International Journal of Hygiene and Environmental Health 222 (2019) 402–409

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Air pollution and Parkinson's disease: A systematic review and meta-analysis up to 2018

Maria-Iosifina Kasdagli[a], Klea Katsouyanni[a,b], Konstantina Dimakopoulou[a], Evangelia Samoli[a,*]

[a] Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[b] Department Population Health Sciences and Department of Analytical, Environmental and Forensic Sciences, School of Population Health & Environmental Sciences, King's College London, London, UK

ARTICLE INFO

Keywords:
Air pollution
Meta-analysis
Parkinson's disease
Systematic review

ABSTRACT

Background: Recent epidemiological findings investigate effects of exposure to air pollution on neurodegenerative disease. We performed a systematic review and meta-analysis to investigate the association between air pollution exposure and Parkinson's disease (PD).

Methods: We performed an extensive literature search in PubMed and Google Scholar databases and further searched for unpublished results in conference abstracts until November 2018. We identified 102 unique studies referring to air pollution and PD, from which 15 were included in the meta-analyses. We applied random-effects models to combine risk estimates and investigated between studies heterogeneity. We assessed publication bias through plots and the Egger's test in cases of sufficient number of studies. We assessed associations accounting for multi-pollutant exposures and effect modification patterns by sex and smoking habits.

Results: We identified 13 reports investigating associations of PD with long-term exposure to regulated air pollutants whilst two reported associations for short-term exposure to $PM_{2.5}$. The pooled relative risk (RR) for incidence of PD following an increase in long-term exposure for 10 $\mu g/m^3$ in $PM_{2.5}$ was 1.06 (95% Confidence Interval (CI): 0.99, 1.14) and in NO_2 1.01 (95%CI: 0.98, 1.03), while for 5 ppb increase in O_3 1.01 (95% CI: 1.00, 1.02) and for 1 mg/m^3 in CO 1.34 (95% CI: 0.85, 2.10); the pooled RR for a hospital admission due to PD after a 10 $\mu g/m^3$ increase in $PM_{2.5}$ short-term exposure was 1.03 (95% CI: 1.01, 1.05). There was high heterogeneity between study-specific results for most of the analyses, attributed to different populations under study. Effects were robust to multi-pollutant adjustment while there were indications of higher particles' effects among non smokers.

Conclusions: We found weak evidence for an association between air pollution, mostly originating from traffic, and PD. Although meta-analysis increases power to detect small associations in rare outcomes, further research is needed to elaborate our suggestive associations. Such results are of public health significance since population aging in developed countries is expected to increase incidence of PD.

1. Introduction

The population of the European Union (EU) on 1/1/2016 was estimated at 510.3 million, with 19.2% aged 65 or over, that corresponds to an increase in this age group of 0.3% compared with the previous year and of 2.4% compared with 10 years earlier. This figure is expected to reach 25% by 2030 (EUROSTAT, 2017). Neurodegenerative disease is an umbrella term for a range of conditions which primarily affect the neurons in the human brain and are strongly linked with age. Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. Among them Parkinson's disease (PD) affects 1–2 per 1,000 of the population at any time with prevalence increasing with age and estimated to affect 1% of the population above 60 years (Tysnes and Storstein, 2017).

The cause of PD is unknown in most cases, although genetic risk factors have been identified, including monogenetic causes that are rare in unselected populations. Some genetic factor can be identified in 5–10% of the patients. Several environmental factors are associated with increased risk of PD. Since 2006, several longitudinal studies have assessed environmental or behavioral factors that seem to modify the risk of developing Parkinson's disease (Ascherio and Schwarzschild,

* Corresponding author. Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, 75 Mikras Asias street, 115 27, Athens, Greece.
E-mail address: esamoli@med.uoa.gr (E. Samoli).

https://doi.org/10.1016/j.ijheh.2018.12.006
Received 3 October 2018; Received in revised form 28 November 2018; Accepted 19 December 2018

2016). Increased risk of Parkinson's disease has been associated with exposure to pesticides, consumption of dairy products, history of melanoma, and traumatic brain injury, whereas a reduced risk has been reported in association with smoking, caffeine consumption, higher serum urate concentrations, physical activity, and use of ibuprofen and other common medications. Researchers in the field call for a need to increase knowledge on genetic and environmental risk factors of PD in order to elucidate its causes and address its primary prevention to promote healthy aging.

Exposure to air pollution has been consistently associated with adverse effects on respiratory and cardiovascular diseases (Andersen et al., 2012; Andersen et al., 2012; Lim et al., 2012; Shah et al., 2013; World Health Organization (WHO), 2013). However, little is currently known about the effects of exposure to air pollution on neurodegenerative diseases such as Parkinson's disease (PD). PD is driven by the loss of dopamine-generating cells in the substantia nigra of the brain (Malapani et al., 1994). Loss of dopaminergic neurons in the pars compacta of the substantia nigra leads to reduced facilitation of voluntary movements. a-synuclein accumulation becomes more widespread in the brain during the progression of PD (Tysnes and Storstein, 2017). Its occurrence entails motor symptoms of bradykinesia, resting tremor, muscle rigidity and postural instability while over the last 10–20 years non-motor symptoms in PD such as positive tests on cardiac sympathetic denervation or olfactory loss have been given considerable attention. PD is the second most common neurodegenerative disease in terms of personal and societal costs (Huse et al., 2005).

