dioxide (NO_2) and PD among participants in the 45 and Up Study, which comprised adults older than 45 years living in New South Wales, Australia.

Methods: We conducted a cross-sectional analysis of long-term exposure to $PM_{2.5}$ and NO_2 concentrations and prevalence of PD using data from around 240,000 cohort members from the 45 and Up Study, NSW. Annual average concentrations of NO_2 and $PM_{2.5}$ were estimated at the participants' residential address using satellite-based land use regression models. Logistic regression was used to quantify the associations between these pollutants and ever physician-diagnosed PD, after adjusting for a range of individual- and area-level covariates.

Results: Among the 236,390 participants with complete data, 1,428 (0.6%) reported physician-diagnosed PD. Annual mean $PM_{2.5}$ and NO_2 concentrations for the cohort were 5.8 and 11.9 $\mu g.m^{-3}$, respectively, and were positively, but not statistically significantly associated with PD. The odds ratio for a 1 $\mu g.m^{-3}$ increase in $PM_{2.5}$ was 1.01 (95% confidence interval (CI): 0.98 – 1.04). The adjusted odds ratio for a 5 $\mu g.m^{-3}$ increase in NO_2 was 1.03 (95% CI: 0.98 – 1.08). In subgroup analyses, larger associations for NO_2 were observed among past smokers (OR 1.11 (95% CI: 1.02 – 1.20) per 5 $\mu g.m^{-3}$ increase).

Conclusions: Overall, we found limited evidence of associations between long-term exposure to NO_2 or $PM_{2.5}$ and PD. The associations observed among past smokers require further corroboration.

Keywords: Parkinson's disease, air pollution, particulate matter, 45 and Up Study

1. Introduction

Parkinson's disease (PD) is a progressive and disabling neurodegenerative disorder, which, after Alzheimer's disease, is the most common neurodegenerative disorder (De Lau and Breteler 2006; Jankovic 2008). The

incidence of PD is low before 50 years of age, after which it increases sharply prior to peaking above 80 years of age (Kalia and Lang 2015). Meta-analyses of world-wide data showed a prevalence of 1,903 PD cases per 100,000 persons older than 80 years (Pringsheim et al. 2014). Studies have found evidence of a greater incidence and prevalence of PD in men compared with women (De Lau and Breteler 2006).

A meta-analysis of the risk factors for PD found lower risk of PD in smokers, with a 40% lower risk in ever smokers (Noyce et al. 2012). However, it is unclear whether the association is causal and what biological mechanisms may be involved (Ritz and Rhodes 2010). Apart from age and smoking, the aetiology of PD is still largely unknown, however, emerging evidence suggests that the interplay between genetic and environmental factors may contribute to the development of PD (Kalia and Lang 2015).

Air pollution, particularly particulate matter (PM), has been implicated as a chronic source of neuroinflammation and reactive oxygen species that may lead to neurological dysfunction (Block and Calderón-Garcidueñas 2009; Genc et al. 2012). Studies that have assessed the associations between long-term exposure to air pollution and PD have shown inconsistent findings (Cerza et al. 2018; C-Y Chen et al. 2017; H Chen et al. 2017a; Finkelstein and Jerrett 2007; Kioumourtzoglou et al. 2015; Lee et al. 2016; Liu et al. 2016; Palacios et al. 2014a; Palacios et al. 2014b; Palacios et al. 2017; Ritz et al. 2016; Shin et al. 2018). Therefore, this study aimed to examine the association between exposure to ambient $PM_{2.5}$ and NO_2 and the risk of PD using the baseline data from an established cohort of more than 265,000 people aged 45 years and older living in New South Wales (NSW), Australia.

2. Methods

2.1. Study population

We conducted a cross-sectional analysis using data from the '45 and Up Study', described in detail elsewhere (45 and Up Study Collaborators 2008). Briefly, the 45 and Up Study was established by the Sax Institute and during 2006 to 2009 recruited 266,969 adults aged 45 years and over in NSW, Australia. Participants were sampled from the Australia's Department of Human Services enrolment database. At recruitment, participants in rural and regional areas were over-sampled to ensure a sufficient sample size for analyses relevant to rural risk factors. Each participant gave signed consent for follow-up and linkage of their information to routine health databases. Participants completed a comprehensive questionnaire at baseline that included information on demographic and social characteristics, personal health behaviours, and health-related data. The study region included all areas of NSW and included a sample size of 266,969 participants.

