Effects of Traffic-Related Air Pollution on Cognitive Function, Dementia Risk and Brain MRI Findings in the Cardiovascular Health Study

Erin O'Brien Semmens

A dissertation
submitted in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy

University of Washington

2012

Reading Committee:

Joel D. Kaufman, Chair

W.T. Longstreth

Adam A. Szpiro

Program Authorized to Offer Degree:

Epidemiology – Public Health

University of Washington

Abstract

Effects of Traffic-Related Air Pollution on Cognitive Function, Dementia Risk and Brain MRI Findings in the Cardiovascular Health Study

Erin O'Brien Semmens

Chair of the Supervisory Committee:
Professor Joel D. Kaufman
Departments of Environmental and Occupational Health Sciences,
Epidemiology and Internal Medicine

Consistent and compelling links between long-term air pollutant exposure and respiratory and cardiovascular disease have been established. Far less is known regarding the impact of air pollution on the brain. Using residence-specific estimates of long-term air pollutant exposure based on regulatory monitors, we investigated the effects of particulate matter < 10 μm in diameter (PM_{10}) and nitrogen dioxide (NO_2) on cognitive decline, dementia risk and brain MRI-detected findings in the Cardiovascular Health Study (CHS), a large cohort of older adults residing in three communities in the U.S. Both pollutants were associated with significantly steeper cognitive decline, assessed by the Modified Mini-Mental State Examination and the Digit Symbol Substitution Test in linear regression analyses with generalized estimating equations. In logistic and Cox regression analyses, neither air pollutant was linked significantly to higher risk of prevalent or incident dementia or Alzheimer's disease. However, a 10 $\mu g/m^3$ elevation in estimated long-term PM_{10} exposure was associated with 2.45-fold increase in odds of prevalent vascular dementia (95% CI: 1.23, 4.86). The same elevation in PM_{10} exposure was associated with a 0.14-unit worse white matter grade (95% CI: 0.01, 0.27), and a 10 ppb

increase in NO_2 exposure was associated with a 0.37-unit worse white matter grade (95% CI: 0.14, 0.61). Worsening white matter between MRIs and MRI-detected infarcts were not significantly associated with PM_{10} or NO_2 exposure. In summary, we found significant associations between estimated long-term exposure to air pollutants and faster rates of cognitive decline, elevated risk of vascular dementia (VaD) and higher white matter grade on brain MRI. Our findings add to the existing strong rationale for limiting exposure to air pollutants.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

There are many I wish to thank, especially my advisor, Joel Kaufman, for his outstanding mentorship. I am fortunate to have worked with such a tremendous researcher, teacher and person. I also wish to express my sincere gratitude to each of my committee members: Annette Fitzpatrick, Will Longstreth, Adam Szpiro and Ken Rice. Each brought valuable expertise in the methods of this research and an interest in my succeeding with the work, which greatly improved its quality. It has been a privilege to work with all of them, and an experience I enjoyed very much.

I would like to acknowledge Helene Margolis, who provided the air pollutant exposure data used in this research and who was a rich source of knowledge, guidance and encouragement; to the Cardiovascular Health Study participants and staff for the generous donation of their time and resources; to Curtis Noonan and Tony Ward who have provided me with on-site mentorship and have been incredibly supportive of my research.

I would like to thank my friends and family for their support and encouragement. I am especially grateful to Elisabeth Beaber, Kathryn Adeney and Kate Gillespie who were wonderful examples as friends and peers and made it possible, in very practical ways, for me to complete this work; to my siblings, Joe, Jocelyn and Susannah, for your interest in my progress and for giving me a wonderful reason to take occasional breaks; to my mom who has so generously helped in all possible ways; and finally to my husband, Dan, whose love and support were so critical in this process, and to my dear daughter, Franny, whose playfulness and good spirit bring joy everyday.

DEDICATION

To my dad, Joseph James O'Brien, who has been in my heart throughout this journey. In honor of his love, encouragement, commitment to family and enjoyment of life.

CHAPTER I.

Introduction

Health Effects of Air Pollution

Decades of research have shown that air pollution, an environmental exposure to which nearly all people are exposed, is an important contributor to morbidity and mortality worldwide, with consistent links between long-term air pollution exposure and respiratory and cardiovascular disease observed in several large cohorts.[1-5] Acute[6] and chronic[7] fine particulate matter ($PM_{2.5}$: PM less than 2.5 μm in diameter) exposures also have been associated with elevated risk of stroke, providing evidence that air pollution affects the vasculature of the brain as well. Exposures generated from traffic, in particular, have been implicated in these health effects[8] with numerous studies demonstrating subclinical and clinical vascular effects associated with living near major roadways[9-11] and elevated $PM_{2.5}$ exposure.[7,12]

The Brain as a Target of Air Pollution

Over the past decade, evidence has begun to accumulate describing the impact of air pollution on the brain. In some of the earliest work exploring the potential contribution of air pollution to neurodegeneration in humans, in autopsied brain tissues, Calderón-Garcidueñas and colleagues observed a significantly greater accumulation of beta-amyloid 42, a peptide associated with amyloid plaques, a pathological hallmark of AD, and elevated expression of various markers of neuroinflammation including cyclooxygenase-2 (COX2) and interleukin-1β (IL-1β) comparing residents of the heavily-polluted Mexico City to those residing in cities with low pollution.[13] In another study, children residing in Mexico City exhibited deficits in several measures of cognitive performance relative to children residing in a different less-polluted city and were more likely to have brain MRI-detected white matter lesions.[14] In Quanzhou, China,

children attending a school in an area with high concentrations of traffic-related pollutants scored significantly lower on neurobehavioral tests than children attending a school in a less polluted area.[15]

Black carbon,[16,17] ozone,[18] proximity to traffic,[19] and an index of ambient air pollution[20] all have been linked cross-sectionally to poorer cognitive function in large epidemiologic studies in children, men and women and older adults. More recently, in the first study of the longitudinal effects of air pollution on cognitive decline, Weuve and colleagues found cognitive decline equivalent to two years of aging associated with 10 $\mu g/m^3$ elevations in estimated long-term fine and coarse PM exposure in a large cohort of older women.[21] Taken together, these studies suggest that air pollution affects not only respiratory and cardiovascular health but that of the brain, a finding of considerable public health importance in an aging population.[22]

Hypothesized Mechanisms

The impact of air pollution on the brain may be mediated by cardiovascular disease. Neurodegenerative and cardiovascular diseases share similar risk factors and often are comorbid conditions.[23] Underlying vascular pathologies often are present in neurodegenerative diseases, suggesting that, in addition to the cardiovascular system, the central nervous system also may be adversely affected by air pollution. Vascular dementia (VaD), a heterogeneous disorder caused by vascular disease, is the second most common form of dementia after Alzheimer's disease (AD), making up approximately 10-20% of all diagnosed dementias.[24,25] In addition, vascular characteristics, specifically the integrity of the vessels of the brain and the presence of cerebral infarcts,[26] may be important in the development of other forms of dementia, with vascular disease being present in 20-40% of cases of AD at autopsy.[27]

Air pollution may influence the brain downstream of cardiovascular disease. In addition, the brain is likely sensitive to the same systemic inflammatory and oxidative stress responses hypothesized to mediate demonstrated relationships between air pollution and increased vascular tone,[28] left ventricular mass[11] and systolic blood pressure,[29] a strong risk factor for VaD. The brain has high metabolic requirements and relatively low concentrations of antioxidant enzymes, making it particularly vulnerable to inflammation and oxidative stress.[30] Other potentially relevant pathways by which air pollution may affect the brain include translocation of ultrafine and fine particles directly from the lungs to other parts of the body through the blood or lymph[31] and transport directly from the nose to brain through deposition in the nasal mucosa and translocation along the olfactory nerve.[32] Studies in animals have demonstrated neurotoxic effects of air pollutant exposure, specifically those of particulate matter, diesel exhaust and ozone.[33-39]

The Cardiovascular Health Study as a Setting to Investigate the Impact of Air Pollution on the Brain

With 10 years of extensive annual clinical examinations to assess risk factors and annual telephone contacts initiating hospitalizations and cardiovascular events ascertainment, the Cardiovascular Health Study (CHS) provides tremendous resources for studying cardiovascular disease, stroke and aging in older adults. The CHS has contributed substantially to clinical knowledge regarding conventional as well as new and potentially modifiable risk factors for subclinical and clinical cardio- and cerebrovascular disease.

CHS investigators have been at the forefront of the investigation of risk factors for cognitive decline, dementia, and cerebrovascular disease in the elderly.[40-46] Researchers have characterized the prevalence and incidence of dementia in CHS as well as the frequency of

different dementia subtypes,[47] each of which may have its own risk profile. This has enabled the investigation of the relationship between cardiovascular disease and dementia as well as identification of, and adjustment for, lifestyle,[48] socioeconomic,[49] medication use[50-52] and genetic[51,53] risk factors not only for dementia but also for more subtle cognitive decline in the elderly. In addition, CHS has performed brain magnetic resonance imaging (MRI) on two occasions,[54] allowing investigators to evaluate risk factors for white matter findings and brain infarcts, both of which are common in the elderly.[42,55] Examples of research utilizing these CHS-assessed structural and functional neurological outcomes are abundant in the literature although the contribution of environmental exposures to these measures of brain health remains largely unexplored in epidemiologic studies.

Summary of Chapters

The studies described herein made use of the rich set of neurological outcomes measured in the CHS. We applied residence-specific estimates of ambient air pollutant exposure, generated as part of a CHS ancillary study, to the cohort. These estimates were based on U.S. Environmental Protection Agency Aerometric Information Retrieval System and California Air Resources Board Ambient Air Quality data. Specifically, the impact of long-term exposure to PM less than 10 μm in diameter (PM_{10}) and nitrogen dioxide (NO_2) on cognitive decline (Chapter II), dementia risk (Chapter III) and brain MRI-detected findings (Chapter IV) was investigated in a large population of older adults to expand our knowledge regarding the health effects of this pervasive environmental exposure.

End Notes

1. Dockery DW, Pope CA, 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med.* Dec 9 1993;329(24):1753-1759.

2. Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. *Environ Health Perspect.* Oct 2000;108(10):941-947.

3. Pope CA, 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *Jama.* Mar 6 2002;287(9):1132-1141.

4. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med.* Mar 15 2006;173(6):667-672.

5. Van Hee VC, Adar SD, Szpiro AA, et al. Exposure to traffic and left ventricular mass and function: the Multi-Ethnic Study of Atherosclerosis. *Am J Respir Crit Care Med.* May 1 2009;179(9):827-834.

6. Wellenius GA, Burger MR, Coull BA, et al. Ambient air pollution and the risk of acute ischemic stroke. *Arch Intern Med.* Feb 13 2012;172(3):229-234.

7. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med.* Feb 1 2007;356(5):447-458.

8. Adar S, Kaufman J. Cardiovascular disease and air pollutants: evaluating and improving epidemiological data implicating traffic exposure. *Inhal Toxicol.* 2007;19 Suppl 1:135-149.

9. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt P. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet.* Oct 2002;360(9341):1203-1209.

10. Hoffmann B, Moebus S, Stang A, et al. Residence close to high traffic and prevalence of coronary heart disease. *Eur Heart J.* Nov 2006;27(22):2696-2702.

11. Van Hee V, Adar S, Szpiro A, et al. Exposure to Traffic and Left Ventricular Mass and Function: The Multi-Ethnic Study of Atherosclerosis. *Am J Respir Crit Care Med.* Jan 2009.

12. Jerrett M, Burnett R, Ma R, et al. Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology.* Nov 2005;16(6):727-736.

13. Calderón-Garcidueñas L, Solt A, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol.* 2008;36(2):289-310.

14. Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain Cogn.* Nov 2008;68(2):117-127.

15. Wang S, Zhang J, Zeng X, Zeng Y, Chen S. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. *Environ Health Perspect.* Oct 2009;117(10):1612-1618.

16. Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. *Am J Epidemiol.* Feb 1 2008;167(3):280-286.

17. Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A, 3rd, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. *Environ Health Perspect.* May 2011;119(5):682-687.

18. Chen JC, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology.* Mar 2009;30(2):231-239.

19. Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environ Res.* Nov 2009;109(8):1004-1011.

20. Zeng Y, Gu D, Purser J, Hoenig H, Christakis N. Associations of environmental factors with elderly health and mortality in China. *Am J Public Health.* Feb 2010;100(2):298-305.

21. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med.* Feb 13 2012;172(3):219-227.

22. Devi S. New studies cast dark cloud over air pollution. *Lancet.* Feb 25 2012;379(9817):697.

23. Ya-Ping J, Ostbye T, Feightner J, Hachinski V. The reciprocal risks of stroke and cognitive impairment in an elderly population. *Alzheimer's & Dementia.* 2006;2:171-178.

24. Fratiglioni L, Launer LJ, Andersen K, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology.* 2000;54(11 Suppl 5):S10-15.

25. Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology.* 2000;54(11 Suppl 5):S4-9.

26. Sonnen J, Larson E, Crane P, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol.* Oct 2007;62(4):406-413.

27. Jellinger KA. Alzheimer disease and cerebrovascular pathology: an update. *J Neural Transm.* May 2002;109(5-6):813-836.

28. Peretz A, Sullivan J, Leotta D, et al. Diesel exhaust inhalation elicits acute vasoconstriction in vivo. *Environ Health Perspect.* Jul 2008;116(7):937-942.

29. Auchincloss A, Diez Roux A, Dvonch J, et al. Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect.* Apr 2008;116(4):486-491.

30. Mattson, M. Mechanisms of neuronal apoptosis and excitotoxicity. *Pathogenesis and neurodegenerative disorders*. Baltimore: Humana Press; 2001:1-20.

31. Peters A, Veronesi B, Calderón-Garcidueñas L, et al. Translocation and potential neurological effects of fine and ultrafine particles a critical update. *Part Fibre Toxicol.* 2006;3:13.

32. Oberdörster G, Sharp Z, Atudorei V, et al. Translocation of inhaled ultrafine particles to the brain. *Inhal Toxicol.* Jun 2004;16(6-7):437-445.

33. Block M, Wu X, Pei Z, et al. Nanometer size diesel exhaust particles are selectively toxic to dopaminergic neurons: the role of microglia, phagocytosis, and NADPH oxidase. *FASEB J.* Oct 2004;18(13):1618-1620.

34. Calderón-Garcidueñas L, Azzarelli B, Acuna H, et al. Air pollution and brain damage. *Toxicol Pathol.*30(3):373-389.

35. Calderón-Garcidueñas L, Maronpot R, Torres-Jardon R, et al. DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic brain inflammation and neurodegeneration. *Toxicol Pathol.*31(5):524-538.

36. Campbell A, Oldham M, Becaria A, et al. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. *Neurotoxicology.* Jan 2005;26(1):133-140.

37. Dorado-Martínez C, Paredes-Carbajal C, Mascher D, Borgonio-Pérez G, Rivas-Arancibia S. Effects of different ozone doses on memory, motor activity and lipid peroxidation levels, in rats. *Int J Neurosci.* 2001;108(3-4):149-161.

38. Rivas-Arancibia S, Vazquez-Sandoval R, Gonzalez-Kladiano D, Schneider-Rivas S, Lechuga-Guerrero A. Effects of ozone exposure in rats on memory and levels of brain and pulmonary superoxide dismutase. *Environ Res.* Jan 1998;76(1):33-39.

39. Sorace A, de Acetis L, Alleva E, Santucci D. Prolonged exposure to low doses of ozone: short- and long-term changes in behavioral performance in mice. *Environ Res.* Feb 2001;85(2):122-134.

40. Bernick C, Kuller L, Dulberg C, et al. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. *Neurology.* Oct 2001;57(7):1222-1229.

41. Kuller L, Longstreth WJ, Arnold A, Bernick C, Bryan R, Beauchamp NJ. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke.* Aug 2004;35(8):1821-1825.

42. Longstreth WJ, Manolio T, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke.* Aug 1996;27(8):1274-1282.

43. Longstreth WJ, Dulberg C, Manolio T, et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* Oct 2002;33(10):2376-2382.

44. Longstreth WJ, Arnold A, Beauchamp NJ, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* Jan 2005;36(1):56-61.

45. Rosano C, Kuller L, Chung H, Arnold A, Longstreth WJ, Newman A. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc.* Apr 2005;53(4):649-654.

46. Newman A, Fitzpatrick A, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *J Am Geriatr Soc.* Jul 2005;53(7):1101-1107.

47. Fitzpatrick A, Kuller L, Ives D, et al. Incidence and prevalence of dementia in the Cardiovascular Health Study. *J Am Geriatr Soc.* Feb 2004;52(2):195-204.

48. Fitzpatrick A, Kuller L, Lopez O, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol.* Mar 2009;66(3):336-342.

49. Elkins J, Longstreth WJ, Manolio T, Newman A, Bhadelia R, Johnston S. Education and the cognitive decline associated with MRI-defined brain infarct. *Neurology.* Aug 2006;67(3):435-440.

50. Sink K, Leng X, Williamson J, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the cardiovascular health study. *Arch Intern Med.* Jul 2009;169(13):1195-1202.

51. Yaffe K, Haan M, Byers A, Tangen C, Kuller L. Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. *Neurology.* May 2000;54(10):1949-1954.

52. Bernick C, Katz R, Smith N, et al. Statins and cognitive function in the elderly: the Cardiovascular Health Study. *Neurology.* Nov 2005;65(9):1388-1394.

53. Haan M, Shemanski L, Jagust W, Manolio T, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA.* Jul 1999;282(1):40-46.

54. Bryan R, Manolio T, Schertz L, et al. A method for using MR to evaluate the effects of cardiovascular disease on the brain: the cardiovascular health study. *AJNR Am J Neuroradiol.* Oct 1994;15(9):1625-1633.

55. Longstreth WJ, Bernick C, Manolio T, Bryan N, Jungreis C, Price T. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. *Arch Neurol.* Sep 1998;55(9):1217-1225.

CHAPTER II.

The Relationship between Long-Term Exposure to Traffic-Related Air Pollutants and Longitudinally-Measured Cognitive Performance in the Cardiovascular Health Study

Background

Cognitive decline adversely affects health and quality of life in aging. Genetic, lifestyle and cardiovascular disease risk factors have been identified,[1] and environmental factors also may also be important. In autopsy studies, higher levels of markers of Alzheimer's disease (AD) and neuroinflammation were observed in brain tissues of residents of the heavily-polluted Mexico City compared to those residing in a city with low pollution.[2] Average levels of these markers were also higher in carriers of at least one apolipoprotein (*APOE)* ε4 allele,[3] the strongest genetic risk factor for AD. Children residing in Mexico City had deficits in several measures of cognitive performance relative to children residing in a less-polluted city and were more likely to have brain MRI-detected white matter lesions.[4] In another ecologic study set in China, lower neurobehavioral test scores were observed in children attending a school in a heavily traffic-polluted area than in children attending a school in a less polluted area.[5]

Recent work has demonstrated associations between air pollution exposure and cognitive performance (Table II.1). Black carbon,[6,7] ozone,[8] proximity to traffic,[9] and an index of ambient air pollution[10] all have been associated with lower cognitive function in large cross-sectional studies in children, men and women and older adults. In a longitudinal study set in a large cohort of older women, cognitive decline equivalent to two years of aging was associated with 10 $\mu g/m^3$ increments in fine and coarse particulate matter (PM) exposure.[11] The aim of our study was to examine the effect of long-term exposure to traffic-related air pollutants on cognitive trajectories over time in a large population of older men and women. We hypothesized that higher air pollutant exposure would be associated with steeper cognitive decline.

Methods

Study population

The Cardiovascular Health Study (CHS) is a large, cohort study of risk factors for cardiovascular disease, funded by the National Heart, Lung and Blood Institute, and has been described elsewhere.[12] To be eligible at baseline, participants were required to be 65 years of age or older, living independently in the community, living in the area over the next three years and not requiring a proxy respondent at baseline. Between 1989-1990, 11,955 individuals randomly selected from Medicare eligibility lists were invited by mail to participate in the study. Four field centers located in Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA recruited 3,654 participants from the randomly selected individuals and an additional 1,547 individuals who met the eligibility criteria and were residing in the same household, for a total of 5,201. Between 1992-1993, an additional 687 African Americans were recruited using a race-specific random selection from Medicare listings. Informed consent was obtained from all 5,888 participants in accordance with Institutional Review Board guidelines at each study center.

Exposure assessment

Etak, Inc. (Menlo Park, CA) generated geocodes by assigning latitude and longitude coordinates for all residential locations ascertained during semiannual contact of CHS participants. It was assumed that a participant moved 3 months prior to contact when geocodes did not match over time. When a geocode was missing for a participant at a particular contact during follow-up, the most recently obtained residential location was utilized. Geocodes for Washington County, MD participants were not sufficiently resolved to warrant exposure

estimation.

Using U.S. Environmental Protection Agency Aerometric Information Retrieval System (Allegheny and Forsyth) and California Air Resources Board Ambient Air Quality (Sacramento) data, Sonoma Technology, Inc. (Petaluma, CA) generated monthly estimates of exposure to PM <10 μm in diameter (PM_{10}) and nitrogen dioxide (NO_2) at residences by first calculating monthly averages for monitoring stations in and near CHS communities. Monthly averages were based on observed 24-hour means with sampling generally occurring every sixth day. Mean pollutant concentrations were then spatially interpolated from monitoring stations to participant residences for each month between 1989-2000.

Inverse distance weighting methods were used to interpolate spatially from monitoring stations to residential locations with a maximum of three monitoring stations included in each interpolation. These methods assume that nearby monitors are most representative of individual exposure and, as a consequence, assign greater weights to concentrations measured at locations closest to participant residences. We included monthly estimates in health effects analyses only when at least one of the monitoring stations used in the interpolation was within 25 kilometers (km), and all were within 50 km of a residence.