Toxicological studies of the human brain and animal experiments, suggest that biologic pathways may be influenced by air pollutants contributing to PD. Neuroinflammation, oxidative stress, and dopamine system–related neurotoxicity associations with air pollution exposures have also been reported (Block and Calderón-Garcidueñas, 2009; Calderón-Garcidueñas et al., 2010; Cannon et al., 2009; Levesque et al. 2011b). For example, olfactory mucosa may act as an entry route for air pollutants affecting the integrity of the central nervous system, according to an animal study which detected oxidative damage and diffuse amyloid plaques in the olfactory bulb of feral dogs living in a high-pollution region of Mexico City (Calderón-Garcidueñas et al., 2010). Further, children in Mexico residing in highly polluted areas, showed inflammation of the olfactory bulb and deficits in olfaction (Calderón-Garcidueñas et al., 2008). Postmortem examination of brain tissues showed elevated amyloid beta 42 (Calderón-Garcidueñas et al., 2008, 2012), hyperphosphorylated tau protein (Calderón-Garcidueñas et al., 2012), and α-synuclein accumulations (Calderón-Garcidueñas et al., 2008) from humans exposed to polluted urban areas. Epidemiologic studies have examined the role of long-term exposure to air pollution in PD risk with inconsistent findings (Palacios, 2017). Indicatively, Palacios et al. (2014a; 2017) reported no association with ambient particles while Liu et al. (2016) and Kirrane et al. (2015) have reported positive associations with particulate matter with aero dynamic diameter less than 10 μm (PM_{10}) or less than 2.5 μm ($PM_{2.5}$). Moreover, the literature investigating exacerbation of PD following short-term exposure of air pollution is very limited (Lee et al., 2017; Zanobetti et al., 2014).

As meta-analysis increases power to detect small associations in rare outcomes such as PD, we performed a systematic review and meta-analysis on existing literature to investigate the effects of either long or short-term exposure to regulated air pollutants on PD in order to address previous inconsistencies.

2. Methods

2.1. Search methods

We performed an extensive search in PubMed and Google Scholar databases and further searched for unpublished results in conference abstracts from the annual conferences of the International Society for Environmental Epidemiology (ISEE), as this is the most relevant Conference for reporting related up to date epidemiological evidence. We a-priory decided to include unpublished work that has been presented in the ISEE conference as we were expecting the number of reports to be rather small and wanted to cover all research that has possibly been done. Our search covered reports published until 7th November 2018 and used as search terms *air pollution* and *Parkinson* disease*. References' lists of retrieved studies were further reviewed for identifying additional literature.

2.2. Inclusion and exclusion criteria

A study was included in the review if it: (1) was an original article investigating exposure to particulate matter with aero dynamic diameter less than 10 μm (PM_{10}), less than 2.5 μm ($PM_{2.5}$), or between 2.5 and 10 μm ($PM_{2.5\text{-}10}$), nitrogen oxides (NO_x) or dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3) and carbon monoxide (CO); (2) referred to adult subjects; (3) was written in English.

Exclusion criteria included: (1) in vivo and in vitro toxicological studies; (2) occupational and pesticides' exposure studies; (3) smoking exposure studies. We also excluded any previous relevant systematic review after confirming that the included studies in these reviews were already identified through our search strategy. MK and KD independently reviewed the literature. When there was disagreement between the two researchers, a final decision was reached after consultation with ES.

2.3. Assessment for risk of bias

We assessed the selected studies for risk of bias using design-specific criteria (separately for cohorts, case-control studies and time-series). Specifically for cohort studies we assessed:1) the description of the sampling method, 2) the diagnosis of PD as doctor-diagnosed (considered low risk), self-reported (high risk) or obtained from records in medical/insurance databases (low risk), 3) the method of air pollution exposure estimation, and specifically whether it used fixed site measurements (high risk), estimates from prediction methods at individual or small spatial scale level (low risk) and further if these estimates were only spatially (high risk) or spatio-temporally (low risk) resolved, 4) whether exposure was back extrapolated and estimated at a time prior to PD diagnosis (low risk) and finally 5) the number of covariates accounted for in the statistical analysis (higher risk in administrative data cohorts or for less than five individual covariates). For case-control studies, we further assessed the selection of controls (population vs hospital-based). Time series studies were assessed for the size of the represented population (low risk for cities over 1 million) and the time period considered (for more than three years low risk), the exposure and outcome definition and the multivariable analysis. Each study was classified as low or high risk of bias per characteristic assessed.

2.4. Data extraction

The following data from eligible studies were extracted using a standard form: (1) authors; (2) year of publication; (3) location; (4) sample size; (5) design of the study; (6) exposure (pollutant studied and exposure estimation methods); (7) duration of follow up/exposure; (8) adjustment variables in multivariable analysis; (9) risk estimates and associated standard errors or confidence intervals (CIs). MK was responsible for the data extraction process under ES supervision. We conducted the corresponding authors of the selected publications in case of missing information or necessary clarifications. Effect estimates were derived from the main statistical model with the maximum number of covariates excluding air pollutants.

2.5. Statistical analysis

Analysis was performed separately for studies assessing short- or long-term exposure to air pollution and by pollutant. As studies reported effect estimates either for continuous exposure (when they assumed linear associations) or by categories (tertiles, quartiles, quintiles) of exposure we performed all analysis using both continuous exposure (for studies that this was provided) and a categorical exposure defined as high vs low, where the high level was defined as the highest study-specific category and the low level as the lowest study-specific category. When exposure was considered as continuous risk estimates were harmonized to estimate risk per 10-μg/m^3 increase in PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, NO_2, NO_x, 1 mg/m^3 increase in CO and a 5 ppb increase in O_3.

