Air Pollution Associated with Cognitive Decline by the Mediating Effects of Sleep Cycle Disruption and Changes in Brain Structure in Adults

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Abstract

The effects of air pollution on sleep and dementia remain unclear. The objective of this study was to investigate the effects of air pollution on cognitive function as mediated by the sleep cycle. A cross-sectional study design was conducted to recruit 4866 subjects on which PSG had been performed. Fifty of them were further given a cognitive function evaluation by the MMSE and CASI as well as brain images by CT and MRI. Associations of 1-year air pollution parameters with sleep parameters, cognitive function, and brain structure were examined. We observed that O_3 was associated with a decrease in arousal, an increase in the N1 stage, and a decrease in the N2 stage of sleep. NO_2 was associated with an increase in the N1 stage, a decrease in the N2 stage, and an increase in REM. $PM_{2.5}$ was associated with a decrease in the N1 stage, increases in the N2 and N3 stages, and a decrease in REM. The N1 and N2 stages were associated with cognitive decline, but REM was associated with an increase in cognitive function. The N1 stage was a mediator of the effects of $PM_{2.5}$ on the concentration domain of the MMSE. O_3 was associated with an increase in the pars orbitalis volume of the left brain. NO_2 was associated with increases in the rostral middle frontal volume, supramarginal gyrus volume, and transverse temporal volume of the left brain, and the pars opercularis volume of the right brain. $PM_{2.5}$ was associated with increases in the pars triangularis volume of the left brain and the fusiform thickness of the right brain. In conclusion, we observed that air pollution was associated with cognitive decline by mediating effects on the sleep cycle with changes in the brain structure in controlling executive, learning, and language functions in adults.

Capsule Of Main Finding

The significance and novelty of this study was that air pollution was associated with cognitive decline by mediating effects on the sleep cycle with changes in brain structure in adults, thereby could increase the risks of dementia.

1. Introduction

Dementia is a group of symptoms of decreasing cognitive function and changes in functional abilities, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. There were 35.6 million people suffering from dementia worldwide in 2010, and this number is increasing by 7.7 million new cases per year (Wortmann, 2012). A clinical diagnosis of dementia is based on a patient's history, symptoms, neurological evaluations, brain scans, and laboratory tests. Recent studies showed that sleep quality (Boothby et al., 1994), cardiovascular diseases, and genetic factors (Hardy, 1996) are major risk factors for dementia.

People spend one-third of their lives sleeping, and sleep is associated with memory consolidation (Diekelmann and Born, 2010) and the cleaning out of metabolic waste products from the brain (Xie et al., 2013). Sleep can be categorized into rapid-eye-movement (REM) and non-REM (NREM) stages. NREM stages are inactive sleep, which can be divided into the N1, N2, and N3 stages. The first sleep stage, N1,

occurs in normal adolescent sleep, which is light sleep. Stage N2 has k complexes and sleep spindles, which function in memory consolidation. Stage N3 is also called deep sleep, which refreshes the body and plays a role in memory consolidation. The REM stage is active sleep in which dreams occur, which benefits memory and learning (Shatzmiller et al., 2010). Our previous reports showed that air pollution was associated with disruption of the sleep cycle in obstructive sleep apnea (OSA) patients (Lo et al., 2021; Tung et al., 2021b). For example, interquartile range (IQR) increases in 1-month particulate matter with an aerodynamic diameter of <2.5 μm ($PM_{2.5}$) and carbon monoxide (CO) levels were associated with a 6.2% (95% confidence interval (CI): 6.1%~6.3%) increase in the N1 stage and 2.0% (95% CI: -3.8%~-0.1%) decrease in the N2 stage. Taken together, air pollution could be a risk factor for disrupting the sleep cycle during sleep.

Previous reports indicated that long-time exposure to $PM_{2.5}$, PM_{10}, and nitrogen dioxide (NO_2) was associated with reductions in sleep quality and sleep efficiency, and increased the risk of sleep apnea (Billings et al., 2019a; Shen et al., 2018). For example, higher levels of PM_{10} were associated with an increased risk of the apnea-hypopnea index (AHI) (Yildiz Gulhan et al., 2020). Short-term exposure to PM_{10} in summer was significantly associated with increases in the respiratory disturbance index (RDI) and the number of instances of desaturation (Zanobetti et al., 2010). In Taiwan, exposure to $PM_{2.5}$ increased the AHI and oxygen desaturation index (ODI) (Shen et al., 2018). An animal study suggested that exposure to 1.5 ppm O_3 produced a linear increase in slow wave sleep and a decrease in the wake duration in rats (Paz and Huitrón-Reséndiz, 1996).

Recent studies revealed that air pollution was associated with cognitive function, dementia, and neuropsychological diseases (Schikowski and Altug, 2020). A longitudinal study of 1806 participants in northern Sweden observed that indoor nitrogen oxides (NOx) were associated with an increased risk of dementia (Oudin et al., 2016). A study in Taiwan indicated that NO_2 and CO were associated with an increased risk of vascular dementia (Li et al., 2019). A cross-sectional study conducted in Southern California showed that NO_2, $PM_{2.5}$, and O_3 were associated with declines in cognitive functions in middle-aged and older people (Gatto et al., 2014). Epidemiological evidence revealed the association of air pollution with sleep or dementia; however, the effects of air pollution on cognitive function via regulation of the sleep cycle remain unclear. The objective of this study was to investigate the associations of air pollution with cognitive function via the sleep cycle.

2. Materials And Methods

2.1. Ethical considerations

This study was approved by the Taipei Medical University-Joint Institution Review Board (TMU-JIRB no. N201910048) (Taipei, Taiwan). The methods were carried out in accordance with the approved protocol.

