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Alzheimer's disease-like cortical atrophy mediates the effect of air pollution on global cognitive function

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ABSTRACT

Little is known about the effect of air pollution on Alzheimer's disease (AD)-specific brain structural pathologies. There is also a lack of evidence on whether this effect leads to poorer cognitive function. We investigated whether, and the extent to which, AD-like cortical atrophy mediated the association between air pollution exposures and cognitive function in dementia-free adults. We used cross-sectional data from 640 participants who underwent brain magnetic resonance imaging and the Montreal Cognitive Assessment (MoCA). Mean cortical thickness (as the measure of global cortical atrophy) and machine learning-based AD-like cortical atrophy score were estimated from brain images. Concentrations of particulate matter with diameters $\leq$ 10 μm (PM_{10}) and $\leq$ 2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2) were estimated based on each participant's residential address. Following the product method, a mediation effect was tested by conducting a series of three regression analyses (exposure to outcome; exposure to mediator; and exposure and mediator to outcome). A 10 $\mu g/m^3$ increase in PM_{10} (β = -1.13; 95 % CI, −1.73 to −0.53) and a 10 ppb increase in NO_2 (β = -1.09; 95 % CI, −1.40 to −0.78) were significantly associated with a lower MoCA score. PM_{10} ($\beta = 0.27$; 95 % CI, 0.06 to 0.48) and NO_2 ($\beta = 0.35$; 95 % CI, 0.25 to 0.45) were significantly associated with an increased AD-like cortical atrophy score. Effects of PM_{10} and NO_2 on MoCA scores were significantly mediated by mean cortical thickness (proportions mediated: 25 %–28 %) and AD-like cortical atrophy scores (13 %–16 %). The findings suggest that air pollution exposures may induce AD-like cortical atrophy, and that this effect may lead to poorer cognitive function in dementia-free adults.

1. Introduction

1.1. Background

Dementia is a major health issue in aging and aged societies. Globally, approximately 55 million people suffered from dementia in 2019, and this number is estimated to more than double in 2050 (World Health Organization 2021). There was a loss of 29 million disability-adjusted life years due to dementia worldwide in 2016 (Nichols et al. 2019). In the Republic of Korea, dementia prevalence doubled from 31 per 1,000 populations in 2008 to 62 per 1,000 populations in 2016 (Choi et al. 2021). It has been well documented that Alzheimer's disease (AD), the most common form of dementia, progresses along a continuum (so-called the 'AD continuum') from preclinical to clinical stages (Jack et al. 2018). The presence of AD pathologies such as amyloid beta and hyperphosphorylated tau accumulations and neurodegeneration

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(manifested as cortical atrophy) in the preclinical stage can be followed by clinically apparent cognitive impairment and dementia. In line with increasing emphasis on biological aspects of dementia, there is a need for a better understanding of mechanisms on how risk factors for dementia impair cognitive function in dementia-free individuals.

Ambient air pollution has been considered a major environmental risk factor for dementia for the past few decades. Population-based evidence suggests that exposure to air pollution is causally associated with the risk of AD and other dementia (Cerza et al. 2019; Delgado-Saborit et al. 2021; Shi et al. 2020). Large population-based studies found that air pollution exposures are associated with poorer cognitive function in dementia-free individuals (Duchesne et al. 2022; Kulick et al. 2020; Power et al. 2011; Wang et al. 2020; Weuve et al. 2012). Given the concept of AD continuum, these associations are supported by neuroimaging studies showing the inverse associations between air pollution exposures and white matter volume, gray matter volume, and cortical thickness (Casanova et al. 2016; Chen et al. 2015; Cho et al. 2020; Power et al. 2018). However, these neuroimaging studies were exploratory and reported mixed findings (including null or positive associations in different parts of the brain regions). Moreover, the observed cortical atrophy associated with air pollution might not be specific to AD pathology. In this context, a previous study used an AD-specific brain structural measure, which was the mean cortical thickness across the brain regions that were selected *a priori* based on literature (Crous-Bou et al. 2020). Recently, a machine learning model was developed to measure the AD-specific similarity of the cortical atrophy pattern on an individual basis (Lee et al. 2018). Use of this more advanced measure may reveal the effect of air pollution exposures on AD-specific brain structural changes in dementia-free adults. Further, it is worth investigating whether the effect of air pollution on AD-specific structural pathology leads to poorer cognitive function, in accordance with the concept of AD continuum. To the best of our knowledge, no study has reported a mediation effect of brain structural findings on the association between air pollution and cognitive function. This work may improve understanding about how air pollution exposures affect brain structures and cognitive function, and the extent to which the effect of air pollution on cognitive function is mediated by AD-specific brain structural pathology.

