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Components of Air Pollution and Cognitive Function in Middle-aged and Older Adults in Los Angeles

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Abstract

While experiments in animals demonstrate neurotoxic effects of particulate matter (PM) and ozone (O₃), epidemiologic evidence is sparse regarding the relationship between different constituencies of air pollution mixtures and cognitive function in adults. We examined cross-sectional associations between various ambient air pollutants [O₃, PM_{2.5} and nitrogen dioxide (NO₂)] and six measures of cognitive function and global cognition among healthy, cognitively intact individuals (n=1,496, mean age 60.5 years) residing in the Los Angeles Basin. Air pollution exposures were assigned to each residential address in 2000–06 using a geographic information system that included monitoring data. A neuropsychological battery was used to assess cognitive function; a principal components analysis defined six domain-specific functions and a measure of global cognitive function was created. Regression models estimated effects of air pollutants on cognitive function, adjusting for age, gender, race, education, income, study and mood. Increasing exposure to PM_{2.5} was associated with lower verbal learning ($\beta = -0.32$ per 10 $\mu\text{g}/\text{m}^3$ PM_{2.5}, 95% CI = $-0.63, 0.00$; $p = 0.05$). Ambient exposure to NO₂ >20 ppb tended to be associated with lower logical memory. Compared to the lowest level of exposure to ambient O₃, exposure above 49 ppb was associated with lower executive function. Including carotid artery intima-media thickness, a measure of subclinical atherosclerosis, in models as a possible mediator did not attenuate effect estimates. This study provides support for cross-sectional associations between increasing levels of ambient O₃, PM_{2.5} and NO₂ and measures of domain-specific cognitive abilities.

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7. CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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Keywords

air pollution; cognitive dysfunction; dementia; particulate matter; ozone; verbal learning

1. INTRODUCTION

Increasing numbers of US adults are living longer (Wood and Walker, 2005) and population growth continues to shift to urban metropolitan areas (Perry et al., 2000). There is thus a growing need to direct efforts to understand adverse cognitive health outcomes relevant to aging populations, including cognitive impairment (CI) and dementia (Comas-Herrera et al., 2007), as well as potential health risks from environmental exposures such as air pollution that are prevalent in urban areas (National Atlas of the United States, 2009). Cognitively impaired persons require nursing home care at twice the rate of cognitively intact persons, and incur significantly greater mental healthcare costs (2009, Coughlin and Liu, 1989, Mackin et al., 2011), making prevention an important priority (Plassman et al., 2008). In urban areas, ambient air pollution is a mixture of gaseous pollutants and particulate matter (PM) that derive from sources mostly related to burning fuel of motor vehicles, diesel-powered transport and equipment and local industrial processes (Dickey, 2000, Lewtas, 2007, Valavanidis et al., 2008). While the aging brain is vulnerable to many environmental insults including urban air pollution, investigations in this emerging field are limited despite the potentially modifiable nature of this exposure.

The association between air pollution and both respiratory and cardiovascular morbidity and mortality has been extensively studied for both acute and chronic ambient PM exposure (Chen et al., 2008, Franchini and Mannucci, 2009, Ghio et al., 2012, Gotschi et al., 2008, Pelucchi et al., 2009), with hypothesized biological pathways including systemic as well as tissue-specific inflammation (Block and Calderon-Garciduenas, 2009, Calderon-Garciduenas et al., 2008b, Kunzli et al., 2005). Cardiovascular disease (CVD) is known to impact cognitive function in later years (O'Brien, 2006), and vascular and metabolic risk factors including high blood pressure, overweight and obesity, diabetes and stroke (Rosamond et al., 2007) have been shown to be inversely associated with cognitive function among middle-aged and older adults (NIH, 2007). Subclinical atherosclerosis measured by carotid artery intima-media thickness (CIMT) has been associated with lower cognitive function (Gatto et al., 2009, Johnston et al., 2004, Muller et al., 2007), and long-term exposure to ambient air pollution has been associated with CIMT (Kunzli, Jerrett, 2005). Many animal studies have reported the effects of air pollutants on the central nervous system (CNS) likely via inflammatory and oxidative stress pathways (Block and Calderon-Garciduenas, 2009, Genc et al., 2012, Gonzalez-Flecha, 2004). Studies of experimental particles simulating PM_{2.5} from tailpipe emissions of motor vehicles raise the question as to whether the blood-brain barrier (BBB) may be breached (Lockman et al., 2004, MohanKumar et al., 2008, Muhlfield et al., 2008). *In vivo* studies with acute and chronic low-level exposures to ozone (O₃), PM, or PM-O₃ mixtures have demonstrated neurotoxic effects in different animal models (Dorado-Martinez et al., 2001, Rivas-Arancibia et al., 1998, Sirivelu et al., 2006, Sorace et al., 2001). Suggested neuropathological evidence of accelerated brain aging has been described in the olfactory and respiratory nasal mucosae, olfactory bulb, and cortex of experimental dogs raised in Mexico City where air pollution is a mixture of O₃, aldehydes, PM, and other components (Calderon-Garciduenas et al., 2008a).