2.2. Study population

A cross-sectional study design was conducted in this research. There were 4866 subjects recruited for this study from January 2015 to April 2019 at a sleep center of a local hospital (New Taipei City, Taiwan). Inclusion criteria were subjects who completed 1-night polysomnography (PSG) and were aged 20~80 years. In addition, 50 subjects who met the above inclusion criteria were given the Mini-Mental State Examination (MMSE) and Cognitive Abilities Screening Instrument (CASI) questionnaires and also underwent brain magnetic resonance imaging (MRI) and computed tomographic (CT) studies. The exclusion criteria were subjects currently using continuous positive airway pressure (CPAP) or uvulopalatopharyngoplasty, had had a tonsillectomy or adenoidectomy, were pregnant, had a fever, regularly consumed alcohol, had a pulmonary disease with oxygen therapy, had a kidney disease on hemodialysis, or had an unstable disease. Basic demographic data were collected, including age, gender, weight in kilograms (kg), height in centimeters (cm), body-mass index (BMI; in kg/m^2), neck circumference (cm), waist circumference (cm), residential address, comorbidities, and the date that they had undergone PSG.

2.3. Air pollution exposure

The geographic distribution of study subjects is shown in Figure S1. Individual-level exposure to air pollutants ($PM_{2.5}$, NO_2, and O_3) was estimated by a hybrid kriging-land-use regression (LUR) approach, which was described in previous studies (Chen et al., 2020; Wu et al., 2018). Briefly, air pollutant data were collected from 71 Taiwan Environmental Protection Administration air quality monitoring stations to develop the prediction model. The Environment Resource Database, Point of Interest, Land use Investigation of Taiwan, Traffic Network Digital Map, Digital Terrain Model, Industrial Development Bureau Database, and Normalized Difference Vegetation Index were used to construct the model. Also, the regression model considered the traffic intensity, weather, population density, industry emissions, elevation, vegetation distribution, the number of temples, and the number of restaurants to calculate residential air pollution levels. Daily $PM_{2.5}$, NO_2, and O_3 concentrations were then aggregated into annual average concentrations for model development. Land-use predictors with a value of Spearman's correlation coefficient of >0.4 with an effect on air pollutants were entered into a stepwise linear regression. Furthermore, a set of pollutant levels was created through a leave-one-out kriging interpolation and added to the LUR model to improve its performance.

2.4. Sleep parameters

One-night sleep parameters were recorded using a digital PSG system (Embla N7000, Medcare, Reykjavik, Iceland) followed by analysis with Somnologica (Medcare). Sleep parameters were re-evaluated by a sleep technician according to AASM criteria (Ruehland et al., 2009). Clinical characteristics for sleep parameters obtained included the total sleep time (TST), sleep efficiency, waking after sleep onset (WASO), arousal, arterial oxygen saturation (SaO_2), the 3% oxygen desaturation index (ODI) and AHI. The definition of hypopnea was nasal airflow decreasing 30%~89% for at least 10 s with arousal or at least 3% desaturation. The definition of apnea was oral airflow reduced by >90% for at least 10 s with or without arousal or desaturation. The AHI (events/h) was the number of hypopneic plus apneic events divided by the TST. Sleep efficiency was defined as the TST divided by time in bed multiplied by 100%.

Waking after sleep onset (WASO) was defined as the duration of awake time after sleep onset. The arousal index was defined as the total number of arousals during sleep. For the sleep cycle, percentages of the TST in NREM sleep stage I (N1%), of the TST in NREM sleep stage II (N2%), of the TST in NREM sleep stage III (N3%), and of the TST in the REM sleep stage (REM%) were collected.

2.5. Cognitive function

The MMSE and CASI (C-2.0) questionnaires were used to evaluate the cognitive function of study subjects. Six cognitive domains were evaluated by the MMSE, including orientation (ranging 0~10), memory registration (0~3), concentration (0~5), delayed recall memory (0~3), language (0~8), and construction 0~1). The total score ranged 0~30. The CASI evaluated nine cognitive domains, including attention (ranging 0~8), orientation 0~18), short-term memory (0~12), long-term memory (0~10), language abilities (0~10), mental manipulation (0~10), verbal fluency (0~10), abstract thinking (0~12), and drawing (0~10), which was estimated by 25 items. The total score ranged 0~100. Scores of the CASI and MMSE decrease with an increasing severity of cognitive impairment (Teng et al., 1994).

2.6. Brain structure

After evaluating cognitive function, the brain pathology of subjects was further examined using brain CT and MRI. CT imaging was performed with a GE Discovery CT750 HD scanner (General Electric, Milwaukee, WI, USA). The CT protocol for subjects was scanning at 240 mAs and 120 kV exposure, and each volumetric scan was made with a total exposure time of 7 min. The reconstructed images had 512 × 512 × 32 voxels with voxel sizes of 0.488 × 0.488 × 5.0 mm. Avizo vers. 7.0 was applied to create three-dimensional models and perform quantitative analysis of white matter changes (WMCs) and gray matter changes (GMCs). Parameters of two-dimensional T1-weighted fluid-attenuated inversion recovery MRI images were as follows: a repetition time of 2132 ms, echo time of 24 ms, auto inverse time of 772 ms, slice thickness of 5 mm, spacing of 2 mm, flip angle of 160°, pixel bandwidth of 208.3 Hz/pixel, bandwidth of 31.25 kHz, matrix size of 300 · 240, field of view of 230 mm, number of excitations of 1.5, and an acquisition time of 1 min 55 s. FreeSurfer vers. 6.0 was used to calculate the volumes and thicknesses of various brain regions on brain MRI images, including the caudal anterior cingulate, caudal middle frontal, cuneus, entorhinal, fusiform, inferior parietal, inferior temporal, isthmus cingulate, lateral occipital, lateral orbitofrontal, lingual, medial orbitofrontal, middle temporal, para hippocampal, paracentral, pars opercularis, pars orbitalis, pars triangularis, peri calcarine, postcentral, posterior cingulate, precentral, precuneus, rostral anterior cingulate, rostral middle frontal, superior frontal, superior parietal, superior temporal, supramarginal, transverse temporal, and insula in the right and left cortices.

2.7. Statistical analyses

All data of air pollution exposure and PSG parameters were treated as continuous variables. To minimize the influence of severe outliers and better achieve a normal distribution of the residuals for PSG parameters, we replaced the extreme low and high values outside of the 1 and 99 percentiles, respectively, using a winsorization approach (Tsai et al., 2012). A normality test was conducted to examine if the data were normally distributed. A linear regression analysis was used to examine associations of 1-year

average levels of O_3, NO_2, and $PM_{2.5}$ with sleep parameters, cognitive function, and brain structures. Covariates for air pollution with sleep parameters were adjusted for age, sex, and the BMI; covariates for air pollution with cognitive function and brain structure were adjusted for educational level. We examined the mediating effect of the sleep cycle between air pollution and cognitive domains with PROCESS. The effects of pollution on sleep parameters, cognitive function, and brain structure were expressed as an estimated regression coefficient (β) multiplied by the IQR of each air pollution (O_3, NO_2, and $PM_{2.5}$). Data were analyzed using R vers. 3.6.1 for linear regressions and SPSS vers. 26 for the PROCESS mediation analysis. Statistical significance was set to $p<0.05$.

