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Effects of Ambient Air Pollution on Brain Cortical Thickness and Subcortical Volume: A Longitudinal Neuroimaging Study

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Keywords
Air pollution · Brain magnetic resonance imaging · Cortical atrophy · Linear mixed model

Abstract

Introduction: Several cross-sectional studies have shown that long-term exposures to air pollutants are associated with smaller brain cortical volume or thickness. Here, we investigated longitudinal associations of long-term air pollution exposures with cortical thickness and subcortical volume. ***Methods:*** In this longitudinal study, we included a prospective cohort of 361 adults residing in four cities in the Republic of Korea. Long-term concentrations of particulate matter with aerodynamic diameters of ≤10 μm (PM10) and ≤2.5 μm (PM2.5) and nitrogen dioxide (NO_2) at residential addresses were estimated. Neuroimaging markers (cortical thickness and subcortical volume) were obtained from brain magnetic resonance images at baseline (August 2014 to March 2017) and at the 3-year follow-up (until September 2020). Linear mixed-effects models were used, adjusting for covariates. ***Results:*** A 10-μg/m^3 increase in PM10 was associated with reduced whole-brain mean (β = −0.45, standard error [SE] = 0.10; $p < 0.001$), frontal (β = −0.53, SE = 0.11; $p < 0.001$) and temporal thicknesses (β = −0.37, SE = 0.12; $p = 0.002$). A 10-ppb increase in NO_2 was associated with a decline in the whole-brain mean cortical thickness (β = −0.23, SE = 0.05; $p < 0.001$), frontal (β = −0.25, SE = 0.05; $p < 0.001$), parietal (β = −0.12, SE = 0.05; $p = 0.025$), and temporal thicknesses (β = −0.19, SE = 0.06; $p = 0.001$). Subcortical structures associated with air pollutants included the thalamus. ***Conclusions:*** Long-term exposures to PM10 and NO_2 may lead to cortical thinning in adults.

Introduction

Ambient air pollution has been considered a significant environmental risk factor for dementia. Epidemiological evidence suggests that long-term exposure to air

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pollution may increase the risks of Alzheimer's disease (AD) and mild cognitive impairment [1–3]. Large population-based studies also found that exposure to air pollution was associated with poor cognitive function in individuals without dementia [4–7]. Given that brain atrophy is a preclinical feature of cognitive decline [8, 9], these associations are supported by numerous neuroimaging studies showing relationships between exposure to air pollution and smaller white and grey matter volumes [10–14]. A few studies have reported the association between exposure to air pollution and a smaller cortical thickness [12, 15, 16], which is a more sensitive measure to detect brain atrophy than cortical volume [17–19].

Given that previous neuroimaging studies were cross-sectional, existing evidence on the effect of air pollution on brain structures does not guarantee a temporal relationship and is based on between-individual comparisons. Longitudinal investigations detecting within-individual brain structural changes associated with exposure to air pollution are warranted. To the best of our knowledge, no study has examined the longitudinal association between exposure to air pollution and cortical thickness in the general adult population. Additionally, current cross-sectional evidence on the effect of air pollution on subcortical structures is conflicting. A study from the United States found that higher levels of particulate matter (PM) were associated with smaller volumes of the thalamus, caudate, putamen, and pallidum, but not with the volume of the hippocampus [13]. Exposure to PM was associated with a decrease in hippocampal volume in a study from the United Kingdom, whereas a study from Spain reported an increase in hippocampal volume [15, 16]. As subcortical structures, such as the hippocampus and thalamus, are frequently involved in the early stages of AD [16, 20], the effect of air pollution exposure on subcortical atrophy must be confirmed using more robust methods. Therefore, we aimed to investigate the longitudinal associations of ambient air pollution with changes in cortical thickness and subcortical volume in a general adult population.

Methods

Study Cohort

The Environmental Pollution-Induced Neurological EFfects (EPINEF) cohort study was launched in 2014 to establish a community-based prospective cohort in the Republic of Korea, covering two metropolitan cities (Seoul and Incheon) and two small cities including rural areas (Wonju and Pyeongchang). The study was designed to explore and understand the neurological effects of environmental pollutants, including PM with an aerodynamic diameter of ≤10 μm (PM10) and a diameter of ≤2.5 μm (PM2.5), and nitrogen dioxide (NO_2). During the baseline survey period from August 2014 to March 2018, individuals aged ≥50 years without known neurological diseases (e.g., dementia, movement disorders, or cerebrovascular disease) were recruited by local advertisements. The survey centres were located at three university-based hospitals: Yonsei University Severance Hospital (Seoul), Gachon University Gil Medical Centre (Incheon), and Wonju Severance Christian Hospital (Wonju and Pyeongchang). Using a standardised survey protocol, the participants underwent questionnaire-based psychometric testing and anthropometric and blood pressure measurements. Blood samples were collected after fasting for ≥12 h and analysed in a central laboratory (Seoul Clinical Laboratory Co. Ltd, Seoul, Korea). Additionally, of the 1,711 participants enrolled during the baseline survey, 998 underwent 3-Tesla brain magnetic resonance imaging (MRI) scans. Of these, 367 participants (180 men and 187 women) underwent a follow-up brain MRI scan until September 2020.

