Cardiovascular and Cognitive Health Effects Associated with Ultrafine Particulate Matter Exposure among Adults in the Boston Puerto Rican Health Study

A thesis submitted by

Laura Corlin

In partial fulfillment of the requirements for the degree of

Master of Science

in

Civil and Environmental Engineering

Tufts University

May 2015

Thesis Committee Chair: Mark Woodin

Thesis Committee Members: Doug Brugge, John Durant, and David Gute

Abstract

Ultrafine particulate matter (UFP, particles < 0.1 μm aerodynamic diameter) may be the most toxic size fraction of particulate matter. However, no longitudinal studies have examined the association between UFP exposure and either biomarkers of cardiovascular disease (CVD) risk or cognitive function among adults. We used data from 812 adults who participated in the Boston Puerto Rican Health Study to assess whether UFP exposure was associated with changes in CVD risk factors and with changes in cognitive function over five years. Residential annual average UFP exposure (measured as particle number concentration or PNC) was assigned using a model accounting for spatial and temporal trends. We adjusted the PNC values for participants' inhalation rate to obtain the particle inhalation rate (PIR). Multilevel linear models with random intercepts for each participant were used to examine the association between UFP exposure and each outcome. We found that UFP concentrations were associated with increases in systolic blood pressure (95% CI for an inter-quartile increase in PNC = 0.3, 1.9 mmHg) and pulse pressure (95% CI = 0.3, 1.4 mmHg), as well as the percent change in C-reactive protein concentrations (95% CI = 1.8, 16.6%) and the cognitive decline rate (95% CI = -0.192, -0.003 points). Each IQR increase in the PIR was associated with diastolic blood pressure levels (95% CI = 0.4 - 1.7 mmHg) and cognitive function scores (95% CI = -0.014, 0.204 points). Effect modification was evident by sex, medication use, employment status, diabetes, smoking, family history of hypertension, depression, and physical activity level. Although future work is needed to validate these results in other populations and certain results found using PNC were inconsistent with results found using the PIR, we found evidence that exposure to UFP is associated with increased levels of CVD risk factors and reduced cognitive function.

Acknowledgements

I would first like to acknowledge the Chair of my committee, Mark Woodin, for his unwavering support and mentorship over the course of both my undergraduate and graduate studies. I cannot thank him enough for his dedication to my personal, academic, and professional growth. I would also like to thank the rest of my committee: Doug Brugge for his leadership on the Boston Puerto Rican Health Study (BPRHS) and the Community Assessment of Freeway Exposure and Healthy Study and for his continuing support of my professional development throughout my undergraduate and graduate years, John Durant for sharing his knowledge about exposure assessment and for the structure he provided over the past two years, and David Gute for his insightful ideas about how to synthesize my findings. In addition to my core committee, I would like to thank Jaime Hart who became a *de facto* member of my committee and who provided invaluable assistance in helping me develop my analytic strategy. I would not be where I am today without each of my committee members. I have truly enjoyed working with them and I value everything they have taught me along the way.

In addition to my committee, I would like to thank several other members of the BPRHS Project Four team. Matt Simon has been a wonderful colleague and I have benefited from his good humor and insightful ideas. I especially appreciate the extra lengths he went to so that I could have the PNC exposure model ready in time for my analysis. I have also greatly enjoyed working with my students, Joanna Stowell and Cara Goodman. In particular, I appreciate their help geocoding all of the participants who moved between study visits.

I am also very appreciative of everyone on the larger BPRHS team. Katy Tucker served as the Principal Investigator of the BPRHS and none of this work would be possible without her. Tammy Scott provided critical assistance in understanding the cognitive measures. Lori Lyn

helped me understand the data set in the context of the study's history. Shilpa Saklani and Esther Carver assisted me in accessing the data. Additionally, I would like to thank the field staff for their dedication.

Many others contributed to my thesis in meaningful ways. Kevin Lane helped me develop the code to assign participants' annual average exposures and has served as an influential role model over the past several years. Wig Zamore was instrumental in helping me find relevant literature, especially in relation to the inhalation rate adjustments. Anne Marie Desmarais helped me learn the toxicology I needed to complete my thesis and helped me formulate my initial research questions. Elena Naumova guided me as I learned about time series analysis. Bobbi White provided expert assistance in interpreting the results of the analysis of the cognitive measures.

I am appreciative to have been able to call Tufts home over the past six years. Each of the CEE faculty and staff members has cultivated a warm and collaborative culture. I would especially like to thank Laura Sacco for coordinating all of the administrative details and for her continued guidance. I am also truly grateful to Kurt Pennell and the Department of Civil and Environmental Engineering for supporting me intellectually and financially throughout the past two years. I would also like to acknowledge the financial support of the Tufts Institute of the Environment and the National Heart, Lung, and Blood Institute (P01 AG023394 and P50 HL105185) for financially supporting this work.

Table of Contents

List of Tables

List of Figures

Chapter 1. Introduction

With approximately 45 million people living, working, or spending time within 300 feet of major roadways (US EPA, 2014), understanding the potential health consequences of traffic-related air pollution is a public health priority. Exposure to ambient particulate matter (PM), a traffic-related pollutant, has been associated with an increased risk of cardiovascular morbidity, cardiovascular mortality, and all-cause mortality (Dockery et al., 1993; Pope et al., 1995; Schwartz & Morris, 1995; Pope III et al., 1999; Peters, Dockery, Muller, & Mittleman, 2001; Künzli et al., 2005; Miller et al., 2007; Gan et al., 2011; Crouse et al., 2012; Beelen et al., 2014). PM exposure has also been associated with cardiovascular disease (CVD) risk factors, such as increased blood pressure and increased levels of biomarkers of systemic inflammation (Hoffmann et al., 2009; Fuks et al., 2011; Coogan et al., 2012; Hennig et al., 2014). In addition to the associations with cardiovascular outcomes, PM exposure has been associated with decreased cognitive function and a faster rate of cognitive decline (Power et al., 2011; Weuve J et al., 2012; Ailshire & Crimmins, 2014; Gatto et al., 2014).

Despite the apparent relationship between exposure to PM pollution and cardiovascular and cognitive outcomes, much less is known about the potential impact of the smallest size fraction of PM. Long-term exposure (averages over months to years) to ultrafine particulate matter (UFP, particles of less than 0.1 μm aerodynamic diameter) is challenging to model in part due to the high spatial and temporal variability (Johansson, Norman, & Gidhagen, 2006). UFP (measured as particle number concentration or PNC) declines exponentially near major roadways with concentrations approximating that of background levels at about 100 m away from roads (Hagler et al., 2009; Zhu et al., 2009). Additionally, there are strong diurnal and seasonal patterns in PNC which seem to be determined partially by changes in meteorological conditions

(Jeong, Evans, Hopke, Chalupa, & Utell, 2006; Durant et al., 2010). Nevertheless, a limited number of environmental epidemiology studies have overcome the challenges of modeling long-term exposure to UFP.

Our research group modeled hourly PNC with 20 m resolution and we found that annual average exposure to UFP is associated with levels of biomarkers of CVD risk among adults participating in the cross-sectional Community Assessment of Freeway Exposure and Health study (Corlin et al., 2014; K. Lane et al., 2015). The only published longitudinal study considering the health effects of long-term exposure found that UFP mass, modeled at a four by four km resolution, was associated with between a two and 18 percent increased risk of ischemic heart disease mortality (Ostro et al., 2015). However, no longitudinal studies have examined the association between long-term exposure to UFP and biomarkers of CVD risk. Similarly, no published studies have considered the relationship between long-term exposure to UFP and cognitive function. In my thesis, I will examine these questions. Specifically, I will assess whether annual average UFP concentrations are associated with blood pressure, C-reactive protein (CRP, a biomarker of systemic inflammation) concentration, and cognitive function measured by scores on the Mini-Mental State Examination (MMSE). I will also assess whether annual average UFP concentrations are associated with changes in these cardiovascular and cognitive measures over five years. I expect that increased UFP exposure will be associated with increased blood pressure, increased CRP, and decreased cognitive function.

As a final objective, I seek to improve air pollution exposure assessment methodology by comparing a novel exposure metric that accounts for participants' inhalation rate against the more traditional metric of PNC. Most studies that have examined the health effects of traffic-related air pollution assume that the residential average pollutant concentration reflects the

biologically effective dose. This assumption is problematic. Even in the unlikely situation that people spend all of their time in micro-environments with ambient exposures equal to their assigned residential average exposure, the biologically effective dose is modulated by several factors other than just the ambient concentration (Bigazzi & Figliozzi, 2014). For example, since inhalation is the primary route of exposure and inhalation rate differs by age, sex, weight, and physical activity (US EPA, 2009), ignoring inhalation rate in exposure assessment may introduce differential exposure misclassification. Specifically, it is known that people inhale more frequently and more deeply during exercise so exposure estimates may be under-estimated for more physically active individuals (Jaques & Kim, 2000; Daigle et al., 2003). Similarly, men and larger individuals are likely to be exposed to higher doses of PM than others, even in environments with the same ambient PNC (US EPA, 2009). To more closely approximate individuals' intake dose of UFP, I multiplied the residential annual average PNC estimates (particles/L) by the average hourly respiratory volume (L of air inhaled/hour) to obtain the average particle inhalation rate (PIR, particles inhaled/hour). While previous studies examining differences in individuals' exposure to UFP by mode of transportation have accounted for inhalation (de Nazelle et al., 2012; Int Panis et al., 2010), no studies of which we are aware have adjusted long-term exposure estimates for average inhalation rate to calculate the PIR. Therefore, throughout my thesis, I will compare PNC and the PIR as exposure metrics for UFP.

Motivation to study UFP exposure as a potential risk factor for CVD and cognitive decline

The primary motivation to study UFP in epidemiology studies comes from the toxicological literature which suggests that UFP may be the most toxic size fraction of PM in terms of cardiovascular and cognitive toxicity. In particular, it is fairly well established that there

is a linear relationship between particle size and total deposition fraction for inhaled PM (Jaques & Kim, 2000; Rissler et al., 2012). Specifically, while the particles initially deposit on the epithelium in the trachea and bronchial airways, the rate at which particles move to the larynx via mucociliary transport depends on the size of the particles. Additionally, of the various size fractions of PM, UFP is most likely to reach the lung through diffusion by Brownian motion and once there, the greater surface area per mass allows more particles to interact directly with the alveoli (Lippmann, Yeates, & Albert, 1980; Kreyling, Semmler-Behnke, & Möller, 2006). The greater surface area of UFP also seems to be related to the increased toxicity of UFP compared to $PM_{2.5}$ since there is a dose-response relationship between surface area and the concentrations of proinflammatory cytokines. This may be related to the relative ease of translocation into the interstitium (Stoeger et al., 2006).

The metabolic differences of UFP compared to larger particles also have a direct bearing on the increased toxicity of these smaller particles. In particular, although both UFP and fine particulate matter ($PM_{2.5,}$ particles of less than 2.5 µm aerodynamic diameter) increase production of oxidants in pulmonary epithelium cells (Shukla et al., 2000), UFP seems to be able to induce oxidative stress more readily. A study examining quinone assays that quantify the reactive oxygen species content of cells found that controlling for mass, UFP could participate in 8.6 times more redox reactions than $PM_{2.5}$ and 21.7 times more redox reactions than coarse particulates (particles of less than 10 µm aerodynamic diameter) (Li et al., 2003). The presence of reactive oxygen species can lead to inflammation responses and vascular toxicity (Gurgueira, Lawrence, Coull, Murthy, & Gonzalez-Flecha, 2002; Sun et al., 2005).

In addition to the putative mechanisms that could lead to vascular toxicity, UFP may affect cognitive function. To the extent that cognitive impairment is due to vascular dementia,

there may be shared mechanisms leading to cardiovascular and cognitive toxicity. Specifically, increased concentrations of circulating cytokines may lead to increased neuroinflammation and oxidative stress within the central nervous system (Block & Calderón-Garcidueñas, 2009). Moreover, and unlike larger size fractions of PM, UFP may exert more direct effects within the brain since it can translocate into the olfactory bulb through the olfactory nerve and it can cross the blood-brain barrier (Oberdörster et al., 2004). It is possible that these effects are mediated through changes in cell-signaling processes that affect transcription of proteins involved in the inflammation response (Kleinman et al., 2008). Although future work is necessary to clarify the specific mechanisms through which UFP may act, there is sufficient toxicological evidence to suggest that it is worth investigating the potential health effects of long-term exposure to UFP.

Thesis overview

Throughout my thesis, I will consider whether UFP exposure is associated with cardiovascular and cognitive outcomes among adults participating in the Boston Puerto Rican Health Study (BPRHS). Chapter 2 gives a detailed description of the methodology, including an overview of the study population, the health data collection, the exposure assessment, and the statistical analyses. Chapter 3 provides the first examination of the associations between long-term exposure to UFP and biomarkers of CVD risk in a longitudinal study. Chapter 4 provides the first analysis of the association between long-term exposure to UFP and cognitive function. In addition to addressing the central research questions of whether UFP exposure is associated with increased levels of CVD risk factors and whether UFP exposure is associated with decreased cognitive function, I hope to address an ongoing debate as to who may be most vulnerable to any cardiovascular or cognitive effects of UFP. In particular, since I am analyzing

data from a population with a high prevalence of chronic disease and low average socioeconomic status, I am interested in addressing the question of whether different sub-populations show varying susceptibility. I also seek to compare two different UFP exposure metrics to gain a fuller understanding of the potential health effects of UFP.

Works Cited

Ailshire, J. A., & Crimmins, E. M. (2014). Fine Particulate Matter Air Pollution and Cognitive Function Among Older US Adults. *American Journal of Epidemiology*, kwu155. http://doi.org/10.1093/aje/kwu155

Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z. J., Weinmayr, G., Hoffmann, B., … Hoek, G. (2014). Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *The Lancet*, *383*(9919), 785–795. http://doi.org/10.1016/S0140-6736(13)62158-3

Bigazzi, A. Y., & Figliozzi, M. A. (2014). Review of Urban Bicyclists' Intake and Uptake of Traffic-Related Air Pollution. *Transport Reviews*, *34*(2), 221–245. http://doi.org/10.1080/01441647.2014.897772

Block, M. L., & Calderón-Garcidueñas, L. (2009). Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends in Neurosciences*, *32*(9), 506–516. http://doi.org/10.1016/j.tins.2009.05.009

Coogan, P. F., White, L. F., Jerrett, M., Brook, R. D., Su, J. G., Seto, E., … Rosenberg, L. (2012). Air Pollution and Incidence of Hypertension and Diabetes Mellitus in Black Women Living in Los Angeles. *Circulation*, *125*(6), 767–772. http://doi.org/10.1161/CIRCULATIONAHA.111.052753

Corlin, L., Woodin, M., Lane, K., Patton, A., Thanikachalam, M., & Brugge, D. (2014). Association of Particle Number Concentration Adjusted for Time-Activity with Blood Pressure and Ankle Brachial Index. *Environmental Health Perspectives - ISEE Abstracts*. Retrieved from http://ehp.niehs.nih.gov/isee/p2-490/

Crouse, D. L., Peters, P. A., van Donkelaar, A., Goldberg, M. S., Villeneuve, P. J., Brion, O., … Burnett, R. T. (2012). Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environmental Health Perspectives*, *120*(5), 708–714. http://doi.org/10.1289/ehp.1104049

Daigle, C. C., Chalupa, D. C., Gibb, F. R., Morrow, P. E., Oberdörster, G., Utell, M. J., & Frampton, M. W. (2003). Ultrafine Particle Deposition in Humans During Rest and Exercise. *Inhalation Toxicology*, *15*(6), 539–552. http://doi.org/10.1080/08958370304468

De Nazelle, A., Fruin, S., Westerdahl, D., Martinez, D., Ripoll, A., Kubesch, N., & Nieuwenhuijsen, M. (2012). A travel mode comparison of commuters' exposures to air pollutants in Barcelona. *Atmospheric Environment*, *59*, 151–159. http://doi.org/10.1016/j.atmosenv.2012.05.013

Dockery, D. W., Pope, C. A., 3rd, Xu, X., Spengler, J. D., Ware, J. H., Fay, M. E., … Speizer, F. E. (1993). An association between air pollution and mortality in six U.S. cities. *The New England Journal of Medicine*, *329*(24), 1753–1759. http://doi.org/10.1056/NEJM199312093292401

Durant, J. L., Ash, C. A., Wood, E. C., Herndon, S. C., Jayne, J. T., Knighton, W. B., … Kolb, C. E. (2010). Short-term variation in near-highway air pollutant gradients on a winter morning. *Atmospheric Chemistry and Physics (Print)*, *10*(2), 5599–5626.

Fuks, K., Moebus, S., Hertel, S., Viehmann, A., Nonnemacher, M., Dragano, N., … Hoffmann, B. (2011). Long-Term Urban Particulate Air Pollution, Traffic Noise, and Arterial Blood

Pressure. *Environmental Health Perspectives*, *119*(12), 1706–1711. http://doi.org/10.1289/ehp.1103564

Gan, W. Q., Koehoorn, M., Davies, H. W., Demers, P. A., Tamburic, L., & Brauer, M. (2011). Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. *Environmental Health Perspectives*, *119*(4), 501–507. http://doi.org/10.1289/ehp.1002511

Gatto, N. M., Henderson, V. W., Hodis, H. N., St. John, J. A., Lurmann, F., Chen, J.-C., & Mack, W. J. (2014). Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. *NeuroToxicology*, *40*, 1–7. http://doi.org/10.1016/j.neuro.2013.09.004

Gurgueira, S. A., Lawrence, J., Coull, B., Murthy, G. G. K., & Gonzalez-Flecha, B. (2002). Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. *Environmental Health Perspectives*, *110*(8), 749–755.

Hagler, G. S. W., Baldauf, R. W., Thoma, E. D., Long, T. R., Snow, R. F., Kinsey, J. S., … Gullett, B. K. (2009). Ultrafine particles near a major roadway in Raleigh, North Carolina: Downwind attenuation and correlation with traffic-related pollutants. *Atmospheric Environment*, *43*(6), 1229–1234. http://doi.org/10.1016/j.atmosenv.2008.11.024

Hennig, F., Fuks, K., Moebus, S., Weinmayr, G., Memmesheimer, M., Jakobs, H., … Hoffmann, B. (2014). Association between Source-Specific Particulate Matter Air Pollution and hs-CRP: Local Traffic and Industrial Emissions. *Environmental Health Perspectives*, *122*(7), 703–710. http://doi.org/10.1289/ehp.1307081

Hoffmann, B., Moebus, S., Dragano, N., Stang, A., Möhlenkamp, S., Schmermund, A., … Jöckel, K.-H. (2009). Chronic Residential Exposure to Particulate Matter Air Pollution and Systemic Inflammatory Markers. *Environmental Health Perspectives*, *117*(8), 1302–1308. http://doi.org/10.1289/ehp.0800362

Int Panis, L., de Geus, B., Vandenbulcke, G., Willems, H., Degraeuwe, B., Bleux, N., … Meeusen, R. (2010). Exposure to particulate matter in traffic: A comparison of cyclists and car passengers. *Atmospheric Environment*, *44*(19), 2263–2270. http://doi.org/10.1016/j.atmosenv.2010.04.028

Jaques, P. A., & Kim, C. S. (2000). Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. *Inhalation Toxicology*, *12*(8), 715–731. http://doi.org/10.1080/08958370050085156

Jeong, C.-H., Evans, G. J., Hopke, P. K., Chalupa, D. J., & Utell, M. (2006). Influence of Atmospheric Dispersion and New Particle Formation Events on Ambient Particle Number Concentration in Rochester, United States, and Toronto, Canada. *Journal of the Air & Waste Management Association*, *56*(4), 431–443. http://doi.org/10.1080/10473289.2006.10464519

Johansson, C., Norman, M., & Gidhagen, L. (2006). Spatial & temporal variations of PM10 and particle number concentrations in urban air. *Environmental Monitoring and Assessment*, *127*(1-3), 477–487. http://doi.org/10.1007/s10661-006-9296-4

Kleinman, M. T., Araujo, J. A., Nel, A., Sioutas, C., Campbell, A., Cong, P. Q., … Bondy, S. C. (2008). Inhaled ultrafine particulate matter affects CNS inflammatory processes and may act via MAP kinase signaling pathways. *Toxicology Letters*, *178*(2), 127–130. http://doi.org/10.1016/j.toxlet.2008.03.001

Kreyling, W. G., Semmler-Behnke, M., & Möller, W. (2006). Ultrafine Particle–Lung Interactions: Does Size Matter? *Journal of Aerosol Medicine*, *19*(1), 74–83. http://doi.org/10.1089/jam.2006.19.74

Künzli, N., Jerrett, M., Mack, W. J., Beckerman, B., LaBree, L., Gilliland, F., … Hodis, H. N. (2005). Ambient Air Pollution and Atherosclerosis in Los Angeles. *Environmental Health Perspectives*, *113*(2), 201–206. http://doi.org/10.1289/ehp.7523

Lane, K., Levy, J., Scammell, M., Patton, A., Durant, J., Mwamburi, M., … Brugge, D. (2015). Effect of time-activity adjustment on exposure assessment for traffic-related ultrafine particles. *Journal of Exposure Science and Environmental Epidemiology*.

Li, N., Sioutas, C., Cho, A., Schmitz, D., Misra, C., Sempf, J., … Nel, A. (2003). Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. *Environmental Health Perspectives*, *111*(4), 455–460.

Lippmann, M., Yeates, D. B., & Albert, R. E. (1980). Deposition, retention, and clearance of inhaled particles. *British Journal of Industrial Medicine*, *37*(4), 337–362.