Studies of air pollution and cognitive dysfunction in humans have previously focused on acute exposure in human volunteers. Short-term exposure to a mixture of diesel exhaust and gaseous pollutants in a chamber study increased the median power frequency in the frontal cortex measured by quantitative EEG (Cruts et al., 2008). Healthy college students with

short-term exposure to carbon monoxide (CO) from kerosene heating stoves used indoors had lower scores on neuropsychological tests indicating dysfunction in multiple areas of cognition (Amitai et al., 1998).

Population-based epidemiologic studies are sparse and limited mainly to examinations of PM pollution among elderly adults (Power et al., 2011, Ranft et al., 2009, Weuve et al., 2012). None of these studies simultaneously examined putative associations between gaseous pollutants and PM with cognitive function. One study using NHANES-III data collected in younger US adults reported associations between O₃ and reduced performance on cognitive tasks requiring attention, short-term memory and coding abilities; associations with PM₁₀ and these tasks were not present after taking into account race/ethnicity and socioeconomic status (Chen and Schwartz, 2009). To the best of our knowledge, previous studies have only reported associations between air pollution exposure and assumed cognitive constructs suggested by neuropsychological tools without performing comprehensive psychometric analyses to assist in the interpretation of possibly heterogeneous results.

We investigated cross-sectional associations between components of ambient urban air pollution [O₃, PM_{2.5} and nitrogen dioxide (NO₂)] from residential exposure, global cognition and six domains of cognitive function in healthy, cognitively intact middle-aged and older adults in the greater Los Angeles area, California. Given the previously-documented strong associations between PM exposure and cardiovascular disease (CVD) (Breton et al., 2012, Kunzli et al., 2010, Kunzli, Jerrett, 2005), this study also assessed whether and to what extent the association between air pollution and cognition may be mediated by subclinical atherosclerosis.

2. MATERIALS AND METHODS

2.1 Study population

Analyses used baseline data obtained prior to randomization from 1,496 healthy, cognitively intact adult participants enrolled in three randomized, double-blind, placebo-controlled clinical trials conducted during 2000–2006 at the University of Southern California (USC) Atherosclerosis Research Unit [B-Vitamin Atherosclerosis Intervention Trial (BVAIT; ClinicalTrials.gov identifier NCT00114400), Women's Isoflavone Soy Health (WISH; NCT00118846) Trial, and Early Versus Late Intervention Trial With Estradiol (ELITE; NCT00114517)] (Henderson et al., 2012, Hodis et al., 2009, Hodis et al., 2011). Briefly, postmenopausal women without clinical evidence of CVD were eligible for WISH and ELITE; otherwise healthy men and postmenopausal women with fasting plasma homocysteine levels ≥ 8.5 $\mu\text{mol/L}$ were eligible for BVAIT. Recruitment occurred over the entire Los Angeles Basin, covering a geographic area of approximately 64,000 km². A total of 5,698 individuals were screened via telephone or in person. Exclusions were made for any clinical signs or symptoms of CVD (n=165), diabetes mellitus or fasting serum glucose ≥ 126 mg/dL (n=137), triglyceride (TG) levels ≥ 500 mg/dL (n=3), hypertension [systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 100 mmHg] (n=13), untreated thyroid disease (n=4), creatinine clearance <70 ml/min or serum creatinine >2.0 mg/dL (n=6), a life threatening disease with prognosis <5 years (n=124), alcohol intake >5 drinks per day/substance abuse (n=4), unwillingness to stop taking vitamin supplements (n=626), current use of hormone therapy (WISH or ELITE) (n=212), hysterectomy and no oophorectomy (ELITE) (n=132), or 6–9 years postmenopausal (ELITE) (n=190). A total of 1,499 subjects were randomized; all participants signed written informed consent approved by the USC Institutional Review Board.