Standard Protocol Approvals, Registrations, and Patient Consents

All the participants provided written informed consent. This study was approved by the Yonsei University Health System Institutional Review Board (approval Nos. 4-2014-0359 and 4-2021-1534).

Exposure Assessment

The PM exposure was quantified in two stages. In the first stage, a total of 429 samples of ambient PM were collected at part of the participants' residential addresses from fall 2016 to summer 2017 to estimate PM concentrations. We estimated the concentrations of ambient PM10 and PM2.5 by season (fall 2016, winter 2016, spring 2017, and summer 2017) using the universal kriging method. In the kriging model, PM concentrations were log-transformed because of their skewed distribution. The universal kriging model consists of mean and variance structures [21]. The mean structure includes the geographical variables associated with each pollutant out of more than 300 geographic variables [22]. Geographical variables were selected by cross-validating the results using the partial least squares method. The variance structure consisted of three parameters (distance reflecting spatial correlation, spatial variation, and non-spatial variation) using the variogram. The performance of the prediction model was evaluated through cross-validation, yielding R^2. The R^2 values for the seasonal PM10 prediction models were 68%, 55%, 28%, and 58% for the spring, summer, fall, and winter, respectively. Those for the seasonal PM2.5 prediction models were 69%, 51%, 21%, and 32% in the spring, summer, fall, and winter, respectively. We finally obtained 1-year average concentrations of PM10 and PM2.5 from seasonal prediction models. In the second stage, because participants' MRI scans were available from 2014, a prediction model spanning from 2014 to 2017 was constructed to address the temporal differences. This model incorporated continuous monitoring data from 289 national air quality stations, adjusting for temporal imbalances using the "Nearest Monitor" method. This approach selected data from the nearest station for each observation. Validation through cross-validation yielded 54% accuracy for the multi-year average model spanning from 2014 to 2017. Furthermore, exposure to NO_2 was quantified using the kriging model method, as described above; the air quality data

implemented in the model development differed from the data used for PM10 and PM2.5. Specifically, the model was constructed utilising annual average concentrations of NO_2, obtained from approximately 300 air quality regulatory monitoring sites, spanning from 2001 to 2016 [22]. By employing this model, NO_2 exposure for each individual was estimated using the annual average concentrations of NO_2 at each participant's residential address.

Acquisition and Analysis of Brain MRI

Brain 3T MRI scans were performed on all participants. Three-dimensional T1-magnetisation prepared rapid gradient-echo images were obtained. During MRI, the participants were placed in the supine position, and the imaging parameters used were: repetition time, 1,900 ms; echo time, 2.93 ms; flip angle, 8°; pixel bandwidth, 170 Hz/pixel; matrix size, 256 × 208; field of view, 256 mm; and the number of excitations (NEX):1, total acquisition. FreeSurfer (version 6.0.0; http://surfer.nmr.mgh.harvard.edu/), a standard software tool for the precise analysis of neuroimaging data [23], was used to estimate cortical thickness and subcortical grey matter volumes using the region-of-interest (ROI)-based method. For each individual, the cortical thicknesses (mm) of six regions (frontal, temporal, parietal, occipital, cingulate, and insular) and the volumes (mm^3) of seven subcortical regions (thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens) were obtained. The whole-brain mean cortical thickness (mm) was estimated by averaging the cortical thicknesses of all the vertices.

Philips 3T Achieva MRI scanners were used in all the baseline and follow-up scans, except for one participant who underwent baseline MRI scan at Gachon University Gil Medical Centre (Siemens 3T Verio MRI scanner). For this participant, Philips scanner-equivalent values were calculated using the method described elsewhere [12].

Covariates

Self-reported information, including sex, socioeconomic factors, and cardiovascular risk factors (i.e., body mass index) were considered as covariates in this study [24]. Socioeconomic factors include marital status (living with a spouse or partner [cohabiting]), residential status (urban living), and educational level (years). Anthropometric measurements (height and weight) were obtained to calculate body mass index (kg/m^2).

Statistical Analysis

Out of 367 participants, a total of 361 individuals were included in the statistical analysis, as they underwent follow-up brain MRI scans and had all air pollution exposure data available (air pollution exposure data for the remaining 6 individuals are yet to be estimated). Longitudinal data analysis (using a linear mixed-effects model with an unstructured covariance matrix) was performed to investigate the association between ambient air pollution and changes in both mean and regional cortical thicknesses. The linear mixed-effects model enabled us to simultaneously consider both within-individual and between-individual variations in mean and regional cortical thicknesses. To control for irregular time intervals between baseline and follow-up MRI scans, age at scan (the baseline and follow-up ages) was included as a time-varying variable in the model (e.g., 65 years old at baseline and 68 years old at follow-up) [25]. Study participants were considered as a random effect. Ambient air pollutant (PM10, PM2.5, and NO_2) concentrations at baseline were included as a fixed-effect exposure variable of interest. Additionally, the analysis included several other variables as fixed effect: sex, years of education, marital status, intracranial volume, and body mass index.

