Journal of Alzheimer's Disease 78 (2020) 1585–1600
DOI 10.3233/JAD-200614
IOS Press

Long-Term Exposure to Air Pollutants and Cognitive Function in Taiwanese Community-Dwelling Older Adults: A Four-Year Cohort Study

Jen-Hau Chen[a], Tsung-Yu Kuo[b], Hwa-Lung Yu[c], Charlene Wu[d], Su-Ling Yeh[e], Jeng-Min Chiou[f], Ta-Fu Chen[g] and Yen-Ching Chen[b,h,*]

[a]*Department of Geriatrics and Gerontology, National Taiwan University Hospital, Taipei, Taiwan*
[b]*Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan*
[c]*Department of Bioenvironmental Systems Engineering, National Taiwan University, Taipei, Taiwan*
[d]*Global Health Program, College of Public Health, National Taiwan University, Taipei, Taiwan*
[e]*Department of Psychology, National Taiwan University, National Taiwan University, Taipei, Taiwan*
[f]*Institute of Statistical Science, Academia Sinica, Taipei, Taiwan*
[g]*Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan*
[h]*Department of Public Health, College of Public Health, National Taiwan University, Taipei, Taiwan*

Accepted 24 September 2020

Abstract.
Background: Previous studies have assessed limited cognitive domains with relatively short exposure to air pollutants, and studies in Asia are limited.
Objective: This study aims to explore the association between long-term exposure to air pollutants and cognition in community-dwelling older adults.
Methods: This four-year prospective cohort study recruited 605 older adults at baseline (2011–2013) and 360 participants remained at four-year follow-up. Global and domain-specific cognition were assessed biennially. Data on $PM_{2.5}$ (particulate matter ≤ 2.5 μm diameter, 2005–2015), PM_{10} (1993–2015), and nitrogen dioxide (NO_2, 1993–2015) were obtained from Taiwan Environmental Protection Administration (TEPA). Bayesian Maximum Entropy was utilized to estimate the spatiotemporal distribution of levels of these pollutants.
Results: Exposure to high-level $PM_{2.5}$ (>29.98 μg/m3) was associated with an increased risk of global cognitive impairment (adjusted odds ratio = 4.56; β = –0.60). High-level PM_{coarse} exposure (>26.50 $\mu g/m^3$) was associated with poor verbal fluency (β = –0.19). High-level PM_{10} exposure (>51.20 $\mu g/m^3$) was associated with poor executive function (β = –0.24). Medium-level NO_2 exposure (>28.62 ppb) was associated with better verbal fluency (β = 0.12). Co-exposure to high concentrations of $PM_{2.5}$, PM_{coarse} or PM_{10} and high concentration of NO_2 were associated with poor verbal fluency ($PM_{2.5}$ and NO_2: β = –0.17; PM_{coarse} and NO_2: β = –0.23; PM_{10} and NO_2: β = –0.21) and poor executive function (PM_{10} and NO_2: β = –0.16). These associations became more evident in women, apolipoprotein ε4 non-carriers, and those with education > 12 years.
Conclusion: Long-term exposure to $PM_{2.5}$ (higher than TEPA guidelines), PM_{10} (lower than TEPA guidelines) or co-exposure to PM_x and NO_2 were associated with poor global, verbal fluency, and executive function over 4 years.

Keywords: Air pollutants, cognitive impairment, cohort study, NO_2, older adults, $PM_{2.5}$, PM_{10}, PM_{coarse}

*Correspondence to: Yen-Ching Chen, ScD, Professor, Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, No. 17, Xu-Zhou Road, Taipei 10055, Taiwan. Tel.: +886 2 33668019; Fax: +886 2 23511955; E-mail: karenchen@ntu.edu.tw.

INTRODUCTION

As population ages rapidly, dementia has become an important health issue in older adults. Alzheimer's disease (AD) is the most common cause of dementia and is characterized by noticeable cognitive and behavioral symptoms that are severe enough to affect daily life [1]. A previous survey study in Taiwan (2011–2013) reported in older adults, the age- and sex-adjusted prevalence for overall dementia and mild cognitive impairment (MCI) were 8.1% and 18.8%, respectively [2], which is higher than the prevalence observed in East Asia (4.98–6.99% in 2015) [3]. Because of the heavy burden on health care and aging society, it is important to prevent cognitive impairment before the clinical manifestation.

Cognitive performance could be assessed by various neuropsychological tests of different domains; these cognitive domains could be classified into memory, attention, language, or executive functioning [4]. During the induction period of dementia, different brain areas are involved in different cognitive functions [4], these changes could serve as potential precursors to dementia. Thus, a cohort study with repeated measure is helpful to clarify the disease progression and possible affected areas in the brain.

Although existing scientific consensuses acknowledge air pollution contributes to cardiovascular and respiratory diseases, studies on cognitive performance started to grow after 2010. Among different sizes of particulate matter (PM), $PM_{2.5}$ ($PM \leq 2.5\mu m$ in diameter) mainly comes from primary combustion emission and secondary particles that were produced by gas-to-particle conversion [5]. $PM_{2.5}$ can penetrate the alveolar gas exchange region of the lungs, mainly deposits in the airway beyond larynx, and thus is known as respirable particles. PM_{coarse} ($PM > 2.5–10\ \mu m$ in diameter) accounts for the majority of visible or obvious form of PM (e.g., black smoke or dust from road, soil, and construction sites) and contains sulfates, nitrates, organic and elemental carbon, sea salts, molds, dust mites pollen, and spores [5]. Existing research indicated the smaller the PM, the more harm to the brain [6]. Our previous case-control study found that long-term exposure to ozone and PM_{10} ($PM \leq 10\ \mu m$ in diameter) at levels lower than the air quality standards of Taiwan Environmental Protection Administration (TEPA) was significantly associated with 2- to 3-fold increased risk of AD and vascular dementia [7]. Because of the heavy burden to dementia, we are hoping to clarify how exposure to air pollutants affect cognitive performance before disease onset.

The majority of previous studies found consistent associations between $PM_{2.5}$ exposure and the risk of cognitive impairment/decline (cohort studies: [8–14]; cross-sectional studies: [15–21]), dementia (AD and vascular dementia) (cohort studies: [11, 22–24]), or brain imaging outcomes such as larger white matter hyperintensity volume and risk of covert brain infarcts (cohort study: [25]). However, this association was not observed in another cross-sectional study [26]. Investigations on the associations between PM_{coarse} exposure and cognitive impairment/decline are limited and positive associations were observed in some studies (cohort study: [8]; cross-sectional study: [17]). Similarly, four cohort studies found positive associations between PM_{10} exposure and the risk of cognitive impairment/decline [9, 10, 14, 27], and another cross-sectional study reported positive association between PM_{10} and dementia [17]. However, these associations were not found in others (cohort studies: [22, 28]; cross-sectional studies: [18, 20]). Regarding NO_2, most of previous studies found that NO_2 exposure was associated with an increased risk of cognitive impairment/decline (cohort studies: [10, 12, 14]; cross-sectional studies: [17]) or dementia (cohort studies: [23, 24, 29]; case-control study: [30]), but such association was not observed in other cross-sectional studies [18, 20, 26]. Taken together, the majority of previous studies found $PM_{2.5}$, PM_{coarse}, PM_{10}, and NO_2 exposure were associated with an increased risk of cognitive impairment/decline or dementia. Different cognitive domains and assessment tools; study design (cohort versus cross-sectional); exposure sources, duration and assessment tools; and geographic locations may explain the inconsistent findings.

Development of dementia may take decades; however, several previous studies 1) collected exposure data over a relatively short duration compared with the disease progression [16, 17, 19, 25], 2) focused on global cognition or limited cognitive domains [11, 12, 15, 16, 21], or 3) used cross-sectional design (about 40% of studies). Because we are simultaneously exposed to multiple air pollutants, investigating co-exposure allows us to clarify the effect of how multipollutants affect cognitive performance in real-life settings. However, the majority of studies examine single pollutant in relation to a health outcome; limited data demonstrate how co-exposure to air pollutants affect cognitive performance over time [27]. In addition, air pollutants tend to vary across geographic

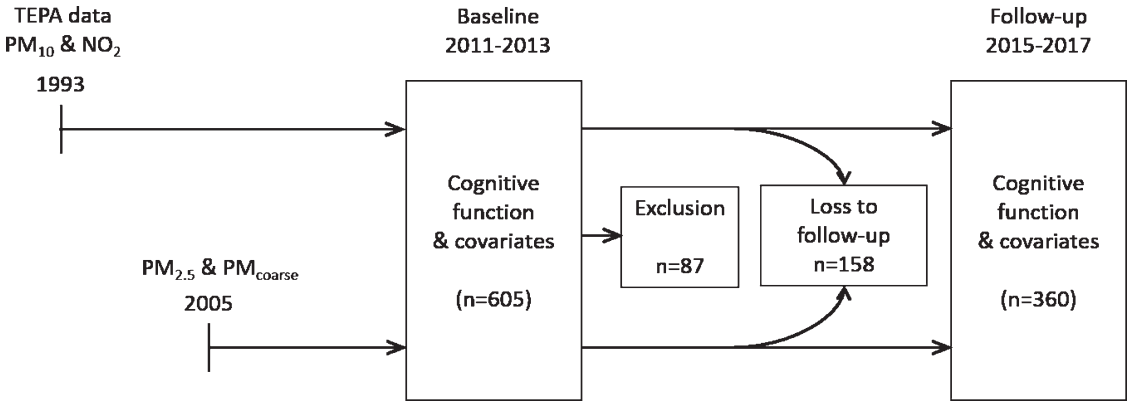

Fig. 1. A conceptual timeline of the present study

locations, but studies in Asian countries are sparse. Therefore, the aim of this study was to explore the association between long-term (11 to 23 years) exposure to air pollutants ($PM_{2.5}$, PM_{coarse}, PM_{10}, and NO_2) and cognitive performance in community-dwelling non-demented older adults in a four-year cohort study. Moreover, this study explored the association of co-exposure to multiple pollutants with cognitive performance. In order to identify subpopulations that are more susceptible to the exposure of air pollutants, we further stratified these associations by apolipoprotein E (*APOE*) ε4 status to assess gene-environment interactions and stratified by other important covariates (e.g., sex and years of education) known to affect the risk of dementia [31].

