Environmental Pollution 271 (2021) 116303

Contents lists available at ScienceDirect

Environmental Pollution

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

Long-term exposure to fine particulate matter and dementia incidence: A cohort study in Hong Kong☆

Jinjun Ran [a, b, *], C. Mary Schooling [a, c], Lefei Han [d], Shengzhi Sun [e], Shi Zhao [d], Xiaohong Zhang [b], King-Pan Chan [a], Fang Guo [a], Ruby Siu-yin Lee [f], Yulan Qiu [b], Linwei Tian [a]

[a] School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China
[b] School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[c] City University of New York, School of Public Health and Health Policy, New York, NY, USA
[d] School of Nursing, Hong Kong Polytechnic University, Hong Kong, China
[e] Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA
[f] Elderly Health Service, Department of Health, Hong Kong, China

ARTICLE INFO

Article history:
Received 9 October 2020
Received in revised form
20 November 2020
Accepted 12 December 2020
Available online xxx

Keywords:
Fine particulate matter
Dementia
Alzheimer's disease
Vascular dementia
Cohort study

ABSTRACT

Recent studies suggested that long-term exposure to fine particulate matter ($PM_{2.5}$) was related to a higher risk of dementia incidence or hospitalizations in western populations, but the evidence is limited in Asian cities. Here we explored the link between long-term $PM_{2.5}$ exposure and dementia incidence in the Hong Kong population and whether it varied by population sub-group. We utilized a Hong Kong Chinese cohort of 66,820 people aged ≥65 years who were voluntarily enrolled during 1998–2001 and were followed up to 2011. Prevalent dementia cases were excluded based on the face-to-face interview at baseline. We ascertained the first occurrence of hospitalization for all-cause dementia and major subtypes during the follow-up period. We assessed $PM_{2.5}$ concentrations using a satellite data-based model with a 1×1 km^2 resolution on the residential address. Cox proportional hazards models were adopted to estimate associations of annual mean $PM_{2.5}$ exposure with dementia incidence, adjusting for potential confounders. We identified 1183 incident cases of all-cause dementia during the follow-up period, of which 655 (55.4%) were cases of Alzheimer's disease, and 334 (28.2%) were those of vascular dementia. We found a positive association between annual mean $PM_{2.5}$ exposure and all-cause dementia incidence in the fully adjusted model. The estimated hazard ratio was 1.06 (95% confidence interval (CI): 1.00, 1.13) per every 3.8 $\mu g/m^3$ increase in annual mean $PM_{2.5}$ exposure. And the estimated HRs for Alzheimer's disease and vascular dementia were 1.03 (95% CI: 0.94, 1.12) and 1.09 (95% CI: 0.98, 1.22), respectively. We did not find effect modifications by age, sex, BMI, hypertension, diabetes, or heart disease on the associations. Results suggest that long-term exposure to $PM_{2.5}$ is associated with a higher risk of dementia incidence in the Asian population.

1. Introduction

Dementia is a syndrome characterized by a deterioration in memory, thinking, behavior, and the ability to perform daily activities. Due to the increasing aging population, the global number of people living with dementia was about 43.8 million in 2016, doubling from the number in 1990 (20.2 million), and is projected to increase to 131.5 million in 2050 (Nichols et al., 2019; Prince et al., 2015). Globally, 2.4 million deaths are attributed to dementia, which ranks as the fifth leading cause of death, and accounted for 28.8 million disability-adjusted life-years in 2016 (Nichols et al., 2019). The cost of dementia was estimated at $818 billion worldwide in 2015 and is likely to have been over a trillion dollars in 2018 (Prince et al., 2015). Since there is no effective treatment, prevention is an attractive strategy to control the surge of dementia incidence and prevalence.

☆ This paper has been recommended for acceptance by Payam Dadvand.

* Corresponding author. School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, G/F, Patrick Manson Building (North Wing), 7 Sassoon Road, Pokfulam, Hong Kong, Hong Kong, China.
E-mail addresses: jimran@hku.hk, jinjunr@sjtu.edu.cn (J. Ran).

https://doi.org/10.1016/j.envpol.2020.116303
0269-7491/

There has been increased interest in the etiological role of ambient fine particulate matter ($PM_{2.5}$, particulate matter with aerodynamic diameter≤2.5 μm) on neurodegeneration. The potential biological mechanisms include oxidative stress and neuroinflammation, accompanied by disruption of the blood-brain barrier (BBB) and microglia activation (Block et al., 2012; Block and Calderón-Garcidueñas, 2009; Genc et al., 2012; Peters et al., 2019). Epidemiological studies have found that long-term exposure to $PM_{2.5}$ is significantly related to cognitive decline, as well as incidence and hospital admissions for Alzheimer's disease (AD) or other dementias in western populations (Ailshire and Crimmins, 2014; Carey et al., 2018; Chen et al., 2017a; Gatto et al., 2014; Kioumourtzoglou et al., 2016; Lee et al., 2019; Oudin et al., 2018; Tonne et al., 2014; Tzivian et al., 2016; Weuve et al., 2012), although not always consistently so (Cerza et al., 2019; Cleary et al., 2018; Loop et al., 2013).

Approximately half of the people living with dementia worldwide are identified in Asian, imposing a heavy burden on the public and health care systems (Prince et al., 2015). The association of $PM_{2.5}$ with dementia is poorly understood in Asian populations since few studies have been performed in Asian cities (Jung et al., 2015), even though Asian cities often have high levels of air pollution (Clean Air Network, 2012). Hong Kong is a densely populated large city located on China's southern coast and has the highest life expectancy around the world. The prevalence of dementia among people aged over 65 was about 7.2% (95% confidence interval (CI): 5.3%, 9.1%) until 2017, slightly higher than the prevalence in mainland China (5.3%, 95% CI: 4.3%, 6.3%) (Wu et al., 2018). We hence took advantage of the Chinese Elderly Health Service (EHS) Cohort to assess the association of long-term exposure to $PM_{2.5}$ with dementia incidence in the older Hong Kong population, and whether the associations were more evident in specific subgroups. We also used admissions for fractures and injuries as a control outcome, as there is no reason to think air pollution affects fractures and injuries.

2. Methods

2.1. Study population

The EHS cohort is a prospective cohort with 66,820 residents aged ≥65 years enrolled during 1998–2001, accounting for nearly 9% of the aged population (65+ years) in Hong Kong (Schooling et al., 2016). The EHS cohort was set to explore the role of Hong Kong as a sentinel for understanding aging in a non-Western context. The individuals voluntarily enrolled in the cohort during 1998–2001 and were followed up till the end of 2011. At baseline (1998–2001), individual information was collected by a face-to-face interview, including demographic characteristics, socioeconomic status (SES), lifestyle, and pre-existing chronic conditions. The interviews were carried out by nurses and doctors using a standardized and structured questionnaire. Informed consents from all participants were obtained during enrollment. Details have been published elsewhere (Ran et al., 2020a, 2020b; Sun et al., 2019). Ethics approval was obtained from the ethics committee of the Department of Health and the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

2.2. Prospective follow-up

Participants were followed from the date of enrollment to date of death or the end of 2011, whichever came first. We obtained dementia incidence during the follow-up period from hospitalization records, obtained from the electronic health record system, administrated by the Hospital Authority. Discharge diagnoses for each patient were coded with ICD-9 (the International Classification of Diseases, 9th version). We identified the incident cases of all-cause dementia, Alzheimer's disease, and vascular dementia based on the principal diagnosis code at discharge referring to a previous study (Frain et al., 2017). Specifically, the classification was: all-cause dementia (ICD-9: 290.0–290.9, 291.2, 294.1, 294.2, 331.0–331.9), Alzheimer's disease (ICD-9: 290.0, 290.2, 290.3, 331.0), and vascular dementia (ICD-9: 290.4). We also used the emergency hospitalizations for fractures and injuries (ICD-9: 800.0–869.1) as a negative control outcome to detect possible bias that may lead to spurious causal inference (Lipsitch et al., 2010).

