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Impact of Long-Term Exposure to Air Pollution on Cognitive Decline in Older Adults Without Dementia

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Abstract.
Background: Air pollution control is necessary to decrease the burden on older adults with cognitive impairment, especially in low- and middle-income countries (LMICs).
Objective: This study retrospectively examined the effect of cumulative exposure to air pollution, including NO_2, SO_2, CO, fine particulate matter $(PM)_{10}$, $PM_{2.5}$, and O_3, on cognitive function in older individuals.
Methods: Community-dwelling older adults who underwent the Mini-Mental State Examination (MMSE) from 2007 to 2018 were included in the analyses. We excluded older individuals diagnosed with dementia at baseline, while those who had completed more than two MMSE tests were included in the longitudinal analyses. Baseline MMSE and changes in MMSE scores were analyzed according to 5-year average concentrations of the district-level air pollutants, after controlling for covariates associated with cognitive decline in older adults.
Results: In total, 884,053 (74.3 ± 7.1 years; 64.1% females) and 398,889 (72.3 ± 6.4 years; 67.0% females) older individuals were included in the cross-sectional and longitudinal analyses, respectively. Older individuals exposed to higher levels of NO_2, SO_2, CO, and PM_{10} showed lower baseline MMSE scores. During follow-up, exposure to higher levels of NO_2, SO_2, CO, and PM_{10} was associated with greater decreases in MMSE scores in older individuals; for O_3, the opposite pattern was observed.
Conclusion: Our findings suggest that exposure to high levels of air pollutants can worsen the cognitive performance of older adults without dementia. Efforts to reduce air pollution in LMICs that have similar levels of pollutants to South Korea are necessary to reduce the burden on older adults with cognitive impairment.

Keywords: Air pollution, cognition, cognitive decline, older adults, South Korea

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INTRODUCTION

The air pollution associated with industrialization is a growing problem implicated in several diseases. Many previous studies have demonstrated the neurotoxicity of air pollutants, as well as convincing associations with neurodegenerative diseases such as Alzheimer's disease [1–7]. In 2020, the Lancet Commission suggested that air pollution is one of the most important factors to target for dementia prevention [8]. They also suggested that the benefits of interventions to address air pollution would be greater in low- and middle-income countries (LMICs) than in developed countries.

Air pollution is mainly composed of gaseous pollutants, such as NO_2, SO_2, CO, and O_3, as well as fine particulate matter (PM) including PM_{10} (aerodynamic diameter ≤ 10 μm) and $PM_{2.5}$ (diameter ≤ 2.5 μm). In urban areas, the major source of air pollutants is traffic (due to direct emission of fossil fuels). O_3 is generated by photochemical reactions of various substances, such as nitrogen oxide (NOx) and carbon-containing compounds. Several systematic reviews have examined the associations of air pollutants with dementia and cognitive decline. In one such review, greater exposure to NO_2/NOx and $PM_{2.5}$ was associated with an increased risk of dementia, while the relationship with cognitive decline was less clear. For O_3, results have been mixed; both positive and negative associations with dementia risk have been reported [9]. Another recent review including both longitudinal and cross-sectional studies showed that, among PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2, and CO, only $PM_{2.5}$ and O_3 were associated with an increased risk of Alzheimer's disease [10]. A small number of longitudinal studies examined the influence of air pollution on performance in repeated cognitive tests. Among three cohort studies investigating cognitive decline over an average period of 5 years, only two showed a significant relationship between exposure to high levels of air pollution and cognitive decline [1, 5, 6]. These inconsistent results may be due to differences in the methods used to analyze air pollution and cognitive function. Also, those studies were conducted in countries with relatively low air pollution (the US, UK, and Sweden), so may not generalize to older populations worldwide.

South Korea is now one of the most economically developed countries in the world, having experienced rapid socioeconomic changes. As economic development was the top priority in South Korea, air pollution regulations were actually started in the 1990s [11]. The levels of air pollutants in South Korea exceed the World Health Organization (WHO) guidelines [12]. In particular, the PM level is higher than in Europe and the US, although it is lower than in China and Taiwan. South Korea has the fastest-aging population in the world, and the increasing number of dementia patients has become a serious social issue. LMICs are also experiencing a rapid increase in dementia cases. Therefore, a longitudinal analysis of the association between air pollution and cognitive health in older South Korean adults could have implications for policies aimed at reducing the effects of air pollution on cognitive health worldwide.

In this study, we performed cross-sectional and longitudinal analyses of the relationship between exposure to air pollutants and cognitive function in non-demented older South Korean adults. We analyzed a 16-year dataset of air pollutants and a 12-year dataset comprising the cognitive test scores of older adults living in Seoul. Data collected by the National Ambient Air Monitoring System (NAMIS) on district-level air pollutants, including NO_2, SO_2, CO, PM_{10}, $PM_{2.5}$, and O_3, were used. We hypothesized that older adults exposed to higher levels of air pollutants would show a greater decline in global cognitive function.

