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# Ozone, Particulate Matter, and Newly Diagnosed Alzheimer's Disease: A Population-Based Cohort Study in Taiwan

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**Abstract**. Several studies with animal research associate air pollution in Alzheimer's disease (AD) neuropathology, but the actual impact of air pollution on the risk of AD is unknown. Here, this study investigates the association between long-term exposure to ozone ($O_3$) and particulate matter (PM) with an aerodynamic diameter equal to or less than 2.5 μm ($PM_{2.5}$), and newly diagnosed AD in Taiwan. We conducted a cohort study of 95,690 individuals' age ≥ 65 during 2001–2010. We obtained $PM_{10}$ and $O_3$ data from Taiwan Environmental Protection Agency during 2000–2010. Since $PM_{2.5}$ data is only accessible entirely after 2006, we used the mean ratio between $PM_{2.5}$ and $PM_{10}$ during 2006–2010 (0.57) to estimate the $PM_{2.5}$ concentrations from 2000 to 2005. A Cox proportional hazards model was used to evaluate the associations between $O_3$ and $PM_{2.5}$ at baseline and changes of $O_3$ and $PM_{2.5}$ during the follow-up period and AD. The adjusted HR for AD was weakly associated with a raised concentration in $O_3$ at baseline per increase of 9.63 ppb (adjusted HR 1.06, 95% confidence interval (CI) 1.00–1.12). Further, we estimated a 211% risk of increase of AD per increase of 10.91 ppb in $O_3$ over the follow-up period (95% CI 2.92–3.33). We found a 138% risk of increase of AD per increase of 4.34 $\mu g/m^3$ in $PM_{2.5}$ over the follow-up period (95% CI 2.21–2.56). These findings suggest long-term exposure to $O_3$ and $PM_{2.5}$ above the current US EPA standards are associated with increased the risk of AD.

Keywords: Air pollution, Alzheimer's disease, neurodevelopment, ozone, particulate matter

## INTRODUCTION

High levels of air pollution, especially ozone ($O_3$) and particulate matter (PM), may be associated with central nervous system diseases including Alzheimer's disease (AD), Parkinson's disease, and stroke [1]. There is currently an increasing interest in the association between air pollution and AD. AD is a predominant age-related neurodegenerative disease that accounts for the major cause of dementia in people older than age 60 years [2]. This disease has afflicted 27.7 million people worldwide and has produced an enormous economic burden (129–159 billion USD) [3]. The major symptom of AD is gradual deterioration in behavior or cognition with impairment of language, praxis, and visuospatial abilities [4, 5]. In Taiwan, AD accounts for two-thirds of dementia and the prevalence rate of AD is 2% among the population aged 65 or older [6]. The incidence rates of AD double every 4.9-year after people reach the age 60 years old grow from 0.17% per year for individual aged 65 to 0.71%, 1.0%, and 2.92% per year, respectively, at 75, 77, and 85 [7]. Both genetic and environmental factors play important roles in the etiology of AD [8]. Short-term changes in the incidence of AD are more likely influenced by

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changes in the environment than by changes in the genetic pool. From the point of view of prevention, there is a growing need to understand the relationship between AD and modifiable environmental exposure, such as exposure to air pollution.

Several toxicological studies of dogs and human autopsies over the past decade have demonstrated that air pollution, mainly $O_3$ and PM, may have adverse impact on the brain and induce AD-like pathology [9–11]. In an animal model, mongrel dogs chronically exposed to high concentrations of $O_3$ and PM would exhibited early and persistent activation of nuclear factor-kappa beta, inducible nitric oxide synthase, alterations in the blood-brain barrier in cortical capillaries, degenerating cortical neurons, apoptotic glial white matter cells, and deposition of apolipoprotein E-positive lipid droplets in smooth muscle cells and pericytes, non-neuritic plaques, and neurofibrillary tangles [9]. In autopsy studies, Calderón-Garcidueñas and colleagues indicated that exposure to severe air pollution is associated with brain inflammation and depositions of amyloid-β 42 ($A\beta_{42}$) peptides—the key characteristic of AD in the frontal cortex and hippocampus [10, 12]. However, the epidemiological evidence characterizing the potential effect of air pollution on AD is still limited [13].

We conducted a prospective 10-year population-based cohort study to assess the associations between exposure to $O_3$ and PM with aerodynamic diameter equal to or less than 2.5 μm ($PM_{2.5}$) and newly diagnosed AD in Taiwan. The design of this study enabled us to verify an appropriate temporality between the hypothesized exposure and outcome and to eliminate the possibility that the presence of the outcome would influence the assessment of exposure.

## MATERIALS AND METHODS

### *Study design*

We conducted a population-based cohort study by retrieving all individuals from the longitudinal health insurance database 2000 (LHID2000). The LHID2000 includes registration files and claim data of ambulatory care expenditures or inpatient expenditures for 1,000,000 individuals systematically and randomly selected from the year 2000 registry of beneficiaries of the National Insurance Research Database (NHIRD). NHIRD is comprised of detailed health care information from more than twenty three million enrollees, representing more than 99% of the entire population in Taiwan. National Health Research Institutes (NHRI) confirmed that there are no significant difference in the gender distribution, age distribution, number of newborns every year, and average insurance payroll amount between LHID2000 and the NHIRD [14]. Because the data were analyzed anonymously, the institute review board specifically waived the need for consent from each subject. This study has been approved by the Institute Review Board of China Medical University Hospital, and it complies with the principles outlined in the Helsinki Declaration.