2.3. Estimation of residential exposure to $PM_{2.5}$

Details about satellite-based $PM_{2.5}$ assessment are given in previous studies (Qiu et al., 2017; Wong et al., 2015). Briefly, we estimated spatiotemporal $PM_{2.5}$ concentrations using aerosol optical depth (AOD) recordings and data from general monitoring stations. AOD, which can indicate troposphere-level $PM_{2.5}$ exposure, was retrieved from US National Aeronautics and Space Administration satellites. It was refined into a resolution of 1×1 km^2 after adjusting for rainy days and humidity (Li et al., 2005). We regressed annual surface extinction coefficients (SEC), for measuring AOD, on corresponding annual mean $PM_{2.5}$ concentrations from four general monitoring, which measured the pollutant in the period 1998–2011. For each year, annual $PM_{2.5}$ exposures at the geographical locations of residential address for each participant were estimated using the same regression equation, with the annual SEC as the explanatory variable. The satellite-based $PM_{2.5}$ assessment was validated and widely utilized to estimate the morbidity or mortality risks of long-term $PM_{2.5}$ exposure in Hong Kong (Qiu et al., 2017; Ran et al., 2020a, 2020b; Sun et al., 2019; Wong et al., 2015). Baseline mean $PM_{2.5}$ concentrations (time-independent) during 1998–2001 was selected as a proxy for long-term $PM_{2.5}$ exposure.

2.4. Covariates

We selected *a priori* the accepted or suspected confounders from the literature, including demographic variables (age, sex, and body mass index (BMI)), SES (education and monthly expenses), behavioral factors (smoking status, drinking, exercise per week), social contact factors (had a regular caregiver, had regular contact with others, participated in any social activities, and had subjective feeling of social isolated), and pre-existing chronic conditions (hypertension, diabetes, heart disease, stroke, and mental illness) (Johansson et al., 2010; Norton et al., 2014; Reitz et al., 2011; Tomata et al., 2020). The types of exercise include walking slowly, stretching exercise, traditional Chinese exercise (Tai Chi, Luk Tung Kuen, Pak Tuen Kam), and aerobic exercise (jogging, swimming, cycling, walking uphill, etc.). Relationships of regular caregiver with our participants included spouse, relatives or family members, neighbors or close friends, volunteers, health or social welfare personnel, etc. Healthcare access for participants in the cohort was probably equitable because the public healthcare system in Hong Kong is virtually free and acts as a safety net for the whole city. We controlled for different sets of potential confounders in the analysis. Model 1 was a univariate model. Model 2 adjusted for age, sex, BMI, education, and monthly expenses. Model 3 was the fully adjusted model, additionally adjusting for smoking status, drinking, exercise, social contact factors, hypertension, diabetes, heart disease, stroke, and mental illness (especially depression and anxiety), based on model 2. All confounders were reported at baseline and considered

as time-independent.

2.5. Statistical analysis

We applied Cox proportional hazards to estimate associations of the incidence of all-cause dementia, Alzheimer's disease, and vascular dementia according to annual mean $PM_{2.5}$ exposure and baseline mean $PM_{2.5}$ exposure. Follow-up time was used as the underlying time scale. The proportional hazards assumption was verified by plots of the scaled Schoenfeld residuals before analysis. Potential confounders were adjusted for, including demographic variables, SES, behavioral factors, social contact factors, and pre-existing chronic conditions, as mentioned above. We estimated the hazard ratios (HRs) with the corresponding 95% confidence intervals (95% CI) per interquartile-range (IQR) increase in $PM_{2.5}$ concentrations. The exposure-response relationships of the $PM_{2.5}$ exposure with the three dementia outcomes were generated using a natural cubic spline with three degrees of freedom for the exposure term in Model 3 based on the minimized Akaike information criterion (AIC). Subgroup analyses were conducted to estimate potential effect modifications by age ($\leq$75 and > 75), sex (male and female), BMI (under/normal weight and overweight/obese), hypertension (yes and no), diabetes (yes and no), and heart disease (yes and no). The statistical significance across the potential effect modifiers was tested by the p-value for the interaction term in model 3.

We performed sensitivity analyses to check the robustness of results by the following strategies. First, we used attained age rather than follow-up time as the time scale. Second, we excluded participants who were diagnosed as incident dementia in the first year or the first three years after enrollment. Third, we excluded participants with baseline mean $PM_{2.5}$ exposure less than 29.70 μg/m^3 (<1% of baseline mean $PM_{2.5}$) and over 42.54 μg/m^3 (>99% of baseline mean $PM_{2.5}$). The two-tail p-value < 0.05 was considered as the result of statistical significance. Statistical analyses were conducted in R environment version 3.6.1 with the 'survival' package for survival analysis.

3. Results

A total of 59,349 participants were followed up after excluding 7126 individuals without accurate geo-coding, covariate, and exposure information, as well as 345 individuals diagnosed with dementia when enrolling. The mean follow-up time is about 10.4 years. Cloud cover problems, usually occurring from February to May, caused partial missing SEC data and then resulted in missing $PM_{2.5}$ estimates (Qiu et al., 2017; Wong et al., 2015). There were 1183 participants newly diagnosed dementia during the follow-up period, accounting for 2.0% of the included participants (59,349). Of the 1183 participants with all-cause dementia, we identified 655 and 334 individuals respectively with the incident Alzheimer's disease and vascular dementia, accounting for 55.4% and 28.2% of the total number of dementia patients (Fig. 1). Fig. 2 shows the spatial distribution of the dementia incident cases and non-dementia participants with varying long-term $PM_{2.5}$ exposure. .

Of those included (59,349 people) at baseline, 2.8% were 85 years or older, 65.6% were women, and 51.8% were overweight or obese. The majority were non-smoker (71.0%), non-drinker (72.2%), and exercised almost every day (72.1%). In terms of social contact, 76% had a regular caregiver, and 97.3% had regular social contacts, including family members, relatives, volunteers, friends, or others. 59.6% participated in any social activities, and only 5.9% had subjective feelings of social isolation. There were 36.0%, 12.3%, 12.3%, 2.9%, and 3.2% individuals with pre-existing hypertension, diabetes, heart disease, stroke, and mental illness at baseline, respectively

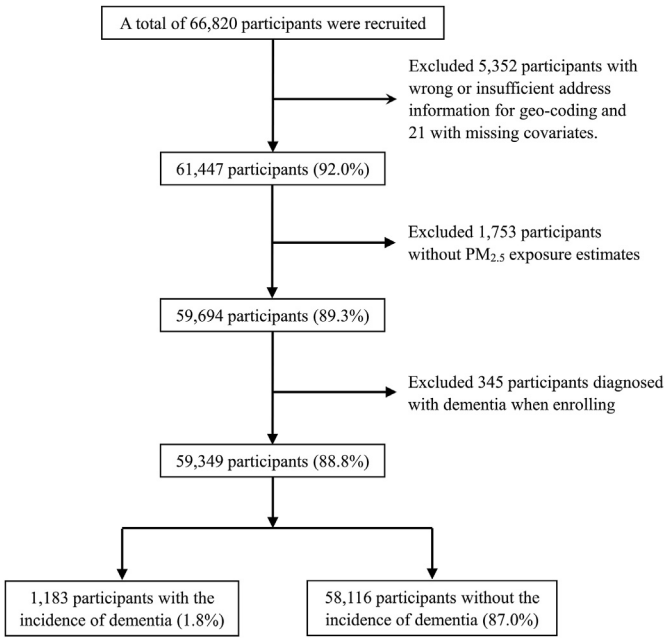

Fig. 1. Description of the inclusion process for the dementia cohort in the analysis.