MATERIALS AND METHODS

Study population

In total, 916,022 adults aged over 60 years were screened for the present study. They underwent the Mini-Mental State Examination (MMSE) in community centers for dementia (CCDs) in Seoul, during the period 2007–2018. Since 2007, these centers have provided services aimed at preventing and screening for dementia, and rehabilitating sufferers. There are 25 CCDs in each district of Seoul. For individuals aged 60 years and above, completing the MMSE every year at a CCD is recommended. Older adults with low MMSE scores (age-, sex-, and education-adjusted z-score < -1.5) are referred for a diagnostic interview with a psychiatrist or neurologist, and also complete a comprehensive neurocognitive test battery. We excluded individuals without information on place of residence, and those diagnosed with dementia at the baseline assessment. Finally, 884,053 participants were included in our cross-sectional analysis; those who completed more than two MMSE tests were also included in the longitudinal analysis ($n = 398{,}889$) (Fig. 1).

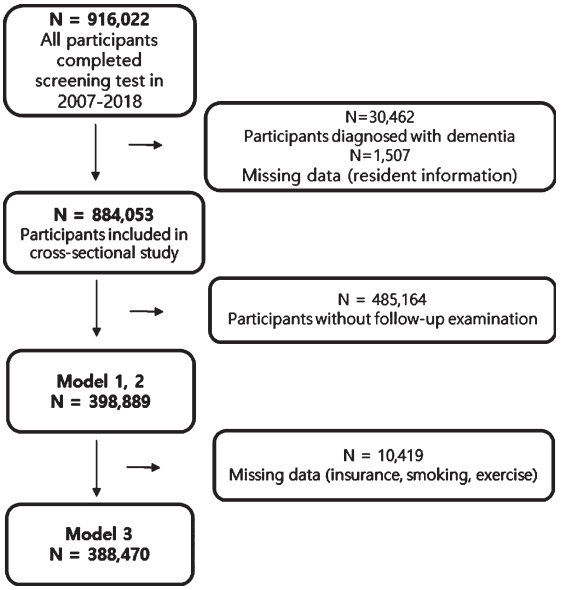

Fig. 1. Flowchart of the study.

Cognitive function

All participants completed the MMSE as a screening test of global cognitive function. Three different tests, all translated into Korean, were used in each CCD: the Korean version of the MMSE used by the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (MMSE-KC), the Korean MMSE (K-MMSE), and the MMSE for Dementia Screening (MMSE-DS) [13–17]. These tests were used to screen 41.5%, 23.4%, and 35.2% of the participants, respectively. Age-, sex-, and education-adjusted normative data for each measure were reported in previous studies and indicated no differences in screening effectiveness among the three tests.

Participants with low MMSE scores (z-score <-1.5) were further examined and classified as cognitively normal, mild cognitive impairment, or dementia. Semi-structured interviews were conducted by psychiatrists and neurologists, and comprehensive neuropsychological tests were completed.

Air pollutants

Every district of Seoul has several sites that monitor air pollutants in real time. The public can access nationwide air pollution data published online by the Korean Ministry of Environment (https://www.airkorea.or.kr). The pollutants are measured in different ways; NO_2 is measured by the chemiluminescent method on an hourly basis, SO_2 by the UV fluorescence method, CO by the non-dispersive infrared method, PM_{10} and $PM_{2.5}$ by the β-ray absorption method, and O_3 by the UV photometric method.

We analyzed the annual mean levels of air pollutants across 25 districts in Seoul from 2003 to 2018. $PM_{2.5}$ data were only available from 2013, so the 5-year dataset for the period 2013–2018 was analyzed. Previous longitudinal studies observed long-term effects of air pollutants (over 3–5 years) [5, 6]. We also matched previous 5-year averages of air pollutants before each MMSE test with each individual's corresponding MMSE scores. If an individual moved to another district during the study period, the levels of air pollutants in the new district were reflected in the analyses. Matched 5-year average concentrations of all air pollutants were subjected to both cross-sectional and longitudinal analyses except $PM_{2.5}$, for which the 1-year average concentration was assessed in cross-sectional analysis.

Covariates

The analyses included demographic factors (age, gender, years of education), socioeconomic factors (marital status, living arrangements, type of medical insurance), vascular risk factors (diabetes mellitus, hypertension, hyperlipidemia, coronary vessel disease, stroke), history of depressive disorder, family history of dementia, and other health-related lifestyle factors (smoking, physical activity) as covariates. The level of physical activity was assessed using the short-form Korean version of the International Physical Activity Questionnaire (IPAQ) [18], and we calculated metabolic equivalent task (MET) hours per week based on the IPAQ data [19]. The MET scores were multiplied by the number of hours per week for each activity type, with the summed values included in the analysis.

Statistical analysis

For the cross-sectional analysis, the baseline MMSE scores of each participant were analyzed according to the 5-year average concentrations of NO_2, SO_2, CO, PM_{10}, and O_3, and the 1-year average concentration of $PM_{2.5}$: the quartiles of individual pollutants were used in a general linear model. Age, sex, years of education, and MMSE type (MMSE-KC, K-MMSE, or MMSE-DS) were adjusted for as covariates.