Outcome ascertainment

The Modified Mini-Mental State Examination (3MSE) and the Digit Symbol Substitution Test (DSST) were performed annually between 1990/1991-1998/1999 for the 3MSE and 1989/90-1998/1999 for the DSST. An extended version of the Mini-Mental State Examination, the 3MSE is a 100-point validated screening test for cognitive impairment that covers 6 core areas of cognitive function.[13,14] The DSST, another widely used tool in the evaluation of cognition, examines attention and psychomotor speed. Subjects are provided with a table of digits (1-9) and corresponding symbols and are asked to fill in as many correct symbols under

the appropriate digit as possible in 90 seconds.[15] Scores range from 0 to 90 points with higher scores indicating better cognitive performance. Several studies have utilized the DSST to examine the effects of various environmental exposures on the brain.[16-18]

Participants who are older and who score poorly on assessments of cognitive performance are less likely to return for follow-up assessments.[19-21] To mitigate this potential bias, CHS investigators evaluated the ability of the Telephone Interview for Cognitive Status (TICS) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) to estimate missing 3MSE for those who did not participate in an annual clinic visit between 1996-1998.[22] In a subset of 405 CHS participants who were administered either the TICS[23] or IQCODE[24] within 30 days of completing the 3MSE, Arnold *et al.* observed that the TICS scores could predict 3MSE scores with good accuracy (Pearson correlation between observed and predicted=0.82). We imputed missing 3MSE scores using TICS and IQCODE scores when available.

Covariate assessment

Data on relevant covariates were collected during annual clinical exams between 1989 and 1999.[12] Covariate values of interest in the current analyses were those obtained during the clinic visit corresponding with the first 3MSE or DSST assessment. The 3MSE was administered beginning at the second examination cycle for the initial cohort and at the fourth for the African American cohort. The DSST was given beginning at the first and fourth examination cycles for the two cohorts. Incident stroke and transient ischemic attack (TIA) were assessed and updated at each annual clinic visit for these analyses.[25] Covariates examined included age at baseline (years), gender, enrollment center, education, income, race (African American/other), body mass index (BMI), physical activity (kilocalories expended per week excluding chores), physical function (instrumental activities of daily life: number of activities with

which participant has difficulty[12]), depression (Centers for Epidemiological Studies Depression[26]), smoking status (never/current/former), alcohol (drinks per week), hypertension (none/borderline; systolic blood pressure (SBP) between140-159 mm Hg or diastolic blood pressure (DBP) between 90-94 mm Hg/hypertensive: SBP ≥ 160 mm Hg or DBP ≥ 95 mm Hg or self-reported history of hypertension and using anti-hypertensive medication), diabetes (none/impaired fasting glucose/diabetes by American Diabetes Association criteria[27]) and prevalent cardiovascular disease at baseline (history of stroke, TIA, myocardial infarction, claudication, angina, or congestive heart failure[28]). *APOE* status was assessed as previously described.[29]

Statistical analysis

The impact of long-term air pollutant exposure on 3MSE and DSST decline over time was analyzed using linear regression with generalized estimating equations (GEE). This approach accounts for correlations between repeated measures of cognitive function on the same person. We applied a working exchangeable correlation structure, which provides optimal efficiency when correlations between repeated measures of cognitive function are equal over time. This approach has been used in previous work examining risk factors for cognitive decline in the CHS population.[30]

We examined the effects of PM_{10} and NO_2 in separate analyses. Air pollutant estimates were available beginning at 3 months prior to study entry, meaning exposure estimates were generated mainly from time intervals occurring after the first cognitive assessment. Long-term air pollutant exposure was included in the analysis in two ways (Figure II.1). First, we estimated cumulative mean PM_{10} and NO_2 exposure from baseline to each cognitive assessment and used this exposure as a time-dependent variable. Previous work has suggested that chronic exposures may be more important than recent exposures.[11] In an effort to use estimates of

exposure generated from data averaged over at least two years, we excluded the first 3MSE score for participants in the initial cohort and the first two 3MSE scores for participants in the African American cohort, as these scores were obtained prior to 2 years after entry into CHS. In our second approach, we modeled PM_{10} and NO_2 exposure as time-independent variables. Long-term exposure in this case was calculated by averaging monthly estimates of air pollutant exposure at participant residences over the first year, first 2 years and first 3 years after entry into the study. We assumed this exposure was representative of long-term exposure occurring before study entry and thus included all cognitive assessments.

All GEE models included main effects for time since baseline cognitive assessment (in years), either PM_{10} or NO_2 (untransformed and continuous) and the product of air pollutant exposure and time, to examine any modification by air pollutant exposure of the rate of cognitive decline. Analyses were also adjusted for age at baseline (continuous), gender, enrollment center, education (4 categories), income (8 categories modeled as grouped linear variable), race, BMI, physical activity, physical function, depression, smoking status, alcohol, hypertension, diabetes and prevalent cardiovascular disease at baseline and the interaction of each covariate with time since baseline with the exception of age. In addition, we evaluated *APOE* genotype as a modifier of the effects of air pollutant exposure on cognitive decline. Rates of cognitive decline are presented as the point decline in 3MSE or DSST score associated with a 10 $\mu g/m^3$ elevation in estimated PM_{10} exposure, analyzed as a continuous variable. A 10 $\mu g/m^3$ increment is commonly utilized in analyses examining the health effects of PM exposure. Less variability was observed in NO_2 exposure, and so differences in rates of cognitive decline were evaluated at 5 parts per billion increments (ppb). We used leave-one-out diagnostics to evaluate the validity of GEE analyses.

Sensitivity analyses

Since the assessment of long-term exposure in our second analytic approach occurred, at least in part, after the first 3MSE for the initial cohort and after the first two 3MSEs for the African American cohort, we examined the impact on results of excluding these examinations so that the complete time interval of exposure estimation occurred prior to cognitive assessment. We also examined whether cognitive decline occurred non-linearly over follow-up time (years) by including follow-up as a 4-level categorical variable (0-2, 2-4, 4-6 and 6+ years) in models. Similarly, we explored potentially non-linear effects of age in statistical models by using age rather than years of follow-up as the time axis of interest. We analyzed quartiles of age (categorical and grouped linear) and compared these results to those observed when age was included as a continuous variable. In addition, we evaluated the influence on findings of excluding 3MSE scores that were imputed based on TICS and IQCODE ascertained through telephone interviews. Finally, since cerebrovascular disease may be in the causal pathway between air pollutant exposure and cognitive decline, we examined the effect on results of adjusting for incident stroke and TIA[25] as time-dependent variables in models.

Results

Estimated air pollutant exposures were significantly correlated with each other (Table II.2). Correlations were particularly strong between PM_{10} estimates generated from at least a two-year interval after entry into the CHS, and all NO_2 estimates regardless of averaging period. PM_{10} and NO_2 concentrations were also significantly correlated as well although not as strongly.

We excluded participants who resided in Washington County, Maryland or far outside of other enrollment centers (n=1,635), had no baseline 3MSE (n=161), moved during follow-up

(n=187), were missing information on relevant covariates (n=505), had improbable numbers of alcoholic beverages consumed per week reported at baseline (n=2) or had air pollutant exposure estimates generated from less than or equal to 9 months/year (n=214). Participants in the highest tertile of estimated PM_{10} exposure did not reside in Forsyth County and were less likely to be African American, have less than a high school education, to be borderline or definite hypertensive and to have at least one copy of the *APOE* ε4 allele (Table II.3). In addition, participants in the highest exposure tertile had higher mean energy expenditures on leisure activities.

Results of analyses examining the effect of cumulative mean PM_{10} exposure updated at each cognitive assessment indicated that a 10 $\mu g/m^3$ elevation in long-term PM_{10} exposure was associated with a -2.6 point (95% CI: -3.1, -1.5) lower 3MSE score and a -1.1 point (95% CI: -2.2, 0.1) lower DSST score (TableII.4). A 5 ppb elevation in long-term NO_2 exposure was associated with a -2.8 point (95% CI: -4.0, -1.6) lower 3MSE score and a -2.0 point (95% CI: -3.0, -0.9) lower DSST score. Increased PM_{10} or NO_2 exposure were not significantly associated with rate of cognitive decline assessed by the DSST, and NO_2 exposure was not significantly associated with rate of cognitive decline assessed by the 3MSE. However, there was a significant interaction between time and PM_{10} exposure (P=0.04), which would suggest that elevated exposure slows the rate of decline in 3MSE score over time (results not shown). Exclusion of imputed 3MSE scores had a small effect (<10% change) on results. Inclusion of incident stroke or TIA in models had no influence on risk estimates, and there was no significant modification by *APOE* genotype of air pollutant effects on rates of cognitive decline.

In analyses using mean values for all covariates, long-term PM_{10} exposure averaged over the first 2 years was associated with significantly faster rates of 3MSE score decline (Figure II.2.a). Effect sizes were similar when a 3 year averaging period was utilized (results not

shown). A similar pattern was observed when long-term exposure was defined as mean exposure during the first year of participation in the CHS; however, the regression coefficients were smaller in magnitude, and the effects were non-significant (results not shown). A significant acceleration of 3MSE score decline was observed for all averaging periods used to evaluate the effects of long-term NO_2 exposure (results shown for 2 year averaging period in Figure II.2.a).

DSST scores declined more rapidly for those exposed to higher concentrations of PM_{10} and NO_2 averaged over the first 2 years of participation in CHS (Figure II.2.b). This acceleration was statistically significant when long-term air pollutant exposure was based on the first year post-entry into the CHS (results not shown). A similar but non-significant pattern was observed when long-term exposure was defined as mean exposure in the first 3 years after study entry.

In sensitivity analyses, we examined the impact on results of excluding exams occurring before the end of the time interval of exposure estimation. The effect of air pollutant exposure on rates of cognitive decline was attenuated substantially by excluding either the first or the first 2 cognitive assessments. This attenuation was lessened by restricting the analysis sample to those with a cognitive assessment at the first clinic visit following the exposure window of interest, and further lessened by restricting the analysis to those under the age of 75 at baseline.

We observed significantly faster decline in 3MSE scores associated with a 10 $\mu g/m^3$ elevation in PM_{10} exposure when we analyzed follow-up time and age more flexibly as 4-level categorical variables (Table II.5.a). Similarly, PM_{10}–associated faster decline in DSST scores was observed regardless of whether follow-up time was analyzed as a continuous or categorical variable (Table II.5.b). Although point estimates were lower (i.e. more negative) for all ages for those exposed to higher PM_{10}, PM_{10}-associated faster decline in DSST scores with age was

significant only when age was examined linearly. Exclusion of imputed 3MSE scores attenuated results only slightly. Although *APOE* genotype is a strong predictor of cognitive decline, there was no significant modification by *APOE* genotype on the effect of air pollutant exposure on 3MSE or DSST scores. Adjustment for incident stroke and TIA had little impact on risk estimates. Leave-one-out diagnostics, although limited, offered some assurance that the GEE analyses presented here are approximately accurate and that the effect estimates are not overly influenced by a few data points.

Discussion

Consistent with previous studies examining the impact of air pollutant exposure on cognition,[6-9,11] we observed a significant relationship between long-term exposure to air pollutants and lower scores on the 3MSE and DSST. When we analyzed exposure as a time-independent variable, assuming exposure early in follow-up of the CHS cohort was a reasonable proxy for long-term exposure occurring prior to enrollment, there was a significant acceleration in the rate of decline over time associated with both long-term PM_{10} and NO_2 exposure. A 10 $\mu g/m^3$ elevation in long-term PM_{10} exposure resulted in a difference in 3MSE score approximately equivalent to that observed between participants one year apart in age at baseline. Weuve *et al*. reported PM-associated cognitive decline equivalent to up to two years of aging in the NHS.[11] Adjustment for cardiovascular or cerebrovascular disease had little impact on our findings, suggesting that air pollutants may affect the brain through pathways independent of those believed to mediate the observed associations between air pollutant exposure and cardiovascular disease and stroke.

With repeated measures of cognition in a large, well-characterized population of older men and women and individual estimates of air pollutant exposure, the CHS provided an excellent setting in which to examine the effects of air pollutants on brain function. However, our study has several notable limitations. Residual confounding, particularly by socioeconomic status, and multiple testing are limitations of our work. However, we adjusted for income, education and CHS community to minimize this concern. In addition, we observed relatively consistent associations between time-independent air pollutant exposure and cognitive decline assessed by the 3MSE and DSST. One of our approaches to modeling exposure relied on estimates based on intervals occurring after baseline cognitive assessments. We expected air pollutant concentrations to be correlated over time and that concentrations observed early in follow-up would be representative of exposure prior to entry into the study. It was reassuring that a similar pattern of effects was observed regardless of averaging period utilized. However, we observed attenuated effects when we excluded examinations occurring prior to exposure windows of interest. Exposure estimates were based exclusively on concentrations observed at nearby monitors and did not account for time spent away from the residence or in traffic or geographic covariates such as proximity to roadways, which may contribute to spatial differences in air pollutant exposures. Also, we utilized TICS and IQCODE scores, when available, to impute 3MSE scores to lessen the effects of informative missingness, which could have resulted in measurement error. However, this error would be expected to be non-differential with respect to air pollution exposure.

In summary, our findings add to the accumulating evidence that ambient air pollution accelerates cognitive decline in an older population, adding to the already compelling rationale for limiting exposure to this modifiable risk factor. Many pathways have been hypothesized to mediate these associations. Further work is required to elucidate underlying mechanisms.

Tables and Figures

Table II.1. Summary of studies examining air pollution effects on cognition

Study	Design	Population	Pollutants	Exposure assessment	Cognitive measures	Significant findings
Suglia *et al.* 2008 [7]	cross-sectional	202 children, mean age (SD): 9.7 (1.7) yrs, residing in Boston, MA	BC	spatiotemporal LUR model to predict annual mean BC (mean: 0.56 μg/m^3, sd: 0.13).	WRAML, K-BIT	IQR elevation in log BC predicted 3-point lower K-BIT composite score and 4-point lower WRAML general index score.
Chen and Schwartz 2009 [8]	cross-sectional	1764 adult NHANES III participants between 1988-91, mean age (SD): 38 (2) yrs	PM_{10}, O_3	IDW methods to estimate annual mean PM_{10} (37 μg/m^3, sd: 13) and O_3 (27 ppb, sd: 5) exposure at census block group centroid in year prior to cognitive assessment.	SRTT, SDST, SDLT	In adjusted models, PM_{10} not associated with cognitive performance but O_3 associated with significantly lower performance on SDST and SDLT.
Ranft *et al.* 2009 [9]	cross-sectional	399 women, mean age (SD): 74 (3) yrs, residing in Germany who had not moved in the previous 20 years	PM_{10}, roadway proximity	nearest monitor used to estimate mean PM_{10} in 5 years prior to baseline examination between 1980-1993 (mean: 48.6 or 45.0 μg/m^3) and between 2002-2006 (mean 28.3 or 25.0 μg/m^3). GIS used to estimate distance to nearest high-traffic roadway.	CERAD-Plus	Living within 50m of high-traffic road was associated with 3.8 lower CERAD-Plus score in women younger than 74 yrs. Trend of significantly lower scores in all women associated with decreasing distance to high-traffic road.
Wang *et al.* 2009 [5]	ecological	282 children, mean age (SD): 9 (0.7) yrs, attending 2 schools in Quanzhou, China	PM_{10}, NO_2	PM_{10} and NO_2 measured at 2 primary schools on 2 consecutive days in May 2005. School A classified as low and B as high exposure.	suite of cognitive assessments	Children attending school in high pollution area has significantly lower scores on 6 of 9 tests.
Zeng *et al.* 2010 [10]	ecological	15,973 residing in China, mean age: 86 yrs	API	API (scored 1-7) in 1995 calculated to exam potential lag between exposure and cognitive effect.	MMSE and cumulative deficits index (DI)	Residents in areas with high air pollutant exposure more likely to have low (<18) MMSE score or high DI (>0.45).
Freire *et al.* 2010 [31]	cross-sectional	210 children residing in urban and rural southern Spain, mean age: 4 yrs	NO_2	LUR model used to predict annual mean NO_2 exposure (5-36 μg/m^3) at residences based on sampling performed during 2 7-day periods (Nov 2005 and Sept 2006).	MSCA	Significant relationship observed only for high NO_2 exposure and gross motor function.
Power *et al.* 2011 [6]	longitudinal	680 men, mean age (SD): 71 (7) yrs, participating in the NAS between 1996-2007	BC	mean of 365 daily estimates (prior to date of first cognitive assessment) of BC predicted by spatiotemporal LUR model.	MMSE and global test of cognitive function	Doubling of estimated BC exposure associated with significantly elevated risk (OR: 1.3; 95% CI: 1.1-1.6) of low MMSE score and lower global cognitive function (equivalent to 1.9 yr age difference).
Calderon-Garciduenas *et al.* 2011 [32]	ecological	20 children from MC and 10 from less-polluted city, mean age SD): 7 (1).	PM, O_3	annual mean concentrations in MC from 2007-2009: 36 (1) μg/m^3.	brain MRI and WISC-R at baseline and year 1	Children living in MC performed worse on several WISC-R subscales.
Weuve *et al.* 2012 [11]	longitudinal	19,409 women (70-81 yrs) in NHS between 1995-2008	$PM_{2.5}$, $PM_{2.5-10}$, PM_{10}	spatiotemporal model to predict exposures at home addresses during different intervals prior to baseline cognitive assessment. Pre-1999 $PM_{2.5}$ model based on seasonal spatial and monthly temporal patterns in $PM_{2.5}$:PM_{10}.	TICS, EBMT, category fluency, Digit Span Backward test	Fine, coarse and thoracic PM associated with faster cognitive decline similar to 1-2 years of increased age.

Abbreviations: BC, black carbon; LUR, land use regression; WRAML, Wide Range Assessment of Memory and Learning; K-BIT, Kaufman Brief Intelligence Test; IQR, interquartile range; NHANES III, Third National Health and Nutrition Examination Survey; IDW, inverse distance weighting; PM_{10}, particulate matter < 10 μm; O_3, ozone; SRTT, simple reaction time test; SDST, symbol-digit substitution test; SDLT, serial-digit learning test; CERAD-Plus, Consortium to Establish a Registry for Alzheimer's Disease; NO_2, nitrogen dioxide; API, air pollution index; MMSE, Mini-Mental State Examination; MSCA, McCarthy Scales of Children's Abilities; NAS, Normative Aging Study; MC, Mexico City; WISC-R, Weschler Intelligence Scale for Children-Revised; TIC, Telephone Interview for Cognitive Status; EBMT, East Boston Memory Test.

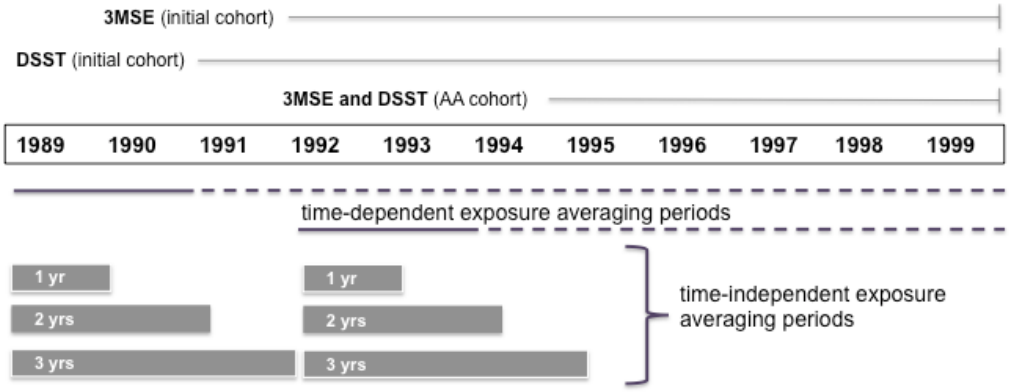


Figure II.1. Timeline of exposure averaging periods and cognitive assessments in CHS

Abbreviations: 3MSE, Modified Mini-Mental State Examination; DSST, Digit Symbol Substitution Test; AA, African American; yr, year.

Table II.2. Summaries and correlations between PM_{10} and NO_2 exposures estimated over various periods after entry into the CHS

	PM_{10} averaged over first:				NO_2 averaged over first:			
	Year	2 Years	3 Years	4 Years	Year	2 Years	3 Years	4 Years
	PM_{10} ($\mu g/m^3$) and NO_2 (ppb) Distributions by Averaging Period							
Mean (SD)	35 (5)	35 (5)	34 (4)	33 (4)	21 (5)	21 (5)	21 (5)	21 (5)
Range	22, 50	21, 46	22, 41	21, 39	12, 31	14, 31	14, 30	14, 30
	PM_{10} ($\mu g/m^3$) and NO_2 (ppb) Spearman Correlations[a] by Averaging Period							
	Year	2 Years	3 Years	4 Years	Year	2 Years	3 Years	4 Years
PM_{10}								
Year	1.00							
2 Years	0.95	1.00						
3 Years	0.92	0.98	1.00					
4 Years	0.89	0.97	0.99	1.00				
NO_2								
Year	0.44	0.47	0.46	0.49	1.00			
2 Years	0.43	0.46	0.48	0.50	0.98	1.00		
3 Years	0.41	0.45	0.47	0.50	0.96	0.99	1.00	
4 Years	0.40	0.44	0.45	0.48	0.97	0.99	0.99	1.00

[a] All Spearman correlation coefficients were statistically significant ($P<0.05$).