Miller, K. A., Siscovick, D. S., Sheppard, L., Shepherd, K., Sullivan, J. H., Anderson, G. L., & Kaufman, J. D. (2007). Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women. *New England Journal of Medicine*, *356*(5), 447–458. http://doi.org/10.1056/NEJMoa054409

Oberdörster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Kreyling, W., & Cox, C. (2004). Translocation of Inhaled Ultrafine Particles to the Brain. *Inhalation Toxicology*, *16*(6-7), 437–445. http://doi.org/10.1080/08958370490439597

Ostro, B., Hu, J., Goldberg, D., Reynolds, P., Hertz, A., Bernstein, L., & Kleeman, M. J. (2015). Associations of Mortality with Long-Term Exposures to Fine and Ultrafine Particles, Species and Sources: Results from the California Teachers Study Cohort. *Environmental Health Perspectives*. http://doi.org/10.1289/ehp.1408565

Peters, A., Dockery, D. W., Muller, J. E., & Mittleman, M. A. (2001). Increased Particulate Air Pollution and the Triggering of Myocardial Infarction. *Circulation*, *103*(23), 2810–2815. http://doi.org/10.1161/01.CIR.103.23.2810

Pope, C. A., Thun, M. J., Namboodiri, M. M., Dockery, D. W., Evans, J. S., Speizer, F. E., & Heath, C. W. (1995). Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults. *American Journal of Respiratory and Critical Care Medicine*, *151*(3_pt_1), 669–674. http://doi.org/10.1164/ajrccm/151.3_Pt_1.669

Pope III, C. A., Verrier, R. L., Lovett, E. G., Larson, A. C., Raizenne, M. E., Kanner, R. E., … Dockery, D. W. (1999). Heart rate variability associated with particulate air pollution. *American Heart Journal*, *138*(5), 890–899. http://doi.org/10.1016/S0002-8703(99)70014-1

Power, M. C., Weisskopf, M. G., Alexeeff, S. E., Coull, B. A., Spiro, A., & Schwartz, J. (2011). Traffic-Related Air Pollution and Cognitive Function in a Cohort of Older Men. *Environmental Health Perspectives*, *119*(5), 682–687. http://doi.org/10.1289/ehp.1002767

Rissler, J., Swietlicki, E., Bengtsson, A., Boman, C., Pagels, J., Sandström, T., … Löndahl, J. (2012). Experimental determination of deposition of diesel exhaust particles in the human respiratory tract. *Journal of Aerosol Science*, *48*, 18–33. http://doi.org/10.1016/j.jaerosci.2012.01.005

Schwartz, J., & Morris, R. (1995). Air Pollution and Hospital Admissions for Cardiovascular Disease in Detroit, Michigan. *American Journal of Epidemiology*, *142*(1), 23–35.

Shukla, A., Timblin, C., BeruBe, K., Gordon, T., McKinney, W., Driscoll, K., … Mossman, B. T. (2000). Inhaled Particulate Matter Causes Expression of Nuclear Factor (NF)- κ B–Related Genes and Oxidant-Dependent NF- κ B Activation *In Vitro*. *American Journal of Respiratory Cell and Molecular Biology*, *23*(2), 182–187. http://doi.org/10.1165/ajrcmb.23.2.4035

Stoeger, T., Reinhard, C., Takenaka, S., Schroeppel, A., Karg, E., Ritter, B., … Schulz, H. (2006). Instillation of six different ultrafine carbon particles indicates a surface area threshold dose for acute lung inflammation in mice. *Environmental Health Perspectives*, *114*(3), 328–333.

Sun, Q., Wang, A., Jin, X., Natanzon, A., Duquaine, D., Brook, R. D., … Rajagopalan, S. (2005). Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA*, *294*(23), 3003–3010. http://doi.org/10.1001/jama.294.23.3003

US EPA. (2009). *Metabolically derived human ventilation rates: a revised approach based upon oxygen consumption rates* (DOCUMENT No. EPA/600/R-06/129F). National Center for Environmental Assessment. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=202543

US EPA, O. (2014). Near Roadway Air Pollution and Health [Overviews & Factsheets]. Retrieved April 21, 2015, from http://www.epa.gov/otaq/nearroadway.htm

Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, & Grodstein F. (2012). Exposure to particulate air pollution and cognitive decline in older women. *Archives of Internal Medicine*, *172*(3), 219–227. http://doi.org/10.1001/archinternmed.2011.683

Zhu, Y., Pudota, J., Collins, D., Allen, D., Clements, A., DenBleyker, A., … Michel, E. (2009). Air pollutant concentrations near three Texas roadways, Part I: Ultrafine particles. *Atmospheric Environment*, *43*(30), 4513–4522. http://doi.org/10.1016/j.atmosenv.2009.04.018

Chapter 2. Methods

Study Population

The Boston Puerto Rican Health Study (BPRHS) is a prospective cohort study designed to investigate the risk factors for allostatic load and cardiovascular disease (CVD) among Puerto Rican adults living in eastern Massachusetts. The methods have been described in detail elsewhere (Katherine L. Tucker et al., 2010). Briefly, participants were recruited through door-to-door enumeration and through community approaches from census tracts in eastern Massachusetts with at least 10 Hispanics ages 45 to 75 years. Individuals were eligible for inclusion in the BPRHS if they were between the ages of 45 and 75 at baseline, they were able to answer questions in English or Spanish, and they self-identified as being of Puerto Rican descent. Only one participant per household was included. Participants were excluded if they had plans to move away from the study area within two years or if they had low cognitive function as measured by the Mini-Mental State Examination (MMSE, scores ≤ 10). The analyses presented in this thesis were further restricted to participants in the BPRHS who lived within 1000 m of our established air pollution monitoring route in Boston at any of the three study visits (n = 809), outside of the 1000 m buffer but within the area bounded by the monitoring route (n = 1 at study visit two), or at a Boston residence at which indoor and outdoor PNC measurements were taken (n = 2 at study visits one and two, n = 1 at study visit three). A map of the Boston monitoring routes, fixed site monitors, and participant residential locations at baseline is given in Figure 2.1.

This study was approved by the Institutional Review Boards at Tufts Medical Center, Northeastern University, and the University of Massachusetts Lowell. All participants provided written informed consent.

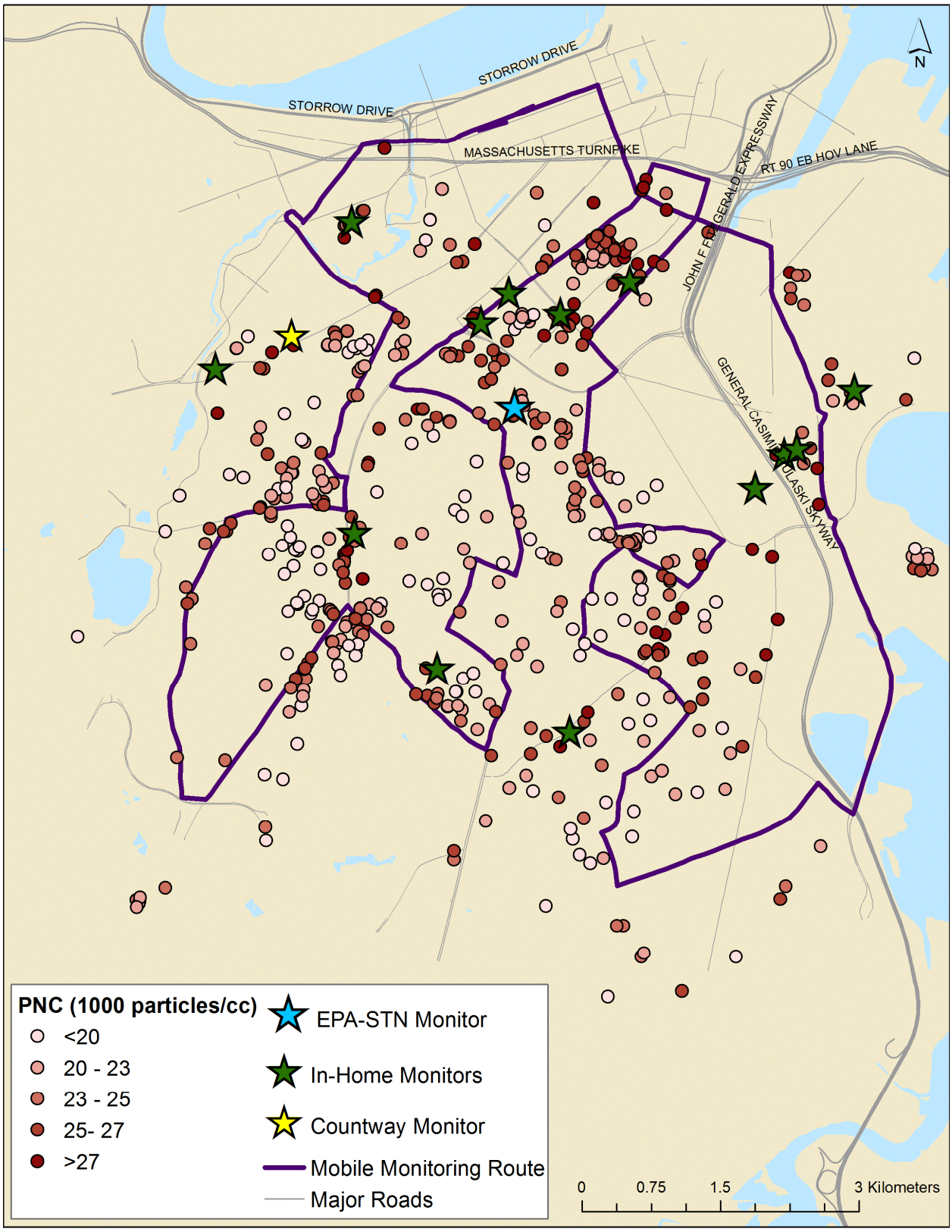

Figure 2.1 Baseline residences of participants, spatial distribution of annual average PNC (by quintiles of exposure at the first study visit), and monitoring locations

Health Data

Participants included in this analysis attended up to three study visits over approximately five years. Baseline visits occurred between 2004 and 2009 (n = 781). The second study visits occurred between 2006 and 2011 (n = 605, mean time between visit one and visit two = 2.2 years). The third study visits occurred between 2009 and 2013 (n = 401, mean time between visit two and visit three = 4.1 years). Study visits were completed in participants' homes. At each study visit, trained Spanish-English bilingual interviewers administered questionnaires asking participants about demographics, psycho-social stressors, health behaviors, and health history. Some variables were only assessed at baseline (educational attainment, current employment status) while other variables were only assessed at the third study visit (family history of various health conditions, exposure to secondhand smoke).

Based on survey responses, several variables were derived. Participants who reported completion of any education above eighth grade were considered to have high educational attainment and participants who reported fewer years of education were considered to have low educational attainment. Smoker status was assessed as current, former, and never smokers. Participants who reported that they had smoked fewer than 100 cigarettes in their life were considered never smokers. Poverty status was determined by comparing participants' total self-reported annual household income to the thresholds released annually by the U.S. Census Bureau (US Census Bureau, 2015). Medication use for various conditions was assessed by asking participants to show the interviewer all of the prescription and over-the-counter medication they currently use.

Validated scales were used to assess physical activity, psychological acculturation, perceived stress, and depression. Physical activity was assessed using a modified Paffenbarger

questionnaire of the Harvard Alumni Activity Survey which has been tested previously in an elderly Puerto Rican population (Paffenbarger et al., 1993; Paffenbarger, Wing, & Hyde, 1978; K. L. Tucker, Bermudez, & Castaneda, 2000). The physical activity scores were given on a scale of 24 to 120 where a score of 24 would suggest that the participant slept or reclined for 24 hours per day while a score of 120 would suggest that a participant engaged in vigorous physical activity for 24 hours per day. Psychological acculturation was determined using a validated scale that addressed participants' psychological attachment to Puerto Rican culture and to mainland U.S. culture (Tropp, Erkut, Coll, Alarcón, & Vázquez García, 1999). To assess participants' stress levels, the Perceived Stress Scale was used. This scale has been tested in other Spanish-speaking populations (Cohen, Kamarck, & Mermelstein, 1983; Ramírez & Hernández, 2007). Participants were considered depressed if they reported taking medications for depression or if they scored at least a 16 on the Center for Epidemiology Studies Depression Scale. This scale has shown good reliability with Hispanic populations, including Puerto Ricans (Mościcki, Locke, Rae, & Boyd, 1989; K. L. Tucker, Falcon, Bianchi, Cacho, & Bermudez, 2000).

The interviewers also assessed anthropometric and blood pressure values at each study visit. Standing height (SECA 214 Portable Stadiometer) and weight (Toledo Weight Plate, Model I5S, Bay State and Systems Inc. Burlington, MA) were measured in duplicate. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an electronic sphygmomanometer (Dinamap^{TM} Model 8260, Critikon, Tampa, FL) in duplicate at three time points during the study visit. The second and third set of blood pressure readings were averaged. Participants were considered hypertensive if they had a SBP of at least 140 mmHg, a DBP of at least 90 mmHg, if they self-reported a diagnosis of hypertension, or if they were taking

medication for hypertension. Pulse pressure (PP) was calculated as the difference between SBP and DBP.

A certified phlebotomist came to the participants' homes to obtain a fasting blood sample. These visits generally occurred the morning after the main study visit. High sensitivity C-reactive protein (CRP) was measured with the Immulite 1000 High Sensitive CRP Kit (LKCRP1) on the Immulite 1000 (Seimens Medical Solutions Diagnostics, Los Angeles, CA). CRP values were natural log transformed due to the skewed distribution. Only CRP values under 51 mg/L were included in the analysis (representing 99% of the measurements) because extreme values may have been more likely to represent acute infections (Clyne & Olshaker, 1999). Cholesterol and triglyceride concentrations were assessed using the Olympus AU400e with Olympus Cholesterol Reagents (OSR6116, OSR6195, and OSR6133, Olympus America Inc., Melville, NY). Triglyceride concentrations were natural log transformed due to the highly right skewed distribution. Serum glucose was also measured using the Olympus AU400e with Olympus Glucose Reagents (OSCR6121, Olympus America Inc., Melville, NY). Participants were considered diabetic if their glucose concentration was at least 126 mg/dL, if they were taking medications for diabetes, or if they self-reported diabetes.

Cognitive Measures

We used the MMSE to assess cognitive function and cognitive decline. The MMSE was developed as a bedside screening tool to assess cognitive impairment and dementia (Folstein, Folstein, & McHugh, 1975). Specifically, the MMSE assesses global cognitive function by considering aspects of orientation, attention, memory, and language skills. At each study visit, participants were asked about their location (state, city, part of the city, address, and floor of the

building) and the time (year, month, date, season, day of the week) to assess their orientation. To assess their attention, memory, and language skills, participants were asked to repeat statements, name objects, recall names of objects, count backwards from 100 by 7s (serial 7s), follow simple instructions to complete an action, write a sentence, and copy a simple geometrical figure. Each correct answer earned one point and participants could score between zero and 30 on the MMSE scale. If a participant did not attempt a question, they did not receive a point for that question and their MMSE was still scored out of 30. Nevertheless, since between 23 and 40 percent of participants did not attempt the serial 7s question at each study visit and this one question was worth up to five points, we considered associations between UFP and MMSE scores among only those participants who attempted to answer this question. Additionally, we considered associations between UFP and MMSE scores on a modified 25 point scale for all participants. The 25 point scale excluded scores for the serial 7s question for all participants. As expected, scores on the MMSE and the Modified MMSE were highly correlated (Pearson's correlation coefficient > 0.85 and $p < 0.001$ at each study visit).

Although we did not consider cognitive impairment as a primary outcome, we did consider effect modification by cognitive impairment status. Previous work has shown that cut-offs for cognitive impairment should be based on individuals' educational attainment (Ardila, Ostrosky-Solis, Rosselli, & Gómez, 2000). Therefore, in the BPRHS, participants with less than a high school education were considered cognitively impaired if they scored less than 21 points, participants with a high school degree were considered cognitively impaired if they scored less than 23 points, and participants with at least some college education were considered cognitively impaired if they scored less than 24 points (Ye et al., 2013). Using these thresholds, between 15 and 22 percent of participants in the BPRHS were considered cognitively impaired at each study

visit. Educational attainment (≤ 8th grade/any high school/> high school) and age were included as covariates in all models of cognitive function and cognitive decline. As noted previously, participants with baseline MMSE scores below 11 were excluded from the study.

Geolocation of Participants' Residences

Participants' baseline residential addresses were geocoded using ArcMap version 9.2. XY coordinate pairs for latitude and longitude were assigned using a three-tiered system consisting of parcel matching, street network matching, and manual refinement using Google Earth (Rioux, Gute, Brugge, Peterson, & Parmenter, 2010). For participants who moved between study visits (n = 97 moved before their second study visit, n = 140 moved before their third study visit), residential addresses for study visits two and three were geocoded in ArcMap version 10.1 using Boston parcel data from 2009 obtained from Tufts GIS Resources. The same geocoding protocol was followed for participants who moved as had been used for geocoding the baseline addresses. The only exception was that addresses which could not be successfully parcel matched with a match score of 100 out of 100 were then geocoded using Google Earth. If there was ambiguity about the residential location within a parcel, as was the case for approximately 14 percent of participants who lived in large housing complexes or where Street View was not available, publically accessible site maps of housing developments were used to verify the locations of participants' residences. If we could not find site maps, we positioned participants at the centroid of the parcel. We were able to geocode 97% of participants' residential locations at their second study visit (41% of whom matched automatically) and 96% of participants' residential locations at their third study visit (38% of whom matched automatically). A randomly selected subset of 12% of the geocoded locations for participants who moved (n = 12 for visit two, n = 18 for visit

three) were independently checked by a second person. All addresses were geocoded to the same parcel and the mean difference in position between the two independently chosen locations was less than 10 m.

PNC Monitoring

Mobile monitoring was conducted with the Tufts Air Pollution Monitoring Laboratory (TAPL) along a ~50 km route covering a ~45 km² area in Boston, MA. As described elsewhere, the TAPL is a recreational vehicle retrofitted with rapid-response gas and particle phase instruments (Padró-Martínez et al., 2012). The mobile monitoring route was chosen to capture the spatial distribution of the participants in Boston and to ensure that PNC values were measured both near and far from major roadways (Figure 2.1). Mobile monitoring sessions lasted between three and six hours and were conducted on 49 days between December, 2011 and November, 2013. In each season, monitoring sessions captured representative traffic and meteorological data for most hours of the day on weekday and weekend days. The TAPL was driven on non-highway streets at between five m/s and 10 m/s so that local changes in pollutant concentrations could be measured. A butanol condensation particle counter (CPC 3775, TSI, Shoreview, MN; D_{50} = 4 nm) was used to measure PNC. A Garmin V GPS (manufacturer-specified accuracy = 3 – 5 m) was used as a master clock to match instrument times so that spatial coordinates could be assigned. The quality control protocols have been described previously (Fuller et al., 2013; Patton et al., 2014). In addition to the mobile monitoring data, the temporal variation in ambient PNC was monitored at the EPA Speciation Trends Network (EPA-STN) site between November, 2011 and November, 2013 (Figure 2.1). Measurements were taken each minute and aggregated at the hourly level (TSI Model 3783 CPC). Data with

instrument errors flagged automatically by the condensation particle counter were removed before data processing.

Exposure Assessment

Each participant was assigned a residential annual average PNC value corresponding to the 365 days prior to each of their study visits. We chose to use annual averages instead of a cumulative exposure measure because participants were in the study for varying lengths of time and the annual averages allowed for a consideration of both cross-sectional and longitudinal relationships. The PNC exposure values were modeled in R using the PNC data. Specifically, an hourly temporal model for PNC variability was developed using the EPA-STN PNC measurements. Covariates in the temporal model included temperature, relative humidity, atmospheric pressure, wind speed, wind direction, day of the week, and rush hour periods. The meteorological and weather data were measured at Logan Airport in Boston. These data were obtained from the National Oceanic and Atmospheric Administration's National Climatic Data Center (National Climatic Data Center, 2015). Modeled PNC estimates were generated from this temporal model for all times during which we also had PNC measurements from mobile monitoring. The differences between the temporally modeled and measured PNC values were then adjusted for spatial variability (20 m resolution) in PNC across the study area using a spatial model for PNC. The spatial model was developed using the measurements obtained from mobile monitoring. Spatial covariates included the distance participants lived from interstate highways, the distance they lived from roads with more than 10,000 vehicles per day (excluding interstates), and the distance they lived from bus routes (Simon, 2015). The distances were

calculated separately for each study visit to account for changes in participants' residential locations. All distance variables were calculated in ArcGIS version 10.1.

Inhalation Adjustment

To more closely approximate participants' uptake dose of particulate matter, we multiplied the annual average PNC estimates (in particles/L) by the hourly respiratory volume (tidal volume * breaths/hour = L of air inhaled/hr) estimates to obtain the average particle inhalation rate (PIR, number of particles inhaled/hr) for each participant. Respiratory volume was estimated using published estimates of sex, age, and physical activity level adjusted ventilation rates (US EPA, 2009) together with data on how many hours per typical weekday and per typical weekend day the BPRHS participants engaged in various levels of physical activity (lying down, sitting, light activity, moderate activity, and vigorous activity). For more details, see Supplement 2.1.

Statistical Analysis

The six primary outcomes considered in this analysis were SBP, DBP, PP, ln(CRP), MMSE scores, and Modified MMSE scores. For each of these outcomes, we developed separate multilevel linear models to consider the potential effect of PNC on the levels of the outcomes over time (PNC/multiple cross-sectional) and to consider the potential effect of PNC on the change in the levels of the outcome over time (PNC/change). For the cognitive analyses, the multiple cross-sectional models were used to assess cognitive function while the change models were used to assess cognitive decline. Additionally, we constructed multilevel linear models to consider the effect of PIR on the levels of the outcomes over time (PIR/multiple cross-sectional)

and to consider the potential effect of PIR on the change in the levels of the outcome over time (PIR/change). All models included random intercepts for each participant. We chose age as the metric for time because it allowed the models to handle the varying frequency and number of study visits between participants (Singer, 2003). Models for change included the baseline level of the outcome variable in the model. All modeling was done in Stata version 13 (StataCorp, 2013).

Other covariates were chosen in a multi-stage process. We chose the initial set of potential covariates based on a literature review of factors that could affect cardiovascular and cognitive outcomes. We then considered the bivariate association between each of these potential covariates in relation to each of the outcomes and in relation to the air pollution exposure measures (PNC and PIR). Then, we built simple models predicting each of the cardiovascular and cognitive outcomes with the air pollution exposure measure and with one other potential covariate. If a variable was 1) associated with the outcome ($p < 0.15$) and 2) was either associated with the air pollution measure ($p < 0.15$) or if it changed the effect estimate for the air pollution measure by at least 10 percent, the variable was considered in the main model. Variables that were not associated with the outcomes ($p < 0.15$) in the multivariate models were dropped. Finally, we assessed the effect of variables that had not been identified initially as confounders in the bivariate analyses but were considered potentially important based on the literature. If these variables were not associated with the outcome ($p < 0.15$) and did not materially change the effect estimates for PNC or PIR, they were left out of the final models. For each of the models, we checked the intra-class correlations to assess the between subject variation in comparison to the within subject variation. We also checked the normality and homoscedasticity of the residual errors in each model.

In the case of highly collinear variables (Pearson's correlation coefficient > 0.40, $p < 0.05$), only the variable that was considered to be a stronger confounder based on its influence on the effect estimates for PNC or the PIR was included in the model. Additionally, we excluded physical activity from the models with the PIR since inhalation rate was dependent on physical activity and physical activity was highly collinear with the PIR (Pearson's correlation coefficient = 0.708, $p < 0.001$). While we also excluded sex from the main PIR models since the PIR was sex-dependent, we conducted sensitivity analyses to determine the effect of including sex. We allowed BMI to be retained in the main models since BMI reflects a different physiological parameter than weight alone. However, sensitivity analyses excluding BMI were also considered.