The first aim of this study was to investigate the associations of air pollution exposures with the AD-specific similarity of the cortical atrophy pattern and global cognitive function. The second aim was to examine whether and the extent to which the AD-specific similarity of the cortical atrophy pattern mediated the association between air pollution exposures and global cognitive function in individuals without dementia.

2. Methods

2.1. Study participants

This study used baseline cross-sectional data from the Environmental Pollution-Induced Neurological EFfects (EPINEF) cohort study (Jang et al. 2021). This community-based cohort consisted of individuals from two metropolitan cities (Seoul and Incheon) and two small cities (Wonju and Pyeongchang) in the Republic of Korea. The inclusion criteria were $\geq$ 50 years of age and the absence of a self-reported history of three neurological disorders (stroke, dementia, and Parkinson's disease). We recruited eligible individuals using local advertisements in the study areas. A total of 1,711 people participated in the baseline survey, which was conducted from August 2014 to March 2017 at three university-based hospitals: Yonsei University Severance Hospital (Seoul), Wonju Severance Christian Hospital (Wonju and Pyeongchang), and Gachon University Gil Medical Center (Incheon). We collected questionnaire-based data on demographic characteristics (age, sex, and education level), lifestyle habits (alcohol consumption and smoking), history of cardiometabolic disease (hypertension, diabetes mellitus, and angina or myocardial infarction), as well as anthropometric measures (height, weight, and body mass index). In order of enrollment, participants were asked to undergo brain 3 T magnetic resonance imaging (MRI). A total of 1,594 participants completed the questionnaires and measurements without missing entries. Of these, 957 participants completed brain MRI using a Philips 3 T Achieva MRI scanner or a Siemens 3 T Verio MRI scanner. The Montreal Cognitive Assessment (MoCA) was conducted only in participants who underwent brain MRI using the Philips 3 T Achieva MRI scanner (n = 640). Written informed consent was obtained from all participants. This study was approved by the Yonsei University Health System Institutional Review Board (approval no. 4–2014-0359 and no. 4–2021-1534).

2.2. Exposure assessment: air pollutants

Individual long-term exposures to particulate matter with aerodynamic diameters $\leq$ 10 μm (PM_{10}) and nitrogen dioxide (NO_2) were assessed as 5-year averages of annual-average concentrations estimated at each participant's residential address before the enrollment year (e.g., 2010–2014 for the first year of enrollment). The annual-average concentrations of PM_{10} and NO_2 were estimated by using the universal kriging model and regulatory air quality monitoring data between 2001 and 2016 from approximately 300 sites, which was described elsewhere (Kim and Song 2017). Long-term exposure to particulate matter with aerodynamic diameters $\leq$ 2.5 μm ($PM_{2.5}$) was estimated as 1-year average concentrations at each participant's residential address in 2015 because nationwide regulatory monitoring data were available from 2015 for $PM_{2.5}$ in the Republic of Korea.

2.3. Outcome assessment: cognitive function

In this study, we evaluated global cognitive function using the Korean version of the Montreal Cognitive Assessment (MoCA-K). The MoCA is a brief cognitive screening tool with high sensitivity for screening patients with mild cognitive impairment (MCI). The MoCA included the cognitive functions of orientation, attention, language, abstraction, visuospatial/executive function, naming, and episodic memory. The highest possible score was 30 points; higher scores reflected better performance. Suspected MCI was defined as a MoCA score $\leq$ 19. The sensitivity, specificity, positive predictive value, and negative predictive value of this cutoff value were 51 %, 97 %, 83 %, and 86 % for discrimination of MCI, respectively (Lee et al. 2008).

2.4. Mediators: global and AD-specific cortical atrophy markers

Three-dimensional T1-magnetization-prepared rapid gradient-echo (3D MP-RAGE) images were obtained via a standardized protocol. Cortical thickness data were obtained for each participant using an automated brain image analysis tool (Inbrain®, MIDAS Information Technology Co., ltd.). As the measure of global cortical atrophy, mean cortical thickness was calculated by averaging the cortical thickness of each mesh vertex. An AD-like cortical atrophy score was also defined as how similar an individual's cortical atrophy pattern was, compared with that of patients with AD. The method used to estimate the AD-like cortical atrophy score was described in a previous study of brain images of 869 cognitively normal individuals and 473 patients with AD (Lee et al. 2018). A relative position of cortical thickness value ('w-score') was calculated based on the distribution of cortical thickness data from approximately 3,000 individuals without dementia. W-scores were corrected for age and education level and entered as feature vectors in a principal component analysis and a linear discriminant analysis for training a group classifier (Belhumeur et al. 1997). The AD-like cortical atrophy score was calculated as the distance between each individual's mapped value and the mean of patients with AD in the linear discriminant analysis space. The accuracy of this model was 91 % for discrimination between individuals with normal cognition and patients