Three sensitivity analyses were performed. First, to effectively control the influence of city of residence [26], a sensitivity analysis was conducted, which involved including residential status as an additional covariate along with the main covariates used in the main analysis. Second, to address potential age-related measurement errors in cortical thickness estimation [27], we performed the analysis including participants under 75 years of age only. This approach also aimed to control for age-related cerebrovascular factors for cortical atrophy such as microbleeds [28–30]. More specifically, individuals aged 75 or older had a 6-times higher prevalence of cerebral microbleeds compared to those under 75 (12.6 vs. 2.2%), as found in the Framingham Original and Offspring Cohorts study [28]. Third, to effectively control age-related matters and geographical variations in air pollution exposure, propensity score matching (PSM) was used in a conservative manner, restricting inclusion to individuals under 75 years old. Propensity score matching, which mimics a randomised intervention, allowed us to obtain two comparable groups living in more- and less-polluted areas by balancing baseline characteristics between the two groups. Specifically, we defined the propensity score as the probability of being assigned to the higher or lower exposure group given a set of individual covariates. To obtain the PSM pairs for each air pollutant (PM10, PM2.5, or NO_2), we generated three subsets of participants. Each subset included individuals with the highest tertile of air pollution concentration (the higher exposure group) and those with the lowest tertile (the lower exposure group). The individuals in the highest and lowest tertiles of air pollution were matched using the greedy nearest neighbourhood matching method (1:1) with a calibre of 0.2 SD for the logit of the estimated propensity score. All covariates, including baseline age, and history of disease (i.e., diabetes and hypertension), were utilised in the PSM analysis, except for intracranial volume. After creating the PSM subsets, the same linear mixed-effects model analyses were repeated adjusting for intracranial volume. Mean differences in cortical thickness (mm) and subcortical volumes (mm^3) between the higher and lower exposure groups were expressed as β-coefficients along with their corresponding 95% confidence intervals.

For all analyses, the strengths of the longitudinal associations were expressed as β-coefficients with corresponding standard errors (SE), otherwise specified. To correct for multiple testing, the FDR method was used. Significance of effect size differences between individuals with and without propensity score matching were tested using the Altman-Bland method and expressed as p for interaction [31]. All statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA).

Results

Characteristics of Study Participants

In this longitudinal study, a total of 361 individuals (176 men and 185 women) were followed for a median (interquartile range [IQR]) of 3 years (2–3 years). Overall, the mean (SD) age was 67.3 (6.0) years at baseline, and 48.8% of the participants were men. The mean (SD) concentrations of PM10, PM2.5, and NO_2 were 45.3

Table 1. Baseline characteristics of study participants

Characteristics	Total (n = 361)
Baseline age, mean (SD)	67.29 (5.97)
Men, n (%)	176 (48.75)
Education level, years, mean (SD)	10.70 (4.23)
Marital status: cohabitating, n (%)	307 (85.04)
Residence status: urban living, n (%)	282 (78.12)
Body mass index, kg/m^2, mean (SD)	24.45 (2.79)
Cortical thickness, mm, mean (SD)	
Whole-brain mean	2.33 (0.10)
Frontal	2.43 (0.11)
Parietal	2.12 (0.12)
Temporal	2.65 (0.12)
Occipital	1.84 (0.10)
Cingulate	2.45 (0.13)
Insula	2.82 (0.15)
Subcortical volume, mm^3, mean (SD)	
Nucleus accumbens	377.84 (73.67)
Amygdala	1,511.89 (212.40)
Hippocampus	3,831.42 (402.24)
Pallidum	1,814.98 (219.21)
Putamen	4,247.69 (500.62)
Caudate	3,083.66 (448.90)
Thalamus	6,475.24 (744.18)
Intracranial volume (1,000 mm^3), mean (SD)	1,520.39 (165.71)

Data are presented as means and standard deviations (SD) of the mean, frequency, and percentage.

(4.5) μm/m^3, 26.1 (0.8) μm/m^3, and 29.6 (9.2) ppb, respectively. The mean (SD) cortical thickness of the whole brain was 2.3 (0.1) mm at baseline. The detailed characteristics of the study participants are presented in Table 1.

Association between Air Pollution and Cortical Thickness

A 10-μg/m^3 increase in PM10 was associated with a decline in the whole-brain mean cortical thickness (β = −0.45, SE = 0.10; p < 0.001). The associations between PM10 and regional cortical thicknesses are presented in Table 2. A 10-μg/m^3 increase in PM10 was associated with declines in the frontal (β = −0.53, SE = 0.11; p < 0.001), temporal (β = −0.37, SE = 0.12; p = 0.002), and insula thicknesses (β = −0.29, SE = 0.15; p = 0.049). After FDR correction, the association between PM10 concentration and cortical thickness remained significant in the frontal and temporal cortices. A 10-ppb increase in NO_2 was associated with a decline in the whole-brain mean cortical thickness (β = −0.23, SE = 0.05; p < 0.001). The associations between NO_2 and regional cortical thicknesses are presented in Table 2. A 10-ppb increase in NO_2 was associated with declines in the frontal (β = −0.25, SE = 0.05; p < 0.001), parietal (β = −0.12, SE = 0.05; p = 0.001), and temporal thicknesses (β = −0.19, SE = 0.06; p = 0.001). After FDR correction, the association between NO_2 concentration and cortical thickness remained significant in the frontal, parietal, and temporal cortices. By contrast, a 10-μg/m^3 increase in PM2.5 was associated with an increase in the whole-brain mean cortical thickness (β = 1.51, SE = 0.56; p = 0.008). The associations between PM2.5 and regional cortical thicknesses are presented in Table 2. A 10-μg/m^3 increase in PM2.5 was associated with increase in the frontal (β = 1.65, SE = 0.64; p = 0.010) and parietal thicknesses (β = 1.61, SE = 0.70; p = 0.022). After FDR correction, the association between PM2.5 concentration and cortical thickness remained significant in the frontal cortex only.