We extracted the risk estimates and corresponding 95% confidence intervals (CIs) from multivariable analysis. Our main analysis used effect estimates based on single pollutant models as only three studies (Cerza et al., 2018; Lee et al., 2016a; Shin et al., 2018) applied two (Cerza et al., 2018), three (Shin et al., 2018) or four pollutant models (Lee et al., 2016a). We meta-analyzed separately effect estimates derived from multi-pollutant models.

We applied random effects models (DerSimonian and Laird, 1986). For each pollutant–outcome analysis we assessed heterogeneity in the risk estimates using the Q test and the I^2 metric (Higgins et al., 2003). In order to investigate possible sources of heterogeneity we carried out a subgroup analysis by study design. We further applied Galbraith plots to distinguish any outlier contributing to the heterogeneity when the meta-analysis included more than six studies and further performed sensitivity analysis by removing one study each time (leave-one-out method) in order to evaluate its influence on the pooled effects. We used funnel plots and Egger's regressions tests to investigate possible publication bias again in cases with a sufficient number of studies. We finally explored effect modification patters by sex and smoking habits as previous research has indicated differences in PD prevalence that may be partly explained by a more complex interaction reflecting sex differences in smoking behavior (Ascherio and Schwarzschild, 2016). We used the STATA statistical software (Corp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP0) and the Review Manager freeware (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3. Results

3.1. Meta-analyses main results

Fig. 1 presents the flowchart of the literature search and the selection of the final sample of the studies included in our meta-analysis. Our search retrieved 102 unique studies, of which 68 were excluded according to our selection criteria, leaving 34 that were selected for full-text eligibility assessment. Of these 17 were excluded as they were non relevant systematic reviews and specifically, 10 were on general neurological problems, one on environmental toxicology, two on gene regulatory mechanisms affected by environmental exposures with disease implications, two completely irrelevant to either air pollution or PD. We retrieved two subject-specific systematic reviews (Hu et al., 2018; Palacios, 2017), among which Palacios et al. (2017) did not provide quantitative estimates while Hu et al. (2018) did not include up to date research from large studies in Europe and Canada (i.e. the studies Cerza et al., 2018; Chen et al., 2017b; Shin et al., 2018) or unpublished results (such as Campos et al., 2015). Our review also addressed short-term exposure effects and associations on categorical exposures relaxing the linearity assumption of an association. We investigated sources of heterogeneity by design, a major issue in the methodology of meta-analysis, and investigated effect modification patters by sex and smoking habits. Further we meta-analyzed separately effect estimates derived from single or multi-pollutant models, while Hu et al. (2018) combined effect estimates derived from single pollutant

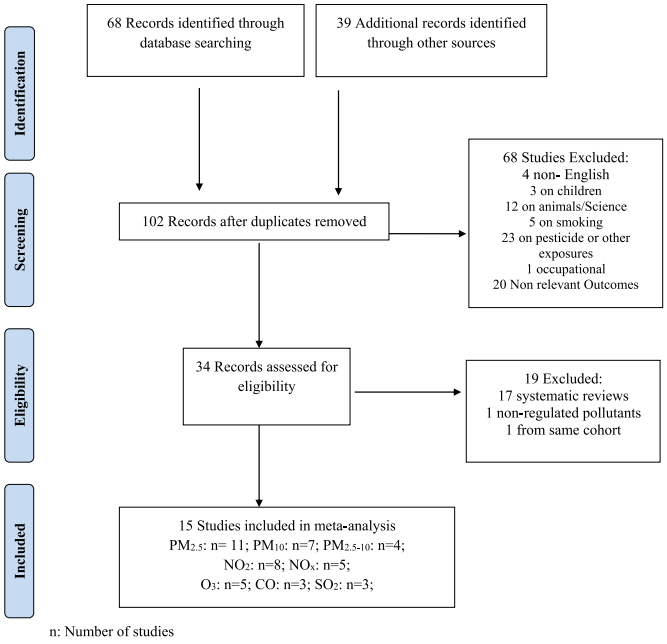


Fig. 1. Flowchart for the systematic literature search on air pollution exposure and risk of Parkinson's disease.

models along with the multi-pollutant adjusted ones from Lee et al (2016a) in Taiwan. We were careful not to include multiple reports from the same study, thus we excluded the use of both Ritz et al. (2015) and Lee et al. (2016b) that were conducted by the same group of investigators using the same data collected in the Danish National Hospital Register, with the only difference that Lee et al. (2016b) focused on gene-environment interaction hence the available sample was slightly smaller. In this case we included the study with the larger sample (Ritz et al., 2015). Finally, Palacios et al. (2014b) was excluded as they investigated exposure to airborne metals (arsenic, antimony, cadmium, chromium, lead, manganese, mercury, and nickel), that were exposures not included in our pre-defined eligibility criteria. Finally, 15 studies were selected for quantitative analysis from which nine investigated associations with long-term exposure to $PM_{2.5}$, seven for PM_{10}, four for $PM_{2.5-10}$, eight for NO_2, five for NO_x, five for O_3, three for CO and three for SO_2, while two reported associations for short-term exposure to $PM_{2.5}$ investigating the risk of aggravation or hospitalization due to PD. Three studies reported effects following exposure to SO_2 two of which regarding long term exposure (Chen et al., 2017a; Lee et al., 2016a). We only meta-analyzed effects associated with high vs low exposure as we could not retrieve a measure of variability for the continuous exposure in Chen et al. (2017a) following unsuccessful communication with the authors to correct for the results reported in the paper (odds ratio 1.20 with 95% CI: 0.99, 1.05).