METHODS

Study population

This four-year cohort study originated from the Taiwan Initiative for Geriatric Epidemiological Research (TIGER, 2011-present), which recruited 605 older adults (aged 65+) from the senior health checkup program of National Taiwan University Hospital (NTUH) at baseline (2011–2013). Among them, 447 (73.9%) participants completed the four-year follow-up (2015–2017). Participants with the following conditions at baseline were excluded: 1) taking medications for treating AD ($n=2$), 2) the score of the Montreal Cognitive Assessment-Taiwanese version (MoCA-T)$\leq$21 [32] (suspected dementia, $n=62$), 3) brain tumor $\geq$ 3 cm ($n=2$), 4) a history of stroke ($n=10$) or head injury with loss of consciousness for more than 30 min ($n=4$), and 5) lack of *APOE* ε4 genotyping data ($n=6$). Furthermore, participants with the following conditions at either baseline or four-year follow-up were also excluded: 1) incomplete address, partial residence (defined as being abroad for over half of the time in the 10 years before the baseline), or actual living place outside of Taipei and Keelung metropolitan area ($n=29$), 2) unreasonable physical activity [$\geq$ 10,000 metabolic equivalent of task (MET)-min/week, $n=2$], and 3) lack of data on any cognitive variables ($n=11$). A total of 360 participants were included for analyses. The research protocol, informed consent, questionnaires, and application forms were approved by the Research Ethics Committee of NTUH. Written informed consent was obtained from all study participants. A conceptual timeline to demonstrate the present study, including participant selection and measures of important variables, is shown in Fig. 1.

Assessment of cognitive performance

At baseline and four-year follow-up, global cognition was assessed by MoCA-T (sensitivity: 92%, specificity: 78%), a score $<$ 24 indicated cognitive impairment and a score $\geq$ 24 indicated normal cognition, this cutoff point has been validated in a Taiwanese population [32]. One point was added to MoCA-T score when a participant had education $\leq$ 12 years. A battery of neuropsychological tests were performed to assess domain-specific cognition (memory, executive function, category/semantic fluency, and attention). In Wechsler Memory Scale-Third Edition (WMS-III), logical memory theme I & II and recall I & II were used to assess verbal episodic memory, and digit span-forward and backward were used to assess attention performance [33]. Verbal

fluency tests were used to assess category/semantic fluency by recording the maximum number of fruits, fish, and vegetables that participants could name in one minute for each category and these scores were then summed up into a composite score. Executive function was assessed by the time (in seconds) to complete Trail Making Test A and B; requiring more time to complete the test would indicate poorer executive function. The scores of the two Trail Making Tests were multiplied by -1 to make them in the same direction of other cognitive variables. To make all cognitive variables comparable, the scores for each cognitive variable at baseline and four-year follow-up were standardized based on the mean and standard deviation (SD) of the score at baseline [34]; higher score is indicative of better cognition.

Exposure assessment of air pollutants

Ambient air quality data were collected from 27 monitoring stations in the Taipei metropolitan area through the Taiwan Air Quality Monitoring Network (TAQMN) established by TEPA [35]. Annual mean concentrations of PM_{10} and NO_2 were available from 1993 to 2015 (23 years), and the $PM_{2.5}$ levels were available between 2005 and 2015 (11 years). PM_{coarse} data were derived by the difference between concentrations of $PM_{2.5}$ and PM_{10}. Bayesian Maximum Entropy (BME) was utilized to estimate the spatiotemporal distribution of levels of these pollutants. If a participant changed residence during the exposure period, address and exposure data were updated accordingly. The level of each air pollutant was then tertiled into low- (T1), medium- (T2), and high-level (T3) exposure. Similar approaches have been adopted in some previous studies to group participants based on their exposure levels [15, 26, 36–38].

Spatiotemporal estimation

BME is an epistemic framework, which distinguishes the general and specific knowledge of the spatiotemporal processes and generates more informative spatiotemporal maps for the variables of interest compared with land-use regression models [39]. The details of BME method and its applications can be referred to previous publications [40–42]. The process of spatiotemporal air pollutants can be characterized by spatiotemporal trend and their covariance. Nested spatiotemporal covariance models were used to characterize the spatiotemporal dependence of the air pollutants to reveal the spatiotemporal processes at different space-time scales [41, 43]. To account for the impact of air pollutants to cognitive impairment, BME method generated the annual cumulative levels of air pollutants at the corresponding residential place for each participant. We designated the exposure timeframe for PM_{10} and NO_2 exposure to begin in 1993, and 2005 for $PM_{2.5}$ because the aforementioned years indicate the time when air quality data became available from the TAQMN. Since participants joined our prospective cohort study between 2011 and 2013; each individual was then followed-up for four years. Thus, each individual's exposure period was 23 and 11 years, respectively. STAR-BME package was used for BME analysis [44, 45].

Statistical analyses

Generalized linear models, coupled with the Generalized Estimation Equations (GEEs) approach to consider within-subject correlations, were used to estimate 1) adjusted odds ratios (aORs) and the corresponding 95% confidence intervals (CIs) for the risk of cognitive impairment (MoCA-T<24 or T1 for the impairment of domain-specific cognition) among participants with high- (T3) and medium-level (T2) exposure versus a low-level (T1) exposure to a specific air pollutant, and 2) the performance of global or domain-specific cognitive function (i.e., the regression coefficient) over 4 years for per unit increase in exposure concentration to a specific air pollutant. The following covariates were adjusted in the regression models: variables with biological importance, variables identified by the stepwise model selection (SLENTRY = 0.10), and variables remained significantly associated with the outcome variables in the multivariable regression models. These variables included sex, age, years of education, *APOE* ε4 status, history of smoking, exposure to environmental tobacco smoke, alcohol drinking, history of hypertension and depressive symptoms, body mass index (BMI), and follow-up time. Stratified analyses were performed by important covariates (e.g., sex, *APOE* ε4 status, and years of education). We also assessed how the performance of cognitive function was affected by co-exposure to air pollutants, i.e., the pairwise combinations of exposure to PM_x ($PM_{2.5}$, PM_{coarse}, or PM_{10}: T1 + T2 versus T3) and NO_2 (T1 + T2 versus T3). SAS version 9.4 (SAS Institute, Cary, NC) was used for statistical analyses. All statistical tests were two sided.

RESULTS

Characteristics of the study population

This study included 360 participants with a repeated measure of demographic characteristics, physical activity, lifestyle, and medical conditions at four-year follow up. The mean age of the participants was 71.9 years old at baseline with an average of 14-year education. At baseline, none of the characteristics of the study population significantly differed across low-, medium-, and high-level exposure of each air pollutant (Table 1).

Spatial and temporal distributions of $PM_{2.5}$, PM_{coarse}, PM_{10}, and NO_2

The annual mean concentration of $PM_{2.5}$ (29.12 $\mu g/m^3$ for 11-year exposure) was higher than TEPA guidelines (15 $\mu g/m^3$), while the annual average level of PM_{10} and NO_2 (50.42 $\mu g/m^3$ and 27.76 ppb for 23-year exposure, respectively) were below the air quality standards (65 $\mu g/m^3$ and 50 ppb, respectively; Supplementary Figure 1 and Supplementary Table 1). The annual mean level of PM_{coarse} was 24.14 $\mu g/m^3$ and TEPA does not have a corresponding standard for this pollutant. The spatial and temporal covariance models (Fig. 2) were used in BME framework, respectively. As the spatial and time lag increased, both the spatial and temporal covariance became smaller. The spatial and temporal covariances of PM_x are different. Among the spatial covariances, $PM_{2.5}$ has a wider spatial correlation range compared to PM_{coarse} and PM_{10}; spatial variability of PM_{10} is smoother compared to $PM_{2.5}$ and PM_{coarse}. However, the smoother variability over time is present in $PM_{2.5}$ and PM_{coarse}, but not in PM_{10}. Elevated $PM_{2.5}$ level was observed in central western Taipei and Taoyuan Cities, possibly attributable to traffic and industrial emissions (Fig. 3).

Associations between air pollutants and cognitive function

The high-level $PM_{2.5}$ exposure (T3: >29.98$\mu g/m^3$) was significantly associated with an increased risk of global cognitive impairment (T3 versus T1: aOR = 4.56, 95% CI = 1.51 to 13.82, $p_{trend} = 0.01$; $\beta = -0.60$, 95% CI = –1.11 to –0.09, $p_{trend} = 0.02$, Table 2). $PM_{2.5}$ exposure was not associated with specific cognitive domains. The high-level PM_{coarse} exposure (T3: >26.50 $\mu g/m^3$) was significantly associated with poor performance of verbal fluency (T3 versus T1: $\beta = -0.19$, 95% CI = –0.37 to –0.01, $p_{trend} = 0.05$). The high-level PM_{10} exposure (T3: >51.20 $\mu g/m^3$) was significantly associated with poor performance of executive function (Trail Making Test A, T3 versus T1: $\beta = -0.24$, 95% CI = –0.41 to –0.06, $p_{trend} = 0.01$). The medium-level NO_2 exposure was associated with better verbal fluency (T2 versus T1: $\beta = 0.12$, 95% CI = 0.0005 to 0.24). PM_{coarse}, PM_{10}, or NO_2 exposure was not related to the performance of global cognition and the remaining cognitive domains.