2.2. Outcome assessment

Persons with PD in the 45 and Up Study were identified from the baseline survey conducted during 2006-2009. Participants reported whether they had ever been diagnosed with PD by a physician and, if so, the age at which the disease was first diagnosed.

2.3. Covariate data

We defined potential covariates *a priori* based on previous studies and known risk or protective factors for PD. Covariate data on age, sex, smoking status, body mass index (BMI), family history of PD, and education were obtained from the 45 And Up Study dataset. The Index of Relative Socioeconomic Disadvantage (IRSD) from the 2006 Census was used as the measure of area level SES. This index is a composite measure of a range of information on income, education, and unemployment for individuals and households within a Census Collection District, a small geographical spatial unit with an average of 220 dwellings in urban areas (ABS 2006). A lower IRSD score indicates relatively greater disadvantage (ABS 2008). Participants' IRSD scores were ranked and grouped into quintiles where category 1 represents the most disadvantaged (lowest SES) and category 5 the least disadvantaged (highest SES).

2.4. Exposure assessment

National satellite-based land use regression (Sat-LUR) models, which had undergone external validation (Knibbs et al. 2014; Knibbs et al. 2016; Knibbs et al. 2018), were used to estimate exposure to ambient NO_2 and $PM_{2.5}$ concentrations. Briefly, Sat-LUR utilises satellite observations and land-use variables to estimate annual average concentrations of both pollutants. Each participant was assigned the 2007 annual average NO_2 and $PM_{2.5}$ concentrations estimated for at the centroid of the mesh block in which they resided. Mesh blocks

are the smallest geographical area defined by the Australian Bureau of Statistics and contain 30-60 dwellings, on average.

2.5. Statistical analyses

The associations between exposure to air pollutants and PD were estimated using multivariable logistic regression models performed separately for each pollutant. Following an approach similar to the European Study of Cohorts for Air Pollution Effects (ESCAPE) study (Beelen et al. 2014), effects of exposure to NO_2 and $PM_{2.5}$ were adjusted for potential confounders, determined *a priori*, in three steps: Model 1) baseline age (in 5-year age groups), and sex; Model 2) Model 1 plus smoking status (current, previous and never smoker), body mass index (BMI) (underweight, normal, overweight, obese), physical activity (sufficient vs insufficient), education (below high school, high school, or university), marital status (single vs partnered), and family history of PD (yes/no); Model 3) Model 2 plus additional adjustment for area-level socioeconomic status (SES) (using Index of Relative Socio Economic Disadvantage). All models (1-3) were run using the Model 3 dataset with no missing covariates (n = 236,390).

Epidemiological studies have consistently observed a lower risk of PD among smokers (Chen et al. 2010). Furthermore, differences in PD incidence (Haaxma et al. 2007) with different risk factors such as diet (Chen et al. 2002) and sex have been suggested. Therefore, we evaluated potential interactions by including a multiplicative interaction with exposure and sex / smoking status in the regression model. We also conducted stratified analyses by sex and baseline smoking status.

To test the robustness of our results, we applied the following sensitivity analyses: 1) Model 3 was further adjusted for alcohol consumption; 2) since previous studies have shown that participants residing in the same area may share similar characteristics and exposure conditions, we applied mixed effect multiple logistic regression models with a random intercept by neighbourhood to account for the potential clustering.

3. Results

Of the 266,969 participants residing in the areas with available $PM_{2.5}$ and NO_2 exposure estimates, 30,579 (11%) were excluded due to missing information on outcome and/or covariates. Of the 236,390 remaining participants, 1,428 (0.6%) reported physician-diagnosed PD. PD cases were more likely to be older, male, to have not completed high school, and were more likely to have a family history of PD (Table 1).