### *Study population*

A representative group comprised 1 million individuals was included at the baseline in 2001. We excluded individuals who had experienced AD prior to the baseline ($n = 182$), and focused on individuals aged 65 years and older at the baseline ($n = 97{,}627$) [15, 16]. The cohort entry constituted a total of 97,627 individuals. A prospective cohort study directed at all the individuals of the cohort was conducted from January 1, 2001 through December 31, 2010. The follow-up time began from the baseline until the diagnosis of AD, termination of insurance, or at the end of the follow-up. A total of 773 individuals (0.79%) were not found upon follow-up during the study period, and the response rate was 99.21%. In the subsequent analyses, we also excluded individuals for whom air pollution information was missing ($n = 1{,}937$). The final study population comprises 95,690 individuals. The flow of data processing is presented in Fig. 1.

### *Outcome of interest*

The database provides personal diagnosis codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We identified individuals who received at least two consensus diagnoses of AD (code 331.0) between January 1, 2001 and December 31, 2010.These individuals were selected as our outcome of interest [17]. Newly diagnosed AD was defined as the first diagnosis of AD. In Taiwan, the coding of AD was assigned by physician based on history, physical examination, laboratory and imaging studies including evidence of progressive medial temporal lobe atrophy on computed tomography (CT) and magnetic resonance image (MRI), the Mini-Mental State Examination [18], National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [19], the Diagnostic and Statistical Manual of Mental Disorders

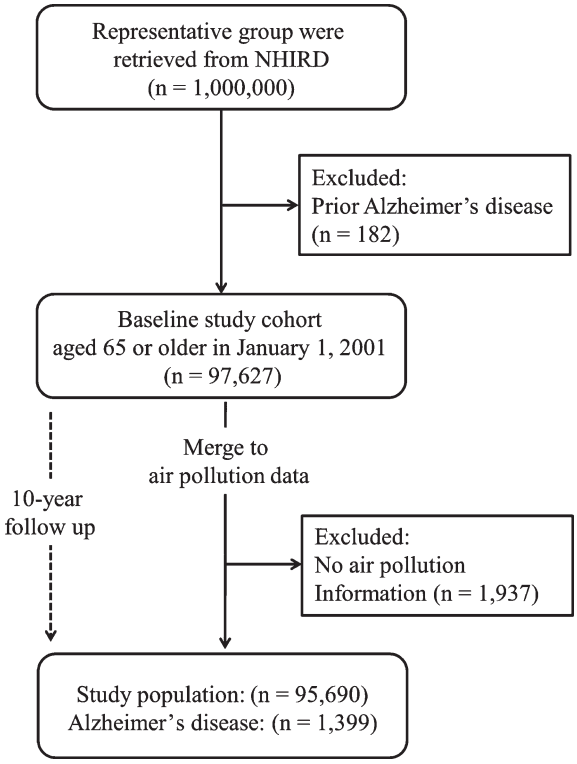


Fig. 1. Flow of data processing of the prospective cohort study.

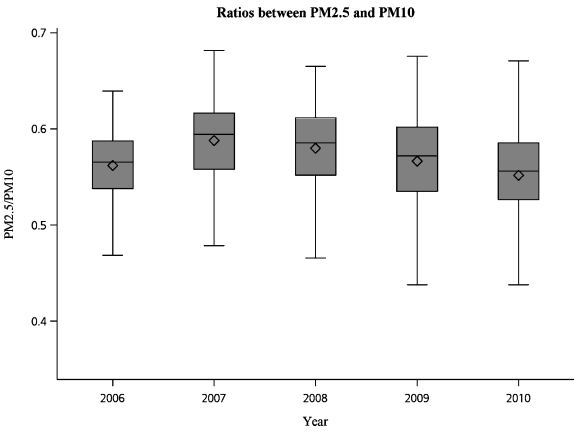


Fig. 2. The ratios between $PM_{2.5}$ and $PM_{10}$ from 2006 to 2010.

(DSM-IV) [20], and Hachinski ischemic score [21]. The National Health Insurance Administration, Ministry of Health and Welfare (NHI) verifies the validity and quality of diagnosis by randomly sampling a constant ratio of claims from every hospital each year and through strict review by an independent group of doctors [22]. In addition, the accuracy of diagnosis of major diseases, such as acute coronary syndrome and ischemic stroke, has been validated [23, 24].

*Exposure assessment*

Hourly $PM_{10}$ and $O_3$ data were available from 70 Taiwan Environmental Protection Agency (EPA) monitoring station on Taiwan's main island from 2000 through 2010. We computed the annual fourth-highest daily maximum 8-hour average ozone concentration based on the 8-hour standard [25] and the annual average of $PM_{10}$ was according to the guidance from US EPA [26]. In addition, we also used hourly data on carbon monoxide (CO), nitrogen dioxide ($NO_2$), and sulfur dioxide ($SO_2$) data from the Taiwan EPA to evaluate the effects of multiple air pollutants. $O_3$, $PM_{10}$, CO, $NO_2$, and $SO_2$ were continuously measured by ultraviolet absorption, beta-gauge, nondispersive infrared absorption, chemiluminescence, and ultraviolet fluorescence, respectively.

The $PM_{2.5}$ data is only accessible entirely after year 2006 in Taiwan. The ratios between $PM_{2.5}$ and $PM_{10}$ were not significantly change from year to year and have a mean value about 0.57 (Fig. 2). We used the mean ratio between $PM_{2.5}$ and $PM_{10}$ during 2006-2010 to estimate the concentrations of $PM_{2.5}$ from 2000 to 2006.

