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Long-term exposure to multiple air pollutants and risk of Parkinson's disease: a population-based multipollutant model study

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ABSTRACT

Background Recent evidence suggests brain-first Parkinson's disease (PD) may start from the olfactory system, indicating potential inhalational exposure to causal agents. We investigated the impact of long-term exposure to various air pollutants on PD incidence using both single- and multi-pollutant models to account for interactions between pollutants.

Methods This retrospective population study used data from Taiwan's National Health Insurance Research Database (2006 and 2018) and included individuals aged 40–65 without PD. Personal exposure levels to various air pollutants, including $PM_{2.5}$, PM_{10}, NO_2, O_3, SO_2 and CO, were calculated using the hybrid Kriging/land-use regression method. Cox regression models were used to analyse the association between pollutants and PD incidence, adjusting for covariates.

Results A total of 5 113 322 individuals without PD (mean age 50.1±6.9 years, 47.3% men) were followed for an average of 11.2±2.4 years, during which 20 694 incident cases of PD were identified. In the single-pollutant model, exposure to $PM_{2.5}$ (HR 2.65 (95% CI 2.59 to 2.72)), PM_{10} (HR 3.13 (3.04 to 3.22)), NO_2 (HR 1.74 (1.68 to 1.80)) and SO_2 (HR 1.68 (1.65 to 1.71)) was associated with an increased risk of PD. These associations remained robust in the multipollutant model. A positive association between exposure to O_3 and an increased risk of PD (HR 1.29 (1.25–1.33)) was observed after adjusting for co-pollutants.

Conclusions This nationwide cohort study employing multiple-pollutant models for considering the interaction effects revealed an association between exposure to multiple air pollutants and the risk of PD, emphasising the need for early prevention strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exposure to air pollutants is inconsistently associate with an increased risk of Parkinson's disease (PD). Few studies have considered the potential interaction between each air pollutant.

WHAT THIS STUDY ADDS

⇒ In the present study, we comprehensively analysed the effects of six major components of air pollution (PM2.5, PM10, NO2, CO, SO2 and O3) using a large population cohort under longitudinal long-term follow-up. By using multipollutant models to consider interaction effects between pollutants and accounting for temperature and humidity as covariates related to global warming, this study uncovered significant associations between long-term exposure to air pollutants (PM2.5, PM10, NO2, SO2 and O3) and increased risks of PD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results emphasise the need for health policies to mitigate the detrimental effects of air pollution on PD, especially on vulnerable populations.

INTRODUCTION

Parkinson's disease (PD) is a common and heterogeneous neurodegenerative disorder with rising global prevalence.[1] Its aetiology involves a complex interplay of ageing, genetics and environmental factors.[1] Recent evidence suggests that the pathological hallmark of PD, neuronal α-synuclein aggregations, may originate in the olfactory bulb or gastrointestinal tract, supporting the brain- and body-first models of PD.[2] Research suggests that altered gut microbiota may trigger body-first PD via the gut-brain axis, while inhaled toxicants could induce α-synuclein pathology in the olfactory system, leading to a brain-first subtype of PD. Identifying harmful environmental triggers offers an opportunity to mitigate PD risks and potentially prevent its onset and progression.

Air pollution is currently the largest environmental risk for premature death in the world.[3] It comprises a complex mixture of hazardous substances, mainly consisting of fine particulate matter (PM), oxides of sulphur and nitrogen, and ground-level ozone (O_3).[3] In vivo mouse studies show that inhaling air pollutants promotes α-synuclein pathology in the olfactory bulb, spreading to PD-vulnerable regions.[4] However, studies on the link between air pollutants and PD incidence have yielded conflicting results. Exposure to traffic-related pollutants, including nitrogen dioxide (NO_2), carbon monoxide (CO) and PM with an aerodynamic diameter <2.5 µm ($PM_{2.5}$) and 10 µm (PM_{10}), has been reported to correlate with higher risk of PD,[5–8] whereas large studies performed in the USA have found no such association.[9] A recent study in Seoul found that exposure to NO2,[8] but

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not other pollutants, is linked to increased PD risk, contrasting with findings from other studies.[5–7] These discrepancies are likely attributed to variations in the study sample size, transportation patterns, exposure to air pollutants and geographic distribution.[10 11] The air pollution levels are worse in Asia than in Europe or North America.[12] Local sources of air pollution, such as automobiles, account for the majority of pollution emissions in Asia.[13] Few studies have considered the potential interaction between each air pollutant. SO_2 and NO_2 are precursors of the formation of sulfate and nitrate PM in the atmosphere and secondary water-soluble ions, which constitute a major portion of $PM_{2.5}$ in Asia.[14] Therefore, $PM_{2.5}$ and the gaseous pollutants SO_2 and NO_2 coexist in the atmosphere and may interact with each other in the process of secondary aerosol pollution. A synergistic interaction between $PM_{2.5}$ and O_3 has been observed via inflammatory pathways.[15] Here, we analysed the effects of six major air pollutants ($PM_{2.5}$, PM_{10}, NO_2, CO, SO_2 and O_3) using a large population cohort under long-term follow-up in Taiwan. We employed both single-pollutant and multipollutant models to account for the confounding and interactive effects arising from the complex interaction between multiple air pollutants.

METHODS

Data source

We used population-based data extracted from Taiwan's National Health Insurance Research Database (NHIRD), which is sourced from the claims data of beneficiaries enrolled in the National Health Insurance (NHI) programme established in 1995. This programme is a mandatory social insurance scheme that provides coverage to up to 99.99% of the Taiwanese population (approximately 23 million people).[16] All records, including demographic characteristics, clinic visits, hospitalisation and disease diagnoses, made by clinical physicians and coded according to the International Classification of Diseases (ICD) 9 and 10 between January 2000 and December 2018 were obtained retrospectively.