with AD. A greater AD-like cortical atrophy score indicated greater similarity to the representative cortical atrophy pattern of patients with AD. The original percentile score data (range, 0 to 100) were converted to z-score data for this study.

2.5. Statistical analysis

Results for general characteristics of the study participants were reported as mean (standard deviation [SD]) or frequency (%) values. Prior to conducting the main analysis, we depicted non-linear relationships between air pollutants and MoCA score, using a generalized additive model (Supplementary Fig. 1). Each air pollutant was entered as a spline variable in the model, with no covariates. The restricted maximum likelihood method was used for selecting degrees of freedom of the spline variable. No remarkable non-linearity with certain thresholds was observed for PM_{10} and NO_2, whereas $PM_{2.5}$ exhibited a very narrow range of concentrations (24.1 to 28.1 μg/m^3) and noticeable non-linearity. Hence, we dichotomized $PM_{2.5}$ data as higher (≥25.7 μg/m^3 [median]) and lower (<25.7 μg/m^3) concentrations.

For the first study aim, we examined associations of exposures (PM_{10}, $PM_{2.5}$, or NO_2) with mediators (mean cortical thickness and AD-like cortical atrophy z-score) and the outcome (MoCA score). We additionally investigated the associations between the mediators and the outcome. We performed linear regression analyses, in which the overall set of covariates consisted of demographics (age and sex), socioeconomic status (years of education), cardiovascular risk factors (history of hypertension, history of diabetes mellitus, history of angina or myocardial infarction, smoking status, alcohol consumption, and body mass index), and enrollment year. Age and years of education were not included in the model regressing the AD-like cortical atrophy score because the score data were corrected for age and education level. Strength of association was expressed as a beta coefficient (per 10 μg/m^3 increase in PM_{10}; of a higher [versus lower] concentration of $PM_{2.5}$; or per 10 ppb increase in NO_2) with a corresponding 95 % confidence interval (CI).

For the second study aim, we conducted a mediation analysis to examine whether each of the cortical atrophy markers ('M', mean cortical thickness or AD-like cortical atrophy score) mediated the effect of each air pollutant ('X', PM_{10}, $PM_{2.5}$, or NO_2) on cognitive function ('Y', MoCA score). Given the two mediators and one outcome, two mediation models were assumed for each air pollutant (Fig. 1). Following the product method (Baron and Kenny 1986), a mediation effect was tested by conducting a series of three regression analyses (X to Y; X to M; and X and M to Y). This procedure yielded beta coefficients for the mediation (or indirect) effect, direct effect, and total effect (the sum of mediation effect and direct effect), and proportion mediated (%) (beta coefficient of effect/beta coefficient of total effect × 100). Beta coefficient 95 % CIs were calculated after 1,000-iteration non-parametric bootstrapping. Considering exposure-mediator, exposure-outcome, and mediator-outcome confounding variables, we used the above-mentioned overall set of covariates in the mediation analysis (Valeri and Vanderweele 2013; VanderWeele 2016); age and years of education were excluded from the model regressing the AD-like cortical atrophy score (as the score data were corrected for age and education level). We also explored exposure-mediator interactions by adding interaction terms to the model regressing MoCA score. No interactions were observed in the regression model including mean cortical thickness (P value = 0.56 for PM_{10}, P value = 0.44 for $PM_{2.5}$, and P value = 0.84 for NO_2) or AD-like cortical atrophy score (P value = 0.38 for PM_{10}, P value = 0.56 for $PM_{2.5}$, and P value = 0.89 for NO_2) as the mediator.

As a sensitivity analysis, we repeated the above analyses using suspected MCI as the outcome. We first examined associations of PM_{10}, $PM_{2.5}$, and NO_2 concentrations with the risk of suspected MCI. We then conducted a mediation analysis, consisting of a linear regression analysis (X to M) and two logistic regression analyses (X to Y; and X and M to Y). We adjusted for the same set of covariates as in the main analysis throughout the whole sensitivity analyses. The mediation effect, direct effect, and total effect were expressed as odds ratios with corresponding 95 % CIs. The proportion mediated (%) was calculated as beta coefficient of effect/beta coefficient of total effect × 100.