Table 1
Baseline characteristics of participants

Sample characteristic	Cross-sectional study ($n = 884,053$)	Longitudinal study ($n = 398,889$)
Baseline age, mean ± SD	74.3 ± 7.1	72.3 ± 6.4
Female, *n* (%)	567,008 (64.1)	267,121 (67.0)
Education, mean ± SD	7.8 ± 5.1	7.4 ± 5.1
Living alone, *n* (%)	191,900 (21.7)	103,777 (26.1)
Medicaid[a], *n* (%)	78,323 (8.9)	44,294 (11.1)
Ever smoker, *n* (%)	192,573 (21.7)	78,527 (19.6)
Level of physical activity[b], mean ± SD	13.9 ± 23.0	15.2 ± 23.4
Vascular risk factors		
Diabetes, *n* (%)	173,973 (19.7)	87,780 (22.0)
Hypertension, *n* (%)	447,982 (50.7)	226,957 (56.9)
Dyslipidemia, *n* (%)	157,878 (17.9)	86,121 (21.6)
Coronary vascular disease, *n* (%)	16,867 (1.9)	10,696 (2.7)
Stroke, *n* (%)	38,683 (4.4)	19,991 (5.0)
Diagnosis of depression, *n* (%)	9,864 (1.1)	5,683 (1.4)
Family history of dementia, *n* (%)	28,118 (3.2)	13,568 (3.4)
Baseline MMSE score, mean ± SD	25.0 ± 4.3	25.2 ± 3.6
Follow-up numbers		
2, *n* (%)		183,087 (45.9)
3, *n* (%)		96,356 (24.1)
4, *n* (%)		54,610 (13.7)
≥5, *n* (%)		64,836 (16.3)
Duration of follow-up (y), mean ± SD		4.20 ± 2.35

MMSE, Mini-Mental State Examination. [a]Participants who were covered by the National Medical Aid program. [b] Physical activity was assessed using a modified Korean version of the International Physical Activity Questionnaire (IPAQ) and then transformed to total metabolic equivalent task (MET) hours per week based on the IPAQ guidelines.

For the longitudinal analysis, individual-level changes in MMSE were analyzed according to time-varying exposure to air pollutants using a generalized estimating equation (GEE) model. Correlations among scores within the same individual were examined using an exchangeable working correlation matrix. The 5-year average concentrations of air pollutants before each MMSE follow-up test were included in the models. Therefore, the changes in air pollutants during the whole follow-up period were reflected in the longitudinal analyses. As stated above, data on $PM_{2.5}$ were only available for the period 2013–2018, so $PM_{2.5}$ was omitted from the longitudinal analysis.

The associations of air pollutants (as continuous and categorical [quartile] variables) with cognitive changes were analyzed. We defined the quartiles of air pollutants based on the data for the whole study period. As the levels of air pollutants changed during the observation period, the quartile for an individual participant would also change according to the ranges of 5-year air pollution at the time before their MMSE examination. The first model was adjusted for age, gender, years of education, baseline MMSE score, MMSE type, and time between the baseline and follow-up visits (Model 1). The second model was also adjusted for vascular risk factors (previous history of diabetes, hypertension, dyslipidemia, coronary heart disease, stroke), diagnosis of depressive disorder, and family history of dementia (Model 2). The third model adjusted for all the covariates included in Model 2, along with type of medical insurance, cohabitation status (living alone or not), smoking status (ever-smoker or not), and level of physical activity. All statistical analyses were performed using SPSS software (version 23.0; IBM Corp., Armonk, NY, USA).

RESULTS

Participant characteristics

Table 1 summarizes the characteristics of the participants included in the cross-sectional ($n = 884,053$) and longitudinal ($n = 398,889$) analyses. For the entire cohort, the mean age at baseline was 74.3 ± 7.1 years; 64.1% of the cohort were female, and the mean years of education were 7.8 ± 5.1. The mean baseline MMSE score was 25.0 ± 4.3. The participants in the longitudinal analysis showed similar demographic characteristics to the overall cohort, although they were slightly younger (72.3 ± 6.4 years). In total,

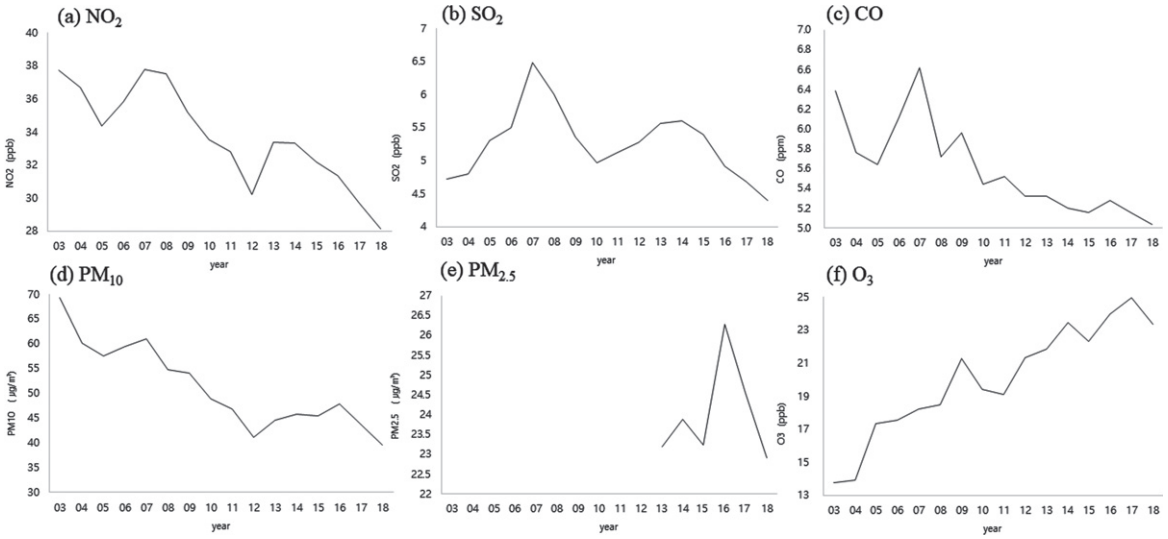

Fig. 2. Pooled estimates of changes in ambient air pollution for all study sites (2003–2018).