Association between Air Pollution and Subcortical Volume

A 10-μg/m^3 increase in PM10 was associated with an increase in the nucleus accumbens (β = −141.84, SE = 68.69; p = 0.040) and with a decline in the thalamus

Table 2. Longitudinal associations of air pollution with cortical thickness and subcortical volume

	PM10			PM2.5			NO_2		
	β	SE	*p* value	β	SE	*p* value	β	SE	*p* value
Cortical thickness									
Frontal	−0.53	0.11	<**0.001***	1.65	0.64	**0.010***	−0.25	0.05	<**0.001***
Parietal	−0.22	0.12	0.053	1.61	0.70	**0.022**	−0.12	0.05	**0.025***
Temporal	−0.37	0.12	**0.002***	0.89	0.68	0.193	−0.19	0.06	**0.001***
Occipital	−0.03	0.09	0.730	0.47	0.58	0.417	−0.06	0.04	0.194
Cingulate	−0.16	0.11	0.170	0.17	0.65	0.789	−0.09	0.05	0.099
Insula	−0.29	0.15	**0.049**	−0.02	0.84	0.979	−0.13	0.07	0.076
Subcortical volume									
Nucleus accumbens	141.84	68.69	**0.040**	426.51	395.09	0.281	56.27	32.99	0.089
Amygdala	124.13	174.27	0.477	−1,511.92	988.07	0.127	47.49	83.57	0.570
Hippocampus	523.29	327.74	0.111	−3,474.63	1,846.39	0.061	316.40	158.37	**0.047**
Pallidum	−226.41	195.87	0.249	−1,014.63	1,108.39	0.361	−94.12	94.67	0.321
Putamen	607.59	357.49	0.090	−123.16	1,980.43	0.950	192.54	173.90	0.269
Caudate	99.57	313.80	0.751	335.47	1,710.63	0.845	52.25	153.29	0.733
Thalamus	−1,195.44	507.56	**0.019***	1,519.06	2,842.62	0.593	−702.74	244.00	**0.004***

Brain cortical thickness was measured in millimetres. β-coefficients (per 10-unit increase in PM10, PM2.5, and NO_2) were from linear mixed models (adjusting for age at scan, sex, education level, marital status, intracranial volume, and body mass index). NO_2, nitrogen dioxide; PM, particulate matter; PM2.5, PM ≤2.5 μm in aerodynamic diameter; PM10, PM ≤10 μm in aerodynamic diameter; SE, standard error. Values less than 0.05 (denoting statistical significance) are in bold. *Significant ($p < 0.05$) after correction for multiple comparisons using the false discovery rate method.

volume (β = −1,195.44, SE = 507.56; $p = 0.019$) (Table 2). The other associations between PM10 and regional subcortical volumes were shown in Table 2. After FDR correction, the association between PM10 concentration and subcortical volume remained significant in the thalamus volume. A 10-ppb increase in NO_2 was associated with an increase in the hippocampus volume (β = 316.40, SE = 158.37; $p = 0.047$) and with a decline in the thalamus volume (β = −702.74, SE = 244.00; $p = 0.004$) (Table 2). The other associations between NO_2 levels and regional subcortical volumes were shown in Table 2. After FDR correction, the association between NO_2 concentration and subcortical volume remained significant in the thalamus volume. There was no association between PM2.5 and brain subcortical volumes.

Sensitivity Analyses

Residential Status

In the sensitivity analysis, which included city of residence as a covariate, a 10-μg/m^3 increase in PM10 was associated with a decline in the whole-brain mean cortical thickness (β = −0.33, SE = 0.10; $p = 0.001$). The associations between PM10 and regional cortical thicknesses were presented in Table 3. A 10-μg/m^3 increase in PM10 was associated with declines in the frontal and temporal cortices, with the associations remaining significant after FDR correction (Table 3). Similarly, a 10-ppb increase in NO_2 was associated with a decline in the whole-brain mean cortical thickness (β = −0.18, SE = 0.05; $p < 0.001$). The associations between NO_2 and regional cortical thicknesses were presented in Table 3. A 10-μg/m^{3}increase in NO_2 was associated with declines in the frontal, temporal, and cingulate cortices. After FDR correction, the associations remained significant for the frontal and temporal cortices (Table 3). By contrast, a 10-μg/m^3 increase in PM2.5 was associated with an increase in the whole-brain mean cortical thickness (β = 1.12, SE = 0.54; $p = 0.022$). A 10-μg/m^3 increase in PM2.5 was associated with increases in the frontal cortex only, with the associations remaining significant after FDR correction (Table 3).