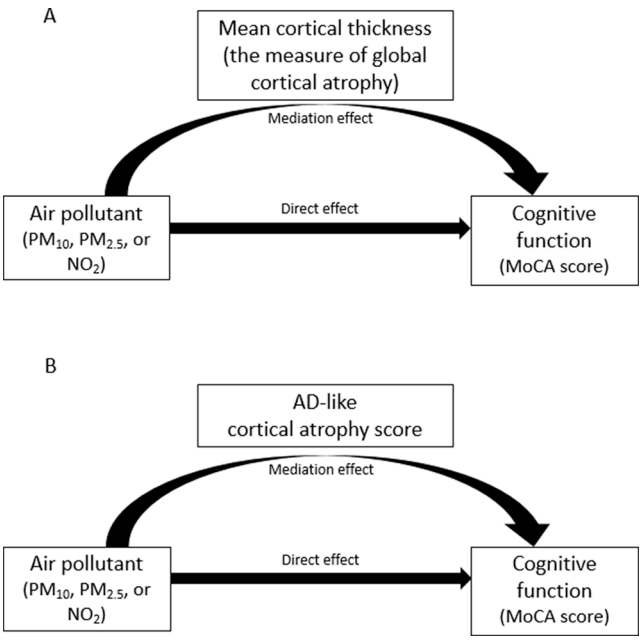

Fig. 1. Causal mediation models tested. PM_{10}: particulate matter, aerodynamic diameters ≤ 10 μm, $PM_{2.5}$: particulates, diameters ≤ 2.5 μm, NO_2: nitrogen dioxide, AD: Alzheimer's disease.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and R statistical software (version 3.4.1, R Foundation) with the 'mgcv' (Wood 2011) and 'mediation' packages (Tingley et al. 2014).

3. Results

3.1. Characteristics of study participants

The mean (SD) age was 67.4 (7.0) years (Table 1). Women were 54.2 % of the total number of participants (n = 347). The mean (SD) concentrations of PM_{10}, $PM_{2.5}$, and NO_2 were 49.7 (5.2) μg/m^3, 25.9 (0.7) μg/m^3, and 27.0 (11.1) ppb, respectively. The mean (SD) value of mean cortical thickness was 2.3 (0.1) mm and that for the AD-like cortical atrophy z-score was −0.8 (1.3). The mean (SD) MoCA score was 22.9 (4.4), and the proportion of suspected MCI (defined as MoCA score ≤ 19) was 18.3 % (n = 117).

3.2. Association between air pollution and cortical atrophy

A 10 μg/m^3 increase in PM_{10} was significantly associated with a reduced mean cortical thickness (β = -0.04 mm; 95 % CI, −0.05 mm to −0.02 mm; P value < 0.001) and increased AD-like cortical atrophy z-score (β = 0.27; 95 % CI, 0.06 to 0.48; P value = 0.013) (Table 2). A higher (versus lower) $PM_{2.5}$ concentration was significantly associated with a reduced mean cortical thickness (β = -0.03 mm; 95 % CI, −0.04 mm to −0.01 mm; P value = 0.001), but not with an AD-like cortical atrophy z-score (β = 0.00; 95 % CI, −0.20 to 0.19; P value = 0.97). A 10 ppb increase in NO_2 was significantly associated with a reduced mean cortical thickness (β = -0.05 mm; 95 % CI, −0.05 mm to −0.04 mm; P value < 0.001) and an increased AD-like cortical atrophy z-score (β = 0.35; 95 % CI, 0.25 to 0.45; P value < 0.001).

Table 1
Characteristics of study participants.

Characteristics	N = 640
Age (years), mean (SD)	67.42 (6.96)
Education level (years), mean (SD)	9.89 (4.35)
Female, n (%)	347 (54.22)
History of hypertension, n (%)	184 (28.75)
History of diabetes mellitus, n (%)	109 (17.03)
History of angina or myocardial infarction, n (%)	55 (8.59)
Smoking status, n (%)	
Current smoker	39 (6.09)
Former smoker	181 (28.28)
Never smoker	420 (65.63)
Alcohol consumption, n (%)	
Currently drinking	284 (44.38)
Not currently drinking	356 (55.63)
Body mass index (kg/m^2), mean (SD)	24.62 (2.93)
Enrollment year, n (%)	
1st (August 2014 to March 2015)	164 (25.63)
2nd (April 2015 to March 2016)	240 (37.50)
3rd (April 2016 to March 2017)	236 (36.88)
Ambient air pollutants, mean (SD)	
PM10, μm/m^3	49.69 (5.19)
PM2.5, μm/m^3	25.85 (0.74)
NO_2, ppb	26.98 (11.09)
Mean cortical thickness (mm), mean (SD)	2.32 (0.11)
AD-like cortical atrophy z-score, mean (SD)	−0.79 (1.26)
Cognitive test (MoCA) score, mean (SD)	22.89 (4.35)
Suspected mild cognitive impairment, n (%)	117 (18.3)

