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Traffic-related air pollution increased the risk of Parkinson's disease in Taiwan: A nationwide study

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ABSTRACT

Background: Ambient air pollution has been associated with many health conditions, but little is known about its effects on neurodegenerative diseases, such as Parkinson's disease (PD). In this study, we investigated the influence of ambient air pollution on PD in a nationwide population-based case–control study in Taiwan.
Methods: We identified 11,117 incident PD patients between 2007 and 2009 from the Taiwanese National Health Insurance Research Database and selected 44,468 age- and gender-matched population controls from the longitudinal health insurance database. The average ambient pollutant exposure concentrations from 1998 through the onset of PD were estimated using quantile-based Bayesian Maximum Entropy models. Basing from logistic regression models, we estimated the odds ratios (ORs) and 95% confidence intervals (CIs) of ambient pollutant exposures and PD risk.
Results: We observed positive associations between NO_x, CO exposures, and PD. In multi-pollutant models, for NO_x and CO above the 75th percentile exposure compared with the lowest percentile, the ORs of PD were 1.37 (95% CI = 1.23–1.52) and 1.17 (95% CI = 1.07–1.27), respectively.
Conclusions: This study suggests that ambient air pollution exposure, especially from traffic-related pollutants such as NO_x and CO, increases PD risk in the Taiwanese population.

1. Introduction

Air pollution has been associated with many health conditions, including adverse birth outcomes and child neurodevelopment, respiratory and cardiovascular diseases, and stroke or cancers (Bentayeb et al., 2012; Chiu et al., 2016; Raaschou-Nielsen et al., 2013; Shah et al., 2015; Stieb et al., 2012). However, little is known about the effects of air pollution on neurodegenerative diseases, such as Parkinson's disease (PD); PD is a disorder affecting millions of people worldwide, with an increasing prevalence in aging populations. PD has been attributed to both genetic and environmental risk factors, which are thought to contribute to the characteristic loss of dopamine neurons in the substantia nigra pars compacta and its related motor and non-motor symptoms. Air pollution has been hypothesized to increase PD risk mainly because of its contributions to neuroinflammation, increased oxidative stress, and dopamine system-related neurotoxicity, as suggested by plausible biologic pathways determined through human and animal data (Block and Calderon-Garciduenas, 2009; Calderon-Garciduenas et al., 2010, 2013; Levesque et al., 2011). For instance, an animal study found oxidative damage and diffuse amyloid plaques in the olfactory bulb of feral dogs living in high-pollution regions of Mexico City (Calderon-Garciduenas et al., 2010). Mexican children residing in highly polluted areas showed inflammation of the olfactory bulb, as well as deficits in olfaction (Calderon-Garciduenas et al., 2008a). Both observations and some additional experimental data by Oberdorster et al. (2004) suggest

Abbreviations: PD, Parkinson's disease; ORs, odds ratios; CIs, confidence intervals; COX2, cyclooxygenase 2; IL-1β, interleukin-1β; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; NO_x, nitrogen oxides; CO, carbon monoxide; SO_2, sulfur dioxide; IRB, Institutional Review Board; NHRI, National Health Research Institute; NHIRD, National Health Insurance Research Database; iPD, idiopathic PD; QBME, quantile-based Bayesian Maximum Entropy; IQR, interquartile range increase; COPD, chronic obstructive pulmonary disease; CCI, Charlson Comorbidity Index.

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that the olfactory mucosa may act as an entry route for air pollutants with possible effects on the brain. Furthermore, upregulation of proinflammatory markers, such as cyclooxygenase 2 (COX2), interleukin-1β (IL-1β), and CD-14; disruption of the blood–brain barrier; and α-synuclein accumulation in post-mortem brains of humans exposed to air pollution have been documented (Calderon-Garciduenas et al., 2008b). These findings suggest that air pollutants may affect the brain via transport of pollutants from the olfactory bulb, thereby increasing systemic inflammation, which contributes to neurodegenerative processes.

Epidemiologic studies have investigated the contribution of airborne metals (e.g., copper, lead, and manganese) to the development of PD (Finkelstein and Jerrett, 2007; Palacios et al., 2014a; Willis et al., 2010). Previous studies have also assessed the associations of PD with other ambient air pollutants (Kirrane et al., 2015; Liu et al., 2016b; Palacios et al., 2014b; Ritz et al., 2015). In the largest case–control study to date conducted in Denmark, we previously reported that long-term traffic-related air pollution, specifically traffic-related nitrogen dioxide (NO_2) exposures, increases PD risk (Ritz et al., 2015). However, a cohort study based on 508 incident PD cases identified from the Nurses' Health Study reported no association between particulate matter exposures and PD (Palacios et al., 2014b). Investigators who have assessed ozone (O_3) and fine particulate matter (particulate matter with an aerodynamic diameter ≤2.5 μm, $PM_{2.5}$) exposures in the Agricultural Health Study cohort with 301 incident and prevalent PD cases reported positive associations for both pollutants (Kirrane et al., 2015). In the present study, we investigated the associations between PD and monitored ambient air pollution exposures (including nitrogen oxides, NO_x; carbon monoxide, CO; sulfur dioxide, SO_2; O_3; and particulate matter with an aerodynamic diameter ≤10 μm, PM_{10}) from a nationwide population-based case–control study in Taiwan.