Co-exposure to PM_x and NO_2

Among different levels of co-exposure to PM_x and NO_2, the exposure concentrations at the highest tertile of both $PM_{2.5}$ and NO_2 were significantly associated with poor performance of verbal fluency (T3 versus T1 + T2: $\beta = -0.17$, 95% CI = –0.30 to –0.03, $p_{trend} = 0.02$, Table 3) compared with medium- to low-level $PM_{2.5}$ and NO_2 exposure. The remaining combinations of different levels of $PM_{2.5}$, PM_{coarse}, or PM_{10} with NO_2 exposure were not associated with the performance of global cognition and the remaining cognitive domains. Secondly, the exposure concentrations at the highest tertile of both PM_{coarse} and NO_2 were significantly associated with poor performance of verbal fluency (T3 versus T1 + T2: $\beta = -0.23$, 95% CI = –0.41 to –0.05, $p_{trend} = 0.01$) compared with medium- to low-level PM_{coarse} and NO_2 exposure. Similarly, the exposure concentrations at the highest tertile of both PM_{10} and NO_2 were significantly associated with poor performance of executive function (T3 versus T1 + T2: $\beta = -0.16$, 95% CI = –0.30 to –0.01, $p_{trend} = 0.04$) and verbal fluency (T3 versus T1 + T2: $\beta = -0.21$, 95% CI = –0.35 to –0.08, $p_{trend} = 0.01$) compared with medium- to low-level PM_{10} and NO_2 exposure.

Stratified analyses by important covariates

For significant associations found between air pollutants and cognitive function over 4 years (Table 2), stratified analyses were performed by important covariates in Fig. 4 (sex, *APOE* $\varepsilon 4$ status, and years of education). Although no significant interaction was observed between exposures to $PM_{2.5}$ or PM_{10} and the aforementioned covariates on global or domain-specific cognition (Fig. 4), significant associations were found in some subgroups after stratification.

Table 1
Characteristics of the study population by levels of air pollutants at baseline (2011–2013, $N = 360$)

Variables	Total	Air pollutants															
		$PM_{2.5}$ ($\mu g/m^3$)				PM_{coarse} ($\mu g/m^3$)				PM_{10} ($\mu g/m^3$)				NO_2 (ppb)			
		Low (T1)	Medium (T2)	High (T3)	*p*	Low (T1)	Medium (T2)	High (T3)	*p*	Low (T1)	Medium (T2)	High (T3)	*p*	Low (T1)	Medium (T2)	High (T3)	*p*
		Mean (SD)															
Age (y)[a]	71.9(4.9)	72.1(5.5)	72.1(4.6)	71.7(4.7)	0.69	72.3(5.3)	71.4(4.8)	72.2(4.7)	0.31	71.7(5.0)	72.5(5.1)	71.6(4.7)	0.28	72.4(5.4)	72.2(4.9)	71.3(4.5)	0.39
Education (y)[a]	14.0(3.4)	13.7(3.1)	14.5(3.5)	13.8(3.6)	0.23	13.5(3.1)	14.2(3.6)	14.3(3.5)	0.07	14.1(2.9)	14.2(3.9)	13.7(3.3)	0.43	13.9(3.4)	14.4(3.2)	13.7(3.6)	0.29
BMI (kg/m^2)[b]	23.8(2.9)	23.9(2.8)	23.9(3.0)	23.6(2.9)	0.70	24.0(3.1)	23.7(2.8)	23.8(2.9)	0.79	23.8(2.5)	24.0(3.1)	23.6(3.1)	0.63	23.8(2.7)	23.9(3.2)	23.7(2.9)	0.86
Physical activity (MET-min/week)[a]	1753.2 (1382.3)	1633.6 (1263.4)	1735.0 (1230.3)	1891.2 (1618.7)	0.61	1578.1 (1183.6)	1805.3 (1346.7)	1876.4 (1581.4)	0.42	1675.5 (1268.3)	1618.7 (1291.7)	1965.5 (1554.8)	0.23	1616.3 (1197.8)	1636.6 (1221.4)	2006.8 (1655.4)	0.37
		N (%)															
Women	195(54.0)	59(49.2)	73(60.8)	62(51.7)	0.16	65(54.2)	66(55.0)	63(52.5)	0.92	67(55.8)	62(51.7)	65(54.2)	0.81	64(53.3)	70(58.3)	60(50.0)	0.42
APOE ε4 carriers	56(15.5)	22(18.3)	18(15.0)	16(13.3)	0.55	18(15.0)	24(20.0)	14(11.7)	0.20	18(15.0)	24(20.0)	14(11.7)	0.20	20(16.7)	21(17.5)	15(12.5)	0.52
Alcohol drinking	88(24.4)	31(25.8)	22(18.3)	35(29.2)	0.14	28(23.3)	27(22.5)	33(27.5)	0.63	32(26.7)	27(22.5)	29(24.2)	0.75	25(20.8)	30(25.0)	33(27.5)	0.48
Cigarette smoking	198(54.9)	74(61.7)	65(54.2)	58(48.3)	0.11	69(57.5)	72(60.0)	56(46.7)	0.09	69(57.5)	62(51.7)	66(55.0)	0.66	73(60.8)	62(51.7)	62(51.7)	0.26
Heart disease	113(31.3)	41(34.2)	33(27.5)	39(32.5)	0.51	37(30.8)	35(29.2)	41(34.2)	0.70	44(36.7)	31(25.8)	38(31.7)	0.19	36(30.0)	41(34.2)	36(30.0)	0.72
Diabetes	61(16.9)	26(21.7)	16(13.3)	15(12.5)	0.10	26(21.7)	14(11.7)	17(14.2)	0.09	20(16.7)	21(17.5)	16(13.3)	0.65	20(16.7)	16(13.3)	21(17.5)	0.65
Hypertension	237(65.7)	78(65.0)	67(55.8)	66(55.0)	0.22	79(65.8)	66(55.0)	66(55.0)	0.14	73(60.8)	71(59.2)	67(55.8)	0.73	72(60.0)	72(60.0)	67(55.8)	0.75
Depressive symptoms	29(8.0)	11(9.2)	8(6.7)	10(8.3)	0.77	14(11.7)	9(7.5)	6(5.0)	0.16	10(8.3)	6(5.0)	13(10.8)	0.25	10(8.3)	9(7.5)	10(8.3)	0.96
COPD	48(13.3)	18(15.0)	13(10.8)	17(14.2)	0.60	18(15.0)	15(12.5)	15(12.5)	0.81	15(12.5)	15(12.5)	18(15.0)	0.81	18(15.0)	15(12.5)	15(12.5)	0.81

[a]Kruskal-Wallis test and [b]analysis of variance were used for continuous variables; Chi square test was used for categorical variables. The annual average levels of the air pollutants in the study population and the corresponding air quality standards can be found in Supplementary Table 1. $PM_{2.5}$, low: <29.00 $\mu g/m^3$; medium: 29.00–29.98 $\mu g/m^3$; high: >29.98 $\mu g/m^3$. PM_{coarse}, low: <22.45 $\mu g/m^3$; medium: 22.45–26.50 $\mu g/m^3$; high: >26.50 $\mu g/m^3$. PM_{10}, low: <49.57 $\mu g/m^3$; medium: 49.57–51.20 $\mu g/m^3$; high: >51.20 $\mu g/m^3$. NO_2, low: <27.47 ppb; medium: 27.47–28.62 ppb; high: >28.62 ppb. T, tertile; SD, standard deviation; BMI, body mass index; MET, metabolic equivalent of task; *APOE*, apolipoprotein; $PM_{2.5,}$ particulate matter ≤ 2.5 μm in diameter; $PM_{coarse,}$ particulate matter > 2.5–10 μm in diameter; $PM_{10,}$ particulate matter ≤ 10 μm in diameter; NO_2, nitrogen dioxide; ppb, parts per billion; COPD, chronic obstructive pulmonary disease.