(Table 1). The newly diagnosed patients with all-cause dementia, Alzheimer's disease, or vascular dementia were more likely to be older, women, and have low education, higher monthly expense, as well as to be smokers or drinkers. They might also take less exercise and felt more isolated. They were also more likely to have had a stroke or mental disease compared with those without the incidence of dementia in the cohort (Table 1 and Table S1). The annual mean $PM_{2.5}$ concentrations for participants were significantly correlated with the incidence of all-cause dementia, Alzheimer's disease, and vascular dementia (Table S2).

In the univariate model, an IQR increase (3.8 μg/m^3) in annual mean $PM_{2.5}$ concentrations was positively associated with the incidence of all-cause dementia, Alzheimer's disease, and vascular disease with HRs of 1.11 (95% CI: 1.04, 1.17), 1.09 (95% CI: 1.00, 1.18), and 1.12 (95% CI: 1.01, 1.24), respectively. After fully adjustment for demographic variables, SES, behavioral factors, and pre-existing chronic conditions, the HR was 1.06 (95% CI: 1.00, 1.13) for all-cause dementia, 1.03 (95% CI: 0.94, 1.12) for Alzheimer's disease, and 1.09 (95% CI: 0.98, 1.12) for vascular dementia per every 3.8 μg/m^3 increase in annual mean $PM_{2.5}$ concentrations. The results using the baseline mean $PM_{2.5}$ were comparable (Table 2). The total number of newly diagnosed cases was 1147 for all-cause dementia, 632 for Alzheimer's disease, and 324 for vascular dementia, after excluding those with incident dementia in the first three years. In this scenario, the observed HRs were 1.07 (95% CI: 1.01, 1.14) for all-cause dementia, 1.04 (95% CI: 0.95, 1.13) for Alzheimer's disease, and 1.09 (95% CI: 0.98, 1.22) for vascular dementia in the fully adjusted model (Table 3). In sensitivity analyses, results were robust when selecting attained age as the time scale and removing participants with baseline mean $PM_{2.5}$ exposure less than 29.53 μg/m^3 (<1% of baseline mean $PM_{2.5}$) (Table S3 and Table S4). After excluding those with baseline mean $PM_{2.5}$ exposure over 44.87 μg/m^3 (>99% of baseline mean $PM_{2.5}$), associations with all-cause dementia and vascular dementia were still observed but the association with Alzheimer's disease mildly waned (Table S5). We found no association of long-term exposure to $PM_{2.5}$ concentration with fractures and injuries in the same statistical framework (Table S6). The exposure-response relationships of dementia HRs with annual

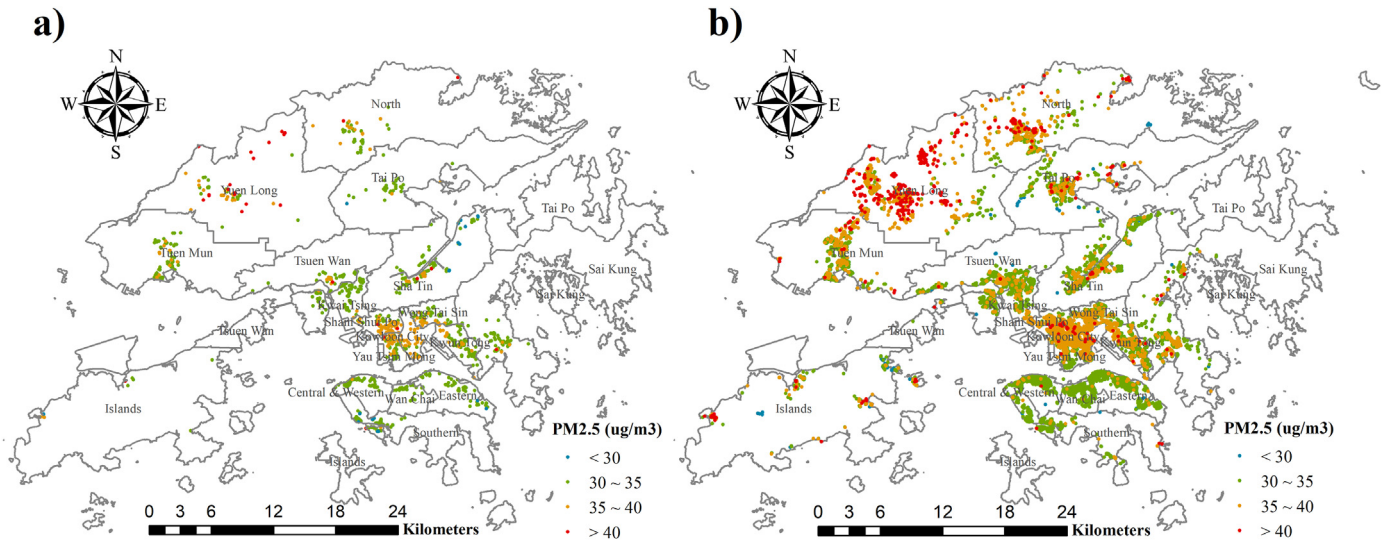

Fig. 2. Spatial distribution of the dementia incident cases and non-dementia participants with varying long-term $PM_{2.5}$ exposure. a) shows the spatial distribution of 1183 dementia incident cases and their corresponding baseline mean $PM_{2.5}$ exposure. b) shows the distribution of 58,116 non-dementia participants.

mean $PM_{2.5}$ exposure were close to linear (Fig. 4 and Figure S3).

We found that HRs of all-cause dementia incidence associated with $PM_{2.5}$ exposure were 1.07 (95% CI: 1.01, 1.15) and 0.97 (95% CI: 0.79, 1.19) in the subgroup living with or without diabetes, respectively. No clear interaction of diabetes on the associations was identified (p-interaction: 0.506) (Fig. 3). A comparable result was observed in the subgroup analyses of Alzheimer's disease (Figure S1 and Figure S2). There was no compelling evidence supporting any potential effect modifications by age, sex, BMI, hypertension, or heart disease of the associations of long-term $PM_{2.5}$ exposure with the dementia outcomes in subgroup analyses. When conducting subgroup analyses by education levels and monthly expense, we found individuals with below primary education had higher incidence risk of all-cause dementia or Alzheimer's disease (Table S7).

4. Discussion

In a cohort study in Hong Kong, an IQR increase in $PM_{2.5}$ concentrations was positively associated with the incident risk of all-cause dementia after adjusting for demographic characteristics, SES, behavioral factors, social contact, and pre-existing chronic conditions. The association with vascular dementia was close to statistical significance, which was consistent with a previous study in Rome (Cerza et al., 2019). Referring to the p-value of model 3 (against its baseline linear version) in Figure S3, we found no (statistical) evidence that the spline model outperformed the linear model for the exposure-response relationship between long-term $PM_{2.5}$ exposure and the incidence of Alzheimer's disease. As such, we considered using a linear model as a proxy to capture the true relationship. Since the HR for Alzheimer's disease was estimated at 1.03 (95% CI: 0.94, 1.12) for the linear model (Table 2), we concluded that the association was not of statistical significance although a positive association was likely. Additionally, we found little evidence of effect modifications by age, sex, BMI, hypertension, diabetes, and heart disease on the association.