The locations of the monitoring stations and air pollution sources were identified and managed by a geographic information system (ArcGIS version 10; ESRI, Redlands, CA, USA). The monitoring data were integrated into yearly point data and interpolated to pollutant surfaces using the inverse distance weighting method (IDW). For the IDW approach, we used the suitable spatial resolution (100.00 m) [27] and 1/square distance methods by using the three closest monitoring stations within 25 kilometer of each grid cell to calculate yearly mean concentration for each air pollutants. To obtain post-code level pollutant concentrations, we were integrated the yearly air pollution data into each post-code area from grid cell and then assigned it to individual by their own post-code number.. Postal codes typically corresponded to one block in urban areas (17.00 square kilometer, SD: 8.56) but were larger in rural areas (154.00 square kilometer, SD: 104.39) with lower population density.

*Covariates*

The characteristics at baseline are listed in the Table 1: age in 2001, gender, income, and other comorbidities. Age is the primary risk factor for AD [28]. To allow non-linear adjustment, age was fitted

Table 1
Demographic data of the study cohort from January 1, 2001 to December 31, 2010

| Characteristic | | AD (%) ($n$ = 1,399) | no AD (%) ($n$ = 94,291) | Person-years | IR[a] | $p$-value[b] |
|---|---|---|---|---|---|---|
| Age | 65–69 | 229 (16.37) | 23,188 (24.59) | 231,555.24 | 9.89 | <0.0001 |
| | 70–73 | 330 (23.59) | 22,808 (24.19) | 228,211.3 | 14.46 | |
| | 74–79 | 461 (32.95) | 25,638 (27.19) | 256,745.88 | 17.96 | |
| | ≥80 | 379 (27.09) | 22,657 (24.03) | 226,216.24 | 16.75 | |
| Gender | Male | 634 (45.32) | 50,937 (54.02) | 508,265.94 | 12.47 | <0.0001 |
| | Female | 765 (54.68) | 43,354 (45.98) | 434,462.72 | 17.61 | |
| Income | Employee | 834 (59.61) | 60,999 (64.69) | 610,206.99 | 13.67 | <0.0001 |
| | Retired | 565 (40.39) | 33,292 (35.31) | 332,521.67 | 16.99 | |
| Diabetes mellitus | No | 714 (51.04) | 63,078 (66.90) | 628,482.19 | 11.36 | <0.0001 |
| | Yes | 685 (48.96) | 31,213 (33.10) | 314,246.47 | 21.80 | |
| Hypertension | No | 223 (15.94) | 34,552 (36.64) | 341,591.01 | 6.53 | <0.0001 |
| | Yes | 1,176 (84.06) | 59,739 (63.36) | 601,137.65 | 19.56 | |
| Myocardial infarction | No | 1,336 (95.50) | 90,228 (95.69) | 902,024.32 | 14.81 | 0.7226 |
| | Yes | 63 (4.50) | 4,063 (4.31) | 40,704.34 | 15.48 | |
| Angina pectoris | No | 1,131 (80.84) | 80,758 (85.65) | 806,444.17 | 14.02 | <0.0001 |
| | Yes | 268 (19.16) | 13,533 (14.35) | 136,284.49 | 19.66 | |
| Stroke | No | 456 (32.59) | 62,323 (66.10) | 619,937.38 | 7.36 | <0.0001 |
| | Yes | 943 (67.41) | 31,968 (33.90) | 322,791.28 | 29.21 | |
| PAD | No | 1,282 (91.64) | 88,733 (94.11) | 886,744.73 | 14.46 | 0.0001 |
| | Yes | 117 (8.36) | 5,558 (5.89) | 55,983.93 | 20.90 | |
| Asthma | No | 1,019 (72.84) | 74,073 (78.56) | 739,414.37 | 17.37 | <0.0001 |
| | Yes | 380 (27.16) | 20,218 (21.44) | 203,314.29 | 24.15 | |
| COPD | No | 441 (31.52) | 48,929 (51.89) | 486,137.52 | 9.07 | <0.0001 |
| | Yes | 958 (68.48) | 45,362 (48.11) | 456,591.14 | 20.98 | |

AD, Alzheimer's disease; COPD, chronic obstructive pulmonary disease; IR, incidence rate; PAD, peripheral arterial disease.[a] Incidence rate per 10,000 person-years.[b] $\chi^2$ tests for categorical variables.

in four indicator variables (70–73, 74–79, and≥80 years with 65–69 years as the reference category). The income levels were classified as retired and non-retired (monthly insurance payment large than zero).

Several comorbidities may be associated with AD including cardiovascular disease [16], cerebrovascular disease [29], diabetes mellitus [30], and hypertension [31]. Asthma and chronic obstructive pulmonary disease (COPD) are also suspected to enhance the pathology of AD [32]. We included diabetes mellitus (ICD-9-CM 250), hypertensive disease (ICD-9-CM 401 to 405), myocardial infarction (ICD-9-CM 410.0 to 410.9), angina pectoris (ICD-9-CM 413), stroke (ICD-9-CM 430 to 434 and 436 to 438), peripheral arterial disease (ICD-9-CM 443.8 to 443.9), asthma (ICD-9-CM 493), and COPD (ICD-9-CM 490 to 496) in the subsequent analyses.