Study population

A cross-comparison of demographic information between data extracted from the NHIRD and National Cause of Death Registry was conducted to exclude individuals who had passed away before the reference year of 2006, as well as records with mismatched sex or year of birth. Among 11 630 373 individuals in the NHIRD who were between 20 and 65 years of age and resided in the western part of Taiwan in 2006, we excluded those age less than 40 years (n=5 306 939) and selected those who were aged between 40 and 65 years (figure 1). This age group was selected because PD typically begins between 60 and 65 years, and prodromal symptoms like constipation, sleep disorders and olfactory dysfunction can appear up to 20 years before motor symptoms.[17] The western part of Taiwan was selected because it has a high population density and retains the measurement data for each air pollutant in all towns (figure 2). We also excluded participants diagnosed before 2006 with PD (n=3401), and those with major depression, dementia, stroke, head injury or catastrophic illness, including myocardial infarction, cancer, systemic lupus erythematous, rheumatoid arthritis and AIDS, due to the potential for secondary parkinsonism (n=1 206 254). Additionally, we excluded patients diagnosed with PD or censored within 1 year of 2006 (n=457), as an exposure period of less than 1 year is unlikely to contribute to the development of PD. To enhance the specificity of disease diagnosis, each condition was defined by having three or more outpatient visits or one hospitalisation with the relevant diagnostic code within 1 year.[18] The ICD code for each disease is recorded in online supplemental table 1.

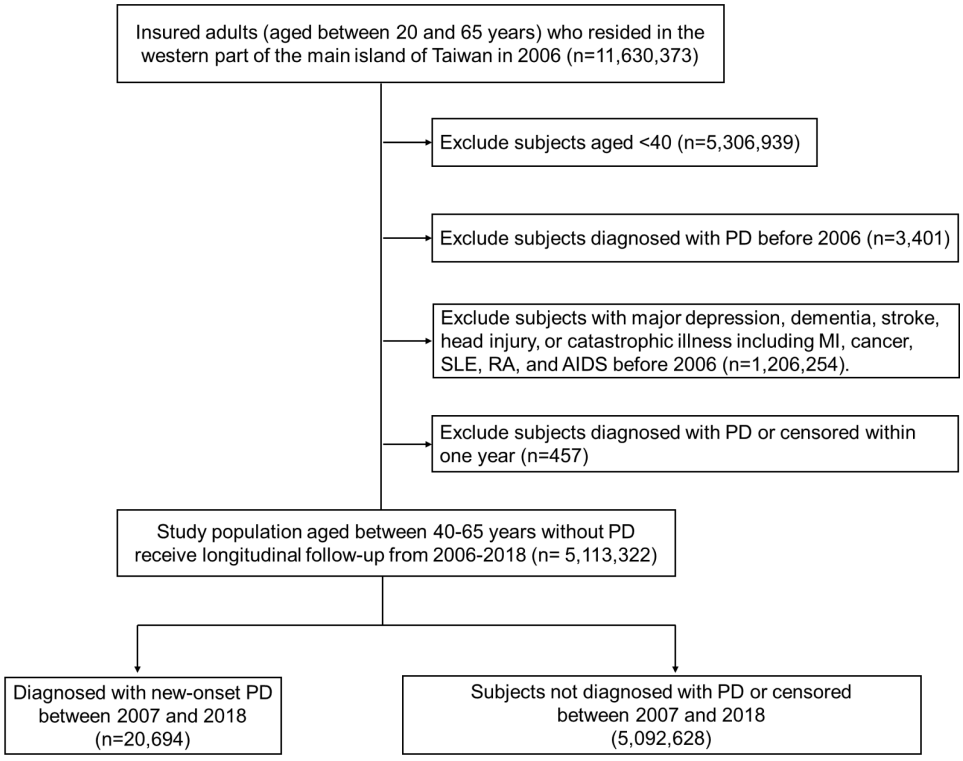

Figure 1 Flowchart of study enrollment and follow-up. MI, myocardial infarction; NHIRD, National Health Insurance Research Database; PD, Parkinson's disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematous.