Table II.3. Selected baseline characteristics of CHS participants who completed a baseline 3MSE by tertile of estimated mean long-term PM_{10} exposure ($\mu g/m^3$)

	Tertile of PM_{10} exposure ($\mu g/m^3$)		
	1	2	3
	< 32.1	32.1-36.5	> 36.5
Characteristic[a]	(n = 1,064)	(n = 1,060)	(n = 1,060)
Site			
Forsyth, NC	83	24	0
Sacramento, CA	17	2	67
Allegheny, PA	<1	75	33
Washington, MD	-	-	-
Age (yrs); mean (SD)	73 (5)	74 (5)	74 (5)
African American	37	27	2
Female	59	56	53
Education			
< high school	34	25	18
high school grad/GED	25	30	28
any vocational school/some college	23	19	30
college graduate/grad or prof. school	19	26	24
Income ≥ $50,000/year	12	19	16
Instrumental ADLs; mean (SD)	0.3 (0.7)	0.3 (0.7)	0.3 (0.7)
Kcals/week leisure activity	1118 (1574)	1033 (1450)	1479 (1731)
Smoking			
former	36	42	43
current	14	13	10
Alcoholic beverages/week; mean(SD)	1.9 (5.6)	2.6 (6.4)	3.6 (7.7)
BMI (kg/m^2); mean (SD)	26.8 (5.0)	26.9 (4.8)	26.5 (4.2)
Diabetes			
impaired fasting glucose	13	15	11
diabetes	16	19	13
Depression score; mean (SD)	4.7 (4.6)	5.6 (5.0)	4.9 (4.5)
Hypertension			
borderline	16	13	13
hypertensive	49	42	37
Cardiovascular disease	20	23	20
Stroke or transient ischemic attack	6	5	5
APOE genotype[b]			
presence of ε4 allele	28	27	23

Abbreviations: SD, standard deviation; ADL, Activities of Daily Living; kcals, kilocalories; BMI, body mass index; *APOE*, apolipoprotein E

[a] Numbers in table refer to percentages unless otherwise noted.

[b] Only participants consenting to the use of their DNA were included (n=2,815).

Table II.4. Associations between time-dependent mean cumulative air pollutant exposure and 3MSE and DSST scores

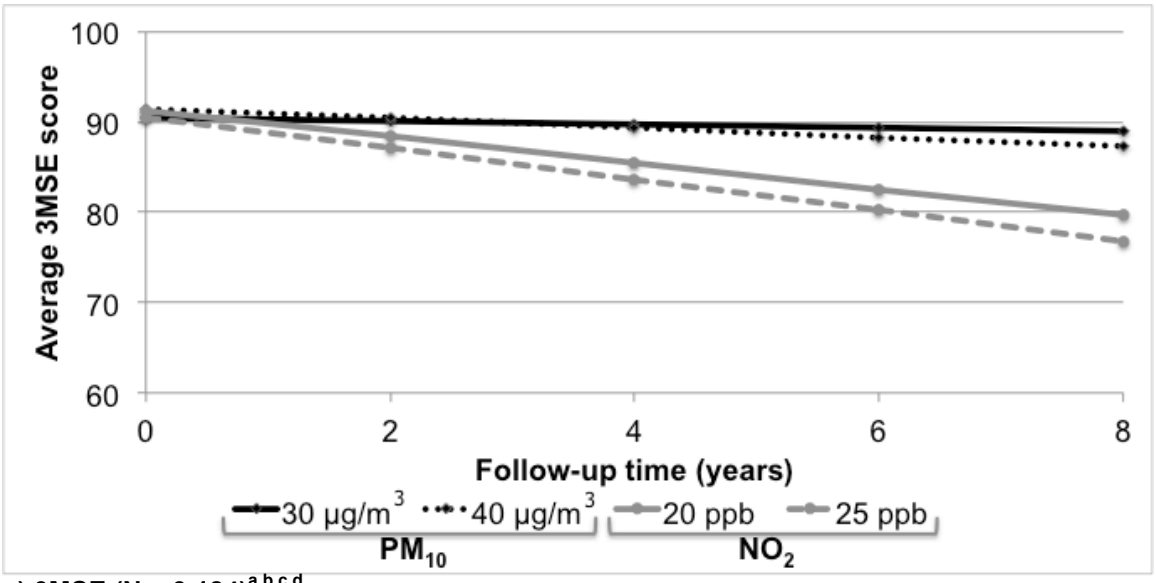
	3MSE			DSST		
	N[a]	β[b]	95% CI	N[a]	β[b]	95% CI
PM_{10}	3,032	-2.6[c]	-3.1, -1.5	3,003	-1.1	-2.2, 0.1
NO_2	3,032	-2.8	-4.0, -1.6	3,003	-2.0	-3.0, -0.9

Abbreviation: 3MSE, Modified Mini-Mental State Examination; DSST, Digit Symbol Substitution Test; CI, confidence interval

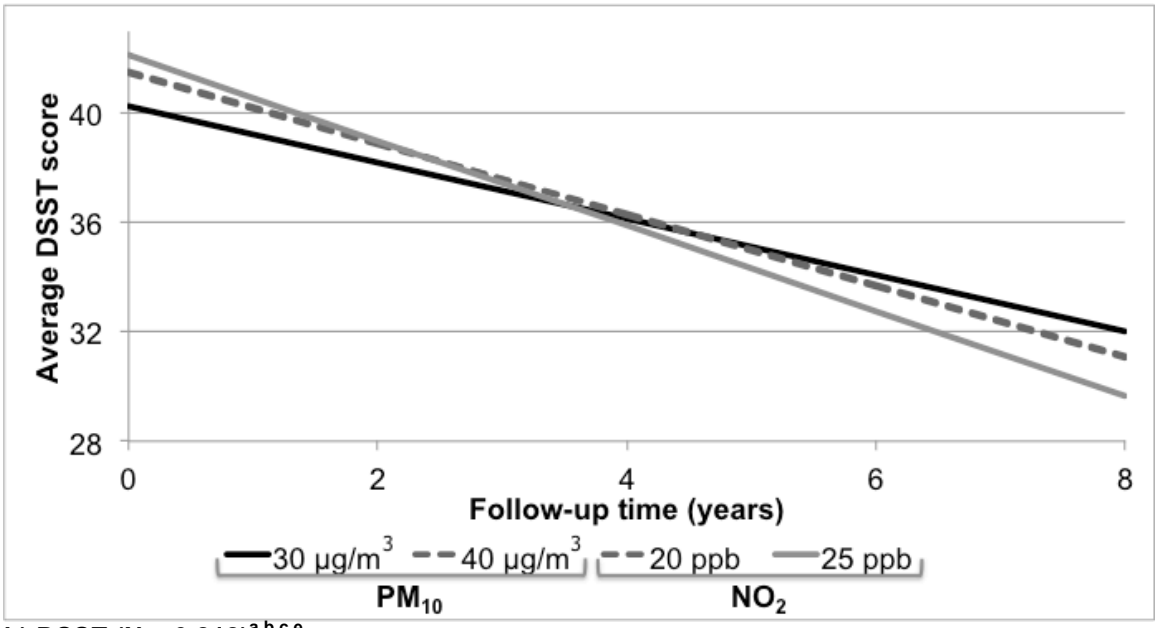
[a] The number of participants included in this analysis is less than 3,184 because participants who had 3MSE or DSST scores from the first 2 examinations only were excluded.

[b] Models adjusted for age at baseline, gender, clinic, education, income, race, BMI, physical function, physical activity, depression, smoking status, alcohol, hypertension, diabetes, prevalent cardiovascular or cerebrovascular disease at baseline and the interaction of each covariate with time since baseline except for age.The number of participants included in this analysis is less than 3,184 because participants who had 3MSE or DSST scores from the first 2 examinations only were excluded.

[c] P-value for interaction of PM_{10} with time = 0.04, indicating slower decline with higher PM_{10} exposure.



a) 3MSE (N = 3,184)[a,b,c,d]



b) DSST (N = 3,212)[a,b,c,e]

Figure II.2. Model-predicted acceleration of decline in 3MSE and DSST scores by estimated long-term air pollutant exposure

[a] Mean baseline 3MSE and DSST scores predicted using mean values for all covariates.
[b] Long-term exposure defined as mean air pollutant in the first 2 years following entry into the CHS.
[c] Models adjusted for age at baseline, gender, CHS community, education, income, race, BMI, physical function, physical activity, depression, smoking status, alcohol, hypertension, diabetes, prevalent cardiovascular or cerebrovascular disease at baseline and the interaction of each covariate with time since baseline except age.
[d] P-value for interaction of PM_{10} with follow-up time = 0.004. P-value for interaction of NO_2 with time = 0.028.
[e] P-value for interaction of PM_{10} with follow-up time = 0.002. P-value for interaction of NO_2 with time = 0.005.

Table II.5. Predicted acceleration of decline in 3MSE and DSST by estimated long-term air pollutant exposure using alternative methods of analyzing time

a) 3MSE (N = 3,184)

Time Axis[a,b]	PM_{10} ($\mu g/m^3$)[c]	Predicted 3MSE score decline				P-value[d]
		$Time_{0\text{-}2\ yrs}$	$Time_{2\text{-}4\ yrs}$	$Time_{4\text{-}6\ yrs}$	$Time_{6+\ yrs}$	
1	30	-	-2.6	-6.0	-7.7	
	40	-	-4.1	-7.2	-8.1	
		Difference	-1.5	-1.2	-0.4	0.004
		Age_{cat0}	Age_{cat1}	Age_{cat2}	Age_{cat3}	
2	30	-	0.4	-4.1	-9.5	
	40	-	-1.7	-6.5	-12.0	
		Difference	-1.3	-2.4	-2.6	0.030
		Age_0	Age_1	Age_2	Age_3	
3	30	-	-3.1	-6.3	-9.4	
	40	-	-4.1	-8.3	-12.4	
		Difference	-1.0	-2.0	-3.0	0.007
		Age_0	Age +3 yrs	Age +6 yrs	Age +9 yrs	
4	30	-	-3.4	-6.8	-10.2	
	40	-	-4.2	-8.4	-12.6	
		Difference	-0.8	-1.6	-2.4	0.005

b) DSST (N = 3,212)

Time Axis[a,b]	PM_{10} ($\mu g/m^3$)[c]	Predicted DSST score decline				P-value[d]
		$Time_{0\text{-}2\ yrs}$	$Time_{2\text{-}4\ yrs}$	$Time_{4\text{-}6\ yrs}$	$Time_{6+\ yrs}$	
1	30	-	-2.5	-5.4	-6.9	
	40	-	-3.2	-7.2	-7.4	
		Difference	-0.7	-1.7	-0.5	0.005
		Age_{cat0}	Age_{cat1}	Age_{cat2}	Age_{cat3}	
2	30	-	-0.6	-3.6	-7.4	
	40	-	-1.4	-4.9	-8.6	
		Difference	-0.8	-1.3	-1.1	0.310
		Age_0	Age_1	Age_2	Age_3	
3	30	-	-2.5	-5.1	-7.6	
	40	-	-3.0	-6.0	-9.0	
		Difference	-0.5	-1.0	-1.4	0.100
		Age_0	Age +3 yrs	Age +6 yrs	Age +9 yrs	
4	30	-	-3.0	-6.1	-9.1	
	40	-	-3.7	-7.4	-11.1	
		Difference	-0.7	-1.3	-2.0	0.002

[a] Time analyzed as follows: 1, follow-up time (years) as a 4-level indicator variable; 2, age at each cognitive assessment as quartiles (categorical); 3, age at each cognitive assessment as quartiles (grouped linear); 4, age at each cognitive assessment in 3-year increments (continuous).

[b] Model 1 adjusted for age at baseline, gender, CHS community, education, income, race, BMI, physical function, physical activity, depression, smoking status, alcohol, hypertension, diabetes, prevalent cardiovascular or cerebrovascular disease at baseline and the interaction of each covariate with time since baseline except age. Models 2-4 adjusted for variables above with the following exceptions: age at each cognitive assessment instead of age at baseline, year of birth and the interaction of each covariate with time-dependent age except for year of birth.

[c] Long-term exposure defined as mean air pollutant in the first 2 years following entry into the CHS.

[d] P-value for interaction of estimated PM_{10} exposure with follow-up time or age assessed using the Wald test.

End Notes

1. Daviglus ML, Plassman BL, Pirzada A, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science. *Arch Neurol.* Sep 2011;68(9):1185-1190.

2. Calderón-Garcidueñas L, Solt A, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol.* 2008;36(2):289-310.

3. Calderon-Garciduenas L, Kavanaugh M, Block M, et al. Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. *J Alzheimers Dis.* Jan 2012;28(1):93-107.

4. Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain Cogn.* Nov 2008;68(2):117-127.

5. Wang S, Zhang J, Zeng X, Zeng Y, Chen S. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. *Environ Health Perspect.* Oct 2009;117(10):1612-1618.

6. Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A, 3rd, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. *Environ Health Perspect.* May 2011;119(5):682-687.

7. Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. *Am J Epidemiol.* Feb 1 2008;167(3):280-286.

8. Chen JC, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology.* Mar 2009;30(2):231-239.

9. Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environ Res.* Nov 2009;109(8):1004-1011.

10. Zeng Y, Gu D, Purser J, Hoenig H, Christakis N. Associations of environmental factors with elderly health and mortality in China. *Am J Public Health.* Feb 2010;100(2):298-305.

11. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med.* Feb 13 2012;172(3):219-227.

12. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol.* Feb 1991;1(3):263-276.

13. McDowell I, Kristjansson B, Hill G, Hébert R. Community screening for dementia: the Mini Mental State Exam (MMSE) and Modified Mini-Mental State Exam (3MS) compared. *J Clin Epidemiol.* Apr 1997;50(4):377-383.

14. Teng E, Chui H. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry.* Aug 1987;48(8):314-318.

15. Wechsler D. *WAIS-R manual*. New York: Psychological Corporation; 1981.

16. Chen J, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology.* Mar 2009;30(2):231-239.

17. Seeber A, Bruckner T, Triebig G. Occupational styrene exposure and neurobehavioural functions: a cohort study with repeated measurements. *Int Arch Occup Environ Health.* Nov 2008.

18. Krieg EJ, Butler M. Blood lead, serum homocysteine, and neurobehavioral test performance in the third National Health and Nutrition Examination Survey. *Neurotoxicology.* Mar 2009;30(2):281-289.

19. Di Bari M, Williamson J, Pahor M. Missing-data in epidemiological studies of age-associated cognitive decline. *J Am Geriatr Soc.* Nov 1999;47(11):1380-1381.

20. Brayne C, Spiegelhalter D, Dufouil C, et al. Estimating the true extent of cognitive decline in the old old. *J Am Geriatr Soc.* Nov 1999;47(11):1283-1288.

21. Anstey K, Luszcz M. Selective non-response to clinical assessment in the longitudinal study of aging: implications for estimating population levels of cognitive function and dementia. *Int J Geriatr Psychiatry.* Aug 2002;17(8):704-709.

22. Arnold A, Newman A, Dermond N, Haan M, Fitzpatrick A. Using telephone and informant assessments to estimate missing Modified Mini-Mental State Exam scores and rates of cognitive decline. The cardiovascular health study. *Neuroepidemiology.* 2009;33(1):55-65.

23. Brandt J, Spence M, Folstein M. The Telephone Interview for Cognitive Status. *Neuropsychiatry, neuropsychology, and behavioral neurology.* 1988;1(2):111-117.

24. Jorm AF, Scott R, Cullen JS, MacKinnon AJ. Performance of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening test for dementia. *Psychol Med.* Aug 1991;21(3):785-790.

25. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Annals of epidemiology.* Jul 1995;5(4):278-285.

26. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. *J Clin Psychol.* Jan 1986;42(1):28-33.

27. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* Jul 1997;20(7):1183-1197.

28. Psaty BM, Kuller LH, Bild D, et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. *Annals of epidemiology.* Jul 1995;5(4):270-277.

29. Kuller LH, Shemanski L, Manolio T, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke.* Feb 1998;29(2):388-398.

30. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *Jama.* Jul 7 1999;282(1):40-46.

31. Freire C, Ramos R, Puertas R, et al. Association of traffic-related air pollution with cognitive development in children. *J Epidemiol Community Health.* Mar 2010;64(3):223-228.

32. Calderon-Garciduenas L, Engle R, Mora-Tiscareno A, et al. Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. *Brain Cogn.* Dec 2011;77(3):345-355.

CHAPTER III.

Exposure to Air Pollutants and Prevalent and Incident Alzheimer's Disease and Vascular Dementia in a Cohort of Older Adults in the Cardiovascular Health Study

Background

Alzheimer's disease (AD), the most widespread neurodegenerative disease and the most common form of dementia, affects an estimated 4.5 million people in the United States.[1] Nearly 50% of adults over the age of 85 have AD,[2] and it is projected that, as the U.S. population ages, the number of people over the age of 85 with AD will quadruple.[1] Apolipoprotein E (*APOE*) has been firmly identified as the strongest genetic risk factor for AD[3] and has also been linked, although less consistently, to vascular dementia (VaD), the second most common cause of dementia after AD.[4] However, the *APOE* epsilon4 (ε4) allele is not present in approximately 40% of AD cases.[5] Other factors likely are important, and much effort has been expended attempting to understand the role of lifestyle, diet and environmental factors that could delay the development, onset and progression of AD.[6] The impact on quality of life and the economic costs associated with AD and other forms of dementia are enormous and growing,[7] making the identification of modifiable risk factors important to public health.

Several studies have shown cross-sectional relationships between air pollution exposure and cognitive performance;[8-12] for example, one found an association between roadway proximity and mild cognitive impairment in older women.[10] Interestingly, significant links were observed between living near a high-traffic road and odor identification, an ability often affected in early AD.[13,14] More recently, Weuve and colleagues observed a longitudinal decline in cognitive performance associated with a 10 $\mu g/m^3$ increment in long-term particulate matter (PM) exposure, equivalent to that observed with two years of aging in a large cohort of older women using refined exposure estimates.[15]

Air pollution is hypothesized to affect the onset of AD by several mechanisms. Cognitive decline and dementia could occur downstream of cardiovascular and cerebrovascular disease,

both of which are associated with elevated risk of subsequent dementia; the brain is likely sensitive to the same systemic inflammatory and oxidative stress responses hypothesized to mediate the demonstrated effects of air pollution on cardiovascular disease, which could affect both AD and VaD risk.[16] Alternatively, air pollution particles may reach the brain directly through particle deposition in the nasal mucosa and translocation along the olfactory nerve or via the systemic circulation through compromised regions of the blood brain barrier (BBB).[16]

In this study, we investigated whether long-term exposure to traffic-related pollutants increases risk of prevalent and incident dementia in older adults participating in the Cardiovascular Health Study (CHS). We examined whether exposures have different impacts on risk of dementia subtypes (AD and VaD) and also explored the influence of *APOE* genotype on these relationships. Our objective was to evaluate a pervasive environmental exposure as a risk factor for a devastating disease and explore possible mechanisms underlying such associations.

Methods

Study population

The Cardiovascular Health Study (CHS) is a large study of risk factors for cardiovascular disease and stroke in older adults residing in four communities in the U.S. as described previously.[17] Participants were recruited from Medicare eligibility lists in two phases between 1989-1990 and 1992-1993 in Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. The present analyses included 3,602 participants in the CHS Cognition Study, who were followed for dementia from 1992-1994 to 1998-1999.[18] Informed consent was obtained from all 5,888 participants in accordance with Institutional Review Board guidelines at each study center. In addition, only participants who consented to use of their

DNA were included in analyses of gene-environment interactions.

Exposure assessment

Exposure to air pollutants was assessed as part of a CHS ancillary study as described in Chapter II. Briefly, monthly estimates of exposure to particulate matter <10 μm in diameter (PM_{10}) and nitrogen dioxide (NO_2) were calculated at monitoring stations in and adjacent to CHS communities. These estimates were then spatially interpolated to the geocoded residences of participants using inverse distance weighting methods. We included monthly estimates only when one of the three monitors used in each interpolation was within 25 kilometers (km) and all were within 50 km of a residence.

Outcome ascertainment

The CHS Cognition Study (CHCS), a CHS ancillary study initiated in 1998, developed and validated a methodology for classifying dementia in a large cohort of participants.[18] The CHCS was able to achieve this goal by rigorously evaluating all participants at one of the study centers (Pittsburgh, PA) and those considered to be at "high-risk" of dementia at the remaining 3 study sites.[19] Due to small numbers, all African American CHCS participants were evaluated for dementia regardless of risk status. Participants were classified as "high-risk" based on a number of factors including vital status, history of stroke, admission to a nursing home, and performance on various measures of cognitive function. Individuals were eligible for the CHCS if they completed at least one Modified Mini-Mental State Examination and a brain MRI between 1992-1994.

Participants were evaluated for dementia using a neuropsychological assessment, which utilized an extensive battery of tests, a detailed neurological examination, and psychiatric screening. The latter comprised a Neuropsychiatric Inventory containing multiple standardized tests assessing specific cognitive domains as well as the Centers for Epidemiologic Studies Depression (CES-D) Scale.[20] Participants were diagnosed with dementia by a neurologist or

psychiatrist at each study site experienced in diagnosing dementia based on a progressive or static cognitive deficit, which affected the subjects' activities of daily living, and a history of normal intellectual function prior to the onset of cognitive impairment. Furthermore, impairments in two cognitive domains, which may or may not have included memory, were required for dementia diagnosis.[19] Investigators did not exclude participants who had died prior to the initiation of the CHCS, but who were otherwise eligible, as this would have resulted in an underestimation of the incidence of dementia in the general population. In addition, this missing data would have biased results of risk factor analyses, as the subtypes of dementia, each likely with their own, if overlapping, causal pathways, exhibit differential mortality and may be associated differentially with air pollutant exposure. Neurologists or psychiatrists relied on performance on cognitive function exams when the deceased were alive, and on medical records, physician questionnaires, and information collected from proxy informants to classify participants who had died prior to 1998. Those participants who exhibited cognitive deficits but who did not meet the criteria for dementia diagnosis were classified as having mild cognitive impairment (MCI).

