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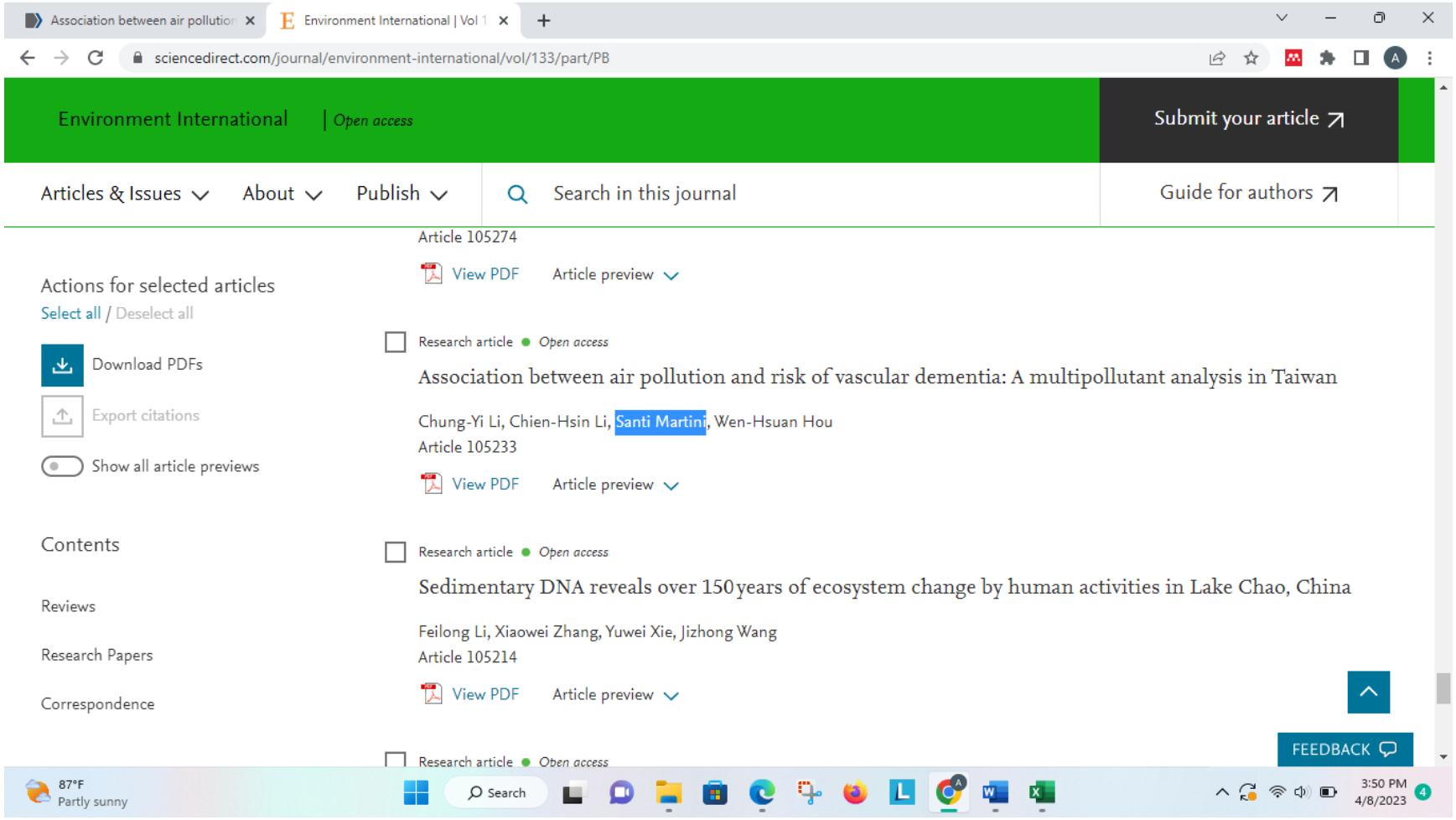
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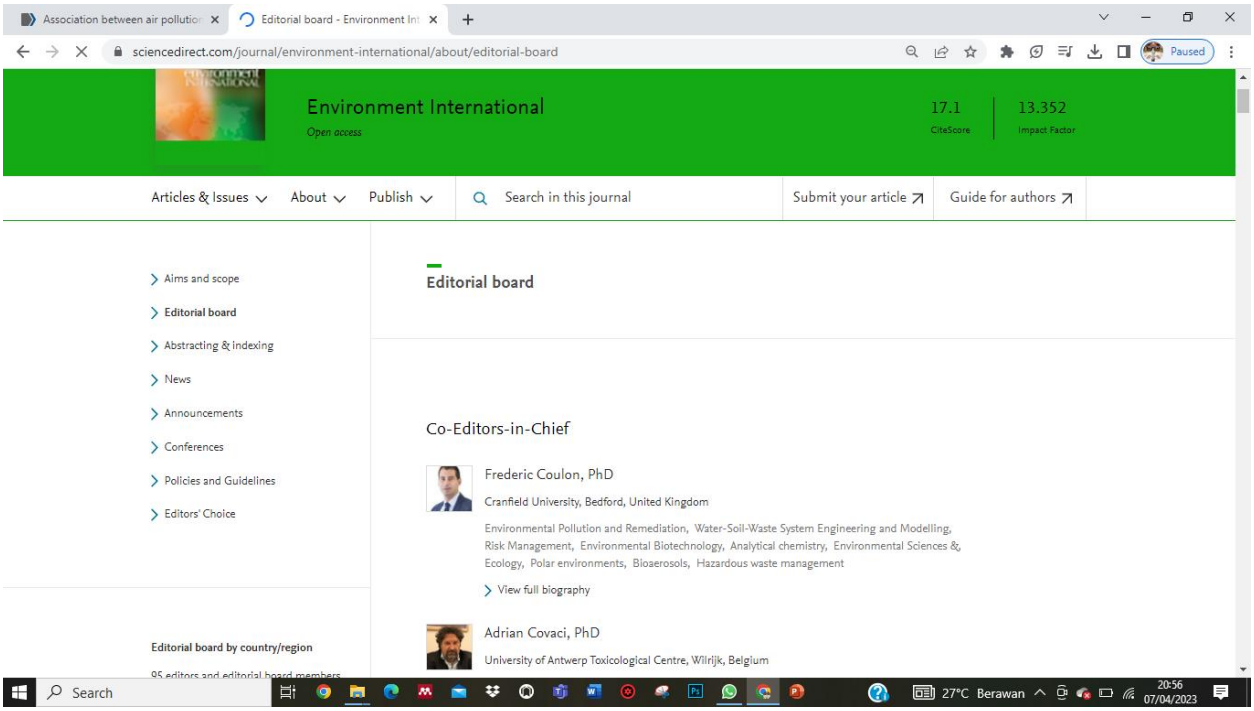
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Association between air pollution and risk of vascular dementia: A multipollutant analysis in Taiwan