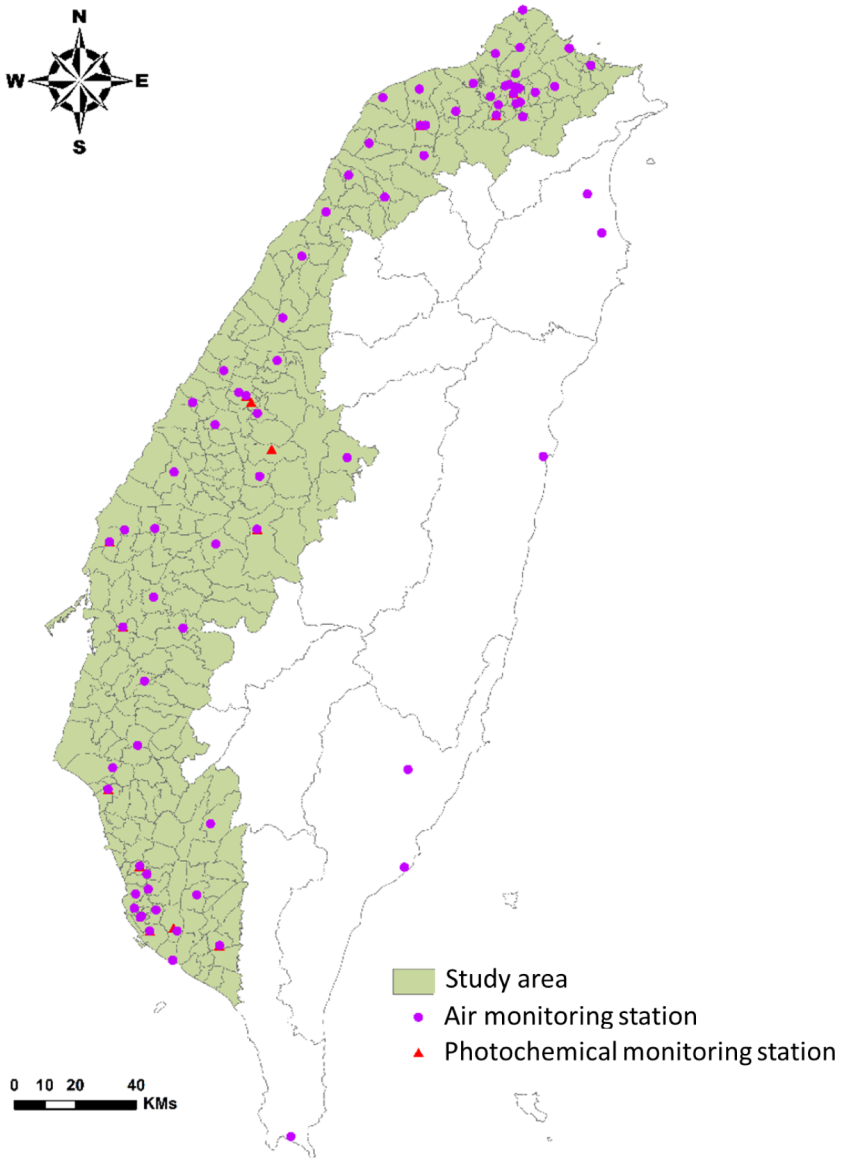

Figure 2 Study area and geographic distribution of air monitoring stations and photochemical monitoring stations.

Standard protocol approval, registration and patient consent

The study was approved by the Institutional Review Board of National Taiwan University Hospital (202002093RIND, 202405076W) and the National Health Research Institute (EC1070901-E). Data from the NHIRD were encrypted to protect privacy, waiving the need for written informed consent. The study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Exposure to air pollution

The Taiwan Environmental Protection Administration (TEPA) provides hourly monitored data on $PM_{2.5}$, PM_{10}, NO_2, O_3, CO and SO_2 from 73 fixed-site air quality monitoring stations across western Taiwan (figure 2). Hourly concentrations of $PM_{2.5}$ and PM_{10} were measured by ß-ray attenuation, CO level by nondispersive infrared, NO_2 by chemiluminescence, SO_2 by ultraviolet fluorescence and O_3 by ultraviolet absorption as described previously.[18] The personal exposure level to each air pollutant was determined as described previously.[18] The average daily concentration of each pollutant was calculated based on at least 16 measures per day and used for further spatial interpolation at a resolution of 50×50 metres using the hybrid Kriging/land-use regression method.[19] The average interpolated pollutant concentrations were calculated at the township level and linked to each participant's annually updated residential address, estimating their exposure dose during follow-up.[18]

Study outcome

Each participant was followed up annually from 2006 to 2018. The outcome of interest was defined as having any hospital discharge diagnosis or having at least three outpatient diagnoses of PD (ICD-9-CM code 332 or ICD-10 code G20). To evaluate the accuracy of the PD diagnostic criteria in our study, a validation study performed at National Taiwan University Hospital, a tertiary referral centre, found that the criteria specificity was 94%.[20] Participants who were lost to follow-up (less than 1% of the NHI database)[20] or died were censored from the analysis.

Covariates

We incorporated individual-level covariates, including age, sex, degree of urbanisation, insured amount and pre-existing

medical comorbidities. The degree of urbanisation was classified into four levels, with level one being the highest urbanised level.[18] The classification was based on population density, the proportion of residents with at least a college-level education, the number of residents >65 years old, the population ratio of agriculture workers and the number of physicians per 100 000 people.[18] Socioeconomic status was evaluated using the insured amount from the NHI and classified into three levels. Pre-existing medical comorbidities including hypertension, diabetes mellitus and viral hepatitis were defined as having at least three outpatient visits or one hospitalisation with relevant diagnostic codes within 1 year. We included viral hepatitis, particularly hepatitis B virus and hepatitis C virus, as potential risk covariates due to their prevalence in Asia and established links to increased PD risk in the population.[21] Ambient temperature and relative humidity data from TEPA air quality stations were included in the analysis, as these factors have been shown to impact PD incidence.[22]

Statistical analysis

All continuous variables are presented as means and SD, and nominal variables as numbers and percentages. A Cox proportional hazards regression model was applied to estimate the HR for PD associated with each IQR increment in the levels of air pollutants. Covariates, including age, sex, degree of urbanisation, insured amount and pre-existing comorbidities, were adjusted in the analysis. Relationships between different air pollutants and environmental factors, including temperature, were assessed using Spearman's correlation test. We employed multipollutant models to address the potential confounding and interaction effects between each pollutant.[23] In the sensitivity analyses, we measured the potential influences of age, sex and pre-existing medical comorbidities on the associations between air pollutants and PD risk, adjusting for the aforementioned covariates. All statistical analyses were performed using SAS (V.9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 5 113 322 participants were included in this study (figure 1). The baseline characteristics showed that the mean age at enrolment was 50.1±6.9 years and 47.3% of enrolled patients were male. Over a mean follow-up of 11.2±2.4 years (totaling 57 508 733 person-years), 20 694 individuals (0.4%) developed incident PD, resulting in an incidence rate of 35.98 per 100 000 person-years. The yearly incident PD cases during follow-up is shown in online supplemental table 2. Elderly age (HR 5.30 (95% CI 5.11 to 5.49) for those ≥50 years old compared with those <50 years old), male sex (HR 1.05 (1.02–1.08) compared with females), rural town inhabitants (HR 1.24 (1.19–1.29) compared with highly urbanised habitants) and pre-existing medical comorbidities were associated with an increased risk of PD (table 1). A higher insured amount was associated with reduced PD risk compared with less medical insurance (HR 0.63 (0.61–0.66)).