Table 1 and Supplementary Table S1 present the final sample of selected studies with their main characteristics. Seven of the selected studies were case-control while eight were cohort studies. Most of the studies were conducted in North America. Also, there was a large variability in the sample sizes and differences in the characteristics for which adjustments have been made within the statistical analysis.

Table 2 presents the pooled effects using either a continuous or categorical exposure. Although a smaller number of studies assessed the associations per exposure category, we opted for their meta-analyses as these results could potentially provide additional information by relaxing the linearity assumption for the association. Further the unpublished work by Campos et al. (2015) only provided information on exposure categories, without the necessary information for the conversion of the respective effect estimates to a continuous measure. Two studies investigated effects in multiple locations: Kirrane et al. (2015)

Table 1
Characteristics of selected epidemiological studies investigating the association between air pollution exposure and Parkinson's disease, sorted by alphabetical order.

Authors, year of publication, country	Study Design	Sample Size	Exposure
Long- term exposure			
Campos et al., (2015), Netherlands[a]	Case - Control	436 cases and 854 controls	$PM_{2.5}$, PM_{10}, $PM_{2.5\text{-}10}$, NO_2, NO_x,
Cerza et al., (2018), Italy	Cohort	1,008,253 subjects with 13,104 incidence cases	$PM_{2.5}$, PM_{10}, $PM_{2.5\text{-}10}$, NO_2, NO_x, O_3
Chen et al., (2017a), Taiwan	Case - Control	1,060 cases and 4,240 controls	PM_{10}, NO_2, NO_x, O_3, CO, SO_2
Chen et al., (2017b), Canada	Cohort	2.2 million subjects with 31,577 incidence cases	$PM_{2.5}$, NO_2
Finkelstein and Jerrett (2007), Canada	Case - Control	509 cases and 52,477 controls	NO_2
Kioumourtzoglou et al., 2015, USA	Cohort	9.8 million with 119,425 cases	$PM_{2.5}$
Kirrane et al., (2015), USA	Case - Control	*North Carolina*: 104 cases and 29,612 controls *Iowa*: 195 cases and 53,024 controls	$PM_{2.5}$, O_3
Lee et al. 2016a, Taiwan	Case - Control	11,117 cases and 44,468 controls	PM_{10}, NO_x, O_3, CO, SO_2
Liu et al., (2016), USA	Case - Control (Nested)	1,556 cases 3,313 controls	$PM_{2.5}$, $PM_{10,}$ NO_2
Palacios et al. 2014a, USA	Women's Cohort	111,769 subjects, with 508 incidence cases	$PM_{2.5}$, PM_{10}, $PM_{2.5\text{-}10}$
Palacios et al., (2017), USA	Men's Cohort	50,352 subjects with 550 incidence cases	$PM_{2.5}$, PM_{10}, $PM_{2.5\text{-}10}$
Ritz et al., 2015, Denmark	Case - Control	1,696 cases and 1,800 controls	NO_2, NO_x, CO
Shin et al., (2018), Canada	Cohort	2.2 million subjects with 38,745 incidence cases	$PM_{2.5}$, NO_2, O_3
Short -term exposure			
Lee et al., (2017), Korea	case - crossover, Population-based Cohort	314 emergency admission cases during 2002–2013	NO_2, SO_2, CO, O_3, $PM_{2.5}$
Zanobetti et al., (2014), USA	Multi-site case - crossover	40,496 hospitalizations during 1999–2010	$PM_{2.5}$

[a] Unpublished study (poster in conference).

investigated particles' effects in Iowa and North Carolina and Finkelstein and Jerrett (2007) NO_2 in Hamilton and Toronto. City-specific estimates were entered in the meta-analysis separately. Regarding long-term exposure to regulated air pollutants none of the associations reached the nominal level of statistical significance, except for O_3 (relative risk (RR): 1.01, 95% CI: 1.00, 1.02 per 5 ppb). However there were strong indications of associations with $PM_{2.5}$ (RR : 1.06 per 10 μg/m^3, 95% CI: 0.99, 1.14) and to a lesser degree with CO (RR per 1 mg/m^3 1.34, 95% CI: 0.85, 2.10) and NO_2 (RR : 1.01 per 10 μg/m^3, 95% CI: 0.98, 1.03). The pooled risk estimates for the other pollutants (PM_{10}, $PM_{2.5\text{-}10}$, NO_x, SO_2) did not suggest an association. Analyses investigating continuous or categorical exposures resulted in similar results for most pollutants. For NO_2 the highest vs lowest study-specific exposure level resulted in a higher pooled effect RR among four case-control studies of 1.06 (95% CI: 0.93, 1.20) with low heterogeneity (I^2 = 14%, p-value = 0.321). Nevertheless, the difference in the pooled NO_2 risks between continuous and categorical exposure assessment was attributed to the different number of included studies, as when we restricted the analysis to the three studies that provided results in both scales the RR per 10 μg/m^3 was 1.09 (95% CI: 0.96, 1.24) and 1.08 (95% CI: 0.95, 1.22) for high vs low exposure. Along the same lines the difference in CO pooled effects when considering continuous or

Table 2
Pooled relative risk estimates (and associated 95% confidence intervals (CI)) from random-effects meta-analysis for the association between long-term exposure to air pollution and Parkinson's disease.