3. Results

3.1. Characteristics of study subjects

Participants' baseline demographic characteristics are summarized in Table 1. The mean age of subjects was 49.5 ± 13.3 years, with 68.8% males. The BMI, neck circumference, and waist circumference were 26.9 ± 4.8 kg/m^2, 37.8 ± 6.9 cm, and 91.7 ± 17.6 cm, respectively. The educational level was 9.7 ± 4.4 years. The sleep efficiency for these subjects was 67.9% ± 20.3%, whereas the WASO was 89.1 ± 63.2 min. The arousal index, SaO_2, 3% ODI, and AHI were 20.1 ± 11.4 events/h, 96.1% ± 1.4%, 21.9 ± 15.3 events/h, and 22.2 ± 15.9 events/h, respectively. Subjects had the highest N2 stage of total sleep (72.0% ± 13.7%), followed by N1 (15.3% ± 15.0%) and REM (11.7% ± 7.7%). As to cognitive functions measured by the MMSE and CASI, we observed the total scores were 23.9 ± 4.3 and 79.8 ± 12.0, respectively. One-year average O_3, NO_2, and $PM_{2.5}$ concentrations were 24.2 ppb, 18.2 ppb, and 28.7 μg/m^3, respectively.

Table 1
Basic characteristics, sleep measures, cognitive function, and air pollution in the study subjects

	All patients (N=4866)
Basic characteristics	
Age (yr)	49.5 ± 13.3
Male (%)	3348 (68.8)
BMI (kg/m^2)	26.9 ± 4.8
Neck (cm)	37.8 ± 6.9
Waist (cm)	91.7 ± 17.6
Education (yr)	9.7 ± 4.4
Sleep parameters	
Total Sleep Time (hr)	4.1 ± 1.2
Sleep Efficiency (%)	67.9 ± 20.3
WASO (min)	89.1 ± 63.2
Arousal Index (events/hr)	20.1 ± 11.4
Mean SaO_2 (%)	96.1 ± 1.4
3% ODI (events/hr)	21.9 ± 15.3
AHI (events/hr)	22.2 ± 15.9
Sleep cycle of total sleep time	
N1 (%)	15.3 ± 15.0
N2 (%)	72.0 ± 13.7
N3 (%)	0.9 ± 2.7
REM (%)	11.7 ± 7.7
Cognitive function (N=50)	
MMSE (range)	
Total score (0-30)	23.9 ± 4.3

Definition of abbreviations: AHI, apnea-hypopnea index; CASI, Cognitive Abilities Screening Instrument; IQR, interquartile range; MMSE, Mini-Mental State Examination; NO_2, nitrogen dioxide; ODI, oxygen desaturation index; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤ 2.5 μm; REM, rapid eye movement; SaO_2, arterial oxygen saturation measured by pulse oximetry; WASO, waking after sleep onset.

	All patients (N=4866)
Orientation (0-10)	8.5 ± 2.0
Memory registration (0-3)	2.9 ± 0.5
Concentration (0-5)	3.7 ± 1.5
Delayed recall memory (0-3)	1.7 ± 1.0
Language (0-8)	6.5 ± 1.2
Construction (0-1)	0.7 ± 0.5
CASI (range)	
Total score (0-100)	79.8 ± 12.0
Orientation (0-18)	15.1 ± 3.7
Long-term memory (0-10)	9.5 ± 1.0
Short-term memory (0-12)	8.4 ± 3.0
Attention (0-8)	6.3 ± 1.3
Mental manipulation (0-10)	7.4 ± 2.5
Abstract thinking (0-12)	8.6 ± 2.0
Language (0-10)	9.2 ± 1.0
Drawing (0-10)	8.9 ± 2.3
Verbal fluency (0-10)	6.3 ± 2.3
Air pollution, mean (IQR)	
O_3, ppb	24.3 (1.0)
NO_2, ppb	18.2 (2.2)
$PM_{2.5}$, μg/m^3	28.7 (3.8)

Definition of abbreviations: AHI, apnea-hypopnea index; CASI, Cognitive Abilities Screening Instrument; IQR, interquartile range; MMSE, Mini-Mental State Examination; NO_2, nitrogen dioxide; ODI, oxygen desaturation index; O_3, ozone; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤ 2.5 μm; REM, rapid eye movement; SaO_2, arterial oxygen saturation measured by pulse oximetry; WASO, waking after sleep onset.

3.2. Associations between air pollution and sleep parameters

Associations of air pollution with sleep parameters are shown in Figure 1. We observed that an IQR increase in O_3 was associated with a decrease of 0.046 events/h in arousal (95% CI: -0.083~-0.009, p<0.05), an 0.122% increase in the N1 stage (95% CI: 0.085~0.160, p<0.05), and a 0.131% decrease in the N2 stage (95% CI: -0.170~-0.092, p<0.05). An IQR increase in NO_2 was associated with a 0.215% increase in the N1 stage (95% CI: 0.148~0.282, p<0.05), a 0.368% decrease in the N2 stage (95% CI: -0.437~-0.299, p<0.05), and a 0.202% increase in the REM stage (95% CI: 0.132~0.271, p<0.05). Also, an IQR increase in $PM_{2.5}$ was associated with a 0.736% decrease in the N1 stage (95% CI: -0.856~-0.617, p<0.05), a 0.827% increase in the N2 stage (95% CI: 0.703~0.950, p<0.05), a 0.129% increase in the N3 stage (95% CI: 0.010~0.248, p<0.05), and a 0.437% decrease in the REM stage (95% CI: -0.562~-0.312, p<0.05).