2.2 Measurements

2.2.1 Air Pollution Exposure Assignment—Employing a GIS-based system, yearly air pollution exposure assignments were derived from measured ambient air quality data spatially mapped to subjects' geocoded residence addresses at year of randomization (2000–2006). These data were initially automatically geocoded to TigerLine files (Navteq, 2006), then manually resolved in a multi-step process similar to that described by McElroy (McElroy et al., 2003). Ambient air quality data were primarily extracted from the Air Quality System (AQS), maintained by the US Environmental Protection Agency (<http://www.epa.gov/ttn/airs/airsaqs/>). A database of O₃ (8 hour maximum), NO₂ (24 hour) and PM_{2.5} (mass, 24 hour) concentrations at monitoring stations was compiled from a June 2008 AQS version. Measurements obtained using Federal Reference Methods and Federal Equivalent Methods were included and supplemented with monthly average O₃, NO₂, and PM_{2.5} concentrations measured in the Southern California Children's Health Study (Peters et al., 2004). Daily, monthly, and annual average concentrations were calculated using a 75% data completeness criterion. The database included measurements from California and border areas of nearby states for calendar years 2000–2006. The density of measurement stations in this regional air monitoring network is every 20 to 40 km in urban areas and 50 to 150 km in rural areas (ARB, 2008).

Annual average concentrations for 2000–2006 from monitoring stations were spatially interpolated to subjects' residential addresses using inverse-distance-squared weighting in a GIS. Specifically, if one or more stations with valid data for a specific year were located within 5 km of a residence, the air pollutant assignment was based solely on local data. If there were no stations within 5 km, air pollutant assignments were calculated from the 3 closest stations with valid data located within 100 km of the residence.

2.2.2 Cognitive Function—Study subjects were administered a battery of 14 cognitive tests (Gatto, Henderson, 2009, Gatto et al., 2008, Henderson, St John, 2012) in a standardized order by one trained psychometrist. The battery was designed to assess a broad array of cognitive abilities, with emphasis on specific tasks used to detect age-associated change in middle-aged and elderly populations, particularly episodic memory and executive function (Table 1).

Three randomized subjects did not undergo cognitive testing; data for 1,496 (99.8%) subjects were included in this study (Table 2). The Center for Epidemiologic Studies Depression Scale (CES-D) scale (Radloff, 1977) was used to assess mood. Demographic factors were assessed by questionnaire.

2.2.3 Subclinical Atherosclerosis—The right common carotid artery was imaged using high resolution B-mode ultrasound (Hodis, Mack, 2009, Hodis, Mack, 2011, Hodis et al., 2001). An image analyst measured carotid artery intima-media thickness (CIMT) of the distal common carotid artery far wall with automated computerized edge detection using an in-house developed software package (patents 2005, 2006, 2011) (Hodis, Mack, 2001, Selzer et al., 2001). CIMT was the average of approximately 70–100 individual measurements between the intima–lumen and media–adventitia interfaces along a 1-cm length just proximal to the carotid artery bulb. This method standardizes the location and the distance over which CIMT is measured and ensures that the same portion of arterial wall is measured in each image and compared within and across all participants. Evaluation of this method demonstrated intraclass correlations of CIMT measurements of 0.97 to 0.99 (Hodis, Mack, 2009, Hodis, Mack, 2011).