This is one of few cohort studies exploring the association of long-term $PM_{2.5}$ exposure with dementia incidence in the Asian population, although many epidemiological studies have been conducted in western populations (Table S8). Two cohort studies in London observed that high exposure to $PM_{2.5}$ concentrations might result in a decline of cognitive function and an increase in incident dementia (Carey et al., 2018; Tonne et al., 2014). They are consistent with a longitudinal study in Northern Sweden, where a 1 $\mu g/m^3$ increase in wood-burning $PM_{2.5}$ was related to dementia incidence with an HR of 1.55 (95% CI: 1.00, 2.41) (Oudin et al., 2016). The findings were partially consistent with another cross-sectional study in the Ruhr region of Germany, where every 1.43 $\mu g/m^3$ increase in $PM_{2.5}$ was related to an odds ratio (OR) of 1.16 (95% CI: 1.05, 1.27) for mild cognitive impairment (Tzivian et al., 2016). A population-based cohort study in Ontario, Canada, where the local air pollution levels are at the lowest around the world, also observed a positive association between long-term exposure to $PM_{2.5}$ concentrations and increased risk of dementia incidence, with an HR of 1.04 (95% CI: 1.03, 1.05) (Chen et al., 2017a). A study of 350,844 Rome residents found that $PM_{2.5}$ exposure was positively related to vascular dementia but negatively associated with Alzheimer's disease (Cerza et al., 2019). Mixed results were observed in the US concerning the association of $PM_{2.5}$ exposure with dementia. Two cohort and two cross-sectional studies reported that $PM_{2.5}$ exposure was significantly related to more cognitive decline and dementia hospitalizations in the US population (Ailshire and Crimmins, 2014; Gatto et al., 2014; Kioumourtzoglou et al., 2016; Lee et al., 2019; Weuve et al., 2012). Studies further found that airborne $PM_{2.5}$ exposure might contribute to white matter loss in older women and might promote pathological brain aging with potentially a more significant impact in $\varepsilon 4$ carriers (an APOE allele) (Cacciottolo et al., 2017; Chen et al., 2015). However, it was also observed that $PM_{2.5}$ exposure was not reliably associated with cognitive impairment and decline in another two studies. One utilized a cohort of 30,239 participants from the 48 contiguous United States recruited between 2003 and 2007, and the other was a longitudinal study compiled by the University of Washington's National Alzheimer's Coordinating Center (NACC) (Cleary et al., 2018; Loop et al., 2013).

To our knowledge, there was only one study conducted in an Asian city. Jung et al. followed a prospective cohort study with 95,690 elderly individuals in Taiwan and found that a 138% (HR: 2.38; 95% CI: 2.21, 2.56) increased risk of Alzheimer's disease per every 4.34 $\mu g/m^3$ increase in ambient $PM_{2.5}$ concentrations after adjusting for age, sex, income, and multiple comorbid conditions (Jung et al., 2015). The association is stronger than our results in

Table 1
Baseline characteristics of the included participants by the incidence of all-cause dementia.

	All participants	Incidence of all-cause dementia		p-value
		Yes	No	
	(n = 59,349)	(n = 1183)	(n = 58,166)	
Annual mean $PM_{2.5}$, μg/m^3	35.2 (3.2)	35.7 (4.1)	35.2 (3.2)	<0.001
Baseline mean $PM_{2.5}$, μg/m^3	33.5 (2.9)	33.7 (3.7)	33.5 (2.9)	0.034
Age, yr, n (%)				<0.001
65–74	42605 (71.8%)	564 (47.7%)	42041 (72.3%)	
75–84	15105 (25.5%)	526 (44.5%)	14579 (25.1%)	
≥85	1639 (2.8%)	93 (7.9%)	1546 (2.7%)	
Sex, n (%)				0.038
Female	38931 (65.6%)	810 (68.5%)	38121 (65.5%)	
Male	20418 (34.4%)	373 (31.5%)	20045 (34.5%)	
BMI, kg/m^2, n (%)				<0.001
<18.5	3110 (5.2%)	96 (8.1%)	3014 (5.2%)	
18.5–23.9	25517 (43.0%)	562 (47.5%)	24955 (42.9%)	
24.0–26.9	18036 (30.4%)	326 (27.6%)	17710 (30.4%)	
≥27.0	12686 (21.4%)	199 (16.8%)	12487 (21.5%)	
Education, n (%)				<0.001
Below primary	26906 (45.3%)	642 (54.3%)	26264 (45.2%)	
Primary	22137 (37.3%)	397 (33.6%)	21740 (37.4%)	
Secondary or above	10306 (17.4%)	144 (12.2%)	10162 (17.5%)	
Monthly expenses, n (%)				<0.001
<1000 HKD	9738 (16.4%)	152 (12.8%)	9586 (16.5%)	
1000–1999 HKD	40894 (68.9%)	811 (68.6%)	40083 (68.9%)	
≥2000 HKD	8717 (14.7%)	220 (18.6%)	8497 (14.6%)	
Smoking status, n (%)				0.013
Never	42161 (71.0%)	819 (69.2%)	41342 (71.1%)	
Quit	11448 (19.3%)	265 (22.4%)	11183 (19.2%)	
Current	5740 (9.7%)	99 (8.4%)	5641 (9.7%)	
Drinking, n (%)				0.003
Never	42864 (72.2%)	870 (73.5%)	41994 (72.2%)	
Quit	5776 (9.73%)	140 (11.8%)	5636 (9.69%)	
Social	8333 (14.0%)	134 (11.3%)	8199 (14.1%)	
Regular	2376 (4.0%)	39 (3.3%)	2337 (4.0%)	
Exercise per week, n (%)				0.001
<1 day	9047 (15.2%)	224 (18.9%)	8823 (15.2%)	
1–6 days	7533 (12.7%)	156 (13.2%)	7377 (12.7%)	
≥7 days	42769 (72.1%)	803 (67.9%)	41966 (72.1%)	
Social contact, n (%)				
Had a regular caregiver	45077 (76.0%)	866 (73.2%)	44211 (76.0%)	0.028
Had regular contact with others	57734 (97.3%)	1117 (94.4%)	56617 (97.3%)	<0.001
Participated in any social activities	35373 (59.6%)	752 (63.6%)	34621 (59.5%)	0.005
Subjective feelings of social isolation	3498 (5.9%)	113 (9.6%)	3385 (5.8%)	<0.001
Pre-existing chronic conditions, n (%)				
Hypertension	21348 (36.0%)	446 (37.7%)	20902 (35.9%)	0.213
Diabetes	7280 (12.3%)	167 (14.1%)	7113 (12.2%)	0.054
Heart disease	7323 (12.3%)	165 (14.0%)	7158 (12.3%)	0.096
Stroke	1727 (2.9%)	64 (5.4%)	1663 (2.9%)	<0.001
Mental illness	1917 (3.2%)	87 (7.4%)	1830 (3.2%)	<0.001

Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; BMI, body mass index.

Table 2
Associations of the incidence of all-cause dementia, Alzheimer's disease, and vascular dementia per IQR increase in annual mean $PM_{2.5}$ and baseline mean $PM_{2.5}$ concentrations.

	All-cause dementia		Alzheimer's disease		Vascular dementia	
	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)
Annual mean $PM_{2.5}$						
Model 1	1183	1.11 (1.04, 1.17)	655	1.09 (1.00, 1.18)	334	1.12 (1.01, 1.24)
Model 2	1183	1.07 (1.01, 1.14)	655	1.04 (0.96, 1.13)	334	1.10 (0.99, 1.22)
Model 3	1183	1.06 (1.00, 1.13)	655	1.03 (0.94, 1.12)	334	1.09 (0.98, 1.22)
Baseline mean $PM_{2.5}$						
Model 1	1183	1.08 (1.03, 1.13)	655	1.06 (1.00, 1.13)	334	1.10 (1.01, 1.19)
Model 2	1183	1.05 (1.01, 1.10)	655	1.03 (0.96, 1.10)	334	1.08 (1.00, 1.17)
Model 3	1183	1.05 (1.00, 1.10)	655	1.02 (0.95, 1.09)	334	1.08 (0.99, 1.17)

Abbreviations: IQR, interquartile range; HR, hazard ratio; CI, confidence interval.
Model 1, univariate model; Model 2, adjusted for age, sex, BMI, education, and monthly expenses; Model 3, adjusted for age, sex, BMI, education, monthly expenses, smoking status, drinking, exercise, had a regular caregiver, had regular contact with others, participated in any social activities, subjective feelings of social isolation, hypertension, diabetes, heart disease, stroke, and mental illness.