3.3. Associations between the sleep cycle and cognitive function

Associations of the sleep cycle with cognitive function as measured by the MMSE and CASI are shown in Table 2. We found that a 10-min increase in wake duration was associated with a 0.365-point decrease in the construction score of the MMSE (95% CI: -0.660~-0.070, p<0.05) and a 0.304-point decrease in the verbal fluency score of the CASI (95% CI: -0.601~-0.006, p<0.05). An increase in 1% of the N1 stage was associated with a 0.420-point decrease in the total MMSE score (95% CI: -0.725~0.115, p<0.05), a 0.411-point decrease in the orientation score of the MMSE (95% CI: -0.722~0.101, p<0.05), and a 0.429-point decrease in the concentration score of the MMSE (95% CI: -0.725~-0.132, p<0.05). An increase in 1% of the N2 stage was associated with a 0.322-point decrease in the language score of the CASI (95% CI: -0.629~-0.015, p<0.05). An increase in 1% of the REM stage was associated with a 0.468-point increase in the total MMSE score (95% CI: 0.193~0.743, p<0.05), a 0.300-point increase in the orientation score of the MMSE (95% CI: < 0.000~0.600, p<0.05), a 0.344-point increase in the concentration score of the MMSE (95% CI: 0.059~0.629, p<0.05), a 0.345-point increase in the language score of the MMSE (95% CI: 0.058~0.631, p<0.05), a 0.302-point increase in the abstract thinking score of the CASI (95% CI: 0.009~0.595, p<0.05), and a 0.458-point increase in the verbal fluency score of the CASI (95% CI: 0.184~0.732, p<0.05).

Table 2
Associations between percent changes in cognitive function scores and the sleep cycle

Percent change in sleep parameters (95% CI)					
Cognitive function	Wake, min	N1, %	N2, %	N3, %	REM, %
MMSE (range)					
Total score (0-30)	-0.178 (-0.487 - 0.131)	**-0.42* (-0.725 - -0.115)**	0.177 (-0.145 - 0.498)	-0.112 (-0.433 - 0.209)	**0.468* (0.193 - 0.743)**
Orientation (0-10)	0.055 (-0.262 - 0.373)	**-0.411* (-0.722 - -0.101)**	0.271 (-0.048 - 0.59)	-0.107 (-0.431 - 0.218)	**0.300* (0 - 0.6)**
Memory registration (0-3)	-0.219 (-0.516 - 0.079)	**-0.323* (-0.629 - -0.017)**	0.247 (-0.06 - 0.555)	0.108 (-0.204 - 0.42)	0.117 (-0.182 - 0.416)
Concentration (0-5)	-0.065 (-0.372 - 0.242)	**-0.429* (-0.725 - -0.132)**	0.256 (-0.053 - 0.565)	-0.076 (-0.391 - 0.239)	**0.344* (0.059 - 0.629)**
Delayed recall memory (0-3)	-0.213 (-0.519 - 0.093)	-0.058 (-0.387 - 0.271)	-0.097 (-0.42 - 0.225)	0.005 (-0.316 - 0.326)	0.256 (-0.043 - 0.554)
Language (0-8)	-0.245 (-0.546 - 0.055)	-0.082 (-0.407 - 0.243)	-0.091 (-0.41 - 0.229)	-0.186 (-0.499 - 0.127)	**0.345* (0.058 - 0.631)**
Construction (0-1)	**-0.365* (-0.66 - -0.07)**	-0.109 (-0.439 - 0.221)	-0.043 (-0.369 - 0.283)	-0.044 (-0.367 - 0.279)	0.27 (-0.03 - 0.569)
CASI (range)					
Total score (0-100)	-0.037 (-0.343 - 0.269)	-0.122 (-0.442 - 0.199)	-0.017 (-0.334 - 0.3)	-0.164 (-0.475 - 0.146)	0.288 (-0.001 - 0.576)

*p<0.05. REM, rapid eye movement; MMSE, Mini-Mental State Examination; CASI, Cognitive Abilities Screening Instrument.

Percent change in sleep parameters (95% CI)					
Orientation (0-18)	0.06 (-0.228 - 0.349)	-0.016 (-0.32 - 0.288)	-0.056 (-0.355 - 0.242)	-0.056 (-0.352 - 0.24)	0.136 (-0.146 - 0.417)
Long term memory (0-10)	-0.007 (-0.317 - 0.304)	0.199 (-0.122 - 0.521)	-0.251 (-0.564 - 0.061)	-0.072 (-0.39 - 0.247)	0.088 (-0.218 - 0.393)
Short term memory (0-12)	-0.212 (-0.519 - 0.095)	-0.028 (-0.358 - 0.302)	-0.102 (-0.425 - 0.221)	-0.135 (-0.455 - 0.184)	0.257 (-0.042 - 0.556)
Attention (0-8)	0.127 (-0.172 - 0.427)	-0.171 (-0.484 - 0.143)	0.111 (-0.2 - 0.421)	-0.131 (-0.438 - 0.176)	0.156 (-0.138 - 0.449)
Mental manipulation (0-10)	0.214 (-0.098 - 0.526)	-0.264 (-0.59 - 0.061)	0.251 (-0.07 - 0.572)	-0.151 (-0.475 - 0.172)	0.095 (-0.218 - 0.407)
Abstract thinking (0-12)	-0.084 (-0.395 - 0.226)	-0.179 (-0.503 - 0.145)	0.042 (-0.281 - 0.365)	-0.199 (-0.513 - 0.116)	**0.302*** **(0.009 - 0.595)**
Language (0-10)	-0.057 (-0.367 - 0.254)	0.198 (-0.124 - 0.52)	**-0.322*** **(-0.629 - -0.015)**	-0.211 (-0.524 - 0.102)	0.247 (-0.05 - 0.544)
Drawing (0-10)	-0.214 (-0.52 - 0.092)	-0.034 (-0.363 - 0.295)	-0.085 (-0.408 - 0.238)	0.099 (-0.22 - 0.419)	0.164 (-0.14 - 0.468)
Verbal fluency (0-10)	**-0.304*** **(-0.601 - -0.006)**	-0.185 (-0.508 - 0.138)	-0.076 (-0.398 - 0.246)	-0.066 (-0.385 - 0.254)	**0.458*** **(0.184 - 0.732)**

*p<0.05. REM, rapid eye movement; MMSE, Mini-Mental State Examination; CASI, Cognitive Abilities Screening Instrument.