During the mean follow-up of 11.2 years, the annual mean concentrations of $PM_{2.5}$, PM_{10} and SO_2 were highest in 2009 and gradually decreased until 2018. The annual mean concentration of O_3 continuously increased during the study period, whereas NO_2 and CO levels remained relatively stable (figure 3). The median concentrations of PM and NO_2 were above the WHO air quality guidelines (15.0 μg/m^3 for $PM_{2.5}$, 45.0 μg/m^3 for PM_{10}, 13.30 ppb for NO_2).[24] The median exposure to each air pollutant was 30.0 (IQR 9.5) μg/m^3 for $PM_{2.5}$, 49.5 (IQR 20.0) μg/m^3 for PM_{10}, 0.46 (IQR 0.21) ppm for CO, 16.8 (IQR 7.4) ppb for NO_2, 3.6 (IQR 1.0) ppb for SO_2 and 30.1 (IQR 4.3) ppb for O_3. Spearman's correlation analysis showed positive associations between the $PM_{2.5}$ and PM_{10} concentrations ($\rho=0.914$; $p<0.05$), as well as between the levels of NO_2 and CO ($\rho=0.893$; $p<0.05$). Conversely, the concentration of O_3 had an inverse relationship with all other pollutants, particularly CO ($\rho=-0.838$; $p<0.05$) and NO_2 ($\rho=-0.699$; $p<0.05$, figure 4). Furthermore, ambient temperature showed positive associations with all pollutants, except O_3, which exhibited an inverse pattern ($\rho=-0.377$; $p<0.05$).

Table 1 The demographic distribution of the study population, incidence and crude HR of Parkinson's disease

	Number	Person-years	Incident PD	Incidence (per 100 000 pyrs)	HR (95% CI)
Total	5 113 322	57 508 733.3	20 694	35.98	
Male	2 420 417	26 855 549.8	9854	36.69	1.05 (1.02 to 1.08)
Age (year)					
< 50	2 602 847	30 511 661.5	3737	12.25	1 (reference)
≥ 50	2 510 475	26 997 071.8	16 957	62.81	5.3 (5.11 to 5.49)
Degree of urbanisation					
1 (highly urbanised)	1 504 569	16 964 687.7	6028	35.53	1 (reference)
2 (intermediately urbanised)	1 710 499	19 292 904.2	6708	34.77	0.98 (0.95 to 1.01)
3 (emerging towns)	942 648	10 745 085.1	3371	31.37	0.88 (0.85 to 0.92)
4 (rural towns)	955 606	10 506 056.3	4587	43.66	1.24 (1.19 to 1.29)
Insured amount (USD/year)					
< $7380	1 118 006	11 784 429.2	5462	46.35	1 (reference)
$7380–$12 924	2 625 359	29 864 036.7	10 475	35.08	0.74 (0.72 to 0.77)
≥ $12 924	1 369 957	15 860 267.4	4757	29.99	0.63 (0.61 to 0.66)
Comorbidity					
Diabetes mellitus	1 148 523	12 753 518.9	5963	46.76	1.44 (1.40 to 1.48)
Hypertension	2 014 080	22 392 863.2	10 436	46.60	1.62 (1.57 to 1.66)
Viral hepatitis A, B or C	430 307	4 799 653.8	1820	37.92	1.07 (1.02 to 1.12)

PD, Parkinson's disease; Pyr, person-years.

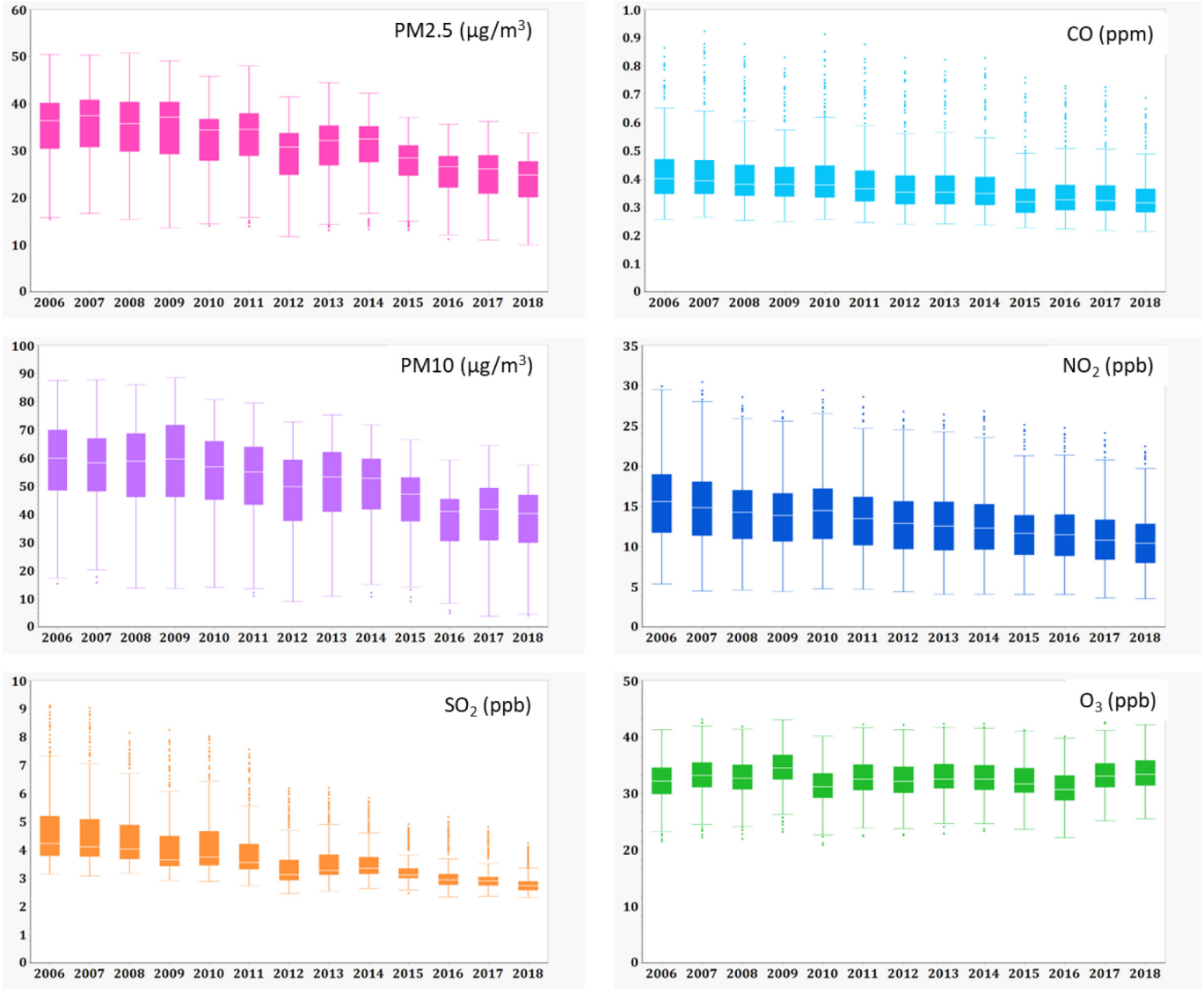

Figure 3 Mean annual concentrations of six studied air pollutants in the western part of Taiwan.