Table 3
Sensitivity analysis for associations of the incidence of all-cause dementia, Alzheimer's disease, and vascular dementia with every IQR increase in annual $PM_{2.5}$ concentrations by excluding participants with incident dementia in the first year and first three years after enrolling.

	All-cause dementia		Alzheimer's disease		Vascular dementia	
	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)
Excluding participants with incident dementia in the first year						
Model 1	1163	1.10 (1.03, 1.16)	640	1.09 (1.01, 1.18)	330	1.08 (0.96, 1.21)
Model 2	1163	1.06 (1.00, 1.13)	640	1.05 (0.96, 1.14)	330	1.06 (0.94, 1.19)
Model 3	1163	1.05 (0.99, 1.12)	640	1.04 (0.95, 1.13)	330	1.05 (0.93, 1.19)
Excluding participants with incident dementia in the first three years						
Model 1	1147	1.11 (1.05, 1.18)	632	1.09 (1.01, 1.19)	324	1.12 (1.01, 1.25)
Model 2	1147	1.08 (1.02, 1.14)	632	1.05 (0.96, 1.14)	324	1.10 (0.99, 1.23)
Model 3	1147	1.07 (1.01, 1.14)	632	1.04 (0.95, 1.13)	324	1.09 (0.98, 1.22)

Abbreviations: IQR, interquartile range; HR, hazard ratio; CI, confidence interval.
Model 1, univariate model; Model 2, adjusted for age, sex, BMI, education, and monthly expenses; Model 3, adjusted for age, sex, BMI, education, monthly expenses, smoking status, drinking, exercise, had a regular caregiver, had regular contact with others, participated in any social activities, subjective feelings of social isolation, hypertension, diabetes, heart disease, stroke, and mental illness.

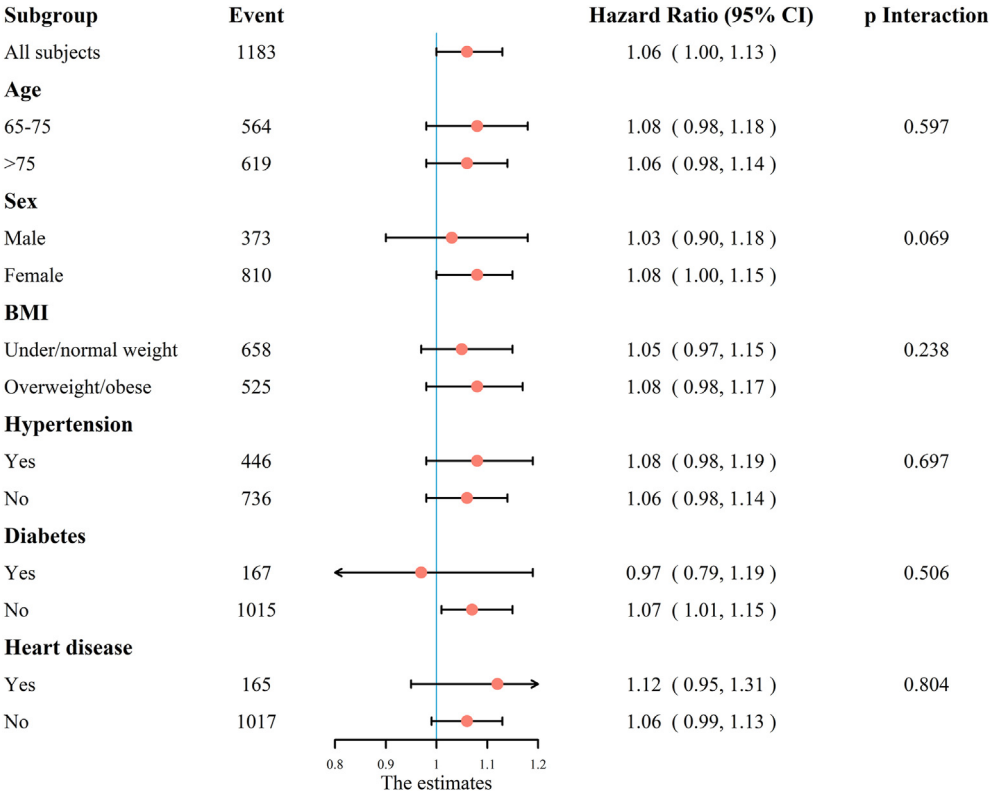

Fig. 3. Associations of all-cause dementia with annual mean $PM_{2.5}$ concentrations in different subgroups (stratified by age, sex, BMI, hypertension, diabetes, and heart disease) in the fully adjusted model (adjusting for age, sex, BMI, education, monthly expenses, smoking status, drinking, exercise, had a regular caregiver, had regular contact with others, participated in any social activities, subjective feelings of social isolation, hypertension, diabetes, heart disease, stroke, and mental illness). The p interaction indicates the result of the interaction effect on the multiplicative scale.

Hong Kong, where we observed the estimated HR was 1.06 (95% CI: 1.00, 1.13) for all-cause dementia and 1.03 (95% CI: 0.94, 1.12) for Alzheimer's disease per every 3.8 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations, probably because the included individuals in our cohort were more health-conscious (71.0% and 72.2% had no smoking and drinking habits, respectively, and 72.1% took daily exercise) and so perhaps less susceptible to the detrimental impacts of air pollution. We could underestimate the true effects of $PM_{2.5}$ exposure in the general elderly population in Hong Kong.

$PM_{2.5}$ can contribute to neuroinflammation and neurodegeneration through indirect and direct pathways (Block and Calderón-Garcidueñas, 2009). Effects of $PM_{2.5}$ can cross from the periphery to the brain partially through systemic inflammation. $PM_{2.5}$ exposure causes pro-inflammatory signals originating in peripheral systems and stimulating a systemic-induced cytokine response, which transfers inflammation to the brain (L. Calderón-Garcidueñas et al., 2008; Lilian Calderón-Garcidueñas et al., 2008a). $PM_{2.5}$ inhalation elevates and mobilizes plasma cytokines into circulation. The circulating cytokines produced in systemic inflammation, especially IL-1β and TNFα, are well known to cause neuroinflammation and neurotoxicity (Perry et al., 2007). However, the effect of cytokines on AD still remains controversial. In addition to neuronal damage, pollutant-induced systemic inflammation may contribute to deteriorating the blood-brain barrier (BBB), enhancing access to the brain (Calderon-Garciduenas et al., 2002). Direct effects of $PM_{2.5}$ on neurodegeneration may be generated