3.4. Mediating effects of the sleep cycle between air pollution and cognitive function

The mediating effects of the sleep cycle between air pollution and cognitive function were examined. As shown in Figure 2, we observed that indirect (mediated) effects of $PM_{2.5}$ with N1 (path a) and N1 with

concentration (path b) were statistically significant with respective regression coefficients (β) of -0.298 and -0.388 (p<0.05). The direct effect of $PM_{2.5}$ on concentration (path c') after controlling for indirect (mediated) effects was a regression coefficient (β) of 0.224 (p=0.108). The total effect (mediated and direct) of $PM_{2.5}$ on concentration (path c) was statistically significant with a regression coefficient (β) of 0.175 (p<0.05). We observed no statistical significance of air pollution on other cognitive domains by the mediation analysis.

3.5. Associations between air pollution and brain structure

Associations of air pollution with brain volumes and thicknesses in different regions are shown in Figures 3 and 4. We observed that an IQR increase in O_3 was associated with a 0.484-mm^3 increase in the pars orbitalis volume in the left brain (95% CI: 0.021~0.948, p<0.05). An IQR increase in NO_2 was associated with a 0.881-mm^3 increase in the rostral middle frontal volume in the left brain (95% CI: 0.061~1.701, p<0.05), a 0.826-mm^3 increase in the supramarginal gyrus volume in the left brain (95% CI: -0.004~1.656, p<0.05), a 0.903-mm^3 increase in the transverse temporal volume in the left brain (95% CI: 0.098~1.708, p<0.05), and a 1.012-mm^3 increase in the pars opercularis volume in the right brain (95% CI: 0.213~1.811, p<0.05). Furthermore, an IQR increase in $PM_{2.5}$ was associated with a 1.870-mm^3 increase in the pars triangularis volume in the left brain (95% CI: 0.465~3.274, p<0.05) and a 1.709-mm increase in the fusiform thickness in the right brain (95% CI: 0.282~3.136, p<0.05). We observed no significant associations of air pollution with gray matter changes or white matter changes.

4. Discussion

Air pollution has been linked to dementia; however, the effects of air pollution on dementia development remain unclear. The novelty of this study was that we examined associations between air pollution and cognitive functions via alterations in sleep cycles. The significance of our results are: (1) air pollution was associated with disruption of sleep quality, (2) air pollution increased the risk of cognitive decline via disrupting the sleep cycle, and (3) changes in brain regions in control of executive, learning, and language functions were associated with air pollution.

This cross-sectional study recruited 4866 subjects who had undergone 1-night PSG measurements in a sleep center in Taipei City. The 1-year average concentrations of air pollution for study subjects in the present study were 24.2 ppb O_3, 18.1 ppb NO_2, and 29.2 μg/m^3 $PM_{2.5}$ as estimated by the LUR model. Exposure levels of air pollution were similar to those of previous studies conducted in Taipei City. One study estimated levels of O_3, NO_2, and $PM_{2.5}$ to be 24.86 ppb, 21.25 ppb, and 22.13 μg/m^3, respectively (Zou et al., 2021). Also, a previous report showed that 1-year average concentrations of O_3, NO_2, and $PM_{2.5}$ were 27.91 ppb, 18.43 ppb, and 18.44 μg/m^3, respectively (Tung et al., 2021c). Levels of O_3 and NO_2, in this study were relatively lower compared to World Health Organization (WHO) air quality guidelines (Organization, 2016). However, the $PM_{2.5}$ level was 1.8-fold higher than the 1-year average

WHO guideline (10 μg/m^3). In this study, subjects were exposed to relatively higher levels of $PM_{2.5}$; however, effects on their health due to air pollution remain unclear.

We observed that air pollution was associated with disruption of sleep quality, in terms of arousal and the sleep cycle. Similar results were observed in our previous reports, indicating that air pollution exposure (i.e., $PM_{2.5}$ and NO_2) was associated with an increase in arousal (Lo et al., 2021; Tung et al., 2021b). The increased risk of arousal events by air pollution may be associated with structural changes and edema due to inflammation in upper airway tissues (Billings et al., 2019b; Tung et al., 2021a). A previous report suggested that air pollution also causes neuroinflammation which limits the growth or repair of nerve tissues and indirectly interrupts the sleep cycle (Bose et al., 2019). Indeed, we found that air pollution was associated with disruption of the sleep cycle. Alterations in light sleep by an increase in the N1 stage and a decrease in the N2 stage were sensitive to O_3 and NO_2, whereas $PM_{2.5}$ was associated with increases in the N2 and N3 stages with decreases in the N1 and deep-sleep REM stages. A previous report showed that $PM_{2.5}$ was associated with an increase in the N1 stage in OSA patients (Lo et al., 2021). Also, $PM_{2.5}$ and NO_2 were associated with an increase in the N1 stage, whereas a decrease in N2 by NO_2 and a decrease in N3 by $PM_{2.5}$ and NO_2 were identified (Tung et al., 2021b). Together, these results suggest that air pollution disrupts the sleep cycle by increasing light sleep during sleep time. Alterations in the sleep cycle due to air pollution could be associated with changes in the upper airway structure. For example, a previous study reported that reduced sleep quality was associated with upper airway edema and inflammation caused by NO_2 (Chen et al., 2019). Short-term exposure to O_3 may interrupt the sleep cycle since this air pollutant can alter the ratio of ventilation and perfusion in the lungs and result in upper airway obstruction (Weinreich et al., 2015). Furthermore, air pollution regulated the serotonin expression level and damaged gamma-aminobutyric acid (GABA) receptors in the mouse brain (Yokota et al., 2013). The reduction in GABA receptors was associated with an increase in sleep fragmentation of the REM stage (Brooks and Peever, 2011), and decreased serotonin levels shortened the REM duration and increased wake times (Monti, 2011). Taken together, air pollution may cause sleep fragmentation and an increase in light sleep, leading to poor sleep quality.