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ABSTRACT

Evidence regarding the association of specific air pollutants with vascular dementia (VaD) risk is limited. In this nested case–control study, we enrolled 831 adults aged > 65 years with VaD (International Classification of Diseases, Ninth Revision, Clinical Modification code 290.4x) newly diagnosed during 2005–2013; 3324 controls were age-, sex-, and VaD diagnosis year–matched with the study patients. Both patients with VaD and controls were selected from among a cohort of one million beneficiaries of Taiwan's National Health Insurance program, all of whom were registered in 2005. Exposure to the mean daily air pollutant concentration, derived from 76 fixed air quality monitoring stations, in 3, 5, and 7 years before VaD diagnosis was assessed using the spatial analysis method (i.e., ordinary kriging) on ArcGIS. A logistic regression model was used to calculate covariate-adjusted odds ratios (ORs) of VaD in relation to specific air pollutants. After potential confounders and other air pollutants were controlled for, high concentrations of coarse particulate matter (10 μm or less in diameter) and carbon monoxide (CO) were sporadically associated with higher OR of VaD. The most prominent association was observed for nitrogen dioxide (NO_2) exposure within 5 and 7 years before diagnosis. Compared with the < 25th percentile of NO_2 exposure, the 25th–50th, 50th–75th, and > 75th percentiles of NO_2 exposure significantly increased ORs (95% confidence intervals): 1.62 (1.28–2.23), 1.61 (1.11–2.33), and 2.22 (1.35–3.65) within 5 years before diagnosis, respectively, and 1.59 (1.20–2.11), 1.65 (1.15–2.37), and 2.05 (1.28–3.28) within 7 years before diagnosis, respectively. We found that higher NO_2 exposure in the past was significantly associated with an elevated risk of VaD. Although less consistent, higher exposure to CO was also associated with a higher risk of VaD. Most NO_2 in cities originates from motor vehicle exhaust; other sources of NO_2 are petrol and metal refining, electricity generation from coal-fired power stations, other manufacturing industries, and food processing. Future studies should investigate associations of VaD with specific sources of NO_2.

1. Introduction

Dementia prevalence has demonstrated a near-exponential increase; it is predicted to increase to 115.4 million worldwide by 2050 according to a report of the World Health Organization Global Burden of Disease Project (Prince et al., 2013). Therefore, with the increasing longevity of the older population, primary prevention of dementia has become a critical public health issue (Norton et al., 2014). Among

Abbreviations: AQMS, air quality monitoring station; CCI, Charlson comorbidity index; CI, confidence interval; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IQR, interquartile range; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; NO_2, nitrogen dioxide; NOx, nitrogen oxide; O_3, ozone; OR, odds ratio; PM_{10}, coarse particulate matter (10 μm or less in diameter); SD, standard deviation; SO_2, sulfur dioxide; VaD, vascular dementia

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various modifiable risk factors, health behavior and comorbidities (e.g., hypertension and diabetes) can be improved through the implementation of personalized intervention strategies; however, from the population perspective, environment-related risk factors such as air pollution can be controlled for (Chen et al., 2009). Power et al. conducted a systematic review of 18 publications that investigated the association of air pollution with cognitive function, cognitive decline, brain imaging, and dementia (Power et al., 2016). Although they provided epidemiologic evidence, along with evidence from other lines of research, supporting a relationship of air pollution exposure with dementia, only one study specifically assessed the relationship between air pollution and vascular dementia (VaD) (Oudin et al., 2016). Killin et al. conducted another review of five studies and suggested a positive association between air pollution and dementia, but only one study included VaD as one of the endpoints (Killin et al., 2016).