Pollutant	[a]Studies	Heterogeneity I [b] (p-value)	Relative Risk (95% CI)
$PM_{2.5}$			
Per 10 μg/m^3	2, 4, 6, 7, 9, 10, 11, 13	86% (< 0.001)	1.06 (0.99, 1.14)
[b]High vs Low exposure	1, 9, 10, 11	0% (0.405)	1.05 (0.92, 1.21)
PM_{10}			
Per 10 μg/m^3	2, 3, 8, 9, 10, 11	58% (0.030)	0.99 (0.96, 1.01)
[b] High vs Low exposure	1, 3, 8, 9, 10, 11	73% (0.002)	1.00 (0.86, 1.18)
$PM_{2.5\text{-}10}$			
Per 10 μg/m^3	2, 10, 11	47% (0.150)	0.97 (0.93, 1.01)
[b] High vs Low exposure	1, 10, 11	0% (0.960)	0.90 (0.74, 1.10)
NO_2			
Per 10 μg/m^3	2, 3, 4, 5, 9, 12, 13	83% (< 0.001)	1.01 (0.98, 1.03)
[b] High vs Low exposure	1, 3, 9, 12	14% (0.321)	1.06 (0.93, 1.20)
NO_x			
Per 10 μg/m^3	2, 3, 8, 12	81% (< 0.001)	1.00 (0.98, 1.03)
[b] High vs Low exposure	1, 3, 8	0% (0.552)	1.04 (0.98, 1.11)
CO			
Per 1 mg/m^3	3, 8, 12	82% (0.004)	1.34 (0.85, 2.10)
[b] High vs Low exposure	3, 8	0% (0.728)	1.04 (0.97, 1.11)
O_3			
Per 5 ppb	2, 3, 7, 8, 13	0% (0.690)	1.01 (1.00, 1.02)
[b] High vs Low exposure	3, 8	77% (0.040)	1.01 (0.81, 1.26)
SO_2			
[b] High vs Low exposure	3, 8	79% (0.030)	0.98 (0.79, 1.21)

[a] References: 1:Campos et al. (2015); 2:Cerza et al. (2018); 3:Chen et al. (2017a); 4: Chen et al. (2017b); 5:Finkelstein and Jerrett (2007); 6:Kioumourtzoglou et al. (2015); 7:Kirrane et al. (2015); 8:Lee et al. (2016a); 9:Liu et al. (2016); 10:Palacios et al. (2014a); 11:Palacios et al. (2017); 12:Ritz et al. (2015); 13:Shin et al. (2018).

[b] Study-specific definition.

categorical exposure was attributed to Ritz et al. (2015) that only provided effect estimates per unit change.

We found evidence of high heterogeneity in all associations assessing continuous exposure metrics, except for O_3 ($I^2 = 0\%$). Supplementary Figure S1 presents the funnel plots for the associations between PD and air pollutants when more than six studies were available, namely for the analysis of $PM_{2.5}$ and NO_2. The small number of studies prohibits statistical assessment of publication bias but nevertheless the plots indicate studies that possibly contribute to the observed heterogeneity, namely Kirrane et al. (2015) for $PM_{2.5}$ and Ritz et al. (2015) and Finkelstein and Jerrett (2007) for NO_2. Pooled effect estimates and the overall heterogeneity were robust to the removal of the indicated studies (for example when removing both cities reported in Kirrane et al. (2015) $PM_{2.5}$ pooled RR changed from 1.06 (95% CI: 0.99, 1.14) with $I^2 = 86\%$ to 1.06 (95% CI: 0.98, 1.14) with $I^2 = 89\%$).

We only identified two studies that investigated risk of PD aggravation following short-term exposure to $PM_{2.5}$. A combination of their results provided a statistically significant pooled RR for hospitalizations of 1.03 (95% CI:1.06, 5.04) per 10 μg/m^3 increase in pollutant concentrations. There was no heterogeneity between study-specific results due to the large CIs of the smaller study by Lee et al. (2017).

The great majority of the published studies included in our meta-analyses were generally considered of low risk of bias for the criteria assessed per design (See Supplemental Figure S2). For long-term associations, most studies clearly defined the sampling method, the great majority used doctor diagnosed PD following medical records and modeling approaches for the spatio-temporal exposure assessment. Most studies also attempted to assign exposure estimates prior to the date of the diagnosis, although the time period considered between studies varied. The use of large electronic administrative databases although provide increased power to detect small associations, lack accurate information on confounders (Cerza et al., 2018; Chen et al., 2017b; Kioumourtzoglou et al., 2015; Shin et al., 2018). Both short term exposure studies had sufficient statistical power as they covered large time periods and populations, used monitoring sites and applied well established statistical analyses methods.

3.2. Investigation of heterogeneity

We performed separate analyses by study design to assess the heterogeneity in the results for long-term exposure to air pollution. In general pooled effect estimates were higher under the case-control design as compared to cohorts, except for O_3 for which results were very similar (RR per 5 ppb 1.01 (95%CI: 1.00, 1.02) for cohorts and (1.00, 95%CI: 0.96, 1.04) for case-control studies with $I^2 = 0\%$ for both sub-groups analyses).