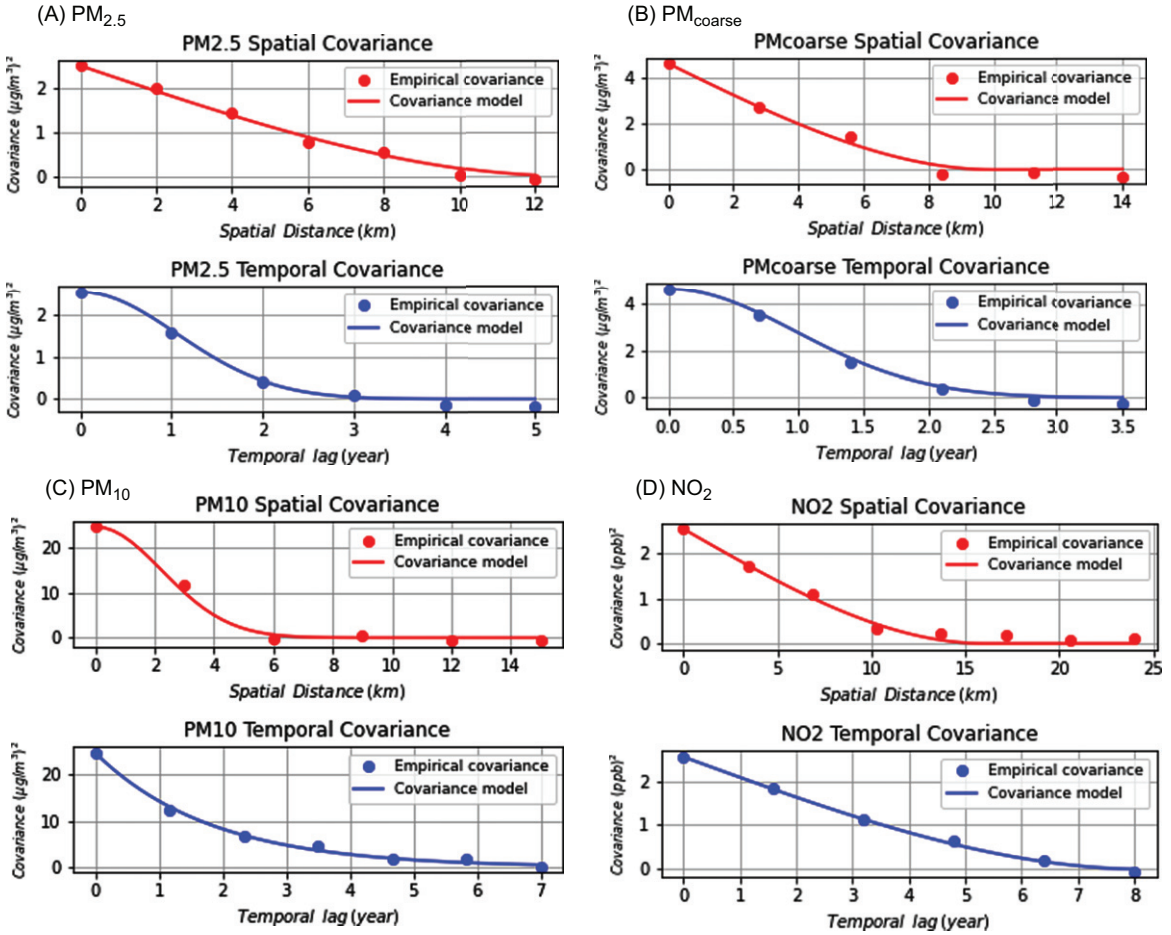

Fig. 2. The spatial (upper)/temporal (lower) covariance model fitting used for Bayesian maximum entropy (BME) estimation: A) particulate matter ≤ 2.5 μm in diameter ($PM_{2.5}$); B) particulate matter > 2.5–10 μm in diameter (PM_{coarse}); C) particulate matter ≤ 10 μm in diameter (PM_{10}); D) nitrogen dioxide (NO_2). X-axis indicates the spatial/temporal lag (km/years); Y-axis indicates the covariance of each air pollutant. Circles are estimated empirical covariance. Curved lines are fitted covariance models, which characterize the spatiotemporal dependence for the annual $PM_{2.5}$, PM_{coarse}, PM_{10}, and NO_2 exposure.

For the association of $PM_{2.5}$ with global cognitive impairment, results became more evident in men (T3 versus T1: aOR = 5.72; p_{trend} =0.05, Fig. 4A), *APOE* ε4 non-carriers (T3 versus T1: aOR = 3.99; p_{trend} =0.03), and participants with education > 12 years (T3 versus T1: aOR = 8.10; p_{trend} =0.03). No significant associations were found in women, *APOE* ε4 carriers, and participants with education ≤ 12 years. For continuous global cognition, results became more evident in women (T3 versus T1: β=–0.83, p_{trend} =0.02, Fig. 4B) and participants with education > 12 years (T3 versus T1: β=–0.72, p_{trend} =0.04). Associations did not reach statistical significance among men, both *APOE* ε4 carriers and non-carriers, and participants with education ≤ 12 years.

For the association of PM_{10} with poor performance of executive function, results became more evident in men (T2 versus T1: β=–0.22; T3 versus T1: β=–0.44; p_{trend} = 0.003, Fig. 4C), *APOE* ε4 non-carriers (T3 versus T1: β=–0.25; p_{trend} = 0.01), and participants with education ≤ 12 years (T3 versus T1: β=–0.34; p_{trend} = 0.02). No significant associations were found in women, *APOE* ε4 carriers, and participants with education > 12 years. For the association of PM_{coarse} with poor performance of verbal fluency, results became more evident in women (T2 versus T1: β=–0.24; p_{trend} = 0.13, Fig. 4D), *APOE* ε4 non-carriers (T3 versus T1: β=–0.21; p_{trend} = 0.03), and participants with education > 12 years (T2 versus T1: β=–0.23; T3 versus T1: β=–0.28; p_{trend} = 0.02). No

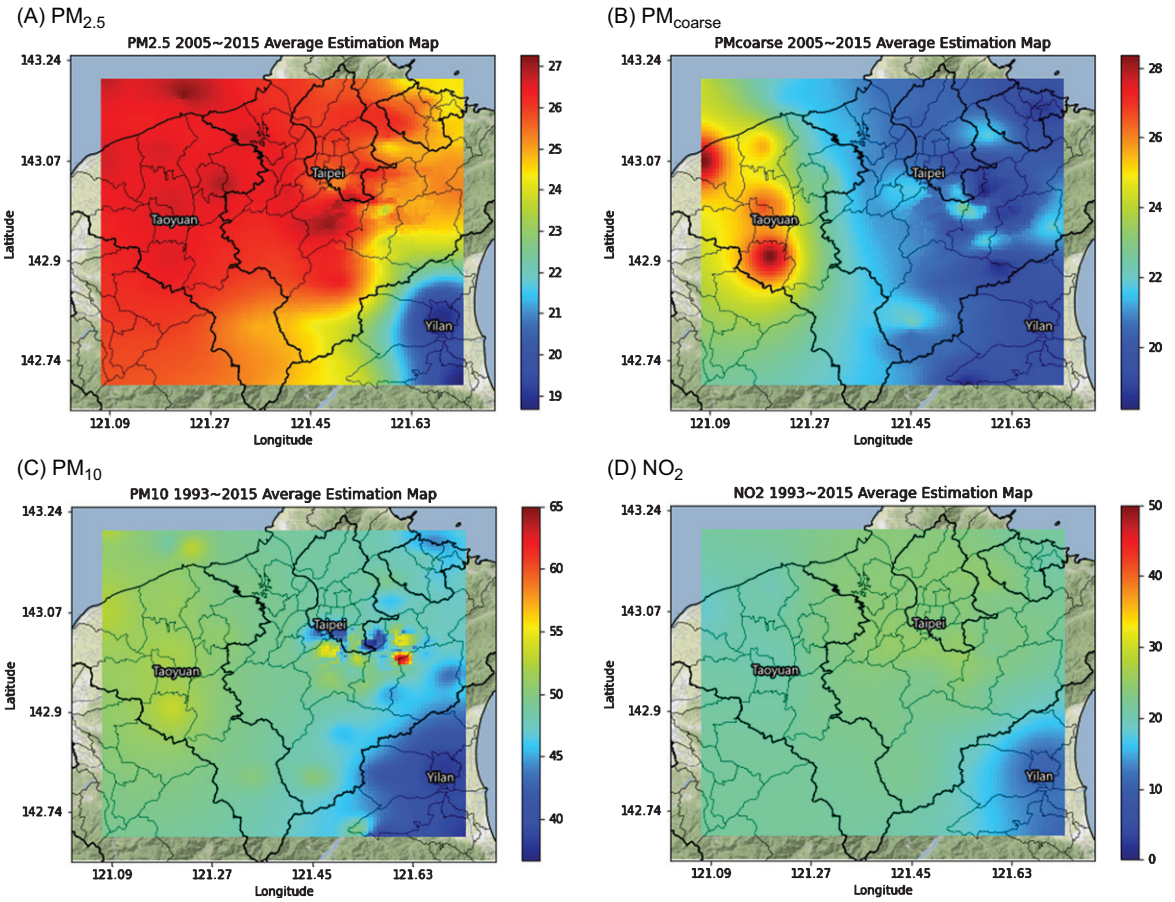

Fig. 3. Fitted covariance model used for Bayesian maximum entropy (BME) estimation in northern Taiwan: A) the average annual $PM_{2.5}$ exposure over 11 years, B) the average annual PM_{coarse} exposure over 11 years, C) the average annual PM_{10} exposure over 23 years, and D) the average annual NO_2 exposure over 23 years. X-axis indicates the longitude of the study area; Y-axis indicates the latitude of the study area.

significant associations were found in men, *APOE* ε4 carriers, and participants with education ≤ 12 years. For the association of NO_2 with better performance of verbal fluency, results became more evident in men (T2 versus T1: β=0.22; $p_{trend} = 0.30$, Fig. 4E), and participants with education > 12 years (T2 versus T1: β=0.15; $p_{trend} = 0.66$). No significant association was found in women, both *APOE* ε4 carriers and non-carriers, and participants with education ≤ 12 years.