In Taiwan, Wu et al. investigated the relationship between air pollution and VaD risk and reported that the highest tertiles of coarse particulate matter (10 μm or less in diameter [PM_{10}]) and ozone (O_3) exposure were significantly associated with increased VaD risk by 109% and 261%, respectively (Wu et al., 2015). In a Swedish study, participants residing in areas with the highest quartile of nitrogen oxide (NOx) exposure had a 47% increase in VaD risk compared with those living in areas with the lowest quartile of NOx exposure (Oudin et al., 2016). Carbon monoxide (CO) may contribute to a 1.60- and 1.75-fold higher incidence of all-cause dementia in patients diagnosed as having CO poisoning than in those without the diagnosis (Lai et al., 2016; Wong et al., 2016). However, some studies have reported no association between air pollution and dementia. Chen et al. (2017a) found no association between O_3 exposure and all-cause dementia incidence; however, they indicated that every 1 interquartile range (1 IQR) increase in NO_2 exposure could significantly result in a 10% increase in dementia risk. Regarding other air pollutants, sulfur dioxide (SO_2), which was investigated only in an in vivo and in vitro study, was observed to induce synaptic dysfunction, leading to a predisposition to cognitive impairment (Yun et al., 2013).

A recent systematic review summarized study findings from the United States, Canada, Taiwan, Sweden, and the United Kingdom and reported inconclusive associations between exposure to specific air pollutants (fine particulate matter of diameter of less than 2.5 μm, NOx, CO, and O_3) and various subtypes of dementia (Peters et al., 2019). In addition, the current epidemiological evidence regarding the association of air pollutants with VaD risk has been neither comprehensive nor consistent, probably due to certain methodological problems. Therefore, in this study, we investigated the associations of VaD risk with short-term (3 years) and long-term (5 or 7 years) exposure to various air pollutants, namely PM_{10}, SO_2, O_3, NO_2, and CO, and considered the related comorbidities.

2. Material and methods

2.1. Research data

We used patient data retrieved from certain data sets of Taiwan's National Health Insurance Research Database (NHIRD), and air pollutant exposure data were obtained from the monitoring data collected by the Taiwan Environmental Protection Administration. Access to the NHIRD was approved by the Review Committee of the National Health Research Institutes. Our study was also approved by the Research Ethics Committee of National Cheng Kung University (approval number 103-010).

The NHIRD contains the medical claims data of the beneficiaries of Taiwan's National Health Insurance (NHI) program, which enrolls > 99% of residents of Taiwan (Hsing and Ioannidis 2015). The NHIRD contains both inpatient and outpatient medical claims from nearly all hospitals and clinics in Taiwan. Each claim includes patients' sociodemographic characteristics, disease diagnosis codes (i.e., International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes), drug information, and treatment costs. In this study, we used the medical claims data of one million people randomly selected from all NHI beneficiaries in 2005.

2.2. Study design and participants

This case–control study was nested within the data of one million people in the NHI as mentioned above. Over 2005–2013, 14368 older adults (aged ≥ 65 years) were treated for all-cause dementia (ICD-9-CM codes 290.0–290.4, 290.8, 290.9, 294.1, and 331.0) (i.e., prevalent cases). These patients were required to have at least two outpatient visits (at least 90 days apart) or one admission for all-cause dementia in a 1-year period after the initial diagnosis. Patients (n = 7315) with a history of dementia, head injury (ICD-9-CM codes 800.804, 850.854.1, 310.2, and 959.01), or Parkinson disease (ICD-9-CM code 332.0) between January 1, 1997, and the date of the first diagnosis of all-cause dementia in 2005–2013 were excluded. Finally, 7053 incident cases of all-cause dementia were included, and among them, 831 were incident cases of VaD (ICD-9-CM code 290.4x). For each patient with VaD, four controls without all-cause dementia, head injury, or Parkinson disease in 1997–2013 were randomly selected and matched by sex, age, and year of diagnosis; finally, 3324 controls were included. The control selection method ensured that controls neither became cases at a late time point nor served as controls for multiple cases.

2.3. Assessment of exposure to air pollutants

Air pollution data for 1998–2013 were retrieved from all 76 fixed-site air quality monitoring stations (AQMSs) supervised by the Taiwan Air Quality Monitoring Network (http://taqm.epa.gov.tw/taqm/en/PsiMap.aspx). We first excluded 10 AQMSs located in industrial parks or remote areas where very few people lived, but we found no apparent differences in the estimated air pollutant concentrations. Therefore, we finally included data from all AQMSs in the analysis.

AQMSs record the hourly concentrations of the following air pollutants: PM_{10} (in $\mu g/m^3$), SO_2 (in parts per billion [ppb]), O_3 (in ppb), nitrogen dioxide (in ppb), and CO (in parts per million [ppm]) (Environmental Protection Administration Executive Yuan). The measurement of various air pollutants at the monitoring stations was performed as follows: PM_{10} through the beta-ray absorption method (F-701 Beta Gauge Particulate Monitor; Verewa/Durag, Hamburg, Germany), SO_2 through ultraviolet fluorescence (EC9850; Ecotech, Knoxfield, Australia), O_3 through a combination of microprocessor control with ultraviolet photometry (EC9810; Ecotech), CO through a non-dispersion cross-modulation infrared analysis method (APMA-360; Horiba Instruments, Pasadena, TX, USA), and NO_2 through chemiluminescence (EC9841; Ecotech).