Relevant data on all "high-risk" participants from 3 of the clinics and all Pittsburgh participants were then collected centrally at the Pittsburgh study site. An adjudication committee reviewed all data including cranial magnetic imaging scans, and classified each participant as having dementia, or not. If dementia was ascertained, its subtype was determined using standardized criteria for AD (National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[21]), VaD (State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria[22]), mixed AD/VaD (both NINCDS-ADRDA and ADDTC criteria) or other. The year of dementia onset and person-years at risk were determined by review of longitudinal data from cognitive tests, medications, depression scores, physical

function measures, and morbid events collected across the annual clinic visits and from information requested in the Dementia Questionnaire. Year of onset could not be determined for MCI. As a result, person-years at risk cannot be calculated for this outcome.

A total of 3,602 of the 5,888 participants satisfied these criteria and were evaluated for dementia. Classification resulted in 227 prevalent and 480 incident cases of dementia over the 5.4 years of average follow-up.[23] Of those with incident dementia, 245 were classified as "pure" AD without VaD, 62 as "pure" VaD without AD, 151 as mixed AD/VaD and 22 as "other." In an effort to validate the sampling strategy employed in the CHCS, investigators examined participants in the Pittsburgh sample to determine the fraction of participants classified as "low-risk" who actually had dementia. Only 4% of the participants in the Pittsburgh study site classified as "low-risk" were diagnosed with dementia. CHCS investigators estimate that approximately 5% of participants with dementia were missed in the other 3 clinics by evaluating only those participants classified as being "high-risk."[18]

Covariate assessment

Data on covariates of interest were collected during annual clinical exams between 1989 and 2000 as described in Chapter II. For the analyses presented here, we were interested in covariate values obtained at the examination a participant participated in that was closest in time but prior to entry into the CHCS. It was assumed that a participant did not participate in a given examination cycle when the exam date and relevant covariates measured during that examination were missing. The prevalence of CHS adjudicated endpoints including myocardial infarction, angina, claudication, stroke, transient ischemic attack, congestive heart failure, stroke and transient ischemic attack (TIA) ascertained during the most recently attended examination were utilized in analyses to ensure disease status was assessed prior to study entry.

Statistical analyses

Logistic regression was used to assess associations between estimated PM_{10} and NO_2 exposure and prevalent dementia which included dementia assessed both prior to and after entry into the CHCS. To maximize sample size, all dementia cases identified by the end of follow-up were defined as prevalent in these analyses. Three separate case groups were examined: all prevalent dementia of any type, AD only cases and any VaD. The control group in all analyses included those free of any dementia by the end of follow-up. Participants identified as having MCI were excluded. Primary analyses adjusted for age (at MRI for prevalent cases at baseline and age at end of follow-up for cases identified as prevalent at the end of follow-up), race (African American or other), sex, education (6 categories, included as grouped linear variable), enrollment center, BMI, smoking status (never/former/current), alcohol (drinks per week), income (8 categories, included as grouped linear variable), LDL and HDL cholesterol, diabetes (normal/impaired fasting glucose/diabetes by ADA criteria), physical function (instrumental activities of daily living: number of activities with which participant has difficulty), kilocalories expended per week excluding chores and depression score (normal: 0-9/ at risk for clinical depression:10+). To examine whether any effect of air pollution on dementia risk was mediated by cerebro- or cardiovascular disease, we additionally adjusted for history of stroke, TIA, myocardial infarction, claudication, angina, congestive heart failure, and hypertension (normotensive/borderline hypertensive/hypertensive) in secondary analyses. We excluded participants missing information on relevant covariates. Robust standard errors were not used in primary analyses. Goodness-of-fit was assessed using the Hosmer and Lemeshow goodness-of-fit test, and influential observations were detected by calculating Pregibon's delta beta statistics.

Associations between air pollutant exposure and time to dementia were estimated using Cox proportional hazards regression, excluding participants with prevalent dementia at baseline and who were diagnosed with mild cognitive impairment during follow-up. Person-years of

follow-up began upon entry into the CHCS (i.e. date of first brain MRI) and ended at the midpoint of the year of dementia onset, death or end of follow-up (June 30, 1999). The validity of proportional hazards assumptions was tested, examining interactions between Schoenfeld residuals and time. Goodness-of-fit was assessed in plots of Cox-Snell residuals. In subanalyses, associations between PM_{10} and NO_2 exposure and time to dementia of particular subtypes (AD only and VaD with or without AD) were evaluated. Participants were censored at VaD onset in analyses evaluating AD risk and at AD onset in analyses evaluating VaD risk. Adjustment variables were the same as those described above. In subanalyses, we evaluated the impact of adjustment on hazard ratio estimates for stroke or TIA status[24] (updated during each exam cycle) as time-dependent covariates, to explore if diagnosed cerebrovascular disease was in the causal pathway between air pollutant exposure and incident dementia.

Exposure intervals of interest for prevalent dementia analyses included one, two and three years prior to entry into the CHCS (Figure III.1). In analyses of incident dementia, we evaluated the exposure intervals above as well as the influence of time-dependent cumulative exposure on time to dementia to investigate the importance of recent exposure (Figure III.1). Specifically, mean PM_{10} and NO_2 exposures from one year prior to entry into the CHCS through dementia onset or censoring were estimated in 6-month increments. Associations are reported as the relative increase in odds or risk associated with a 10 $\mu g/m^3$ or 10 ppb elevation in estimated mean long-term PM_{10} or NO_2 exposure.

The presence of at least one copy of the APOE $\varepsilon 4$ allele, age and sex were explored as potential modifiers of the effects of long-term PM_{10} and NO_2 exposure on dementia risk, overall and by subtype. Effect modification was evaluated by including a multiplicative interaction term (i.e. exposure variable*potential effect modifier) among the covariates. Likelihood ratio tests were used to test if the fit of the models with and without the interaction term were significantly different.

Results

Prevalent dementia

Most characteristics were similar for CHS participants across tertiles of long-term PM_{10} exposure prior to entry into the CHCS (Table III.1). However, relative to participants in the highest tertile of PM_{10} exposure, those in the lowest tertile had lower mean energy expenditures on leisure activities, were more likely to reside in Forsyth County, less likely to have graduated from high school and less likely to have an elevated depression score. PM_{10} exposure was highest in Sacramento County, and NO_2 exposure was highest in Allegheny County (Figure III.2). Pollutant concentrations generally declined over the course of CHS follow-up, explaining why higher mean estimates were observed over longer averaging periods.

No significant associations were observed between long-term exposure to either PM_{10} or NO_2 and overall prevalent dementia or dementia caused by AD only (Table III.2). After adjustment for covariates, a strong relationship was observed between PM_{10} exposure in the one and two years prior to CHCS entry and any prevalent VaD. Specifically, a 10 $\mu g/m^3$ elevation in mean PM_{10} exposure in the 2 years prior to CHCS entry was associated with a 2.45-fold increase in odds of VaD (95% CI: 1.23, 4.86). This association was attenuated but not eliminated after further adjustment for history of stroke, TIA, hypertension or other prevalent cardiovascular disease. The pattern was similar with long-term NO_2 exposure, but associations were not statistically significant. No significant interactions between air pollutant exposure and *APOE* genotype, age or sex were observed in analyses of all dementia, AD only and any VaD (results not shown). Hosmer Lemeshow goodness-of-fit tests suggest models examining the relationship between air pollutants (regardless of exposure averaging period) and any prevalent dementia fit reasonably well (data not shown). However, tests approached significance in

assessments of models examining the relationship of PM_{10} averaged over the 3 years prior to CHCS entry and AD and VaD. Observations with Pregibon's delta beta statistics greater than 0.2 were identified; however, their exclusion from analyses resulted in even higher odds ratios.

Incident dementia

No significant associations were observed between long-term cumulative mean long-term exposure to PM_{10} and overall prevalent dementia, dementia caused by AD only or VaD (Table III.3). Similar to analyses of prevalent dementia, the point estimates were highest for VaD and lowest for AD only; however, none of the associations was statistically significant. Little change in risk estimates was observed after adjustment for additional variables beyond age, race, sex, enrollment center, education and income. As in prevalent dementia analyses, no significant interactions between air pollutant exposure and *APOE* genotype, age or sex were observed in analyses of all dementia, AD only and any VaD. Findings were similar when we examined associations between time-independent air pollutant exposure and dementia (results not shown). Examination of Schoenfeld and Cox-Snell residuals indicated no significant violation of proportional hazards assumptions in all incident dementia analyses, and reasonably good fit for overall dementia, respectively. Concerns with goodness-of-fit arose in analyses of incident AD and VaD; however, fit improved after adjustment for *APOE* genotype.

Discussion

Estimated long-term PM_{10} or NO_2 exposure was not associated with overall prevalent dementia of any cause or AD only (i.e. without VaD). The presence of any *APOE* ε4 allele resulted in odds ratios describing air pollutant and AD relationships that were greater in magnitude, but these interactions were not statistically significant. In contrast, we saw a relationship between PM_{10} and any prevalent VaD (alone or mixed with AD). Although the

magnitudes of the effect estimates were similar, a significant relationship was not observed in analyses of incident VaD in those free of dementia at baseline.

A large, well-characterized population with over 8 years of follow-up, the CHS provided a unique setting to examine the relationship between air pollutant exposure and dementia, overall and by subtype. Nonetheless limitations should be noted. Exposure measurement error is present as estimates were based on inverse distance weighting methods, which utilize pollutant concentrations at potentially distant monitors to estimate exposure at residences, which are assumed to be representative of true, personal exposure. In addition, we had exposure information for participants only in old age with a mean age of 80 years at entry into the CHCS. Lifetime exposures likely are most relevant in dementia. In the current study, the period of exposure estimation may well have occurred after the initiation of an underlying disease process believed to begin years before dementia diagnosis. The exposure windows examined here preceded all identified incident dementia in those free of dementia at CHCS baseline. In contrast, prevalent dementia at baseline of the CHCS could have been diagnosed anytime prior to the air pollutant exposure averaging period. However, to the extent that mean exposure averaged over various periods preceding study entry approximated long-term exposure, our findings provide evidence that long-term exposure to air pollutants may contribute to the development of VaD. Also, statistical models may have been mis-specified, and residual confounding could be present. We examined associations between two air pollutants averaged over various time periods and dementia by subtype. With the high number of statistical tests performed, we would expect to observe a significant association by chance alone, and the findings with respect to prevalent VaD should be considered with the multiple testing burden in mind. Finally, we should point out also that the methods for ascertaining time to dementia and distinguishing subtypes could have resulted in misclassification of disease. The methods were unconventional in that they employed a historical assessment of prospectively-collected data in

CHS. Only those considered “high risk” and who were still alive between 1998-1999 underwent an in-person, detailed neuropsychological evaluation. As a result, misclassification likely occurred when distinguishing those who had prevalent dementia at baseline, were at risk for incident dementia and developed MCI. Specifically, the “at risk” population likely includes participants in the early stages of dementia. However, we expect misclassification was non-differential with respect to exposure status and would have resulted in attenuated effect estimates.

Numerous studies have demonstrated associations between air pollution exposure and cognition. The findings presented here are the first to suggest that long-term exposure to PM_{10} may be important in dementia, the most extreme manifestation of age-related cognitive decline. Given the consistently observed relationship between air pollution and cardiovascular disease, it is not surprising that air pollution would be most strongly related to VaD and that adjustment for previous stroke or TIA would weaken this association. Although additional studies are required, our findings provide some evidence that vascular processes may explain, at least in part, associations between air pollutant exposure and cognitive decline.

Tables and Figures

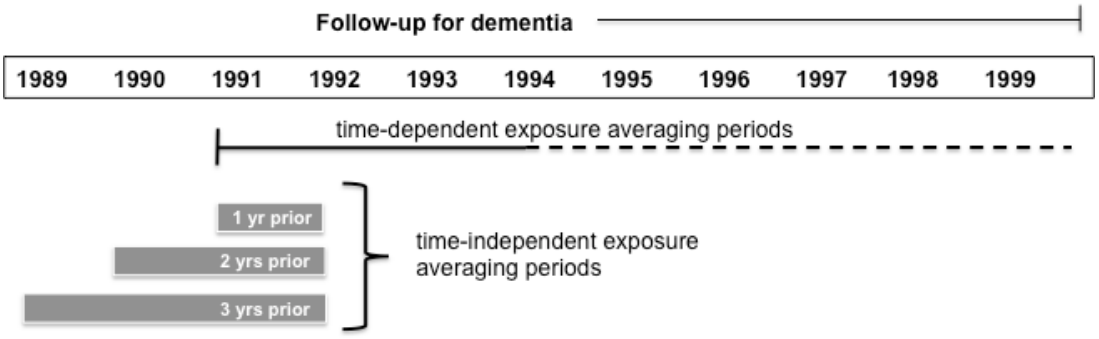
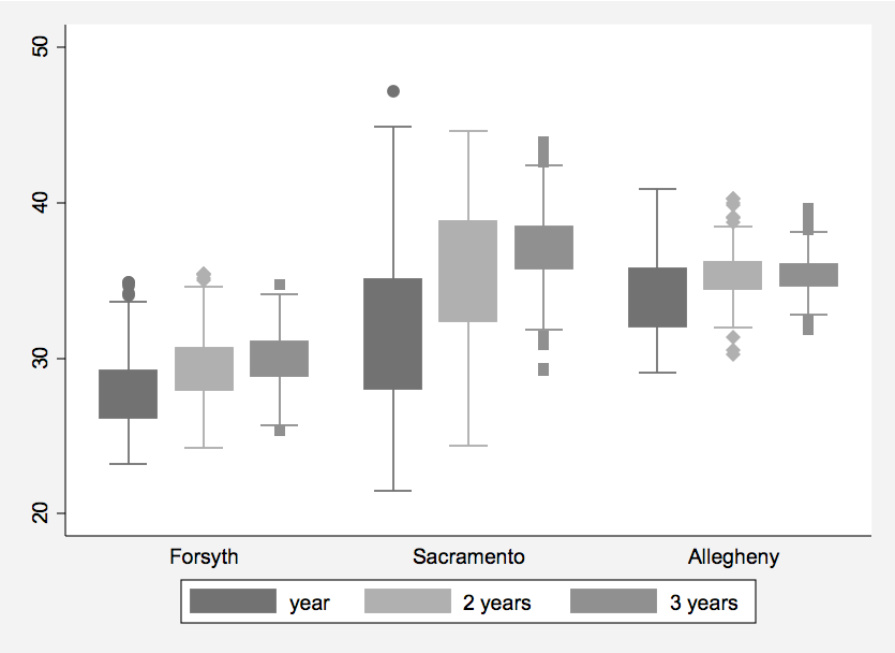


Figure III.1. Timeline of exposure averaging periods and dementia follow-up in CHS

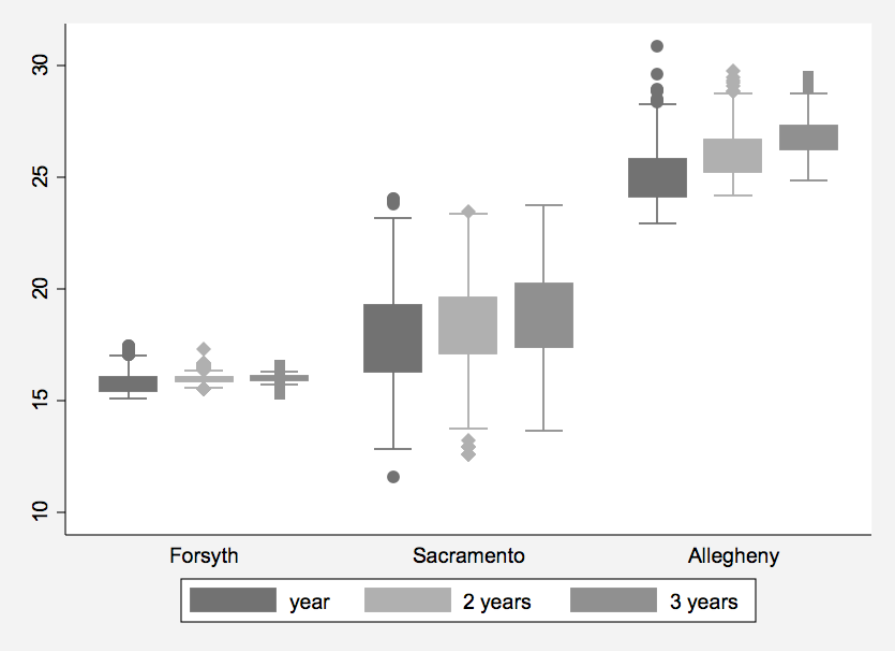
Table III.1. Selected characteristics of CHCS participants by tertile of estimated mean PM_{10} exposure ($\mu g/m^3$) in the 2 years prior to study entry

	Tertile of PM_{10} exposure ($\mu g/m^3$)		
	1	2	3
	< 31.2	31.2-34.9	> 34.9
Characteristic[a]	(n = 532)	(n = 530)	(n = 531)
Site			
Forsyth, NC	82	18	1
Sacramento, CA	17	51	37
Allegheny, PA	< 1	32	62
Washington, MD	-	-	-
Age (yrs); mean (SD)	80 (5)	81 (4)	81 (4)
African American	5	3	5
Female	57	58	55
Education			
< high school	24	14	12
high school grad/GED	28	30	27
any vocational school	11	10	9
some college	14	19	19
college graduate	12	16	16
grad. or prof. school	11	12	18
Instrumental ADLs; mean (SD)	0.4 (0.8)	0.3 (0.7)	0.3 (0.6)
Kcals/week leisure activity; mean (SD)	1207 (1628)	1296 (1614)	1351 (1617)
Smoking			
former	42	45	46
current	9	8	9
Alcoholic beverages/week; mean(SD)	2 (5)	3 (5)	3 (8)
BMI (kg/m^2); mean (SD)	26 (4)	26 (4)	26 (4)
LDL chol. (mg/dl); mean (SD)	124 (31)	127 (33)	127 (32)
HDL chol. (mg/dl); mean (SD)	53 (14)	53 (15)	55 (15)
Diabetes			
impaired fasting glucose	10	10	10
diabetes	11	12	11
Elevated depression score	10	11	16
Hypertension			
borderline	16	15	14
hypertensive	37	38	33
Cardiovascular disease	20	20	23
Stroke or transient ischemic attack	5	5	8
APOE genotype[b]			
presence of ε4 allele	25	25	21

[a] Numbers in table refer to percentages unless otherwise noted.
[b] Only participants consenting to the use of their DNA were included (n=1,436).



a) PM_{10}[a]



b) NO_2[a]

Figure III.2. Air pollutant concentrations averaged over the one, two and three years prior to entry into the CHCS by enrollment center

[a] Boxes, whiskers and points indicate the interquartile range, the upper and lower adjacent values and outliers, respectively.

Table III.2. Associations between a 10 μg/m^3 and 10 ppb elevation in long-term PM_{10} and NO_2 exposure and prevalent dementia, overall and by subtype

			Model 1[a]		Model 2[b]	
Averaging period	N	cases n (%)	OR (95% CI)	P-value	OR (95% CI)	P-value
Any dementia						
PM_{10}						
Year	1593	305 (19)	1.31 (0.89, 1.94)	0.174	1.14 (0.76, 1.70)	0.519
2 Years	1593	305 (19)	1.28 (0.77, 2.12)	0.347	1.15 (0.69, 1.93)	0.593
3 Years	1506	279 (19)	0.92 (0.41, 2.07)	0.838	0.92 (0.40, 2.11)	0.849
NO_2						
Year	1592	304 (19)	1.48 (0.57, 3.86)	0.424	1.04 (0.39, 2.79)	0.931
2 Years	1592	304 (19)	0.87 (0.30, 2.58)	0.808	0.67 (0.22, 2.01)	0.473
3 Years	1528	283 (19)	0.54 (0.16, 1.82)	0.319	0.49 (0.14, 1.70)	0.263
AD						
PM_{10}						
Year	1439	151 (10)	0.82 (0.46, 1.46)	0.493	0.81 (0.45, 1.45)	0.478
2 Years	1439	151 (10)	0.82 (0.40, 1.69)	0.592	0.82 (0.39, 1.70)	0.591
3 Years	1369	142 (10)	0.59 (0.20, 1.76)	0.344	0.57 (0.19, 1.73)	0.324
NO_2						
Year	1439	151 (10)	0.94 (0.23, 3.77)	0.930	0.89 (0.22, 3.61)	0.875
2 Years	1439	151 (10)	0.50 (0.11, 2.38)	0.387	0.47 (0.10, 2.24)	0.341
3 Years	1390	145 (10)	0.34 (0.06, 1.83)	0.210	0.33 (0.06, 1.80)	0.203
VaD						
PM_{10}						
Year	1423	135 (9)	2.33 (1.39, 3.91)	0.001	1.71 (1.00, 2.92)	0.048
2 Years	1423	135 (9)	2.45 (1.23, 4.86)	0.011	2.08 (1.02, 4.24)	0.044
3 Years	1347	120 (9)	1.98 (0.63, 6.21)	0.242	1.98 (0.61, 6.48)	0.256
NO_2						
Year	1422	134 (9)	3.35 (0.93, 12.08)	0.065	1.71 (0.45, 6.54)	0.429
2 Years	1422	134 (9)	2.26 (0.52, 9.90)	0.280	1.42 (0.31, 6.63)	0.653
3 Years	1366	121 (9)	1.15 (0.21, 6.21)	0.874	1.08 (0.19, 6.20)	0.931

[a] Model 1 adjusted for age at enrollment in CHCS, sex, race (African American/other), enrollment center and education (less than high school/ high school graduate/any vocational school/any college/college graduate/graduate or professional school). BMI, smoking status (never/former/current), alcohol (drinks per week), income (8 categories), LDL and HDL cholesterol, diabetes (normal/impaired fasting glucose/diabetes by ADA criteria), physical function (instrumental activities of daily living: number of activities with which participant has difficulty), physical activity (kilocalories expended per week excluding chores) and depression score (normal: 0-9/ at risk for clinical depression:10+).