$PM_{2.5}$ and NO_2 concentrations were relatively low (Table 2). Mean $PM_{2.5}$ and NO_2 concentrations estimated at the participants' residences were 5.8 and 11.9 $\mu g.m^{-3}$, respectively.

Table 1: Characteristics of the 236,390 45 and up study participants according to PD diagnosis at baseline.

Characteristic	No PD	PD
n (%)	234,962 (99.4)	1,428 (0.6)
Mean age, years (SD)	62.4 (11.0)	71.4 (10.5)
Male, %	47.4	56.5
Education, %		
completed some high school	33.7	43.5
completed High school	42.4	39.8
Completed University	23.9	16.6
Smoking status, %		
Current	7.2	5.3
Past	35.9	33.9
Never	56.8	60.7

Family history of PD, %	4.6	12.4
Area level SES, %		
1, most disadvantaged	20.0	25.4
2	20.0	19.5
3	20.0	18.6
4	20.0	20.0
5, least disadvantaged	20.0	16.5

Table 2: $PM_{2.5}$ and NO_2 summary statistics, 45 and Up Study.

Pollutant	N	Mean	Median	SD	Range	10th pct.	25th pct.	75th pct.	90th pct.	IQR
$PM_{2.5}$ ($\mu g.m^{-3}$)	236,362	5.75	6.00	1.66	0.10 – 10.30	3.40	4.60	7.00	7.70	2.40
NO_2 ($\mu g.m^{-3}$)	236,390	11.92	10.58	5.76	4.21 – 71.20	5.68	7.22	15.66	19.98	8.44

The associations between annual mean exposure to $PM_{2.5}$ and NO_2 and PD are shown in table 3. Further adjustments for covariates had little effects on the crude ORs for the association between exposure to the air pollutants and PD (Table 3). As Model 3 was adjusted for the greatest number of covariates chosen *a priori* it was chosen as the main model for all further analyses.

Overall, exposures to ambient $PM_{2.5}$ and NO_2 were positively, but not statistically significantly associated with ever physician-diagnosed PD (Table 3). $PM_{2.5}$ and NO_2 exposures were associated with a higher odds of PD among men compared with women, however, the inclusion of sex as an interaction term was not statistically significant (Table 4).

Table 3: Exposure to $PM_{2.5}$ and NO_2 and odds of PD.

		OR (95% CI)		
Pollutant	PD cases	Model 1	Model 2	Model 3
$PM_{2.5}$ *(per 1 $\mu g.m^{-3}$ change in $PM_{2.5}$)*	1,428	1.02 (0.99 – 1.05)	1.01 (0.98 – 1.05)	1.01 (0.98 – 1.04)
NO_2 *(per 5 $\mu g.m^{-3}$ change in NO_2)*	1,428	1.01 (0.97 – 1.06)	1.02 (0.97 – 1.07)	1.03 (0.98 – 1.08)

Model 1: adjusted for age and sex
Model 2: model 1 plus education, smoking status, physical activity, marital status, BMI and family history of PD
Model 3: model2 plus area level socio-economic status

Table 4: Exposure to $PM_{2.5}$ and NO_2 and risk of PD, stratified by sex. Odds ratios are for 1 and 5 $\mu g.m^{-3}$ changes in $PM_{2.5}$ and NO_2 concentrations, respectively.

By sex	Male (n = 110,542)		Female (n = 125,848)		*p*-Int
	PD cases	OR and 95% CI	PD cases	OR and 95% CI	
$PM_{2.5}$	807	1.02 (0.97 – 1.06)	621	1.00 (0.95 – 1.05)	0.88

NO_2	807	1.05 (0.98 – 1.12)	621	1.01 (0.94 – 1.09)	0.28

All models were adjusted for age, education, smoking status, physical activity, BMI, family history of PD, and area level socio-economic status

The inclusion of smoking status as an interaction term was statistically significant for NO_2 (p = 0.02 but not $PM_{2.5}$ (p = 0.51). In the sub-analysis stratified by smoking (Table 5), exposure to NO_2 was associated with an increased risk of PD among past smokers, OR = 1.11 (1.02 – 1.20) per unit increase in $PM_{2.5}$, while no such associations were found in current or never smokers. Application of the mixed effect model did not materially alter the effect estimates.