After adjusting for covariates, the single-pollutant model showed that exposure to higher concentrations of $PM_{2.5}$ (HR 2.65 (95% CI 2.59 to 2.72) per IQR increment), PM_{10} (HR 3.13 (3.04–3.22) per IQR increment), CO (HR 1.82 (1.75–1.89) per IQR increment), NO_2 (HR 1.74 (1.68–1.80) per IQR increment) and SO_2 (HR 1.68 (1.65–1.71) per IQR increment) is associated with an increased risk of PD, whereas elevated O_3 levels were associated with a lower incidence of PD (HR 0.77 (0.75–0.79) per IQR increment; table 2). Considering the mutual interactions between each air pollutant,[14 25] we examined the effect of each pollutant, adjusting for other multiple air pollutants. In the two-pollutant model, $PM_{2.5}$ (HR 2.29–2.74), NO_2 (HR 1.29–1.97) and SO_2 (HR 1.32–1.61) remained positively associated with increased PD risk after adjusting for each other. The association of PM_{10} (HR 1.76–3.07), CO (HR 1.34–1.79) and O_3 (HR 0.81–0.93) with PD risk remained significant after adjusting for $PM_{2.5}$, NO_2 and SO_2, respectively (table 2). In the multipollutant model, after concomitantly adjusting for the levels of $PM_{2.5}$, NO_2 and SO_2, we observed that exposure to $PM_{2.5}$ (HR 2.51 (95% CI 2.45 to 2.58)), NO_2 (HR 1.76 (1.70–1.83)), PM_{10} (HR 1.25 (1.18–1.33)) and SO_2 (HR 1.15 (1.13–1.18)) was positively associated with a higher incidence of PD. However, the association between exposure to CO and the incidence of PD became insignificant after adjusting for multiple air pollutants. Notably, after adjusting for co-pollutants, higher concentrations of O_3 were associated with an increased risk of PD (HR 1.29 (1.25–1.33)).

In sensitivity analyses, we found that traffic-related pollutants NO2 and CO had a greater impact on younger individuals, males and those without pre-existing medical comorbidities. The associations between $PM_{2.5}$, PM_{10} and PD risk were stronger in participants without chronic disorders. Specifically, $PM_{2.5}$ was more strongly associated with PD risk in individuals under 50 compared with those over 50 (online supplemental table 3).

DISCUSSION

Using a national population cohort with longitudinal follow-up data, our findings revealed that long-term exposure to air pollutants, including $PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3, is associated with an increased risk of incident PD. Notably, these associations remained robust after mutual adjustment for the potential interactions of other co-pollutants in the multipollutant model. The sensitivity analysis showed that the adverse impacts of air pollutants on PD risk are particularly significant among populations

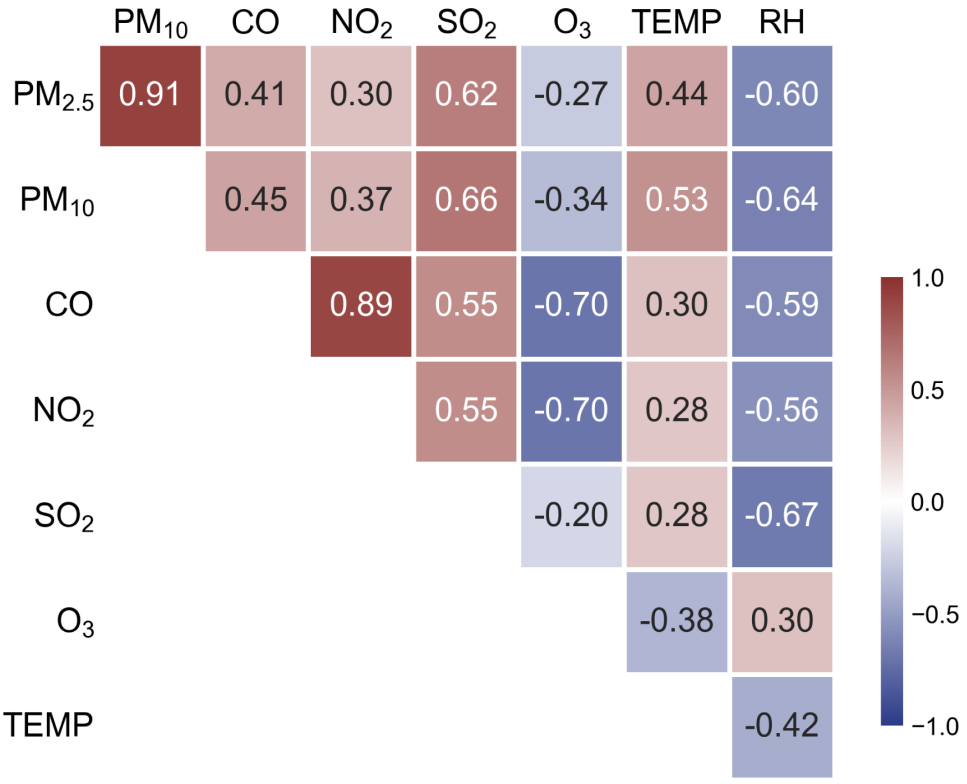

Figure 4 Spearman's correlation analysis of the relationships between different air pollutants and environmental factors, including temperature and humidity. RH, relative humidity; TEMP, ambient temperature.

that are younger, male or residents without chronic systemic diseases.