In the present study, the sleep cycle was associated with cognitive function according to results of the MMSE and CASI. We found that increases in the wake, N1, and N2 stages were associated with cognitive decline, whereas an increase in REM sleep was associated with increases in cognitive functions. These results suggest that sleep quality plays an important role in maintaining cognitive functions. Increases in the wake and N1 percentages were associated with reduced cognitive function by MMSE scores in elderly females (Blackwell et al., 2006). Another study in China suggested that patients with abnormal cognitive function had a higher N1 stage percentage compared to normal participants (Liu et al., 2020). The unique brainwave feature in the N2 stage sleep spindle was associated with memory consolidation, and a decrease in the N2 percentage was associated with cognitive decline (Liu et al., 2020). Furthermore, REM sleep is associated with memory and learning ability (Shatzmiller et al., 2010). One study suggested that sleep with an insufficient REM percentage might not allow processing for memory consolidation, thereby affecting cognitive function (Vertes and Eastman, 2000). Also, a low percentage of REM sleep was

associated with an increased risk of developing dementia (Pase et al., 2017). Taken together, the sleep cycle may be a mediator of cognitive function after air pollution exposure.

Next, we investigated the mediating effects of the sleep cycle between air pollution and cognitive function in study subjects. We found that $PM_{2.5}$ was associated with a decrease in the N1 stage, whereas the N1 stage was associated with a decrease in concentration. Notably, we found the direct effect of $PM_{2.5}$ was insignificantly associated with concentration. This result suggests that the N1 stage fully mediates between $PM_{2.5}$ and concentration. Previous studies also showed that $PM_{2.5}$ was associated with MMSE domains (Aretz et al., 2020; Yao et al., 2021). Also, NO_2 and O_3 were found to be associated with cognitive function measurements (Chen et al., 2021; Crous-Bou et al., 2020). Therefore, the sleep cycle is essential to maintaining cognitive function and is associated with dementia.

To further understand pathological changes in the brain due to air pollution, we examined associations between air pollution and brain structures. We observed that air pollution was associated with increases in the brain volume and thickness in certain regions associated with executive, learning, and language functions. First, O_3 and NO_2 were associated with increased volumes of the pars orbitalis, rostral middle frontal, supra marginal, transverse temporal, and pars opercularis. Previous reports indicated that the pars orbitalis is related to language function (Ben Shalom and Poeppel, 2008), the rostral middle frontal is involved in executive function (Nakamura-Palacios et al., 2014), the supra marginal is related to memory function (Rubinstein et al., 2021), and the transverse temporal is involved in language function (Ardila et al., 2016). O_3 and NO_2 were associated with damage to the integrity of the blood-brain barrier (BBB) (Rivas-Arancibia et al., 2010; Thiel et al., 2001), which elevated oxidative stress and neurotoxicity and disrupted BBB functions (Yan et al., 2015). An *in vivo* study found that exposure to O_3 at 0.25 ppm (4 h/day for 4 weeks) increased the brain volume and caused brain cell and tissue injury (Rivas-Arancibia et al., 2010). Furthermore, we found associations of $PM_{2.5}$ with an increased volume of the pars triangularis and increased thickness of the fusiform of the brain. The pars trangularis is linked to language function (Yuan et al., 2021), and the fusiform cortical thickness is related to memory function (Zhao et al., 2021). Previous studies showed that $PM_{2.5}$ was associated with increased thicknesses of the occipital and cingulate lobes (Cho et al., 2020). Also, coarse particulate matter ($PM_{2.5-10}$) was associated with an increase in the cerebellum volume (Lubczyńska et al., 2020). Brain volume enlargement with oxidative-inflammatory responses was also observed *in vivo* after 3 and 6 months of exposure to low-level $PM_{2.5}$ in Taipei City (Shih et al., 2018). Air pollution-induced brain inflammation could cause edema (Shih et al., 2018), leading to sleep cycle disturbances and increased risks of cognitive decline.

There are some limitations to our study. The sample size for cognitive function measurement should be increased in the future. Information on comorbidities was not collected in this study, which should be included in future work. Other cofactors such as socioeconomic status, alcohol, smoking, noise exposure, and physical activities, should be considered in the future. Indoor air pollution and the chemical composition of $PM_{2.5}$ should be included in future work.

5. Conclusions

In conclusion, we observed that air pollution was associated with cognitive decline by mediating effects on the sleep cycle with changes in brain structure in adults. Furthermore, changes in brain regions in control of executive, learning, and language functions were associated with air pollution. Our results suggest that sleep cycle disruption by air pollution could increase the risks of dementia.

Abbreviations List

3% ODI 3% oxygen desaturation index

AHI Apnea–Hypopnea Index

SaO_2 arterial oxygen saturation

BMI body mass index

CO carbon monoxide

CASI Cognitive Abilities Screening Instrument

CT computed tomography

CPAP continuous positive airway pressure

GABA gamma-aminobutyric acid

GMC grey matter changes

IQR interquartile range

LUR land-use regression

MRI magnetic resonance imaging

MMSE Mini-Mental State Examination

NO_2 nitrogen dioxide

NOx nitrogen oxides

NREM non-rapid-eye-movement

ODI oxygen desaturation index

PM_{10} particulate matter less than 10 μm in aerodynamic diameter

$PM_{2.5}$ particulate matter less than 2.5 μm in aerodynamic diameter

PSG polysomnography

REM rapid-eye-movement

RDI respiratory disturbance index

TST total sleep time

WASO wake after sleep onset

WMC white matter changes

WHO World Health Organization

Declarations

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

HCC and CCL contributed to the completion of interpretation of the data and the manuscript. **HCC and WTL** contributed substantially to the concept, design, interpretation of the data, and completion of the study and manuscript. **YHL, TCC, YTF, YCL, and YYC** contributed to brain image collection and analyses. **DW** contributed to dementia data collection. **LK, and CYT** contributed to sleep data collection. **CDW, KJC and TYC** contributed to air pollution data collection. **YLL, and KFH** contributed to critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Taipei Medical University-Joint Institutional Review Board (TMU-JIRB no. N201910048; Taipei, Taiwan).