Abbreviations. SD: standard deviation, PM_{10}: particulate matter, aerodynamic diameter ≤ 10 μm, $PM_{2.5}$: particulate matter, aerodynamic diameter ≤ 2.5 μm, NO_2: nitrogen dioxide, AD: Alzheimer's disease, MoCA: Montreal Cognitive Assessment.

3.3. Association between air pollution and cognitive function

Increases in PM_{10} (β = -1.13; 95 % CI, −1.73 to −0.53; *P* value < 0.001), $PM_{2.5}$ (β = -0.69; 95 % CI, −1.23 to −0.14; *P* value = 0.014), and NO_2 (β = -1.09; 95 % CI, −1.40 to −0.78; *P* value < 0.001) were significantly associated with a lower MoCA score (Table 2). A 0.1 mm increase in mean cortical thickness was associated with a higher MoCA score (β = 0.91; 95 % CI, 0.62 to 1.19; *P* value < 0.001). An increase in AD-like cortical atrophy z-score was associated with a lower MoCA score (β = -0.63; 95 % CI, −0.88 to −0.39; *P* value < 0.001). In the sensitivity analysis, increases in PM_{10} (odds ratio, 2.22; 95 % CI, 1.26 to 3.92) and NO_2 (1.73; 1.28 to 2.33) were significantly associated with the risk of suspected MCI (Supplementary Fig. 2). A higher (versus lower) $PM_{2.5}$ concentration was associated with an increased risk of suspected MCI, which did not exhibit statistical significance (odds ratio, 1.52; 95 % CI, 0.92 to 2.52).

3.4. Mediating effect of cortical atrophy on the association between air pollution and cognitive function

The mediation effect of mean cortical thickness on the association between PM_{10} and MoCA score was statistically significant (β = -0.32; 95 % CI, −0.54 to −0.15; *P* value < 0.001); the proportion mediated was 28.0 % (95 % CI, 12.4 % to 63.1 %; *P* value = 0.002) (Table 3). The mediation effect of AD-like cortical atrophy z-score on the association between PM_{10} and MoCA score was statistically significant (β = -0.17; 95 % CI, −0.37 to −0.03; *P* value = 0.014); the proportion mediated was 13.2 % (95 % CI, 2.4 % to 29.5 %; *P* value = 0.014). The mediation effect of mean cortical thickness on the association between $PM_{2.5}$ and MoCA score was statistically significant (β = -0.23; 95 % CI, −0.40 to −0.10; *P* value < 0.001); the proportion mediated was 32.8 % (95 % CI, 12.0 % to 134.1 %; *P* value = 0.014). The mediation effect of AD-like cortical atrophy z-score on the association between $PM_{2.5}$ and MoCA score was not statistically significant (β = 0.00; 95 % CI, −0.13 to 0.14; *P* value = 0.99). The mediation effect of mean cortical thickness on the association between NO_2 and MoCA score was statistically significant (β = -0.28; 95 % CI, −0.46 to −0.11; *P* value = 0.002); the proportion mediated was 25.3 % (95 % CI, 9.4 % to 45.1 %; *P* value = 0.002). The mediation effect of AD-like cortical atrophy z-score on the association between NO_2 and MoCA score was statistically significant (β = -0.19; 95 % CI, −0.33 to −0.08; *P* value < 0.001); the proportion mediated was 15.8 % (95 % CI, 7.2 % to 27.4 %; *P* value < 0.001).

Table 2
Associations between exposures (air pollutants), mediators (mean cortical thickness and AD-like cortical atrophy score), and the outcome (cognitive test score).