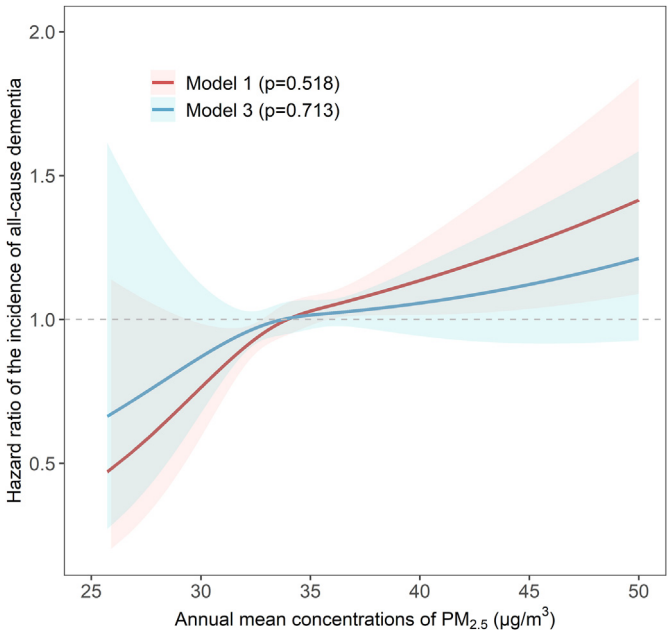

Fig. 4. Exposure-response relationship of the hazard ratio of the all-cause dementia incidence with annual mean $PM_{2.5}$ concentrations in the univariate model and fully adjusted model (adjusting for age, sex, BMI, education, monthly expenses, smoking status, drinking, exercise, had a regular caregiver, had regular contact with others, participated in any social activities, subjective feelings of social isolation, hypertension, diabetes, heart disease, stroke, and mental illness). The red line indicates the curve in model 1 (univariate model), and the blue line shows the result in model 3 (fully adjusted model). The p-value shows the result of the linearity test, and p-value > 0.05 suggests that the relationship is close to linear.

based on the particles and absorbed toxic compounds. An animal model observed the translocation of the particles into the brain after inhalation and nasal instillation of particles (Oberdörster et al., 2004). Particles, especially ultrafine particulate matter (UFPM), are proposed as an ideal vehicle to transport transition metals and lipopolysaccharides into neurons since they can easily penetrate cell membranes (Geiser et al., 2005). Numerous compounds are neurotoxic, such as manganese and aluminum. Studies found that exposure to manganese and aluminum particles might result in dopaminergic neurotoxicity or BBB damage (Burton and Guilarte, 2009; Chen et al., 2008).

Microglia activation and BBB disruption are documented as cellular mechanisms of neuroinflammation (Block and Calderón-Garcidueñas, 2009; Peters et al., 2019). Microglia can be activated by particle-induced cytokines, endogenous disease proteins (accumulation of Amyloid β-42 and α-Synuclein), and neuronal death (Block et al., 2007; Lilian Calderón-Garcidueñas et al., 2008b). Microglia activation can be a chronic source of pro-inflammatory molecules (TNFα, IL-1β, and IFNγ) and oxidative stress through dopaminergic neurotoxicity and the upregulation of mRNA of pro-inflammatory cytokines, which drives neurodegenerative progress in the brain (Block et al., 2007). Particles have been identified in brain capillaries and parenchyma, suggesting a capacity to interact with and pass through the BBB (Lilian Calderón-Garcidueñas et al., 2008b). Particle-induced ROS and cytokines can reduce the viability of brain microvascular endothelial cells and the expression of tight junction proteins, which enhance access to the brain and further impinge upon neuropathology (Chen et al., 2008; Hartz et al., 2008).

We found little evidence of effect modification by age, sex, BMI, hypertension, diabetes, and heart disease in the $PM_{2.5}$-related dementia risks, possibly due to their heightened baseline risk profile that would mask the multiplicative effect from $PM_{2.5}$ exposure. We observed a potentially higher $PM_{2.5}$-related incident risk of dementia among participants without diabetes (HR: 1.07; 95% CI: 1.01, 1.15) than that among counterparts (HR: 0.97; 95% CI: 0.79, 1.19) though no clear effect modification was identified (p-interaction: 0.506). While in the study of Chen et al. the estimated risk of incident dementia was significantly higher in the subgroup living without diabetes (p-interaction: 0.030) (Chen et al., 2017a). One possible explanation is the selection bias, that is, people with diabetes may die before they have a chance to get dementia. However, more studies were warranted to explore the multifaceted reasons from other aspects, such as medication or nutrition.

Caution should be exercised when interpreting our results. First, participants in the EHS cohort are not the whole Hong Kong elderly population though the number of included participants accounted for approximately 9% of older people in Hong Kong (Schooling et al., 2016). The enrolled participants were more health-conscious because they voluntarily enrolled in the cohort. The volunteer selection bias might bias our results to null. Second, yearly residential $PM_{2.5}$ exposure was estimated using a satellite data-based model with 1×1 km^2 resolution. The model has been validated and has been used in previous studies (Qiu et al., 2017; Ran et al., 2020a, 2020b; Sun et al., 2019; Wong et al., 2015). Exposure measurement error is possible and would bias towards the null. Third, undiagnosed dementia might exist because only the principal diagnosis code at discharge was used. However, missing diagnosis is likely independent of $PM_{2.5}$ exposure given universal healthcare in Hong Kong. This nondifferential misclassification would underestimate the true health effects of air pollution. Fourth, due to data unavailability, we cannot test surrogate effects or interaction effects with other prevalent environmental factors, especially other pollutants from transportation (Chen et al., 2017b), green space (Dadvand et al., 2015; Gascon et al., 2015), or UFPM. The UFPM would also be a determinator responsible for neuroinflammation since it has a large surface-to-volume ratio and easily penetrates cell membranes (Block and Calderón-Garcidueñas, 2009; Peters et al., 2019). Fifth, we only obtained long-term exposure to $PM_{2.5}$ concentration by a satellite data-based model. The exposure assessments for other pollutants, such as nitrogen dioxide or ozone, were not available up to now. Further study would focus on the multiple-pollutant model for fitting associations of more air pollutants with the incidence of dementia when data are available. Additionally, we did not evaluate the cognitive function of each participant at baseline. Their baseline cognitive functions were not controlled in models in our analyses. More studies were warranted to explore further the potential mediation effect of cognitive decline on the pathway from long-term $PM_{2.5}$ exposure to the dementia incidence. And we did not have the information about the time of residence in the participants before enrollment. Therefore, we could not evaluate the previous $PM_{2.5}$ exposure before enrollment for each participant. Last but not the least, we cannot rule out potential selection bias and residual confounding by unmeasured aspects of SES. However, it would unlikely substantially bias our estimates because our negative control gave no association.

5. Conclusions

We observed that long-term exposure to $PM_{2.5}$ concentrations was positively related to the incidence of all-cause dementia in a large population-based cohort in Hong Kong. We observed no evidence of effect modifications by age, sex, BMI, hypertension, diabetes, and heart disease on the association. Our findings may contribute to the evidence of $PM_{2.5}$-induced risks on neurodegeneration in the Asian population.

Funding support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to thank the Environmental Protection Department of Hong Kong for providing air pollution data, thank the Elderly Health Services of Department of Health for the cohort data, and also thank the Hospital Authority for the hospitalization data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2020.116303.

Credit author statement

Jinjun Ran, Conceptualization, Methodology, Formal analysis, Writing – original draft. C.Mary Schooling, Supervision, Writing – review & editing; Lefei Han, Validation, Visualization, Writing – review & editing; Shengzhi Sun, Methodology, Validation, Writing – review & editing; Shi Zhao, Methodology, Writing – review & editing; Xiaohong Zhang, Visualization; King-Pan Chan, Software, Investigation; Fang Guo: Visualization, Validation; Ruby Siu-yin Lee, Investigation, Resources, Data curation; Yulan Qiu, Conceptualization, Methodology; Linwei Tian: Supervision, Project administration.

References

Ailshire, J.A., Crimmins, E.M., 2014. Fine particulate matter air pollution and cognitive function among older US adults. Am. J. Epidemiol. 180, 359–366. https://doi.org/10.1093/aje/kwu155.

Block, M.L., Calderón-Garcidueñas, L., 2009. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 32, 506–516. https://doi.org/10.1016/j.tins.2009.05.009.