In terms of subcortical volumes, a 10-ppb increase in NO_2 was associated with a decline only in the thalamus volume (β = −570.87, SE = 248.41; $p = 0.022$), with the associations remaining significant after FDR correction. The other associations between NO_2 levels and regional subcortical volumes were shown in Table 3. By contrast, a 10-μg/m^3 increase in PM10 was associated with an increase in the nucleus accumbens (β = 143.55, SE = 69.07;

Table 3. Longitudinal associations of air pollution with cortical thickness and subcortical volume including city of residence

	PM10			PM2.5			NO_2		
	β	SE	*p* value	β	SE	*p* value	β	SE	*p* value
Cortical thickness									
Frontal	−0.48	0.11	<**0.001***	1.59	0.63	**0.012***	−0.23	0.05	<**0.001***
Parietal	−0.05	0.11	0.637	0.88	0.61	0.149	−0.03	0.05	0.581
Temporal	−0.30	0.11	**0.010***	0.81	0.65	0.215	−0.16	0.06	**0.005***
Occipital	0.07	0.09	0.395	0.46	0.51	0.368	0.01	0.04	0.858
Cingulate	−0.18	0.11	0.124	0.15	0.64	0.815	−0.11	0.06	**0.049**
Insula	−0.28	0.15	0.061	−0.02	0.84	0.980	−0.13	0.07	0.064
Subcortical volume									
Nucleus accumbens	143.55	69.07	**0.038**	414.71	394.99	0.295	49.88	33.45	0.137
Amygdala	184.00	173.88	0.291	−1,471.05	981.79	0.135	80.39	84.61	0.343
Hippocampus	531.10	330.72	0.109	−3,491.92	1,844.57	0.059	289.05	161.45	0.074
Pallidum	−189.88	197.12	0.336	−1,057.44	1,108.19	0.341	−75.78	96.39	0.432
Putamen	712.40	361.60	0.050	−113.87	1,977.35	0.954	227.82	178.47	0.203
Caudate	148.93	319.66	0.642	318.04	1,708.73	0.853	94.68	158.42	0.550
Thalamus	−853.69	505.64	0.092	1,513.86	2,800.41	0.589	−570.87	248.41	**0.022**

Brain cortical thickness was measured in millimetres. β-coefficients (per 10-unit increase in PM10, PM2.5, and NO_2) were from linear mixed models (adjusting for age at scan, sex, education level, marital status, intracranial volume, body mass index, and residential status). NO_2, nitrogen dioxide; PM, particulate matter; PM2.5, PM ≤2.5 μm in aerodynamic diameter; PM10, PM ≤10 μm in aerodynamic diameter; SE, standard error. Values less than 0.05 (denoting statistical significance) are in bold. *Significant ($p < 0.05$) after correction for multiple comparisons using the false discovery rate method.

$p = 0.038$), but this association did not remain significant after FDR correction. There was no association between PM2.5 and brain subcortical volumes (Table 3).

Individuals under 75 Years Old

In the sensitivity analysis constrained to individuals under 75 years old, a 10-μg/m^3 increase in PM10 was associated with a decline in the whole-brain mean cortical thickness (β = −0.86, SE = 0.11; $p < 0.001$). The associations between PM10 and regional cortical thicknesses are presented in Table 4. A 10-μg/m^3 increase in PM10 was associated with declines in the frontal (β = −0.94, SE = 0.13; $p < 0.001$), parietal (β = −1.19, SE = 0.14; $p < 0.001$), temporal (β = −0.76, SE = 0.14; $p < 0.001$), cingulate (β = −0.27, SE = 0.13; $p = 0.040$), and insula thicknesses (β = −0.65, SE = 0.17; $p < 0.001$), with the associations remaining significant in the frontal, parietal, temporal, and insula cortices after FDR correction (Table 4). Similarly, a 10-ppb increase in NO_2 was associated with a decline in the whole-brain mean cortical thickness (β = −0.45, SE = 0.05; $p < 0.001$). The associations between NO_2 and regional cortical thicknesses are presented in Table 4. A 10-ppb increase in NO_2 was associated with declines in the frontal (β = −0.46, SE = 0.06; $p < 0.001$), parietal (β = −0.62, SE = 0.07; $p < 0.001$), temporal (β = −0.35, SE = 0.07; $p < 0.001$), cingulate (β = −0.15, SE = 0.06; $p = 0.021$), and insula thicknesses (β = −0.30, SE = 0.09; $p = 0.001$), with these associations remaining significant even after FDR correction (Table 4).

In terms of subcortical volumes, a 10-μg/m^3 increase in PM10 was associated with a decline in the pallidum (β = −565.11, SE = 231.16; $p = 0.015$) and thalamus volumes (β = −2423.21, SE = 574.30; $p < 0.001$), with the association remaining significant only in the thalamus volume after FDR correction (Table 4). A 10-ppb increase in NO_2 was associated with a decline in the pallidum (β = −294.22, SE = 113.40; $p = 0.010$) and thalamus volumes (β = −2032.81, SE = 562.48; $p < 0.001$), with these associations remaining significant even after FDR correction (Table 4). No association was found between PM2.5 and brain cortical thicknesses or subcortical volumes.