	β(95 % CI)	p
Exposure to mediator (mean cortical thickness)		
PM_{10}	−0.04 (-0.05 to −0.02)	<0.001
$PM_{2.5}$	−0.03 (-0.04 to −0.01)	0.001
NO_2	−0.05 (-0.05 to −0.04)	<0.001
Exposure to mediator (AD-like cortical atrophy z-score)		
PM_{10}	0.27 (0.06 to 0.48)	0.013
$PM_{2.5}$	0.00 (-0.20 to 0.19)	0.97
NO_2	0.35 (0.25 to 0.45)	<0.001
Exposure to outcome (cognitive test score)		
PM_{10}	−1.13 (-1.73 to −0.53)	<0.001
$PM_{2.5}$	−0.69 (-1.23 to −0.14)	0.014
NO_2	−1.09 (-1.40 to −0.78)	<0.001
Mediator to outcome (cognitive test score)		
Mean cortical thickness	0.91 (0.62 to 1.19)	<0.001
AD-like cortical atrophy z-score	−0.63 (-0.88 to −0.39)	<0.001

Abbreviations. AD: Alzheimer's disease, MoCA: Montreal Cognitive Assessment, PM_{10}: particulate matter, aerodynamic diameters ≤ 10 μm, $PM_{2.5}$: particulates, diameters ≤ 2.5 μm, NO_2: nitrogen dioxide, CI: confidence interval.
Footnotes: A greater AD-like cortical atrophy z-score indicates greater similarity to the representative cortical atrophy pattern of patients with AD. Beta coefficients (per 10-unit increase in PM_{10} and NO_2; median [25.7 μg/m^3] or higher versus lower $PM_{2.5}$; per 0.1 mm increase in mean cortical thickness; per 1 increase in AD-like cortical atrophy z-score) were from linear regression models, adjusted for age, sex, years of education, history of hypertension, history of diabetes mellitus, history of angina or myocardial infarction, smoking status, alcohol consumption, body mass index, and enrollment year. Age and years of education were not included in the model regressing the AD-like cortical atrophy score because scores were age- and education level-corrected.

3.5. Mediating effect of cortical atrophy on the association between air pollution and suspected mild cognitive impairment

The mediation effect of mean cortical thickness on the association between PM_{10} and suspected MCI was statistically significant (odds ratio, 1.002; 95 % CI, 1.000 to 1.010); the proportion mediated was 17.0 % (95 % CI, 2.6 % to 55.3 %) (Supplementary Table). The mediation effect of AD-like cortical atrophy z-score on the association between PM_{10} and suspected MCI was statistically significant (odds ratio, 1.001; 95 % CI, 1.000 to 1.004); the proportion mediated was 10.8 % (95 % CI, 1.3 % to 28.7 %). The mediation effect of mean cortical thickness on the association between NO_2 and suspected MCI was not statistically significant (odds ratio, 1.006; 95 % CI, 0.997 to 1.020). The mediation effect of AD-like cortical atrophy z-score on the association between NO_2 and suspected MCI was statistically significant (odds ratio, 1.005; 95 % CI, 1.001 to 1.010); the proportion mediated was 17.8 % (95 % CI, 4.1 % to 41.3 %). For $PM_{2.5}$, none of the proportions mediated

Table 3
Mediating effects of mean cortical thickness and AD-like cortical atrophy scores on associations between air pollution and cognitive test scores.

Mediator		Outcome: Cognitive test (MoCA) score					
		Exposure to PM_{10}		Exposure to $PM_{2.5}$		Exposure to NO_2	
		β(95 % CI)	p	*β*(95 % CI)	p	*β*(95 % CI)	p
Mean cortical thickness	Mediation effect	−0.32 (-0.54 to −0.15)	<0.001	−0.23 (-0.40 to −0.10)	<0.001	−0.28 (-0.46 to −0.11)	0.002
	Direct effect	−0.81 (-1.41 to −0.24)	0.012	−0.46 (-0.98 to 0.10)	0.11	−0.82 (-1.16 to −0.49)	<0.001
	Total effect	−1.13 (-1.72 to −0.59)	0.002	−0.69 (-1.23 to −0.13)	0.014	−1.09 (-1.41 to −0.81)	<0.001
	*Proportion Mediated, %**	28.0 (12.4 to 63.1)	0.002	32.8 (12.0 to 134.1)	0.014	25.3 (9.4 to 45.1)	0.002
AD-like cortical atrophy z-score	Mediation effect	−0.17 (-0.37 to −0.03)	0.014	0.00 (-0.13 to 0.14)	0.99	−0.19 (-0.33 to −0.08)	<0.001
	Direct effect	−1.11 (-1.70 to −0.58)	<0.001	−0.66 (-1.19 to −0.13)	0.012	−1.01 (-1.31 to −0.72)	<0.001
	Total effect	−1.28 (-1.87 to −0.73)	<0.001	−0.66 (-1.19 to −0.11)	0.024	−1.20 (-1.51 to −0.91)	<0.001
	*Proportion Mediated, %**	13.2 (2.4 to 29.5)	0.014	−0.3 (-39.6 to 26.7)	0.99	15.8 (7.2 to 27.4)	<0.001