These hourly data recorded at each AQMS were further averaged into daily mean concentrations in this study. We retrospectively assessed every individual's mean daily mean exposure to the aforementioned air pollutants during three periods: 3, 5, and 7 years before VaD diagnosis. Calculating the daily concentration of various air pollutants and averaging the daily concentrations across different lengths of exposure (i.e., 3, 5, and 7 years) were performed to be consistent with exposure guidelines set by the Taiwan Environmental Protection Agency or the World Health Organization, which utilize 24-h and 1-year exposure standards as guidelines for PM_{10}, NO_2, and SO_2 as well as 8-h exposure standards for SO_2 and CO.

The air pollutant concentration was estimated for the center point coordinator of each of the 316 city districts and townships all over Taiwan through spatial analysis (i.e., ordinary kriging) on ArcGIS Desktop (version 10 software; ESRI Inc., Redlands, CA, USA), a frequently used software program (Coogan et al., 2012; Huang et al., 2015; Wang et al., 2015). The spatial interpolation and cross-validation approach interpolated the exposure concentration to a regular grid

($250 \times 250\,m^2$) across Taiwan. Cross-validation was based on the pollutant data of the AQMSs within 3 km outside the city district and township boundaries. Because the NHIRD provides no information on moving of residence by patients, we used only the city district and township details on the date of VaD diagnosis as patients' residence for exposure assessment. Supplemental Fig. 1 is a map showing locations of 76 AQMSs and all patients and controls.

2.4. Potential confounders

In addition to matching variables (i.e., sex, age, and year of VaD diagnosis), some personal characteristics and comorbidities presumably associated with VaD risk were included in the analysis, including history of hypertension (ICD-9-CM codes 401–405) (Weuve et al., 2012), diabetes (ICD-9-CM code 250) (Biessels et al., 2006; Cheng et al., 2012; Gudala et al., 2013), hyperlipidemia (ICD-9-CM codes 272.0–272.4) (Anstey et al., 2008; Muangpaisan and Brayne, 2010), cerebrovascular disease (ICD-9-CM codes 430–438) (Bejot et al., 2018; Wellenius et al., 2012), chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 490–496) (Liao et al., 2015), and disease burden indicated by the Charlson comorbidity index (CCI) (Charlson et al., 1987). Information on comorbidities was retrieved from inpatient/outpatient claims between January 1, 1997 and the date of VaD diagnosis.

In addition, individuals' monthly income, urbanization level of the residential city district or township, and city district– or township–specific median family income were included in the analysis, because studies have reported that the lower the socioeconomic status, the higher the VaD risk (Beydoun et al., 2014; Russ et al., 2013). We also adjusted data for the urbanization level of the residential city district or township to minimize the potential confounding effects of differences in medical care accessibility and availability and to account for the possible urban–rural differences in the quality of diagnostic techniques (Tan et al., 2005).

2.5. Statistical analysis

We first compared the characteristics between the study patients and controls. The mean daily concentration of individuals' air pollutant exposure was calculated and compared between the study patients and controls. In addition, Pearson's correlation coefficients were calculated to indicate the strength of pairwise associations of concentrations among various air pollutants. Pearson's correlation coefficients for the association between NO_2 and CO ($r = 0.895–0.928$) indicated a strong correlation (Supplemental Table 1); thus, to prevent potential collinearity problems, we did not include NO_2 and CO simultaneously in the multipollutant models. By using conditional logistic regression model, we calculated crude and covariate-adjusted odds ratios (ORs) to estimate the relative VaD risk in relation to specific air pollutant exposures determined at various time points before VaD diagnosis. The potential confounders adjusted for in the multivariate regression model included all variables listed in Table 1 and various air pollutants.

Because air pollution has been found to be associated with increased risks of various diseases such as cerebrovascular disease and diabetes (which are also risk factors for dementia), we further conducted sensitivity analyses by excluding select comorbidities and the CCI score from adjustment in order to assess potential mediation by comorbidities in the temporal pathway between air pollution and VaD. All statistical analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA). A p value of < 0.05 was considered statistically significant.

3. Results

The mean ± standard deviation (SD) values of ages were similar for patients and controls at 79.08 ± 7.14 years and 79.08 ± 7.13 years, respectively. Male subjects accounted for 53.1% of both patients and controls. The monthly income, urbanization level, and city district– or township–specific median family annual income were similarly distributed between patients and controls. However, compared with controls, patients were more likely to have a history of comorbidities, including hypertension, diabetes, hyperlipidemia, stroke, and COPD (83.4% vs. 67.5%, 40.7% vs. 26.3%, 32.5% vs. 27.7%, 63.2% vs. 21.3%, and 33.3% vs. 31.1%, respectively). In addition, patients had a higher mean CCI than controls (3.43 ± 2.36 vs. 2.36 ± 2.26).

Table 2 presents the mean concentrations of various air pollutant exposures at different time points before VaD diagnosis in patients and controls. Compared with controls, patients demonstrated higher mean daily NO_2 exposure but slightly lower PM_{10}, SO_2, and O_3 exposure. By contrast, the mean CO concentration remained similar between patients and controls.