Propensity Score Matching

The associations between exposure to air pollution (PM10, PM2.5, NO_2) and the brain cortical thickness and subcortical volume for individuals with and without PSM showed no statistically significant differences across any regions of brain cortical thickness and subcortical volume (data not shown). The higher (vs. lower) PM10 group had reduced whole-brain mean cortical thickness (β = −0.090;

Table 4. Longitudinal associations of air pollution with cortical thickness and subcortical volume of individuals under 75 years old

	PM10			PM2.5			NO_2		
	β	SE	*p* value	β	SE	*p* value	β	SE	*p* value
Cortical thickness									
Frontal	−0.94	0.13	<**0.001***	1.36	0.79	0.085	−0.46	0.06	<**0.001***
Parietal	−1.19	0.14	<**0.001***	1.42	0.86	0.100	−0.62	0.07	<**0.001***
Temporal	−0.76	0.14	<**0.001***	0.45	0.84	0.596	−0.35	0.07	<**0.001***
Occipital	−0.15	0.11	0.176	0.31	0.72	0.667	−0.10	0.05	0.076
Cingulate	−0.27	0.13	**0.040**	−0.11	0.78	0.892	−0.15	0.06	**0.021***
Insula	−0.65	0.17	<**0.001***	−0.17	1.06	0.872	−0.30	0.09	**0.001***
Subcortical volume									
Nucleus accumbens	145.01	84.08	0.086	594.69	512.32	0.247	65.78	41.04	0.110
Amygdala	129.87	211.84	0.540	−372.03	1,276.82	0.771	52.72	103.24	0.610
Hippocampus	302.37	384.82	0.433	−2,368.45	2,262.72	0.296	205.97	189.06	0.277
Pallidum	−565.11	231.16	**0.015**	488.77	1,379.28	0.723	−294.22	113.40	**0.010***
Putamen	225.79	405.49	0.578	824.89	2,305.19	0.721	−11.38	200.10	0.955
Caudate	−109.37	356.04	0.759	2,515.09	1,973.38	0.203	−73.20	176.12	0.678
Thalamus	−2,423.21	574.30	<**0.001***	5,827.83	3,357.11	0.084	−1,323.93	280.70	<**0.001***

Brain cortical thickness was measured in millimetres. β-coefficients (per 10-unit increase in PM10, PM2.5, and NO_2) were from linear mixed models (adjusting for age at scan, sex, education level, marital status, intracranial volume, and body mass index). NO_2, nitrogen dioxide; PM, particulate matter; PM2.5, PM ≤2.5 μm in aerodynamic diameter; PM10, PM ≤10 μm in aerodynamic diameter; SE, standard error. Values less than 0.05 (denoting statistical significance) are in bold. *Significant ($p < 0.05$) after correction for multiple comparisons using the false discovery rate method.

95% confidence intervals [CI] = −0.143 to −0.037). The higher (vs. lower) PM10 group had reduced the frontal, parietal, temporal, and occipital cortices, with these associations remaining significant even after FDR correction (Fig. 1a). The higher (vs. lower) NO_2 group had reduced whole-brain mean cortical thickness (β = −0.050; 95% CI = −0.072 to −0.028). The higher (vs. lower) NO_2 group had reduced the frontal, parietal, temporal, occipital, cingulate, and insula cortices, with the association remaining significant in the frontal, parietal, temporal, and occipital cortices (Fig. 1e). There was no significant association between PM2.5 and brain cortical thickness after PSM (Fig. 1c). None of the associations between exposure to PM (PM10 and PM2.5) and NO_2 and subcortical volumes were found to be statistically significant after PSM (Fig. 1b, d, f). We found no significant differences in association strength between the results from the main analysis and the analyses after PSM.

Discussion

In this 3-year prospective cohort study, we aimed to investigate the longitudinal associations of long-term exposure to PM10, PM2.5, and NO_2 with changes in brain cortical thickness and subcortical volume. Despite the relatively short follow-up period, repeated measurements of brain cortical thickness and subcortical volume enabled us to detect within-individual changes associated with exposure to air pollution. We used a linear mixed-effects model considering both within- and between-individual variations. To ensure robustness of our findings, we conducted sensitivity analyses controlling for the influence of participants' city of residence and reducing age-related measurement errors in cortical thickness estimation. In addition, PSM method was used to reduce confounding by individual-level characteristics related to both ageing and geographical areas, specifically addressing air pollution exposure. The main finding was that long-term exposures to PM10 and NO_2 were associated with reductions in both cortical thickness and subcortical volume. Specifically, exposure to PM10 was associated with reduced thicknesses of frontal and temporal cortices, while exposure to NO_2 was associated with reduced thicknesses of frontal, parietal, and temporal cortices. Both PM10 and NO_2 exposures were also associated with reduced thalamus volume. After PSM, exposures to PM10 and NO_2 were associated with broader regions of the brain cortex, including frontal, parietal, temporal,