Abbreviations. AD: Alzheimer's disease, MoCA: Montreal Cognitive Assessment, PM_{10}: particulate matter, aerodynamic diameters ≤ 10 μm, $PM_{2.5}$: particulates, diameters ≤ 2.5 μm, NO_2: nitrogen dioxide, CI: confidence interval.
Footnotes: Beta coefficients (per 10-unit increase in PM_{10} and NO_2; median [25.7 μg/m^3] or higher versus lower $PM_{2.5}$) from causal mediation models with bootstrapping (1,000 iterations). Mediation models were adjusted for age, sex, years of education, history of hypertension, history of diabetes mellitus, history of angina or myocardial infarction, smoking status, alcohol consumption, body mass index, and enrollment year. Age and years of education were not included in the model regressing the AD-like cortical atrophy score because scores were age- and education level-corrected.
* Proportion mediated = beta coefficient of mediation effect/beta coefficient of total effect × 100.

were statistically significant.

4. Discussion

This study investigated the effect of air pollution exposures on cortical atrophy, and, for the first time, found that this effect led to poorer cognitive function and suspected MCI in individuals without dementia. We used an AD-specific cortical atrophy marker that is a novel, machine learning-based approach used to assess AD pathology on brain MRI. One main finding was that PM_{10} and NO_2 exposures were associated with both global cortical atrophy and AD-like cortical atrophy. PM_{10} and NO_2 exposures were also associated with poorer cognitive function. These associations were mediated by both global cortical atrophy and AD-like cortical atrophy. Global cortical atrophy contributed 28 % to the association between PM_{10} and MoCA score, and AD-like cortical atrophy contributed 13 %. Global cortical atrophy contributed 25 % to the association between NO_2 and MoCA score, and AD-like cortical atrophy contributed 16 %. In contrast, the association between $PM_{2.5}$ and MoCA score was only mediated by global cortical atrophy, which contributed 33 % to the association.

Neuroimaging studies have examined brain regions associated with air pollution exposures; their findings vary (Casanova et al. 2016; Chen et al. 2015; Cho et al. 2020; Power et al. 2018). These varied results may imply that some brain regions are particularly susceptible to air pollution exposure and, simultaneously, provide insights into the mechanism of how air pollution exposure increases the risk of AD. To examine whether air pollution exposures induce AD-specific brain structural changes, a neuroimaging study estimated AD signatures for cortical thickness by averaging cortical thicknesses in brain regions selected based on previous literature (Crous-Bou et al. 2020). This previous study found inverse associations of PM_{10} and NO_2 concentrations with the AD signature measure, with borderline significance. In the present study, we used a measure for AD-specific cortical atrophy similarity developed using machine learning of brain MRI data from individuals with normal cognition and patients with AD (with 91 % of accuracy) (Lee et al. 2018). We found that increased concentrations of PM_{10} and NO_2 were significantly associated with greater similarity of an individual's cortical atrophy pattern to that of a patient with AD. It is noteworthy that $PM_{2.5}$ was not significantly associated with AD-specific cortical atrophy score in the present study, aligned with the previous study using AD signatures for cortical atrophy (Crous-Bou et al. 2020). Collectively, we suggest that PM_{10} and NO_2 exposures may induce neurodegeneration (manifested as cortical atrophy) in the AD-specific manner. Exposure to $PM_{2.5}$ may promote global cortical atrophy, but this effect might not involve AD-specific pathology. The other AD pathologies such as brain beta-amyloid and tau burden may also be associated with air pollution exposures in individuals without dementia, as demonstrated in recent studies (Alemany et al. 2021; Ma et al. 2022). Future studies need to examine whether the effect of air pollution exposures on beta-amyloid and tau burden induces AD-specific cortical atrophy and, consequently, cognitive impairment.