Block, M.L., Elder, A., Auten, R.L., Bilbo, S.D., Chen, H., Chen, J.C., Cory-Slechta, D.A., et al., 2012. The outdoor air pollution and brain health workshop. Neurotoxicology 33, 972–984. https://doi.org/10.1016/j.neuro.2012.08.014.

Block, M.L., Zecca, L., Hong, J.S., 2007. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat. Rev. Neurosci. 8, 57–69. https://doi.org/10.1038/nrn2038.

Burton, N.C., Guilarte, T.R., 2009. Manganese neurotoxicity: lessons learned from longitudinal studies in nonhuman primates. Environ. Health Perspect. 117, 325–332. https://doi.org/10.1289/ehp.0800035.

Cacciottolo, M., Wang, X., Driscoll, I., Woodward, N., Saffari, A., Reyes, J., Serre, M.L., Vizuete, W., Sioutas, C., Morgan, T.E., Gatz, M., Chui, H.C., Shumaker, S.A., Resnick, S.M., Espeland, M.A., Finch, C.E., Chen, J.C., 2017. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. Transl. Psychiatry 7. https://doi.org/10.1038/tp.2016.280.

Calderon-Garciduenas, L., Azzarelli, B., Acuna, H., R, G., T, G., Osnaya, N., Monroy, S., 2002. Air pollution and brain damage. Toxicol. Pathol. 30, 373–389.

Calderón-Garcidueñas, Lilian, Mora-Tiscareño, A., Ontiveros, E., Gómez-Garza, G., Barragán-Mejía, G., Broadway, J., Chapman, S., Al, E., 2008a. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain Cognit. 68, 117–127. https://doi.org/10.1016/j.bandc.2008.04.008.

Calderón-Garcidueñas, Lilian, Solt, A.C., Henríquez-Roldán, C., Torres-Jardón, R., Nuse, B., Herritt, L., Villarreal-Calderón, R., Osnaya, N., Stone, I., García, R., Brooks, D.M., González-Maciel, A., Reynoso-Robles, R., Delgado-Chávez, R., Reed, W., 2008b. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β-42 and α-synuclein in children and young adult. Toxicol. Pathol. 36, 289–310. https://doi.org/10.1177/0192623307313011.

Calderón-Garcidueñas, L., Villarreal-Calderon, R., Valencia-Salazar, G., Henríquez-Roldán, C., Gutiérrez-Castrellón, P., Coria-Jiménez, R., Torres-Jardón, R., Al, E., 2008. Systemic inflammation, endothelial dysfunction, and activation in clinically healthy children exposed to air pollutants. Inhal. Toxicol. 20, 499–506. https://doi.org/10.1080/08958370701864797.

Carey, I.M., Anderson, H.R., Atkinson, R.W., Beevers, S.D., Cook, D.G., Strachan, D.P., Dajnak, D., Gulliver, J., Kelly, F.J., 2018. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. BMJ Open 8, 1–11. https://doi.org/10.1136/bmjopen-2018-022404.

Cerza, F., Renzi, M., Gariazzo, C., Davoli, M., Michelozzi, P., Forastiere, F., Cesaroni, G., 2019. Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study. Environ. Heal. A Glob. Access Sci. Source 18, 1–12. https://doi.org/10.1186/s12940-019-0511-5.

Chen, H., Kwong, J.C., Copes, R., Hystad, P., van Donkelaar, A., Tu, K., Brook, J.R., Goldberg, M.S., Martin, R.V., Murray, B.J., Wilton, A.S., Kopp, A., Burnett, R.T., 2017a. Exposure to ambient air pollution and the incidence of dementia: a population-based cohort study. Environ. Int. 108, 271–277. https://doi.org/10.1016/j.envint.2017.08.020.

Chen, H., Kwong, J.C., Copes, R., Tu, K., Villeneuve, P.J., van Donkelaar, A., Hystad, P., Martin, R.V., Murray, B.J., Jessiman, B., Wilton, A.S., Kopp, A., Burnett, R.T., 2017b. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. Lancet 389, 718–726. https://doi.org/10.1016/S0140-6736(16)32399-6.

Chen, J.C., Wang, X., Wellenius, G.A., Serre, M.L., Driscoll, I., Casanova, R., McArdle, J.J., Manson, J.E., Chui, H.C., Espeland, M.A., 2015. Ambient air pollution and neurotoxicity on brain structure: evidence from women's health initiative memory study. Ann. Neurol. 78, 466–476. https://doi.org/10.1002/ana.24460.

Chen, L., Yokel, R.A., Hennig, B., Toborek, M., 2008. Manufactured aluminum oxide nanoparticles decrease expression of tight junction proteins in brain vasculature. J. Neuroimmune Pharmacol. 3, 286–295. https://doi.org/10.1007/s11481-008-9131-5.

Clean Air Network, 2012. Hong Kong Air Quality Review January~ June, 2012 (Hong Kong).

Cleary, E.G., Cifuentes, M., Grinstein, G., Brugge, D., Shea, T.B., 2018. Association of low-level ozone with cognitive decline in older adults. J. Alzheim. Dis. 61, 67–78. https://doi.org/10.3233/JAD-170658.

Dadvand, P., Nieuwenhuijsen, M.J., Esnaola, M., Forns, J., Basagaña, X., Alvarez-Pedrerol, M., Rivas, I., López-Vicente, M., De Pascual, M.C., Su, J., Jerrett, M., Querol, X., Sunyer, J., 2015. Green spaces and cognitive development in primary schoolchildren. Proc. Natl. Acad. Sci. U. S. A 112, 7937–7942. https://doi.org/10.1073/pnas.1503402112.

Frain, L., Swanson, D., Cho, K., Gagnon, D., Lu, K.P., Betensky, R.A., Driver, J., 2017. Association of cancer and Alzheimer's disease risk in a national cohort of veterans. Alzheimer's Dementia 13, 1364–1370. https://doi.org/10.1016/j.jalz.2017.04.012.

Gascon, M., Mas, M.T., Martínez, D., Dadvand, P., Forns, J., Plasència, A., Nieuwenhuijsen, M.J., 2015. Mental health benefits of long-term exposure to residential green and blue spaces: a systematic review. Int. J. Environ. Res. Publ. Health 12, 4354–4379. https://doi.org/10.3390/ijerph120404354.

Gatto, N.M., Henderson, V.W., Hodis, H.N., St John, J.A., Lurmann, F., Chen, J.C., Mack, W.J., 2014. Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. Neurotoxicology 40, 1–7. https://doi.org/10.1016/j.neuro.2013.09.004.

Geiser, M., Rothen-Rutishauser, B., Kapp, N., Schürch, S., Kreyling, W., Schulz, H., Semmler, M., Im Hof, V., Heyder, J., Gehr, P., 2005. Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. Environ. Health Perspect. 113, 1555–1560. https://doi.org/10.1289/ehp.8006.

Genc, S., Zadeoglulari, Z., Fuss, S.H., Genc, K., 2012. The adverse effects of air pollution on the nervous system. J. Toxicol. 2012. https://doi.org/10.1155/2012/782462.

Hartz, A.M.S., Bauer, B., Block, M.L., Hong, J.-S., Miller, D.S., 2008. Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier. Faseb. J. 22, 2723–2733. https://doi.org/10.1096/fj.08-106997.

Johansson, L., Guo, X., Waern, M., Östling, S.Ö., Gustafson, D., Bengtsson, C., Skoog, I., 2010. Midlife psychological stress and risk of dementia: a 35-year longitudinal population study. Brain 133, 2217–2224. https://doi.org/10.1093/brain/awq116.

Jung, C.R., Lin, Y.T., Hwang, B.F., 2015. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. J. Alzheim. Dis. 44, 573–584. https://doi.org/10.3233/JAD-140855.