### *Statistical methods*

The difference in the proportion of categorical variables among AD group and the group without AD was presented by chi-square statistics. The incidences of newly diagnosed AD were calculated per 10,000 person-years. A Cox proportional hazard model which takes into account confounding factors was used to investigate the association between air pollutants and newly diagnosed AD [33]. For the analyses of the time to diagnosis of AD, each individual's observation time was censored at the year when the insurance was terminated, the patient died due to another cause, or at the end of the follow-up. In order to examine the associations between newly diagnosed AD with the baseline and changes of air pollution concentration over the follow-up period, we considered two exposure indicators. First, concentration of each air pollutant at baseline was denoted by the concentration of each air pollutant in the year prior to the baseline (year 2000). Second, change in each air pollutant between the follow-up period and baseline, was defined as the concentrations at the end of follow-up period minus the baseline concentration of each air pollutant in the analyses. A positive value of change was indicated when the concentration at baseline increases over time while a negative value of change was observed when the concentration at baseline decreased over time. The correlation between baseline and change of each air pollutant were highly correlated (i.e., the correlation between baseline and change of $PM_{10}$ was $-0.63$). To avoid potential collinearity problems, we did not include these two exposure indicators in the same model. The effect of each pollutant on the risk of newly diagnosed AD was estimated as the hazard ratio (HR) per interquartile range of 9.63 and 10.91 ppb for the

baseline of $O_3$ and the change in $O_3$ over the follow-up period, the interquartile range of 13.21 and 4.34 $\mu g/m^3$ for the baseline of $PM_{2.5}$ and the change in $PM_{2.5}$ over the follow-up period, along with 95% confidence intervals (CIs). We treated age, gender, income, and other comorbidities as covariates in the Cox proportional hazards model. A stepwise selection procedure was used to select potential confounders in the relation to air pollutants and the risk of newly diagnosed AD. Finally, we adjusted for age, gender, income, diabetes mellitus, hypertensive disease, myocardial infarction, stroke, asthma, and COPD ($p < 0.05$) in the final model. Further, we also fitted the two-pollutant models of $O_3$ and $PM_{10}$ with CO, $NO_2$, and $SO_2$ separately. The two pollutant models provide estimates of the independent effects of $O_3$ and $PM_{10}$ controlling for the second pollutant in the models; correlation coefficients among air pollutants equal or larger than 0.4 were excluded in the models. All analyses were conducted using SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC).

## RESULTS

### *Baseline characteristics*

A total of 1,399 individuals were diagnosed with AD within the cohort of 95,690 individuals from January 1, 2001 to December 31, 2010. The incidence rate was 14.83 per 10,000 person-years. These newly diagnosed AD individuals included 765 females (54.68%) and 834 non-retired individuals (59.61%). In our study, most newly diagnosed AD individuals were older, from ages 74 to 79 (incidence rate (IR) = 17.96 per 10,000 person-years), female (IR = 17.61 per 10,000 person-years), and retired individuals (IR = 16.99 per 10,000 person-years). The common comorbidities were hypertensive disease (84.06% of AD individuals), COPD (68.48% of AD individuals), stroke (67.41% of AD individuals), and diabetes mellitus (48.96% of AD individuals) (Table 1).

### *Air pollution*

The mean of annual 4th maximum of daily max 8-hour average $O_3$ concentration was 92.64 ppb (standard deviation (SD), 13.47) with a range from 34.75 to 137.65 ppb; the mean of annual average of $PM_{10}$ was 59.25 $\mu g/m^3$ (SD, 15.76) with a range of 18.18 to 108.35 $\mu g/m^3$; the mean of annual average of $PM_{2.5}$ was 33.56 $\mu g/m^3$ (SD, 9.20) with a range of 10.36 to 61.76 $\mu g/m^3$ during 2000–2010. The trends of $O_3$, $PM_{10}$, and $PM_{2.5}$ based on 70 sites during study period are shown in Figs. 3–5, respectively. As shown in Table 2, the mean of $O_3$ at baseline was 88.97 ppb (SD, 7.80) with a range of 52.79 to 106.74 ppb in the AD

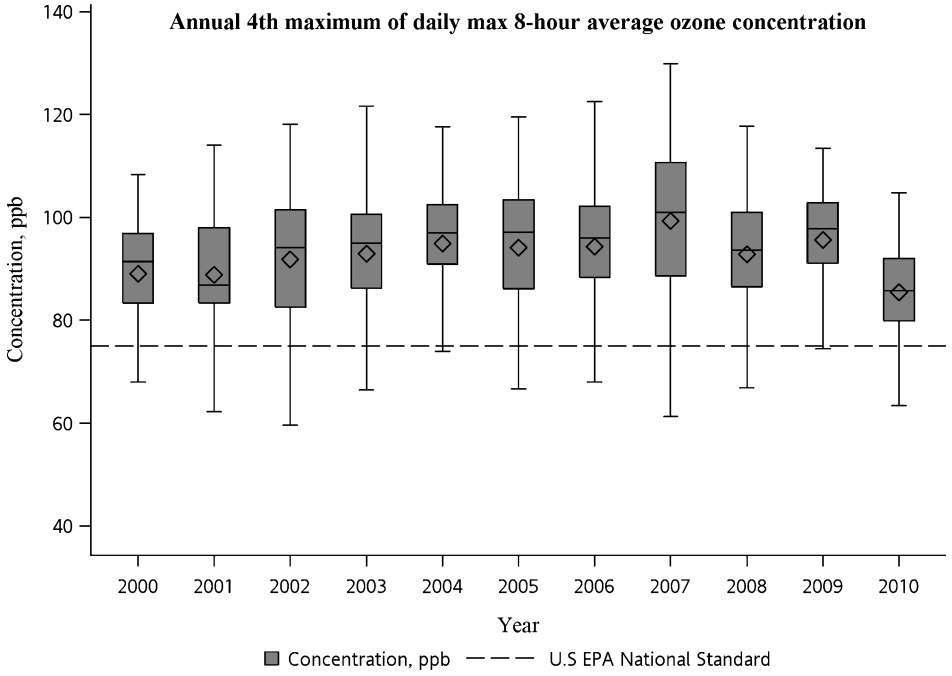


Fig. 3. The trend of annual 4th maximum of daily max 8-hour average ozone concentration in Taiwan during 2000-2010.