DISCUSSION

This study found that 11-year exposure to elevated $PM_{2.5}$ levels (annual mean higher than that established by TEPA) was associated with poor global cognition over four-year follow-up. An 11-year exposure to elevated PM_{coarse} levels or a 23-year exposure to elevated PM_{10} levels (annual mean lower than that established by TEPA) was significantly associated with poor verbal fluency. These associations became more evident in women and *APOE* ε4 non-carriers, and participants with education > 12 years. Additionally, the co-exposure to PM_x and NO_2 was significantly associated with poor verbal fluency; co-exposure to PM_{10} and NO_2 was significantly associated with poor executive function. Taken together, we found that PM_{10}, PM_{coarse}, $PM_{2.5}$, and NO_2 exposure affected different cognitive function (e.g., global or domain-specific cognition). Different cognitive domains were associated with PM_x exposure, which may be attributable to different sources of PM, adsorbed compounds presented on PM, geographic locations of sample collection, seasons, the deposit locations in the airway, and the ability of traverse traditional barriers in the lung or the blood-brain barrier [46]. In addition, this study found that the perfor-

Table 2
Association between air pollutants and cognitive function over four-year follow up ($N = 360$)

Air pollutants		Global cognition by MoCA-T		Cognitive domain specific tests					
		Binary aOR (95% CI)	Continuous β (95% CI)	Logical memory β (95% CI)	Executive function β (95% CI)	Trail Making Test A β (95% CI)	Trail Making Test B β (95% CI)	Verbal fluency β (95% CI)	Attention β (95% CI)
$PM_{2.5}$	T1	1.00	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	T2	2.23(0.76, 6.55)	–0.26(–0.73, 0.21)	0.11(–0.08, 0.30)	0.02(–0.11, 0.15)	0.12(–0.04, 0.28)	–0.08(–0.24, 0.09)	0.04(–0.10, 0.19)	0.07(–0.07, 0.21)
	T3	**4.56(1.51, 13.82)**	**–0.60(–1.11, –0.09)**	0.16(–0.06, 0.39)	–0.11(–0.26, 0.05)	–0.01(–0.19, 0.17)	–0.21(–0.43, 0.005)	–0.07(–0.22, 0.08)	–0.12(–0.29, 0.04)
	P_{trend}	**0.01**	**0.02**	0.15	0.18	0.96	0.06	0.40	0.17
PM_{coarse}	T1	1.00	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	T2	0.95(0.42, 2.14)	–0.29(–0.74, 0.15)	0.12(–0.08, 0.33)	0.03(–0.14, 0.21)	–0.04(–0.22, 0.14)	0.11(–0.12, 0.33)	–0.14(–0.30, 0.02)	0.02(–0.14, 0.18)
	T3	1.03(0.43, 2.47)	–0.15(–0.65, 0.35)	0.04(–0.18, 0.27)	–0.06(–0.24, 0.12)	–0.10(–0.29, 0.09)	–0.01(–0.24, 0.23)	**–0.19(–0.37, –0.01)**	–0.01(–0.17, 0.16)
	P_{trend}	0.95	0.62	0.77	0.48	0.30	0.87	**0.05**	0.92
PM_{10}	T1	1.00	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	T2	1.50(0.62, 3.63)	–0.24(–0.65, 0.17)	–0.06(–0.25, 0.13)	–0.09(–0.22, 0.04)	–0.12(–0.26, 0.02)	–0.08(–0.27, 0.12)	–0.12(–0.24, 0.002)	–0.04(–0.18, 0.11)
	T3	1.61(0.52, 4.96)	–0.28(–0.80, 0.25)	–0.17(–0.40, 0.06)	–0.13(–0.29, 0.02)	**–0.24(–0.41, –0.06)**	–0.05(–0.26, 0.17)	–0.12(–0.27, 0.02)	–0.08(–0.25, 0.10)
	P_{trend}	0.42	0.30	0.15	0.10	**0.01**	0.69	0.11	0.39
NO_2	T1	1.00	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	T2	0.41(0.16, 1.02)	0.15(–0.25, 0.56)	–0.01(–0.17, 0.15)	0.10(–0.03, 0.22)	0.12(–0.02, 0.26)	0.08(–0.07, 0.23)	**0.12(0.0005, 0.24)**	0.09(–0.03, 0.20)
	T3	1.21(0.40, 3.68)	–0.26(–0.82, 0.31)	0.14(–0.08, 0.36)	0.10(–0.08, 0.27)	0.14(–0.05, 0.34)	0.05(–0.17, 0.28)	–0.01(–0.18, 0.16)	–0.02(–0.19, 0.16)
	P_{trend}	0.97	0.53	0.28	0.21	0.12	0.55	0.74	0.90

Generalized estimating equations were used to estimate aORs [for binary MoCA-T: ≥24 (normal) versus < 24 (impaired)] and β coefficients (continuous cognitive variables) adjusted for age, sex, years of education, *APOE* ε4 status, history of smoking and drinking, depressive symptoms, body mass index, and follow-up time (baseline: 2011–2013; follow-up: 2015–2017). The numbers in bold indicate statistically significant findings ($p < 0.05$). The annual average levels of the air pollutants in the study population and the corresponding air quality standards can be found in Supplementary Table 1. MoCA-T, Montreal Cognitive Assessment-Taiwanese version; aOR, adjusted odds ratio; CI, confidence interval; Ref., reference group; $PM_{2.5,}$ particulate matter ≤ 2.5 μm in diameter; $PM_{coarse,}$ particulate matter > 2.5–10 μm in diameter; $PM_{10,}$ particulate matter ≤ 10 μm in diameter; NO_2, nitrogen dioxide; ppb, parts per billion.

Table 3
Coexposure to PM_x and NO_2 on cognitive function over four-year follow up ($N = 360$)

Air pollutants	Global cognition by MoCA-T		Cognitive specific tests					
	Binary aOR (95% CI)	Continuous β (95% CI)	Logical memory β (95% CI)	Executive function β (95% CI)	Trail Making Test A β (95% CI)	Trail Making Test B β (95% CI)	Verbal fluency β (95% CI)	Attention β (95% CI)
$PM_{2.5}$ (T1 + T2)								
NO_2 (T1 + T2)	1.00	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
NO_2 (T3)	0.95(0.27, 3.37)	–0.24(–0.85, 0.38)	0.03(–0.25, 0.30)	–0.01(–0.15, 0.14)	–0.02(–0.19, 0.15)	0.0038(–0.20, 0.21)	–0.15(–0.31, 0.01)	0.09(–0.06, 0.25)
$PM_{2.5}$ (T3)								
NO_2 (T1 + T2)	2.44(0.19, 30.86)	–0.60(–1.41, 0.20)	–0.10(–0.40, 0.20)	–0.29(–0.67, 0.10)	–0.17(–0.49, 0.14)	–0.40(–1.03, 0.22)	–0.03(–0.33, 0.27)	–0.08(–0.39, 0.23)
NO_2 (T3)	1.80(0.66, 4.88)	–0.27(–0.72, 0.17)	0.12(–0.06, 0.31)	–0.09(–0.22, 0.05)	–0.08(–0.25, 0.09)	–0.10(–0.27, 0.07)	**–0.17*(–0.30, –0.03)**	–0.09(–0.26, 0.07)
P_{trend}	0.29	0.19	0.23	0.15	0.32	0.17	**0.02**	0.26
PM_{coarse} (T1 + T2)								
NO_2 (T1 + T2)	1.00	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
NO_2 (T3)	1.58(0.38, 6.56)	–0.45(–1.07, 0.17)	0.10(–0.19, 0.38)	0.02(–0.16, 0.20)	–0.03(–0.23, 0.18)	0.07(–0.16, 0.30)	–0.15(–0.32, 0.03)	–0.03(–0.24, 0.17)
PM_{coarse} (T3)								
NO_2 (T1 + T2)	0.95(0.37, 2.44)	–0.0002(–0.51, 0.51)	–0.06(–0.27, 0.16)	–0.05(–0.22, 0.12)	–0.04(–0.23, 0.14)	–0.04(–0.25, 0.17)	–0.06(–0.24, 0.11)	–0.01(–0.18, 0.16)
NO_2 (T3)	1.60(0.49, 5.23)	–0.26(–0.83, 0.31)	0.07(–0.16, 0.30)	–0.12(–0.29, 0.06)	–0.13(–0.33, 0.06)	–0.10(–0.33, 0.13)	**–0.23(–0.41, –0.05)**	–0.05(–0.23, 0.14)
P_{trend}	0.52	0.44	0.67	0.21	0.20	0.44	**0.01**	0.63
PM_{10} (T1 + T2)								
NO_2 (T1 + T2)	1.00	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
NO_2 (T3)	0.94(0.22, 3.94)	–0.37(–0.91, 0.17)	0.19(–0.03, 0.41)	0.02(–0.15, 0.19)	0.05(–0.15, 0.25)	0.004(–0.23, 0.23)	–0.07(–0.26, 0.12)	–0.16(–0.34, 0.01)
PM_{10} (T3)								
NO_2 (T1 + T2)	0.48(0.16, 1.47)	0.08(–0.46, 0.61)	–0.11(–0.31, 0.08)	–0.04(–0.19, 0.11)	–0.12(–0.31, 0.08)	0.03(–0.13, 0.19)	0.02(–0.11, 0.15)	–0.08(–0.24, 0.08)
NO_2 (T3)	1.27(0.44, 3.64)	–0.08(–0.57, 0.41)	0.03(–0.18, 0.24)	–0.08(–0.21, 0.06)	**–0.16(–0.30, –0.01)**	–0.01(–0.19, 0.18)	**–0.21*(–0.35, –0.08)**	–0.05(–0.22, 0.13)
P_{trend}	0.89	0.74	0.93	0.28	**0.04**	0.98	**0.01**	0.40

Generalized estimating equations were used to estimate aORs [for binary MoCA-T: ≥24 (normal) versus < 24 (impaired)] and β coefficients (continuous cognitive variables) adjusted for age, sex, years of education, *APOE ε4* status, history of smoking and drinking, depressive symptoms, body mass index, and follow-up time (baseline: 2011–2013; follow-up: 2015–2017). The numbers in bold indicate statistically significant findings ($p < 0.05$). *Results remained significant after correction for multiple tests by using false discovery rate. The annual average levels of the air pollutants in the study population and the corresponding air quality standards can be found in Supplementary Table 1. MoCA-T, Montreal Cognitive Assessment-Taiwanese version; aOR, adjusted odds ratio; CI, confidence interval; Ref, reference group; $PM_{2.5,}$ particulate matter ≤ 2.5 μm in diameter; $PM_{coarse,}$ particulate matter > 2.5–10 μm in diameter; $PM_{10,}$ particulate matter ≤ 10 μm in diameter; NO_2, nitrogen dioxide; ppb, parts per billion.