2.3 Statistical Analyses

Because historical address data were not available, air pollution exposure estimates were averaged for the residential address where the subject lived during the year when cognitive assessment was conducted and the prior year. Variables for continuous exposure were scaled to 10 parts per billion (ppb) for O₃, NO₂, and to 10 ug/m³ for PM_{2.5}, and categorized into tertiles of exposure.

For subjects who were unable to complete one or more tests in the neuropsychological battery (n=60, < 0.5% of total tests), age-, gender- and education-specific mean values for the given test from the study population were imputed in order to conserve sample size for analyses. Small reductions (averaging 0.8%) in variances of the tests resulted from imputations, which were made for < 0.5% of the total number of tests administered. There were no appreciable differences in results or conclusions if subjects with imputed values were excluded from analyses.

To construct cognitive factors, a principal components analysis with an orthogonal varimax rotation was performed on the 14 cognitive tests in the neuropsychological battery. Following methods of Cattell (Cattell, 1966), a scree plot of successive eigenvalues was used to identify number of principal components; six factors (Table 1) accounted for 76.9% of total variance. Individual cognitive tests with loadings >0.59 were used to construct scores for the factors, reflecting domain-specific cognitive abilities (Table 1). For each subject, a score for each factor was calculated by summing the z-scores of component cognitive tests. A measure of global cognition was calculated as the sum of z-scores on each of the tests in the battery, weighted by the sum of the inverse covariances of scores with other tests.

Examination of simple scatter plots indicated possible non-linear relationships between air pollution exposures and global cognition (Figure 1). Linear regression models with simple continuous and categorical (tertiles) terms for air pollution measures were utilized to estimate associations with cognition measures. Final models included demographic characteristics that were significant univariate correlates of global cognition, including age, race/ethnicity (Caucasian, African-American, Latino and Asian-American/Pacific Islander/ Native American), gender, highest educational level achieved (high school or less, some college, Bachelor's degree and graduate/professional degree), household income (<30,000, 30,000–49,999, 50,000–69,999, 70,000–99,999 and 100,000 dollars/year), and mood (CES-D total score, in quartiles). An indicator term for the fixed effect of study (BVAIT, WISH, ELITE) was included. Separate models analyzed each pollutant. Beta coefficients (β) and 95% confidence intervals (CI) of β were estimated. Additional models examined whether CIMT mediated relationships between air pollutants and cognition by assessing the change in magnitude of air pollution effect estimates when CIMT was included in models. Multiple linear regression model residual diagnostics showed limited evidence of departures from model assumptions of linearity, homoskedasticity, and normality, thus linear regression methods were retained and no data transformations done. All analyses used SAS version 9.2 (SAS Institute Inc., Cary, NC, USA.).

3. RESULTS

The study population had a mean ($\pm$ SD) age of 60.5 ($\pm$ 8.1) years (Table 2). The majority were women (79.4%), Caucasian (66.2%) and 62.5% had a Bachelor's or graduate degree. The mean body-mass index (BMI) was 27.3 ($\pm$ 5.2) kg/m² and 39.5% of subjects were either current or former smokers. Annual average exposure to air pollutants (O₃, NO₂, PM_{2.5}) varied geographically across Southern California where study participants resided over the seven-year period (Figure 2, for the year 2006).

Exposure to O₃, NO₂, or PM_{2.5} was not associated with age. Men had higher exposure to NO₂ (29.1 ± 7.1 versus 24.3 ± 6.3 ppb, $p < 0.0001$) and PM_{2.5} (20.2 ± 3.5 versus 16.5 ± 3.3 ug/m³, $p < 0.0001$) than women, whereas women had greater exposure to O₃ (40.5 ± 5.2 versus 37.7 ± 5.7 ppb, $p < 0.0001$). Caucasian participants had greater O₃ exposure, but less exposure to NO₂, and PM_{2.5} compared to Latino, African-American or Asian participants (p -values < 0.05). Education and income were not associated with O₃ exposure, but participants with lower educational levels or household incomes had greater exposure to NO₂ and PM_{2.5}. Exposure to NO₂ ($r = 0.12$, $p < 0.0001$) and PM_{2.5} ($r = 0.20$, $p < 0.0001$) were positively correlated with SBP. O₃, NO₂, or PM_{2.5} were not correlated with CIMT and were minimally correlated with BMI (all $r < 0.10$).