In addition to the primary models, we wanted to determine whether effect modification was present. For the cardiovascular outcomes, we conducted stratified analyses by sex, hypertension medication use (or cardiovascular medication use for ln(CRP)), family history of hypertension (or CVD for ln(CRP)), diabetes, statin medication use, smoking, and employment status at baseline. We also conducted a sensitivity analysis excluding the 89 participants who self-reported at least one previous heart attack or stroke at their baseline study visit. For the cognitive outcomes, we conducted stratified analyses by sex, cognitive impairment status, baseline age (< 65/≥ 65 years of age), depression, baseline employment status, smoking, hypertension medication use, family history of diabetes, diabetes, physical activity level tertile, and BMI (between 18.5 and 25 kg/m²/≥ 30 kg/m²). We also conducted sensitivity analyses excluding the participants who self-reported at least one previous heart attack or stroke at their baseline study visit and excluding the 368 participants who had low educational attainment.

Due to attrition and resulting concerns about potential selection bias, several measures were taken. First, variables that were only assessed at the third study visit, such as secondhand

smoke exposure, family history of hypertension, and family history of CVD, were not included in the primary models because this would have cut the sample size approximately in half. If these variables were identified as potentially important confounders, however, the effect of these variables was assessed by adding them back to the final models. Second, we considered whether demographic and health characteristics differed between participants who completed the study compared to participants who dropped out after either the first or second study visits. Additionally, we conducted a sensitivity analysis excluding the 51 participants who died before they completed their third study visit.

Although the covariates for the 24 primary models (PNC/multiple cross-sectional, PIR/multiple cross-sectional, PNC/change, PIR/change for each of the outcomes - SBP, DBP, PP, ln(CRP)), MMSE, and Modified MMSE) were chosen independently since each model reflected a different substantive question, we also sought to directly compare the effect estimates for PNC and the effect estimates for PIR. Therefore, we constructed secondary models with the same set of covariates for the parallel models for each outcome (e.g. PNC/multiple cross-sectional and PIR/multiple cross-sectional or PNC/change and PIR/change). If sex or physical activity were included as covariates in the PNC models, the parallel PIR models were built without these covariates. Additionally, to facilitate direct comparisons between the models with PNC and with the PIR, we scaled all results to the inter-quartile range of 4.6 thousand particles/cm^3 and 6.1 billion particles inhaled/hour for PNC and PIR, respectively.

Supplement 2.1 Inhalation rate adjustment

The published estimates for age and sex-specific minute respiratory volume (reported as L of oxygen inhaled/min-kg) adjusted for weight and physical activity level were developed using two national data sets (US EPA, 2009). We used the age and sex-specific values as coefficients in the algorithm to calculate the average number of particles inhaled per hour. As an example, for a male participant in his 50s, the algorithm for the average number of particles inhaled hourly would be:

Step 1. Average number of liters of air breathed in hourly =
[(5 week days * body weight in kg * 60 minutes per hour)
*(0.07*number of hours sleeping or lying down during a weekday
+ 0.07*number of sedentary hours during a weekday
+ 0.17*number of hours engaging in light physical activity during a weekday
+ 0.38*number of hours engaging in moderate physical activity during a weekday
+ 0.68*number of hours engaging in vigorous physical activity during a weekday)
+ (2 weekend days * body weight in kg * 60 minutes per hour)
*(0.07*number of hours sleeping or lying down during a weekend day
+ 0.07*number of sedentary hours during a weekend day
+ 0.17*number of hours engaging in light physical activity during a weekend day
+ 0.38*number of hours engaging in moderate physical activity during a weekend day +
0.68*number of hours engaging in vigorous physical activity during a weekend day)]
/(7 days of the week * 24 hours)

Step 2. Average number of particles inhaled hourly (PIR) = PNC (particles/ cm^3) * 1000 (cm^3/L) * average number of liters of air breathed in hourly.

Works Cited

Ardila, A., Ostrosky-Solis, F., Rosselli, M., & Gómez, C. (2000). Age-Related Cognitive Decline During Normal Aging: The Complex Effect of Education. *Archives of Clinical Neuropsychology*, *15*(6), 495–513. http://doi.org/10.1016/S0887-6177(99)00040-2

Clyne, B., & Olshaker, J. S. (1999). The C-reactive protein1. *The Journal of Emergency Medicine*, *17*(6), 1019–1025. http://doi.org/10.1016/S0736-4679(99)00135-3

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A Global Measure of Perceived Stress. *Journal of Health and Social Behavior*, *24*(4), 385. http://doi.org/10.2307/2136404

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. http://doi.org/10.1016/0022-3956(75)90026-6

Fuller, C. H., Brugge, D., Williams, P. L., Mittleman, M. A., Lane, K., Durant, J. L., & Spengler, J. D. (2013). Indoor and outdoor measurements of particle number concentration in near-highway homes. *Journal of Exposure Science and Environmental Epidemiology*, *23*(5), 506–512. http://doi.org/10.1038/jes.2012.116

Mościcki, E. K., Locke, B. Z., Rae, D. S., & Boyd, J. H. (1989). Depressive symptoms among Mexican Americans: the Hispanic Health and Nutrition Examination Survey. *American Journal of Epidemiology*, *130*(2), 348–360.

National Climatic Data Center. (2015). Land-Based Station Data. Retrieved March 16, 2015, from http://www.ncdc.noaa.gov/data-access/land-based-station-data

Padró-Martínez, L. T., Patton, A. P., Trull, J. B., Zamore, W., Brugge, D., & Durant, J. L. (2012). Mobile monitoring of particle number concentration and other traffic-related air pollutants in a near-highway neighborhood over the course of a year. *Atmospheric Environment*, *61*, 253–264. http://doi.org/10.1016/j.atmosenv.2012.06.088

Paffenbarger, R. S., Hyde, R. T., Wing, A. L., Lee, I. M., Jung, D. L., & Kampert, J. B. (1993). The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *The New England Journal of Medicine*, *328*(8), 538–545. http://doi.org/10.1056/NEJM199302253280804

Paffenbarger, R. S., Wing, A. L., & Hyde, R. T. (1978). Physical activity as an index of heart attack risk in college alumni. *American Journal of Epidemiology*, *108*(3), 161–175.

Patton, A. P., Collins, C., Naumova, E. N., Zamore, W., Brugge, D., & Durant, J. L. (2014). An Hourly Regression Model for Ultrafine Particles in a Near-Highway Urban Area. *Environmental Science & Technology*, *48*(6), 3272–3280. http://doi.org/10.1021/es404838k

Ramírez, M. T. G., & Hernández, R. L. (2007). Factor structure of the Perceived Stress Scale (PSS) in a sample from Mexico. *The Spanish Journal of Psychology*, *10*(1), 199–206.

Rioux, C. L., Gute, D. M., Brugge, D., Peterson, S., & Parmenter, B. (2010). Characterizing Urban Traffic Exposures Using Transportation Planning Tools: An Illustrated Methodology for Health Researchers. *Journal of Urban Health : Bulletin of the New York Academy of Medicine*, *87*(2), 167–188. http://doi.org/10.1007/s11524-009-9419-7

Simon, M. (2015, March 23). use of countway data in the PNC model?

Singer, J. D. (2003). *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence* (1 edition). Oxford ; New York: Oxford University Press.

StataCorp. (2013). *Stata Statistical Software: Release 13.* College Station, Tx: StataCorp LP.

Tropp, L. R., Erkut, S., Coll, C. G., Alarcón, O., & Vázquez García, H. A. (1999). Psychological Acculturation: Development of a New Measure for Puerto Ricans on the U.S. Mainland. *Educational and Psychological Measurement*, *59*(2), 351–367. http://doi.org/10.1177/00131649921969794

Tucker, K. L., Bermudez, O. I., & Castaneda, C. (2000). Type 2 diabetes is prevalent and poorly controlled among Hispanic elders of Caribbean origin. *American Journal of Public Health*, *90*(8), 1288–1293.

Tucker, K. L., Falcon, L. M., Bianchi, L. A., Cacho, E., & Bermudez, O. I. (2000). Self-reported prevalence and health correlates of functional limitation among Massachusetts elderly Puerto Ricans, Dominicans, and non-Hispanic white neighborhood comparison group. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *55*(2), M90–97.

Tucker, K. L., Mattei, J., Noel, S. E., Collado, B. M., Mendez, J., Nelson, J., … Falcon, L. M. (2010). The Boston Puerto Rican Health Study, a longitudinal cohort study on health disparities in Puerto Rican adults: challenges and opportunities. *BMC Public Health*, *10*(1), 107. http://doi.org/10.1186/1471-2458-10-107

US Census Bureau, D. I. S. (2015). US Census Bureau Poverty main page. Retrieved March 15, 2015, from http://www.census.gov/hhes/www/poverty/data/threshld/

US EPA. (2009). *Metabolically derived human ventilation rates: a revised approach based upon oxygen consumption rates* (DOCUMENT No. EPA/600/R-06/129F). National Center for Environmental Assessment. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=202543

Ye, X., Scott, T., Gao, X., Maras, J. E., Bakun, P. J., & Tucker, K. L. (2013). Mediterranean diet, healthy eating index 2005, and cognitive function in middle-aged and older Puerto Rican adults. *Journal of the Academy of Nutrition and Dietetics*, *113*(2), 276–281.e1–3. http://doi.org/10.1016/j.jand.2012.10.014

Chapter 3. Associations between exposure to ultrafine particulate matter and changes in biomarkers of cardiovascular disease over five years

Introduction

Exposure to high levels of particulate matter (PM) pollution is associated with an increased risk of cardiovascular morbidity, cardiovascular mortality, and all-cause mortality (Dockery et al., 1993; Pope et al., 1995; Schwartz & Morris, 1995; Pope III et al., 1999; Peters et al., 2001; Künzli et al., 2005). In fact, the most recent Global Burden of Disease study estimated that over 3.2 million deaths each year are attributable to ambient air pollution (Lim et al., 2012). Exposure to high concentrations of PM over many months or years may pose particularly important cardiovascular morbidity and mortality risks (Miller et al., 2007; Beelen et al., 2008; Puett et al., 2009; Gan et al., 2011; Crouse et al., 2012). For example, the European Study of Cohorts for Air Pollution Effects (ESCAPE), one of the largest investigations into the association between long-term exposure to PM and all-cause mortality, found that an increase of five $\mu g/m^3$ in ambient average fine particulate matter ($PM_{2.5}$, particles of less than 2.5 µm aerodynamic diameter) concentration was associated with a two to 13 percent increase in an individuals' likelihood of death over an average of 13.9 years of follow-up (Beelen et al., 2014). In an analysis of a sub-sample from this population, long-term average exposure concentrations of both $PM_{2.5}$ and coarse particulate matter (PM_{10}, particles of less than 10 µm aerodynamic diameter) were associated with incident coronary events (Cesaroni et al., 2014).

In addition to the clear associations between exposure to PM pollution and cardiovascular morbidity and mortality, PM exposure has been associated with cardiovascular disease (CVD) risk factors, such as increased blood pressure and increased concentrations of biomarkers of systemic inflammation. One cross-sectional study with nearly 4300 participants between 45 and 75 years of age found significant positive associations between the residential annual average

$PM_{2.5}$ and PM_{10} concentration with blood pressure, even after adjusting for daily temperature and exposure to traffic-related noise (Fuks et al., 2011). Another cross-sectional study using data from over 130,000 adults participating in the National Health Interview Survey found that each 10 µg/m³ increase in annual average exposure to $PM_{2.5}$ was significantly associated with a five percent increase in the likelihood of having self-reported hypertension (Johnson & Parker, 2009).

The relationship between air pollution and blood pressure has also been considered in a number of longitudinal studies. The Black Women's Health Study featured the first analysis that examined the risk of incident hypertension in relation to air pollution exposure. The researchers found that each 10 µg/m³ increase in $PM_{2.5}$ exposure was associated with a 48 percent increase in the incidence of hypertension after 10 years (95% CI = 0.95 – 2.31). Furthermore, there was a significant association between nitrogen oxides (NO_x, a traffic-related air pollutant) and hypertension even after controlling for $PM_{2.5}$ exposure (Coogan et al., 2012). In contrast, a Danish cohort study of over 57,000 adults ages 50-64 found that one and five year average exposure to NO_x was significantly inversely associated with blood pressure levels at baseline and NO_x exposure was not associated with incident hypertension over five years (Sorensen et al., 2012). Furthermore, traffic-related air pollutants, including $PM_{2.5}$ and PM_{10}, were not significantly associated with blood pressure levels among participants in ESCAPE. However, when the ESCAPE analysis was restricted to participants for whom at least three consecutive blood pressure readings were taken, $PM_{2.5}$ was significantly associated with blood pressure levels among individuals taking medications for hypertension (Fuks et al., 2014).

The literature on long-term associations between $PM_{2.5}$ and PM_{10} with biomarkers of systemic inflammation is somewhat less well developed. A Taiwanese study found significant associations between one-year average PM exposure with both blood pressure levels and

interleukin-6 (a cytokine associated with inflammation) concentrations (Chuang, Yan, Chiu, & Cheng, 2010). Other studies have found associations between long term exposure to traffic-related pollutants and C-reactive protein (CRP). For example, in an analysis of baseline data from the German Heinz Nixdorf Recall Study, annual average $PM_{2.5}$ concentrations were significantly associated with increased CRP and fibrinogen levels among men, but not among women (Hoffmann et al., 2009). In a longitudinal analysis from this study, annual average $PM_{2.5}$ concentrations were associated with changes in CRP levels among all participants (Hennig et al., 2014).

Despite the apparent relationship between exposure to PM pollution and cardiovascular outcomes, much less is known about the potential cardiovascular impact of the smallest size fraction of PM. Ultrafine particulate matter (UFP, particles of less than 0.1 µm aerodynamic diameter) may represent the most relevant PM size fraction in terms of cardiovascular toxicity. Compared to the larger size fractions, UFP can penetrate most deeply into the lungs, the particles have greater total surface area with which to interact with epithelial cells potentially inducing oxidative stress responses, and the particles are more likely to cross biological barriers such as the blood-brain barrier (Donaldson et al., 2002; Stoeger et al., 2006; Oberdörster et al., 2004; Kreyling et al., 2006).

The limited epidemiological literature on UFP has predominately focused on acute health effects of exposure. The findings have been inconsistent in terms of the association with blood pressure. One recent study from our team in the Boston area found that exposure to UFP (measured as particle number concentration or PNC), but not black carbon or $PM_{2.5}$, was associated with both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Chung et al., 2015). In another study that measured participants' blood pressure each waking hour for five

consecutive days during two times of the year, there were significant associations between traffic-related pollutants and blood pressure among older adults with a history of coronary artery disease. However, increased PNC was only significantly associated with increased blood pressure among individuals when they had participated in physical activity within the previous hour, possibly due to a mechanism mediated through the autonomic nervous system. In contrast, individuals in this study who were not on statin medication (used predominately to lower cholesterol) had a significant inverse relationship between PNC exposure and both SBP and DBP (R. Delfino et al., 2010). In a third study, researchers similarly found evidence for an inverse association between PNC exposure and acute changes in DBP, although they found a positive association between PNC exposure and acute changes in SBP (Rich et al., 2012). The difference in results obtained in these studies is likely attributable to factors other than differences in protocol or study design. One three-city study with consistent protocols across the cities found null associations among participants in one city, positive associations among participants in a second city, and inverse associations among participants in the third (Ibald-Mulli et al., 2004).

As with the literature regarding the potential association between UFP and blood pressure, there is inconsistent evidence for an association between UFP and acute levels of biomarkers of systemic inflammation. The prospective Normative Aging Study found that weekly average PNC exposure was associated with fibrinogen levels while PNC exposure was not associated with CRP (Zeka, Sullivan, Vokonas, Sparrow, & Schwartz, 2006). Similarly, a prospective cohort study of myocardial infarction survivors found that 24-hour average PNC was not associated with CRP concentration, although it was associated with interleukin-6 concentration (Ruckerl et al., 2007). Other studies, however, have found significant positive associations between PNC exposure averaged over very short time periods and CRP, especially

among older individuals and among overweight or obese participants (Rückerl et al., 2006; Yue et al., 2007; R. J. Delfino et al., 2008; Hertel et al., 2010). It is possible that source composition of the air pollutants or local variability in concentrations is driving the disparate results and that different exposure assessment methods could dramatically affect the results. This may have been the case in another recent analysis from our team in the Boston metropolitan area that found that PNC measured at a central fixed site was associated with levels of several biomarkers of systemic inflammation while PNC measured at a near-highway fixed site was not (Fuller et al., 2015).

The research on the potential health consequences of UFP exposure averaged over longer time frames (months to years) is even more limited than the literature on the acute health effects of exposure. In the cross-sectional Community Assessment of Freeway Exposure and Health Study (CAFEH), our research team found modest associations between PNC averaged over one year and SBP levels, particularly among diabetic participants and among white, non-Hispanic participants (Corlin et al., 2014). Additionally, we found positive associations between PNC and CRP, especially after controlling for the body mass index (BMI), smoking status, and race and nativity of the participants (K. Lane et al., 2015). The only published longitudinal analysis of the chronic health effects of UFP considered UFP mass modeled on a four by four km grid, rather than near-roadway PNC. Researchers followed over 100,000 predominately white, non-Hispanic female teachers in California from 2001 through 2007 and found that UFP mass concentration was significantly associated with ischemic heart disease mortality (hazard ratio = 1.10, 95% CI = 1.02 – 1.18) but that UFP mass was not significantly associated with all-cause, cardiovascular, or pulmonary mortality (Ostro et al., 2015).

Due to the paucity of literature on the potential health effects of long-term exposure to UFP, we sought to investigate the relationship between UFP and cardiovascular risk factors in the prospective Boston Puerto Rican Health Study (BPRHS) (Katherine L. Tucker et al., 2010). In this study population, proximity to traffic has been previously associated with changes in CRP levels over two years, particularly among individuals taking insulin for diabetes (Rioux, Tucker, et al., 2010; Rioux, Tucker, Brugge, Gute, & Mwamburi, 2011). To build on this work, we wanted to assess 1) whether ambient annual UFP concentrations were associated with blood pressure and CRP levels over five years and 2) whether ambient annual UFP concentrations were associated with changes in blood pressure and CRP levels over five years.

In addition, we sought to compare the traditional approach of assigning average exposure concentrations to a novel and exploratory method that may more closely approximate the biologically relevant dose of UFP. Specifically, since the amount of UFP that can exert a biological effect should be directly related to the dose of inspired pollutant (Borm, Schins, & Albrecht, 2004; Bigazzi & Figliozzi, 2014), we adjusted the ambient annual average exposure concentrations by a factor representing each individual's respiratory volume to obtain the average hourly particle inhalation rate (PIR). Since the PIR represents a different type of exposure metric than PNC, we wanted to directly compare the strength of association between the two exposure metrics with the cardiovascular risk factors to gain a fuller understanding of the potential health effects of UFP.

Results

Demographic and health characteristics of the participants at each study visit are summarized in Table 3.1. The majority of participants were female (69.0%) and 52.9% of the participants had attained more than an eighth grade level of education. At each study visit, over 70 percent of participants reported a total household income under 120 percent of the federal poverty line. Although the mean age at baseline was 57.0 (standard deviation (SD) = 7.4), over 11 percent of participants had already suffered at least one heart attack or stroke, nearly three-quarters were hypertensive, almost half were diabetic, and two-thirds were depressed. The mean physical activity score at baseline was 31.8 (SD = 4.7), the mean at visit two was 31.3 (SD = 4.5), and the mean at visit three was 31.8 (SD = 6.2). Compared to the baseline visit, participants' mean perceived stress scores and participants' mean HDL cholesterol levels increased significantly by the third study visit ($p < 0.001$ for each). Additionally, by the third study visit, more participants had hypertension ($p < 0.001$), more had suffered a heart attack or stroke ($p = 0.008$), more had diabetes ($p = 0.036$), more were taking medications for hypertension ($p < 0.001$), more were taking medications for CVD ($p < 0.001$), and more were taking statin medications ($p < 0.001$). At baseline, the mean SBP was 134 mmHg, the mean DBP was 81 mmHg, the mean PP was 54 mmHg, and the mean CRP concentration was 5.9 mg/L.

The participants included in the present analysis were representative of the larger BPRHS population (n = 1499) in terms of demographic and health characteristics. At baseline, there were no statistically significant differences in mean age ($t = 0.11$, $p = 0.913$), BMI ($t = 0.76$, $p = 0.446$), SBP ($t = 1.08$, $p = 0.280$), DBP ($t = 0.41$, $p = 0.685$), or ln(CRP) ($t = 0.08$, $p = 0.935$). There were also no statistically significant differences in the proportion of females ($z = 1.38$, $p = 0.167$), people with low educational attainment ($z = 0.73$, $p = 0.46$), or people who lived below

120 percent of the federal poverty line ($z = -0.81$, $p = 0.418$). At the second and third study visits, demographic and health characteristics were also similar between the sub-set of participants represented in this analysis and those participants in the parent study.