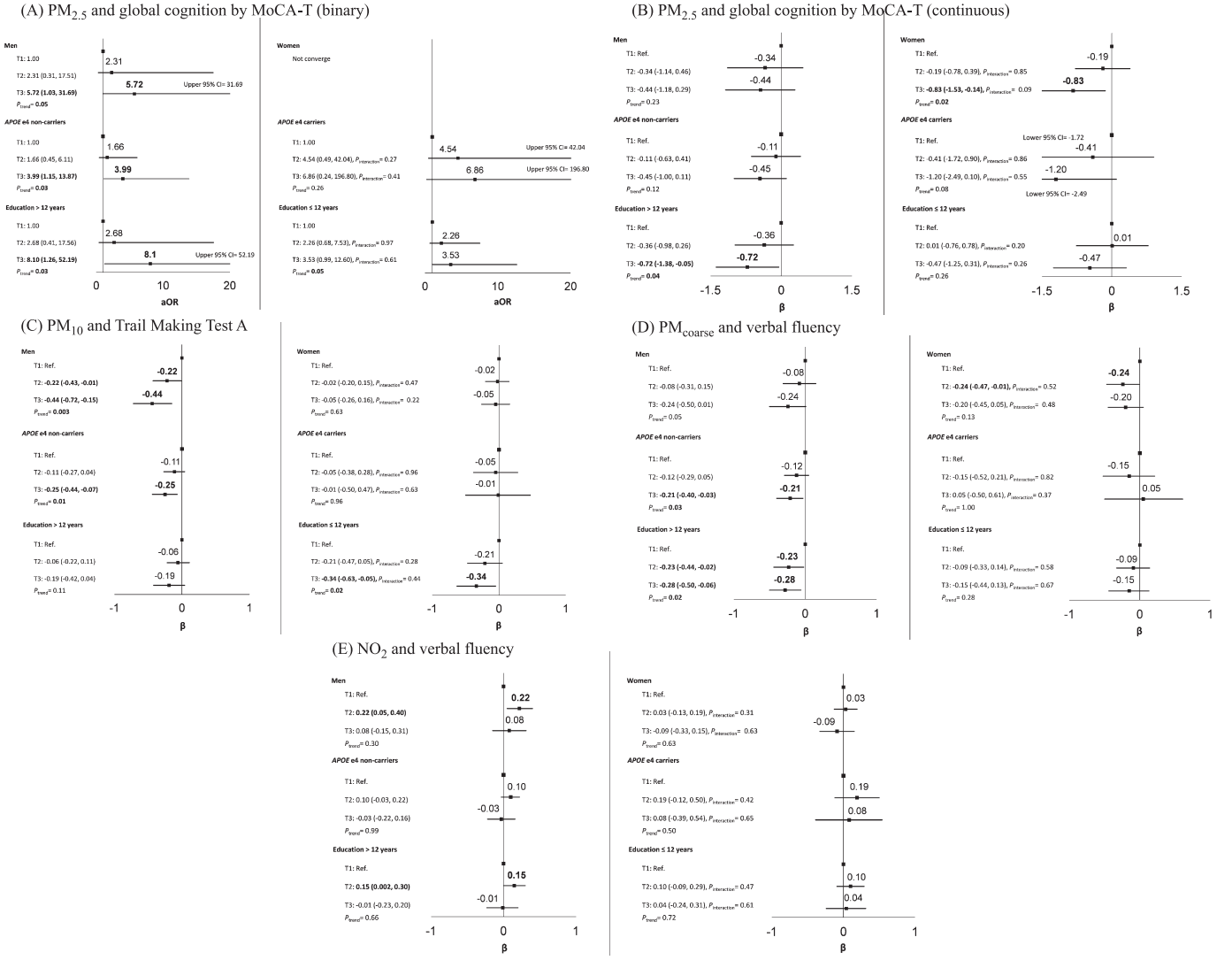

Fig. 4. Association between air pollutants and cognition over 4 years stratified by important variables ($N = 360$). A) $PM_{2.5}$ and global cognition by MoCA-T (binary), B) $PM_{2.5}$ and global cognition by MoCA-T (continuous), C) PM_{10} and Trail Making Test A, D) PM_{coarse} and verbal fluency, and E) NO_2 and verbal fluency. Numbers in bold indicated statistically significant findings ($p < 0.05$).

mance of verbal fluency was consistently affected by long-term PM_{coarse}, PM_{10}, and NO_2 exposure. Verbal fluency includes language, semantic memory, and executive function [47, 48] and is related to the prefrontal cortex (especially inferior frontal gyrus and middle frontal gyrus) of the brain [49, 50]. In sum, different air pollutants may be associated with either global or specific cognitive domains.

Air pollutants enter the human body through the olfactory bulb and nasal epithelial cells or via mechanical inhalation [6]. Some toxic compounds present on the surface of PM, such as manganese, polyaromatic hydrocarbons, and lipopolysaccharides, could affect the central nervous system through neurons directly or through the activation of microglial cells [46]. PM absorption could trigger the generation of proinflammatory cytokines and causes systematic or brain inflammation. The subsequent oxidative stress and its product, reactive oxygen species, can compromise the blood-brain barrier, which leads to the damage of neurons, the accumulation of Aβ, and the formation of senile plague, and subsequently affects cognitive function [46]. Instead of targeting specific cognitive domain(s), high-level $PM_{2.5}$ exposure may have moderate effect on each domain. However, the aggregated effect of $PM_{2.5}$ from all cognitive domains may explain the significant association between $PM_{2.5}$ exposure and the impairment of global cognition. In addition, Taiwan is an island country with subtropical climate, the high relative humidity may result in the adsorption of endotoxin on PM_{coarse} and PM_{10} [51], which may partially explain our findings on long-term PM_{10} or PM_{coarse} exposure affecting verbal fluency and executive function. Taken together, more studies are needed to clarify the toxicologic characteristics of air pollutants on different cognitive domains.

Our finding of 11-year $PM_{2.5}$ exposure with poor global cognition was consistent with previous studies (cohort studies: [8–14]; cross-sectional studies: [15–21]). In addition, we found that PM_{coarse} exposure was associated with poor verbal fluency. However, few studies explored verbal fluency in relation to PM_{coarse} exposure, and our finding was consistent with a previous cross-sectional study [17]. Furthermore, few studies explored executive function in relation to air pollution. We found that 23-year high-level PM_{10} exposure was associated with poor executive function, which was consistent with a previous cohort study [28], but the other cohort study did not observe an association [10]. The significant findings we found were in Trail Making Test A but not Test B. It is possible that participants with high-level exposure to air pollutant had slower response in Trail Making Test A. In addition, after the assessment using Trail Making Test A, participants become more familiar with this type of test, which may also explain the non-significant finding in Trail Making Test B. In addition, this study found that exposure to elevated PM_{coarse} or co-exposure to elevated PM_x and NO_2 were associated poor verbal fluency or poor executive function (especially for PM_{10} and NO_2 co-exposure), which should be attributable to the detrimental effect of PM_x exposure because NO_2 showed mild protective effect. Various brain areas have been related to the age-related decline in executive function (Trail Making Test), which include smaller grey matter volume in the dorsolateral and ventrolateral prefrontal cortex, medial prefrontal cortex, frontal pole, right inferior frontal gyrus, temporal lobe, insular cortex, caudate, globus pallidus, posterior parietal lobe, occipital cortex, and the cerebellum [52–54].

Furthermore, this study found that 23-year NO_2 exposure lower than TEPA standard was associated with better verbal fluency, which was inconsistent with limited previous studies (cross-sectional studies: [17, 18, 20]). Among these studies, one study found inversed association (cross-sectional study: [17]) and two other found no association (cross-sectional studies: [18, 20]) between NO_2 exposure and verbal fluency. Previous animal studies revealed that exposure to NO_2 has shown to generate excitotoxicity, which affects the synaptic plasticity [55] and resulted in the accumulation and formation of Aβ and senile plaque via nitrification [56]; the subsequent neuronal apoptosis then affects cognitive function [56]. The protective finding in our study may be due to the long-term NO_2 exposure lower than the TEPA standard and the following rationale. NO_2 may participate with nitrotyrosination in the brain [57], which was observed in AD brain [58]. However, moderate nitrotyrosination has also been found in healthy people [59–61], which implies low-level nitration is needed to maintain physiological function [57]. As a whole, more experimental studies are needed to clarify the underlying mechanism of NO_2 exposure on human brain.

This study has the following strengths. First, since the progression of dementia may take decades, the collection of long-term exposure data started before the commencement of this study (from 2005–2015 for $PM_{2.5}$ and PM_{coarse}; from 1993–2015 for PM_{10} and NO_2) and the design of cohort study allowed us to clarify the association between past exposure

to air pollutants and cognitive performance over four-year follow-up. Secondly, few studies explored cognitive domains; assessment tools were also highly heterogeneous. This study assessed both global and domain-specific cognition (i.e., memory, executive function, verbal fluency, and attention), which allowed us to identify the effect of air pollutants on different cognitive domain(s). Thirdly, to account for the fact that multiple air pollutants coexist in the ambient environment, our analysis on the association between single-pollutant and cognitive function adjusted for other air pollutants. Fourthly, few studies explored the effect of co-exposure to air pollutants on cognition-related outcomes; we also assessed the co-exposure to these pollutants to clarify possible synergistic effect. Our exposure data were estimated from BME, which used both spatial and temporal data to estimate individual exposure over time; change in residency during the exposure period were noted to improve the accuracy of exposure estimation. Last but not least, this study included *APOE* $\varepsilon 4$ status to assess important gene-environment interactions.