Kioumourtzoglou, M.A., Schwartz, J.D., Weisskopf, M.G., Melly, S.J., Wang, Y., Dominici, F., Zanobetti, A., 2016. Long-term PM2.5 exposure and neurological hospital admissions in the northeastern United States. Environ. Health Perspect. 124, 23–29. https://doi.org/10.1289/ehp.1408973.

Lee, M., Schwartz, J., Wang, Y., Dominici, F., Zanobetti, A., 2019. Long-term effect of fine particulate matter on hospitalization with dementia. Environ. Pollut. 254, 112926. https://doi.org/10.1016/j.envpol.2019.07.094.

Li, C., Lau, A.K.H., Mao, J., Chu, D.A., 2005. Retrieval, validation, and application of the 1-km aerosol optical depth from MODIS measurements over Hong Kong. IEEE Trans. Geosci. Rem. Sens. 43, 2650–2658. https://doi.org/10.1109/TGRS.2005.856627.

Lipsitch, M., Tchetgen Tchetgen, E., Cohen, T., 2010. Negative Controls: a tool for detecting confounding and bias in observational studies. Epidemiology 21,

383–388. https://doi.org/10.1097/EDE.0b013e3181d61eeb.
Loop, M.S., Kent, S.T., Al-Hamdan, M.Z., Crosson, W.L., Estes, S.M., Estes, M.G., Quattrochi, D.A., Hemmings, S.N., Wadley, V.G., McClure, L.A., 2013. Fine particulate matter and incident cognitive impairment in the REasons for geographic and racial differences in stroke (REGARDS) cohort. PloS One 8, 1–9. https://doi.org/10.1371/journal.pone.0075001.
Nichols, E., Szoeke, C.E.I., Vollset, S.E., Abbasi, N., Abd-Allah, F., Abdela, J., Aichour, M.T.E., et al., 2019. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18, 88–106. https://doi.org/10.1016/S1474-4422(18)30403-4.
Norton, S., Matthews, F.E., Barnes, D.E., Yaffe, K., Brayne, C., 2014. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 13, 788–794. https://doi.org/10.1016/S1474-4422(14)70136-X.
Oberdörster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Kreyling, W., Cox, C., 2004. Translocation of inhaled ultrafine particles to the brain. Inhal. Toxicol. 16, 437–445. https://doi.org/10.1080/08958370490439597.
Oudin, A., Forsberg, B., Adolfsson, A.N., Lind, N., Modig, L., Nordin, M., Nordin, S., Adolfsson, R., Nilsson, L.G., 2016. Traffic-related air pollution and dementia incidence in Northern Sweden: a longitudinal study. Environ. Health Perspect. 124, 306–312. https://doi.org/10.1289/ehp.1408322.
Oudin, A., Segersson, D., Adolfsson, R., Forsberg, B., 2018. Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. PloS One 13, 1–15. https://doi.org/10.1371/journal.pone.0198283.
Perry, V.H., Cunningham, C., Holmes, C., 2007. Systemic infections and inflammation affect chronic neurodegeneration. Nat. Rev. Immunol. 7, 161–167.
Peters, R., Ee, N., Peters, J., Booth, A., Mudway, I., Anstey, K.J., 2019. Air pollution and dementia: a systematic review. J. Alzheim. Dis. 70, S145–S163. https://doi.org/10.3233/JAD-180631.
Prince, M., Wimo, A., Guerchet, M., Ali, G.-C., Wu, Y.-T., Prina, M., 2015. World Alzheimer Report 2015: the global impact of dementia. An analysis of prevalence, incidence, costs and trends. Alzheimer's Dis. Int.
Qiu, H., Sun, S., Tsang, H., Wong, C.-M., Lee, R.S., Schooling, C.M., Tian, L., 2017. Fine particulate matter exposure and incidence of stroke: a cohort study in Hong Kong. Neurology 88, 1709–1717. https://doi.org/10.1212/WNL.0000000000003903.
Ran, J., Sun, S., Han, L., Zhao, S., Chen, D., Guo, F., Li, J., Qiu, H., Lei, Y., Tian, L., 2020a. Fine particulate matter and cause-specific mortality in the Hong Kong elder patients with chronic kidney disease. Chemosphere 247, 125913. https://doi.org/10.1016/j.chemosphere.2020.125913.
Ran, J., Yang, A., Sun, S., Han, L., Li, J., Guo, F., Zhao, S., Yang, Y., Mason, T.G., Chan, K.-P., Lee, R.S.-Y., Qiu, H., Tian, L., 2020b. Long-term exposure to ambient fine particulate matter and mortality from renal failure: a retrospective cohort study in Hong Kong, China. Am. J. Epidemiol. 189, 602–612. https://doi.org/10.1093/aje/kwz282.
Reitz, C., Brayne, C., Mayeux, R., 2011. Epidemiology of alzheimer disease. Nat. Rev. Neurol. 7, 137–152. https://doi.org/10.1038/nrneurol.2011.2.
Schooling, C.M., Chan, W.M., Leung, S.L., Lam, T.H., Lee, S.Y., Shen, C., Leung, J.Y., Leung, G.M., 2016. Cohort profile: Hong Kong department of health elderly health service cohort. Int. J. Epidemiol. 45, 64–72. https://doi.org/10.1093/ije/dyu227.
Sun, S., Cao, W., Qiu, H., Ran, J., Lin, H., Shen, C., Siu-Yin Lee, R., Tian, L., 2019. Benefits of physical activity not affected by air pollution: a prospective cohort study. Int. J. Epidemiol. 1–11. https://doi.org/10.1093/ije/dyz184.
Tomata, Y., Li, X., Karlsson, I.K., Mosing, M.A., Pedersen, N.L., Hägg, S., 2020. Joint impact of common risk factors on incident dementia: a cohort study of the Swedish Twin Registry. J. Intern. Med. https://doi.org/10.1111/joim.13071.
Tonne, C., Elbaz, A., Beevers, S., Singh-Manoux, A., 2014. Traffic-related air pollution in relation to cognitive function in older adults. Epidemiology 25, 674–681. https://doi.org/10.1097/EDE.0000000000000144.
Tzivian, L., Dlugaj, M., Winkler, A., Hennig, F., Fuks, K., Sugiri, D., Schikowski, T., Jakobs, H., Erbel, R., Jöckel, K.H., Moebus, S., Hoffmann, B., Weimar, C., 2016. Long-term air pollution and traffic noise exposures and cognitive function: a cross-sectional analysis of the Heinz Nixdorf Recall study. Environ. Health Perspect. 124, 1361–1368. https://doi.org/10.1080/15287394.2016.1219570.
Weuve, J., Puett, R.C., Schwartz, J., Yanosky, J.D., Laden, F., Grodstein, F., 2012. Exposure to particulate air pollution and cognitive decline in older women. Arch. Intern. Med. 172, 219–227. https://doi.org/10.1001/archinternmed.2011.683.
Wong, C.M., Lai, H.K., Tsang, H., Thach, T.Q., Neil Thomas, G., Lam, K.B.H., Chan, K.P., Yang, L., Lau, A.K.H., Ayres, J.G., Lee, S.Y., Chan, W.M., Hedley, A.J., Lam, T.H., 2015. Satellite-based estimates of long-term exposure to fine particles and association with mortality in elderly Hong Kong residents. Environ. Health Perspect. 123, 1167–1172. https://doi.org/10.1289/ehp.1408264.
Wu, Y.T., Ali, G.C., Guerchet, M., Matthew Prina, A., Chan, K.Y., Prince, M., Brayne, C., 2018. Prevalence of dementia in mainland China, Hong Kong and Taiwan: an updated systematic review and meta-analysis. Int. J. Epidemiol. 47, 709–719. https://doi.org/10.1093/ije/dyy007.