The components of air pollution were themselves correlated: O₃ was strongly inversely correlated with both NO₂ ($r = -0.77$; $p < 0.0001$) and PM_{2.5} ($r = -0.62$; $p < 0.0001$), while NO₂ and PM_{2.5} were strongly positively correlated ($r = 0.80$; $p < 0.0001$). CIMT was not correlated with any of the six cognitive factors or the measure of global cognition.

None of the air pollutants were significantly associated with global cognition. Increasing exposure to PM_{2.5} was associated with lower verbal learning ($\beta = -0.32$ per 10 ug/m³ PM_{2.5}, 95% CI = $-0.63, 0.00$; $p = 0.05$). The magnitude of the association was not very different between men ($\beta = -0.41$ per 10 ug/m³, 95% CI = $-0.99, 0.17$) and women ($\beta = -0.29$ per 10 ug/m³, 95% CI = $-0.67, 0.09$), or in adults aged 60 and older ($\beta = -0.25$ per 10 ug/m³, 95% CI = $-0.68, 0.17$) compared to those younger than 60 years ($\beta = -0.39$ per 10 ug/m³, 95% CI = $-0.87, 0.09$). Compared to study participants with exposure to ambient PM_{2.5} 15 ug/m³, those with greater exposure levels (in tertiles) had lower verbal learning (Table 3).

Ambient exposure to NO₂ >20 ppb tended to be associated with lower logical memory ($\beta = -0.62$, 95% CI = $-1.35, 0.11$; $p = 0.095$) compared to exposure 10ppb.

Compared to the ambient O₃ 34 ppb, exposure above 49 ppb was associated with lower executive function ($\beta = -0.66$, 95% CI = $-1.35, 0.03$; $p = 0.059$). However, mid-range O₃ exposure (34–49 ppb) was also associated with a higher logical memory factor score (Table 3), which appeared to be driven by the effect in women ($\beta = 0.46$, 95% CI = $0.09, 0.83$) and in adults aged 60 and older ($\beta = 0.51$, 95% CI = $0.11, 0.91$).

Including CIMT in models with air pollutants and these cognitive factors had a negligible ($<3\%$) impact on any of the effect estimates.

4. DISCUSSION

In this study of 1,496 middle-aged and older healthy, cognitively intact adults living in the Los Angeles area, specific components of ambient air pollution were associated with lower cognitive function in certain domains of abilities, but not with an overall composite measure of cognition. Greater exposure to PM_{2.5} was associated with lower verbal learning performance. NO₂ exposure was inversely associated with logical memory abilities. Higher O₃ exposure tended to be associated with lower executive functioning, but was also associated with higher logical memory, particularly in women and adults aged 60 and older. For PM_{2.5}, the estimated decrement in verbal learning for each 10 ug/m³ exposure is approximately 30 percent greater than the expected decline associated with each additional year of age, and about 20 percent greater than the beta estimate associated with a high school education or less (compared to a graduate or professional degree). Results importantly suggest that associations between air pollutants prevalent in urban areas and decreased cognitive abilities were present - albeit at small to modest magnitudes of effect estimates - among community-dwelling middle-aged and older adults who are otherwise healthy and not exhibiting any symptoms of cognitive dysfunction.

Existing population-based epidemiologic studies primarily examined PM exposure among elderly adults and limited areas of cognitive function. Long-term exposure to black carbon, a marker for traffic-related air pollution, was associated with lower scores on the Mini-Mental State Examination among 680 older US men (mean age 71 years)(Power, Weisskopf, 2011). Traffic-related PM pollution was also associated with global cognitive decline (measured by a neuropsychological battery of six tests) but not specifically with verbal memory among elderly US females aged 70–81 years in the Nurses' Health Study(Weuve, Puett, 2012). Shorter distance from residence to a busy road (an indicator of traffic-related air pollution) was associated with lower scores overall on a neuropsychological battery among 243 elderly German women aged 68–74 years(Ranft, Schikowski, 2009). PM exposure was also associated with lower attention/processing speed, but not olfactory discrimination. In contrast to previous work, our study uniquely examined both gaseous and PM exposures with several specific cognitive domains in addition to a composite assessment of global cognition. Our study population was an average of 10 years younger than previous cohorts studied; generally air pollutant-cognition associations did not depend on age or sex. Because selection criteria established a study population that was cognitively intact even at the extreme end of the age spectrum, we were unable to examine pollution effects on adults with more prominent cognitive deficits. An advantage of including younger, cognitively intact adults is that it allowed for an examination of study hypotheses while reducing noise from expected age-associated declines in cognitive function prevalent in elderly populations.