This study has some limitations; firstly, the study area was confined to Taipei metropolis, therefore, our findings may not be generalizable to other areas of Taiwan. Secondly, participation bias may occur because study participants were recruited from the health checkup program at baseline and tended to be healthier than the general population. However, after the four-year follow up, health status of these participants decreased and became similar to the general population. Therefore, we anticipate participation bias diminished over time in cohort studies [62, 63]. Thirdly, occupation before retirement may affect the association between exposure to air pollutants and the risk of cognitive impairment. After stratification by the occupational complexity, which was defined by Stern et al. [64] (low complexity: housewife, unskilled/semiskilled, skilled trade or craft, or clerical/office worker; high complexity: managerial, professional, or skilled workers), we found that the high-complexity group had similar findings with the whole population; the findings in the low-complexity group are less significant, especially in PM_{10} and NO_2 exposure (data not shown). It is possible that almost all participants had been retired while they were recruited into this cohort during 2011–2013. Therefore, the effect of occupation may be attenuated as the number of years since retirement increased. Fourthly, this study used quantiles to categorize the levels of air pollutants in part because the results from the pollutant as a continuous variable was not significant, which may be attributable to the annual average exposure levels of PM_{10}, and NO_2 being lower than TEPA standards. It is also possible that the study participants, all of whom are community-dwelling older adults, have better overall health status compared to hospitalized patients; therefore, per unit increase in exposure concentration may not have a significant impact on their cognitive performance. In addition, chunking the continuous variable into increments of 10 $\mu g/m^3$ also resulted in the majority of the data in a single category. Therefore, this study adopted the quantile approach for grouping the exposure. Lastly, despite the estimation of long-term exposure to air pollutants, this study was unable to identify the critical time period in which cognitive function is most severely affected by exposure to air pollutants.

In conclusion, this four-year prospective study found that long-term (11 years) exposure to $PM_{2.5}$ levels higher than the current TEPA guideline values was significantly associated with cognitive impairment, signaling that the reduction of emission resources may be helpful to lower the risk of cognitive related outcome. In our single-pollutant exposure scenario, long-term (23 years) exposure to ambient PM_{10} levels lower than the TEPA standards were associated poor cognitive function; co-exposure to both PM_{10} and NO_2 revealed the same association. Notably, because these non-significant associations occurred at exposure concentrations lower than air quality guidelines established by TEPA, our results indicate that lowering the current national air quality standards for both PM_{10} and NO_2 may be warranted in order to protect older adults from cognitive impairment. Equally important, the co-exposure of various air pollutants should be considered while evaluating the subsequent health outcomes in epidemiologic studies. Lastly, conducting prospective studies with long-term co-exposure period is suitable for exploring the association of air pollutants with cognitive function, which not only reflect the real-life exposure scenario to air pollutants but also allow us to clarify the effect of air pollution on the progression of cognitive impairment or dementia over time.

ACKNOWLEDGMENTS

This study was supported by the Ministry of Science and Technology in Taiwan (100-2314-B-002-103, 101-2314-B-002-126-MY3, 103-2314-B-002-033-MY3, and 104-2314-B-002-038-MY3, 107-2314-B-002-186-MY3, 107-2314-B-002-230,

108-2314-B-002-128-MY2) and a grant from Academia Sinica. We acknowledge Prof. Tsun-Jen Cheng's professional suggestions on neurotoxicology.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-0614r3).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD200614

REFERENCES

[1] Alzheimer's Association, 2020 Alzheimer's Disease Facts and Figures, https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf, Accessed May 11, 2020.

[2] Sun Y, Lee HJ, Yang SC, Chen TF, Lin KN, Lin CC, Wang PN, Tang LY, Chiu MJ (2014) A nationwide survey of mild cognitive impairment and dementia, including very mild dementia, in Taiwan. *PLoS One* **9**, e100303.

[3] World Health Organization, The Epidemiology and Impact of Dementia, https://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf, Accessed May 11, 2020.

[4] Harvey PD (2019) Domains of cognition and their assessment. *Dialogues Clin Neurosci* **21**, 227-237.

[5] Kelly FJ, Fussell JC (2012) Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. *Atmos Environ* **60**, 504-526.

[6] Underwood E (2017) The polluted brain. *Science* **355**, 342-345.

[7] Wu YC, Lin YC, Yu HL, Chen JH, Chen TF, Sun Y, Wen LL, Yip PK, Chu YM, Chen YC (2015) Association between air pollutants and dementia risk in the elderly. *Alzheimers Dement* **1**, 220-228.

[8] Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F (2012) Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med* **172**, 219-227.

[9] 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.

[10] Schikowski T, Vossoughi M, Vierkotter A, Schulte T, Teichert T, Sugiri D, Fehsel K, Tzivian L, Bae IS, Ranft U, Hoffmann B, Probst-Hensch N, Herder C, Kramer U, Luckhaus C (2015) Association of air pollution with cognitive functions and its modification by APOE gene variants in elderly women. *Environ Res* **142**, 10-16.

[11] Cacciottolo M, Wang X, Driscoll I, Woodward N, Saffari A, Reyes J, Serre ML, Vizuete W, Sioutas C, Morgan TE (2017) Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. *Transl Psychiatry* **7**, e1022.

[12] Tallon LA, Manjourides J, Pun VC, Salhi C, Suh H (2017) Cognitive impacts of ambient air pollution in the National Social Health and Aging Project (NSHAP) cohort. *Environ Int* **104**, 102-109.

[13] Wurth R, Kioumourtzoglou M-A, Tucker KL, Griffith J, Manjourides J, Suh H (2018) Fine particle sources and cognitive function in an older Puerto Rican cohort in Greater Boston. *Environ Epidemiol* **2**, e022.

[14] Kulick ER, Elkind MSV, Boehme AK, Joyce NR, Schupf N, Kaufman JD, Mayeux R, Manly JJ, Wellenius GA (2020) Long-term exposure to ambient air pollution, APOE-ε4 status, and cognitive decline in a cohort of older adults in northern Manhattan. *Environ Int* **136**, 105440.

[15] Ailshire JA, Crimmins EM (2014) Fine particulate matter air pollution and cognitive function among older US adults. *Am J Epidemiol* **180**, 359-366.

[16] Ailshire JA, Clarke P (2015) Fine particulate matter air pollution and cognitive function among U.S. older adults. *J Gerontol B Psychol Sci Soc Sci* **70**, 322-328.

[17] Tzivian L, Dlugaj M, Winkler A, Hennig F, Fuks K, Sugiri D, Schikowski T, Jakobs H, Erbel R, Jockel KH, 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. *J Toxicol Environ Health A* **79**, 1057-1069.

[18] Tzivian L, Dlugaj M, Winkler A, Weinmayr G, Hennig F, Fuks KB, Vossoughi M, Schikowski T, Weimar C, Erbel R, Jöckel KH, Moebus S, Hoffmann B (2016) Long-term air pollution and traffic noise exposures and mild cognitive impairment in older adults: A cross-sectional analysis of the Heinz Nixdorf Recall Study. *Environ Health Perspect* **124**, 1361-1368.

[19] Ailshire J, Karraker A, Clarke P (2017) Neighborhood social stressors, fine particulate matter air pollution, and cognitive function among older U.S. adults. *Soc Sci Med* **172**, 56-63.

[20] Tzivian L, Jokisch M, Winkler A, Weimar C, Hennig F, Sugiri D, Soppa VJ, Dragano N, Erbel R, Jockel KH, Moebus S, Hoffmann B (2017) Associations of long-term exposure to air pollution and road traffic noise with cognitive function-An analysis of effect measure modification. *Environ Int* **103**, 30-38.

[21] Salinas-Rodríguez A, Fernández-Niño JA, Manrique-Espinoza B, Moreno-Banda GL, Sosa-Ortiz AL, Qian ZM, Lin H (2018) Exposure to ambient PM2.5 concentrations and cognitive function among older Mexican adults. *Environ Int* **117**, 1-9.

[22] Jung CR, Lin YT, Hwang BF (2015) Ozone, particulate matter, and newly diagnosed Alzheimer's disease: A population-based cohort study in Taiwan. *J Alzheimers Dis* **44**, 573-584.

[23] Chen H, Kwong JC, Copes R, Hystad P, van Donkelaar A, Tu K, Brook JR, Goldberg MS, Martin RV, Murray BJ (2017) Exposure to ambient air pollution and the incidence of dementia: A population-based cohort study. *Environ Int* **108**, 271-277.

[24] Chen H, Kwong JC, Copes R, Tu K, Villeneuve PJ, van Donkelaar A, Hystad P, Martin RV, Murray BJ, Jessiman B, Wilton AS, Kopp A, Burnett RT (2017) Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: A population-based cohort study. *Lancet* **389**, 718-726.

[25] Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, Li W, Schwartz J, Koutrakis P, DeCarli C (2015) Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. *Stroke* **46**, 1161-1166.

[26] Gatto NM, Henderson VW, Hodis HN, St John JA, Lurmann F, Chen JC, Mack WJ (2014) Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. *Neurotoxicology* **40**, 1-7.