All patients received written information and provided informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

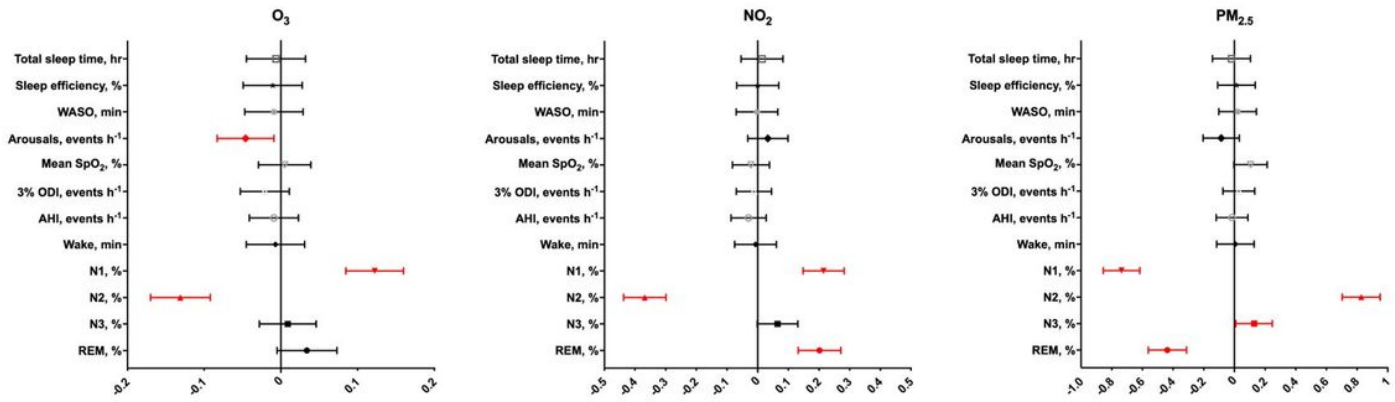

Figure 1

Associations of O3, NO2, and particulate matter with an aerodynamic diameter of <2.5 μM (PM2.5) with sleep parameters. Red indicates statistical significance with p<0.05.

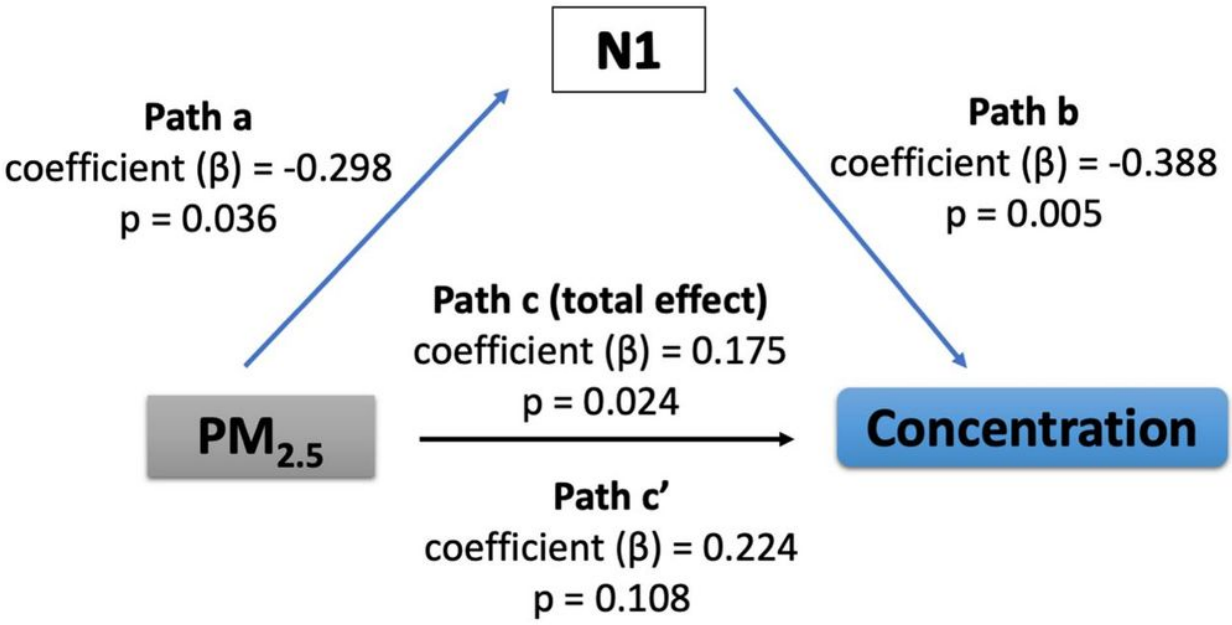

Figure 2

Mediation analysis of sleep cycle between particulate matter with an aerodynamic diameter of <2.5 μm (PM2.5) and the cognitive concentration domain. Depicted is the path diagram (including regression coefficients and p values) of the mediation analysis demonstrating that the N1 stage mediates the effects of PM2.5 on the cognitive concentration domain of the Mini-Mental State Examination. All four requirements for a mediation effect were satisfied: path a, path b, and path c were significant.