[b] Model 2 adjusted for Models 1 covariates and history of stroke, transient ischemic attack, cardiovascular disease (myocardial infarction, claudication, angina or congestive heart failure) and hypertension (normotensive/borderline hypertensive/hypertensive.

Table III.3. Adjusted hazard ratios (HRs) describing associations between a 10 μg/m^3 elevation in long-term PM_{10} and exposure and incident dementia, overall and by subtype

			Model 1[a]	Model 2[b]	Model 3[c]
Averaging period	cases	subjects	HR (95% CI)	HR (95% CI)	HR (95% CI)
PM_{10}					
dementia	258	1709	1.29 (0.66, 2.51)	1.31 (0.67, 2.58)	1.31 (0.69, 2.48)
AD	129	1709	1.00 (0.36, 2.77)	1.03 (0.37, 2.92)	1.01 (0.34, 2.98)
VaD	114	1709	1.98 (0.79, 4.93)	1.99 (0.79, 5.02)	1.90 (0.88, 4.12)

[a] Model 1 was stratified on sex and enrollment center and adjusted for age at enrollment in CHCS (continuous), race (African American/other), education (grouped linear: less than high school/ high school graduate/any vocational school or college/college graduate or graduate or professional school), income (8 categories modeled as grouped linear variable) and smoking status (never/former/current).

[b] Model 2 was stratified on sex and enrollment center and adjusted for Model 1 covariates and BMI, alcohol (drinks per week), LDL and HDL cholesterol, diabetes (normal/impaired fasting glucose/diabetes by ADA criteria), physical function (instrumental activities of daily living: number of activities with which participant has difficulty), physical activity (kilocalories expended per week excluding chores) and depression score (normal: 0-9/ at risk for clinical depression:10+).

[c] Model 3 was stratified on sex, enrollment center and history of stroke/TIA and adjusted for Models 1 and 2 covariates and history of cardiovascular disease (myocardial infarction, claudication, angina or congestive heart failure) and hypertension (normotensive/borderline hypertensive/hypertensive).

End Notes

1. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol.* Aug 2003;60(8):1119-1122.

2. Evans D, Funkenstein H, Albert M, et al. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. *JAMA.* Nov 1989;262(18):2551-2556.

3. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *Jama.* Oct 22-29 1997;278(16):1349-1356.

4. Yin YW, Li JC, Wang JZ, et al. Association between apolipoprotein E gene polymorphism and the risk of vascular dementia: A meta-analysis. *Neurosci Lett.* Apr 11 2012;514(1):6-11.

5. Bird TD. Alzheimer Disease Overview. *Gene Reviews* 2010; http://www.ncbi.nlm.nih.gov/books/NBK1161/. Accessed April 9, 2012.

6. Daviglus ML, Plassman BL, Pirzada A, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science. *Arch Neurol.* Sep 2011;68(9):1185-1190.

7. Wimo A, Jonsson L, Gustavsson A, et al. The economic impact of dementia in Europe in 2008-cost estimates from the Eurocode project. *Int J Geriatr Psychiatry.* Aug 2010;26(8):825-832.

8. Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A, 3rd, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. *Environ Health Perspect.* May 2011;119(5):682-687.

9. Chen JC, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology.* Mar 2009;30(2):231-239.

10. Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environ Res.* Nov 2009;109(8):1004-1011.

11. Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. *Am J Epidemiol.* Feb 1 2008;167(3):280-286.

12. Wang S, Zhang J, Zeng X, Zeng Y, Chen S. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. *Environ Health Perspect.* Oct 2009;117(10):1612-1618.

13. Serby M, Larson P, Kalkstein D. The nature and course of olfactory deficits in Alzheimer's disease. *Am J Psychiatry.* Mar 1991;148(3):357-360.

14. Doty RL. The olfactory system and its disorders. *Semin Neurol.* Feb 2009;29(1):74-81.

15. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med.* Feb 13 2012;172(3):219-227.

16. Genc S, Zadeoglulari Z, Fuss SH, Genc K. The adverse effects of air pollution on the nervous system. *J Toxicol.* 2012;2012:782462.

17. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol.* Feb 1991;1(3):263-276.

18. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. *Neuroepidemiology.* Jan-Feb 2003;22(1):1-12.

19. Lopez O, Kuller L, Fitzpatrick A, Ives D, Becker J, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. *Neuroepidemiology.*22(1):1-12.

20. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. *J Clin Psychol.* Jan 1986;42(1):28-33.

21. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* Jul 1984;34(7):939-944.

22. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology.* Mar 1992;42(3 Pt 1):473-480.

23. Fitzpatrick AL, Kuller LH, Lopez OL, Kawas CH, Jagust W. Survival following dementia onset: Alzheimer's disease and vascular dementia. *J Neurol Sci.* Mar 15 2005;229-230:43-49.

24. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Annals of epidemiology.* Jul 1995;5(4):278-285.

CHAPTER IV.

The Relationship between Prevalent and Incident Brain MRI Findings and Air Pollutant Exposure in the Cardiovascular Health Study

Background

The impact of air pollutants on cardiovascular morbidity is well established. Numerous studies have demonstrated adverse effects of air pollutant exposure on cardiovascular health measures[1] including systemic inflammation,[2,3] blood pressure,[4] heart rate variability,[5-8] vascular function,[9,10] altered cardiac structure and function,[11,12] cardiac electrical abnormalities[13] and atherosclerosis.[10,14] In the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air), estimated short- and long-term exposure to fine particulate matter were significantly associated with measurements on retinal photography, providing evidence that air pollution adversely influences the microvasculature.[9] Interestingly, in the Cardiovascular Health Study (CHS) cohort, those with small vessel disease of the retina compared to those without such retinal findings were at higher risk of brain infarcts and poorer white matter grade on magnetic resonance imaging (MRI),[15] which are themselves markers of small vessel disease and also linked to cognitive decline.[16-18] Thus, damage to the microvasculature could be an intermediate linking air pollution exposure and cognitive outcomes.

Although much of the focus of air pollution research has been on respiratory and cardiovascular effects, evidence from human studies describing adverse impacts of air pollutants on the brain is beginning to accumulate. Comparing autopsied brain tissues from residents of the heavily polluted Mexico City to those of cities with low pollution, investigators observed elevated expression of various markers of neuroinflammation and a significantly greater accumulation of beta-amyloid 42, a pathological hallmark of Alzheimer's disease.[19] In another study, children residing in Mexico City exhibited deficits in several measures of cognitive performance relative to children residing in a less-polluted city and were more likely to have brain MRI-defined white matter lesions.[20] Similar MRI findings were evident in dogs from

the same cities with brain tissue showing on pathologic examination vascular subcortical changes associated with neuroinflammation. In a small controlled-exposure study utilizing a blinded randomized crossover design, a significant relationship was observed between exposure to dilute diesel exhaust and increases in brain activity measured by quantitative electroencephalography,[21] providing experimental evidence that traffic-related air pollution can affect brain function in humans under experimental conditions. A relationship between air pollutant exposure and brain effects has been observed in several epidemiologic studies. Black carbon, ozone, particulate matter and proximity to traffic have been implicated in these effects.[22-27]

Our objective here was to investigate the relationship between long-term air pollutant exposure and subclinical or covert brain MRI-defined findings, namely in people without a history of transient ischemic attack (TIA) or stroke. Specifically, we hypothesized that long-term exposure to particulate matter less than 10 μm in aerodynamic diameter (PM_{10}) and to nitrogen dioxide (NO_2) would be associated with MRI-defined white matter grade and infarcts in the Cardiovascular Health Study (CHS) cohort of older adults living in four communities in the United States. Although the underlying pathology of these MRI findings is not understood completely, brain infarcts and white matter lesions have demonstrated adverse consequences including cognitive impairment,[28,29] incident stroke,[30,31] and cardiovascular events.[32]

Methods

Study population

The Cardiovascular Health Study (CHS) is a large, observational study of risk factors for cardiovascular disease as described previously[33] and in Chapters II and III. Participants were non-institutionalized adults 65 years of age or older at baseline recruited from 4 U.S.

communities including Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. 5,201 participants were recruited between 1989-1990, and an additional 687 African Americans were recruited between 1992-1993. A subset of the cohort underwent brain MRI scanning between 1991-1994 and between 1997-1999. These participants were younger and healthier than the cohort as a whole. Informed consent was obtained from all 5,888 participants in accordance with Institutional Review Board guidelines at each study center.

Exposure assessment

Residence-specific estimates of long-term exposure to particulate matter <10 μg in diameter (PM_{10}) and nitrogen dioxide (NO_2) were generated using inverse distance weighting methods as described in Chapters II and III. Estimates were based on U.S. Environmental Protection Agency Aerometric Information Retrieval System (Allegheny and Forsyth Counties) and California Air Resources Board Ambient Air Quality (Sacramento County) data spatially interpolated to the geocoded residential locations of CHS participants in all study communities except for Washington County.

Outcome ascertainment

All CHS participants were invited to undergo brain MRI scans twice during follow-up, first between November 1991 and May 1994 (n = 3,660) and again between May 1997 and December 1999 (n = 2,313). A total of 2,116 participants underwent brain MRI scanning on both occasions. The scanning protocol included sagittal T1-weighted localizer images and axial T1, spin density and T2 weighted images.[34] Axial images had 5-mm thickness without interslice gaps. Those who were willing and had no contraindications for the scan were younger, healthier, and more educated than those who did not. At a centralized reading center, neuroradiologists, without knowledge of clinical information of participating individuals, identified brain infarcts and estimated white matter grade. Infarcts were defined as a region of abnormal

signal intensity in a vascular distribution that lacked mass effect and were at least 3 millimeters in maximum diameter. White matter grade was scored on a 10-point scale using library templates. To improve reliability of measures of change in white matter grade, initial and follow-up scans were reread in 2001-2002 side-by-side by raters blinded to both the original grade and order of the scans.[18]

Covariate assessment

Data on covariates of interest were collected during annual clinical examinations between 1989 and 2000. For the analyses presented here, we were interested in covariate values obtained at the examination an individual participated in that was closest in time but prior to the brain MRI. When the examination date and relevant covariates measured during that examination were missing, an individual was assumed not to have participated in that examination cycle. The CHS adjudicated endpoints included myocardial infarction, angina, claudication, stroke, transient ischemic attack (TIA), and congestive heart failure.[35] The prevalence of these endpoints ascertained during the most recently attended examination was utilized in analyses to ensure disease status was assessed prior to the MRI. Participants with a history of transient ischemic attack or stroke prior to the MRI were excluded.

Statistical analyses

To maximize the sample size for analyses, we used generalized estimating equations (GEE) with robust standard errors to estimate associations between long-term PM_{10} and NO_2 exposure and repeated measures of prevalent white matter grade (modeled as a continuous and binary variable) and infarcts (presence/absence). GEE methods account for within-participant correlations between multiple measurements on the same person. Those with an infarct < 3 mm in maximum diameter, which were not reliably measured, were excluded in infarct analyses except as subsequently described. Exposure intervals of interest included

mean exposure in the one, two, three and four years preceding each MRI. Pollutant concentrations varied by season. As a result, in an effort to use estimates representative of annual exposure, we included in analyses only those one, two, three and four year averages generated from at least 9, 18, 27 and 36 months, respectively. Primary analyses adjusted for sex, clinic, age at MRI, education, race, date of MRI, physical activity, BMI, smoking and diabetes. Secondary analyses also adjusted for LDL and HDL cholesterol, hypertension, use of hypertension medications, statins or diuretics, any prevalent cardiovascular disease, MRI-detected infarcts in white matter grade analyses and white matter grade in MRI-detected infarct analyses.

We also evaluated relationships between PM_{10} and NO_2 exposure and worsening white matter grade (using grade ascertained in scan re-reads) and incident infarcts in the subset of the cohort with both brain MRI scans in logistic regression models. Exposure intervals of interest included mean exposure in the one, two and three years preceding each MRI as well as mean exposure between MRIs. Primary and secondary analyses were adjusted for the variables above as well as time between scans and infarct at initial scan in white matter worsening analyses and white matter grade at the initial MRI in incident infarct analyses. Associations are reported as the either an increase in white matter grade or relative increase in odds of white matter worsening or MRI-detected infarct associated with a 10 $\mu g/m^3$ or 10 ppb elevation in estimated mean long-term PM_{10} or NO_2 exposure. These are increments commonly used in studies examining the health effects of air pollutant exposure. Robust standard errors were not used in primary logistic regression analyses. Leave-one-out diagnostics were utilized to provide an approximation of the validity of GEE analyses. Goodness-of-fit of logistic regression models was assessed using the Hosmer and Lemeshow goodness-of-fit test, and influential observations were detected by calculating Pregibon's delta beta statitistics.

Sensitivity analyses

In sensitivity analyses, we explored the effect of additional adjustment for income at baseline and *APOE* as well as the number of alcoholic beverages consumed per week and creatinine, both ascertained at the exam closest in time to the MRI. Also, given the improved reliability of the variables used to calculate change in white matter grade from scan re-reads, we examined the effect of using scan re-read variables in analyses of PM_{10} and NO_2 effects on repeated measures of white matter grade. The scan re-read variables were not used in primary analyses as they were available only for the subset of the cohort who had both brain MRIs. In addition, we performed analyses restricted to the primary subject in each household to examine the sensitivity of our findings to within-household clustering as some participants in this study resided in the same household as another subject. Finally, risk factor profiles of lacunar infarcts may differ by size.[36] Specifically, beyond the common risk factors of age, hypertension and smoking, a recent study demonstrated that diabetes and glycated hemoglobin were the strongest risk factors for small infarcts (≤ 7mm) whereas LDL cholesterol appeared to be the most important risk factor for larger infarcts (8-20mm).[36] To explore the possibility that air pollutant associations may differ by infarct size, we evaluated the relationship between PM_{10} and NO_2 and the following case groups: any infarct ≤7 mm in maximum diameter, which included the presence of lesions < 3 mm; and any infarct 8-20 mm in maximum diameter. The control group in all analyses was comprised of those free of an infarct of any size.

Results

Characteristics generally were similar for CHS participants across tertiles of long-term PM_{10} exposure for each scan examined separately (Table IV.1). Notable exceptions included site and smoking status with few participants residing in Allegheny County in the lowest tertile

for either scan and more former smokers in the highest tertile of exposure for the second MRI. PM_{10} exposure was highest prior to the first MRI in Sacramento County and prior to the second MRI in Allegheny County (Figure IV.1). NO_2 exposure was highest in Allegheny County regardless of MRI. Pollutant concentrations generally declined over the course of CHS follow-up resulting in higher mean estimates generated based on longer averaging periods. The greatest variability in exposure was observed in Sacramento County and Allegheny County. Estimated air pollutant exposures were significantly correlated with each other for each MRI (Table IV.2). Correlations were particularly strong between PM_{10} estimates generated from at least a two-year interval before the first MRI, all PM_{10} estimates for periods preceding the second MRI, and all NO_2 estimates regardless of MRI. PM_{10} and NO_2 were significantly correlated as well although not as strongly.

Mean white matter grade worsened between MRIs, and both prevalent and incident infarcts were common in the CHS population (Table IV.3). A 10 $\mu g/m^3$ and 10 ppb difference in mean PM_{10} and NO_2 exposure (averaged over the prior 1, 2, 3 and 4 years preceding an MRI scan) was associated with higher (i.e. worse) white matter grade in fully-adjusted linear models (Table IV.4). In logistic models in which exposure was averaged over the 2 years preceding an MRI, those exposed to 10 $\mu g/m^3$ higher PM_{10} levels had 1.32-fold (95% CI: 1.04, 1.68) greater odds of having white matter grade greater than 2, and those exposed to 10 ppb higher NO_2 levels had 1.58-fold (95% CI: 1.07, 2.32) greater odds of having white matter grade greater than 2 (Table IV.5). Odds ratios describing associations over different exposure intervals were smaller in magnitude and nonsignificant. Elevated PM_{10} and NO_2 exposure, over any averaging period, was not significantly associated with worsening white matter between MRIs in analyses restricted to those who participated in serial brain MRIs (Table IV.6), and the effect of air

pollutant exposure on white matter grade did not depend significantly on APOE ε4 status (results not shown).

Greater exposure to either pollutant was not positively associated with prevalent (Table IV.7) or incident (Table IV.8) infarcts regardless of exposure averaging period used. The magnitude of the ORs generally indicated reduced, and in some case significantly reduced, odds of infarct associated with higher air pollutant exposure. Secondary adjustment variables had little influence on overall conclusions. Similar results were observed when alternate case definitions were used, which examined air pollutant effects on MRI-detected infarcts ≤ 7 mm (or 10 mm) in maximum diameter (with or without inclusion of infarcts less than or equal to 3 mm in maximum diameter) or MRI-detected infarcts 8-20 mm.

Leave-one-out diagnostics provided some, if limited, assurance that GEE analyses presented here are valid and not overly influenced by particular observations. Hosmer Lemeshow goodness-of-fit tests suggest logistic regression analyses examining the relationship between air pollutants (regardless of exposure averaging period) and incident brain MRI findings did not have significant problems with fit with the exception of the analysis examining the relationship between PM_{10} averaged over the three years prior to the initial MRI and worsening white matter. Observations with Pregibon's delta beta statistics greater than 0.2 were identified in both white matter worsening and incident infarct analyses; however, their exclusion from analyses did not change overall conclusions.

Discussion

In this study of older adults residing in three U.S. communities, results suggested that long-term exposure to traffic-related pollutants is associated with subclinical or covert white

matter lesions. Age is a consistently identified strong risk factor for white matter lesions, and the effect of a 10 μg/m^3 increase in PM_{10} on white matter grade seen in the present study was equivalent approximately to an increase of 1.5-2.5 years of age, depending on the period over which the exposure was averaged. The primary results were from a repeated measures analysis in which the relationship between air pollutant exposure, treated as a time-dependent variable, and white matter grade on MRI was assessed. No relationship was observed between air pollutant exposure and white matter worsening in those who had two brain MRIs. This may be because there truly is no relationship or the time period between MRIs was too short to observe air pollutant-associated white matter worsening. Alternatively, the lack of a significant association may be a consequence of the smaller sample size in analyses of white matter worsening.

Previous work has demonstrated significant cross-sectional and longitudinal links between exposure to traffic-related pollutants and cognitive impairment.[22-24,26,27] In an ecologic study of MRI findings in children living in a high- versus low-pollution cities, over half of children with high exposure had MRI-defined white matter hyperintensities compared to only one residing in a low-pollution city.[20] The findings were corroborated in dogs from the same cities. Although our results must be interpreted with caution, the associations reported here suggest that air pollution affects the brain's white matter. Higher white matter grade, though clinically unrecognized or covert, is not without adverse consequences as it has been linked to cognitive impairment and functional decline in addition to being a significant predictor of future vascular events affecting the brain and the heart. White matter grade was correlated with serum interleukin-6 (IL-6) and C-reactive protein (CRP), plasma markers measured in the CHS study population.[37] Both are well-recognized biomarkers of the inflammatory response that may mediate the effects of air pollution on the brain. Further work is required to determine if white matter injury may be in the pathway between air pollution exposure and cognitive decline.

Unexpectedly, no associations were observed between MRI-detected brain infarcts and any air pollutant over any averaging period. White matter injury and brain infarcts are both thought to be manifestations of small vessel disease,[38] and we expected that if air pollution affected one, it would affect the other through the same pathway. Possibly, the significant associations between the air pollutants and higher white matter grade occurred by chance. Alternatively, air pollution may affect white matter through a mechanism less likely to influence risk of infarcts.

This study has a number of strengths including individual, residence-specific air pollutant exposure estimates, serial brain MRI imaging, and extensive information on potentially confounding factors for this large cohort. It has limitations as well. Participants who underwent MRI scanning were younger and healthier than those who did not and younger and healthier than those in the general elderly population. Possibly those who experienced an infarct or white matter worsening were less likely to have an MRI. Also, exposure measurement error exists as estimates were based on inverse distance weighting methods, which utilize pollutant concentrations at monitors to estimate exposure at residences. Moreover, we evaluated the effects of two pollutants averaged over several time periods on prevalent and incident brain MRI-detected outcomes. Given the multiple statistical tests utilized, we would expect to see significant associations due to chance alone. However, associations between air pollutants and repeated measures of white matter grade were consistently significant in fully-adjusted analyses regardless of pollutant or exposure averaging period used, lessening the multiple testing concern somewhat. In addition, there was a consistent lack of a significant association between either air pollutant and MRI-detected infarcts.

In summary, our findings suggest a relationship between long-term exposure to air pollutants and a specific brain MRI finding in the white matter. The findings in this cohort of older adults are consistent with a prior study in children.[20] We did not find an association with

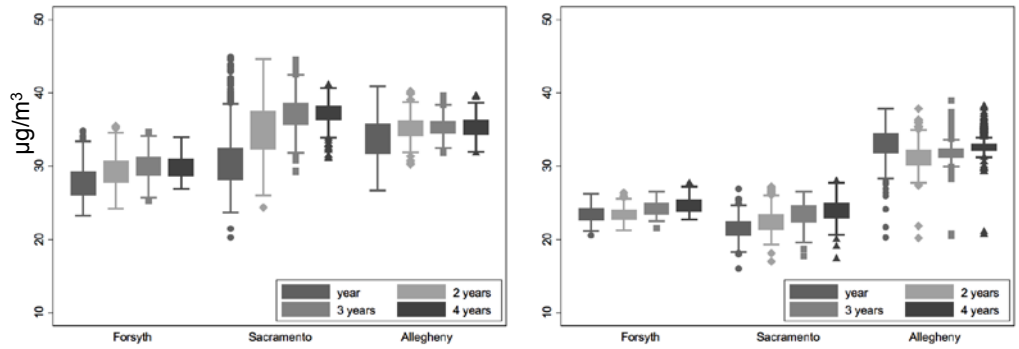
brain infarcts raising the possibility that air pollutants may affect white matter by toxic rather than vascular mechanisms. Evaluation of the effects of air pollutants on the white matter in animal studies and in other cohorts in which brain MRIs have already been performed is necessary to confirm these results and advance our understanding of the mechanism by which air pollutants affect the brain.