We observed a significant association between the exposure levels to PM, both $PM_{2.5}$ and PM_{10}, and an increased risk of PD, with these effects persisting in both two-pollutant or multi-pollutant model analyses. PM is a major pollutant that poses a significant threat to human health, including PD.[3] Our findings align with previous studies conducted in China, North America, and the UK, demonstrating that long-term exposure to higher levels of $PM_{2.5}$ is linked to an increased incidence of PD, whereas results from other regions, such as Finland, Italy, the Netherlands, Australia, Israel and South Korea have yielded no obvious association (online supplemental table 4).[8] Notably, the risk of PD is not increased in Seoul,[8] which is geographically near to our region. The median concentration of $PM_{2.5}$ (30.0 $\mu g/m^3$) was higher in in the current study than in Seoul (26.5 $\mu g/m^3$), which may be attributed to the main sources of $PM_{2.5}$ in our population being traffic emissions and coal combustion. Consistently, given that motorcycles are the main transportation system in our region,[26] the transportation system could partially explain why the sensitivity analysis revealed that the adverse impacts of air pollutants on PD risk are particularly significant among populations that are younger, male or residents without chronic diseases. Additionally, the most influential

Table 2 The adjusted HR of PD for each IQR increment in air pollutant levels

		Two-pollutant model			
	Single pollutant model	Model 1 (adjusted for $PM_{2.5}$)	Model 2 (adjusted for NO_2)	Model 3 (adjusted for SO_2)	Multiple pollutants model*
Air pollutant	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI
$PM_{2.5}$	2.65 (2.59 to 2.72)	–	2.74 (2.67 to 2.80)	2.29 (2.23 to 2.35)	2.51 (2.45 to 2.58)
PM_{10}	3.13 (3.04 to 3.22)	1.76 (1.66 to 1.87)	3.07 (2.99 to 3.16)	2.65 (2.56 to 2.73)	1.25 (1.18 to 1.33)
CO	1.82 (1.75 to 1.89)	1.79 (1.72 to 1.86)	1.34 (1.26 to 1.42)	1.47 (1.42 to 1.54)	1.05 (0.99 to 1.11)
NO_2	1.74 (1.68 to 1.80)	1.97 (1.91 to 2.04)	–	1.29 (1.25 to 1.34)	1.76 (1.70 to 1.83)
SO_2	1.68 (1.65 to 1.71)	1.32 (1.29 to 1.34)	1.61 (1.58 to 1.64)	–	1.15 (1.13 to 1.18)
O_3	0.77 (0.75 to 0.79)	0.93 (0.90 to 0.95)	0.91 (0.89 to 0.94)	0.81 (0.79 to 0.83)	1.29 (1.25 to 1.33)

Single-pollutant model: adjusted for sex; age; degree of urbanisation; insured amount; diabetes mellitus; hypertension; viral hepatitis A, B or C; ambient temperature; and relative humidity.
Two-pollutant model: covariates including sex, age, degree of urbanisation, insured amount, diabetes mellitus, hypertension, viral hepatitis, ambient temperature and relative humidity were adjusted in all the models.
Model 1: adjusted for covariates and $PM_{2.5}$. Model 2: adjusted for covariates and NO_2. Model 3: adjusted for covariates and SO_2.
*Multiple-pollutant model: single-pollutant model plus co-pollutants. For $PM_{2.5}$, adjustments are made for NO_2 and SO_2. For NO_2, adjustments are made for $PM_{2.5}$ and SO_2. For SO_2, adjustments are made for $PM_{2.5}$ and NO_2. For PM_{10}, CO, and O_3, adjustments are made for $PM_{2.5}$, NO_2, and SO_2.
PD, Parkinson's disease.

climate factors on $PM_{2.5}$ are temperature and rainfall. The higher mean temperature and humidity in our region compared with Seoul may also explain the difference in our results. The ultrafine particles (≤0.1 µm) included among $PM_{2.5}$ could cross the blood-brain barrier in humans. $PM_{2.5}$ can contain heavy metals, including arsenic and manganese, which have been implicated in the pathogenesis of basal ganglia degeneration.[27] Other specific components of $PM_{2.5}$, particularly nitrate and organic matter, are positively associated with PD progression.[28] Furthermore, PD experimental models have demonstrated that $PM_{2.5}$ can trigger the formation of toxic α-synuclein fibrils, impair mitochondrial function and disrupt autophagy, and activate microglia through the NF-κB pathway and the NLRP3 inflammasome, leading to neurodegeneration.[4 29] We found a significant association between PM_{10} and increased PD risk, even after adjusting for other pollutants. Associations between PM_{10} and risk of PD have been reported in a large cohort in China but was not observed in studies conducted in other regions. [8 10 11] As PM_{10} are course particles that cannot cross the blood-brain barrier, studies have shown that PM_{10} induces endothelial dysfunction and neuroinflammation in in vivo models.[30] Furthermore, the genetic background in various ethnicities provides different susceptibilities to PM for PD development, which may strengthen the detrimental effect of PM_{10} on PD risk.[10]

NO_2, primarily from road traffic, was found to increase PD risk in this study, consistent with findings from South Korea, Canada, Israel and most European countries (online supplemental table 4).[8] Animal studies show that NO2 causes brain toxicity, leading to mitochondrial dysfunction, microglial activation, amyloid and τ accumulation, synaptic dysfunction and neuronal degeneration.[31] CO, a traffic-related pollutant, was positively associated with PD risk in the single-pollutant model, but this association became non-significant after adjusting for other pollutants. Although higher concentrations of CO interfere with oxygen capacity, mitochondrial impairment and subsequent neurotoxicity, physiological levels of CO act as a signalling gas that modulates immune function and exerts a neuroprotective effect through upregulating the Nrf2 pathway.[32–34] Over the past decade, pollutant levels have generally decreased (except ozone), with no significant changes in concentrations between 2006 and 2018. SO_2, primarily from power plants and industrial facilities, has decreased due to air pollution control programmes and changes in traffic patterns, including bus electrification and the phase-out of heavy-duty diesel vehicles. We first showed that long-term SO_2 exposure increases the risk of PD, while previous studies in South Korea and Israel found no significant association between ambient SO_2 levels and PD risk.[8 35] SO_2 in ambient air primarily originates from the burning of fossil fuels, such as coal or oil, and the major sources of SO_2 in Taiwan are coal-fired power plants and industrial activities.[13] Inhalation of SO_2 has been found to promote peripheral inflammatory responses and trigger oxidative stress, ultimately leading to neuronal loss in the brain.[36] In rodent models, simultaneous exposure to SO_2 and $PM_{2.5}$ leads to τ pathology and subsequent cortical neuronal degeneration, a phenomenon that does not occur with exposure to either pollutant alone.[37] Our results indicate that the harmful influence of ambient air SO_2 on PD should not be overlooked.