Specifically, per 10 μg/m^3 in $PM_{2.5}$ the pooled RR was 1.06 (95% CI: 0.98, 1.15) for cohort studies (n = 6) with high heterogeneity ($I^2 = 91\%$, p-value < 0.001) and 1.19 (95% CI: 0.71, 1.97) for case-control studies (n = 3 studies including two city-specific estimates) with moderate heterogeneity ($I^2 = 29\%$, p-value = 0.250) (Fig. 2). Further, when we excluded the cohort study by Kioumourtzoglou et al. (2015) as a possible source of heterogeneity, the pooled risk estimate was only slightly reduced to 1.03 (95%CI: 0.97, 1.11), as was also the heterogeneity in the study-specific results ($I^2 = 83\%$, p-value < 0.001). We considered this study as a potential source of bias as it investigated the association between long-term exposure to $PM_{2.5}$ and the risk of first hospitalization due to PD that most probably reflects an exacerbation in PD, whilst all other studies used doctor-diagnosed incident PD.

Regarding long-term exposure to PM_{10}, subgroup analyses by study design supported the absence of an association in cohorts (pooled RR 0.99, 95% CI: 0.97, 1.00 per 10 μg/m^3 with no heterogeneity $I^2 = 0\%$), while for case-control studies the RR was 1.03 (95% CI: 0.83, 1.28) with high heterogeneity ($I^2 = 83\%$, p-value < 0.001). Therefore, the heterogeneity in the pooled estimates for particles was not attributed to the different study designs.

There were five city-specific effect estimates for the association between long-term exposure to NO_2 and PD under a case-control design (Fig. 2) that revealed a pooled risk of RR 1.07 (95%CI: 0.97, 1.18), which was greatly driven by the results in Ritz et al.(2016), as excluding the latter the RR dropped to 1.02 (95%CI: 0.94, 1.10). High heterogeneity remained within case–control studies ($I^2 = 71\%$ including Ritz et al. (2015) and 50% excluding it). Results from the cohort studies indicated no association with NO_2.

Regarding long-term exposure to CO, three studies reported relevant estimates, two of which were performed in Taiwan and one in Denmark. When we excluded the Danish study, the pooled RR reduced from 1.34 (95%CI: 0.85, 2.10) to 1.09 (95% CI: 1.00, 1.20), while all heterogeneity was removed. The RR in Denmark (2.43, 95% CI: 1.52, 3.88) was statistically significant different to the pooled RR in the two Taiwanese studies (p < 0.001).

3.3. Multi-pollutant adjusted meta-analysis and effect modification patters

Few studies reported multi-pollutant model effect estimates or effect modification patterns reducing the power of the meta-analyses. Supplementary Table S2 presents meta-analyses' results from the studies that reported both single and multi-pollutant models' effect estimates indicating that adjustment for other pollutants did not affect the pooled estimates.

Regarding effect modification by sex or smoking habits (Supplementary Table S3), although pooled effects were not statistically different between subgroups analysis (either by sex or smoking) there was a consistent indication in the analysis of particles ($PM_{2.5}$ and PM_{10}) of higher effects among non smokers with no heterogeneity ($I^2 = 0\%$).

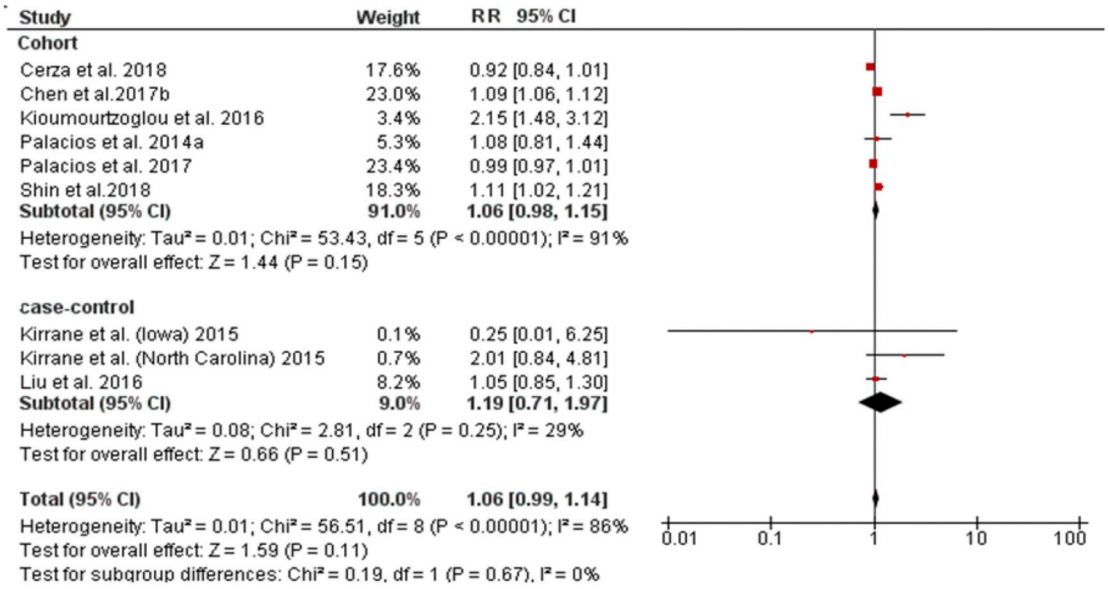
4. Discussion

We conducted meta-analyses of studies investigating the association between exposure to air pollution and Parkinson's disease. There were indications of associations with long-term exposures to $PM_{2.5}$, CO, NO_2 and O_3 among which only the last one reached the nominal level of significance. As we did not find an association with either PM_{10} or $PM_{2.5\text{-}10}$ the particles effects may be attributed to differential penetration in the respiratory tract depending on size but also to differential chemical compositions. Further short-term exposure to $PM_{2.5}$ was significantly associated with the aggravation of the disease. As vehicle traffic is the main source of NO_2 and CO, as well as an important source of $PM_{2.5}$, our results point to an adverse effect originating from traffic-related air pollution. This potential association is also supported by the results of Chen et al. (2017b) that reported a hazard ratio for PD incidence 1.01 (95% CI: 0.98, 1.04) for people living less than 50 m from a major traffic road versus those living further than 300 m.