Tables and Figures

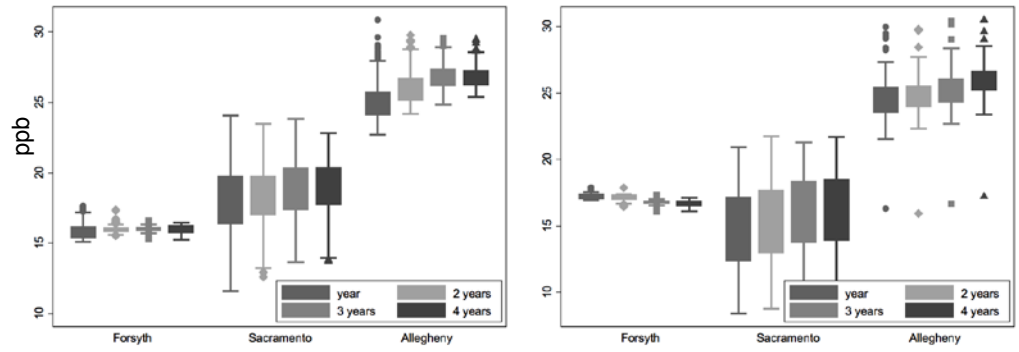
Table IV.1. Selected characteristics of CHS participants who underwent brain MRI scanning by tertile of estimated mean PM_{10} exposure in the 2 years prior to MRI

	First MRI (1991-1994)			Second MRI (1997-1999)		
	Tertile of PM_{10} exposure ($\mu g/m^3$)			Tertile of PM_{10} exposure ($\mu g/m^3$)		
	< 31.3	31.3-34.9	> 34.9	< 23.1	23.1-27.1	> 27.1
Characteristic[a]	(n = 624)	(n = 624)	(n = 623)	(n = 461)	(n = 459)	(n = 460)
Site						
Forsyth, NC	82	15	1	28	58	0
Sacramento, CA	18	46	36	71	42	1
Allegheny, PA	< 1	39	63	<1	0	99
Washington, MD	-	-	-	-	-	-
Age (yrs); mean (SD)	75 (5)	76 (5)	75 (5)	79 (4)	79 (4)	79 (4)
African American	7	5	6	23	15	23
Female	58	58	57	62	58	58
Education						
< high school	27	18	14	20	22	15
high school grad/GED	28	29	28	30	25	29
> high school	46	53	58	50	53	56
Instrumental ADLs; mean(SD)	0.3 (0.7)	0.3 (0.6)	0.3 (0.6)	0.4 (0.8)	0.4 (0.8)	0.3 (0.8)
Kcals/week leisure activity; mean (SD)	1178 (1594)	1268 (1635)	1326 (1573)	1071 (1481)	1303 (1656)	908 (1118)
Smoking						
former	41	45	47	44	39	52
current	9	8	9	7	7	7
BMI (kg/m^2); mean (SD)	26 (4)	26 (4)	26 (4)	27 (4)	26 (4)	27 (4)
Any diuretic use	22	19	20	29	27	21
Any statin use	3	6	5	14	10	16
LDL chol. (mg/dl); mean (SD)	124 (32)	125 (33)	128 (33)	127 (32)	124 (32)	127 (32)
HDL chol. (mg/dl); mean (SD)	54 (15)	53 (15)	55 (15)	56 (15)	55 (14)	53 (14)
Diabetes						
impaired fasting glucose	9	10	9	5	7	6
diabetes	12	10	10	12	12	14
Hypertension						
borderline	16	16	13	11	12	9
hypertensive	38	37	32	48	44	45
Hypertension medication	42	43	43	56	52	55
Cardiovascular disease[b]	19	21	22	23	22	27

[a] Numbers represent percentages unless otherwise indicated.
[b] Prevalent cardiovascular disease includes a history of angina, myocardial infarction, claudication or congestive heart failure.



a) PM_{10} (first and second MRI)[a]



b) NO_2 (first and second MRI)[a]

Figure IV.1. Air pollutant concentrations averaged over the one, two, three and four years prior to each brain MRI, by enrollment center

[a] Boxes, whiskers and points indicate the interquartile range, the upper and lower adjacent values and outliers, respectively.

Table IV.2. Summaries and Spearman correlations between PM_{10} and NO_2 exposure estimated over various periods preceding each MRI

a) First MRI (N = 1,587)[a]

	PM_{10} averaged over preceding:				**NO_2 averaged over preceding:**			
	Year	2 Years	3 Years	4 Years	Year	2 Years	3 Years	4 Years
PM_{10} averaged over preceding:								
Year	1.00							
2 Years	0.89	1.00						
3 Years	0.59	0.83	1.00					
4 Years	0.52	0.73	0.94	1.00				
NO_2 averaged over preceding:								
Year	0.74	0.68	0.42	0.36	1.00			
2 Years	0.78	0.77	0.55	0.48	0.95	1.00		
3 Years	0.78	0.79	0.56	0.50	0.93	0.98	1.00	
4 Years	0.76	0.77	0.55	0.49	0.92	0.97	0.98	1.00

b) Second MRI (N = 1,559)[a]

	PM_{10} averaged over preceding:				**NO_2 averaged over preceding:**			
	Year	2 Years	3 Years	4 Years	Year	2 Years	3 Years	4 Years
PM_{10} averaged over preceding:								
Year	1.00							
2 Years	0.91	1.00						
3 Years	0.84	0.88	1.00					
4 Years	0.86	0.96	0.93	1.00				
NO_2 averaged over preceding:								
Year	0.80	0.77	0.84	0.78	1.00			
2 Years	0.79	0.79	0.84	0.80	0.94	1.00		
3 Years	0.77	0.76	0.83	0.78	0.94	0.97	1.00	
4 Years	0.77	0.76	0.82	0.79	0.92	0.97	0.98	1.00

[a] All Spearman correlation coefficients were statistically significant ($P<0.05$).

Table IV.3. Prevalence and incidence of brain MRI findings at first and second scans

	First MRI		Second MRI	
	N	%	N	%
White matter grade				
Mean (SD)	1,864	2.1 (1.4)	1,378	2.5 (1.6)
Grade > 2	1,864	31	1,378	42
Worsening	-	-	1,026	28
MRI-detected infarcts ≥ 3mm				
prevalent	1,572	24	1,174	23
incident	-	-	676	13

Table IV.4. Associations between long-term exposure to PM_{10} (10 µg/m^3 increment) and NO_2 (10 ppb increment) exposure and white matter grade (continuous) in repeated measures analyses

		Primary Model[a]		Secondary Model[b]	
Averaging period	N[c]	β_1 (95% CI)	P-value	β_1 (95% CI)	P-value
PM_{10}					
Year	3050	0.12 (0.01, 0.23)	0.033	0.13 (0.02, 0.23)	0.024
2 Years	2918	0.14 (0.01, 0.27)	0.029	0.15 (0.03, 0.28)	0.019
3 Years	2836	0.18 (0.05, 0.31)	0.005	0.21 (0.08, 0.33)	0.002
4 Years	2571	0.13 (-0.01, 0.27)	0.076	0.17 (0.03, 0.31)	0.021
NO_2					
Year	3052	0.26 (0.05, 0.47)	0.017	0.27 (0.05, 0.48)	0.015
2 Years	2932	0.37 (0.14, 0.61)	0.002	0.39 (0.15, 0.62)	0.001
3 Years	2876	0.35 (0.09, 0.61)	0.009	0.36 (0.10, 0.62)	0.006
4 Years	2602	0.35 (0.06, 0.64)	0.018	0.40 (0.12, 0.68)	0.005

[a] Adjusted for sex, clinic, age at MRI, education, race, date of MRI, physical function and activity, BMI, smoking and diabetes.
[b] Adjusted for primary model covariates and LDL and HDL cholesterol, hypertension, hypertension medications, statin use, diuretic use, any prevalent cardiovascular disease and prevalent infarct.
[c] N refers the number of MRIs performed.

Table IV.5. Associations between long-term exposure to PM_{10} (10 µg/m^3 increment) and NO_2 (10 ppb increment) exposure and white matter grade > 2 in repeated measures analyses

		Primary Model[a]		Secondary Model[b]	
Averaging period	N[c]	OR (95% CI)	P-value	OR (95% CI)	P-value
PM_{10}					
Year	3385	1.17 (0.96, 1.43)	0.122	1.20 (0.98, 1.47)	0.074
2 Years	3242	1.26 (1.00, 1.59)	0.048	1.32 (1.04, 1.68)	0.022
3 Years	3152	1.18 (0.94, 1.49)	0.148	1.27 (1.00, 1.61)	0.051
4 Years	2856	1.13 (0.89, 1.44)	0.304	1.24 (0.96, 1.61)	0.101
NO_2					
Year	3387	1.27 (0.91, 1.77)	0.153	1.31 (0.93, 1.85)	0.128
2 Years	3257	1.50 (1.04, 2.18)	0.031	1.58 (1.07, 2.32)	0.020
3 Years	3194	1.32 (0.88, 1.95)	0.176	1.35 (0.89, 2.05)	0.152
4 Years	2883	1.23 (0.80, 1.90)	0.342	1.33 (0.85, 2.09)	0.215

[a] Adjusted for sex, clinic, age at MRI, education, race, date of MRI, physical function and activity, BMI, smoking and diabetes.
[b] Adjusted for primary model covariates and LDL and HDL cholesterol, hypertension, hypertension medications, statin use, diuretic use, any prevalent cardiovascular disease and prevalent infarct.
[c] N refers the number of MRIs performed.

Table IV.6. Longitudinal associations between long-term exposure to PM_{10} (10 µg/m^3 increment) and NO_2 (10 ppb increment) exposure and worsening white matter grade in CHS participants who underwent serial brain MRIs

		Primary Model[a]		Secondary Model[b]	
Averaging period	N	OR (95% CI)	P-value	OR (95% CI)	P-value
PM_{10}					
Year	1111	1.15 (0.72, 1.85)	0.557	1.08 (0.67, 1.75)	0.740
2 Years	1027	1.14 (0.60, 2.16)	0.687	1.08 (0.57, 2.06)	0.814
3 Years	990	0.98 (0.40, 2.36)	0.958	0.90 (0.37, 2.19)	0.808
4 Years	814	1.57 (0.50, 4.91)	0.435	1.39 (0.44, 4.42)	0.578
NO_2					
Year	1111	1.04 (0.41, 2.66)	0.933	0.93 (0.36, 2.41)	0.884
2 Years	1032	0.73 (0.24, 2.22)	0.584	0.64 (0.21, 1.98)	0.442
3 Years	1015	0.56 (0.17, 1.80)	0.327	0.47 (0.14, 1.54)	0.212
4 Years	829	1.18 (0.29, 4.83)	0.817	1.01 (0.24, 4.27)	0.990

[a] Adjusted for sex, clinic, age at MRI, education, race, physical function and activity, BMI, smoking, diabetes, time between scans and grade at initial scan.
[b] Adjusted for primary model covariates and LDL and HDL cholesterol, hypertension, hypertension medications, statin use, diuretic use, any prevalent cardiovascular disease and prevalent infarct.

Table IV.7. Associations between long-term exposure to PM_{10} (10 µg/m^3 increment) and NO_2 (10 ppb increment) exposure and infarcts in repeated measures analyses

		Primary Model[a]		Secondary Model[b]	
Averaging period	N[c]	OR (95% CI)	P-value	OR (95% CI)	P-value
PM_{10}					
Year	2881	0.92 (0.73, 1.16)	0.489	0.91 (0.71, 1.17)	0.471
2 Years	2746	0.87 (0.65, 1.16)	0.335	0.83 (0.61, 1.13)	0.231
3 Years	2677	0.79 (0.61, 1.04)	0.094	0.74 (0.55, 0.99)	0.045
4 Years	2442	0.75 (0.57, 1.00)	0.049	0.71 (0.52, 0.96)	0.029
NO_2					
Year	2881	0.83 (0.55, 1.23)	0.350	0.77 (0.51, 1.24)	0.310
2 Years	2757	0.74 (0.47, 1.17)	0.202	0.68 (0.42, 1.10)	0.112
3 Years	2702	0.77 (0.48, 1.26)	0.301	0.72 (0.43, 1.21)	0.218
4 Years	2466	0.77 (0.45, 1.30)	0.328	0.70 (0.40, 1.21)	0.200

[a] Adjusted for sex, clinic, age at MRI, education, race, date of MRI, physical function and activity, BMI, smoking and diabetes.
[b] Adjusted for primary model covariates and LDL and HDL cholesterol, hypertension, hypertension medications, statin use, diuretic use, any prevalent cardiovascular disease and white matter grade.
[c] N refers the number of MRIs performed.

Table IV.8. Associations between long-term exposure to PM_{10} (10 µg/m^3 increment) and NO_2 (10 ppb increment) exposure and incident infarcts in CHS participants who underwent serial brain MRIs and had no infarcts on initial scan

Averaging period	N	OR (95% CI)	P-value	OR (95% CI)	P-value
PM_{10}					
Year	740	0.58 (0.26, 1.27)	0.170	1.01 (0.40, 2.57)	0.983
2 Years	676	0.62 (0.21, 1.83)	0.390	1.70 (0.42, 6.84)	0.458
3 Years	659	0.37 (0.09, 1.56)	0.175	0.71 (0.12, 4.14)	0.707
4 Years	524	0.68 (0.11, 4.19)	0.682	0.90 (0.11, 7.65)	0.922
NO_2					
Year	740	0.69 (0.16, 3.01)	0.623	0.69 (0.15, 3.28)	0.644
2 Years	681	0.80 (0.14, 4.62)	0.801	0.91 (0.14, 5.96)	0.921
3 Years	667	0.88 (0.14, 5.47)	0.891	0.99 (0.14, 6.81)	0.989
4 Years	559	0.57 (0.07, 4.41)	0.580	0.43 (0.05, 3.70)	0.444

[a] Adjusted for sex, clinic, age at MRI, education, race, physical activity, BMI, smoking, diabetes and time between scans.

[b] Adjusted for primary model covariates and LDL and HDL cholesterol, hypertension, hypertension medications, statin use, diuretic use, any prevalent cardiovascular disease and white matter grade at initial scan.

End Notes

1. Gill EA, Curl CL, Adar SD, et al. Air pollution and cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. *Prog Cardiovasc Dis.* Mar-Apr 2011;53(5):353-360.

2. Peters A, Frohlich M, Doring A, et al. Particulate air pollution is associated with an acute phase response in men; results from the MONICA-Augsburg Study. *Eur Heart J.* Jul 2001;22(14):1198-1204.

3. Seaton A, Soutar A, Crawford V, et al. Particulate air pollution and the blood. *Thorax.* Nov 1999;54(11):1027-1032.

4. Auchincloss AH, Diez Roux AV, Dvonch JT, et al. Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect.* Apr 2008;116(4):486-491.

5. Park SK, Auchincloss AH, O'Neill MS, et al. Particulate air pollution, metabolic syndrome, and heart rate variability: the multi-ethnic study of atherosclerosis (MESA). *Environ Health Perspect.* Oct 2010;118(10):1406-1411.

6. Park SK, O'Neill MS, Vokonas PS, Sparrow D, Schwartz J. Effects of air pollution on heart rate variability: the VA normative aging study. *Environ Health Perspect.* Mar 2005;113(3):304-309.

7. Liao D, Duan Y, Whitsel EA, et al. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. *Am J Epidemiol.* Apr 15 2004;159(8):768-777.

8. Whitsel EA, Quibrera PM, Christ SL, et al. Heart rate variability, ambient particulate matter air pollution, and glucose homeostasis: the environmental epidemiology of arrhythmogenesis in the women's health initiative. *Am J Epidemiol.* Mar 15 2009;169(6):693-703.

9. Adar SD, Klein R, Klein BE, et al. Air Pollution and the microvasculature: a cross-sectional assessment of in vivo retinal images in the population-based multi-ethnic study of atherosclerosis (MESA). *PLoS Med.* 2010;7(11):e1000372.

10. Diez Roux AV, Auchincloss AH, Franklin TG, et al. Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol.* Mar 15 2008;167(6):667-675.

11. Van Hee VC, Adar SD, Szpiro AA, et al. Exposure to traffic and left ventricular mass and function: the Multi-Ethnic Study of Atherosclerosis. *Am J Respir Crit Care Med.* May 1 2009;179(9):827-834.

12. Van Hee VC, Adar SD, Szpiro AA, et al. Common genetic variation, residential proximity to traffic exposure, and left ventricular mass: the multi-ethnic study of atherosclerosis. *Environ Health Perspect.* Jul 2010;118(7):962-969.

13. Van Hee VC, Szpiro AA, Prineas R, et al. Association of long-term air pollution with ventricular conduction and repolarization abnormalities. *Epidemiology.* Nov 2011;22(6):773-780.

14. Kaufman JD. Does air pollution accelerate progression of atherosclerosis? *J Am Coll Cardiol.* Nov 23 2010;56(22):1809-1811.

15. Longstreth W, Jr., Larsen EK, Klein R, et al. Associations between findings on cranial magnetic resonance imaging and retinal photography in the elderly: the Cardiovascular Health Study. *Am J Epidemiol.* Jan 1 2007;165(1):78-84.

16. Kuller LH, Shemanski L, Manolio T, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke.* Feb 1998;29(2):388-398.

17. Longstreth WT, Jr., Dulberg C, Manolio TA, et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* Oct 2002;33(10):2376-2382.

18. Longstreth WT, Jr., Arnold AM, Beauchamp NJ, Jr., et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* Jan 2005;36(1):56-61.

19. Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol.* 2008;36(2):289-310.

20. Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain Cogn.* Nov 2008;68(2):117-127.

21. Cruts B, van Etten L, Tornqvist H, et al. Exposure to diesel exhaust induces changes in EEG in human volunteers. *Part Fibre Toxicol.* 2008;5:4.

22. Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A, 3rd, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. *Environ Health Perspect.* May 2011;119(5):682-687.

23. Chen JC, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology.* Mar 2009;30(2):231-239.

24. Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environ Res.* Nov 2009;109(8):1004-1011.

25. Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. *Am J Epidemiol.* Feb 1 2008;167(3):280-286.

26. Wang S, Zhang J, Zeng X, Zeng Y, Chen S. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. *Environ Health Perspect.* Oct 2009;117(10):1612-1618.

27. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med.* Feb 13 2012;172(3):219-227.

28. Mosley TH, Jr., Knopman DS, Catellier DJ, et al. Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study. *Neurology.* Jun 28 2005;64(12):2056-2062.

29. Pantoni L, Leys D, Fazekas F, et al. Role of white matter lesions in cognitive impairment of vascular origin. *Alzheimer Dis Assoc Disord.* Oct-Dec 1999;13 Suppl 3:S49-54.

30. Bernick C, Kuller L, Dulberg C, et al. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. *Neurology.* Oct 9 2001;57(7):1222-1229.

31. Kuller LH, Longstreth WT, Jr., Arnold AM, Bernick C, Bryan RN, Beauchamp NJ, Jr. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke.* Aug 2004;35(8):1821-1825.

32. Longstreth WT, Jr., Arnold AM, Kuller LH, et al. Progression of magnetic resonance imaging-defined brain vascular disease predicts vascular events in elderly: the Cardiovascular Health Study. *Stroke.* Oct;42(10):2970-2972.

33. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol.* Feb 1991;1(3):263-276.

34. Bryan RN, Manolio TA, Schertz LD, et al. A method for using MR to evaluate the effects of cardiovascular disease on the brain: the cardiovascular health study. *AJNR Am J Neuroradiol.* Oct 1994;15(9):1625-1633.

35. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Annals of epidemiology.* Jul 1995;5(4):278-285.

36. Bezerra DC, Sharrett AR, Matsushita K, et al. Risk factors for lacune subtypes in the Atherosclerosis Risk in Communities (ARIC) Study. *Neurology.* Jan 10 2011;78(2):102-108.

37. Fornage M, Chiang YA, O'Meara ES, et al. Biomarkers of Inflammation and MRI-Defined Small Vessel Disease of the Brain: The Cardiovascular Health Study. *Stroke.* Jul 2008;39(7):1952-1959.

38. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol.* Jul 2010;9(7):689-701.

CHAPTER V.

Conclusions

Context of Findings

Around the time publications describing the relationship between air pollution and stroke began to emerge,[1-4] provocative studies were published comparing the brains of canines[5] and humans[6] living in Mexico City to the brains of residents of a control city. PM concentrations regularly greatly exceed National Ambient Air Quality Standards (NAAQS) in Mexico City, whereas air quality is comparatively good in the control city. Neuroinflammation, Alzheimer's disease (AD)-like pathology and compromised blood-brain barrier (BBB) integrity all were evident in the brains of Mexico City residents. This and subsequent work provided evidence that high concentrations of air pollutants may influence not only neuroinflammation and neuropathology but also cognition and risk of MRI-detected white matter hyperintensities through vascular-independent pathways.[7,8] While the findings from this series of studies were intriguing, there were limitations including small numbers of subjects, the potential for confounding by other city-specific factors and the lack of individual-level estimates of exposure. Questions remained, and chief among them is whether extreme exposure to air pollutants was necessary in order for air pollutants to have neurotoxic effects.