Table 3.1. Characteristics of the participants by study visit

	Study Visit One (2004 - 2009)			Study Visit Two (2006 - 2011)			Study Visit Three (2009 - 2013)		
	N	mean	95%CI	N	mean	95%CI	N	mean	95%CI
Primary cardiovascular risk factors									
SBP (mmHg)	758	134.4	(133.1 - 135.7)	600	136.8	(135.3 - 138.3)	385	135.2	(133.3 - 137.1)
DBP (mmHg)	757	80.8	(80.0 - 81.6)	600	80.4	(79.6 - 81.3)	385	75.3	(74.3 - 76.3)
Pulse pressure (mmHg)	757	53.6	(52.5 - 54.6)	600	56.4	(55.1 -57.7)	385	59.9	(58.2 - 61.5)
ln(CRP mg/L)	753	1.2	(1.1 - 1.3)	576	1.1	(1.0 - 1.2)	220	1.4	(1.2 - 1.5)
Demographics and Health Biomarkers									
Age	781	57.0	(56.5 - 57.6)	605	59.2	(58.6 - 59.7)	401	63.0	(62.3 - 63.8)
BMI (kg/m²)	774	31.7	(31.3 - 32.2)	585	31.6	(31.1 - 32.1)	358	31.1	(30.5 - 31.8)
Glucose (mg/dL)	755	121.6	(118.0 - 125.2)	577	118.4	(114.3 - 122.5)	356	119.8	(114.1 - 125.5)
HDL (mg/dL)	763	44.3	(43.4 - 45.2)	594	46.5	(45.4 - 47.5)	361	46.7	(45.1 - 48.3)
LDL (mg/dL)	746	107.4	(104.9 - 110.0)	585	109.7	(106.8 - 112.6)	359	105.5	(101.9 - 109.2)
ln(triglycerides mg/dL)	763	5.0	(4.9 - 5.0)	594	4.9	(4.9 - 4.9)	361	4.8	(4.8 - 4.9)
Physical activity score	778	31.8	(31.5 - 32.2)	603	31.3	(31.0 - 31.7)	399	31.8	(31.2 - 32.4)
Perceived stress	778	23.0	(22.3 - 23.7)	603	22.5	(21.7 - 23.2)	394	28.4	(27.7 - 29.1)
Air Pollution Exposure									
Distance from nearest interstate highway (m)	781	1850	(1770 - 1930)	605	1770	(1690 - 1860)	401	1710	(1610 - 1810)
Distance from nearest major road (m)	781	250	(230 - 260)	605	240	(220 - 260)	401	250	(230 - 270)
Inhalation rate (L/hr)	774	580	(560 - 590)	588	560	(540 - 570)	368	580	(550 - 600)
PNC exposure (1000 particles/cc)	781	23.7	(23.4 - 23.9)	605	23.4	(23.1 - 23.6)	401	23.0	(22.7 - 23.4)
Particle inhalation rate (billion particles/hr)	774	13.6	(13.0 - 14.0)	588	13.0	(13.0 - 13.0)	368	13.3	(13.0 - 14.0)
	N	n	%	N	n	%	N	n	%
Demographics									
Female	781	538	68.9	605	428	70.7	399	287	71.9
Smoker status									
Current smoker	779	184	23.6	604	133	22.0	387	74	19.1
Former smoker	779	253	32.5	604	199	33.0	387	145	37.5
Never smoker	779	342	43.9	604	272	45.0	387	168	43.4
Secondhand smoke	NA			NA			381	76	19.9
Educational attainment									
Any education through 8th grade	776	368	47.4	603	289	47.9	397	199	50.1
More than 8th grade	776	408	52.6	603	314	52.1	397	198	49.9
Income <120% federal poverty threshold	733	523	71.4	568	427	75.2	358	277	77.4
Employed	683	147	21.5	NA			NA		
Marital status									
Married	777	252	32.4	603	203	33.7	400	119	29.8
Single	777	111	14.3	603	92	15.3	400	69	17.3
Divorced	777	314	40.4	603	233	38.6	400	143	35.8
Widowed	777	100	12.9	603	75	12.4	400	69	17.3
Health Characteristics									
Previous heart attack or stroke	779	89	11.4	605	95	15.7	398	70	17.6
Cardiovascular medication	778	456	58.6	602	396	65.8	392	291	74.2
Family history CVD	NA			NA			323	228	70.6
Hypertensive (medication, measurements, self-reported diagnosis)	774	558	72.1	600	460	76.7	389	324	83.3
Hypertension medication	778	409	52.6	602	352	58.5	392	271	69.1
Family history hypertension	NA			NA			329	265	80.6
Diabetic (medication, measurements, diagnosis)	761	349	45.9	589	279	47.4	373	201	53.9
Family history diabetes	NA			NA			343	222	64.7
Statins (antilipemic medication)	778	292	37.5	602	283	47.0	392	217	55.4
Depression (medication or CESD ≥ 16)	767	508	66.2	600	376	62.7	393	254	64.6
Anxiety medications	778	153	19.7	602	134	22.3	392	101	25.8
Respiratory medications	778	197	25.3	602	175	29.1	392	122	31.1

Exposure distributions

Among all of the observations included in this analysis, the mean distance participants resided from the nearest interstate highway was nearly 1.80 km (1.85 km at baseline, 1.77 km at visit two, and 1.71 km at visit three). The mean distance participants resided from the nearest road segment with more than 10,000 vehicles per day (excluding interstates) was 0.25 km (0.25 km at baseline, 0.24 km at visit two, and 0.25 km at visit three). The median residential annual average PNC was 24,000 particles/cm³ and this was stable across the time period of the study. The range was 22,000 particles/cm³ (minimum =10000 particles/cm³, maximum = 32,000 particles/cm³) and the inter-quartile range was 4600 particles/cm³. The median PIR was 12.3 billion particles inhaled/hr and this did not change significantly across the time period of the study ($\chi^2 = 2.8$, $p = 0.245$). The range was 50.7 billion particles inhaled/hr (minimum =3.7 billion particles inhaled/hr, maximum = 54.4 billion particles inhaled/hr) and the inter-quartile range was 6.1 billion particles inhaled/hr. Table 3.2 shows the distributions of PNC and PIR overall and Figure 3.1 shows the distributions of PNC and PIR stratified by study visit. The spatial distribution of PNC exposure was shown in Figure 2.1 (see Chapter 2).

Table 3.2. Exposure distributions for PNC and PIR

	PNC (1000 particles/cc) (N = 1788)	PIR (1 billion inhaled/hr) (N = 1730)
Mean	23.4	13.3
Minimum	10.4	3.7
25th percentile	21.3	9.6
Median	24.0	12.3
75th percentile	25.9	15.7
Maximum	32.1	54.4
Range	21.7	50.7
IQR	4.6	6.1

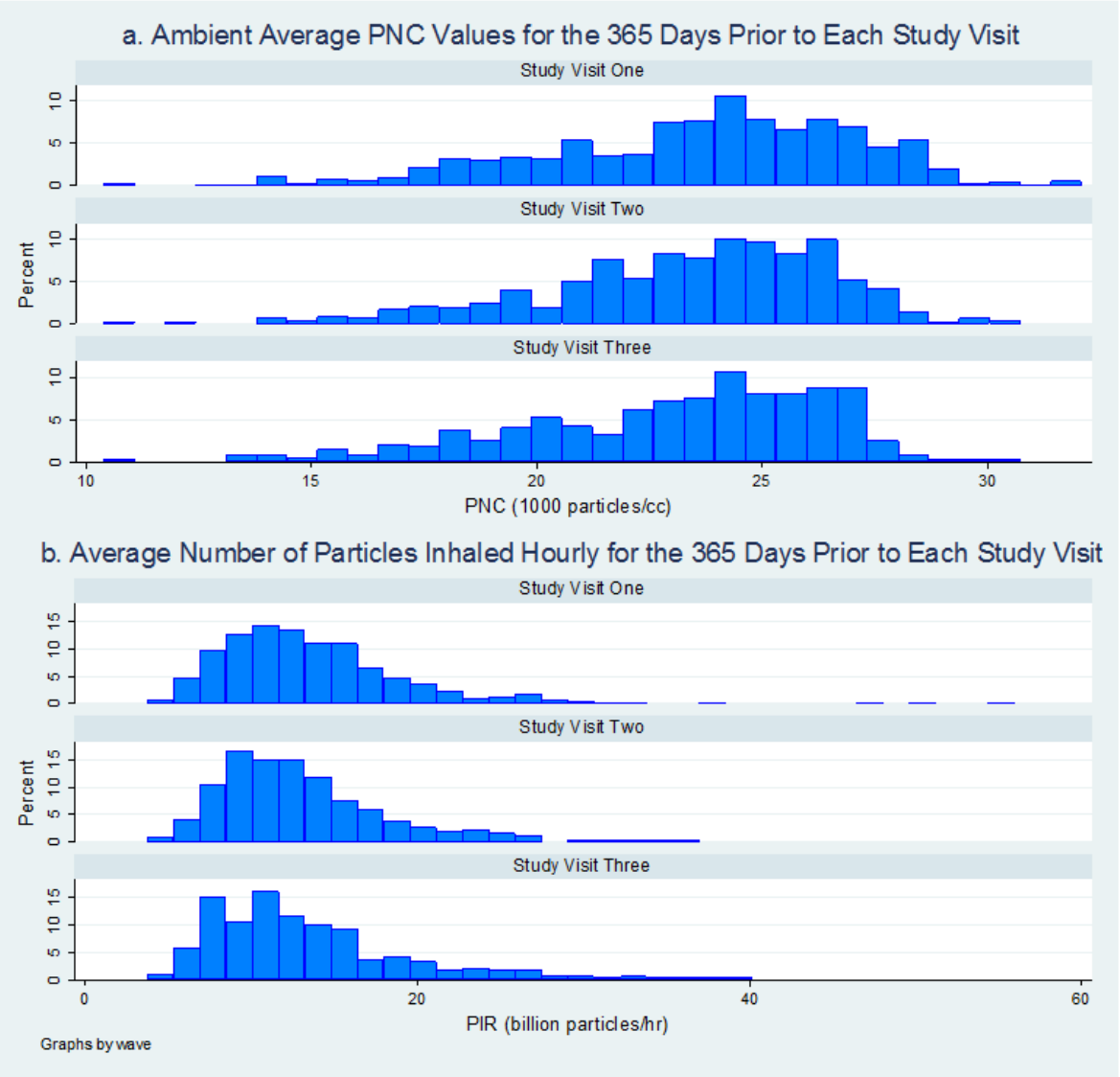

Figure 3.1. Distribution of PNC and PIR by study visit

Of note, while both physical activity and PNC were included in the algorithm to calculate the PIR, physical activity and the PIR were more strongly correlated than were PNC and the PIR (Table 3.3). Additionally, while sex, physical activity levels, and weight were not significant predictors of PNC exposure ($p = 0.565$, 0.518, and 0.358, respectively), all three were significant predictors of the PIR ($p < 0.001$ for each). Age was significantly inversely associated with both PNC and the PIR ($p = 0.001$ and $p < 0.001$, respectively).

Table 3.3 Pearson's correlation coefficients between PNC, PIR, and physical activity

	Study visit one			Study visit two			Study visit three		
		PIR	PNC		PIR	PNC		PIR	PNC
coefficient	PNC	0.342		PNC	0.337		PNC	0.366	
p value		0.000			0.000			0.000	
n		774			588			368	
coefficient	Physical activity	0.696	-0.059	Physical activity	0.685	-0.064	Physical activity	0.755	0.022
p value		0.000	0.098		0.000	0.119		0.000	0.664
n		774	778		588	603		368	399

Associations with CVD risk factors

Overall, PNC was more strongly associated with changes in blood pressure levels while the PIR was more strongly associated with blood pressure levels in the multiple cross-sectional models. While the following sections give greater detail, the primary results for the blood pressure measures are summarized in Figure 3.2.

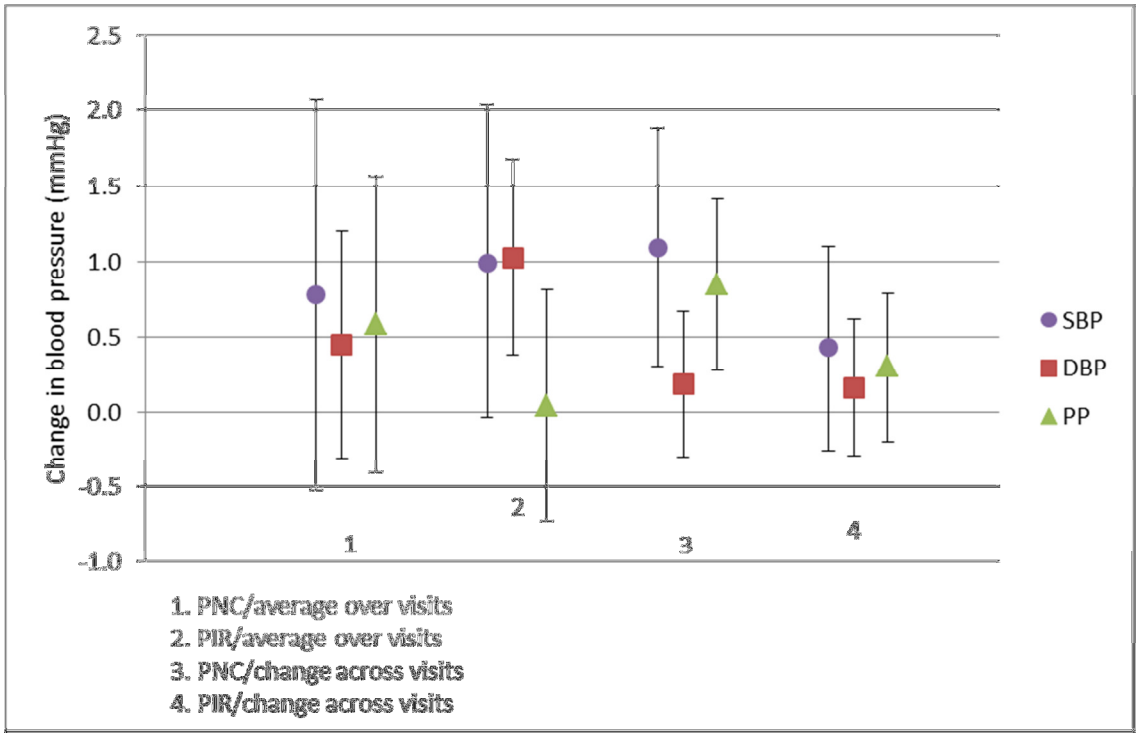

Figure 3.2. Change in blood pressure (mmHg) with an inter-quartile increase in PNC or PIR

Main models adjusted for:

1. SBP (n = 783): age, education, sex, BMI, high-density lipoprotein (HDL) cholesterol, ln(triglycerides), hypertension medication, anxiety medication, year of baseline visit, and marital status;
   DBP (n = 777): age, sex, BMI, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, ln(triglycerides), diabetes, year of baseline visit, and marital status;
   PP (n = 780): age, education, LDL cholesterol, hypertension medication, diabetes, marital status, and smoking
2. SBP (n = 776): age, education, BMI, LDL cholesterol, HDL cholesterol, ln(triglycerides), hypertension medication, anxiety medication, year of baseline visit, and marital status;
   DBP (n = 779): age, BMI, LDL cholesterol, HDL cholesterol, ln(triglycerides), year of baseline visit, marital status, and smoking;
   PP (n = 776): age, education, LDL cholesterol, hypertension medication, diabetes, marital status, and smoking
3. SBP (n = 765): baseline SBP, age, sex, LDL cholesterol, HDL cholesterol, hypertension medication, and year of baseline visit;
   DBP (n = 758): baseline DBP, age, sex, BMI, LDL cholesterol, HDL cholesterol, diabetes, physical activity, and perceived stress;
   PP (n = 769): baseline PP, age, HDL cholesterol, hypertension medication, diabetes, perceived stress, psychological acculturation, and year of baseline visit
4. SBP (n = 759): baseline SBP, age, education, LDL cholesterol, HDL cholesterol, hypertension medication, and year of baseline visit;
   DBP (n = 759): baseline DBP, age, LDL cholesterol, ln(triglycerides), perceived stress, and diabetes;
   PP (n = 765): baseline PP, age, HDL cholesterol, hypertension medication, diabetes, perceived stress, psychological acculturation, and year of baseline visit

Systolic blood pressure

PNC was associated with SBP in a multiple cross-sectional model controlling only for age, although the association was not significant (95% CI for change in SBP with each additional 4600 particles/cm³ = -0.09 mmHg – 2.47 mmHg [Table 3S1.1 in Supplement 3.1]). The association was attenuated after controlling for relevant confounding variables (95% CI for change in SBP with each IQR increase in PNC = -0.52 mmHg – 2.07 mmHg [Figure 3.2]). The effect estimate for PNC was relatively robust to different choices of covariates. However, effect modification was evident by sex. For females, PNC was positively and significantly associated with mean SBP levels (95% CI = 0.09 mmHg – 3.35 mmHg) while for males, PNC was inversely and not significantly associated with mean SBP (95% CI = -3.56 mmHg – 0.75 mmHg). Additionally, the effect estimate for PNC was larger in people who reported that they had never smoked (95% CI = -0.17 mmHg – 4.09 mmHg) compared to former smokers (95% CI = -2.88 mmHg – 1.47 mmHg) or current smokers (95% CI = -2.76 mmHg – 2.02 mmHg).

As with PNC, the association between the PIR and mean SBP levels was attenuated after controlling for relevant confounders. In a model controlling only for age, each additional 6.1 billion particles inhaled per hour was associated with a significant increase of 1.19 mmHg in mean SBP (95% CI = 0.16 mmHg – 2.22 mmHg [Table 3S1.1]). By comparison, after controlling for relevant confounders, each IQR increase in PIR was associated with only a 0.99 mmHg increase in mean SBP (95% CI = -0.04 mmHg – 2.04 mmHg [Figure 3.2]). Additionally, while the covariates used in the primary PNC and PIR models were slightly different, if the PIR model were run with the same set of covariates as the PNC model (except for sex, which was excluded since it was already accounted for in the inhalation rate), the effect estimates for PNC and PIR would be roughly equivalent (95% CI for an IQR increase in PIR = -0.05 mmHg – 2.09

mmHg). Including sex had no substantive effect on the PIR effect estimates. Nevertheless, stratifying by self-reported statin medication use and hypertension medication use suggests that the association between PIR and SBP is stronger among those not taking medications for chronic conditions (Table 3S1.1). Additionally, the effect estimate for the PIR seemed to be somewhat stronger among individuals who were employed at baseline (95% CI = -0.04 mmHg – 3.37 mmHg) compared to those who were not (95% CI = -1.19 mmHg – 1.71 mmHg).

In contrast to the trends observed in the multiple cross-sectional models, PNC seemed to be more strongly associated with changes in SBP over five years than did the PIR. Each IQR increase of PNC was significantly associated with a 1.09 mmHg increase in SBP (95% CI = 0.30 mmHg – 1.88 mmHg [Figure 3.2 and Table 3S1.1]), while each IQR increase in PIR was not significantly associated with changes in mean SBP over time (95% CI = -0.26 mmHg – 1.10 mmHg). This overall trend was observed regardless of covariate selection and in a PIR/change model using the same set of covariates as the primary PNC/change model (excluding sex), the effect estimate for PIR was materially unchanged (95% CI = -0.28 mmHg – 1.06 mmHg).

Effect modification was evident for both the PNC/change model and the PIR/change model. The association between PNC and changes in SBP was stronger among non-diabetics, among individuals not on statins, among individuals without a family history of hypertension, and among females while the effect estimates of PIR were higher among non-diabetics, among those not taking statins, and among those not taking hypertension medications. Additionally, the association between the PIR and change in SBP was stronger among current smokers than among former smokers or among individuals who reported never smoking (Table 3S1.1).

Diastolic blood pressure

In the multiple cross-sectional models, PNC was not significantly associated with mean DBP levels (95% CI for change in DBP with each additional 4600 particles/cm³ = -0.31 mmHg – 1.21 mmHg [Figure 3.2]). The effect estimate for PNC was not affected by the inclusion of other potential confounders, such as education or hypertension medications (details not shown). It was also unchanged if the same variables were used to predict DBP levels as were used to predict SBP levels. The only sub-population in which PNC seemed to be associated with DBP was in people who reported that they had never smoked. Among these individuals, each IQR increase in PNC was significantly associated with a 1.23 mmHg higher mean DBP (95% CI = 0.012 mmHg – 2.34 mmHg).

Although PNC was not significantly associated with mean DBP levels, each additional 6.1 billion particles inhaled per hour was associated with a significant increase of 1.03 mmHg in mean DBP (95% CI = 0.38 mmHg – 1.68 mmHg [Figure 3.2]). Including the same set of covariates in the PIR model as in the PNC model for DBP (excluding sex) did not substantively change the effect estimate for the PIR. However, the effect estimate for the PIR was attenuated when sex was added and was augmented when BMI was excluded from the model. Additionally, the association between the PIR and DBP was attenuated among individuals not employed at baseline and among non-diabetics (Table 3S1.2). Clear effect modification was also evident by sex. Among males, the PIR was associated with DBP levels (95% CI = 1.05 mmHg – 2.90 mmHg) while in females, there was a non-significant inverse association between PNC and DBP levels (95% CI = -1.31 mmHg – 0.32 mmHg).

In the models for change, neither PNC nor the PIR was significantly associated with changes in the mean DBP. PNC was not associated with changes in DBP levels in any of the

stratified analyses. This was in contrast to the significant associations observed between PNC and changes in the levels of SBP over five years but it was concordant with the non-significant trends observed for the association between the PIR and SBP. Also similarly to the trends observed with SBP, the association between the PIR and changes in the level of DBP was stronger among current smokers, among non-diabetics, among participants without a family history of hypertension, and among participants not taking hypertension medication (Table 3S1.2).

Pulse pressure

PNC was not significantly associated with mean PP levels in the multiple cross-sectional model with all participants combined (95% CI for change in PP with each additional 4600 particles/cm³ = -0.40 mmHg – 1.57 mmHg [Figure 3.2]). However, analogously to the trends observed for SBP in the PNC/multiple cross-sectional model, sex modified the relationship between PNC and PP. Among men, there was a strong inverse association between PNC and PP levels (95% CI = -3.38 mmHg – -0.07 mmHg) while in women, there was an equally strong positive association between PNC and PP levels (95% CI = 0.39 mmHg – 2.82 mmHg). Although PNC was not significantly associated with PP levels in any other sub-group, the data suggest that there may also be a stronger association between PNC and PP levels among people not taking hypertension medication and among people with a family history of hypertension (Table 3S1.3 in Supplement 3.1). In contrast, the PIR was not significantly associated with mean PP levels in the primary multiple cross-sectional model (95% CI for change in PP levels with each IQR increase in PIR = -0.73 mmHg – 0.81 mmHg) or in any of the stratified analyses (Table 3S1.3).

The trends for change in PP in relation to PNC and PIR were similar to the trends for change in SBP in relation to these measures. Specifically, an IQR increase in PNC exposure was significantly associated with an increase of 0.85 mmHg in PP (95% CI = 0.28 mmHg – 1.42 mmHg) while the PIR was not (95% CI for change in PP with an IQR increase in PIR = -0.20 mmHg – 0.79 mmHg). Additionally, and also analogously to the trends for SBP, the association between PNC and PP was stronger among non-diabetics, among individuals not on statins, and among females. The association between the PIR and PP was also stronger, although not statistically significant, among individuals who did not take statins and among individuals who did not take hypertension medication (Table 3S1.3). The association between the PIR and changes in PP was only significant among females (95% CI = 0.07 mmHg – 1.47 mmHg).

C-reactive protein

In contrast to the blood pressure measures, the only significant association between UFP exposure and CRP was seen in the PNC/multiple cross-sectional model (Figure 3.3). Neither PNC nor the PIR were significantly associated with changes in CRP levels over five years after controlling for confounders. This finding was robust to covariate selection and effect modification was not evident (Table 3S1.4 in Supplement 3.1).