Table 3 shows crude and adjusted ORs of VaD in association with exposure to various air pollutants in 5 years before VaD diagnosis. After potential confounders and other air pollutants were controlled for, higher levels of NO_2 exposure were associated with significantly elevated OR (95% confidence interval [CI]) for VaD at the 25th–50th, 50th–75th, and > 75th percentiles compared with the < 25th percentile: 1.62 (1.28–2.23), 1.61 (1.11–2.33), and 2.22 (1.35–3.65), respectively. Moreover, every 1 IQR and 1-ppb increase in NO_2 exposure in 5 years before VaD diagnosis was significantly associated with increased VaD risk, with covariate-adjusted ORs (95% CIs) of 1.28 (0.98–1.66) and 1.05 (0.99–1.11), respectively.

For PM_{10}, we noted a significantly elevated adjusted OR (95% CI) of 1.27 (1.01–1.61) for the 25th–50th percentile of exposure compared with the < 25th percentile of exposure. In addition, the 50th–75th percentile of CO exposures was significantly associated with the increased adjusted OR (95% CI) of 1.55 (1.10–2.19). However, SO_2 or O_3 exposure had no significant association with VaD risk.

Supplemental Tables 2 and 3 present the association of air pollution exposure in 3 and 7 years before VaD diagnosis, respectively. Compared with the < 25th percentile, only the 25th–50th percentile of NO_2 exposure and the 50th–75th percentile of CO exposure were significantly associated with elevated ORs, with ORs (95% CI) of 1.29 (1.01–1.65) and 1.36 (1.01–1.85), respectively (Supplemental Table 2). The results for exposure in 7 years before VaD were very similar to those for exposure in 5 years before VaD. A dose gradient patterns were observed for NO_2 exposure in 7 years before VaD diagnosis: 1.59 (1.20–2.11), 1.65 (1.15–2.37), and 2.05 (1.28–3.28), respectively. Moreover, every 1 IQR and 1-ppb increase in NO_2 exposure in 7 years before VaD diagnosis was significantly associated with increased VaD risk, with covariate-adjusted ORs (95% CIs) of 1.30 (1.02–1.65) and 1.06 (1.01–1.11), respectively. In addition, the 25th–50th, 50th–75th, and > 75th percentiles of CO exposure in 7 years before VaD diagnosis were all significantly associated with increased adjusted ORs (95% CIs) of 1.46 (1.11–1.93), 1.53 (1.10, 2.13), and 1.53 (1.03, 2.27), respectively (Supplemental Table 3).

Sensitivity analyses showed slight increases in most of the ORs indicating the association between NO_2 exposure in the past 5 years and VaD diagnosis. An even more obvious increase in ORs for the relationship between CO and VaD was observed (Table 3). The results of sensitivity analyses suggested potential mediation by certain comorbidities, such as cerebrovascular disease and diabetes, in the temporal pathway between exposure to NO_2 or CO and VaD.

4. Discussion

This large-scale study included a representative sample of older adults in Taiwan. The results revealed that higher NO_2 exposure levels in 3, 5, and 7 years before VaD diagnosis were significantly and positively associated with an increased risk of VaD. Although less consistent, CO exposure also had a slightly but significantly negative influence on VaD risk. SO_2 and O_3 exposures were not associated with

Table 1
Characteristics of patients and controls.

	Patients		Controls		
	n	%	*n*	%	*p* value[a]
Age (years)					NA
65–69	91	10.9	364	10.9	
70–74	139	16.7	556	16.7	
75–79	185	22.3	740	22.3	
≥80	416	50.1	1664	50.1	
Mean ± SD	79.08 ± 7.14		79.08 ± 7.13		
Sex					NA
Female	390	46.9	1560	46.9	
Male	441	53.1	1764	53.1	
Monthly income, NTD					0.2440
Dependent	337	40.5	1233	37.1	
≤15,840	193	23.2	772	23.2	
15,841–22,800	283	34.1	1229	37.0	
22,801–28,800	4	0.5	39	1.2	
28,801–36,300	4	0.5	9	0.2	
36,301–45,800	7	0.8	26	0.8	
> 45,800	3	0.4	16	0.5	
Urbanization					0.3666
Urban	493	59.3	1982	59.6	
Satellite	276	33.2	1049	31.6	
Rural	62	7.5	293	8.8	
Township-specific median family annual income quartiles[a], NTD					0.2485
≤Q1	226	27.2	814	24.5	
> Q1–Q2	203	24.4	908	27.3	
> Q2–Q3	195	23.5	791	23.8	
> Q3	207	24.9	811	24.4	
Mean ± SD	438,100 ± 198,000		445,900 ± 192,700		0.2951
History of comorbidities					
Hypertension	693	83.4	2244	67.5	< 0.0001
Diabetes	338	40.7	873	26.3	< 0.0001
Hyperlipidemia	270	32.5	919	27.7	0.0057
Cerebrovascular disease	525	63.2	708	21.3	< 0.0001
COPD	277	33.3	1032	31.1	0.2044
Charlson comorbidity index					
0	59	7.1	754	22.7	< 0.0001
1	118	14.2	708	21.3	
2	154	18.5	563	16.9	
≥3	500	60.2	1299	39.1	
Mean ± SD	3.43 ± 2.36		2.36 ± 2.26		
Total	**831**		**3324**		

SD, standard deviation; COPD, chronic obstructive pulmonary disease; NTD, New Taiwan Dollars. US$1 ≅ NTD30.
International Classification of Diseases, Ninth Revision, Clinical Modification codes: hypertension (401–405), diabetes (250), hyperlipidemia (272.0–272.4), cerebrovascular disease (430–438), and chronic obstructive pulmonary disease (490–496).
[a] Q1 = 414,000, Q2 = 520,000, Q3 = 575,000.