A number of studies have since demonstrated consistent links between air pollution exposure and poorer performance on cognitive assessments in several different populations exposed to a range of concentrations of various air pollutants. Three of these employed ecological designs in high-exposure settings and are thus subject to the same limitations of the Calderón-Garcidueñas research. However, the four cross-sectional studies, for which residence-specific exposure estimates were available, demonstrated significant associations between black carbon (BC),[9] ozone,[10] proximity to high-traffic roadways[11] and nitrogen dioxide (NO_2)[12] and measures of intelligence, psychomotor speed, memory, attention and gross motor

function. Power *et al*. examined the effect of BC on repeated measures of the Mini-Mental State Exam (MMSE), a validated screening test for dementia, as well as several other cognitive assessments in older men participating in the Normative Aging Study. These authors observed significantly lower scores associated with higher BC exposures but did not report any acceleration of cognitive decline over time or if such a relationship was evaluated. In the most recent study, Weuve and colleagues observed significantly faster cognitive decline in older women in the Nurses' Health Study (NHS) exposed to elevated concentrations of PM. Importantly, mean $PM_{2.5}$ concentrations, regardless of the time window of exposure utilized, were below the NAAQS for fine PM.

Four of the nine studies examining air pollutant effects on cognition, and both longitudinal, studies utilized spatiotemporal model-generated estimates of exposure to BC, NO_2 and PM of three size fractions and found that traffic-related exposures may be particularly harmful. However, it is not clear which pollutant is most toxic or if these measures act as surrogates for other traffic-related exposures such as ultra-fine particles or even noise, which can be correlated with traffic-related exposures.[13] Together, these epidemiologic studies indicate that the developing, developed and aging brain are sensitive to exposure to air pollutants. Interestingly, in the three studies in which adjustment for prevalent cardiovascular disease was possible, there was no attenuation of risk estimates observed when cardiovascular risk factors were included in statistical models, providing some suggestion that the causal pathway between air pollutant exposure and decreased cognitive function may be independent of vascular pathology. Little additional evidence for the relevant biologic pathways is available from the studies published to date.

Summary of Air Pollutant Effects in the Cardiovascular Health Study

The findings presented in the preceding chapters describe the effects of long-term air pollutant exposure on various measures of brain health in the Cardiovascular Health Study (CHS) cohort. We defined *long-term* in different ways for each of the analyses, and exposure averaging periods and associated effects are summarized in Table V. A consistent approach across all chapters was the use of averaging periods over multiple years. The primary rationale for evaluating the effects of exposure on brain outcomes averaged over one, two or three years was to establish whether an association was consistent over various periods of time and not simply an artifact of the particular averaging period chosen. Exposure estimates were based entirely on concentrations observed at regulatory monitors, and we expect the specific monitors utilized in inverse distance weighting methods changed from year to year. The objective of using averaging periods of different lengths was to smooth out air pollutant measurements that were unrepresentative of longer-term exposure.

When possible, exposure averaging periods preceding outcome ascertainment were utilized. Follow-up for dementia and brain MR imaging began during the fourth CHS clinical examination cycle meaning that the exposure intervals of interest could precede outcome measurement. However, cognitive assessments began at study entry for the DSST and at the second examination cycle for the 3MSE. Air pollutant exposure was not estimated prior to study entry, and, as a result, long-term exposure averaging periods occurred after baseline cognitive assessments. Excluding the first or first two cognitive assessments was not desirable as more participants completed earlier, rather than later, cognitive assessments. We also examined time-dependent exposures in analyses of each brain outcome to evaluate the importance of recent exposure.

The approach used to examine the effects of long-term air pollutant exposure on the

brain in our study has advantages, as noted above; however, concerns with this strategy warrant discussion. First, recruitment of participants in CHS occurred over several years, and clinical examinations were conducted over 1-2 years, meaning that the exposure averages utilized in analyses occur over different calendar periods for different participants. Different calendar years may be more or less representative of true long-term exposure, either due to different monitors being in use during the averaging period or short-term fluctuations in air pollutants. Second, the approach described above is limited in its ability to allow for the comparison of results between analyses. Consistent results regardless of air pollutant examined or averaging period utilized in cognitive decline and white matter grade analyses lessen these concerns somewhat. However, air pollutant averages for a fixed calendar year (or years) based not just on monitored concentrations but also on other predictors of exposure would lessen concerns further.

Our main findings were significant associations between estimated long-term exposure to PM_{10} and NO_2 and faster rates of cognitive decline, elevated risk of vascular dementia (VaD) and higher prevalent white matter grade on brain MRI. Our cognitive decline analyses benefitted from repeated measures of cognitive performance assessed by the Modified Mini-Mental State Exam (3MSE), a test of global cognition scored from 1-100. Relative to the MMSE, the 3MSE more precisely captures differences in cognitive abilities and reduces ceiling effects compared to the MMSE, which occurs when individuals achieve the maximum score but would have scored more highly if the exam had tested for higher performance. Two of the three published studies examining the effects of PM_{10} on cognition in adults observed no association. One [10] of these studies averaged exposure only over the year preceding the cognitive assessment at the centroid of the census block group in which the participant resided. Although we do not expect our PM_{10} estimates to be appreciably more resolved than those generated at the block group level, we do expect longer-term exposures are more biologically important and

also that the residential stability of the CHS population was greater than that observed in the NHANES III study of younger adults. The other study [11] in which no PM_{10} effect was observed had less variability in exposure, which could have affected the ability to detect an association. Our results are consistent with those observed in the NHS population[14] although we observed a slower rate of PM-associated decline, when compared to that observed with age, which may be due to the fact that we used a different cognitive assessment tool and also less spatially-resolved estimates of exposure. Our findings with respect to NO_2 effects were generally similar to those observed for PM_{10}, which may be due to the significant correlation between these pollutants in our study. In addition, both pollutants were associated with faster decline in Digit Symbol Substitution Test (DSST) performance in CHS.

The assessment of dementia in CHS allowed us to examine the contribution of air pollutants to the most debilitating manifestation of cognitive decline. Moreover, the assessment by subtype provided insight into potential underlying mechanisms. We observed significant relationships between long-term PM_{10} exposure and VaD but not AD. The findings were attenuated, though not completely, by inclusion of history of stroke or transient ischemic attack in models. PM_{10} exposure may have resulted in vascular pathology and/or damage to the white matter of the brain, which was part of the classification criteria of possible VaD in CHS.[15] This white matter damage may or may not have occurred through vascular mechanisms. Our findings did not provide evidence for a link between chronic air pollutant exposure and AD. The absence of a detected association with AD may be because there is, contrary to the Calderón-Garcidueñas findings, no relationship between air pollutants and AD or because those in the preclinical stages of AD related to chronic air pollution exposure may have been less likely to participate in the study. Alternatively, exposure earlier in life may be more important than exposure in old age in AD, which, relative to other dementia subtypes, progresses very slowly.[16]

Long-term exposure to both PM_{10} and NO_2 were linked with higher (i.e. worse) white

matter grade detected on brain MRI. The observed increase in white matter grade associated with 10 μg/m^3 higher estimated long-term PM_{10} exposure was similar to that observed with approximately 2 years of aging in our dataset, depending on the exposure averaging period used. There was no relationship between exposure and prevalent brain infarcts, suggesting that a vascular mechanism alone may not be responsible for the observed effects on brain white matter. Air pollutants may reach the brain directly though nasal routes or through a compromised BBB and exert direct toxic effects on brain white matter as described following exposure to radiation, chemotherapeutics, and occupational solvents.[17]

Our analyses were conducted in a large, residentially-stable and well-characterized population of older adults but have several notable limitations. Potentially important factors not taken into account include neighborhood characteristics (e.g. mean education and income at the census tract level) and dietary intake, both of which plausibly could be related to both air pollutant exposure and cognitive decline and brain MRI findings. We attempted to address this through adjustment for enrollment center and individual-level confounders such as education and income.

We relied on estimated ambient PM_{10} and NO_2 estimates generated using inverse distance weighting methods, averaging concentrations observed at nearby monitors to estimate exposure at residences, an approach with several limitations. Basing estimates on the location of participants' residences ignores actual time spent in and outside the home, time spent commuting in traffic and time spent at the workplace that may be in area with different exposure characteristics. Estimates are based on ambient monitors and ignore infiltration rates between outdoor and indoor air and do not include estimates of indoor sources of air pollution exposure. In addition, we were unable to construct long-term residential histories prior to study entry. This limits our ability to assess exposure during time periods likely relevant to the development of dementia, for example. Furthermore, predicted pollutant concentrations were estimated from a

spatial surface that is likely overly-smoothed as a result of a sparse network of monitoring stations, particularly in Forsyth County, which likely resulted in large errors in estimates and an inability to detect the true variability in exposure between individuals. However, we expect that exposure misclassification would be non-differential with respect to the brain health measures examined and would limit our ability to detect associations rather than artificially inflate risk estimates.

Another limitation to our work is that we examined only PM_{10} and NO_2 effects. PM_{10} is comprised of both fine PM (≤ 2.5 μm in diameter) and coarse PM (>2.5 and ≤ 10 μm in diameter), which have different primary sources and health effect profiles. It is not clear if one size fraction is most important or if both contribute to the observed results. NO_2 is a marker of traffic and industrial emissions and exhibits a high level of spatial variability that could not be captured by our approach to exposure estimation. In addition, significant correlations between ambient PM_{10} and NO_2 were present. As a result, observed associations between NO_2 and effects on the brain may have been due to PM exposure. Also, it is possible that observed effects are not from either of the evaluated pollutants but from other correlated exposures.

Although it is not practical in a large cohort study to have monitors at each residential location or to have each participant wear a personal monitor, improvement on our exposure estimates is possible using more advanced modeling approaches. More refined estimates of exposure, which in addition to information from stationary monitors, would incorporate geographic covariates (e.g. proximity to major roadways, traffic density, population density and percentage of urbanization) and likely capture more within-city spatial variability. In addition, they would allow for the estimation of exposure for CHS participants residing in Washington County, Maryland, substantially increasing the sample size for analyses.

Finally, we examined the effects of long-term air pollutant exposure, defining long-term in several different ways, on many measures of brain health. The high number of statistical

tests raises the concern of multiple testing, whereby we would expect to observe significant findings even if there were no true relationship between air pollutants and cognition, dementia or MRI-detected findings. We observed wide confidence intervals in our analyses of PM_{10} and prevalent VaD, and a significant relationship was not observed between NO_2 and VaD, raising concerns about whether this is a real or chance finding. We have the most confidence in our cognitive decline and white matter grade findings as the significant results were consistent across different exposure averaging periods and both pollutants examined.

Extensions of the Current Analyses and Additional Questions

Extensions of the presented analyses may provide evidence for pathways important in the observed air pollutant effects. First, serum interleukin-6 (IL-6) and C-reactive protein (CRP), plasma biomarkers of inflammation, were measured on CHS participants at baseline, and both were correlated with prevalent white matter grade ≥ 2.[18] Adjusting for these biomarkers in analyses would enable us to investigate the importance of a systemic inflammatory response in the PM-induced effects on the brain. Second, although *APOE* genotype did not modify air pollutant effects in our analyses, other genetic variants important in Alzheimer's disease[19] and white matter grade[20] have been identified. Although a large sample size and likely a multi-cohort study would be required, exploration of gene-environment interactions may identify potentially sensitive populations as well as relevant mechanistic pathways.

The results of the analyses investigating the effects of air pollutant exposure on several measures of brain health raise questions for future research. For example, is air pollution more strongly linked to deficits in particular domains of cognitive function, or can recent exposure modify an individual's cognitive trajectory following elevated long-term exposure? Does long-term exposure accelerate cognitive decline in prevalent dementia cases? To what extent do

white matter lesions mediate the observed effects? These questions all can be addressed in the CHS cohort. Much can be learned as well from investigating these questions in other cohorts, comprised of populations of various ages, underlying sensitivities and comorbidities, measured phenotypes and, particularly, in cohorts in which air pollutant exposures have been or can be well-characterized.

Conclusions

Our findings largely are consistent with previous work investigating air pollutant effects on the brain, and our dementia analyses add to earlier work by examining the contribution of air pollution to dementia, a disease endpoint of great importance to public health. In addition, in novel analyses, we demonstrated that the brain white matter may be a target of chronic exposure to air pollutants. It is well established that air pollution is an important contributor to respiratory and cardiovascular disease. The findings presented here add to the already-compelling rationale for, and suggest a substantial public health benefit from, limiting exposure to air pollutants.

Table V. Summary of exposure averaging periods used in analyses examining the effects of air pollutant exposure on the brain

Outcome	Exposure averaging period	First year outcome measured		Outcome frequency	Significant finding
		initial cohort	AA cohort		
3MSE	mean cumulative exposure (time-dependent) from 3 months prior to study entry through the month prior to each exam. The first cognitive assessment used in this analysis occurred AFTER 2 years of exposure estimates had accumulated.	1990-1	1992-3	annual	PM_{10} and NO_2 associated with lower 3MSE score but neither accelerates rate of cognitive decline over time.
3MSE	mean exposure from 3 months prior to study entry through first 12 months in study (all cognitive assessments included)	1990-1	1992-3	annual	Higher NO_2 associated with significantly faster decline (i.e. time*NO_2 interaction significant); similar trend observed with PM_{10} but interaction term not significant (P=0.178).
3MSE	mean exposure from 3 months prior to study entry through first 24 months in study (all cognitive assessments included)	1990-1	1992-3	annual	Both pollutants associated with significantly faster cognitive decline.
3MSE	mean exposure from 3 months prior to study entry through first 36 months in study (all cognitive assessments included)	1990-1	1992-3	annual	Both pollutants associated with significantly faster cognitive decline.
DSST	mean cumulative exposure (time-dependent) from 3 months prior to study entry through the month prior to each exam. The first cognitive assessment used in this analysis occurred AFTER 2 years of exposure estimates had accumulated.	1989-90	1992-3	annual	NO_2 but not PM_{10} associated with lower DSST score, but neither accelerates rate of cognitive decline over time.
DSST	mean exposure from 3 months prior to study entry through first 12 months in study (all cognitive assessments included)	1989-90	1992-3	annual	Both pollutants associated with significantly faster cognitive decline.
DSST	mean exposure from 3 months prior to study entry through first 24 months in study (all cognitive assessments included)	1989-90	1992-3	annual	Both pollutants associated with significantly faster cognitive decline.
DSST	mean exposure from 3 months prior to study entry through first 36 months in study (all cognitive assessments included)	1989-90	1992-3	annual	Neither pollutant associated with significantly faster decline (P for interaction=0.12 for PM_{10} and 0.06 for NO_2).
prevalent dementia prevalent AD prevalent VaD	mean air pollutant exposure in the 1 year prior to entry into the CHS Cognition Study (CHCS). Entry into the CHCS ranged from 1992-1994.	1992-4	1992-4	follow-up through 1999	Neither pollutant associated prevalent dementia. Neither pollutant associated prevalent AD. PM_{10} associated with higher risk of VaD.
prevalent dementia prevalent AD prevalent VaD	mean air pollutant exposure in the 2 years prior to entry into CHCS. Entry into the CHCS ranged from 1992-1994.	1992-4	1992-4	follow-up through 1999	Neither pollutant associated prevalent dementia. Neither pollutant associated prevalent AD. PM_{10} associated with higher risk of VaD.

Table V, continued.

Outcome	Exposure averaging period	First year outcome measured: initial cohort	First year outcome measured: AA cohort	Outcome frequency	Significant finding
prevalent dementia	mean air pollutant exposure in the 3 years prior to entry into CHCS. Entry into the CHCS ranged from 1992-1994.	1992-4	1992-4	follow-up through 1999	Neither pollutant associated with prevalent dementia.
prevalent AD					Neither pollutant associated with prevalent AD.
prevalent VaD					PM_{10} point estimate similar to that obtained above but non-significant
incident dementia	cumulative mean air pollutant exposure (time-dependent) beginning 1 year prior to entry into CHCS (1992-4) through dementia onset or censoring.	1992-4	1992-4	follow-up through 1999	No association.
incident AD					No association.
incident VaD					No significant association but HR≅2 and close to significant.
incident dementia	mean air pollutant exposure in the 1 year prior to entry into CHCS. Entry into the CHCS ranged from 1992-1994.	1992-4	1992-4	follow-up through 1999	No association.
incident AD					No association.
incident VaD					No association.
incident dementia	mean air pollutant exposure in the 2 years prior to entry into CHCS. Entry into the CHCS ranged from 1992-1994.	1992-4	1992-4	follow-up through 1999	No association.
incident AD					No association.
incident VaD					No association.
incident dementia	mean air pollutant exposure in the 3 years prior to entry into CHCS. Entry into the CHCS ranged from 1992-1994.	1992-4	1992-4	follow-up through 1999	No association.
incident AD					No association.
incident VaD					No association.
prevalent WMG	mean air pollutant exposure in the 1 year prior to each brain MRI. First MRI was between 1991-4 and the second between 1997-9.	1991-4	1991-4	twice	Significant associations with both pollutants.
prevalent infarct					No association.
prevalent WMG	mean air pollutant exposure in the 2 years prior to each brain MRI. First MRI was between 1991-4 and the second between 1997-9.	1991-4	1991-4	twice	Significant associations with both pollutants.
prevalent infarct					No association.
prevalent WMG	mean air pollutant exposure in the 3 years prior to each brain MRI. First MRI was between 1991-4 and the second between 1997-9.	1991-4	1991-4	twice	Significant associations with both pollutants.
prevalent infarct					Significant association of PM_{10} with reduced risk of infarct.
prevalent WMG	mean air pollutant exposure in the 4 years prior to each brain MRI. First MRI was between 1991-4 and the second between 1997-9.	1991-4	1991-4	twice	Significant associations with both pollutants.
prevalent infarct					Significant association of PM_{10} with reduced risk of infarct.
worsening WMG	mean air pollutant exposure between first and second MRI.	1991-4	1991-4	twice	No association.
incident infarct					No association.
worsening WMG	mean air pollutant exposure in the 1 year prior to first brain MRI.	1991-4	1991-4	twice	No association.
incident infarct					No association.

Table V, continued.

Outcome	Exposure averaging period	First year outcome measured: initial cohort	First year outcome measured: AA cohort	Outcome frequency	Significant finding
worsening WMG	mean air pollutant exposure in the 2 years prior to first brain MRI.	1991-4	1991-4	twice	No association.
incident infarct					No association.
worsening WMG	mean air pollutant exposure in the 3 years prior to first brain MRI.	1991-4	1991-4	twice	No association.
incident infarct					No association.
worsening WMG	mean air pollutant exposure in the 4 years prior to first brain MRI.	1991-4	1991-4	twice	No association.
incident infarct					No association.

Abbreviations: 3MSE, Modified Mini-Mental State exam; DSST, digit symbol substitution test; AD, Alzheimer's disease; VaD, vascular dementia; WMG, white matter grade.

End Notes

1. Maheswaran R, Elliott P. Stroke mortality associated with living near main roads in England and wales: a geographical study. *Stroke.* Dec 2003;34(12):2776-2780.

2. Maheswaran R, Haining RP, Brindley P, et al. Outdoor air pollution and stroke in Sheffield, United Kingdom: a small-area level geographical study. *Stroke.* Feb 2005;36(2):239-243.

3. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med.* Feb 1 2007;356(5):447-458.

4. Wellenius GA, Schwartz J, Mittleman MA. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *Stroke.* Dec 2005;36(12):2549-2553.

5. Calderon-Garciduenas L, Azzarelli B, Acuna H, et al. Air pollution and brain damage. *Toxicol Pathol.* May-Jun 2002;30(3):373-389.

6. Calderon-Garciduenas L, Reed W, Maronpot RR, et al. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. *Toxicol Pathol.* Nov-Dec 2004;32(6):650-658.

7. Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain Cogn.* Nov 2008;68(2):117-127.

8. Calderon-Garciduenas L, Mora-Tiscareno A, Styner M, et al. White Matter Hyperintensities, Systemic Inflammation, Brain Growth, and Cognitive Functions in Children Exposed to Air Pollution. *J Alzheimers Dis.* Apr 18 2012.

9. Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. *Am J Epidemiol.* Feb 1 2008;167(3):280-286.

10. Chen JC, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology.* Mar 2009;30(2):231-239.

11. Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environ Res.* Nov 2009;109(8):1004-1011.

12. Freire C, Ramos R, Puertas R, et al. Association of traffic-related air pollution with cognitive development in children. *J Epidemiol Community Health.* Mar 2010;64(3):223-228.

13. Allen RW, Adar SD. Are both air pollution and noise driving adverse cardiovascular health effects from motor vehicles? *Environ Res.* Jan 2011;111(1):184-185.

14. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med.* Feb 13 2012;172(3):219-227.

15. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. *Neuroepidemiology.* Jan-Feb 2003;22(1):1-12.

16. Fitzpatrick AL, Kuller LH, Lopez OL, Kawas CH, Jagust W. Survival following dementia onset: Alzheimer's disease and vascular dementia. *J Neurol Sci.* Mar 15 2005;229-230:43-49.

17. Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. *N Engl J Med.* Aug 9 2001;345(6):425-432.

18. Fornage M, Chiang YA, O'Meara ES, et al. Biomarkers of Inflammation and MRI-Defined Small Vessel Disease of the Brain: The Cardiovascular Health Study. *Stroke.* Jul 2008;39(7):1952-1959.

19. Seshadri S, Fitzpatrick AL, Ikram MA, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *Jama.* May 12 2010;303(18):1832-1840.

20. Fornage M, Debette S, Bis JC, et al. Genome-wide association studies of cerebral white matter lesion burden: the CHARGE consortium. *Ann Neurol.* Jun 2011;69(6):928-939.

BIBLIOGRAPHY

1. 2012 Alzheimer's disease facts and figures. *Alzheimers Dement.* Mar 2012;8(2):131-168.

2. Abbey DE, Mills PK, Petersen FF, Beeson WL. Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. *Environ Health Perspect.* Aug 1991;94:43-50.

3. Abrahamowicz M, Schopflocher T, Leffondre K, du Berger R, Krewski D. Flexible modeling of exposure-response relationship between long-term average levels of particulate air pollution and mortality in the American Cancer Society study. *J Toxicol Environ Health A.* Aug 22-Oct 10 2003;66(16-19):1625-1654.