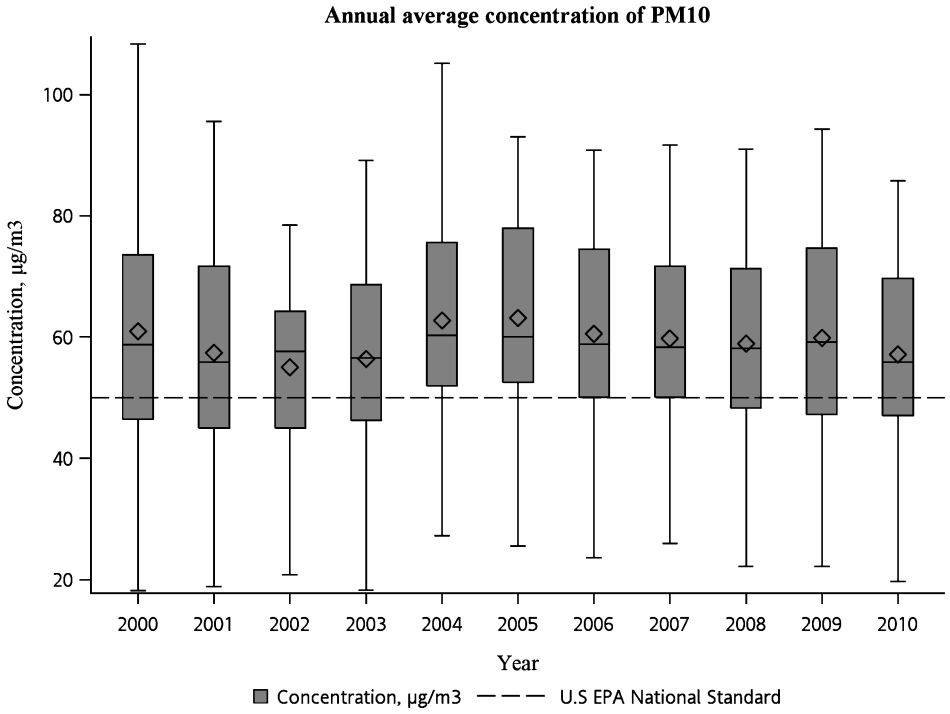


Fig. 4. The trend of annual average concentration of $PM_{10}$ in Taiwan during 2000-2010.

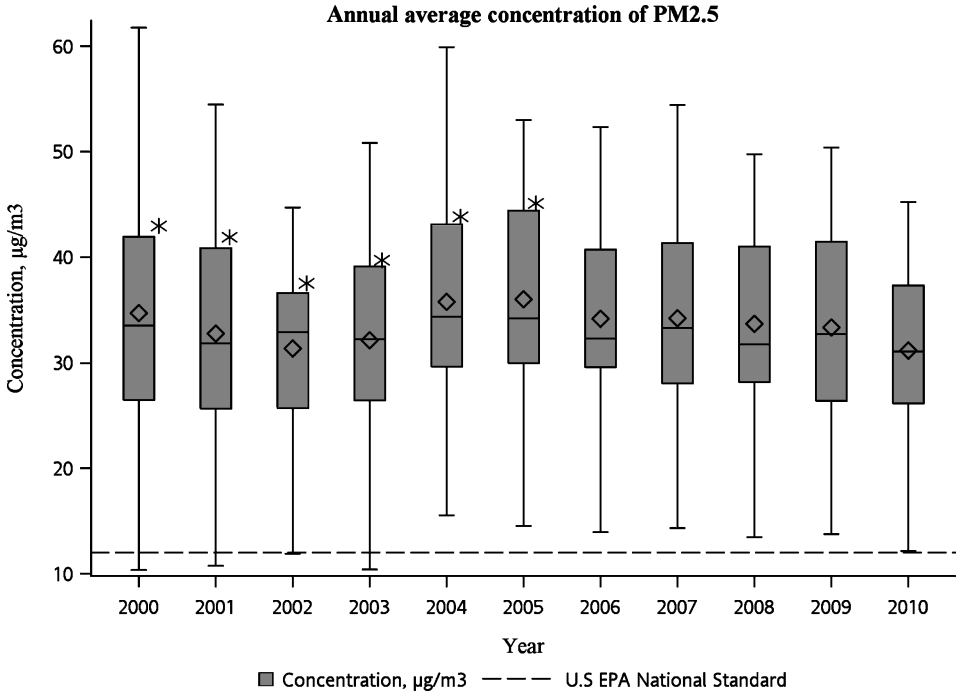


Fig. 5. The trend of annual average concentration of $PM_{2.5}$ in Taiwan during 2000-2010. (*: The concentration of $PM_{2.5}$ in the year was estimated from $PM_{10}$).

Table 2
Mean and distribution of air pollutants at baseline and change during follow-up period from January 1, 2001 to December 31, 2010

| Pollutant | AD | N | Mean | SD | Max | Min | Range | Q1 | Q3 |
|---|---|---|---|---|---|---|---|---|---|
| $O_3$ (ppb) | | | | | | | | | |
| Baseline | YES | 1,399 | 88.97 | 7.80 | 106.74 | 52.79 | 53.95 | 85.12 | 94.41 |
| | NO | 94,291 | 88.50 | 8.93 | 106.81 | 52.79 | 54.03 | 84.70 | 94.33 |
| Change | YES | 1,399 | 4.40 | 9.64 | 34.85 | −24.65 | 59.49 | −2.07 | 10.83 |
| | NO | 94,291 | −3.26 | 8.17 | 25.53 | −24.65 | 50.18 | −9.41 | 1.29 |
| $PM_{2.5}$ ($\mu g/m^3$) | | | | | | | | | |
| Baseline | YES | 1,399 | 34.40 | 8.60 | 55.86 | 16.79 | 39.07 | 27.83 | 41.14 |
| | NO | 94,291 | 34.32 | 8.68 | 55.86 | 16.06 | 39.80 | 27.76 | 40.96 |
| Change | YES | 1,399 | −0.13 | 4.04 | 15.89 | −15.32 | 31.21 | −2.36 | 2.48 |
| | NO | 94,291 | −2.50 | 3.79 | 8.48 | −16.85 | 25.33 | −4.34 | −0.18 |