2. Materials and methods

2.1. Human subjects

This study was approved by the Institutional Review Board of the Taipei City Hospital (TCHIRB-10404119-W). Informed consent from each participant was not required because of the use of anonymous data. An agreement with the Computer-Processed Personal Data Protection and regulations of the National Health Research Institute was signed by the data analyst and researchers.

2.2. Subjects

Taiwan implemented its National Health Insurance program on March 1, 1995. In 2014, 99.9% of Taiwan's 23 million residents were enrolled to this program (Administration, N.H. I, 2014). Information on all health-related services, including clinic visits, hospitalizations, and prescriptions, is recorded in national databases. All databases can be linked to each other by encrypted personal identification numbers.

We conducted a population-based case–control study involving 11,117 patients aged 35 years or older with a first hospital or outpatient clinic contact for PD (ICD-9-CM code 332.0) between 2007 and 2009; these patients did not undergo a prior PD diagnosis between 2002 and 2006, according to the Taiwanese National Health Insurance Research Database (NHIRD). To increase the specificity of identifying idiopathic PD (iPD) when relying on diagnosis codes (ICD-9-CM), we applied the following criteria to our incident iPD subjects: (1) subjects who received at least three prescriptions of anti-PD medications (Anatomical Therapeutic Chemical, ATC code N04B) after the first PD diagnosis and (2) the first and last outpatient or inpatient visit within our study period (i.e., 2007–2010) should have been at least 90 days apart. In addition, we excluded 1) subjects who had received a diagnostic code of secondary PD (ICD-9-CM code 332.1); 2) those who had received any neuroleptic medication (ATC code N05A) prescription within 180 days prior to their first PD diagnosis; and 3) those diagnosed with dementia (ICD-9-CM codes 290 and 331) prior to their first PD diagnosis during the study period.

To identify the earliest possible date of iPD diagnosis, we defined the first hospital or outpatient record with a PD diagnosis or the first prescription of a PD medication (ATC code N04B) after 2007 as the index date on the basis of the registration data available after 2002, i.e., we excluded those with PD diagnoses or PD medication prescriptions between 2002 and 2006. Through density sampling, up to four age-matched (i.e., age at index date) and sex-matched controls were selected per case from the longitudinal health insurance database in 2000 (LHID 2000). This database includes registration files and inpatient, outpatient, and prescription information for 1 million individuals randomly selected from the year 2000 registry of beneficiaries of NHIRD and followed through 2010. We also validated the criteria that we applied to identify iPD cases from registry databases by analyzing the medical charts of 290 subjects who were randomly selected from all PD patients treated in En Chu Kong Hospital, a tertiary referral center in northern Taiwan, between January 2012 and October 2012. Among the 290 iPD patients, 245 were confirmed by chart review; in addition, 6 iPD cases were identified and confirmed by chart review, but these cases did not meet our registry data based on eligibility criteria for iPD, resulting in sensitivity, specificity, positive predictive, and negative predictive values of 97.6%, 92.3%, 98.8%, and 85.7%, respectively.

2.3. Assessment of air pollution exposure

We developed quantile-based Bayesian Maximum Entropy (QBME) models of CO, NO_x, SO_2, O_3, and PM_{10} from 1998 through 2009 to estimate the space–time distribution of these pollutants' daily concentrations for Taiwan. We estimated the subjects' exposure to ambient air pollution by averaging the daily exposures over a period starting from 1998 or their first record in the registration file after 1998 up to the participant's index date. $PM_{2.5}$ was not monitored for the entire country until 2005; thus, this pollutant was not included in our study. Considering the lack of residential information, we compiled ambient pollutant estimates according to their space–time distribution based on a township (space) daily (time) scale, which is similar to the approach used in a previous study (Chang et al., 2014). We assessed exposures for individuals at the township level according to the location of the clinic in which each participant most frequently sought treatment for acute upper respiratory infections (ICD-9-CM codes 460). Most residents attended a neighborhood clinic for mild respiratory diseases (Wu et al., 2015), indicating that each person probably lives within close proximity of such a clinic. For subjects without any record for a clinic visit for acute upper respiratory infection during the study period ($n = 2358$), the exposure assessments were based on the location (at the township level) of their health insurance registration.

To obtain township-level pollutant concentrations, we estimated the daily concentration for each grid centroid by averaging the daily concentrations of grids within each township for each pollutant. We used a grid size of 5 km × 5 km for counties/cities with less dense air monitoring networks and a size of 1 km × 1 km for counties/cities with denser air monitoring networks. Depending on population density, the average township area is 176.5 km^2 (SD = 264.2) in rural areas and 28.9 km^2 (SD = 25.1) in urban areas. Details of QBME modeling have been described elsewhere (Yu and Wang, 2013). In brief, QBME modeling is a novel quantile-based geostatistical approach based on the Bayesian Maximum Entropy framework that accounts for nonstationary and nonhomogeneous characteristics of ambient air pollution (Yu and Wang, 2013). To obtain nationwide ambient pollutant estimates, the QBME modeling integrates both the monitoring network data from the Taiwanese Environmental Protection Agency and secondary information (e.g., background pollutant concentrations monitored at Lu-Lin station located in a high mountain area) to account for uncertainties in ambient pollutant levels in areas without monitoring stations