Table 5: Exposure to $PM_{2.5}$ and NO_2 and risk of PD, by smoking status. Odds ratios are for 1 and 5 $\mu g.m^{-3}$ changes in $PM_{2.5}$ and NO_2 levels, respectively.

By smoking status	Current smokers		Past smokers		Never smokers		*p*-Int
	PD cases	OR and 95% CI	PD cases	OR and 95% CI	PD cases	OR and 95% CI	
$PM_{2.5}$	76	1.00 (0.87 – 1.14)	485	1.03 (0.98 – 1.09)	867	1.00 (0.96 – 1.04)	0.51
NO_2	76	0.91 (0.73 – 1.13)	485	1.11 (1.02 – 1.20)	867	1.00 (0.94 – 1.06)	0.02

All models were adjusted for age, sex, education, physical activity, marital status, BMI, family history of PD, and area level socio-economic status

4. Discussion

In this study, we found positive, but not statistically significant associations between exposure to low level $PM_{2.5}$ and NO_2 and self-reported physician-diagnosed PD. The associations with NO_2 was statistically significant in past smokers while no such associations were found in current and non-smokers.

Studies that have examined the associations between long-term exposure to PM_{10}, $PM_{2.5}$ and NO_2 and PD are summarised in Table 6. Nine of 11 studies found positive associations with five results being statistically significant. Two reported negative associations. Studies have also found positive statistically significant associations with NO_2 more often than $PM_{2.5}$. The different findings across the literature may be ascribed to varying population characteristics, study designs and different PM chemical compositions at different locations.

Table 6: Summary table on the literature on associations between air pollution and PD

Author, year	Study design	Location	Population, n (age year)	Pollutant	Association	Statistically significant
This study	Cross-sectional	Australia	232,053 (>= 45 years at baseline)	$PM_{2.5}$	Positive	No
				NO_2	Positive	No
Palacios et al. (2014b)	Prospective cohort	USA	111,769 (30-55 at baseline, women)	PM_{10}	Positive	No
				$PM_{2.5}$	Positive	No
				$PM_{2.5-10}$	Negative	No
Kirrane et al. (2015)	Cross-sectional	USA	83,343 (12 – 92 at enrolment)	Ozone	Positive	No
				$PM_{2.5}$	Positive	No
Lee et al. (2016)	Case-control	Taiwan	11,117 cases	NOx	Positive	Yes
			44,468 controls	SO2	Negative	Yes

				CO	Positive	Yes
				Ozone	Positive	Yes
				PM_{10}	No associations	NA
Liu et al. (2016)	Case-control	USA	1,556 cases	NO_2	Negative	No
			3,313 controls	PM_{10}	Positive	No
				$PM_{2.5}$	Positive	No
Ritz et al. (2016)	Case-control	Denmark	1,696 cases	NO_2	Positive	Yes
			1,800 controls			
C-Y Chen et al. (2017)	Case-control	Taiwan	1,060 cases	SO_2	Positive	No
			4,240 controls	CO	Negative	No
				Ozone	Positive	No
				PM_{10}	Positive	Yes
				NO_2	Positive	No
H Chen et al. (2017b)	Population-based cohort	Canada	2,165,282 (55 – 85 years at entry)	Traffic proximity	Positive	Yes
Palacios et al. (2017)	Prospective cohort	USA	50,352 (40 – 75 years at enrolment, men	PM_{10}	Negative	No
				$PM_{2.5}$	Negative	No
				$PM_{2.5-10}$	Negative	No
Cerza et al. (2018)	Population-based cohort	Italy	1,008,253 (> 50)	NO_2	Negative	No
				Ozone	Positive	No
				PM_{10}	Negative	No
				$PM_{2.5}$	Negative	No
				$PM_{2.5-10}$	Negative	No
				$PM_{2.5\ absorbance}$	Negative	No
Shin et al. (2018)	Population-based cohort	Canada	2,194,519 (55 - 85 years)	NO_2	Positive	Yes
				Ozone	Positive	Yes
				$PM_{2.5}$	Positive	Yes

Air pollution, particularly PM, has been implicated in the aetiology of neurological dysfunction (Block and Calderón-Garcidueñas 2009; Genc et al. 2012). Evidence suggests that air pollution can induce neuroinflammation, oxidative stress, microglial activation which can contribute to central nervous system pathology (Genc et al. 2012).