4. Adar SD, Klein R, Klein BE, et al. Air Pollution and the microvasculature: a cross-sectional assessment of in vivo retinal images in the population-based multi-ethnic study of atherosclerosis (MESA). *PLoS Med.* 2010;7(11):e1000372.

5. Allen RW, Adar SD. Are both air pollution and noise driving adverse cardiovascular health effects from motor vehicles? *Environ Res.* Jan 2011;111(1):184-185.

6. Anthony DC, Montine TJ, Valentine WM, Graham DG. Toxic Responses of the Nervous System. In: Klaassen CD, ed. *Casarett & Doull's Toxicology: the Basic Science of Poisons*. 6th ed. New York: McGraw Hill; 2001.

7. Auchincloss AH, Diez Roux AV, Dvonch JT, et al. Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect.* Apr 2008;116(4):486-491.

8. Barnes DE, Haight TJ, Mehta KM, Carlson MC, Kuller LH, Tager IB. Secondhand Smoke, Vascular Disease, and Dementia Incidence: Findings From the Cardiovascular Health Cognition Study. *Am J Epidemiol.* Jan 5 2010.

9. Bernick C, Kuller L, Dulberg C, et al. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. *Neurology.* Oct 9 2001;57(7):1222-1229.

10. Bird TD. Alzheimer Disease Overview. *Gene Reviews* 2010; http://www.ncbi.nlm.nih.gov/books/NBK1161/. Accessed April 9, 2012.

11. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci.* Sep 2009;32(9):506-516.

12. Borenstein AR, Copenhaver CI, Mortimer JA. Early-life risk factors for Alzheimer disease. *Alzheimer Dis Assoc Disord.* Jan-Mar 2006;20(1):63-72.

13. Brandt J, Spence M, Folstein M. The Telephone Interview for Cognitive Status. *Neuropsychiatry, neuropsychology, and behavioral neurology.* 1988;1(2):111-117.

14. Brook RD. Cardiovascular effects of air pollution. *Clin Sci (Lond).* Sep 2008;115(6):175-187.

15. Brook RD, Rajagopalan S, Pope CA, 3rd, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation.* Jun 1 2010;121(21):2331-2378.

16. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health.* Sep 1998;88(9):1337-1342.

17. Brunekreef B, Beelen R, Hoek G, et al. Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: the NLCS-AIR study. *Res Rep Health Eff Inst.* Mar 2009(139):5-71; discussion 73-89.

18. Calderon-Garciduenas L, Azzarelli B, Acuna H, et al. Air pollution and brain damage. *Toxicol Pathol.* May-Jun 2002;30(3):373-389.

19. Calderon-Garciduenas L, Engle R, Mora-Tiscareno A, et al. Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. *Brain Cogn.* Dec 2011;77(3):345-355.

20. Calderon-Garciduenas L, Franco-Lira M, Henriquez-Roldan C, et al. Urban air pollution: influences on olfactory function and pathology in exposed children and young adults. *Exp Toxicol Pathol.* Jan 2010;62(1):91-102.

21. Calderon-Garciduenas L, Kavanaugh M, Block M, et al. Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. *J Alzheimers Dis.* Jan 2012;28(1):93-107.

22. Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain Cogn.* Nov 2008;68(2):117-127.

23. Calderon-Garciduenas L, Mora-Tiscareno A, Styner M, et al. White Matter Hyperintensities, Systemic Inflammation, Brain Growth, and Cognitive Functions in Children Exposed to Air Pollution. *J Alzheimers Dis.* Apr 18 2012.

24. Calderon-Garciduenas L, Reed W, Maronpot RR, et al. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. *Toxicol Pathol.* Nov-Dec 2004;32(6):650-658.

25. Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol.* 2008;36(2):289-310.

26. Chen JC, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology.* Mar 2009;30(2):231-239.

27. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology.* Mar 1992;42(3 Pt 1):473-480.

28. Clark NM, Gong M, Brown RW, et al. Influences on childhood asthma in low-income communities in China and the United States. *J Asthma.* Jul-Aug 2005;42(6):493-497.

29. Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. *Science.* Oct 29 1993;262(5134):689-695.

30. Cromley EK, McLafferty SL. *GIS and Public Health*. New York: Guilford Press; 2002.

31. Cruts B, van Etten L, Tornqvist H, et al. Exposure to diesel exhaust induces changes in EEG in human volunteers. *Part Fibre Toxicol.* 2008;5:4.

32. Daviglus ML, Plassman BL, Pirzada A, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science. *Arch Neurol.* Sep 2011;68(9):1185-1190.

33. Debette S, Bis JC, Fornage M, et al. Genome-wide association studies of MRI-defined brain infarcts: meta-analysis from the CHARGE Consortium. *Stroke.* Feb 2010;41(2):210-217.

34. Devi S. New studies cast dark cloud over air pollution. *Lancet.* Feb 25 2012;379(9817):697.

35. Diez Roux AV, Auchincloss AH, Astor B, et al. Recent exposure to particulate matter and C-reactive protein concentration in the multi-ethnic study of atherosclerosis. *Am J Epidemiol.* Sep 1 2006;164(5):437-448.

36. Diez Roux AV, Auchincloss AH, Franklin TG, et al. Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol.* Mar 15 2008;167(6):667-675.

37. Diggle P. *Analysis of longitudinal data*. Oxford; New York: Oxford University Press; 2002.

38. Dockery DW, Pope CA, 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med.* Dec 9 1993;329(24):1753-1759.

39. Doty RL. The olfactory system and its disorders. *Semin Neurol.* Feb 2009;29(1):74-81.

40. Elder A, Gelein R, Silva V, et al. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. *Environ Health Perspect.* Aug 2006;114(8):1172-1178.

41. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *Jama.* Oct 22-29 1997;278(16):1349-1356.

42. Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. *N Engl J Med.* Aug 9 2001;345(6):425-432.

43. Fitzpatrick AL, Kuller LH, Ives DG, et al. Incidence and prevalence of dementia in the Cardiovascular Health Study. *J Am Geriatr Soc.* Feb 2004;52(2):195-204.

44. Fitzpatrick AL, Kuller LH, Lopez OL, Kawas CH, Jagust W. Survival following dementia onset: Alzheimer's disease and vascular dementia. *J Neurol Sci.* Mar 15 2005;229-230:43-49.

45. Fornage M, Chiang YA, O'Meara ES, et al. Biomarkers of Inflammation and MRI-Defined Small Vessel Disease of the Brain: The Cardiovascular Health Study. *Stroke.* Jul 2008;39(7):1952-1959.

46. Fornage M, Debette S, Bis JC, et al. Genome-wide association studies of cerebral white matter lesion burden: the CHARGE consortium. *Ann Neurol.* Jun 2011;69(6):928-939.

47. Freire C, Ramos R, Puertas R, et al. Association of traffic-related air pollution with cognitive development in children. *J Epidemiol Community Health.* Mar 2010;64(3):223-228.

48. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol.* Feb 1991;1(3):263-276.

49. Genc S, Zadeoglulari Z, Fuss SH, Genc K. The adverse effects of air pollution on the nervous system. *J Toxicol.* 2012;2012:782462.

50. Gerlofs-Nijland ME, van Berlo D, Cassee FR, Schins RP, Wang K, Campbell A. Effect of prolonged exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain. *Part Fibre Toxicol.* 2010;7:12.

51. Gill EA, Curl CL, Adar SD, et al. Air pollution and cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. *Prog Cardiovasc Dis.* Mar-Apr 2011;53(5):353-360.

52. Gold G, Kovari E, Hof PR, Bouras C, Giannakopoulos P. Sorting out the clinical consequences of ischemic lesions in brain aging: a clinicopathological approach. *J Neurol Sci.* Jun 15 2007;257(1-2):17-22.

53. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *Jama.* Jul 7 1999;282(1):40-46.

54. Haber SN, Calzavara R. The cortico-basal ganglia integrative network: the role of the thalamus. *Brain Res Bull.* Feb 16 2009;78(2-3):69-74.

55. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med.* May 1965;58:295-300.

56. Huber A, Stuchbury G, Burkle A, Burnell J, Munch G. Neuroprotective therapies for Alzheimer's disease. *Curr Pharm Des.* 2006;12(6):705-717.

57. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Annals of epidemiology.* Jul 1995;5(4):278-285.

58. Jellinger KA. Recent advances in our understanding of neurodegeneration. *J Neural Transm.* Sep 2009;116(9):1111-1162.

59. Jerrett M, Arain A, Kanaroglou P, et al. A review and evaluation of intraurban air pollution exposure models. *J Expo Anal Environ Epidemiol.* Mar 2005;15(2):185-204.

60. Jorm AF, Scott R, Cullen JS, MacKinnon AJ. Performance of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening test for dementia. *Psychol Med.* Aug 1991;21(3):785-790.

61. Kang JH, Weuve J, Grodstein F. Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. *Neurology.* Jul 13 2004;63(1):101-107.

62. Kaufman JD. Does air pollution accelerate progression of atherosclerosis? *J Am Coll Cardiol.* Nov 23 2010;56(22):1809-1811.

63. Kleinbaum DG, Klein M. *Logistic regression : a self-learning text*. New York, NY: Springer-Verlag; 2002.

64. Kleinbaum DG, Klein M. Survival analysis a self-learning text. 2005; http://www.myilibrary.com?id=133454.

65. Koepsell TD, Weiss NS. Epidemiologic methods : studying the occurrence of illness. 2003:ix, 513 p.

66. Kohlmeier L, Bellach B. Exposure assessment error and its handling in nutritional epidemiology. *Annu Rev Public Health.* 1995;16:43-59.

67. Krewski D, Burnett RT, Goldberg MS, et al. Overview of the reanalysis of the Harvard Six Cities Study and American Cancer Society Study of Particulate Air Pollution and Mortality. *J Toxicol Environ Health A.* Aug 22-Oct 10 2003;66(16-19):1507-1551.

68. Kuller LH, Longstreth WT, Jr., Arnold AM, Bernick C, Bryan RN, Beauchamp NJ, Jr. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke.* Aug 2004;35(8):1821-1825.

69. Kuller LH, Lopez OL, Newman A, et al. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology.* Jan-Feb 2003;22(1):13-22.

70. Kuller LH, Shemanski L, Manolio T, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke.* Feb 1998;29(2):388-398.

71. Kunzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager IB. Association between lifetime ambient ozone exposure and pulmonary function in college freshmen--results of a pilot study. *Environ Res.* Jan 1997;72(1):8-23.

72. Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. *Environ Health Perspect.* Oct 2000;108(10):941-947.

73. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med.* Mar 15 2006;173(6):667-672.

74. Liao D, Duan Y, Whitsel EA, et al. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. *Am J Epidemiol.* Apr 15 2004;159(8):768-777.

75. Longstreth WT, Jr., Arnold AM, Beauchamp NJ, Jr., et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* Jan 2005;36(1):56-61.

76. Longstreth WT, Jr., Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. *Arch Neurol.* Sep 1998;55(9):1217-1225.

77. Longstreth WT, Jr., Dulberg C, Manolio TA, et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* Oct 2002;33(10):2376-2382.

78. Longstreth WT, Jr., Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke.* Aug 1996;27(8):1274-1282.

79. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. *Neuroepidemiology.* Jan-Feb 2003;22(1):1-12.

80. Maheswaran R, Elliott P. Stroke mortality associated with living near main roads in England and wales: a geographical study. *Stroke.* Dec 2003;34(12):2776-2780.

81. Maheswaran R, Haining RP, Brindley P, et al. Outdoor air pollution and stroke in Sheffield, United Kingdom: a small-area level geographical study. *Stroke.* Feb 2005;36(2):239-243.

82. Maheswaran R, Haining RP, Pearson T, Law J, Brindley P, Best NG. Outdoor NOx and stroke mortality: adjusting for small area level smoking prevalence using a Bayesian approach. *Stat Methods Med Res.* Oct 2006;15(5):499-516.

83. Maheswaran R, Pearson T, Smeeton NC, Beevers SD, Campbell MJ, Wolfe CD. Impact of outdoor air pollution on survival after stroke: population-based cohort study. *Stroke.* May 2010;41(5):869-877.

84. Maheswaran R, Pearson T, Smeeton NC, Beevers SD, Campbell MJ, Wolfe CD. Outdoor air pollution and incidence of ischemic and hemorrhagic stroke: a small-area level ecological study. *Stroke.* Jan 2012;43(1):22-27.

85. Maheswaran R, Strachan DP, Elliott P, Shipley MJ. Trends in stroke mortality in Greater London and south east England--evidence for a cohort effect? *J Epidemiol Community Health.* Apr 1997;51(2):121-126.

86. Mattson. Mechanisms of neuronal apoptosis and excitotoxicity. *Pathogenesis and neurodegenerative disorders*. Baltimore: Humana Press; 2001:1-20.

87. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* Jul 1984;34(7):939-944.

88. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med.* Feb 1 2007;356(5):447-458.

89. Mills NL, Donaldson K, Hadoke PW, et al. Adverse cardiovascular effects of air pollution. *Nat Clin Pract Cardiovasc Med.* Jan 2009;6(1):36-44.

90. Nelson LM, Tanner CM, VanDenEeden SK, McGuire V. *Neuroepidemiology: From Principles to Practice*. New York: Oxford University Press; 2004.

91. Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *J Am Geriatr Soc.* Jul 2005;53(7):1101-1107.

92. Newman AB, Walter S, Lunetta KL, et al. A meta-analysis of four genome-wide association studies of survival to age 90 years or older: the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. *J Gerontol A Biol Sci Med Sci.* May 2010;65(5):478-487.

93. O'Brien JT. Vascular cognitive impairment. *Am J Geriatr Psychiatry.* Sep 2006;14(9):724-733.

94. O'Neill MS, Diez-Roux AV, Auchincloss AH, et al. Airborne particulate matter exposure and urinary albumin excretion: the Multi-Ethnic Study of Atherosclerosis. *Occup Environ Med.* Aug 2008;65(8):534-540.

95. Oberdorster G, Elder A, Rinderknecht A. Nanoparticles and the brain: cause for concern? *J Nanosci Nanotechnol.* Aug 2009;9(8):4996-5007.

96. Oberdorster G, Sharp Z, Atudorei V, et al. Translocation of inhaled ultrafine particles to the brain. *Inhal Toxicol.* Jun 2004;16(6-7):437-445.

97. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. *J Clin Psychol.* Jan 1986;42(1):28-33.

98. Park SK, Auchincloss AH, O'Neill MS, et al. Particulate air pollution, metabolic syndrome, and heart rate variability: the multi-ethnic study of atherosclerosis (MESA). *Environ Health Perspect.* Oct 2010;118(10):1406-1411.

99. Park SK, O'Neill MS, Vokonas PS, Sparrow D, Schwartz J. Effects of air pollution on heart rate variability: the VA normative aging study. *Environ Health Perspect.* Mar 2005;113(3):304-309.

100. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol.* Feb 2007;7(2):161-167.

101. Peters A, Frohlich M, Doring A, et al. Particulate air pollution is associated with an acute phase response in men; results from the MONICA-Augsburg Study. *Eur Heart J.* Jul 2001;22(14):1198-1204.

102. Peters A, Veronesi B, Calderon-Garciduenas L, et al. Translocation and potential neurological effects of fine and ultrafine particles a critical update. *Part Fibre Toxicol.* 2006;3:13.

103. Pope CA, 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *Jama.* Mar 6 2002;287(9):1132-1141.

104. Pope CA, 3rd, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation.* Jan 6 2004;109(1):71-77.

105. Post SG, Whitehouse PJ, Binstock RH, et al. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *Jama.* Mar 12 1997;277(10):832-836.

106. Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A, 3rd, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. *Environ Health Perspect.* May 2011;119(5):682-687.

107. Psaty BM, Kuller LH, Bild D, et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. *Annals of epidemiology.* Jul 1995;5(4):270-277.

108. Qin L, Wu X, Block ML, et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia.* Apr 1 2007;55(5):453-462.

109. Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environ Res.* Nov 2009;109(8):1004-1011.

110. Rivest S, Lacroix S, Vallieres L, Nadeau S, Zhang J, Laflamme N. How the blood talks to the brain parenchyma and the paraventricular nucleus of the hypothalamus during systemic inflammatory and infectious stimuli. *Proc Soc Exp Biol Med.* Jan 2000;223(1):22-38.

111. Schwartz J. Air pollution and blood markers of cardiovascular risk. *Environ Health Perspect.* Jun 2001;109 Suppl 3:405-409.

112. Seaton A, Soutar A, Crawford V, et al. Particulate air pollution and the blood. *Thorax.* Nov 1999;54(11):1027-1032.

113. Serby M, Larson P, Kalkstein D. The nature and course of olfactory deficits in Alzheimer's disease. *Am J Psychiatry.* Mar 1991;148(3):357-360.

114. Seshadri S, Fitzpatrick AL, Ikram MA, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *Jama.* May 12 2010;303(18):1832-1840.

115. Shadlen MF, Siscovick D, Fitzpatrick AL, Dulberg C, Kuller LH, Jackson S. Education, cognitive test scores, and black-white differences in dementia risk. *J Am Geriatr Soc.* Jun 2006;54(6):898-905.

116. Sink KM, Leng X, Williamson J, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med.* Jul 13 2009;169(13):1195-1202.

117. Squire LR. *Fundamental neuroscience*. Amsterdam; Boston: Elsevier / Academic Press; 2008.

118. Stampfer MJ. Cardiovascular disease and Alzheimer's disease: common links. *J Intern Med.* Sep 2006;260(3):211-223.

119. Stolp HB, Dziegielewska KM, Ek CJ, Potter AM, Saunders NR. Long-term changes in blood-brain barrier permeability and white matter following prolonged systemic inflammation in early development in the rat. *Eur J Neurosci.* Dec 2005;22(11):2805-2816.

120. Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. *Am J Epidemiol.* Feb 1 2008;167(3):280-286.

121. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *Jama.* Dec 21 2005;294(23):3003-3010.

122. Thomas D, Stram D, Dwyer J. Exposure measurement error: influence on exposure-disease. Relationships and methods of correction. *Annu Rev Public Health.* 1993;14:69-93.

123. Thomas DC. Statistical methods in environmental epidemiology. 2009; http://public.eblib.com/EBLPublic/PublicView.do?ptiID=472393.

124. Twisk JWR. *Applied longitudinal data analysis for epidemiology : a practical guide*. Cambridge, UK; New York: Cambridge University Press; 2003.

125. Van Hee VC, Adar SD, Szpiro AA, et al. Exposure to traffic and left ventricular mass and function: the Multi-Ethnic Study of Atherosclerosis. *Am J Respir Crit Care Med.* May 1 2009;179(9):827-834.

126. Van Hee VC, Adar SD, Szpiro AA, et al. Common genetic variation, residential proximity to traffic exposure, and left ventricular mass: the multi-ethnic study of atherosclerosis. *Environ Health Perspect.* Jul 2010;118(7):962-969.

127. Van Hee VC, Kaufman JD, Budinger GR, Mutlu GM. Update in environmental and occupational medicine 2009. *Am J Respir Crit Care Med.* Jun 1;181(11):1174-1180.

128. Wang S, Zhang J, Zeng X, Zeng Y, Chen S. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. *Environ Health Perspect.* Oct 2009;117(10):1612-1618.

129. Wellenius GA, Burger MR, Coull BA, et al. Ambient air pollution and the risk of acute ischemic stroke. *Arch Intern Med.* Feb 13 2012;172(3):229-234.

130. Wellenius GA, Schwartz J, Mittleman MA. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *Stroke.* Dec 2005;36(12):2549-2553.

131. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *Jama.* Sep 22 2004;292(12):1454-1461.

132. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med.* Feb 13 2012;172(3):219-227.

133. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology.* Jan;23(1):119-128.

134. White E, Armstrong BK, Saracci R. *Principles of exposure measurement in epidemiology: collecting, evaluating, and improving measures of disease risk factors*. Second ed. New York: Oxford University Press; 2008.

135. Whitsel EA, Quibrera PM, Christ SL, et al. Heart rate variability, ambient particulate matter air pollution, and glucose homeostasis: the environmental epidemiology of arrhythmogenesis in the women's health initiative. *Am J Epidemiol.* Mar 15 2009;169(6):693-703.

136. Wong DW, Yuan L, Perlin SA. Comparison of spatial interpolation methods for the estimation of air quality data. *J Expo Anal Environ Epidemiol.* Sep 2004;14(5):404-415.

137. Yin YW, Li JC, Wang JZ, et al. Association between apolipoprotein E gene polymorphism and the risk of vascular dementia: A meta-analysis. *Neurosci Lett.* Apr 11 2012;514(1):6-11.

138. Zeger SL, Thomas D, Dominici F, et al. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ Health Perspect.* May 2000;108(5):419-426.

139. Zeng Y, Gu D, Purser J, Hoenig H, Christakis N. Associations of environmental factors with elderly health and mortality in China. *Am J Public Health.* Feb 2010;100(2):298-305.

140. Cruts B, Driessen A, van Etten L, et al. Reply to comment on Cruts et al. (2008), "Exposure to diesel exhaust induces changes in EEG in human volunteers" by Valberg et al. *Part Fibre Toxicol.* 2008;5:11.

141. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* Jul 1997;20(7):1183-1197.

VITA

Erin O'Brien Semmens was born in Scranton, Pennsylvania and grew up nearby in Clarks Summit, Pennsylvania. Following the completion of her undergraduate studies in Biology and Political Science at Duke University in 2002, she joined the Jesuit Volunteer Corps and assisted low-income family law clients. She returned to school and earned a Master of Public Health degree in Environmental and Occupational Health from the University of Washington in 2007. In 2012, she earned a Doctor of Philosophy in Epidemiology from the University of Washington. She currently resides in Missoula, Montana with her husband, Dan, daughter, Franny, and dog Maggie.