Max, maximum; Min, minimum; 4th-$O_3$, fourth-highest daily maximum average 8-hour ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter equal to or less than 2.5 μm; Q1, 25 percentile; Q3, 75 percentile; SD, standard deviation.

group and a mean of 88.50 ppb (SD, 8.93) with a range of 52.79 to 106.81 ppb in group without AD. The mean of $PM_{2.5}$ at baseline was 34.40 $\mu g/m^3$ (SD, 8.60) with a range of 16.79 to 55.86 $\mu g/m^3$ in the AD group and a mean of 34.32 $\mu g/m^3$ (SD, 8.68) with a range of 16.06 to 55.86 $\mu g/m^3$ in the group without AD. The change of $O_3$ was positive (mean change = 4.40 ppb, SD, 9.64) in the AD group, showing an increased trend over time while a negative change was found in the group without AD (mean change = −3.26 ppb, SD, 8.17). There was almost no change in $PM_{10}$ concentration in the AD group (mean change = −0.13 $\mu g/m^3$, SD, 4.04) while a negative change of $PM_{10}$ was observed in the group without AD (mean change = −2.50 ppb, SD, 3.79).

The concentration of $O_3$ at baseline was moderately and positively correlated with $PM_{2.5}$ ($r = 0.40$) at baseline. The concentrations of $SO_2$ at baseline were highly correlated with $NO_2$ ($r = 0.45$) and $PM_{2.5}$($r = 0.51$) (Table 3). The changes in $PM_{2.5}$ were moderately correlated with $NO_2$ ($r = 0.33$) and $SO_2$ ($r = 0.32$) (Table 4).

### *Air pollution and the risk of newly diagnostic AD*

The adjusted HR for newly diagnosed AD was weakly positively associated with the raised concentration in $O_3$ at baseline per increase of 9.63 ppb (IQR) (adjusted HR = 1.06, 95% CI: 1.00, 1.12) (Table 5), and the adjusted HR change slightly after controlling for second pollutants (adjusted HR = 1.10, 95% CI: 1.03, 1.17 with CO at baseline; adjusted HR = 1.06, 95% CI: 0.99, 1.13 with $NO_2$ at baseline; adjusted HR = 1.04, 95% CI: 0.98, 1.11 with $SO_2$ at baseline) (Table 6). We estimated a 211% risk of the increase of newly diagnosed AD per increase of 10.91 ppb (IQR) in $O_3$ over the follow-up period (adjusted HR = 3.12, 95%

Table 3
Correlations of air pollutants' concentration at baseline

| | Baseline CO | Baseline $NO_2$ | Baseline $O_3$ | Baseline $PM_{10}$ | Baseline $SO_2$ |
|---|---|---|---|---|---|
| Baseline CO | 1.00 | **0.84***** | −0.23*** | −0.02*** | 0.21*** |
| Baseline $NO_2$ | | 1.00 | 0.07*** | 0.21*** | **0.45***** |
| Baseline $O_3$ | | | 1.00 | **0.40** *** | 0.19*** |
| Baseline $PM_{10}$ | | | | 1.00 | **0.51***** |
| Baseline $SO_2$ | | | | | 1.00 |

$NO_2$, nitrogen dioxides; $PM_{2.5}$, particulate matter with aerodynamic diameter equal to or less than 2.5 μm; $SO_2$, sulfur dioxide; $O_3$, fourth-highest daily maximum average 8-hour ozone; CO, carbon monoxide. ***$p$-value < 0.0001. Bold: Pearson correlation coefficient > 0.4.

Table 4
Correlations of changes in air pollutants' concentration during follow-up period

| | Change CO | Change $NO_2$ | Change $O_3$ | Change $PM_{10}$ | Change $SO_2$ |
|---|---|---|---|---|---|
| Change CO | 1.00 | 0.36*** | 0.10*** | 0.04*** | 0.19*** |
| Change $NO_2$ | | 1.00 | −0.05*** | 0.33*** | 0.27*** |
| Change $O_3$ | | | 1.00 | −0.26*** | 0.01 |
| Change $PM_{10}$ | | | | 1.00 | 0.32*** |
| Change $SO_2$ | | | | | 1.00 |

$NO_2$, nitrogen dioxides; $PM_{10}$, particulate matter with aerodynamic diameter equal to or less than 10 μm; $SO_2$, sulfur dioxide; $O_3$, fourth-highest daily maximum average 8-hour ozone; CO, carbon monoxide. ***$p$-value < 0.0001.

Table 5
Crude and adjusted hazard ratios with 95% confidence intervals (CIs) of newly diagnosed Alzheimer's disease (AD), corresponding to $O_3$ and $PM_{2.5}$ exposure at baseline as well as change of concentrations during follow-up period

| | Crude HR (95% confidence interval) | Adjusted HR[a] (95% confidence interval) |
|---|---|---|
| $O_3$ | | |
| The HR of AD per 9.63 ppb increase in baseline $O_3$ | 1.06(1.00, 1.13) | 1.06 (1.00, 1.12) |
| The HR of AD per 10.91 ppb increase in change $O_3$ | 3.11 (2.91, 3.32) | 3.12 (2.92, 3.33) |
| $PM_{2.5}$ | | |
| The HR of AD per 13.21 $\mu g/m^3$ increase in baseline $PM_{2.5}$ | 1.01 (0.93, 1.09) | 1.03 (0.95, 1.11) |
| The HR of AD per 4.34 $\mu g/m^3$ increase in change $PM_{2.5}$ | 2.41 (2.24, 2.59) | 2.38 (2.21, 2.56) |

$M_{2.5}$, particulate matter with aerodynamic diameter equal to or less than 2.5 $\mu m$; $O_3$, fourth-highest daily maximum average 8-hour ozone. [a]Adjusted HR was adjusted for age, gender, income, diabetes mellitus, hypertensive disease, myocardial infarction, stroke, asthma and chronic obstructive pulmonary disease.