In the multiple cross-sectional model, however, exposure to an additional 4600 particles/cm^3 was significantly associated with a 9.2 percent higher mean level of CRP (95% CI = 1.8 – 16.6 percent). After adding baseline employment status to the model (and dropping the 98 participants without employment data), the association with PNC was attenuated (95% CI = -0.2 – 25.8 percent). The association between an IQR increase in PNC and CRP levels was stronger among people who reported that they never smoked (95% CI = 2.3 – 22.5 percent) than

among former smokers (95% CI = -1.8 – 21.6 percent) and among current smokers (95% CI = -20.2 – 14.7 percent). Additionally, PNC was significantly associated with the percent change in CRP levels among people taking medication for CVD and among people without a family history of CVD but there was no significant association between PNC and CRP among people who were not taking medications for CVD or who did have a family history of CVD (Table 3S1.4).

Despite the significant associations between PNC exposure and CRP levels, as well as a proportionately strong association between the PIR and CRP levels in a model adjusted only for age (95% CI for percent change in CRP with each increase of 6.1 billion particles inhaled hourly = 2.4 – 14.0), the PIR was not associated with CRP levels after controlling for relevant covariates (95% CI = -9.2 – 2.4 percent) (Figure 3.3). The association between the PIR and CRP concentration was also weaker than that of PNC in the multiple cross-sectional models controlling for an identical set of covariates. Nevertheless, the PIR was inversely and significantly associated with CRP concentrations among current smokers (95% CI = -32.9 – -1.2 percent) and among diabetics (95% CI = -17.1 – -0.6 percent). There was also an inverse association between the PIR and CRP levels among people without a family history of CVD, although this association was not statistically significant (95% CI = -22.0 – 1.2 percent).

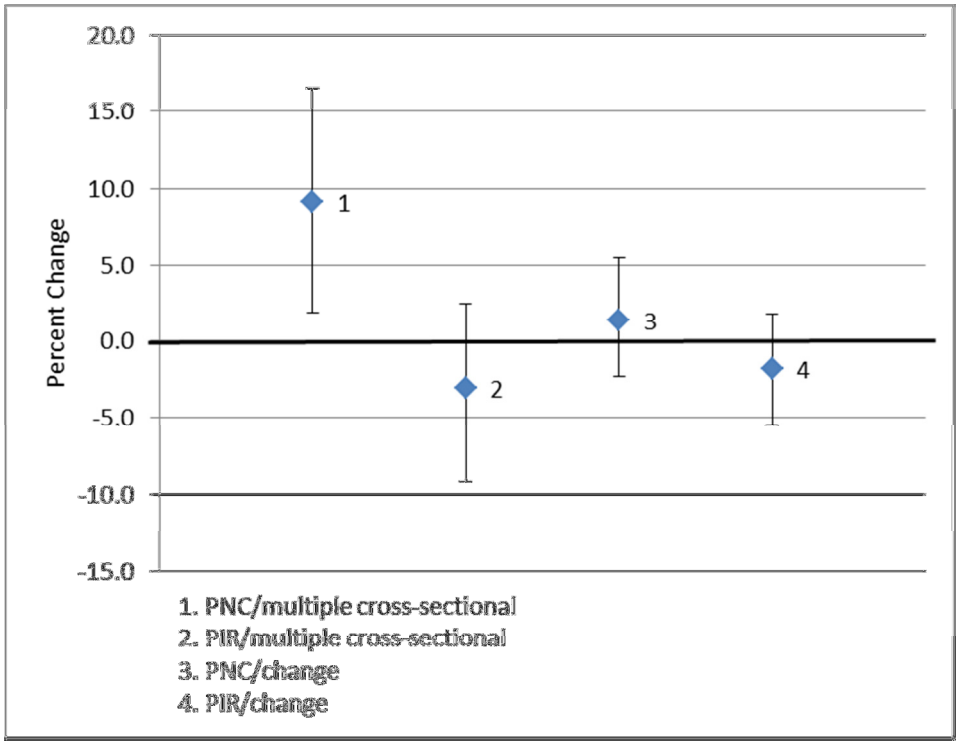

Figure 3.3. Percent change in CRP (mg/L) with an interquartile increase in PNC or PIR

Main models adjusted for:
1. Age, sex, education, BMI, LDL cholesterol, HDL cholesterol, ln(triglycerides), and diabetes; n = 764
2. Age, education, BMI, LDL cholesterol, HDL cholesterol, ln(triglycerides), diabetes, and anxiety medication; n = 764
3. Baseline ln(CRP), age, education, BMI, LDL cholesterol, HDL cholesterol, and marital status; n = 753
4. Baseline ln(CRP), age, education, BMI, LDL cholesterol, HDL cholesterol, and marital status; n = 753

Sensitivity analyses

Sensitivity analyses excluding people who died before their third study visit did not change the results materially for any of the outcomes. Similarly, excluding participants who self-reported a previous heart attack or stroke before their first study visit did not change the overall conclusions. The only exception was that the association between PNC and the levels of CRP was attenuated in the multiple cross-sectional model (95% CI for percent change = -0.5 – 14.7 percent). Details on these sensitivity analyses are provided in Supplement 3.1.

Discussion

Overall, we found evidence that UFP exposure is associated with increased levels of biomarkers of CVD risk, especially among certain sub-populations. This is consistent with the toxicological and epidemiological literature suggesting that UFP exposure may have cardiovascular consequences.

Associations with PNC

Our first objective was to determine whether long-term exposure to UFP was associated with blood pressure and CRP levels among Puerto Rican adults residing in Boston. We found that among all participants, PNC was not significantly associated with SBP, DBP, or PP levels but that PNC was significantly associated with CRP concentrations. For each of the biomarkers, the multiple cross-sectional associations with PNC were stronger among people who reported never smoking compared to either current or former smokers. For SBP, PP, and CRP, the associations with PNC were also stronger among females. Furthermore, there were significant associations between PNC and changes in SBP and changes in PP over five years. These associations were stronger among females, among non-diabetics, among people without a family history of hypertension, and among people not taking statins.

The inconsistency in the strength of associations of PNC with the various blood pressure measures is reflected in the literature, perhaps due to differences in how exposure or outcome were measured. In a study of individuals with coronary artery disease, for example, PNC was not significantly associated with acute changes in blood pressure except when participants had recently engaged in moderate to strenuous physical activity (R. Delfino et al., 2010). In contrast, a study of 76 patients who had experienced a recent cardiac event found positive associations

between UFP and acute changes in SBP but inverse associations between UFP and acute changes in DBP (Rich et al., 2012). Furthermore, while we found no significant associations between long-term exposure to PNC and DBP except among never smokers, previous work by our team in a different population suggested that short-term exposure to PNC was significantly associated with DBP but not with SBP or PP (Chung et al., 2015). Despite some of the inconsistencies between our study and the studies of acute changes in blood pressure, it is probable that consistently high UFP exposure over months or years could have different physiological consequences than high exposure over hours or days.

In support of the idea that long-term exposure to particulate matter may be associated with changes in blood pressure, the Black Women's Health Study found that increased $PM_{2.5}$ exposure was associated with an increased incidence of hypertension (Coogan et al., 2012). In our models for changes in blood pressure, however, PNC was only significantly associated with SBP and PP. This may be due, in part, to the differential trends for the blood pressure measures over time. Both SBP and PP increased with participants' age while DBP decreased with participants' age and these trends were consistent among participants who were not taking medication for hypertension. Among adults aged 60 years and older, PP is most predictive of coronary heart disease risk (95% CI for the hazard ratio for a 10 mmHg increase in PP = 1.16 – 1.33), followed by SBP (95% CI for a 10 mmHg increase in SBP = 1.11 – 1.24), and then DBP (95% CI for a 10 mmHg increase in DBP = 0.99 – 1.27). Moreover, when SBP and DBP are considered jointly, DBP has an inverse association with coronary heart disease risk among older adults (Franklin et al., 2001). Taken together, these results suggest that the blood pressure trends that we observed for long-term exposure to PNC are consistent with increased CVD risk.

Similarly, each IQR increase in PNC was significantly associated with more than a nine percent higher mean CRP concentration in the multiple cross-sectional model. This association is consistent, although perhaps slightly weaker, than that found between long-term PNC exposure and CRP among a different population participating in a cross-sectional study in the Boston metropolitan area (K. Lane et al., 2015). As in that study, BMI, sex, and smoking affected the effect estimates for PNC in this analysis by more than 10 percent. However, after controlling for confounders, smoking was not a significant predictor of CRP levels in our population. Nevertheless, smoking still modified the relationship between PNC and CRP. Specifically, the associations were strongest among never smokers and were weakest among current smokers. Despite evidence that tobacco smoke and particulate matter may act at least partially through different physiological pathways (Curjuric et al., 2012), previous work has also found that the associations between particulate matter exposure and chronic health effects are strongest among never-smokers (Pope et al., 2002), possibly because smokers already have constant low-grade inflammation (Yasue et al., 2006). Furthermore, our finding that long-term PNC exposure was associated with mean CRP levels is consistent with several studies examining the relationship between UFP and acute changes in CRP (Rückerl et al., 2006; Yue et al., 2007; R. J. Delfino et al., 2008; Hertel et al., 2010), although not all studies (Zeka et al., 2006; Ruckerl et al., 2007). As with the inconsistencies reported in the blood pressure literature, it is possible that differences are due to varying exposure assessment methodologies. This idea is supported by a recent study in the Boston metropolitan area that found significant associations between UFP measured at a central site and biomarkers of systemic inflammation but found no significant associations between modeled residential UFP exposures and these same biomarkers (Fuller et al., 2015).

We did not find associations between PNC and CRP after controlling for participants' baseline CRP levels. Since 55% of participants had CRP values greater than three mg/L at baseline (indicative of high cardiovascular risk), a substantial increase in mean CRP levels may not be possible to observe for a substantial subset of our study population (Pearson et al., 2003). Indeed, age was not a significant predictor for CRP concentrations in our study, even controlling for baseline CRP levels. However, even among the participants with CRP concentrations below three mg/L at baseline, there was no significant association between PNC and changes in CRP concentrations.

The differences observed between the multiple cross-sectional models and the change models are not unique to our study (Adar et al., 2013) and reflect the different underlying research questions these models address. The multiple cross-sectional models assess the associations between UFP exposure and levels of the biomarkers while the change models consider the association between UFP and the rate of change over time of biomarker levels. For biomarkers, such as CRP, which did not change substantially over the course of the study, the multiple cross-sectional models are likely to show stronger associations. However, if there had been a significant association in the change models, this would be stronger evidence for a potential causative role for UFP.

Comparing PNC and PIR

In addition to presenting the first longitudinal analysis of the association between long-term exposure to near-roadway UFP and biomarkers of CVD risk, we also developed an algorithm to calculate the average PIR and then compared PNC and PIR as measures of UFP exposure. Although one previous study calculated the PIR by multiplying PNC by the amount of

air inhaled per minute, no other studies of which we are aware estimated the annual average PIR using published estimates of minute respiratory volume in combination with data on how many hours per typical weekday and per typical weekend day participants engaged in defined levels of physical activity (Int Panis et al., 2010). The previous study found that participants' exposure to UFP was greater while cycling than while driving in some cities, but not in others. In contrast, other studies that did not account for inhalation found inconsistent results regarding relative PNC estimates for cyclists compared to PNC estimates for people in vehicles (Kaur, Nieuwenhuijsen, & Colvile, 2005; Boogaard, Borgman, Kamminga, & Hoek, 2009). Thus, controlling for inhalation rate may influence the results of epidemiological analyses.

Of note, there are fundamental differences in what PNC and the PIR measure physiologically. It is possible that someone with a high PIR was exposed to very low PNC but had a high average inhalation rate. In this case, the particle deposition fraction and clearance rate may be the most relevant factors in whether that person will experience any health effects associated with long-term exposure to UFP (Lippmann et al., 1980; Leikauf, 2010). This situation is particularly relevant for certain sub-populations, such as males and those with greater physical activity, who have higher inhalation rates and thus may be at greater risk from potential health consequences of exposure over time. In particular, during exercise, deposition of inhaled particles typically exceeds predictions based on the size of the particles (Daigle et al., 2003). In our study, we found some evidence that associations between the PIR and blood pressure (particularly DBP) were higher among males than among females. Additionally, as might be expected if there were a true association between UFP and DBP levels over time, the association between the PIR and DBP in males was stronger than the association between PNC and DBP in males.

Although we may generally expect people who inhale more particles per hour to be more susceptible to high ambient concentrations, if people are inhaling more pollutants because they are physically active, they may be less vulnerable to potential health effects from air pollution because they are healthier overall and because exercise is associated with better cardiovascular health (O'Neill et al., 2005; Wheeler et al., 2006; Forastiere et al., 2007). However, healthier individuals in our study appeared to be somewhat more susceptible, overall. Specifically, we found stronger associations between PIR and blood pressure among people who were not taking hypertension medications, among people not taking statin medications, and among people who were employed at baseline than among people who were perhaps likely to be less healthy overall. Additionally, these associations with PIR were stronger than the associations with PNC. While it is possible that healthier people are in fact more susceptible, it is also possible that it is easier to observe associations among people who are not taking medications, such as statins, that could help counteract the negative effects of PM exposure on vascular health (Schwartz et al., 2005; Miyata, Bai, Vincent, Sin, & Eeden, 2012; Miyata et al., 2013).

Nevertheless, the PIR was not more strongly associated with all of the outcomes. In particular, the associations between PNC and changes in SBP over time were stronger than associations between the PIR and changes in SBP over time. Additionally, PNC was more strongly associated with PP overall and among every sub-group in the study except for people taking hypertension medication. Similarly, PNC was more strongly associated with CRP, except in diabetics and in current smokers. Therefore, it remains possible that healthier people are less susceptible to at least certain health effects of UFP or, assuming that the PIR is a better measure of exposure, it is possible that UFP is not associated with PP or CRP.

As a final note, it seems that PNC and PIR may measure different physiological processes. PNC was more closely associated with changes in blood pressure while the PIR was more closely associated with the levels of blood pressure in the multiple cross-sectional analyses. It is possible, for example, that PNC may be a stronger measure for chronic health effects while the PIR may be more relevant for acute health effects. Although we did not test associations with acute health effects, in our future work, we will include short-term exposure to UFP in the health association models.

Limitations and next steps

While we have participant data from 2004 through 2013, we only monitored UFP concentrations from December 2011 through November 2013. Although this limits our ability to evaluate the modeled estimates to some degree, much of the temporal variability in PNC exposure is explained by meteorological conditions and we do have historical data for these parameters (Noble et al., 2003; Kozawa, Winer, & Fruin, 2012). Additionally, we were able to compare our modeled estimates to PNC measurements at a fixed site within our study region (Countway Library, Figure 2.1) (Harvard Clean Air Research Center, 2015) and we were able to compare our modeled estimates to PNC measurements at the homes of five participants. These comparisons suggest that the PNC model captured seasonal trends quite well, but over-predicted PNC, especially between 2006 and 2011 (Supplement 3.2). To account for annual trends not captured within the PNC model, we tested a term for the year participants started the study in the health association models. This term was significant in most of the blood pressure models but not in the CRP models. It seems unlikely that the temporal trends in blood pressure were due to differences in blood pressure measurement technique as there were no clear trends in mean blood

pressure by year participants started the study, with the exception of 2005 when the mean PP and SBP were significantly lower than other years.

Despite the generally strong performance of the PNC model at predicting ambient residential exposure, the model development was predicated on a number of critical assumptions. First, by constructing an hourly PNC model, we assumed that the PNC trends predicted by the temporal model were stable over the course of an hour. Given the year-long averaging period for PNC, however, this is unlikely to be a serious limitation. In contrast, assuming that the spatial variability in UFP was constant with time may have been more problematic to the exposure assessment. We know that the Massachusetts Bay Transportation Authority upgraded many of its vehicles to burn cleaner fuels (MBTA, 2007; Jessen, 2010) and that there were a number of major construction projects in Boston during the study period which may have affected the spatial variability in PNC. Notably among these projects, the Big Dig ended most construction only in 2006 (MassDOT, 2014). These projects could have generated particulate matter and they could have affected traffic patterns which both would have affected the spatial variability in PNC (Fruin, Westerdahl, Sax, Sioutas, & Fine, 2008; Weichenthal, Farrell, Goldberg, Joseph, & Hatzopoulou, 2014). Future work to address the question of consistency in spatial variability over time will consider how traffic density has changed with time across our study area. Additionally, given more resources, it may have been preferable to jointly consider the spatial variability of UFP with mobile monitoring and atmospheric dispersion models as this has been shown to improve the predictive ability (Zwack, Hanna, Spengler, & Levy, 2011). This could have helped improve the relatively low R^2 of 0.37 in the exposure model.

Development of the spatial inputs for the PNC model presented another set of challenges that could have introduced error. Since distances to highways, major roadways, and bus routes

were critical spatial factors, the geocoding process could have been a source of error. In particular, the geocoding process was not identical at each study visit. For all of the participants' baseline residences, geocoding was completed prior to the availability of the present version of Street View for Boston. This limited the ability to visually check that each parcel was in fact properly identified and possibly resulted in greater average positional error at baseline than for the other two study visits. Even for the participants for whom it was possible to verify street addresses within Street View, placing participants within the centroid of parcels can still result in substantial positional error if the parcels are large (K. J. Lane et al., 2013). Although we found publically accessible building plans or site maps to better place participants within parcels for approximately 14 percent of the participants who moved, we could not do this in every case due to lack of publically accessible information.

Furthermore, we assumed that a 365 day averaging period for PNC represented the most relevant window for long-term exposure. Although this is common practice in studies considering the associations between traffic-related air pollution and blood pressure or systemic inflammation (Chen & Schwartz, 2008; Chuang et al., 2010; Fuks et al., 2011; Sørensen et al., 2012), it is possible that the critical averaging window for UFP differs from that of other pollutants. Additionally, our results may be confounded by acute changes in blood pressure or CRP levels due to fluctuations in UFP exposure immediately prior to the participants' study visits. Our future work will consider the effect of including a measure of short-term exposure to UFP in the health model. Future work will also consider the influence of excluding participants who have spent substantial portions of time outside of Boston in the year prior to their study visit as these participants likely have poorly characterized annual ambient average exposure values.

Beyond the limitations in assessing participants' residential annual average PNC exposure, this measure is still only a proxy for participants' true exposure to UFP. Participants are not home 100 percent of the time and exposure concentrations can vary dramatically within different micro-environments in which participants spend their time. Previous work has shown that adjusting the hourly PNC exposure values by a factor determined by participants' time in micro-environments (inside the home, outside the home, work, highway, other) reduces misclassification as those who live closer to major roadways tend to have over-estimated exposure values which are reduced after accounting for their time-activity patterns (K. J. Lane et al., 2013). However, in the BPRHS, we do not have data on which hours of the day participants spent in different micro-environments so we cannot make these adjustments. We also did not incorporate data on the indoor-outdoor ratio for PNC at the participants' residences so we are assuming that the concentrations outside the home are equivalent to the concentrations within the home. This assumption is likely reasonable as previous work in Somerville, MA has suggested that the indoor-outdoor ratio may approach one, indicating that the overall gradient between indoor concentrations and outdoor concentrations is zero (Fuller et al., 2013).

Furthermore, while we attempted to more closely estimate participants' intake dose through adjustment of the residential annual average concentration by inhalation rate, we were not able to validate our algorithm since we do not have data available on participants' actual respiratory volume. Future work is needed to validate this approach. Additionally, it is likely that the PIR algorithm is only valid among individuals who do not have major respiratory problems, such as chronic obstructive pulmonary disease. This is because the total residence time of PM in the lungs is greater in individuals with chronic obstructive pulmonary disease, likely resulting in more accumulation and systemic distribution of PM (Brown, Zeman, & Bennett, 2002). In the

future, we will do a sensitivity analysis restricting the population to only those participants who are non-smokers and who are not taking medications for respiratory conditions. Additionally, we will conduct a sensitivity analysis excluding people in the highest percentile of physical activity since several of these extremely high (>50.4 points) physical activity scores are inconsistent with the participants' physical activity scores at other study visits and these participants' physical activity values generally resulted in extremely high (>30.7 billion particles inhaled/hour) PIR estimates. As a final check on our inhalation rate adjustment, we will consider whether participants' physical activity occurred in places that were likely to be highly polluted or not since this could give insight into whether these physically active participants were likely to be inhaling more particles per hour.

From an exposure assessment perspective, a final critical limitation was that we assessed exposure to UFP without regard to its constituent parts or to other pollutants with which it may interact. It is possible that the biological mechanisms through which UFP acts involve interactions with other pollutants (Brook et al., 2004; R. Delfino et al., 2009). Future work with multi-pollutant models will be necessary to address this critically important question (Dominici, Peng, Barr, & Bell, 2010; Billionnet, Sherrill, & Annesi-Maesano, 2012).

From a health analysis perspective, our study also had several limitations. The most critical was the amount of attrition and resulting potential for selection bias. Only 45 percent of the 812 participants contributed data at all three time points. Although the baseline characteristics of participants who stayed in the study through their third visit were similar to those who dropped out, we plan to predict participants' propensity to drop out and then conduct a sensitivity analysis weighting observations by the inverse probability of these propensity scores. We will be able to validate our propensity scores to some extent since we have health data on 82

participants who remained in the BPRHS even though they moved out of Boston before their third study visit.

Additionally, we considered the potential impact of the high mortality rate among our participants. The 51 participants who died before their third study visit were older, more likely to be male, were more likely to have had a previous heart attack or stroke, had lower LDL cholesterol, and had lower triglycerides concentrations at baseline. Of perhaps greatest interest, participants who died prior to their third study visit had significantly higher PNC exposures at baseline (mean for those who died = 25,000 particles/cm^3, mean for those who did not die = 24,000 particles/cm^3, $p = 0.029$). While we do not have data available on the causes of death and there is no evidence for bivariate cross-sectional associations between baseline exposure to PNC and baseline blood pressure or CRP, it is possible that there was an association between PNC and changes in the levels of the biomarkers that contributed to the participants' deaths. However, excluding the participants who died prior to their third study visit did not affect the results for any of the biomarkers.

Nevertheless, there is a concern that since our participants on average were quite sick at baseline, it may have been difficult to observe changes in the levels of their cardiovascular risk factors. Alternatively, it is possible that these participants with poor physical health would have been the most susceptible to additional environmental stressors (Pope et al., 2015). At baseline, over half of our participants had CRP values indicative of high cardiovascular risk and 72 percent were hypertensive (Pearson et al., 2003). We did not exclude these participants from the main analysis since we were concerned about the sample size and because we were interested both in the levels and the changes in levels of these biomarkers. However, we could restrict the

population to those participants who had lower CRP levels and were not hypertensive and then test whether UFP exposure is associated with the risk of developing high CRP or hypertension.