Using neurobehavioral data from NHANES-III for 1,764 adult participants (aged 37.5 ± 10.9 years), Chen and Schwartz(Chen and Schwartz, 2009) showed that annual O₃ exposure aggregated at the county level was associated with reduced performance on cognitive tasks requiring attention, short-term memory and coding abilities but not reaction time; decrements were equivalent to 3.5 and 5.3 years of aging-related decline in cognitive performance. Our observations that O₃ exposure may be related to lower executive function is consistent with these data given the involvement of attention in executive function(Lezak et al., 2004). In rats, acute inhalation of O₃ has been shown to cause memory impairment and decreases in motor activity(Dorado-Martinez, Paredes-Carbajal, 2001). Mechanisms by which O₃ may affect neurodegenerative processes involve elevations in free radicals contributing to oxidative stress states(Calderon-Garciduenas, Solt, 2008b, Dorado-Martinez, Paredes-Carbajal, 2001).

Pathways have been proposed by which long-term exposure to PM could result in neurodegeneration(Calderon-Garciduenas, Mora-Tiscareno, 2008a, Ranft, Schikowski, 2009). The central translocation theory suggests that, once crossing the BBB, small PM particles, which may be covered with biocontaminants (e.g., endotoxins) or contain transition metals, may induce and propagate a cascade of free radical activities that can damage lipids, nucleic acids, and proteins of target neural cells on contact, and stimulate inflammatory cytokine release(Balasubramanian et al., 2013, Lockman, Koziara, 2004, MohanKumar, Campbell, 2008, Muhlfeld, Rothen-Rutishauser, 2008). Ambient PM exposure enhances neuroinflammatory markers in rodent brain(Gerlofs-Nijland et al.). Rats with prolonged exposure to diesel exhaust at levels comparable to those humans experience in tunnels, workplaces or traffic hot spots showed regionally-specific brain neuroinflammatory responses. Specifically levels of pro-inflammatory cytokines tumor necrosis factor alpha (TNF- α) and interleukin-1 alpha (IL-1 α) increased in the striatum after PM exposure, but not in the cortex, hippocampus or cerebellum(Campbell et al., 2009). Animal studies have also demonstrated that PM activates the stress axis and causes neurodegeneration in oxidative stress-prone animals(MohanKumar, Campbell, 2008). Differential responses to air pollution exposure may vary by brain region or genetic factors that determine susceptibility to CNS inflammation(Campbell, Araujo, 2009). Alterations of the BBB, degenerated cortical neurons, apoptotic glial cells, and neurofibrillary tangles have

been observed, as well as changes suggestive of oxidative stress-mediated damage(Calderon-Garciduenas, Mora-Tiscareno, 2008a).

The association between chronic PM air pollutant exposure and cardiovascular morbidity and mortality is well established(Franchini and Mannucci, 2009). Thus, mechanisms by which CVD could act on cognition could also link PM pollution to cognitive outcomes. Atherosclerosis, heart disease or stenosis of arteries causing vascular obstructions can result in reduced blood flow to the brain and diminished delivery of oxygen(Crowley, 2004). In populations that are cognitively normal, small decreases in brain oxygen may explain some individual differences in cognitive performance, with cumulative effects over time contributing to declines in cognitive function. In our study, the association between PM_{2.5} and verbal learning was not appreciably altered when CIMT was included in models suggesting that subclinical atherosclerosis may not be a strong mediator of this relationship and further, that an effect of PM air pollution on this area of cognition may act through pathways other than atherosclerosis, such as inflammation and free radical initiation(Kelly et al., 1995). Exposure to air pollutants could lead to cerebrovascular dysregulation through vasoconstriction caused by free radical processes at the arterial wall (peroxidation of NO₂, for example)(Barregard et al., 2006, Schulz et al., 2011). Deficits in certain cognitive abilities may be explained by their association with areas of the brain that are more vulnerable to effects of pollutants (effectively causing cerebral hypoxemia).