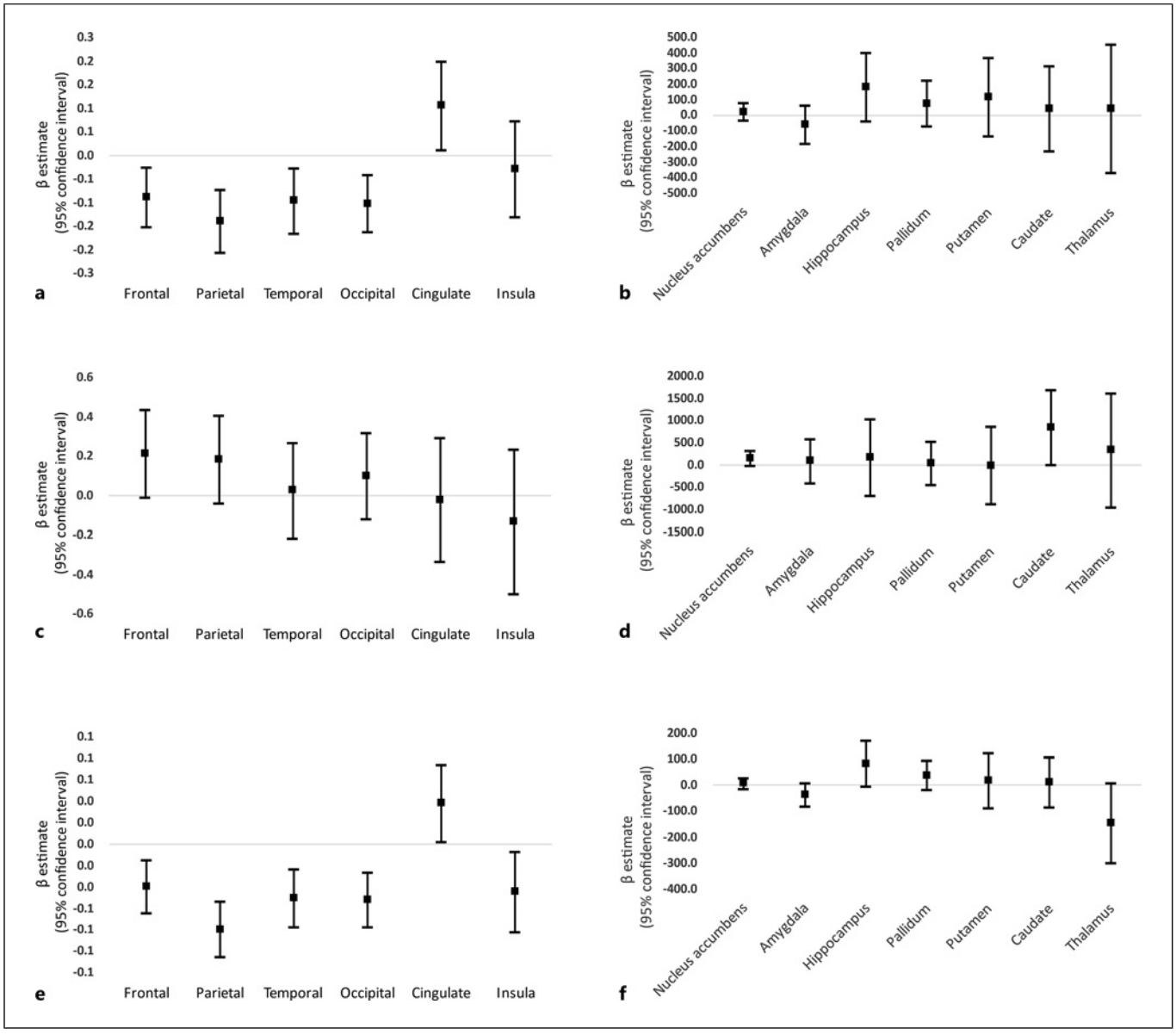

Fig. 1. Results of associations between baseline air pollution and subcortical volume reduction and cortical thickness of EPINEF cohort after propensity score marching. **a** Association between cortical thickness change and PM10 concentrations. **b** Association between subcortical volume change and PM10 concentrations. **c** Association between cortical thickness change and PM2.5 concentrations. **d** Association between subcortical volume change and PM2.5 concentrations. **e** Association between cortical thickness change and NO_2 concentrations. **f** Association between subcortical volume change and NO_2 concentrations. The variables used in the propensity score marching included all covariates except intracranial volume. Linear mixed models were adjusted for intracranial volume. NO_2, nitrogen dioxide; PM, particulate matter; PM2.5, PM ≤2.5 μm in aerodynamic diameter; PM10, PM ≤10 μm in aerodynamic diameter.

cingulate, and insula cortices, as well as pallidum and thalamus volumes.