The issue of poor health at baseline additionally suggests issues of generalizability. All of our study participants were of Puerto Rican descent, most had a very low socioeconomic status measured by either income or educational attainment, and most had at least one chronic health condition at baseline. It is possible that in a healthier population, the associations between UFP and biomarkers of CVD risk would differ. This idea is supported by the evidence for interactions by hypertension medication use, statin medication use, cardiovascular medication use, and diabetes. Longitudinal studies of the potential associations between long-term exposure to UFP and CVD risk are needed in other populations to address the question of varying susceptibility.

In addition to the limitations with respect to generalizability, we are missing data on certain key covariates for at least two study visits for every participant. For employment history, we only have data at baseline. This is a limitation because we would otherwise want to do a sensitivity analysis restricting the population to only those participants who did not work at each study visit since the assigned residential annual average exposure values would likely be more valid for these participants. For other variables, such as family history of various chronic diseases, we only have data from participants who were present at the third study visit. If we included these potentially important confounders, we would lose approximately half of our sample size. While we assessed the influence of these variables, they ideally could have been included in the primary analysis.

An additional limitation in our analysis was the large number of comparisons. It is thus possible that some of the significant findings occurred by chance. However, even most of the non-statistically significant results had positive point estimates with confidence intervals strongly

favoring positive values. If the significant positive associations that we found were due to chance, it would be more likely that the other findings would have point estimates distributed around zero, rather than around positive point estimates.

As with any epidemiology study, it is possible that we neglected to adequately control for important confounding variables. There are potential concerns, for example, with participants' self-reported smoking behavior and compliance with medication use. We also did not assess the role nutrition may play in terms of confounding or modifying the associations between UFP exposure and CVD risk factors. Additionally, while we have each participant's genome completely sequenced, we did not attempt to assess any gene-environment interactions within this analysis. Our future work will address this critical question.

Overall contributions

The work presented here advances the field in three primary ways. First, this is the first study to consider longitudinal associations between long-term UFP exposure and CVD risk factors. Although there has been one published longitudinal assessment of the potential health effects of UFP exposure, the researchers of that study were not interested in primary UFP from traffic-related sources. Rather, they used four km grids to model regional variations in UFP mass (Ostro et al., 2015). In contrast, we considered UFP measured as PNC with a spatial resolution of 20 m. Second, this is the first study to our knowledge that has adjusted residential annual average exposure concentrations by inhalation rate to obtain the PIR for participants in a longitudinal study. We are thus advancing air pollution exposure assessment methodologies by proposing a way to more closely estimate intake dose. Finally, we found that both PNC and PIR are associated with CVD risk factor levels over five years. Although future work is needed to

validate these findings, our analysis has potential policy implications as the EPA has been waiting for evidence from longitudinal studies before deciding whether UFP should be regulated at the federal level.

Supplement 3.1 Effect estimates among sub-populations

Significant associations ($p < 0.05$) are denoted with an asterisk.

Table 3S1.1. Change in SBP with an IQR increase in PNC or PIR

	SBP - Multiple cross-sectional								SBP - Change							
	PNC (particles/cc)				Particles inhaled per hour				PNC (particles/cc)				Particles inhaled per hour			
	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p
Adjusted only for age (and baseline level for change models)	1.19	-0.09	2.47	0.067	1.19	0.16	2.22	0.024*	1.01	0.22	1.80	0.012*	0.23	-0.41	0.88	0.482
Overall†	0.78	-0.52	2.07	0.242	0.99	-0.04	2.04	0.061	1.09	0.30	1.88	0.007*	0.43	-0.26	1.10	0.221
Excluding people with a previous heart attack or stroke by baseline (n = 89)	0.98	-0.40	2.35	0.164	1.10	0.00	2.19	0.050	0.97	0.10	1.83	0.029*	0.45	-0.26	1.17	0.214
Excluding people who died before y5 (n = 51)	0.79	-0.55	2.13	0.249	0.90	-0.16	1.95	0.096	1.11	0.29	1.94	0.008*	0.36	-0.32	1.05	0.300
Sex																
Male	-1.40	-3.56	0.75	0.203	1.07	-0.54	2.67	0.194	0.57	-0.58	1.72	0.330	0.02	-0.91	0.95	0.969
Female	1.72	0.09	3.35	0.039*	-0.07	-1.51	1.37	0.923	1.27	0.24	2.30	0.015*	0.37	-0.63	1.36	0.470
Smoker status																
Current	-0.37	-2.76	2.02	0.761	1.13	-1.01	3.28	0.300	1.28	-0.27	2.83	0.105	1.37	-0.32	3.04	0.112
Former	-0.70	-2.88	1.47	0.525	0.80	-1.09	2.68	0.407	1.04	-0.37	2.44	0.150	0.56	-0.67	1.79	0.374
Never	1.96	-0.17	4.09	0.071	0.98	-0.61	2.58	0.226	0.69	-0.49	1.87	0.250	0.03	-0.88	0.93	0.950
Baseline employment status																
Yes	0.37	-2.55	3.29	0.804	1.67	-0.04	3.37	0.056	0.82	-0.94	2.58	0.360	0.35	-0.71	1.40	0.517
No	0.40	-1.14	1.93	0.612	0.26	-1.19	1.71	0.725	0.74	-0.20	1.68	0.121	0.15	-0.77	1.06	0.759
Family history of hypertension																
Yes	0.87	-1.20	2.94	0.410	0.57	-0.92	2.07	0.454	1.34	-0.12	2.81	0.073	-0.17	-1.18	0.84	0.742
No	0.68	-3.78	5.14	0.765	-0.08	-3.17	3.02	0.960	2.73	0.68	4.79	0.009	1.29	-0.47	3.05	0.151
Hypertension medication use																
Yes	0.31	-1.36	1.99	0.713	0.02	-1.49	1.53	0.984	1.11	-0.06	2.28	0.063	-0.32	-1.24	0.59	0.490
No	0.82	-0.93	2.56	0.359	1.53	0.18	2.87	0.026*	0.81	-0.09	1.71	0.079	1.07	0.18	1.97	0.018*
Statin medication use																
Yes	0.58	-1.39	2.54	0.563	-0.35	-2.28	1.58	0.723	1.09	-0.27	2.44	0.117	-0.22	-1.57	1.13	0.748
No	0.79	-0.92	2.49	0.367	1.71	0.44	2.98	0.008*	1.12	0.18	2.07	0.020*	0.63	-0.13	1.40	0.105
Diabetic																
Yes	-0.28	-1.97	1.41	0.746	0.74	-0.84	2.32	0.360	0.87	-0.36	2.11	0.166	-0.12	-1.18	0.94	0.826
No	1.14	-0.80	3.07	0.248	0.82	-0.57	2.21	0.250	1.10	0.06	2.13	0.037*	0.81	-0.08	1.68	0.074
Covariates†	age, education, sex, BMI, HDL cholesterol, ln(triglycerides), hypertension medication, anxiety medication, year of baseline visit, marital status				age, education, BMI, LDL cholesterol, HDL cholesterol, ln(triglycerides), hypertension medication, anxiety medication, year of baseline visit, marital status				baseline SBP, age, sex, LDL cholesterol, HDL cholesterol, hypertension medication, year of baseline visit				baseline SBP, age, education, LDL cholesterol, HDL cholesterol, hypertension medication, year of baseline visit			

Table 3S1.2. Change in DBP with an IQR increase in PNC or PIR

	DBP - Multiple cross-sectional								DBP - Change							
	PNC (particles/cc)				Particles inhaled per hour				PNC (particles/cc)				Particles inhaled per hour			
	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p
Adjusted only for age (and baseline level for change models)	0.46	-0.28	1.20	0.221	1.11	0.49	1.73	<0.001*	0.18	-0.29	0.64	0.448	0.12	-0.33	0.56	0.611
Overall†	0.45	-0.31	1.21	0.245	1.03	0.38	1.68	0.002*	0.18	-0.30	0.67	0.460	0.16	-0.29	0.62	0.478
Excluding people with a previous heart attack or stroke by baseline (n = 89)	0.41	-0.39	1.21	0.311	0.99	0.31	1.67	0.005*	0.06	-0.47	0.59	0.821	0.19	-0.29	0.67	0.441
Excluding people who died before y5 (n = 51)	0.40	-0.38	1.17	0.318	0.98	0.32	1.63	0.004*	0.17	-0.34	0.67	0.523	0.11	-0.35	0.57	0.634
Sex																
Male	0.96	-0.44	2.36	0.177	1.98	1.05	2.90	<0.001*	0.63	-0.17	1.43	0.122	0.51	-0.16	1.17	0.137
Female	0.17	-0.73	1.07	0.710	-0.49	-1.31	0.32	0.235	model would not converge				-0.41	-1.01	0.18	0.174
Smoker status																
Current	0.15	-1.30	1.60	0.843	1.23	0.00	2.45	0.050	0.38	-0.55	1.31	0.421	0.86	-0.05	1.78	0.066
Former	-0.80	-2.17	0.57	0.253	1.16	-0.05	2.37	0.061	-0.16	-1.00	0.68	0.707	-0.07	-0.96	0.81	0.867
Never	1.23	0.12	2.34	0.029*	0.89	-0.05	1.83	0.063	0.30	-0.41	1.02	0.410	0.12	-0.50	0.73	0.708
Baseline employment status																
Yes	0.89	-0.81	2.59	0.307	1.56	0.38	2.73	0.010*	-0.35	-1.42	0.72	0.522	0.05	-0.66	0.77	0.880
No	0.42	-0.47	1.31	0.356	0.77	-0.10	1.65	0.082	0.24	-0.34	0.82	0.414	0.00	-0.65	0.65	0.994
Family history of hypertension																
Yes	0.13	-1.00	1.27	0.817	0.65	-0.32	1.61	0.190	0.07	-0.86	0.99	0.882	-0.37	-1.04	0.31	0.288
No	0.28	-2.06	2.61	0.816	0.79	-0.63	2.21	0.275	0.32	-0.90	1.54	0.609	1.29	0.29	2.29	0.011*
Hypertension medication use																
Yes	0.69	-0.30	1.67	0.174	1.17	0.24	2.09	0.013*	0.36	-0.35	1.06	0.320	-0.13	-0.75	0.49	0.684
No	-0.11	-1.21	1.00	0.849	1.02	0.12	1.93	0.027*	-0.07	-0.66	0.51	0.804	0.51	-0.06	1.08	0.080
Statin medication use																
Yes	0.77	-0.38	1.91	0.19	1.07	-0.07	2.21	0.067	0.00	-0.77	0.76	0.992	-0.01	-0.87	0.85	0.983
No	0.32	-0.73	1.36	0.55	1.27	0.48	2.07	0.002	0.35	-0.26	0.98	0.261	0.27	-0.24	0.77	0.299
Diabetic																
Yes	0.49	-0.59	1.57	0.372	1.26	0.34	2.18	0.007*	0.08	-0.69	0.86	0.831	-0.21	-0.93	0.51	0.568
No	0.17	-0.86	1.20	0.748	0.73	-0.17	1.63	0.114	0.22	-0.38	0.81	0.475	0.56	0.02	1.10	0.043*
Covariates†	age, sex, BMI, LDL cholesterol, HDL cholesterol, ln(triglycerides), diabetes status, year of baseline visit, marital status				age, BMI, LDL cholesterol, HDL cholesterol, ln(triglycerides), year of baseline visit, marital status, smoker status				baseline DBP, age, sex, BMI, LDL cholesterol, HDL cholesterol, diabetes status, physical activity, perceived stress				baseline DBP, age, LDL cholesterol, ln(triglycerides), perceived stress, diabetes status			

Table 3S1.3. Change in PP with an IQR increase in PNC or PIR

	PP - Multiple cross-sectional								PP - Change							
	PNC (particles/cc)				Particles inhaled per hour				PNC (particles/cc)				Particles inhaled per hour			
	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p
Adjusted only for age (and baseline level for change models)	0.91	-0.08	1.90	0.073	0.10	-0.66	0.85	0.800	0.89	0.31	1.46	0.003*	0.18	-0.29	0.66	0.451
Overall†	0.58	-0.40	1.57	0.247	0.04	-0.73	0.81	0.910	0.85	0.28	1.42	0.003*	0.30	-0.20	0.79	0.237
Excluding people with a previous heart attack or stroke by baseline (n = 89)	0.76	-0.26	1.78	0.146	0.20	-0.62	1.01	0.640	0.78	0.17	1.38	0.012*	0.25	-0.26	0.76	0.337
Excluding people who died before y5 (n = 51)	0.52	-0.50	1.54	0.315	0.07	-0.71	0.85	0.866	0.94	0.35	1.53	0.002*	0.31	-0.20	0.81	0.229
Sex																
Male	-1.72	-3.38	-0.07	0.041*	-0.86	-2.10	0.38	0.174	0.02	-0.88	0.92	0.964	-0.29	-1.01	0.45	0.446
Female	1.61	0.39	2.82	0.010*	0.66	-0.34	1.68	0.196	1.24	0.51	1.97	0.001*	0.77	0.07	1.47	0.030*
Smoker status																
Current	0.18	-1.75	2.12	0.851	-0.18	-1.90	1.54	0.838	1.02	-0.23	2.26	0.108	0.62	-0.60	1.83	0.323
Former	0.00	-1.61	1.62	0.996	-0.33	-1.63	0.96	0.615	0.83	-0.29	1.95	0.146	0.56	-0.32	1.43	0.217
Never	0.90	-0.69	2.48	0.268	0.32	-0.84	1.46	0.592	0.76	-0.02	1.55	0.056	-0.03	-0.68	0.62	0.922
Baseline employment status																
Yes	-0.66	-2.71	1.39	0.530	-0.06	-1.15	1.02	0.911	0.64	-0.40	1.69	0.230	0.37	-0.25	0.98	0.244
No	0.37	-0.83	1.57	0.545	-0.56	-1.65	0.54	0.319	0.59	-0.12	1.30	0.102	0.08	-0.63	0.79	0.819
Family history of hypertension																
Yes	1.13	-0.38	2.65	0.143	-0.81	-3.45	1.83	0.547	1.16	0.13	2.19	0.027*	0.08	-0.61	0.77	0.817
No	-0.22	-3.57	3.12	0.897	0.11	-0.92	1.13	0.831	2.10	0.52	3.67	0.009*	-0.02	-1.74	1.69	0.977
Hypertension medication use																
Yes	0.07	-1.27	1.41	0.917	-0.81	-1.97	0.35	0.169	0.84	0.01	1.67	0.047	-0.07	-0.77	0.63	0.850
No	1.08	-0.24	2.41	0.109	0.68	-0.22	1.57	0.138	0.77	0.10	1.44	0.025	0.60	-0.02	1.22	0.058
Statin medication use																
Yes	0.17	-1.35	1.68	0.832	-0.89	-2.35	0.57	0.232	0.92	-0.04	1.87	0.059	-0.23	-1.26	0.82	0.673
No	0.79	-0.43	2.01	0.204	0.50	-0.35	1.35	0.251	0.71	0.06	1.36	0.032*	0.49	-0.04	1.01	0.068
Diabetic																
Yes	-0.35	-1.67	0.95	0.594	-0.05	-1.31	1.20	0.935	0.63	-0.34	1.60	0.203	0.13	-0.62	0.90	0.726
No	1.00	-0.43	2.43	0.169	0.04	-0.87	0.94	0.935	0.95	0.25	1.64	0.008*	0.37	-0.27	1.00	0.263
Covariates†	age, education, LDL cholesterol, hypertension medication, diabetes status, marital status, smoker status				age, education, LDL cholesterol, hypertension medication, diabetes status, marital status, smoker status				baseline PP, age, HDL cholesterol, hypertension medication, diabetes status, perceived stress, psychological acculturation, year of baseline visit				baseline PP, age, HDL cholesterol, hypertension medication, diabetes status, perceived stress, psychological acculturation, year of baseline visit			

Table 3S1.4. Percent change in CRP with an IQR increase in PNC or PIR

	CRP - Multiple cross-sectional								CRP - Change							
	PNC (particles/cc)				Particles inhaled per hour				PNC (particles/cc)				Particles inhaled per hour			
	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p	beta for an IQR increase	95% L	95% U	p
Adjusted only for age (and baseline level for change models)	10.12	2.30	17.48	0.011*	7.93	2.44	14.03	0.006*	1.38	-2.76	5.06	0.568	3.66	0.00	7.32	0.066
Overall†	9.20	1.84	16.56	0.013*	-3.05	-9.15	2.44	0.238	1.38	-2.30	5.52	0.469	-1.83	-5.49	1.83	0.335
Excluding people with a previous heart attack or stroke by baseline (n = 89)	7.36	-0.46	14.72	0.062	-4.27	-9.76	1.22	0.143	0.92	-3.68	5.06	0.710	-3.05	-6.71	1.22	0.169
Excluding people who died before y5 (n = 51)	8.28	1.38	15.64	0.022*	-2.44	-8.54	3.05	0.345	0.92	-3.22	4.60	0.729	-1.83	-5.49	1.83	0.343
Sex																
Male	11.50	-1.84	24.84	0.093	-2.44	-12.20	7.93	0.669	4.14	-2.76	11.50	0.246	-3.05	-8.54	2.44	0.290
Female	8.74	0.00	17.48	0.045*	2.44	-4.27	9.76	0.436	-0.46	-5.06	4.60	0.905	1.22	-3.66	6.71	0.593
Smoker status																
Current	-2.76	-20.24	14.72	0.769	-17.08	-32.94	-1.22	0.033*	4.60	-4.60	13.34	0.319	-4.27	-14.64	6.10	0.416
Former	9.66	-1.84	21.62	0.095	-6.71	-16.47	3.05	0.192	-0.46	-6.90	6.44	0.945	-1.83	-7.93	4.88	0.614
Never	12.42	2.30	22.54	0.017*	3.05	-4.27	9.76	0.458	1.38	-4.14	6.90	0.580	-1.22	-6.10	4.27	0.730
Baseline employment status																
Yes	9.20	-4.14	22.08	0.184	1.22	-6.71	9.76	0.737	-4.60	-13.34	4.14	0.288	-3.05	-8.54	2.44	0.261
No	7.36	-1.84	16.10	0.114	-4.27	-12.20	4.27	0.328	2.76	-1.84	7.82	0.213	0.00	-5.49	6.10	0.929
Family history of cardiovascular disease																
Yes	3.68	-7.82	14.72	0.530	0.61	-8.54	9.15	0.899	-1.38	-7.82	5.06	0.674	-2.44	-9.15	4.88	0.539
No	15.18	0.46	29.90	0.046*	-10.37	-21.96	1.22	0.087	0.46	-11.04	12.42	0.915	-9.15	-17.69	0.00	0.056
Cardiovascular medication use																
Yes	10.12	1.38	19.32	0.027*	-3.66	-10.37	3.66	0.338	1.84	-2.76	6.90	0.413	-3.66	-8.54	1.83	0.190
No	7.82	-4.14	20.24	0.196	-4.27	-12.81	4.27	0.335	0.92	-5.52	7.82	0.750	0.00	-6.10	5.49	0.960
Statin medication use																
Yes	11.04	-0.46	22.54	0.057	-0.61	-9.76	8.54	0.926	2.30	-3.68	8.74	0.439	3.66	-3.05	9.76	0.283
No	5.52	-3.68	14.72	0.253	-4.88	-12.20	1.83	0.165	0.92	-4.14	6.44	0.664	-3.66	-8.54	0.61	0.113
Diabetic																
Yes	9.66	-0.92	20.70	0.075	-9.15	-17.08	-0.61	0.036*	1.84	-3.68	7.82	0.514	-4.88	-10.37	1.22	0.101
No	8.74	-0.92	18.40	0.081	0.00	-7.32	7.32	0.976	1.38	-4.14	6.44	0.647	0.61	-4.88	5.49	0.889
Covariates†	age, sex, education, BMI, LDL cholesterol, HDL cholesterol, ln(triglycerides), diabetes status				age, education, BMI, LDL cholesterol, HDL cholesterol, ln(triglycerides), diabetes status, anxiety medication				baseline ln(CRP), age, education, BMI, LDL cholesterol, HDL cholesterol, marital status				baseline ln(CRP), age, education, BMI, LDL cholesterol, HDL cholesterol, marital status			

Supplement 3.2. Comparing modeled and measured PNC values at Countway Library

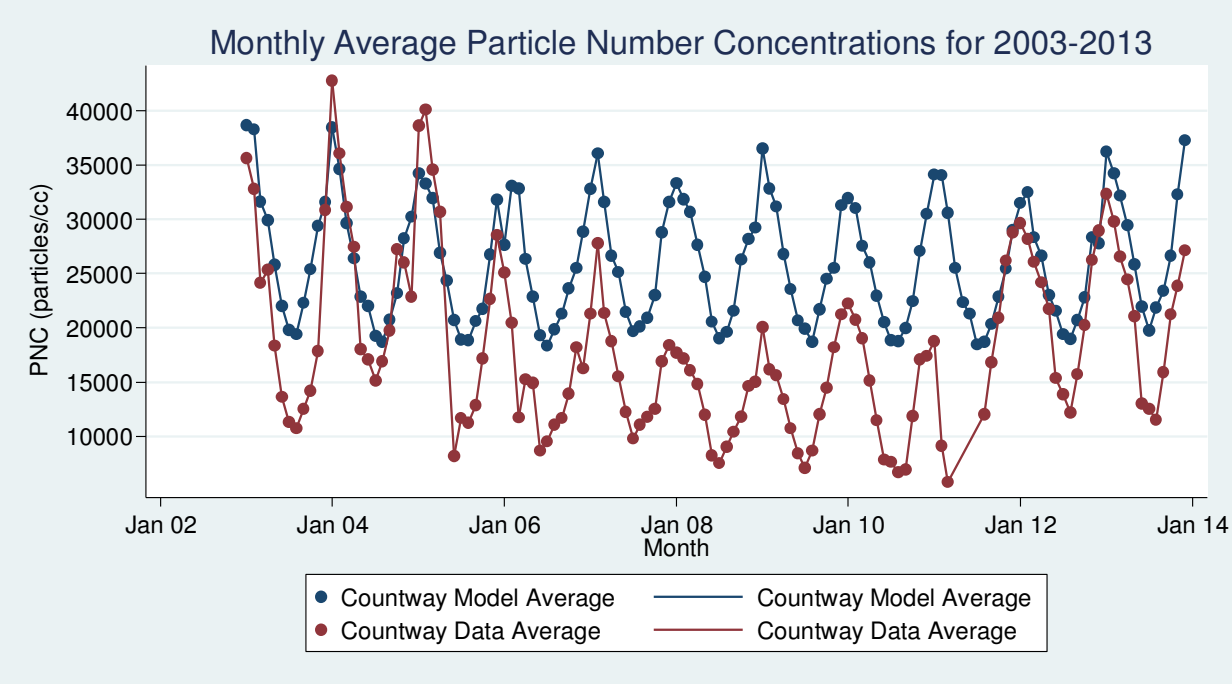

Figure 3S2.1: Modeled and measured PNC values at Countway Library

Data from the Harvard School of Public Health at the Countway Library of Medicine were obtained through the financial support of USEPA (Grant RD 83479801) and NIEHS (Grant PO1ES009825) (Harvard Clean Air Research Center, 2015). Modeled values were predicted for Countway Library using our team's UFP exposure model described in Chapter 2.