45.9% of the participants in the longitudinal analysis completed two MMSE tests, while 16.3% completed more than five. The mean follow-up duration was 4.20 ± 2.35 years.

Ambient air pollutants

During the period 2003–2018, the levels of NO_2 (mean = 34.0 ppb; min = 28.2 ppb; max = 37. ppb), SO_2 (mean = 5.30 ppb; min = 4.40 ppb; max = 6.48 ppb), CO (mean = 0.60 ppm; min = 0.50 ppm; max = 0.66 ppm), and PM_{10} (mean = 52.0 $\mu g/m^3$; min = 39.6 $\mu g/m^3$; max = 69.3 $\mu g/m^3$) showed decreasing trends in Seoul, whereas an increasing trend was seen for O_3 (mean = 20 ppb; min = 14 ppb; max = 25 ppb). The observation period was not sufficient to identify a pattern of change in $PM_{2.5}$ (mean = 24.3 $\mu g/m^3$; min = 22.9 $\mu g/m^3$; max = 26.3 $\mu g/m^3$) (Fig. 2).

Figure 3 shows the mean concentrations of six air pollutants during the study period by district. The levels of most of the pollutants tended to be higher in western districts, although a higher level of O_3 was observed in northern districts. Correlation analyses among air pollutants revealed that areas with higher levels of NO_2 showed lower levels of O_3 ($r = -0.60$, $p = 0.001$).

Cross-sectional associations between exposure to air pollutants and cognitive function

Table 2 shows the distribution of baseline MMSE scores across air pollutant quartiles. Older adults living in areas with higher levels of NO_2, SO_2, CO, and PM_{10}, but not $PM_{2.5}$ or O_3, showed lower MMSE scores after controlling for age, sex, years of education, and type of MMSE. Adjustment for additional covariates, such as vascular risk factors, history of depression, family history of dementia, socioeconomic status, smoking, and physical activity, did not change the significance of the findings.

Longitudinal associations of time-varying cumulative exposure to air pollutants with cognitive decline

Older adults living in districts with higher levels of NO_2, SO_2, CO, and PM_{10} showed greater declines in MMSE scores than those living in areas with relatively low levels of these air pollutants. These results remained significant, for both categorical (quartile) and continuous measures of air pollutants, after controlling for age, sex, years of education, and type of MMSE (Tables 3 and 4). These associations were also seen in Models 2 and 3. In contrast, older adults exposed to high levels of O_3 did not show cognitive decline, except for those in the highest versus lowest O_3 quartile in Model 3 (Table 3).

DISCUSSION

This study revealed associations between exposure to air pollutants and the cognitive function of older adults living in a metropolitan area of South Korea via