Several cross-sectional neuroimaging studies have investigated the link between air pollution and cortical thickness on brain MRI among middle-aged and elderly individuals [12, 15, 32, 33]. These studies have explored brain atrophy regions associated with AD, including the frontal, parietal, temporal, and insular lobes, all showing an inverse association with long-term exposure to ambient air pollution. We previously used a

cross-sectional sample of the EPINEF cohort to investigate the associations of PM10, PM2.5, and NO_2 with cortical thickness and subcortical volume. We found significant associations between PM10 and smaller frontal and temporal thicknesses [12]. In the present study, a longitudinal sample from the EPINEF cohort showed similar associations in extensive brain areas, including the frontal, parietal, temporal, and insular lobes. We also reported a smaller temporal thickness associated with an increase in PM2.5 [12]. Although our main analysis did not find an association between PM2.5 and temporal thickness, the sensitivity analysis after PSM showed associations in additional brain regions such as the frontal, parietal, and temporal cortices. We also previously found that NO_2 exposure was associated with smaller frontal, parietal, temporal, and insula thicknesses [12]. Similar associations were observed in the main and sensitivity analyses in the present study. Interestingly, our previous study showed positive associations between exposures to PM10 and NO_2 and cingulate and occipital thicknesses [12]. However, after a 3-year follow-up in the present study, we found that PM10 and NO_2 exposures were associated with reduced thicknesses in these regions. Here, we employed more robust methods involving a prospective longitudinal study design to detect within-individual changes in brain structures. This study confirmed the inverse association between air pollution exposure and cortical thickness that we previously observed. Furthermore, our findings suggest that exposure to air pollution may lead to thinning of broader cortical regions.

Most neuroimaging studies in this field have investigated the link between air pollution and volumes of subcortical structures such as the hippocampus (a frequently studied subcortical region related to AD) [12, 13, 15, 16, 20]. However, the findings of these studies have been mixed. While some epidemiological studies have shown no significant associations between air pollution and hippocampal volume, others have reported positive or inverse relationships [10, 11, 13, 15, 16]. Our previous study using the EPINEF cohort demonstrated that PM10, PM2.5, and NO_2 exposures were associated with smaller hippocampal volumes [12]. However, in our present follow-up study, we did not observe any associations between air pollution exposure and hippocampal volume. Instead, we found a significant association between air pollution exposure and the thalamus volume in the main analysis, and both thalamus and pallidum volumes in the sensitivity analysis after PSM. The thalamus is another important subcortical structure that is involved in the early stages of AD. Our findings align with previous research showing reductions in thalamus volume associated with exposures to PM10 and NO_2 [13]. Consistent with our previous cross-sectional study, the current study also showed that PM10 and NO_2 exposures were associated with a reduced thalamic volume in both main and PSM analyses. Our results suggest that exposure to PM may contribute to atrophy of the subcortical structures involved in the development of AD, such as the thalamus and pallidum.

The present study had several limitations First, the relatively small sample size and short follow-up period may have led to insufficient statistical power to detect an association between air pollution and changes in cortical thickness and subcortical volume. Despite this limitation, this was the first study to examine the longitudinal association between air pollution and brain atrophy, demonstrating significant associations across extensive brain regions (Table 1). In our cohort, the whole-brain cortical thickness decreased by 0.005 mm (SE = 0.001; $p < 0.001$), which was similar to the average cortical thinning observed in a previous study among individuals transitioning from their 60s to their 70s in Korea (0.007 mm in women; 0.006 mm in men) [34]. Although we did not find a significant decrease in average cortical thickness within individuals over a 3-year follow-up period in our cohort, future studies with longer follow-up periods (≥3-year follow-up period) were warranted to detect additional changes in brain structures associated with exposure to air pollution. The additional information can be found in the online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000539467). Second, the present study may be susceptible to selection bias as this study included participants who underwent both baseline and follow-up brain MRI scans. To recruit participants in the follow-up study, research nurses contacted those who participated in the baseline brain MRI study in order of enrolment. A total of 361 participants who had completed follow-up brain MRI scans and had available air pollution exposure data until September 2020 were included in this longitudinal study. Moreover, to reduce selection bias, we compared characteristics between individuals with baseline magnetic resonance images only and those with follow-up images. No significant differences were found in mini-mental state examination scores between participants who underwent follow-up MRI (median, 27.0; IQR, 25.0, 29.0) and those who did not (median, 28.0; IQR, 26.0, 29.0) ($p = 0.834$) (online suppl. Table 2) [12]. Lastly, we acknowledge the potential for residual confounding by individual-

and contextual-level factors (e.g., neighbourhood socioeconomic status, noise, greenness, population density).

In summary, this longitudinal neuroimaging study demonstrated that PM and NO_2 exposures were associated with cortical thinning in the frontal, parietal, temporal, cingulate, and insular lobes over a 3-year follow-up period. Exposure to PM was also associated with reductions in thalamus volume. We added robust evidence to the existing literature on the neurotoxic effects of the ambient air pollution, highlighting its impact on structural changes in the brain over time.

Statement of Ethics

All the participants provided written informed consent. This study was approved by the Yonsei University Health System Institutional Review Board (approval Nos. 4-2014-0359 and 4-2021-1534). The authors declare that the procedures were followed according to the Declaration of Helsinki.

Conflict of Interest Statement

None declared.

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Author Contributions

J.K.: formal analysis, investigation, writing – original draft, and project administration. J.S.: investigation and project administration. Y.N.: methodology, software, investigation, writing – review and editing, and funding acquisition. S.K.: methodology, investigation, and funding acquisition. S.L.: methodology, software, investigation, resources, and funding acquisition. S.K.: methodology, writing – review and editing, and funding acquisition. J.C. and C.K.: conceptualisation, methodology, writing – review and editing, supervision, and funding acquisition.

Data Availability Statement

Anonymised data not published within this article will be made available by request from any qualified investigator.

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