VaD.

NO_2, one of the most frequently investigated air pollutants, has been frequently observed to increase the risk of dementia (Chang et al., 2014), probably by increasing the risks of neurodegenerative and cerebrovascular diseases (Andersen et al., 2012; Lisabeth et al., 2008; Migliore and Coppede, 2009; Turin et al., 2012), which are the principal contributors to dementia (Knopman, 2007; O'Brien, 2006). Our study results corroborate previous findings, suggesting that increased NO_2 exposure significantly increases VaD incidence, and the results of our sensitivity analyses suggested that the link between NO_2 and VaD might be partially mediated by certain comorbidities, such as stroke. NO_2 exposure has been found to be associated with cardiovascular admission (Ab Manan et al., 2018). In a UK study, people living in areas with the highest fifth of NO_2 concentration (> 41.5 μg/m^3) had a significantly higher risk of AD, but not of VaD, than did those living in areas with the lowest fifth of NO_2 concentration (< 31.9 μg/m^3) (Carey et al., 2018). Nonetheless, in contrast to our study, in which 51% of patients with VaD were aged > 80 years, the UK study included only younger patients (< 80 years). The positive relationship between NO_2 inhalation and VaD has also been implied using animal models, demonstrating that NO_2 may elicit pathological changes and molecular excitotoxicity of synaptic plasticity (Li and Xin 2013). Nevertheless, in a US study of middle-aged adults conducted in 2014, no significant correlation was noted between NO_2 exposure and global cognitive function (Gatto et al., 2014).

Although less consistent, our study also noted that higher exposure to CO, especially in 5 or 7 years before VaD diagnosis, significantly increased VaD risk. In addition to traffic sources, CO can be derived from fossil fuel combustion from stationary sources, such as power plants and heating appliances, or from natural gas. Studies have revealed similar results: VaD incidence was 1.37- to 1.61-fold higher in the higher quartiles of a CO-exposed cohort than in its counterpart (Chang et al., 2014; Chen et al., 2013). The mechanisms underlying the association between CO and VaD risk may be as follows: CO exposure reduces the oxygen-carrying capacity of blood and induces oxidative stress and inflammatory responses, which in turn cause end-organ brain damage (Parkinson et al., 2002).

PM_{10}, a particulate air pollutant, is derived primarily from fossil fuel

Table 2
Mean daily exposure of patients and controls to various air pollutants in 3, 5, and 7 years before vascular dementia diagnosis.

Air pollutants	Past 3 years		Past 5 years		Past 7 years	
	Mean ± SD	Min.–Max.	Mean ± SD	Min.–Max.	Mean ± SD	Min.–Max.
PM_{10} (μg/m^3)						
Patients	56.89 ± 11.08	33.23–81.22	57.10 ± 10.73	33.41–80.03	57.07 ± 10.56	31.98–79.17
Controls	58.06 ± 11.54	31.85–82.76	58.23 ± 11.20	31.28–80.37	58.21 ± 11.08	29.19–79.44
SO_2 (ppb)						
Patients	4.10 ± 1.00	1.82–7.64	4.09 ± 1.01	1.70–7.56	4.09 ± 1.05	1.68–8.08
Controls	4.15 ± 1.08	1.49–7.66	4.14 ± 1.09	1.38–7.62	4.14 ± 1.13	1.39–8.25
O_3 (ppb)						
Patients	26.97 ± 1.84	22.43–32.09	26.65 ± 1.92	21.38–31.07	25.99 ± 2.08	20.01–30.94
Controls	27.14 ± 1.87	20.34–31.84	26.83 ± 1.96	20.37–31.04	26.16 ± 2.11	19.03–30.90
NO_2 (ppb)						
Patients	18.40 ± 3.07	9.60–24.52	18.79 ± 3.08	9.54–24.86	19.23 ± 3.09	9.52–25.70
Controls	18.17 ± 3.06	9.45–24.64	18.55 ± 3.07	9.17–24.91	18.99 ± 3.09	9.52–25.66
CO (ppm)						
Patients	0.54 ± 0.11	0.31–0.80	0.56 ± 0.11	0.33–0.84	0.58 ± 0.12	0.35–0.88
Controls	0.54 ± 0.11	0.33–0.80	0.55 ± 0.11	0.34–0.84	0.57 ± 0.12	0.35–0.88

SD, standard deviation; CO, carbon monoxide; PM_{10}, coarse particulate matter (10 μm or less in diameter); SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone.

Table 3
Crude and adjusted odds ratios of vascular dementia in association with various air pollutant exposures in 5 years before vascular dementia diagnosis.