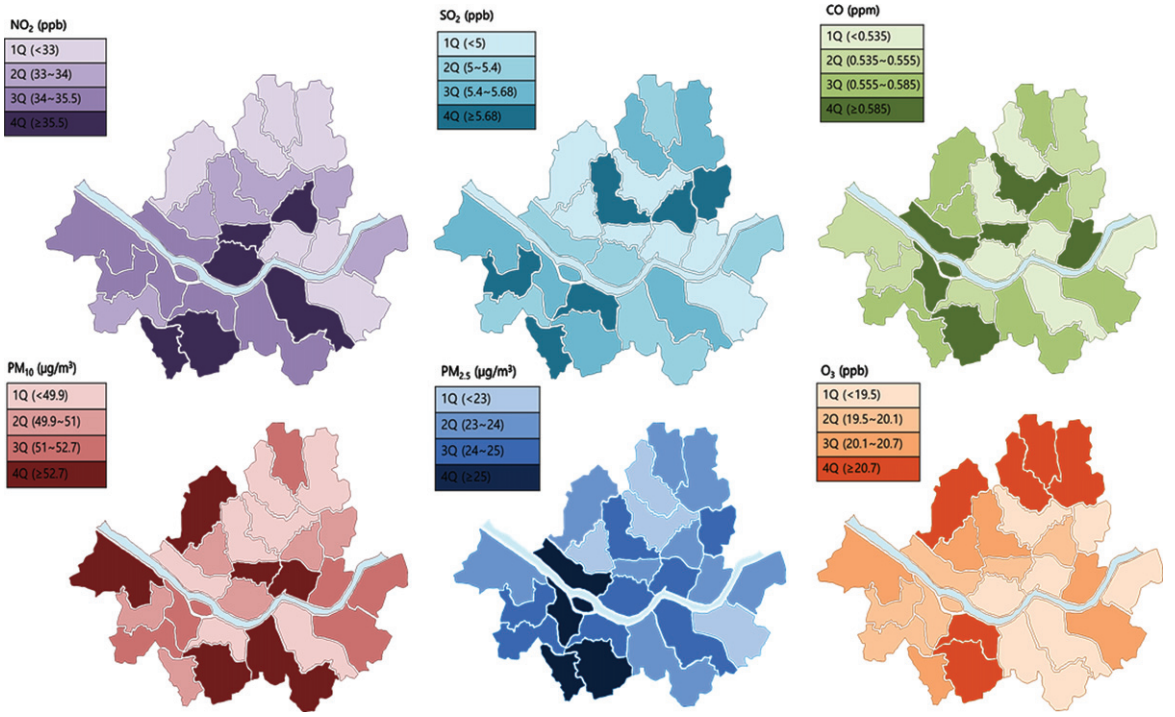

Fig. 3. District-level mean concentrations of air pollutants during the study period (2003–2018) in Seoul.

Table 2
Baseline MMSE scores across the level of air pollutants (quartile groups)

	NO_2 [a]			SO_2 [b]			CO [c]		
	MMSE (mean ± SD)	Adjusted difference [g]	*p*	MMSE (mean ± SD)	Adjusted difference	*p*	MMSE (mean ± SD)	Adjusted difference	*p*
Quartile 1	24.78 ± 4.85	Ref		24.71 ± 4.83	Ref		24.83 ± 4.75	Ref	
Quartile 2	24.79 ± 4.71	0.075	< 0.0001	24.83 ± 4.65	–0.265	< 0.0001	24.70 ± 4.71	–0.365	< 0.0001
Quartile 3	24.57 ± 4.68	–0.265	< 0.0001	24.58 ± 4.79	–0.215	< 0.0001	24.48 ± 4.61	–0.359	< 0.0001
Quartile 4	24.46 ± 4.60	–0.411	< 0.0001	24.38 ± 4.60	–0.161	< 0.0001	24.42 ± 4.72	–0.352	< 0.0001
	PM_{10} [d]			$PM_{2.5}$ [e]			O_3 [f]		
	MMSE (mean ± SD)	Adjusted difference	*p*	MMSE (mean ± SD)	Adjusted difference	*p*	MMSE (mean ± SD)	Adjusted difference	*p*
Quartile 1	25.06 ± 4.73	Ref		24.96 ± 4.82	Ref		24.46 ± 4.66	Ref	
Quartile 2	24.74 ± 4.81	0.101	< 0.0001	24.88 ± 4.72	0.267	< 0.0001	24.50 ± 4.70	0.220	< 0.0001
Quartile 3	24.49 ± 4.76	–0.424	< 0.0001	25.10 ± 4.65	0.214	< 0.0001	24.73 ± 4.73	0.353	< 0.0001
Quartile 4	24.29 ± 4.52	–0.652	< 0.0001	25.10 ± 4.63	0.168	< 0.0001	24.95 ± 4.78	0.613	< 0.0001

NO_2, nitrogen dioxide; SO_2, sulfur dioxide; CO, carbon monoxide; PM10, fine particulate matter ≤ 10 μm in aerodynamic diameter; PM2.5, fine particulate matter ≤ 2.5 μm in aerodynamic diameter; O_3, ozone; ppm: parts per million; ppb, parts per billion; O_3, ozone. [a]NO_2: 1Q under 31.8 ppb, 2Q 31.8 ppb to 34.2 ppb, 3Q 34.2 ppb to 36.2 ppb, 4Q over 36.2 ppb. [b]SO_2: 1Q under 4.9 ppb, 2Q 4.9 ppb to 5.4 ppb, 3Q 5.4 ppb to 6.0 ppb, 4Q over 6.0 ppb. [c]CO: 1Q under 0.52 ppm, 2Q 0.52 ppm to 0.58 ppm, 3Q 0.58 ppm to 0.61 ppm, 4Q over 0.61 ppm. [d]PM10:1Q under 46.4 μg/m^3, 2Q 46.4 μg/m^3 to 50.0 μg/m^3, 3Q 50.0 μg/m^3 to 54.9 μg/m^3, 4Q over 54.9 μg/m^3. [e]PM2.5:1Q under 23 μg/m^3, 2Q 23 μg/m^3 to 24 μg/ m^3, 3Q 24 μg/m^3 to 25 μg/ m^3, 4Q over 25 μg/m^3 groups. [f]O_3: 1Q under 18.6 ppb, 2Q 18.6 ppb to 20.4 ppb, 3Q 20.4 ppb to 21.8 ppb, 4Q over 21.8 ppb. [g]Adjusted for age, sex, education, and type of MMSE test.

cross-sectional and longitudinal analyses. Exposure to higher levels of NO_2, SO_2, CO, and PM_{10} was associated with a worse cognitive test performance at baseline and a greater decrease in global cognitive function over the longest follow-up periods of 11 years. However, exposure to high levels of O_3 was not associated with cognitive decline.