Cerza et al. (2018) reported departures from linearity for the associations between PD and long-term exposure to O_3, NO_2, $PM_{2.5}$, hence our meta-analysis comparing effects for high vs low pollutant exposures complement and verify the results using continuous exposures. As smoking decreases PD risk (Ascherio and Schwarzschild, 2016) it is possible that it acts as an effect modifier in the association with air pollution exposure masking the small effects that environmental exposures are expected to have on morbidity. Indeed we found higher effects of $PM_{2.5}$ and PM_{10} among non –smokers using the limited number of studies that provided the relevant information.

Only recently epidemiological studies have investigated the effect of air pollution exposure to the central nervous system. In particular, the associations between air pollution and incidence of dementia, Alzheimer's disease, Parkinson's disease and stroke have been investigated, but the findings were inconclusive (Calderón-Garcidueñas et al., 2004; Finkelstein and Jerrett, 2007; Palacios et al., 2014a; Ritz et al., 2015; Willis et al., 2010; Wu et al., 2015). Nevertheless, most

A. $PM_{2.5}$ (per 10 μg/m^3)



B. NO_2 (per 10 μg/m^3)

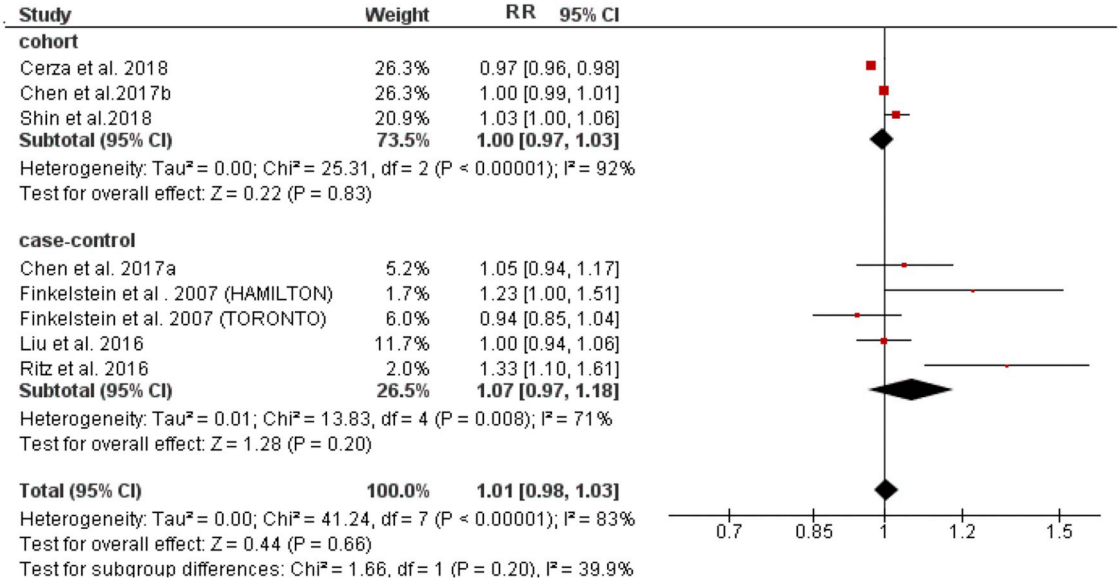


Fig. 2. Subgroup analyses for the association between long-term exposure to $PM_{2.5}$ and NO_2 and the risk of Parkinson's disease by study design.

previous studies and reviews have focused on association between air pollution exposure and cognitive function, as studies investigating rare outcomes such as PD are not cost effective and generally lack power. A review (Tzivian et al., 2015) on the effect of long-term exposure to outdoor air pollution on cognitive function in adults assessed findings from 13 studies that varied both by design and assessment of cognitive function. The authors concluded that findings support a possible role of air pollutants on neurocognitive function decline. An updated review (Clifford et al., 2016) identified six more studies and proposed that although there is likely an effect in brain life in late decline, more studies are needed to elaborate the association. Recently Hu et al. (2018) published a meta-analysis on long-term exposure to air pollution and PD using a smaller number of studies. The authors concluded that NO_2, NO_x, CO and O_3 exposure were associated with an increased risk of PD as they report small but statistically significant pooled RRs (slightly above 1). The adverse effect of these pollutants is in accordance with our results although only O_3 retained its statistical significance after the inclusion of newly published results (Cerza et al., 2018; Shin et al., 2018). Further we report a lower and non significant CO (RR: 1.34 per 1 mg/m3) effect, as Hu et al. (2018, RR: 1.65 per 1 ppb) include in the pooled RR two studies from the same sample hence violating the assumption of inclusion of independent studies in meta-analysis, as discussed in the Methods section. Regarding $PM_{2.5}$, Hu et al. (2018) report a 1.21 increase in PD using six city-specific

studies, while our results indicate a 1.06 increase per 10 μg/m^3 using eight city-specific estimates. Both analyses do not report associations with PM_{10} or $PM_{2.5\text{-}10}$.