Period and level of exposure[a]	Odds ratio (95% CI)		
	Crude models	Adjusted models[b]	Sensitivity analysis[c]
PM_{10} (μg/m^3)			
< 25th percentile	1.00	1.00	1.00
25th–50th percentile	**1.27 (1.01, 1.60)**	**1.27 (1.01, 1.61)**	1.28 (1.00, 1.65)
50th–75th percentile	0.93 (0.73, 1.18)	0.89 (0.69, 1.13)	0.82 (0.63, 1.07)
> 75th percentile	0.91 (0.65, 1.28)	0.86 (0.61, 1.22)	0.77 (0.53, 1.11)
Per 1-IQR increase	0.92 (0.75, 1.14)	0.89 (0.72, 1.10)	0.81 (0.65, 1.02)
Per 10-μg/m^3 increase	1.00 (0.99, 1.01)	0.99 (0.98, 1.01)	0.99 (0.98, 1.00)
SO_2 (ppb)			
< 25th percentile	1.00	1.00	1.00
25th–50th percentile	1.10 (0.86, 1.41)	1.11 (0.87, 1.43)	1.15 (0.88, 1.50)
50th–75th percentile	1.11 (0.81, 1.51)	1.16 (0.84, 1.59)	1.24 (0.88, 1.74)
> 75th percentile	0.96 (0.66, 1.40)	0.98 (0.67, 1.44)	1.07 (0.71, 1.62)
Per 1-IQR increase	0.95 (0.80, 1.12)	0.93 (0.79, 1.11)	1.00 (0.84, 1.20)
Per 1-ppb increase	0.96 (0.84, 1.09)	0.95 (0.83, 1.08)	1.00 (0.87, 1.16)
O_3 (ppb)			
< 25th percentile	1.00	1.00	1.00
25th–50th percentile	0.91 (0.72, 1.14)	0.90 (0.71, 1.14)	0.91 (0.71, 1.16)
50th–75th percentile	0.76 (0.57, 1.00)	0.80 (0.60, 1.06)	0.79 (0.59, 1.08)
> 75th percentile	0.77 (0.55, 1.06)	0.83 (0.60, 1.16)	0.77 (0.54, 1.09)
Per 1-IQR increase	0.95 (0.78, 1.14)	1.02 (0.84, 1.24)	0.97 (0.79, 1.20)
Per 1-ppb increase	0.98 (0.92, 1.05)	1.01 (0.94, 1.08)	0.99 (0.92, 1.06)
NO_2 (ppb)			
< 25th percentile	1.00	1.00	1.00
25th–50th percentile	**1.30(1.01, 1.66)**	**1.62 (1.28, 2.23)**	**1.71 (1.29, 2.27)**
50th–75th percentile	1.04(0.74, 1.46)	**1.61 (1.11, 2.33)**	**1.64 (1.13, 2.38)**
> 75th percentile	1.16(0.78, 1.74)	**2.22 (1.35, 3.65)**	**2.30 (1.39, 3.80)**
Per 1-IQR increase	1.09(0.87, 1.36)	1.28 (0.98, 1.66)	1.28 (0.98, 1.66)
Per 1-ppb increase	1.02(0.97, 1.07)	1.05 (0.99, 1.11)	1.04 (0.99, 1.12)
CO (ppm)			
< 25th percentile	1.00	1.00	1
25th–50th percentile	1.15 (0.86, 1.53)	1.17 (0.88, 1.56)	**1.40 (1.06, 1.62)**
50th–75th percentile	**1.50 (1.07, 2.12)**	**1.55 (1.10, 2.19)**	**1.61 (1.14, 2.27)**
> 75th percentile	1.27 (0.82, 1.95)	1.17 (0.76, 1.79)	**1.55 (1.01, 2.37)**
Per 1-IQR increase	1.05 (0.88, 1.26)	1.12 (0.99, 1.28)	1.13 (0.90, 1.41)
Per 1-ppm increase	1.50 (0.48, 4.71)	1.78 (0.56, 5.61)	1.95 (0.56, 6.83)

IQR, Interquartile range; SD, Standard deviation; CI, Confidence interval.
$p < .05$ is indicated by bold type.
[a] IQRs for PM_{10}, SO_2, O_3, NO_2, and CO were 19.88 μg/m^3, 1.23 ppb, 3.01 ppb, 4.69 ppb, and 0.18 ppm, respectively.
[b] In addition to the adjustment for the covariates listed in Table 1, the models were adjusted for the following air pollutants: SO_2, O_3, and NO_2 for PM_{10}; PM_{10}, O_3, and NO_2 for SO_2; PM_{10}, SO_2, and NO_2 for O_3; PM_{10}, SO_2, and O_3 for NO_2; and PM_{10}, SO_2, and O_3 for CO.
[c] The analysis was conducted by repeating adjusted models but excluding select comorbidities and the Charlson comorbidity index score from the models.

combustion from both motor vehicles and stationary sources such as power plants. This PM type can enter the airways (Deng et al., 2019), can be transmitted through the blood–brain barrier, can be deposited in the brain, and can cause neuroinflammation and central nervous system disease (Block and Calderon-Garciduenas, 2009). In the present study, we noted that PM_{10} exposure significantly increased VaD risk, consistent with the results of Canadian (Chen et al., 2017b) and German (Ranft et al., 2009) studies reporting that chronic traffic-related PM exposure may be involved in the pathogenesis of neurodegenerative diseases. In addition, the association between chronic PM exposure and cardiovascular morbidity and mortality has been well established (Franchini and Mannucci, 2009). Thus, chronic PM exposure–related cardiovascular disease (CVD), which potentially affects cognition and thus links PM to adverse cognitive outcomes, leading to cerebrovascular dysregulation through vasoconstriction caused by free radical reactions at the arterial wall (Barregard et al., 2006; Schulz et al., 2011).