[27] Lo YTC, Lu YC, Chang YH, Kao S, Huang HB (2019) Air pollution exposure and cognitive function in Taiwanese older adults: A repeated measurement study. *Int J Environ Res Public Health* **16**, 2976.
[28] Ranft U, Schikowski T, Sugiri D, Krutmann J, Krämer U (2009) Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environ Res* **109**, 1004-1011.
[29] Chang KH, Chang MY, Muo CH, Wu TN, Chen CY, Kao CH (2014) Increased risk of dementia in patients exposed to nitrogen dioxide and carbon monoxide: A population-based retrospective cohort study. *PLoS One* **9**, e103078.
[30] Li CY, Li CH, Martini S, Hou WH (2019) Association between air pollution and risk of vascular dementia: A multipollutant analysis in Taiwan. *Environ Int* **133**, 105233.
[31] Chen JH, Lin KP, Chen YC (2009) Risk factors for dementia. *J Formos Med Assoc* **108**, 754-764.
[32] Tsai CF, Lee WJ, Wang SJ, Shia BC, Nasreddine Z, Fuh JL (2012) Psychometrics of the Montreal Cognitive Assessment (MoCA) and its subscales: Validation of the Taiwanese version of the MoCA and an item response theory analysis. *Int Psychogeriatr* **24**, 651-658.
[33] Wechsler D (1997) *Wechsler Memory Scale for Adults, 3rd Ed*, Psychological Corporation, San Antonio, TX.
[34] Nooyens AC, Baan CA, Spijkerman AM, Verschuren WM (2010) Type 2 diabetes and cognitive decline in middle-aged men and women: The Doetinchem Cohort Study. *Diabetes Care* **33**, 1964-1969.
[35] Environmental Protection Administration Executive Yuan R.O.C (Taiwan), Taiwan air quality monitoring network, https://airtw.epa.gov.tw/ENG/default.aspx, Accessed May 11, 2020.
[36] Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, Nordin S, Adolfsson R, Nilsson LG (2016) Traffic-related air pollution and dementia incidence in Northern Sweden: A longitudinal study. *Environ Health Perspect* **124**, 306-312.
[37] Cleary EG, Cifuentes M, Grinstein G, Brugge D, Shea TB (2018) Association of low-level ozone with cognitive decline in older adults. *J Alzheimers Dis* **61**, 67-78.
[38] Carey IM, Anderson HR, Atkinson RW, Beevers SD, Cook DG, Strachan DP, Dajnak D, Gulliver J, Kelly FJ (2018) Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. *BMJ Open* **8**, e022404.
[39] Yu HL, Wang CH, Liu MC, Kuo YM (2011) Estimation of fine particulate matter in Taipei using landuse regression and bayesian maximum entropy methods. *Int J Environ Res Public Health* **8**, 2153-2169.
[40] Christakos G, Hristopulos D (1998) *Spatiotemporal environmental health modelling: A tractatus stochasticus*, Springer US.
[41] Christakos G, Serre ML (2000) BME analysis of spatiotemporal particulate matter distributions in North Carolina. *Atmos Environ* **34**, 3393-3406.
[42] Christakos G, Bogaert P, Serre M (2001) *Tmeporal GIS*: Advanced Functions for Field-Based Applications. Springer-Verlag Berlin Heidelberg.
[43] Yu HL, Wang CH (2010) Retrospective prediction of intraurban spatiotemporal distribution of PM2.5 in Taipei. *Atmos Environ* **44**, 3053-3065.
[44] Yu HL, Ku SC, Kolovos A (2016) A GIS tool for spatiotemporal modeling under a knowledge synthesis framework. *Stoch Envrion Res Risk Assess* **30**, 665-679.
[45] Yu HL, Ku SJ, Kolovos A (2012) Advanced space-time predictive analysis with STAR-BME. *Proceedings of the 20th International Conference on Advances in Geographic Information Systems*, 593-596.
[46] Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, Cory-Slechta DA, Costa D, Diaz-Sanchez D, Dorman DC, Gold DR, Gray K, Jeng HA, Kaufman JD, Kleinman MT, Kirshner A, Lawler C, Miller DS, Nadadur SS, Ritz B, Semmens EO, Tonelli LH, Veronesi B, Wright RO, Wright RJ (2012) The outdoor air pollution and brain health workshop. *Neurotoxicology* **33**, 972-984.
[47] Mueller KD, Koscik RL, LaRue A, Clark LR, Hermann B, Johnson SC, Sager MA (2015) Verbal fluency and early memory decline: Results from the Wisconsin Registry for Alzheimer's Prevention. *Arch Clin Neuropsychol* **30**, 448-457.
[48] Whiteside DM, Kealey T, Semla M, Luu H, Rice L, Basso MR, Roper B (2016) Verbal fluency: Language or executive function measure? *Appl Neuropsych Adult* **23**, 29-34.
[49] Gaillard WD, Sachs BC, Whitnah JR, Ahmad Z, Balsamo LM, Petrella JR, Braniecki SH, McKinney CM, Hunter K, Xu B, Grandin CB (2003) Developmental aspects of language processing: fMRI of verbal fluency in children and adults. *Hum Brain Mapp* **18**, 176-185.
[50] Costafreda SG, Fu CHY, Lee L, Everitt B, Brammer MJ, David AS (2006) A systematic review and quantitative appraisal of fMRI studies of verbal fluency: Role of the left inferior frontal gyrus. *Hum Brain Mapp* **27**, 799-810.
[51] Huang KL, Liu SY, Chou CC, Lee YH, Cheng TJ (2017) The effect of size-segregated ambient particulate matter on Th1/Th2-like immune responses in mice. *PLoS One* **12**, e0173158.
[52] Newman LM, Trivedi MA, Bendlin BB, Ries ML, Johnson SC (2007) The relationship between gray matter morphometry and neuropsychological performance in a large sample of cognitively healthy adults. *Brain Imaging Behav* **1**, 3-10.
[53] Pa J, Possin KL, Wilson SM, Quitania LC, Kramer JH, Boxer AL, Weiner MW, Johnson JK (2010) Gray matter correlates of set-shifting among neurodegenerative disease, mild cognitive impairment, and healthy older adults. *J Int Neuropsychol Soc* **16**, 640-650.
[54] Ruscheweyh R, Deppe M, Lohmann H, Wersching H, Korsukewitz C, Duning T, Bluhm S, Stehling C, Keller SS, Knecht S (2013) Executive performance is related to regional gray matter volume in healthy older individuals. *Hum Brain Mapp* **34**, 3333-3346.
[55] Li H, Xin X (2013) Nitrogen dioxide (NO(2)) pollution as a potential risk factor for developing vascular dementia and its synaptic mechanisms. *Chemosphere* **92**, 52-58.
[56] Kummer MP, Hermes M, Delekarte A, Hammerschmidt T, Kumar S, Terwel D, Walter J, Pape HC, Konig S, Roeber S, Jessen F, Klockgether T, Korte M, Heneka MT (2011) Nitration of tyrosine 10 critically enhances amyloid beta aggregation and plaque formation. *Neuron* **71**, 833-844.
[57] Picon-Pages P, Garcia-Buendia J, Munoz FJ (2019) Functions and dysfunctions of nitric oxide in brain. *Biochim Biophys Acta Mol Basis Dis* **1865**, 1949-1967.
[58] Smith MA, Richey Harris PL, Sayre LM, Beckman JS, Perry G (1997) Widespread peroxynitrite-mediated damage in Alzheimer's disease. *J Neurosci* **17**, 2653-2657.
[59] Ill-Raga G, Palomer E, Ramos-Fernandez E, Guix FX, Bosch-Morato M, Guivernau B, Tajes M, Valls-Comamala V, Jimenez-Conde J, Ois A, Perez-Asensio F, Reyes-Navarro M, Caballo C, Gil-Gomez G, Lopez-Vilchez I, Galan AM, Alameda F, Escolar G, Opazo C, Planas AM, Roquer J, Valverde MA, Munoz FJ (2015) Fibrinogen nitrotyrosination after ischemic stroke impairs thrombol-

ysis and promotes neuronal death. *Biochim Biophys Acta* **1852**, 421-428.

[60] Guix FX, Wahle T, Vennekens K, Snellinx A, Chavez-Gutierrez L, Ill-Raga G, Ramos-Fernandez E, Guardia-Laguarta C, Lleo A, Arimon M, Berezovska O, Munoz FJ, Dotti CG, De Strooper B (2012) Modification of gamma-secretase by nitrosative stress links neuronal ageing to sporadic Alzheimer's disease. *EMBO Mol Med* **4**, 660-673.

[61] Ramos-Fernandez E, Tajes M, Palomer E, Ill-Raga G, Bosch-Morato M, Guivernau B, Roman-Degano I, Eraso-Pichot A, Alcolea D, Fortea J, Nunez L, Paez A, Alameda F, Fernandez-Busquets X, Lleo A, Elosua R, Boada M, Valverde MA, Munoz FJ (2014) Posttranslational nitroglycative modifications of albumin in Alzheimer's disease: Implications in cytotoxicity and amyloid-beta peptide aggregation. *J Alzheimers Dis* **40**, 643-657.

[62] Benfante R, Reed D, MacLean C, Kagan A (1989) Response bias in the Honolulu Heart Program. *Am J Epidemiol* **130**, 1088-1100.

[63] Strotmeyer ES, Arnold AM, Boudreau RM, Ives DG, Cushman M, Robbins JA, Harris TB, Newman AB (2010) Long-term retention of older adults in the Cardiovascular Health Study: Implications for studies of the oldest old. *J Am Geriatr Soc* **58**, 696-701.

[64] Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R (1994) Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* **271**, 1004-1010.