Works Cited

Adar, S. D., Sheppard, L., Vedal, S., Polak, J. F., Sampson, P. D., Diez Roux, A. V., … Kaufman, J. D. (2013). Fine Particulate Air Pollution and the Progression of Carotid Intima-Medial Thickness: A Prospective Cohort Study from the Multi-Ethnic Study of Atherosclerosis and Air Pollution. *PLoS Med*, *10*(4), e1001430. http://doi.org/10.1371/journal.pmed.1001430

Beelen, R., Hoek, G., van den Brandt, P. A., Goldbohm, R. A., Fischer, P., Schouten, L. J., … Brunekreef, B. (2008). Long-Term Effects of Traffic-Related Air Pollution on Mortality in a Dutch Cohort (NLCS-AIR Study). *Environmental Health Perspectives*, *116*(2), 196–202. http://doi.org/10.1289/ehp.10767

Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z. J., Weinmayr, G., Hoffmann, B., … Hoek, G. (2014). Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *The Lancet*, *383*(9919), 785–795. http://doi.org/10.1016/S0140-6736(13)62158-3

Bigazzi, A. Y., & Figliozzi, M. A. (2014). Review of Urban Bicyclists' Intake and Uptake of Traffic-Related Air Pollution. *Transport Reviews*, *34*(2), 221–245. http://doi.org/10.1080/01441647.2014.897772

Billionnet, C., Sherrill, D., & Annesi-Maesano, I. (2012). Estimating the Health Effects of Exposure to Multi-Pollutant Mixture. *Annals of Epidemiology*, *22*(2), 126–141. http://doi.org/10.1016/j.annepidem.2011.11.004

Boogaard, H., Borgman, F., Kamminga, J., & Hoek, G. (2009). Exposure to ultrafine and fine particles and noise during cycling and driving in 11 Dutch cities. *Atmospheric Environment*, *43*(27), 4234–4242. http://doi.org/10.1016/j.atmosenv.2009.05.035

Borm, P. J. A., Schins, R. P. F., & Albrecht, C. (2004). Inhaled particles and lung cancer, part B: Paradigms and risk assessment. *International Journal of Cancer*, *110*(1), 3–14. http://doi.org/10.1002/ijc.20064

Brook, R. D., Franklin, B., Cascio, W., Hong, Y., Howard, G., Lipsett, M., … Tager, I. (2004). Air Pollution and Cardiovascular Disease A Statement for Healthcare Professionals From the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation*, *109*(21), 2655–2671. http://doi.org/10.1161/01.CIR.0000128587.30041.C8

Brown, J. S., Zeman, K. L., & Bennett, W. D. (2002). Ultrafine Particle Deposition and Clearance in the Healthy and Obstructed Lung. *American Journal of Respiratory and Critical Care Medicine*, *166*(9), 1240–1247. http://doi.org/10.1164/rccm.200205-399OC

Cesaroni, G., Forastiere, F., Stafoggia, M., Andersen, Z. J., Badaloni, C., Beelen, R., … Peters, A. (2014). Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. *BMJ*, *348*, f7412. http://doi.org/10.1136/bmj.f7412

Chen, J.-C., & Schwartz, J. (2008). Metabolic Syndrome and Inflammatory Responses to Long-Term Particulate Air Pollutants. *Environmental Health Perspectives*, *116*(5), 612–617. http://doi.org/10.1289/ehp.10565

Chuang, K.-J., Yan, Y.-H., Chiu, S.-Y., & Cheng, T.-J. (2010). Long-term air pollution exposure and risk factors for cardiovascular diseases among the elderly in Taiwan. *Occupational and Environmental Medicine*, oem.2009.052704. http://doi.org/10.1136/oem.2009.052704

Chung, M., Wang, D. D., Rizzo, A. M., Gachette, D., Delnord, M., Parambi, R., … Brugge, D. (2015). Association of PNC, BC, and PM2.5 Measured at a Central Monitoring Site with Blood Pressure in a Predominantly Near Highway Population. *International Journal of Environmental Research and Public Health*, *12*(3), 2765–2780. http://doi.org/10.3390/ijerph120302765

Coogan, P. F., White, L. F., Jerrett, M., Brook, R. D., Su, J. G., Seto, E., … Rosenberg, L. (2012). Air Pollution and Incidence of Hypertension and Diabetes Mellitus in Black Women Living in Los Angeles. *Circulation*, *125*(6), 767–772. http://doi.org/10.1161/CIRCULATIONAHA.111.052753

Corlin, L., Woodin, M., Lane, K., Patton, A., Thanikachalam, M., & Brugge, D. (2014). Association of Particle Number Concentration Adjusted for Time-Activity with Blood Pressure and Ankle Brachial Index. *Environmental Health Perspectives - ISEE Abstracts*. Retrieved from http://ehp.niehs.nih.gov/isee/p2-490/

Crouse, D. L., Peters, P. A., van Donkelaar, A., Goldberg, M. S., Villeneuve, P. J., Brion, O., … Burnett, R. T. (2012). Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environmental Health Perspectives*, *120*(5), 708–714. http://doi.org/10.1289/ehp.1104049

Curjuric, I., Imboden, M., Nadif, R., Kumar, A., Schindler, C., Haun, M., … Probst-Hensch, N. M. (2012). Different Genes Interact with Particulate Matter and Tobacco Smoke Exposure in Affecting Lung Function Decline in the General Population. *PLoS ONE*, *7*(7). http://doi.org/10.1371/journal.pone.0040175

Daigle, C. C., Chalupa, D. C., Gibb, F. R., Morrow, P. E., Oberdörster, G., Utell, M. J., & Frampton, M. W. (2003). Ultrafine Particle Deposition in Humans During Rest and Exercise. *Inhalation Toxicology*, *15*(6), 539–552. http://doi.org/10.1080/08958370304468

Delfino, R. J., Staimer, N., Tjoa, T., Polidori, A., Arhami, M., Gillen, D., … Sioutas, C. (2008). Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. *Environmental Health Perspectives*, *116*(7), 898–906. http://doi.org/http://dx.doi.org/10.1289/ehp.11189

Delfino, R., Staimer, N., Tjoa, T., Gillen, D., Polidori, A., Arhami, M., … Sioutas, C. (2009). Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. *Environmental Health Perspectives*, *117*(8), 1232–8. http://doi.org/http://dx.doi.org/10.1289/ehp.0800194

Delfino, R., Tjoa, T., Gillen, D. L., Staimer, N., Polidori, A., Arhami, M., … Longhurst, J. (2010). Traffic-related Air Pollution and Blood Pressure in Elderly Subjects With Coronary Artery Disease. *Epidemiology (Cambridge, Mass.)*, *21*(3). http://doi.org/10.1097/EDE.0b013e3181d5e19b

Dockery, D. W., Pope, C. A., 3rd, Xu, X., Spengler, J. D., Ware, J. H., Fay, M. E., … Speizer, F. E. (1993). An association between air pollution and mortality in six U.S. cities. *The New England Journal of Medicine*, *329*(24), 1753–1759. http://doi.org/10.1056/NEJM199312093292401

Dominici, F., Peng, R. D., Barr, C. D., & Bell, M. L. (2010). Protecting Human Health from Air Pollution: Shifting from a Single-Pollutant to a Multi-pollutant Approach. *Epidemiology (Cambridge, Mass.)*, *21*(2), 187–194. http://doi.org/10.1097/EDE.0b013e3181cc86e8

Donaldson, K., Brown, D., Clouter, A., Duffin, R., MacNee, W., Renwick, L., … Stone, V. (2002). The pulmonary toxicology of ultrafine particles. *Journal of Aerosol Medicine: The Official Journal of the International Society for Aerosols in Medicine*, *15*(2), 213–220. http://doi.org/10.1089/089426802320282338

Forastiere, F., Stafoggia, M., Tasco, C., Picciotto, S., Agabiti, N., Cesaroni, G., & Perucci, C. A. (2007). Socioeconomic status, particulate air pollution, and daily mortality: Differential exposure or differential susceptibility. *American Journal of Industrial Medicine*, *50*(3), 208–216. http://doi.org/10.1002/ajim.20368

Franklin, S. S., Larson, M. G., Khan, S. A., Wong, N. D., Leip, E. P., Kannel, W. B., & Levy, D. (2001). Does the Relation of Blood Pressure to Coronary Heart Disease Risk Change With Aging? The Framingham Heart Study. *Circulation*, *103*(9), 1245–1249. http://doi.org/10.1161/01.CIR.103.9.1245

Fruin, S., Westerdahl, D., Sax, T., Sioutas, C., & Fine, P. M. (2008). Measurements and predictors of on-road ultrafine particle concentrations and associated pollutants in Los Angeles. *Atmospheric Environment*, *42*(2), 207–219. http://doi.org/10.1016/j.atmosenv.2007.09.057

Fuks, K., Moebus, S., Hertel, S., Viehmann, A., Nonnemacher, M., Dragano, N., … Hoffmann, B. (2011). Long-Term Urban Particulate Air Pollution, Traffic Noise, and Arterial Blood Pressure. *Environmental Health Perspectives*, *119*(12), 1706–1711. http://doi.org/10.1289/ehp.1103564

Fuks, K., Weinmayr, G., Foraster, M., Dratva, J., Hampel, R., Houthuijs, D., … Hoffmann, B. (2014). Arterial Blood Pressure and Long-Term Exposure to Traffic-Related Air Pollution: An Analysis in the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Environmental Health Perspectives*. http://doi.org/10.1289/ehp.1307725

Fuller, C. H., Brugge, D., Williams, P. L., Mittleman, M. A., Lane, K., Durant, J. L., & Spengler, J. D. (2013). Indoor and outdoor measurements of particle number concentration in near-highway homes. *Journal of Exposure Science and Environmental Epidemiology*, *23*(5), 506–512. http://doi.org/10.1038/jes.2012.116

Fuller, C. H., Williams, P. L., Mittleman, M. A., Patton, A. P., Spengler, J. D., & Brugge, D. (2015). Response of biomarkers of inflammation and coagulation to short-term changes in central site, local, and predicted particle number concentrations. *Annals of Epidemiology*. http://doi.org/10.1016/j.annepidem.2015.02.003

Gan, W. Q., Koehoorn, M., Davies, H. W., Demers, P. A., Tamburic, L., & Brauer, M. (2011). Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. *Environmental Health Perspectives*, *119*(4), 501–507. http://doi.org/10.1289/ehp.1002511

Harvard Clean Air Research Center. (2015). Harvard Clean Air Research Program. Retrieved March 23, 2015, from http://www.hsph.harvard.edu/clarc/index.html

Hennig, F., Fuks, K., Moebus, S., Weinmayr, G., Memmesheimer, M., Jakobs, H., … Hoffmann, B. (2014). Association between Source-Specific Particulate Matter Air Pollution and hs-CRP: Local Traffic and Industrial Emissions. *Environmental Health Perspectives*, *122*(7), 703–710. http://doi.org/10.1289/ehp.1307081

Hertel, S., Viehmann, A., Moebus, S., Mann, K., Bröcker-Preuss, M., Möhlenkamp, S., … Hoffmann, B. (2010). Influence of short-term exposure to ultrafine and fine particles on systemic inflammation. *European Journal of Epidemiology*, *25*(8), 581–592. http://doi.org/10.1007/s10654-010-9477-x

Hoffmann, B., Moebus, S., Dragano, N., Stang, A., Möhlenkamp, S., Schmermund, A., … Jöckel, K.-H. (2009). Chronic Residential Exposure to Particulate Matter Air Pollution and Systemic Inflammatory Markers. *Environmental Health Perspectives*, *117*(8), 1302–1308. http://doi.org/10.1289/ehp.0800362

Ibald-Mulli, A., Timonen, K. L., Peters, A., Heinrich, J., Wolke, G., Lanki, T., … Pekkanen, J. (2004). Effects of particulate air pollution on blood pressure and heart rate in subjects with cardiovascular disease: a multicenter approach. *Environmental Health Perspectives*, *112*(3), 369–377.

Int Panis, L., de Geus, B., Vandenbulcke, G., Willems, H., Degraeuwe, B., Bleux, N., … Meeusen, R. (2010). Exposure to particulate matter in traffic: A comparison of cyclists and car passengers. *Atmospheric Environment*, *44*(19), 2263–2270. http://doi.org/10.1016/j.atmosenv.2010.04.028

Jessen, K. (2010). MBTA Launches Hybrid Buses [Text]. Retrieved March 31, 2015, from http://blog.mass.gov/transportation/mbta/mbta-launches-hybrid-buses/

Johnson, D., & Parker, J. D. (2009). Air pollution exposure and self-reported cardiovascular disease. *Environmental Research*, *109*(5), 582–589. http://doi.org/10.1016/j.envres.2009.01.001

Kaur, S., Nieuwenhuijsen, M., & Colvile, R. (2005). Personal exposure of street canyon intersection users to PM2.5, ultrafine particle counts and carbon monoxide in Central London, UK. *Atmospheric Environment*, *39*(20), 3629–3641. http://doi.org/10.1016/j.atmosenv.2005.02.046

Kozawa, K. H., Winer, A. M., & Fruin, S. A. (2012). Ultrafine particle size distributions near freeways: Effects of differing wind directions on exposure. *Atmospheric Environment*, *63*, 250–260. http://doi.org/10.1016/j.atmosenv.2012.09.045

Kreyling, W. G., Semmler-Behnke, M., & Möller, W. (2006). Ultrafine Particle–Lung Interactions: Does Size Matter? *Journal of Aerosol Medicine*, *19*(1), 74–83. http://doi.org/10.1089/jam.2006.19.74

Künzli, N., Jerrett, M., Mack, W. J., Beckerman, B., LaBree, L., Gilliland, F., … Hodis, H. N. (2005). Ambient Air Pollution and Atherosclerosis in Los Angeles. *Environmental Health Perspectives*, *113*(2), 201–206. http://doi.org/10.1289/ehp.7523

Lane, K. J., Kangsen Scammell, M., Levy, J. I., Fuller, C. H., Parambi, R., Zamore, W., … Brugge, D. (2013). Positional error and time-activity patterns in near-highway proximity studies: an exposure misclassification analysis. *Environmental Health*, *12*, 75. http://doi.org/10.1186/1476-069X-12-75

Lane, K., Levy, J., Scammell, M., Patton, A., Durant, J., Mwamburi, M., … Brugge, D. (2015). Effect of time-activity adjustment on exposure assessment for traffic-related ultrafine particles. *Journal of Exposure Science and Environmental Epidemiology*.

Leikauf, L. G. (2010). Toxic Responses of the Respiratory System. In C. Klaassen & J. B. Watkins (Eds.), *Casarett and Doull's Essentials of Toxicology* (Vols. 1–2nd). New York: McGraw-Hill.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., ..., … Memish, Z. A. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, *380*(9859), 2224–2260. http://doi.org/10.1016/S0140-6736(12)61766-8

Lippmann, M., Yeates, D. B., & Albert, R. E. (1980). Deposition, retention, and clearance of inhaled particles. *British Journal of Industrial Medicine*, *37*(4), 337–362.
MassDOT. (2014). The Big Dig - Highway Division. Retrieved March 23, 2015, from http://www.massdot.state.ma.us/highway/TheBigDig.aspx
MBTA. (2007). *Capital Investment Program FY2008 - FY2012*. Retrieved from https://www.google.com/search?q=Capital+Investment+Program+FY2008+-+FY2012+mbta&ie=utf-8&oe=utf-8
Miller, K. A., Siscovick, D. S., Sheppard, L., Shepherd, K., Sullivan, J. H., Anderson, G. L., & Kaufman, J. D. (2007). Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women. *New England Journal of Medicine*, *356*(5), 447–458. http://doi.org/10.1056/NEJMoa054409
Miyata, R., Bai, N., Vincent, R., Sin, D. D., & Eeden, S. F. V. (2012). Novel properties of statins: suppression of the systemic and bone marrow responses induced by exposure to ambient particulate matter (PM10) air pollution. *American Journal of Physiology - Lung Cellular and Molecular Physiology*, *303*(6), L492–L499. http://doi.org/10.1152/ajplung.00154.2012
Miyata, R., Hiraiwa, K., Cheng, J. C., Bai, N., Vincent, R., Francis, G. A., … Van Eeden, S. F. (2013). Statins attenuate the development of atherosclerosis and endothelial dysfunction induced by exposure to urban particulate matter (PM10). *Toxicology and Applied Pharmacology*, *272*(1), 1–11. http://doi.org/10.1016/j.taap.2013.05.033
Noble, C. A., Mukerjee, S., Gonzales, M., Rodes, C. E., Lawless, P. A., Natarajan, S., … Neas, L. M. (2003). Continuous measurement of fine and ultrafine particulate matter, criteria pollutants and meteorological conditions in urban El Paso, Texas. *Atmospheric Environment*, *37*(6), 827–840. http://doi.org/10.1016/S1352-2310(02)00935-4
Oberdörster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Kreyling, W., & Cox, C. (2004). Translocation of Inhaled Ultrafine Particles to the Brain. *Inhalation Toxicology*, *16*(6-7), 437–445. http://doi.org/10.1080/08958370490439597
O'Neill, M. S., Veves, A., Zanobetti, A., Sarnat, J. A., Gold, D. R., Economides, P. A., … Schwartz, J. (2005). Diabetes Enhances Vulnerability to Particulate Air Pollution–Associated Impairment in Vascular Reactivity and Endothelial Function. *Circulation*, *111*(22), 2913–2920. http://doi.org/10.1161/CIRCULATIONAHA.104.517110
Ostro, B., Hu, J., Goldberg, D., Reynolds, P., Hertz, A., Bernstein, L., & Kleeman, M. J. (2015). Associations of Mortality with Long-Term Exposures to Fine and Ultrafine Particles, Species and Sources: Results from the California Teachers Study Cohort. *Environmental Health Perspectives*. http://doi.org/10.1289/ehp.1408565
Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., Criqui, M., … Vinicor, F. (2003). Markers of Inflammation and Cardiovascular Disease Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*, *107*(3), 499–511. http://doi.org/10.1161/01.CIR.0000052939.59093.45
Peters, A., Dockery, D. W., Muller, J. E., & Mittleman, M. A. (2001). Increased Particulate Air Pollution and the Triggering of Myocardial Infarction. *Circulation*, *103*(23), 2810–2815. http://doi.org/10.1161/01.CIR.103.23.2810
Pope, C. A., 3rd, Burnett, R. T., Thun, M. J., Calle, E. E., Krewski, D., Ito, K., & Thurston, G. D. (2002). Lung cancer, cardiopulmonary mortality, and long-term exposure to fine

particulate air pollution. *JAMA: The Journal of the American Medical Association*, *287*(9), 1132–1141.

Pope, C. A., Thun, M. J., Namboodiri, M. M., Dockery, D. W., Evans, J. S., Speizer, F. E., & Heath, C. W. (1995). Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults. *American Journal of Respiratory and Critical Care Medicine*, *151*(3_pt_1), 669–674. http://doi.org/10.1164/ajrccm/151.3_Pt_1.669

Pope, C. A., Turner, M. C., Burnett, R. T., Jerrett, M., Gapstur, S. M., Diver, W. R., … Brook, R. D. (2015). Relationships Between Fine Particulate Air Pollution, Cardiometabolic Disorders, and Cardiovascular Mortality. *Circulation Research*, *116*(1), 108–115. http://doi.org/10.1161/CIRCRESAHA.116.305060

Pope III, C. A., Verrier, R. L., Lovett, E. G., Larson, A. C., Raizenne, M. E., Kanner, R. E., … Dockery, D. W. (1999). Heart rate variability associated with particulate air pollution. *American Heart Journal*, *138*(5), 890–899. http://doi.org/10.1016/S0002-8703(99)70014-1

Puett, R. C., Hart, J. E., Yanosky, J. D., Paciorek, C., Schwartz, J., Suh, H., … Laden, F. (2009). Chronic Fine and Coarse Particulate Exposure, Mortality, and Coronary Heart Disease in the Nurses' Health Study. *Environmental Health Perspectives*, *117*(11), 1697–1701. http://doi.org/10.1289/ehp.0900572

Rich, D. Q., Zareba, W., Beckett, W., Hopke, P. K., Oakes, D., Frampton, M. W., … Utell, M. J. (2012). Are ambient ultrafine, accumulation mode, and fine particles associated with adverse cardiac responses in patients undergoing cardiac rehabilitation? *Environmental Health Perspectives*, *120*(8), 1162–1169. http://doi.org/10.1289/ehp.1104262

Rioux, C. L., Tucker, K. L., Brugge, D., Gute, D. M., & Mwamburi, M. (2011). Traffic Exposure in a Population with High Prevalence Type 2 Diabetes - Do Medications Influence Concentrations of C-Reactive Protein? *Environmental Pollution (Barking, Essex : 1987)*, *159*(8-9), 2051–2060. http://doi.org/10.1016/j.envpol.2010.12.025

Rioux, C. L., Tucker, K. L., Mwamburi, M., Gute, D. M., Cohen, S. A., & Brugge, D. (2010). Residential Traffic Exposure, Pulse Pressure, and C-reactive Protein: Consistency and Contrast among Exposure Characterization Methods. *Environmental Health Perspectives*, *118*(6), 803–811. http://doi.org/10.1289/ehp.0901182

Ruckerl, R., Greven, S., Ljungman, P., Aalto, P., Antoniades, C., Bellander, T., … Peters, A. (2007). Air Pollution and Inflammation (Interleukin-6, C-Reactive Protein, Fibrinogen) in Myocardial Infarction Survivors. *Environmental Health Perspectives*, *115*(7), 1072–1080. http://doi.org/10.1289/ehp.10021

Rückerl, R., Ibald-Mulli, A., Koenig, W., Schneider, A., Woelke, G., Cyrys, J., … Peters, A. (2006). Air Pollution and Markers of Inflammation and Coagulation in Patients with Coronary Heart Disease. *American Journal of Respiratory and Critical Care Medicine*, *173*(4), 432–441. http://doi.org/10.1164/rccm.200507-1123OC

Schwartz, J., & Morris, R. (1995). Air Pollution and Hospital Admissions for Cardiovascular Disease in Detroit, Michigan. *American Journal of Epidemiology*, *142*(1), 23–35.