The global burden of ground-level O3 and its health impacts has steadily increased, especially in East Asia. While studies in Canada and Taiwan show a positive link between long-term O3 exposure and PD incidence, others report null or even negative associations with PD risk or progression.[8 11 13] Our study initially found a negative association between O3 levels and PD incidence in the single-pollutant model, which turned positive after adjusting for other pollutants. O_3 is a secondary pollutant formed primarily from the chemical reaction between oxides of nitrogen and volatile organic compounds. Given that O_3 interacts with multiple pollutants,[15 38] our multipollutant model suggested a potential, long-term adverse effect of O_3 on the incidence of PD. Experimental studies show that chronic O3 exposure causes oxidative stress, triggering neuroinflammation, altered synaptic plasticity and hippocampal neuronal loss.[39] Clarifying the role of O_3 in PD pathogenesis remains an important area for future research.

The strength of this study lies in using data from a large, well-characterised nationally representative cohort with long-term follow-up in Asia. Using this cohort, we were able to incorporate the annually updated information on residence, demographic characteristics and medical history in all participants. The novelty of this study is that we comprehensively evaluated six different types of air pollutants and used the multi-pollutant model for considering the interaction effects between each pollutant to validate the findings from the single-pollutant analysis. We also considered temperature and humidity as covariates, as global warming has been shown to worsen the air quality. However, our study has several limitations. First, a causal inference cannot be made because this is an observational study. Further experimental research is needed to clarify the mechanisms by which these pollutants contribute to PD pathogenesis. Second, the measurement of outcomes relied on diagnostic codes, which introduces the possibility of misclassification. To enhance the specificity of disease diagnosis, we incorporated the number of medical institution visits into the diagnostic criteria, which has been shown and validated to improve accuracy in diagnosing PD.[26] Third, we did not adjust for several PD-associated protective or risk factors, such as smoking, exposure to pesticides, education level, occupations, physical activity, dietary habits, caffeine consumption and genetic variations, as this information was not accessible in the NHIRD. Additionally, much of western Taiwan is densely developed and populated, with areas combining metropolitan, residential and industrial zones, making it hard to distinguish between them. To minimise environmental interference, we adjusted for urbanisation and socioeconomic status, which are linked to PD risk and may affect exposure to neurotoxic agents.[40] Fourth, we were unable to examine the association between exposure duration and PD risk at the individual participant level. Additionally, this study did not examine the time trend effect of air pollutants on PD incidence due to sample size limitations and the need to avoid multiple comparisons, representing an important avenue for future research. Future studies should include more precise air pollutant measurements, along with personal factors like occupational history, transportation patterns, lifestyle and interactions between environmental PD risks.

In conclusion, our multipollutant models reveal significant associations between long-term exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3 and increased PD risk. These findings highlight the complex relationship between air pollution and PD, stressing the need for health policies to reduce pollution's impact. Our results emphasise the importance of monitoring air quality in high-risk populations and incorporating air pollution exposure into PD risk assessments. Additionally, they support community-based strategies and patient counselling to minimise exposure, potentially reducing PD incidence and progression.