The present study revealed that SO_2 and O_3 did not have significant effects on VaD risk. A recent systematic review reported the association of increased SO_2 exposure with a slightly increased cardiovascular admission risk (Ab Manan et al., 2018). A previous study also documented the biological effects of SO_2 on ion channels, which led to the development of CVD (Yu et al., 2018). However, our study revealed no significant association of SO_2 with VaD risk. Because most petrochemical industries in Taiwan are located in the metropolitan area of Kaohsiung, the second largest city of Taiwan, we speculated that many patients and controls with higher SO_2 exposure were from the Kaohsiung metropolitan area, where people generally have a higher education level, which is a protective factor of dementia. Although we considered personal and neighborhood socioeconomic indicators in our analysis, we could not directly adjust for education level, which may have attenuated the association between SO_2 and VaD risk.

Wu et al. reported that long-term exposure to the highest tertile of O_3 ($\geq$21.56 ppb) significantly increased VaD risk by approximately twofold (Wu et al., 2015). Moreover, Chen and Schwartz reported that each 10-ppb increase in annual O_3 concentration was associated with a 3.5–5.3-year-equivalent aging-related decline in cognitive performance (Chen and Schwartz, 2009). However, in this study, we did not note a significant association between ambient O_3 exposure and VaD risk. Future relevant studies are thus warranted.

This study has some limitations. First, the air pollution data from AQMSs may not necessarily reflect the air pollution level in the inhabited areas, even though we used modeling techniques; this may have biased our results and attenuated the true relationship between air pollutants and VaD risk. Exposure information bias may also have been introduced because we could not obtain detailed information on our patients' and controls' mobility at the selected exposure time points before VaD diagnosis. Second, information on VaD diagnosis completely relied on the claims data from the NHIRD; this may have resulted in a potential disease misclassification bias despite the requirement that one must have two or more VaD diagnoses in an outpatient setting or one or more admissions in 1 year in order to be considered as a patient with VaD. Because such disease misclassification was unlikely to be related to the air pollution exposure level, it tends to be non-differential misclassification bias, which would lead to underestimation rather than overestimation of the association between air pollution and VaD. Thus, our study tended to provide conservative results for the association between air pollutants and VaD risk. We further determined the specialty of physicians who provided VaD diagnosis for the 831 patients in our study and noted that 67.4% (560 of 831) of patients were diagnosed by neurologists, and 20.3% (169 of 831) were diagnosed by psychiatrists. In Taiwan, neurologists and psychiatrists usually perform serum evaluation (including a complete blood count and biochemistries, iron, thyroid hormone, vitamin B_{12}, folate, and syphilis), psychological examination, and brain imaging (computed tomography or magnetic resonance imaging) to confirm the diagnosis of dementia (Cheng et al., 2019). A high percentage of VaD cases were diagnosed by either neurologists or psychiatrists, which provides reassurance that the case definition adopted in our study can be considered to be valid.

Third, although we excluded the influence of certain known risk factors for dementia, the residual influence of some other risk factors for VaD might have existed because the claims data from Taiwan's NHIRD do not include information on the education level, blood work (e.g., *APOE* ε4 allele), anthropometric parameters (e.g., body mass index), and lifestyle factors (e.g., exercise, diet, and smoking). A lower education level (Caamano-Isorna et al., 2006), presence of the *APOE* ε4 allele (Gachupin et al., 2016), being underweight (Park et al., 2019), no exercise (Park et al., 2019; Toots et al., 2017), a non-Mediterranean diet (Aridi et al., 2017), and the lack of certain micronutrients and macronutrients (Solfrizzi et al., 2017) may increase cognitive dysfunction risk. Moreover, no information is available on the family history of CVD. Hereditary arteriopathy (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is related to VaD and vascular cognitive impairment risks (Kalaria, 2016). Owing to incomplete adjustment for the aforementioned known risk factors for dementia, a potential for residual confounding cannot be entirely excluded. We included personal monthly income and residential city district– or township-specific family annual income in the analyses; this could minimize the potential confounding effects of socioeconomic status.

Certain statistical problems were encountered in this study. Because the air pollution level shows a strong temporal trend, the inter-correlations of air pollutant exposure levels in the three periods studied would be high. Such a strong temporal trend in air pollution exposure makes it difficult to separate the short-term effect (e.g., 3 years) from the long-term effect (e.g., 7 years) of air pollution. We tried but failed to control for air pollutant levels in the other two periods when analyzing VaD risk in relation to exposure in a specific period, mainly because of the problem of collinearity among air pollutant exposure levels across the three time points. This statistical problem may have limited specific interpretations of our findings regarding the exposure time points within which the air pollutant exposure was the most relevant to VaD risk. Moreover, owing to a high correlation between NO_2 and CO that could cause the problem of collinearity, we were unable to include both pollutants simultaneously in the model. Thus, it was not possible in our study to separately assess the effects of NO_2 and CO on VaD.

5. Conclusions

VaD risk was significantly associated with higher exposure to NO_2. The relationship between air pollutants and increased VaD risk might be potentially mediated by certain comorbidities, such as cerebrovascular disease. Additional experimental studies exploring the potential mechanisms and pathogenesis underlying the association between NO_2 and VaD risk are warranted.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105233.

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