NO_2 and CO are mainly emitted from motor vehicles, while SO_2 is mainly emitted during manufacturing processes [20]. Adverse effects on the

Table 3
Associations of air pollutant (quartile groups) with longitudinal changes in MMSE

	Model 1[a] (n = 398,889)		Model 2[b] (n = 398,889)		Model 3[c] (n = 388,470)	
Air pollutant	Estimate [95% CI]	p	Estimate [95% CI]	p	Estimate [95% CI]	p
NO_2						
Quartile 1	Ref					
Quartile 2	0.010 [–0.010, 0.030]	0.346	0.009 [–0.011, 0.030]	0.360	0.009 [–0.012, 0.029]	0.386
Quartile 3	–0.053 [–0.073, –0.033]	0.012	–0.052 [–0.072, –0.031]	< 0.0001	–0.045 [–0.065, –0.025]	< 0.0001
Quartile 4	–0.120 [–0.141, –0.099]	< 0.0001	–0.118 [–0.139, –0.097]	< 0.0001	–0.103[–0.125, –0.082]	< 0.0001
time	–0.084 [–0.083, –0.076]	< 0.0001	–0.086 [–0.087, –0.080]	< 0.0001	–0.081[–0.085, –0.078]	< 0.0001
SO_2						
Quartile 1	Ref					
Quartile 2	–0.048 [–0.067, –0.028]	< 0.0001	–0.047 [–0.066, –0.027]	< 0.0001	–0.048 [–0.068, –0.028]	< 0.0001
Quartile 3	–0.043 [–0.063, –0.024]	< 0.0001	–0.042 [–0.062, –0.023]	< 0.0001	–0.039 [–0.058, –0.020]	< 0.0001
Quartile 4	–0.139 [–0.161, –0.116]	< 0.0001	–0.137 [–0.159, –0.114]	< 0.0001	–0.131 [–0.153, –0.109]	< 0.0001
time	–0.080[–0.083, –0.076]	< 0.0001	–0.080[–0.083, –0.076]	< 0.0001	–0.079 [–0.082, –0.075]	< 0.0001
CO						
Quartile 1	Ref		Ref		Ref	
Quartile 2	–0.136 [–0.156, –0.116]	< 0.0001	–0.135 [–0.155, –0.116]	< 0.0001	–0.134 [–0.154, –0.114]	< 0.0001
Quartile 3	0.008 [–0.014, 0.029]	0.963	0.007 [–0.015, 0.028]	0.768	0.010 [–0.012, 0.031]	0.401
Quartile 4	–0.066 [–0.085, –0.047]	< 0.0001	–0.065 [–0.084, –0.046]	< 0.0001	–0.062 [–0.081, –0.043]	< 0.0001
time	–0.077 [–0.081, –0.074]	< 0.0001	–0.077[–0.081, –0.074]	< 0.0001	–0.077 [–0.081, –0.074]	< 0.0001
PM_{10}						
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.106 [0.086, 0.126]	< 0.0001	0.106 [0.086, 0.126]	< 0.0001	0.103 [0.083, 0.123]	< 0.0001
Quartile 3	0.062 [0.033, 0.104]	< 0.0001	0.062 [0.033, 0.104]	< 0.0001	0.061 [0.040, 0.081]	< 0.0001
Quartile 4	–0.094 [–0.114, –0.073]	< 0.0001	–0.094 [–0.114, –0.073]	< 0.0001	–0.089 [–0.109, –0.068]	< 0.0001
time	–0.093 [–0.097, –0.090]	< 0.0001	–0.094 [–0.098, –0.090]	< 0.0001	–0.092 [–0.096, –0.088]	< 0.0001
O_3						
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.114 [0.096, 0.132]	< 0.0001	0.113 [0.095, 0.131]	< 0.0001	0.106 [0.088, 0.124]	< 0.0001
Quartile 3	0.131 [0.111, 0.152]	< 0.0001	0.131 [0.111, 0.151]	< 0.0001	0.125 [0.105, 0.145]	< 0.0001
Quartile 4	0.143 [0.122, 0.164]	< 0.0001	0.144 [0.122, 0.165]	< 0.0001	0.133 [0.111, 0.154]	< 0.0001
time	–0.089 [–0.093, –0.086]	< 0.0001	–0.090 [–0.093, –0.086]	< 0.0001	–0.088 [–0.092, –0.084]	< 0.0001

MMSE, Mini-Mental State Examination; PM_{10}, particulate matter with aerodynamic diameter of less than 10 μm; CO, carbon monoxide; O_3, ozone; NO_2, nitrogen dioxide; SO_2, sulfur dioxide. [a]Model 1 = adjusted for age, gender, years of education, baseline MMSE score, type of MMSE test, and time from baseline assessment. [b]Model 2 = Model 1 plus adjusted for numbers of vascular risks, diagnosis of depression, and family history of dementia. [c]Model 3 = Model 2 plus adjusted for socioeconomic status, living alone, smoking, and level of physical activity. NO_2: 1Q under 30.8 ppb, 2Q 30.8 ppb to 32.6 ppb, 3Q 32.6 ppb to 34.4 ppb, 4Q over 34.4 ppb. SO_2: 1Q under 4.8 ppb, 2Q 4.8 ppb to 5.2 ppb, 3Q 5.2 ppb to 5.8 ppb, 4Q over 5.8 ppb. CO: 1Q under 0.50 ppm, 2Q 0.50 ppm to 0.54 ppm, 3Q 0.54 ppm to 0.58 ppm, 4Q over 0.58 ppm. PM_{10}: 1Q under 44.2 μg/m3, 2Q 44.2 μg/m3 to 46.4 μg/m3, 3Q 46.4 μg/m3 to 48.2 μg/m3, 4Q over 48.2 μg/m3. O_3: 1Q under 20 ppb, 2Q 20 ppb to 21.6 ppb, 3Q 21.6 ppb to 22.8 ppb, 4Q over 22.8 ppb.