Animal studies have found that exposure to different ambient air pollutants such as urban fine particles, diesel exhaust, and ultrafine particles causes elevated proinflammatory cytokines and oxidative stress in the brain (Cheng et al. 2016; Levesque et al. 2011; Mumaw et al. 2016). PM uptake is thought to take place through olfactory neurons (Calderón-Garcidueñas et al. 2008) and ultrafine PM (< 100 nm) can translocate to the central nervous system where they can activate innate immune response.

Ultrafine particle concentration correlates better with NO_2 than $PM_{2.5}$ in ambient air (Eeftens et al. 2015) since NO_2 and ultrafine particles are both more affected by traffic related air pollution compared with $PM_{2.5}$. Therefore, NO_2 may better represents exposure to ultrafine particles. This may explain the higher associations we observed with NO_2 and the fact that studies in the literature have found stronger associations between PD and NO_2 than $PM_{2.5}$. This suggests the need to conduct epidemiological studies to assess the associations between long-term exposure to the ultrafine particles and PD.

We did not find any evidence showing a modifying effect of sex on the associations between exposure to air pollution and PD. Cerza et al. (2018) found negative associations between exposure to PM absorbance and Nitrogen oxides with incidence of PD in women while no such association were observed in men. Generally, lower rates of PD have been reported for women in the literature (Van Den Eeden et al. 2003) which may be due to the protective effect of the activity of oestrogen (Haaxma et al. 2007).

Smoking has been consistently reported as a protective factor for PD. A systematic and meta-analysis of PD and cigarette smoking found consistent statistically significant negative (protective) associations, RR = 0.46 (0.42 – 0.51), between smoking and risk of PD (Breckenridge et al. 2016). We also saw a non-significant protective effect of smoking.

We found positive associations between exposure to NO_2 and PD in past smokers (OR = 1.11 (1.02 – 1.20)) while there was no such association in current and never smokers. To our knowledge, this is the first study showing significant modifying effect of smoking status on the associations of air pollution with PD. However, we do not know why past smokers would have a greater risk than current or never smokers. The protective effect of smoking overall was noted, as consistent with the literature.

Ritz et al. (2016) found higher associations between long-term exposure to air pollution and PD in current smokers while the opposite effect of smoking was found in another study (Liu et al. 2016). These findings as well as what we found in this study suggest the possibility of smoking acting as an effect modifier on the casual pathway of exposure to air pollution and PD.

A major strength of our study is its large size and the detailed individual-level information collected on potential confounders. PD cases were identified based on the questionnaire filled in by participants at baseline. Therefore, we may have biased outcome measures.

Moreover, we only had limited cases of PD despite having a large cohort. The small number of cases together with exposure misclassification may result in reduced ability to detect modest associations. In addition, we used the cross-sectional study design, therefore, our findings should be interpreted as associations rather than causality or effects. We plan to conduct future analyses on this study cohort using follow-up data of the cohort.

We also assumed that the 2007 annual average pollutant concentrations were good approximations of their long-term exposure. Knibbs et al. (2014) found a small temporal change in the spatial pattern of NO_2 concentrations between 2006-2011. Therefore, we assumed that the exposures participants in 2007 was representative of the long-term exposures. We assessed the historical $PM_{2.5}$ measurements and found that year-to-year differences in spatial pattern of $PM_{2.5}$ concentrations were small and therefore we assumed this year to be representative of annual averages of previous years.

5. Conclusions

In summary, we found limited evidence for associations between exposures to NO_2 or $PM_{2.5}$ and PD. The associations with NO_2 was stronger and statistically significant in past smokers which warrants further investigation on the modifying effects of smoking.

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