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REFERENCES

1 Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet* 2021;397:2284–303.
2 Borghammer P, Just MK, Horsager J, *et al*. A postmortem study suggests a revision of the dual-hit hypothesis of Parkinson's disease. *NPJ Parkinsons Dis* 2022;8:166.
3 Fuller R, Landrigan PJ, Balakrishnan K, *et al*. Pollution and health: a progress update. *Lancet Planet Health* 2022;6:e535–47.
4 Liu Z, Sokratian A, Duda AM, *et al*. Anionic nanoplastic contaminants promote Parkinson's disease–associated α-synuclein aggregation. *Sci Adv* 2023;9.
5 Ritz B, Lee P-C, Hansen J, *et al*. Traffic-Related Air Pollution and Parkinson's Disease in Denmark: A Case-Control Study. *Environ Health Perspect* 2016;124:351–6.
6 Nunez Y, Boehme AK, Weisskopf MG, *et al*. Fine Particle Exposure and Clinical Aggravation in Neurodegenerative Diseases in New York State. *Environ Health Perspect* 2021;129:27003.
7 Kasdagli M-I, Katsouyanni K, Dimakopoulou K, *et al*. Air pollution and Parkinson's disease: A systematic review and meta-analysis up to 2018. *Int J Hyg Environ Health* 2019;222:402–9.
8 Jo S, Kim Y-J, Park KW, *et al*. Association of NO2 and Other Air Pollution Exposures With the Risk of Parkinson Disease. *JAMA Neurol* 2021;78:800–8.
9 Palacios N, Fitzgerald KC, Hart JE, *et al*. Air Pollution and Risk of Parkinson's Disease in a Large Prospective Study of Men. *Environ Health Perspect* 2017;125:087011.
10 Huang Y-M, Ma Y-H, Gao P-Y, *et al*. Genetic susceptibility modifies the association of long-term air pollution exposure on Parkinson's disease. *NPJ Parkinsons Dis* 2024;10:23.
11 Kirrane EF, Bowman C, Davis JA, *et al*. Associations of Ozone and PM2.5 Concentrations With Parkinson's Disease Among Participants in the Agricultural Health Study. *J Occup Environ Med* 2015;57:509–17.
12 Wise J. Pollution: 90% of world population breathes air that exceeds WHO targets on particulate matter. *BMJ* 2023;380:615.
13 Lee P-C, Liu L-L, Sun Y, *et al*. Traffic-related air pollution increased the risk of Parkinson's disease in Taiwan: A nationwide study. *Environ Int* 2016;96:75–81.
14 Gao X, Xue L, Wang X, *et al*. Aerosol ionic components at Mt. Heng in central southern China: abundances, size distribution, and impacts of long-range transport. *Sci Total Environ* 2012;433:498–506.
15 Bouthillier L, Vincent R, Goegan P, *et al*. Acute effects of inhaled urban particles and ozone: lung morphology, macrophage activity, and plasma endothelin-1. *Am J Pathol* 1998;153:1873–84.
16 Hsieh C-Y, Su C-C, Shao S-C, *et al*. Taiwan's National Health Insurance Research Database: past and future. *Clin Epidemiol* 2019;11:349–58.
17 Roos DS, Klein M, Deeg DJH, *et al*. Prevalence of Prodromal Symptoms of Parkinson's Disease in the Late Middle-Aged Population. *J Parkinsons Dis* 2022;12:967–74.
18 Pan S-C, Huang C-C, Chin W-S, *et al*. Association between air pollution exposure and diabetic retinopathy among diabetics. *Environ Res* 2020;181:108960.
19 Chen T-H, Hsu Y-C, Zeng Y-T, *et al*. A hybrid kriging/land-use regression model with Asian culture-specific sources to assess NO_2 spatial-temporal variations. *Environ Pollut* 2020;259:113875.
20 Lin C-H, Wu R-M, Chang H-Y, *et al*. Preceding pain symptoms and Parkinson's disease: a nationwide population-based cohort study. *Eur J Neurol* 2013;20:1398–404.
21 Tsai H-H, Liou H-H, Muo C-H, *et al*. Hepatitis C virus infection as a risk factor for Parkinson disease: A nationwide cohort study. *Neurology (ECronicon)* 2016;86:840–6.
22 Bougea A, Papagiannakis N, Simitsi A-M, *et al*. Ambiental Factors in Parkinson's Disease Progression: A Systematic Review. *Medicina (Kaunas)* 2023;59:294.
23 Ku T, Ji X, Zhang Y, *et al*. PM2.5, SO2 and NO2 co-exposure impairs neurobehavior and induces mitochondrial injuries in the mouse brain. *Chemosphere* 2016;163:27–34.
24 WHO Guidelines Approved by the Guidelines Review Committee. WHO global air quality guidelines: particulate matter (PM(25) and PM(10)), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva World Health Organization; 2021.
25 Qu Y, Wang T, Yuan C, *et al*. The underlying mechanisms of PM2.5 and O3 synergistic pollution in East China: Photochemical and heterogeneous interactions. *Sci Total Environ* 2023;873:162434.
26 Lin C-Y, Liao Y. Perceptions of activity-supportive environment and motorcycle use among urban Taiwanese adults. *BMC Public Health* 2017;17:665.
27 Willis AW, Evanoff BA, Lian M, *et al*. Metal emissions and urban incident Parkinson disease: a community health study of Medicare beneficiaries by using geographic information systems. *Am J Epidemiol* 2010;172:1357–63.
28 Chou CCK, Lung S-C, Hsiao T-C, *et al*. Regional and urban air quality in east Asia: Taiwan. In: Akimoto H, Tanimoto H, eds. *Handbook of Air Quality and Climate Change*. Singapore: Springer Nature Singapore, 2023: 469–506.
29 Wang Y, Li C, Zhang X, *et al*. Exposure to PM2.5 aggravates Parkinson's disease via inhibition of autophagy and mitophagy pathway. *Toxicology* 2021;456.
30 Guo L, Zhu N, Guo Z, *et al*. Particulate matter (PM10) exposure induces endothelial dysfunction and inflammation in rat brain. *J Hazard Mater* 2012;213–214:28–37.
31 Yan W, Ji X, Shi J, *et al*. Acute nitrogen dioxide inhalation induces mitochondrial dysfunction in rat brain. *Environ Res* 2015;138:416–24.
32 Dreyer-Andersen N, Almeida AS, Jensen P, *et al*. Intermittent, low dose carbon monoxide exposure enhances survival and dopaminergic differentiation of human neural stem cells. *PLoS One* 2018;13:e0191207.
33 Rose KN, Zorlu M, Fassini A, *et al*. Neuroprotection of low dose carbon monoxide in Parkinson's disease models commensurate with the reduced risk of Parkinson's among smokers. *NPJ Parkinsons Dis* 2024;10:152.
34 Siracusa R, Voltarelli VA, Salinaro AT, *et al*. NO, CO and H2S: A trinacrium of bioactive gases in the brain. *Biochem Pharmacol* 2022;202:115122.
35 Karakis I, Yarza S, Zlotnik Y, *et al*. Contribution of Solar Radiation and Pollution to Parkinson's Disease. *Int J Environ Res Public Health* 2023;20:2254.
36 Yao G, Yue H, Yun Y, *et al*. Chronic SO2 inhalation above environmental standard impairs neuronal behavior and represses glutamate receptor gene expression and memory-related kinase activation via neuroinflammation in rats. *Environ Res* 2015;137:85–93.

37 Ku T, Chen M, Li B, *et al*. Synergistic effects of particulate matter ($PM_{2.5}$) and sulfur dioxide (SO_2) on neurodegeneration via the microRNA-mediated regulation of tau phosphorylation. *Toxicol Res* 2017;6:7–16.
38 Fu Y, Zhang W, Li Y, *et al*. Association and interaction of O3 and NO2 with emergency room visits for respiratory diseases in Beijing, China: a time-series study. *BMC Public Health* 2022;22:2265.
39 Velázquez-Pérez R, Rodríguez-Martínez E, Valdés-Fuentes M, *et al*. Oxidative Stress Caused by Ozone Exposure Induces Changes in P2X7 Receptors, Neuroinflammation, and Neurodegeneration in the Rat Hippocampus. *Oxid Med Cell Longev* 2021;2021:3790477.
40 Ben-Shlomo Y, Darweesh S, Llibre-Guerra J, *et al*. The epidemiology of Parkinson's disease. *Lancet* 2024;403:283–92.