This is the first study to our knowledge to evaluate cognitive effects from and exposure to ambient NO₂ and the first to report possible associations with logical memory. The positive association between logical memory and O₃ exposure is not understood. O₃ exposure was not correlated with education or income, arguing against the possibility that the result was an artifact of participants with higher income and education living in areas of higher O₃ pollution in Los Angeles. Potential relationships with this area of cognitive function need to be further examined. Measurement error is a concern for air pollution data because pollution levels vary over time and space. Even though exposure assignments were derived from one of the most comprehensive air monitoring systems in the US, where monitoring stations are typically located 20 to 30 km apart, pollutant concentrations are known to vary on smaller spatial scales than can be resolved with regional air monitoring networks. Nevertheless, a strength of the exposure assessment herein compared to many other studies is the availability of data for multiple pollutants with fine spatial resolution across the study region. This study is limited to a cross-sectional examination since historical residential address data for subjects were not available with which to base estimates of longer term exposure. In addition, the exclusion of participants with clinical CVD and overt CVD risk factors limits generalizability of study results. This study did not consider the contribution to cognitive dysfunction from other environmental contaminants characteristic of urban areas, such as heavy metals or point source industrial emissions. Our study is only the second to evaluate cognitive effects of exposure to fine particulate air pollution. Our study included a robust, in depth assessment of cognitive function using a neuropsychological battery that permitted an examination of multiple domains of cognition and estimation of pollutant-cognitive ability specific associations.

5. CONCLUSIONS

In summary, this study provides support for cross-sectional associations between higher exposure to O₃, PM_{2.5} and NO₂ and lower cognitive abilities in specific domains among healthy, cognitively intact older adults. Additional, longer term studies are needed that focus more comprehensively on the multiple components of air pollution, measure specific areas of cognition, as well as include younger adults in order to examine air pollution associations while reducing the amount of variation from expected age-related declines in cognitive

function prevalent in elderly populations. If the causal link between cognitive decline and exposure to neurotoxic ambient air pollution in urban areas is further substantiated, public health recommendations could be directed towards modifying environmental air pollution through policy or legislation.

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Highlights

The aging brain is vulnerable to the effect of urban air pollution.

Investigations into cognitive effects in human populations are limited.

Our study included healthy cognitively intact older adults.

We studied exposure to O₃, PM_{2.5} and NO₂

Exposure to air pollution was inversely associated with cognitive abilities.

Figure 1.
Relationships between components of air pollution (O₃, NO₂, PM_{2.5}) and Global Cognitive Function

Figure 2.
Geographic variability in components of air pollution (O₃, NO₂, PM_{2.5}) in Southern California with Study Participants' Addresses, 2006

Constructed Cognitive Factors and Individual Component Tests from Neuropsychological Test Battery

Table 1

Cognitive Factor Name	Component Tests
Executive Function	Symbol Digit Modalities Test Trail Making Test, Part B Letter-Number Sequencing (Wechsler Memory Scale, 3rd Edition (WMS-III) Shipley Institute of Living Scale, Abstraction Subtest
Verbal Learning	California Verbal Learning Test, 2nd edition, immediate recall (IR) and delayed recall (DR)
Logical Memory	paragraph recall – IR and DR (WMS-III)
Visual Processing	Judgment of Line Orientation, Form H Block design (Wechsler Adult Intelligence Scale, 2nd Edition (WAIS-III))
Visual Episodic Memory	Faces, IR and DR (WMS-III)
Semantic Memory	Category fluency - animal naming, 60 seconds Boston Naming Test, 30-item version

Table 2

Characteristics of Study Population (n=1,496)