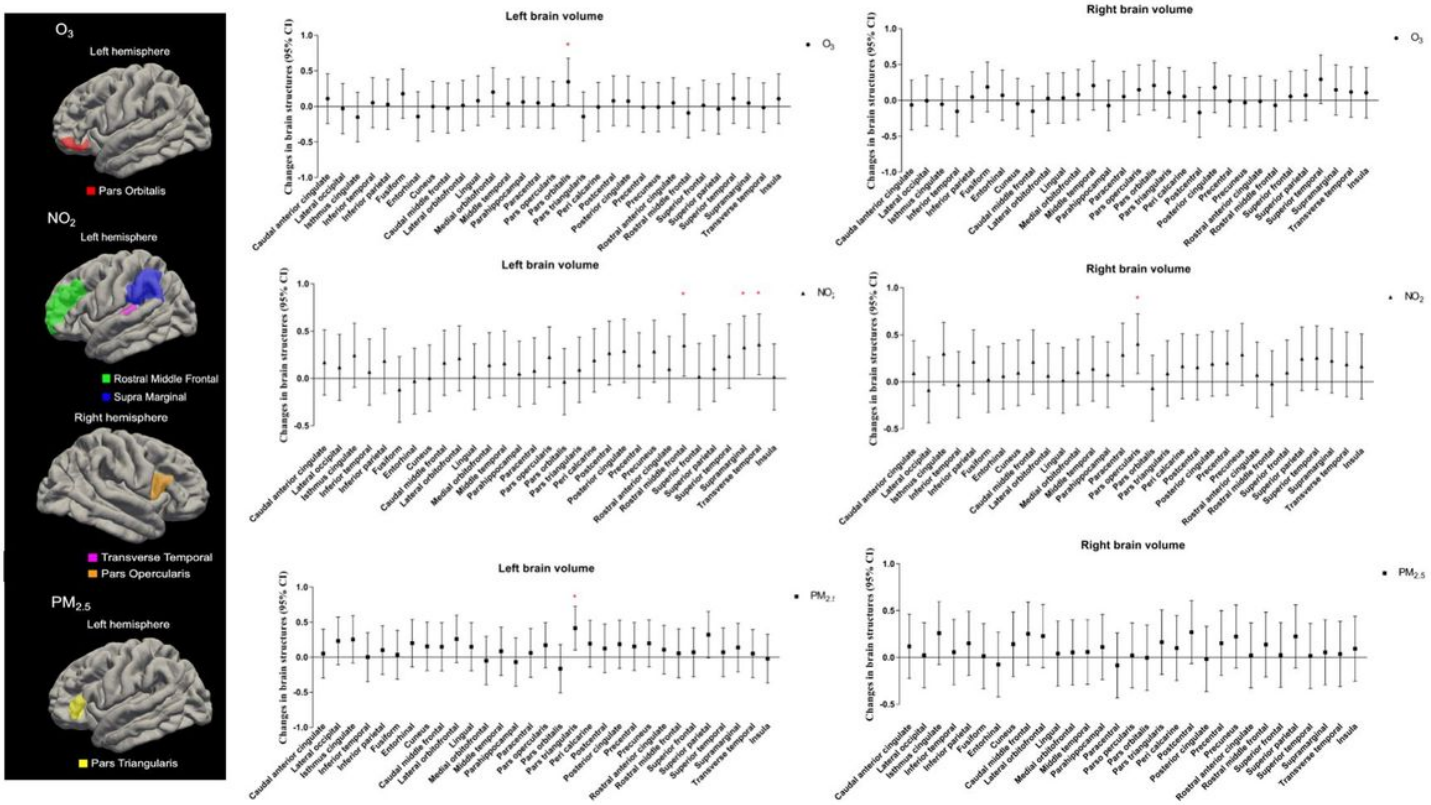

Figure 3

Associations of air pollution with left and right brain volumes. * p<0.05.

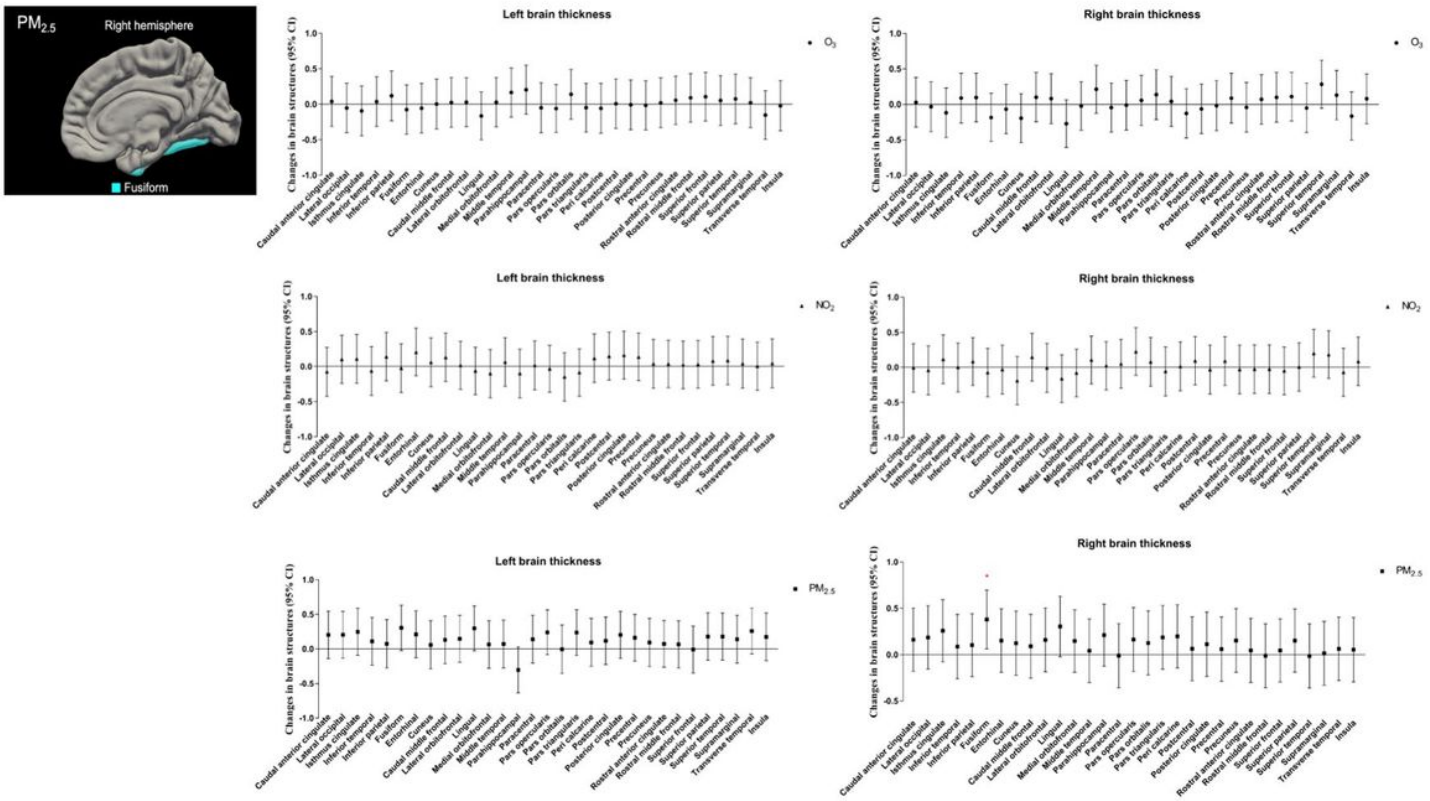

Figure 4

Associations of air pollution with left and right brain thicknesses. * p<0.05.

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