Table 4
Associations of air pollutants (continuous) with longitudinal changes in MMSE

	Model 1[a] (n = 398,889)		Model 2[b] (n = 398,889)		Model 3[c] (n = 388,470)	
Air pollutant	Estimate [95% CI]	p	Estimate [95% CI]	p	Estimate [95% CI]	p
NO_2	–0.020 [–0.023, –0.018]	< 0.0001	–0.020 [–0.023, –0.018]	< 0.0001	–0.018 [–0.021, –0.015]	0.1009
SO_2	–0.081 [–0.093, –0.070]	< 0.0001	–0.080 [–0.092, –0.069]	< 0.0001	–0.076 [–0.088, –0.065]	< 0.0001
CO	–0.021 [–0.033, –0.009]	< 0.0001	–0.021 [–0.033, –0.009]	< 0.0001	–0.019 [–0.031, –0.007]	< 0.0001
PM_{10}	–0.009 [–0.011, –0.007]	< 0.0001	–0.009 [–0.011, –0.007]	< 0.0001	–0.008 [–0.010, –0.006]	< 0.0001
O_3	0.023 [0.019, 0.026]	< 0.0001	0.023 [0.019, 0.026]	< 0.0001	0.023 [–0.017, 0.024]	< 0.0001

MMSE, Mini-Mental State Examination; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; CO, carbon monoxide; PM_{10}, particulate matter with aerodynamic diameter of less than 10 μm; O_3, ozone. [a]Model 1 = adjusted for age, gender, years of education, baseline MMSE score, type of MMSE test, and time from baseline assessment. [b]Model 2 = Model 1 plus adjusted for numbers of vascular risk factors, diagnosis history of depression, and family history of dementia. [c]Model 3 = Model 2 plus adjusted for socioeconomic status, living alone, smoking, and physical activity.

respiratory and cardiovascular systems of these pollutants have been well-documented [21, 22]. Negative effects of NOx on neurological function and memory have also been suggested [1], as well as an increased risk of dementia [2–4, 23]. Although few studies on the effects of SO_2 exposure on cognitive function have been conducted, one study showed adverse effects of this pollutant on the cerebrovascular system [24]. Regarding CO exposure, accidental CO poisoning has been shown to cause headache, dizziness, and coma as well as cognitive impairment [25], and ambient CO may be a risk factor for dementia [3].

The present study confirmed longitudinal associations of NO_2, SO_2, and CO with cognitive decline in older adults residing in an urban area. NO_2, SO_2, and CO mainly enter the body through the respiratory tract and can affect the brain via the blood circulation. Pollutants can also enter the brain through the nose, increasing the production of reactive oxygen species (ROS) and affecting the mitochondrial respiratory system and cellular energy utilization [26, 27]. Impaired cellular metabolism can cause neuronal apoptosis and structural brain damage [28] and the expression of Alzheimer's disease-related proteins (amyloid-β [Aβ] and tau) is affected by pollutants. In animal studies, rats exposed to SO_2 showed increased levels of proinflammatory cytokines, as well as overproduction of Aβ in the brain [29]. Moreover, increased expression of tau protein was observed in patients with CO poisoning [30]. These findings suggest that air pollutants from motor vehicles and manufacturing processes play an important role in cognitive impairment and the development of neurodegenerative diseases. Fortunately, due to global policies aimed at reducing these pollutants, NO_2, SO_2, and CO levels have shown a gradual decrease in many countries, including South Korea.

Recently, the adverse health effects of PM on cognitive function have been attracting more attention. In Seoul, although the overall level of PM_{10} is decreasing, the number of days with very high levels of PM (defined as $PM_{10} \geq 151\ \mu g/m^3$ or $PM_{2.5} \geq 76\ \mu g/m^3$) is in fact increasing [20]. Studies from the UK and China showed that increased levels of PM_{10} were related to poorer cognitive function in older adults [6, 31], although the Chinese study used an air pollution index that also included NO_2 and SO_2. A longitudinal relationship of PM_{10} exposure with cognitive decline was confirmed in our analyses, even in relatively healthy older adults without dementia. PM_{10} induces the expression of several inflammatory factors, including interleukin (IL)-1, tumor necrosis factor-alpha, and IL-6, after entering the body. These systemic inflammatory factors can disrupt the blood-brain-barrier and thus reach the central nervous system (CNS). Subsequent microglial activation triggers oxidative stress and neuroinflammation, which can lead to cognitive impairment [32, 33]. Recent studies using amyloid imaging also suggested that PM_{10} can promote Aβ deposition in the brain and thus increase the risk of Alzheimer's disease [34, 35].