There was heterogeneity among study-specific estimates in all associations between air pollutants and PD, except for O_3. Although previous findings also reported heterogeneity (Hu et al., 2018), we further explored potential sources. Heterogeneity remained in the subgroup analyses and there was no statistically significant difference between the pooled estimates of the cohort vs the case-control studies. Removal of potentially influential studies only slightly accounted for heterogeneity decrease. Particularly CO presented higher effects in Denmark as compared to Taiwan. Although the comparison is restricted by the limited number of studies, possible sources for this discrepancy include the different exposure assessment models used as well as possibly different underlying concentration response associations. As levels of CO were slightly lower in Denmark (mean 0.55 mg/m^3 vs 0.62 mg/m^3 in Asia), higher effects could be attributed to a supra-linear association, although the studies did not evaluate the concentration response associations. Denmark's air pollution levels are also lower than those observed in Southern and Eastern Europe, but similar to other western industrialized countries in which the most important source is the emission of exhaust gas (Eeftens et al., 2012). Another possible explanation may be the slightly larger population of people aged above 65 years in Denmark over Taiwan (19.4% vs 13.7%) resulting in a larger pool of sensitive population, as previous studies have shown that air pollution effects are larger among the elderly (Indexmundi.com, 2018).

Potential neurotoxic effects of air pollution are likely to be exposure specific, time-dependent and dose-dependent (Block et al., 2012).Toxicological studies have proposed possible biological mechanisms underlying potential associations that are mainly related to the oxidative stress induced by air pollutants' exposure. Animal experiments have shown that inhaled particles penetrate the olfactory bulb and end up in the brain through the nasal cavity (Block et al., 2012), cause a reduction in dopaminergic neurons in the substantia nigra (Veronesi et al., 2005), increase alpha-cellulose in the mesenchephalus (Levesque et al., 2011a) and activate the deviated protein response in the striatum of the brain (Guerra et al., 2013). Other animal studies have shown that O_3 exposure is associated with cumulative damage to the brains of rodents, and its inhalation seemed to produce impaired nigral cell morphology and loss of dopamine neurons in rats (Angoa-Pérez et al., 2006; Guevara-Guzmán et al., 2009; Pereyra-Muñoz et al., 2006). NOx can cause damage to the neurons via olfactory bulb, nasal epithelium and the lungs through diffusion or capture and carriage by red blood cells across the blood-brain-barrier (Tse, 2017). NOx and cytokines, released by pulmonary inflammation activate the microglia to upregulate the expression of inducible and neuronal nitric oxide synthase. As a result, increases in oxidative stress, neurotoxicity and neurodegeneration have been reported. CO bonds with hemoglobin, forming carbon-oxyhemoglobin (HbCO), which does not transport oxygen. Oxygen is required to form levodopa. Consequently, CO may interfere with the availability of oxygen in the brain, although the exact mechanism in relation to Parkinson's has not been investigated (viartis.net, 2010). Schwela (2000) argued that ambient CO may act through other pathways than COHb formation, and at lower levels those pathways may dominate the observed adverse health effects. Nevertheless it remains unclear if associations with CO are causal or CO acts as a proxy for combustion particles. Overall, most toxicological studies have focused on particles' effects, while mechanisms for gaseous pollutants need further research.

One of the limitations of our meta-analysis is the relatively small number of studies, as the association between exposure to air pollution and PD has attracted interest only recently. Further our pooled effect estimates reflect the quality of the research done in the topic. Although all studies were carefully planned they were restricted by the inherent limitations of air pollution epidemiology including measurement error in the exposure estimates and lack of confounders in the analysis of administrative data. Recent research has shown that if anything measurement error in air pollution that incorporates a mixture of classical and Berkson error would be expected to lead to smaller effects and loss of power in most cases (Samoli and Butland, 2017). Further the administrative studies included in our review have applied several sensitivity analyses to account for potential bias from missing individual confounders and their results were robust. Additionally, the different reporting of exposure indices in continuous or categorical scales prohibited the inclusion of all studies in both analyses. Studies that used categorical exposures did not provide the corresponding descriptive information relative to the sample size in each exposure level to enable harmonization of categories between studies. Nevertheless, the meta-analyses results using pollutants as continuous variables were similar to those using exposures as categorical (high vs. low), with any differences mainly attributed to the different included studies. Only three studies reported effects from multi-pollutant models hindering an in depth investigation of multi-pollutant exposure effects, although our findings supported the robustness of single pollutant analyses. Our meta-analysis had limited power for the investigation of effect modification patterns by sex or smoking patterns due to the small number of studies that reported effects. Hence it is proposed that future research should further investigate multi-pollutant exposures and effect modification patterns.

Finally, the vast majority of the studies included in the meta-analysis are located in developed countries and specifically in North America, so the generalization of results in developing countries requires attention, and reveals the need for relevant research in other countries. This investigation will not only help to understand the impact of air pollution on the risk of disease but also to understanding the mechanisms involved in the development of PD.

Despite these limitations, our meta-analysis has indicated small but consistent adverse associations between PD and long-term exposure to $PM_{2.5}$, NO_2, O_3 and CO, and aggravation of the disease with short-term exposure to $PM_{2.5}$. The continuing investigation of the role of environmental risk factors for the development or aggravation of this multifactorial disease is of public health significance, especially considering the aging of the population in developed countries.

Acknowledgments

This study was part of a Master Thesis conducted in the context of the MSc Program in Biostatistics of Medical School of National and Kapodistrian University of Athens, Greece.

The work presented did not receive any funding. The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijheh.2018.12.006.

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