Variable	Mean $\pm$ SD or Number (%)
Age (years)	60.5 $\pm$ 8.1
Female	1,188 (79.4)
Race/Ethnicity	
Caucasian	991 (66.2)
African-American	156 (10.4)
Hispanic	201 (13.4)
Asian/Pac Island/Native Am	148 (9.9)
Educational Level	
High school or less	139 (9.3)
Some college	438 (29.3)
Bachelor's degree	378 (25.3)
Graduate/professional degree	541 (36.2)
Study	
BVAIT	504 (33.7)
WISH	349 (23.3)
ELITE	643 (43.0)
Body-mass index (kg/m²)^a	27.3 $\pm$ 5.2
Current/Former Smoker^b	590 (39.5)
Blood Pressure (mmHg)^c	
Systolic	121.2 $\pm$ 16.0
Diastolic	76.7 $\pm$ 9.7
CES-D score	15.6 $\pm$ 8.4
CIMT (mm)	0.77 $\pm$ 0.12

^a
n=1,489^b
n=1,495^c
n=1,490

Table 3

Beta Coefficients (95% Confidence Intervals) from Linear Regression Models^a of Associations between Components of Ambient Air Pollution and Measures of Cognition for 1,496 BVAIT, WISH and ELITE Study Participants

Component of Air Pollution ^f	Area of Cognitive Function					
	Global Cognition	Executive Function	Verbal Learning	Logical Memory	Visual Memory	Semantic Memory
8-hour O₃ (ppb)						
> 49	-0.08 (-0.45, 0.28)	-0.66 (-1.35, 0.03) ^b	-0.20 (-0.63, 0.23)	0.24 (-0.21, 0.68)	0.01 (-0.42, 0.44)	-0.12 (-0.50, 0.26)
34-49	0.05 (-0.19, 0.29)	-0.23 (-0.68, 0.22)	-0.13 (-0.41, 0.16)	0.31 (0.01, 0.60) ^d	0.12 (-0.16, 0.40)	0.08 (-0.17, 0.33)
34	ref	ref	ref	ref	ref	ref
<i>p-trend</i>	0.81	0.07	0.33	0.15	0.80	0.75
24-hour NO₂ (ppb)						
> 20	-0.32 (-0.92, 0.28)	-0.01 (-1.13, 1.11)	-0.04 (-0.75, 0.67)	-0.62 (-1.35, 0.11) ^e	-0.26 (-0.97, 0.45)	-0.24 (-0.87, 0.39)
10-20	-0.36 (-0.96, 0.27)	-0.15 (-1.30, 1.01)	0.03 (-0.70, 0.76)	-0.54 (-1.29, 0.22)	-0.15 (-0.88, 0.58)	-0.29 (-0.94, 0.35)
10	ref	ref	ref	ref	ref	ref
<i>p-trend</i>	0.74	0.53	0.59	0.16	0.25	0.95
24-hour PM_{2.5} (ug/m³)						
> 17	-0.15 (-0.38, 0.08)	-0.06 (-0.49, 0.37)	-0.37 (-0.64, -0.10) ^c	-0.12 (-0.40, 0.16)	-0.19 (-0.46, 0.08)	-0.07 (-0.31, 0.16)
15-17	-0.01 (-0.21, 0.22)	0.04 (-0.36, 0.44)	-0.24 (-0.49, 0.01) ^b	0.16 (-0.10, 0.42)	-0.11 (-0.36, 0.14)	-0.03 (-0.25, 0.20)
15	ref	ref	ref	ref	ref	ref
<i>p-trend</i>	0.23	0.81	0.007	0.49	0.16	0.54

^aModels adjusted for age (continuous), race/ethnicity (Caucasian, African-American, Latino and Asian-American/Pacific Islander/Native American), gender, highest educational level achieved (high school or less, some college, Bachelor's degree and graduate/professional degree), household income (<30,000, 30,000-49,999, 50,000-69,999, 70,000-99,999 and 100,000 dollars/year), mood (CES-D total score, in quartiles), and study (BVAIT, WISH, ELITE)

^bp=0.059

^cp=0.008

^dp=0.04

^ep<0.10

^ftwo-year average of air pollution levels assessed for the residential address where the subject lived during the year cognitive assessment was conducted and the prior year during the period 2000-2006