Several studies showed that high levels of $PM_{2.5}$ affect cognitive function in older adults [5, 6] with some reporting that $PM_{2.5}$ exposure increases the risk of dementia [2, 36]. However, in other studies, $PM_{2.5}$ exposure was not associated with cognitive impairment [37, 38], similar to our results. As we only had $PM_{2.5}$ data from 2013 onward, we analyzed the 1-year average $PM_{2.5}$ concentration, as opposed to the 5-year average concentrations analyzed for the other pollutants; this might explain our unexpected results. Moreover, the level of $PM_{2.5}$ in Seoul is higher (range: 19–29 $\mu g/m^3$) than in the US (1.3–19.8 $\mu g/m^3$) [23, 38], although it is lower than in other Asian countries, such as Taiwan and China (10.7–122.3 $\mu g/m^3$) [24, 36]. The ambient $PM_{2.5}$ concentration exceeding regulatory standards may have contributed to the lack of significant findings in our study. In addition, the $PM_{2.5}$ levels were within a narrow range throughout the study area. Thus, the moderate levels and small variation of $PM_{2.5}$ could also have contributed to the lack of association of $PM_{2.5}$ with cognitive impairment in the present study. Alternatively, it is possible that PM_{10} and $PM_{2.5}$ act differently in the body; the absorption and deposition of PM in the airway can be influenced by the size of the particles [33]. PM_{10} induces a greater inflammatory reaction than $PM_{2.5}$, which may be explained by the endotoxins in PM_{10} [39].

Although the O_3 level is relatively low in Seoul (20–22.8 ppb) compared to other cities (typically > 26 ppb) [24, 36, 38, 40], we nevertheless found that it increased over the study period. Increased O_3 is known to be associated with global temperature increases, as well as changes in the NO_2/NOx emission ratio from motor vehicles [41]. In the present study, O_3 generally did not show an association with cognitive decline in older adults. Previous studies reported inconsistent findings: some suggested that higher O_3 increased the risk of dementia [34, 36], while others showed no such association, or even an inverse one [2, 23, 40]. Another study revealed that O_3 was not associated with Aβ deposition in the

brain [42]. As a possible explanation for these negative results, inhaled gases like O_3 cannot enter the CNS directly; rather, they can provoke chronic lung inflammation and affect the brain indirectly through proinflammatory factors [36]. In addition, we found a negative correlation between the levels of O_3 and NO_2 in Seoul: districts showing higher levels of O_3 had lower levels of NO_2, where this low NO_2 might explain our finding of a general lack of association between O_3 exposure and cognitive impairment. Some studies also reported negative correlations of O_3 with various other air pollutants [43–45], and a study conducted in South Korea revealed that higher O_3 was associated with a lower risk of Meniere's disease [46]. The biological mechanisms underlying these results should be studied further.

Strengths and limitations

The present study had several strengths. First, we included a large number of relatively healthy older adults without dementia. The total number of older adults (aged ≥ 65 years) in Seoul was 1,561,139 in 2020, and more than half of these ($n = 884,053$) were included in our analyses; this was achieved via our community-based dementia screening and follow-up program. Second, we analyzed long-term observational data, with the longest follow-up duration of 11 years. Also, we analyzed time-varying concentrations of air pollutants to obtain insight into the effects of changing air pollutant levels on cognitive decline in older adults. Third, we adjusted for important confounders that affect cognitive function in older adults, such as vascular risk factors, history of depression, family history of dementia, socioeconomic status, smoking, and physical activity. As this study was conducted in a single metropolitan city with homogenous environmental and socioeconomic conditions, local differences among districts were not adjusted for. Finally, the air pollutant data in this study were obtained at ground-level sites in each district, which differs from some previous studies estimating ambient air pollution according to the proximity of the nearest major road [6, 7] or using a land use regression model [1, 4].

Some limitations of this study should be also discussed. First, our data were collected retrospectively from a CCD database, and there may have been a selection bias toward healthier older adults worried about dementia; such individuals are likely to have undergone tests at CCDs more frequently. Therefore, prospectively designed studies are needed to confirm our results. Second, this study was conducted in a single metropolitan city, so the air pollutant levels were within a narrow range. Nevertheless, even small differences in the levels of each pollutant could explain variations in cognitive function among the older adults. Our findings could inform policies aimed at mitigating the deleterious effects of air pollution worldwide, especially on cognitive function in the older population; the results indicate that even a small decrease could be beneficial. Third, our air pollutant exposure estimates were based on each individual's address and data from district-level monitoring sites; whether participants traveled to other regions during the daytime was not considered. However, we assumed that the participants were unlikely to travel frequently to other districts, as most of them were retired. Fourth, although most of the analyses showed significant results the actual effect size was small. Our large sample size which may contribute to detect theses small effects should be considered in interpreting our results. Fifth, we used the MMSE to assess older adults' cognitive function. However, this instrument has limitations for measuring cognitive decline in a healthy population, such as our subjects, due to the ceiling effect. Although significant changes in MMSE scores were found in this study, the MMSE may have limited sensitivity for detecting mild cognitive changes in cognitively healthy participants. Also, we did not investigate whether the impact of air pollution on cognitive decline would show differences between cognitively normal group and mild cognitive impairment group. Lastly, even though the observational period of this study was longer than in previous studies, an even longer duration would be beneficial for detecting clinically meaningful cognitive decline, including the development of dementia.

Conclusion

This study suggests that long-term exposure to high levels of NO_2, SO_2, CO, and PM_{10} is associated with cognitive decline in older adults without dementia. Our findings support the efforts of LMICs to reduce air pollution, with a view to reducing the public health burden imposed by cognitive impairment in older adults.

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-5120r2).

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