Although it is readily assumed that cortical atrophy precedes cognitive impairment, there is a lack of evidence suggesting that the effect of air pollution on preclinical cortical atrophy can lead to clinically apparent cognitive impairment. This study was the first to demonstrate that brain cortical atrophy mediated the effect of air pollution exposures on cognitive function in individuals without dementia. More specifically, the pathway through global cortical atrophy contributed 25 %–28 % to the total effect of PM_{10} or NO_2 exposures on cognitive function, and that through AD-like cortical atrophy contributed 13 %–16 %. One hypothesis based on these findings is that there are mediators other than gray matter cortical atrophy. For example, white matter changes (e.g., small brain infarcts) and burden of beta-amyloid and tau proteins are known to be associated with air pollution exposures (Alemany et al. 2021; Ma et al. 2022; Wilker et al. 2015) as well as faster cognitive decline (Chun et al. 2022; Hamilton et al. 2021; Shen et al. 2020). These pathologies might contribute to the linkage between air pollution and cognitive function. Another hypothesis is that a pathway through non-AD-like cortical atrophy exists in the relationship between air pollution exposures and cognitive function. Some studies found that air pollution exposures are associated with increased risks of vascular dementia (Li et al. 2019) and Parkinson's disease (Jo et al. 2021; Ritz et al. 2016). Cortical atrophy due to these non-AD types of dementia might also have a mediating role in the association between air pollution and cognitive function. Notwithstanding we did not provide evidence on these non-AD-related mechanisms or other AD pathologies such as amyloid beta and tau burden, the efforts to detect preclinical AD-specific brain structural phenotypes associated with air pollution exposures may widen the window of opportunity for early intervention with a view to reducing the burden of AD, the most common form of dementia, attributable to air pollution exposures.

There are several limitations to be noted. First, we performed a mediation analysis using cross-sectional data, in which brain images (for mediators) and MoCA scores (for outcomes) were collected at the same point in time. However, the mediation hypothesis we tested was formulated on sufficient evidence that preclinical cortical atrophy precedes cognitive impairment given the concept of AD continuum (Jack et al. 2013; Jack et al. 2010). Second, the AD-like cortical atrophy score we used may not be generalizable to other populations, as the machine learning-based scoring algorithm was developed using data from

patients with AD and individuals with normal cognition in the Republic of Korea (Lee et al. 2018). Although one study found no differences in AD-like cortical atrophy patterns between ethnic populations (Fan et al. 2019), our results based on the AD-like cortical atrophy scoring method may require replication in other populations. Third, the prediction of $PM_{2.5}$ concentrations was performed using air pollution monitoring data in 2015 only (as the nationwide monitoring of $PM_{2.5}$ commenced in 2015 in the Republic of Korea). This means that the baseline survey preceded the exposure data in participants who were enrolled in 2014 (n = 116, 18.1 %). We disregarded temporality and only considered spatial variation in $PM_{2.5}$ within the study areas in the year 2015, which may be the reason for the narrow range of $PM_{2.5}$ concentrations from 24.1 to 28.1 μg/m^3 (mean, 25.9 μg/m^3; SD, 0.7 μg/m^3) in our study population. This insufficient exposure variation might have led to the null association between $PM_{2.5}$ and AD-like cortical atrophy. Last, we could only define 'suspected MCI' using the MoCA, a screening tool for MCI. To minimize the possibility of overestimating prevalence of suspected MCI, we applied the cutoff value (≤19 points) that yielded the highest positive predictive value (83 %) to discriminate MCI (Lee et al. 2008). The prevalence of suspected MCI in our study population was 18 %, which was similar to that from a *meta*-analysis including over 0.2 million community-dwelling individuals aged 50 years or older (mean, 16 %; 95 % CI, 13 to 18 %) (Bai et al. 2022).

In summary, we found that PM_{10} and NO_2 exposures were associated with global cortical atrophy, AD-like cortical atrophy, and cognitive function. Both global and AD-like cortical atrophy mediated the associations of PM_{10} and NO_2 exposures with cognitive function. Almost 30 % of the effect of PM_{10} or NO_2 exposures on cognitive function was mediated by global cortical atrophy, and up to 16 % of the effect was mediated by AD-like cortical atrophy. This study found that the effects of PM_{10} and NO_2 exposures on cognitive function were partly explained by global cortical atrophy and AD-like cortical atrophy.

CRediT authorship contribution statement

Jaelim Cho: Conceptualization, Methodology, Writing – original draft. **Heeseon Jang:** Data curation, Software, Visualization. **Hyunji Park:** Data curation, Software, Visualization. **Young Noh:** Data curation, Investigation, Methodology, Writing – review & editing. **Jungwoo Sohn:** Data curation, Investigation. **Sang-Baek Koh:** Data curation, Investigation. **Seung-Koo Lee:** Investigation, Methodology. **Sun-Young Kim:** Data curation, Methodology, Writing – review & editing. **Changsoo Kim:** Supervision, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

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