Table 6
Adjusted hazard ratios with 95% confidence intervals (CIs) of newly diagnosed Alzheimer's disease, corresponding to $O_3$ and $PM_{2.5}$ exposure at baseline as well as change concentrations during follow period in two pollutant models

| Pollutant | IQR | Controlling pollutant | Adjusted HR[a] (95% CI) |
|---|---|---|---|
| Baseline $O_3$ | 9.63 ppb increase | Baseline CO | 1.10 (1.03, 1.17) |
| Baseline $O_3$ | 9.63 ppb increase | Baseline $NO_2$ | 1.06 (0.99, 1.13) |
| Baseline $O_3$ | 9.63 ppb increase | Baseline $SO_2$ | 1.04 (0.98, 1.11) |
| Baseline $PM_{2.5}$ | 13.21 $\mu g/m^3$ increase | Baseline CO | 1.03 (0.95, 1.12) |
| Baseline $PM_{2.5}$ | 13.21 $\mu g/m^3$ increase | Baseline $NO_2$ | 0.99 (0.91, 1.07) |
| Change $O_3$ | 10.91 ppb increase | Change CO | 3.40 (3.16, 3.65) |
| Change $O_3$ | 10.91 ppb increase | Change $NO_2$ | 3.42 (3.20, 3.65) |
| Change $O_3$ | 10.91 ppb increase | Change $PM_{10}$ | 3.52 (3.29, 3.77) |
| Change $O_3$ | 10.91 ppb increase | Change $SO_2$ | 3.23 (3.02, 3.46) |
| Change $PM_{2.5}$ | 4.34 $\mu g/m^3$ increase | Change CO | 2.17 (2.03, 2.33) |
| Change $PM_{2.5}$ | 4.34 $\mu g/m^3$ increase | Change $NO_2$ | 2.23 (2.07, 2.41) |
| Change $PM_{2.5}$ | 4.34 $\mu g/m^3$ increase | Change $O_3$ | 2.43 (2.30, 2.57) |
| Change $PM_{2.5}$ | 4.34 $\mu g/m^3$ increase | Change $SO_2$ | 2.34 (2.17, 2.52) |

$NO_2$, nitrogen dioxides; $PM_{2.5}$, particulate matter with aerodynamic diameter equal to or less than 2.5 $\mu m$; $SO_2$, sulfur dioxide; $O_3$, fourth-highest daily maximum average 8-hour ozone; CO, carbon monoxide. [a]Adjusted HR was adjusted for age, gender, income, diabetes mellitus, hypertensive disease, myocardial infarction, stroke, asthma and chronic obstructive pulmonary disease.

CI: 2.92, 3.33), and we observed a slight increase after controlling for CO, $NO_2$ $PM_{10}$, and $SO_2$ (adjusted HR varying from 3.23 to 3.52) (Table 6). The unadjusted HR per increase of 13.21 $\mu g/m^3$ (IQR) increase in $PM_{2.5}$ at baseline was 1.01 (95% CI: 0.93, 1.09), and the adjusted HR was 1.03 (95% CI: 0.95, 1.11). In addition, the adjusted HRs changed slightly after controlling for CO and $NO_2$ (adjusted HR = 1.03, 95% CI: 0.95, 1.12 with CO at baseline; adjusted HR = 0.99, 95% CI: 0.91, 1.07 with $NO_2$ at baseline). We found a 138% risk of increase of newly diagnosed AD per increase of 4.34 $\mu g/m^3$ (IQR) in $PM_{2.5}$ over the follow-up period (adjusted HR = 2.38, 95% CI: 2.21, 2.56) (Table 5), was and estimates remained stable when additional pollutants were added (Table 6).

## DISCUSSION

In this population-based cohort study, higher concentrations of $O_3$ exposure were associated with increased risk of newly diagnosed AD. We found that individuals exposed to a 10.91 ppb increase in $O_3$ over the follow-up period had a 211% increase risk of newly diagnosed AD. In addition, we used $PM_{10}$ data to estimate the concentration of $PM_{2.5}$ during 2000–2005 and also found individuals exposed to a 4.34 $\mu g/m^3$ increase in $PM_{2.5}$ over the follow-up period had a 138% increased risk of newly diagnosed AD.

Cognition is defined as a combination of domains, including attention, learning, memory, language, visuospatial skills, and executive functions [8]. Reasons for cognitive decline range from age-related decline and mild cognitive impairment, to severe dementia such as AD [8]. A few studies have elaborated associations between air pollution, mainly $O_3$ and PM, and cognitive decline. Long-term exposure to $PM_{2.5}$ and $PM_{10}$ has been also associated with significantly faster cognitive decline in older US women [34]. For German women aged 68–74 years, living within 50 m from a busy road (an indicator of traffic-related air pollution) was associated with worse scores on a

neuropsychological test battery [35]. Increasing levels of annual exposure to $O_3$ was associated with reduce cognitive performance such as coding ability, short-term memory, and attention in US adults [36]. A recent study also suggested that exposures to higher concentrations of $O_3$ and $PM_{2.5}$ are associated with lower executive function and verbal learning, respectively [37]. Consistently, the present study found the risk of newly diagnosed AD increased with increasing concentrations of $O_3$ and $PM_{2.5}$.

Air pollution may transfer from peripheral organs to the brain through systemic inflammation [1]. Exposure to $O_3$ may induce the release of pro-inflammatory mediators from the lungs [38]. Chronic lung inflammation may result in systemic inflammation that impacts blood vessels [39]. Cytokine derived from systemic inflammation may also cross the blood-brain barrier [40] and lead to active microglia [41]. Microglial activation is an early event in the process of AD [42]. Activated microglia releases secondary inflammation mediators and reactive oxygen species such as superoxide, NO, tumor necrosis factor-$\alpha$, interleukin 1$\beta$; this may intensify neuroinflammation and lead to brain damage [41].

Oxidative stress is also a vital pathogenesis and etiology of AD [13, 43, 44] which may lead to lipid peroxidation, protein oxidation, and DNA oxidation in brain [45–47]. A$\beta_{42}$ deposition is the key characteristic of AD. This kind of deposition first works against oxidative damage in the initial stage of AD, but ultimately evolves into a prooxidant only and exacerbates oxidative stress in the AD brain [48]. Ambient air is a complex of variety individual pollutants that are free radical ($NO_2$) or have the ability to drive free radical reaction ($O_3$ and PM) [49]. Acute or chronic $O_3$ exposure may generate oxidative stress that leads to brain lipid peroxidation [50, 51], neuronal morphological and ultrastructural changes [52], and memory deterioration [53].

According to the studies conducted locally in Taiwan, which indicated vehicle emissions, secondary aerosols, and biomass burning were the major source of $PM_{2.5}$ in urban regions [54–57]. Fang and colleagues found the annual average metal concentration in the $PM_{2.5\text{-}10}$ were $360.6 \pm 115.8$ ng/m$^3$ for iron (Fe), $92.1 \pm 54.7$ ng/m$^3$ for magnesium (Mg), $90.6 \pm 54.9$ ng/m$^3$ for lead (Pb), $40.3 \pm 33.9$ ng/m$^3$ for zinc (Zn), $9.0 \pm 13$ ng/m$^3$ for chromium (Cr), $4.3 \pm 8.1$ ng/m$^3$ for nickel (Ni), $3.8 \pm 6.2$ ng/m$^3$ for cadmium (Cd), $12.8 \pm 11.8$ ng/m$^3$ for copper (Cu), and $7.5 \pm 3.4$ ng/m$^3$ for manganese (Mn); in the $PM_{2.5}$ were $162.8 \pm 163.3$ ng/m$^3$ for Fe, $37.9 \pm 50.8$ ng/m$^3$ for Mg, $283.1 \pm 252.2$ ng/m$^3$ for Pb, $177.8 \pm 103$ ng/m$^3$ for Zn, $33.5 \pm 48$ ng/m$^3$ for Cr, $11.8 \pm 29.9$ ng/m$^3$ for Ni, $4.3 \pm 8.5$ ng/m$^3$ for Cd, $11.5 \pm 19.9$ ng/m$^3$ for Cu, $19.1 \pm 20.5$ ng/m$^3$ for Mn [57], they also found the average concentrations of particle-bound polycyclic aromatic hydrocarbons including in $PM_{2.5}$ was 56 ng/m$^3$ [58] in central Taiwan. PM itself may influence the brain directly; ultrafine PM (<100 nm) may diffuse from the lung to other organs such as the liver, kidney, heart, and brain [59]. The nasal olfactory is a critical portal by which nano-sized PM may directly enter the brain through the olfactory bulb and reach the cerebral cortex, hippocampus, cerebellum and brainstem [60, 61]. Abundant nano-sized PMs were identified in the cytoplasm of the olfactory bulb neurons after long term air pollution exposure [12]. Once PMs reach the brain, they could provide stimulus that induces the production of proinflammatory cytokines [1]. Ambient PM may result in brain inflammation in mice [62], dogs [9], and humans [10]. In addition, adsorbed compounds present on the PM surface include polycyclic aromatic hydrocarbons and oxidant metals which are neurotoxic [1].

This study has three strengths. First, the NHIRD covered 99% of the entire population in Taiwan. Thus, we have a sufficient, prospective, and population base database from the year 2001 that allow us to test the relationship between air pollutants and newly diagnosed AD. In addition, we included 95,690 individuals hence the analysis approach may provide more statistical power than case-control designs and provide benefits in studying rare outcomes. Second, the longer follow-up period provides an opportunity to explore the association between the risk of newly diagnosed AD and long-term cumulative exposure. Third, this is the first study of its kind to be conducted among an Asian population. However, this study also has several limitations that should be noted. First, we are not able to adjust for confounders such as genetic information (for example apolipoprotein E type 4 alleles) [63], smoking [64], body mass index [65], metals [66, 67], and occupational exposure [68], because no such detailed information is available in the NHIRD. Also, we were not able to evaluate subtypes of AD using NHIRD. Second, we were unable to investigate how the specific pollutants or mix of pollutants might have influenced in AD, because we did not have information on compositions and source of $PM_{2.5}$ from Taiwan EPA.

The present study found that risk of newly diagnosed AD may increase by 211% for individuals suffering from a 10.91 ppb increase in $O_3$ over 10 years during follow-up period. In addition, a 4.34 $\mu$g/m$^3$ increase

in $PM_{2.5}$ over the follow-up period may lead to a 138% increase in the risk of newly diagnosed AD. These findings suggest that improved ambient air quality, especially when it comes to $O_3$ and $PM_{2.5}$, might decrease the risk of newly diagnosed AD. The implications of these finding for public health are urgent because air pollution is a common and notorious environmental issue.

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