Schwartz, J., Park, S. K., O'Neill, M. S., Vokonas, P. S., Sparrow, D., Weiss, S., & Kelsey, K. (2005). Glutathione-S-Transferase M1, Obesity, Statins, and Autonomic Effects of Particles. *American Journal of Respiratory and Critical Care Medicine*, *172*(12), 1529–1533. http://doi.org/10.1164/rccm.200412-1698OC

Sørensen, M., Hoffmann, B., Hvidberg, M., Ketzel, M., Jensen, S. S., Andersen, Z. J., … Raaschou-Nielsen, O. (2012). Long-Term Exposure to Traffic-Related Air Pollution

Associated with Blood Pressure and Self-Reported Hypertension in a Danish Cohort. *Environmental Health Perspectives*, *120*(3), 418–424. http://doi.org/10.1289/ehp.1103631

Stoeger, T., Reinhard, C., Takenaka, S., Schroeppel, A., Karg, E., Ritter, B., … Schulz, H. (2006). Instillation of six different ultrafine carbon particles indicates a surface area threshold dose for acute lung inflammation in mice. *Environmental Health Perspectives*, *114*(3), 328–333.

Tucker, K. L., Mattei, J., Noel, S. E., Collado, B. M., Mendez, J., Nelson, J., … Falcon, L. M. (2010). The Boston Puerto Rican Health Study, a longitudinal cohort study on health disparities in Puerto Rican adults: challenges and opportunities. *BMC Public Health*, *10*(1), 107. http://doi.org/10.1186/1471-2458-10-107

Weichenthal, S., Farrell, W., Goldberg, M., Joseph, L., & Hatzopoulou, M. (2014). Characterizing the impact of traffic and the built environment on near-road ultrafine particle and black carbon concentrations. *Environmental Research*, *132*, 305–310. http://doi.org/10.1016/j.envres.2014.04.007

Wheeler, A., Zanobetti, A., Gold, D. R., Schwartz, J., Stone, P., & Suh, H. H. (2006). The Relationship between Ambient Air Pollution and Heart Rate Variability Differs for Individuals with Heart and Pulmonary Disease. *Environmental Health Perspectives*, *114*(4), 560–566.

Yasue, H., Hirai, N., Mizuno, Y., Harada, E., Itoh, T., Yoshimura, M., … Ogawa, H. (2006). Low-Grade Inflammation, Thrombogenicity, and Atherogenic Lipid Profile in Cigarette Smokers. *Circulation Journal*, *70*(1), 8–13. http://doi.org/10.1253/circj.70.8

Yue, W., Schneider, A., Stölzel, M., Rückerl, R., Cyrys, J., Pan, X., … Peters, A. (2007). Ambient source-specific particles are associated with prolonged repolarization and increased levels of inflammation in male coronary artery disease patients. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *621*(1–2), 50–60. http://doi.org/10.1016/j.mrfmmm.2007.02.009

Zeka, A., Sullivan, J. R., Vokonas, P. S., Sparrow, D., & Schwartz, J. (2006). Inflammatory markers and particulate air pollution: characterizing the pathway to disease. *International Journal of Epidemiology*, *35*(5), 1347–1354. http://doi.org/10.1093/ije/dyl132

Zwack, L. M., Hanna, S. R., Spengler, J. D., & Levy, J. I. (2011). Using advanced dispersion models and mobile monitoring to characterize spatial patterns of ultrafine particles in an urban area. *Atmospheric Environment*, *45*(28), 4822–4829. http://doi.org/10.1016/j.atmosenv.2011.06.019

Chapter 4. Associations between exposure to ultrafine particulate matter and changes in cognitive function over five years

Introduction

As the U.S. population ages over the next 40 years, the prevalence of Alzheimer's dementia is expected to nearly triple from 4.7 million adults living with Alzheimer's in 2010 to 13.8 million by 2050 (Hebert, Weuve, Scherr, & Evans, 2013). In addition to the substantial and increasing burden of Alzheimer's, mild cognitive impairment is pervasive in the U.S. with between three and 19 percent of elderly adults affected (Gauthier et al., 2006). Identifying modifiable risk factors for cognitive impairment is therefore a public health priority. Education, physical activity, smoking, depression, obesity, cardiovascular disease, and diabetes are among the known modifiable risk factors for cognitive impairment and dementia (Kivipelto et al., 2001; Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Winblad et al., 2004; Anstey, Sanden, Salim, & O'Kearney, 2007; Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). Another modifiable risk factor may be traffic-related air pollution. In particular, traffic-related air pollution may affect cognitive function through mechanisms mediated by an increased concentration of circulating cytokines leading to increased neuroinflammation and oxidative stress within the central nervous system (Block & Calderón-Garcidueñas, 2009). Additionally, the smallest size fraction of particulate matter, ultrafine particulate matter (UFP, particles < 0.1 µm aerodynamic diameter) may exert effects within the brain since particles in this size range can cross the blood-brain barrier (Oberdörster et al., 2004).

Despite the public health need to identify modifiable risk factors for cognitive decline and the biologically plausible routes through which traffic-related air pollutants may lead to cognitive decline, few studies have addressed this question directly. There have been several studies that examined associations between proximity to roadways and cognitive function among

older adults. One longitudinal study of 400 adults found that proximity to major roadways was significantly associated with mild cognitive impairment among adults younger than 75 years of age (Ranft, Schikowski, Sugiri, Krutmann, & Krämer, 2009). Another study followed 765 adults over 65 years of age for a median interval of 16.8 months. Proximity to roadways was inversely associated with cognitive function on a number of cognitive measures. However, proximity to major roadways was only significantly associated with Mini-Mental State Examination (MMSE, a validated scale for global cognitive function) scores among people with more than a high school education and among younger members of the cohort (≤ 77 years). Moreover, in this study, only 10 percent of participants lived within 100 meters (m) of major roadways and approximately two-thirds lived more than 500 m from major roadways so the ability to assess near-roadway exposure was limited (Wellenius et al., 2012). Additionally, by using proximity as a proxy for participants' exposure to pollutants, exposure misclassification was likely.

Nevertheless, the results of the proximity studies have been largely corroborated by studies that have considered the association between modeled or measured air pollution and cognitive function. In the Nurses' Health Study, for example, women who had greater exposure to fine particulate matter ($PM_{2.5}$, particles with less than 2.5 µm aerodynamic diameter) and coarse particulate matter (PM_{10}, particles with less than 10 µm aerodynamic diameter) experienced a faster rate of cognitive decline. Using data from three waves of cognitive assessments over seven years, each 10 µg/m³ increase in exposure to $PM_{2.5}$ and to PM_{10} was associated with a cognitive performance decline trajectory similar to that of individuals one to two years older (Weuve J et al., 2012). Similarly, for men in the Normative Aging Study, a doubling of log-transformed black carbon exposure levels over 11 years was associated with cognitive scores equivalent to those of individuals 1.9 years older (Power et al., 2011).

Recent cross-sectional studies have found similar deficits in cognitive function among older adults exposed to high levels of regional traffic-related air pollution. Adults residing in census tracts with higher $PM_{2.5}$ concentrations had significantly worse cognitive function scores on the Telephone Interview for Cognitive Status, a scale similar to the MMSE in terms of the types of questions asked (Ailshire & Crimmins, 2014). However, in one cross-sectional study of nearly 1500 generally well-educated (> 90 percent had at least some college education) adults, none of annual average ozone, nitrogen dioxide, or $PM_{2.5}$ exposures was significantly associated with global cognitive function (Gatto et al., 2014). Nevertheless, particular domains of cognitive abilities, such as verbal learning or executive function, were significantly associated with concentrations of at least one pollutant. Similarly, in a cross-sectional study of 1764 adults participating in NHANES (mean age = 37.4 years, SD = 10.9), ozone but not PM_{10} exposure was associated with reduced cognitive function (Chen & Schwartz, 2009).

Although the studies that have considered the relationship between PM exposure and cognitive function have found significant associations, no longitudinal studies that we are aware of have considered the relationship between UFP exposure and cognitive decline. Since UFP may act through both direct and indirect mechanisms to affect cognitive function, we sought to examine both the relationship between UFP and cognitive function over five years and the relationship between UFP and cognitive decline over five years among adults participating in the longitudinal Boston Puerto Rican Health Study (BPRHS).

Additionally, we sought to compare the traditional approach of assigning ambient average exposure concentrations (measured as particle number concentration or PNC) to a novel method of assigning exposure which accounts for the sex and age-specific rate at which pollutants are inhaled. Since the physiological response is affected by both the ambient

concentration and the inhalation rate, we adjusted the residential annual average exposure concentrations by a factor representing each individual's respiratory volume to obtain the average hourly particle inhalation rate (PIR). While the PIR captures a slightly different physiological dynamic than PNC, we wanted to compare the strength of association between the two exposure metrics with cognitive function to provide a fuller understanding of any potential cognitive effects of UFP.

Results

Demographic characteristics of the sample, a comparison of our sample to the larger BPRHS population, and exposure distributions have been presented previously (Chapter 3). Table 4.1 shows the mean MMSE scores for each study visit, stratified by educational attainment, by age group (in decades), by quartile of PNC exposure, and by quartile of PIR. Note that in the BPRHS, only about half of participants had completed more than an eighth grade education and only 16 percent had any education beyond high school. A larger proportion of participants with lower educational attainment did not attempt the serial 7s question and participants with higher educational attainment scored significantly higher ($p < 0.001$ for all comparisons). In a bivariate analysis, age was also a significant predictor of cognitive function ($p < 0.001$ for both MMSE and Modified MMSE scores) and of changes in cognitive function ($p = 0.029$ for MMSE, $p = 0.032$ for Modified MMSE). Specifically, prior to age 50, MMSE scores were relatively constant with age but among participants ages 50-80, MMSE scores decreased linearly with age in our cohort. Additionally, in the multilevel models, MMSE scores showed significant decline by study visit ($p = 0.001$).

Table 4.1. Mean MMSE and Modified MMSE scores by study visit stratified by education, age, and UFP exposure

	Study visit 1			Study visit 2			Study visit 3		
	n	mean	SD	n	mean	SD	n	mean	SD
Educational Attainment									
Any education through 8th grade									
MMSE	204	23.4	2.9	192	22.3	3.2	96	22.7	3.0
Modified MMSE	368	20.5	2.7	276	20.7	2.6	192	20.8	2.4
Any high school									
MMSE	217	25.0	2.5	182	24.5	2.5	93	24.8	2.9
Modified MMSE	285	22.0	1.9	220	22.1	1.8	137	22.4	1.8
Post high school									
MMSE	110	26.3	2.3	83	25.9	2.3	46	26.5	2.7
Modified MMSE	123	23.0	1.6	88	23.1	1.3	57	22.9	1.8
Age Group									
40s									
MMSE	94	25.2	2.7	43	24.6	2.7	0	NA	NA
Modified MMSE	127	22.1	2.3	50	22.4	2.1	0	NA	NA
50s									
MMSE	251	25.0	2.7	220	24.2	3.0	91	25.0	2.6
Modified MMSE	365	21.8	2.2	277	21.8	2.3	143	22.3	1.9
60s									
MMSE	159	24.2	2.7	154	23.5	3.2	96	24.0	3.6
Modified MMSE	240	21.0	2.5	200	21.4	2.3	169	21.6	2.3
70s and 80s									
MMSE	29	22.4	4.0	30	22.6	3.6	49	23.3	3.4
Modified MMSE	49	19.6	2.8	59	20.7	2.6	78	20.8	2.5
PNC Exposure									
Lowest quartile (< 21300 particles/cc)									
MMSE	140	25.0	3.2	95	24.3	3.3	69	25.0	3.2
Modified MMSE	195	21.8	2.6	128	21.7	2.4	112	22.2	2.0
2nd quartile (21300 - 23999)									
MMSE	111	24.7	2.7	134	23.8	3.2	57	23.9	3.4
Modified MMSE	176	21.3	2.2	174	21.6	2.3	96	21.5	2.3
3rd quartile (24000 - 25899)									
MMSE	131	24.3	2.5	124	23.6	3.2	59	23.8	3.0
Modified MMSE	186	21.3	2.4	155	21.5	2.4	96	21.4	2.4
Highest quartile (≥ 25900 particles/cc)									
MMSE	151	24.7	2.9	104	23.8	2.8	51	24.3	3.2
Modified MMSE	224	21.4	2.5	129	21.4	2.3	86	21.5	2.4
PIR Exposure									
Lowest quartile (< 9.6 billion particles inhaled/hr)									
MMSE	111	24.1	2.4	122	23.2	3.4	51	23.9	3.4
Modified MMSE	170	21.1	2.8	154	21.1	2.7	104	21.5	2.5
2nd quartile (9.6 - 12.29 billion particles inhaled/hr)									
MMSE	129	24.4	2.9	100	23.6	3.3	50	24.5	3.3
Modified MMSE	205	21.2	2.6	138	21.4	2.4	82	21.9	2.5
3rd quartile (12.3 - 15.69 billion particles inhaled/hr)									
MMSE	128	24.7	2.7	111	24.0	3.1	53	24.8	3.3
Modified MMSE	190	21.4	2.3	142	21.6	2.3	84	21.7	2.1
Highest quartile (≥ 15.7 billion particles inhaled/hr)									
MMSE	162	25.1	2.5	118	24.5	2.6	63	24.4	2.6
Modified MMSE	209	22.0	2.1	138	22.2	2.0	88	21.9	1.7

Associations with UFP

Adjusting for relevant covariates, PNC was inversely associated with MMSE scores while the PIR was significantly and positively associated with MMSE scores. PNC was also significantly associated with the rate of cognitive decline as measured by the Modified MMSE but the PIR was not associated with the rate of cognitive decline. (Figure 4.1).

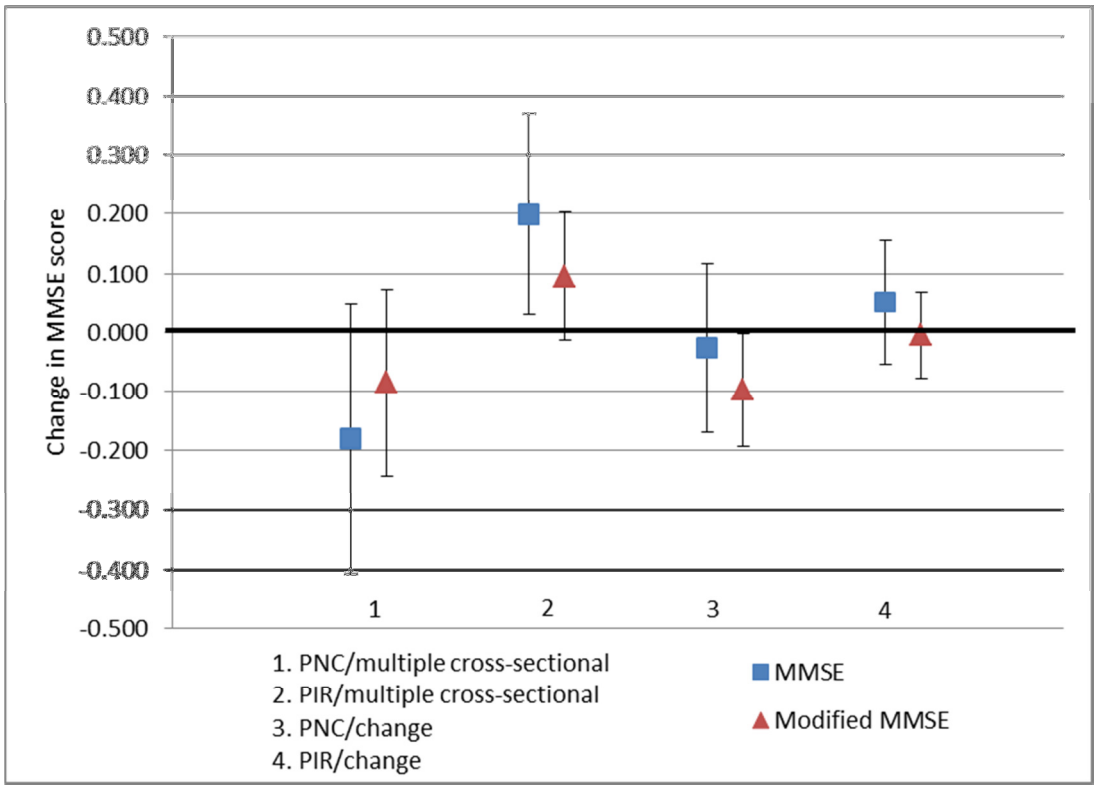

Figure 4.1. Change in MMSE score with an interquartile increase in PNC or PIR

Main models adjusted for:
1. MMSE (n = 658): age, education, sex, marital status, anxiety medications, and physical activity;
   Modified MMSE (n = 795): age, education, sex, depression, marital status, psychological acculturation;
2. MMSE (n = 643): age, education, depression, marital status, anxiety medications, diabetes;
   Modified MMSE (n = 791): age, education, depression, marital status, psychological acculturation;
3. MMSE (n = 539): baseline MMSE score, age, education, diabetes;
   Modified MMSE (n = 799): baseline Modified MMSE score, age, education, sex, marital status, psychological acculturation, perceived stress;
4. MMSE (n = 544): baseline MMSE score, age, education, statin medications;
   Modified MMSE (n = 795): baseline Modified MMSE score, age, education, marital status, psychological acculturation, perceived stress

Multiple cross-sectional associations

PNC was inversely associated with MMSE scores after controlling for relevant covariates, although this association was not statistically significant (95% CI for an IQR increase in PNC = -0.407, 0.046 points, Figure 4.1 and Table 4.2). Including a PNC by sex interaction term in the main model substantially increased the effect estimate for PNC (95% CI = -0.911, -0.157 points) and the interaction term was significant. Additionally, if we controlled for family history of hypertension, the association became significant but 328 participants were dropped due to missing data (95% CI = -0.598, -0.005 points, details not shown). Excluding family history of hypertension from the model, the inverse association between PNC and MMSE scores was significant among males, individuals who were not cognitively impaired, individuals who were younger than 65 years of age at baseline, individuals who were not taking hypertension medication, individuals without a family history of diabetes, individuals without diabetes, and individuals who had physical activity scores in the top tertile (Table 4.2). Additionally, there were non-statistically significant inverse associations between PNC and cognitive function scores among people who were depressed, among people who were not employed at baseline, and among former smokers (Table 4.2). However, PNC was not associated with the Modified MMSE scores (95% CI = -0.243, 0.073 points) except in a model controlling for family history of diabetes (95% CI = -0.386, 0.009 points) where a non-significant association was observed. Additionally, PNC was associated with Modified MMSE scores among those who were not cognitively impaired, those without hypertension medications, and those without a family history of diabetes (Table 4.2). There were also non-significant associations between PNC and the Modified MMSE scores among participants who were unemployed at baseline, among former smokers, and among individuals in the bottom tertile of physical activity (Table 4.2).

In contrast to the inverse associations observed between PNC and MMSE scores, an increased PIR was significantly associated with increased MMSE scores (95% CI for an IQR increase in PIR = 0.030, 0.369 points, Figure 4.1 and Table 4.3). Significant positive associations between the PIR and MMSE scores were apparent among females, among people who had not experienced a previous heart attack or stroke, among diabetics, among people with a family history of diabetes, and among people with BMIs in the normal range (Table 4.2). Additionally, non-significant positive associations were apparent between the PIR and MMSE scores among former smokers, among never smokers, among people who were not taking medications for hypertension, among people who had physical activity scores in the lowest two tertiles, and among obese people (Table 4.2). Associations between the PIR and the Modified MMSE scores showed similar trends, although the effect estimates for PIR were attenuated. Specifically, there was a non-significant positive association between the PIR and Modified MMSE scores in the main model (95% CI = -0.014, 0.204 points). While the only significant association between the PIR and the Modified MMSE scores was among people without a previous heart attack or stroke, diabetes, family history of diabetes, depression, and smoking all modified the association between the PIR and Modified MMSE scores (Table 4.2).

In order to explore the positive associations observed between increases in the PIR and cognitive function, we designed a post-hoc analysis to determine the relative influence of PNC and physical activity on cognitive function. In the main PNC/multiple cross-sectional model, neither PNC nor physical activity was significantly associated with MMSE scores, although the effect estimates had opposite signs (as given above, 95% CI for an IQR increase in PNC = -0.407, 0.046 points; 95% CI for an IQR increase in physical activity = -0.003, 0.047 points). When we restricted the main PNC/multiple cross-sectional model to only those participants with

physical activity scores in the second and third quartiles, PNC was not associated with MMSE scores (95% CI for an IQR increase in PNC = -0.416, 0.224 points). In contrast, when we restricted the main PNC/multiple cross-sectional model to only those participants with PNC scores in the second and third quartiles, physical activity was an independent predictor of MMSE scores (95% CI for an IQR increase in physical activity = 0.010, 0.081 points).

Associations between UFP and change in cognitive function

Despite the associations between PNC and the PIR with global cognitive function scores in the multiple cross-sectional analyses, neither PNC nor PIR was associated with changes in MMSE scores over time (Figure 4.1 and Table 4.3). However, strong effect modification was evident by sex. In males, PNC was significantly and inversely associated with changes in MMSE score (95% CI for an IQR increase in PNC = -0.454, -0.006 points) while in females, PNC was positively and non-significantly associated with changes in MMSE scores (95% CI = -0.046, 0.290). Furthermore, PNC was significantly associated with cognitive decline as measured by the Modified MMSE (95% CI = -0.192, -0.003 points). The association was stronger among males, among people who were not employed at baseline, among former smokers, among people who were not taking hypertension medication, and among people who had physical activity scores in the bottom tertile (Table 4.3).

Sensitivity analyses

We conducted two primary sensitivity analyses. First, we considered whether the high mortality rate (6.5 percent over the study period) affected the results. We found that excluding participants who died prior to their third study visit slightly attenuated the associations between

PNC and MMSE scores (95% CI for an IQR increase in PNC = -0.393, 0.073 points) and between the PIR and the Modified MMSE scores (95% CI for an IQR increase in PIR = -0.029, 0.192 points). Otherwise, excluding these participants had no material effect on the results. Furthermore, neither baseline MMSE scores nor baseline Modified MMSE scores differed significantly between participants who died before their third study visit and participants who did not die ($p = 0.324$ and $p = 0.384$, respectively).

Excluding people without at least some high school education had a greater effect on the results. Among participants with more than an eighth grade education, the association between PNC and change in MMSE scores was attenuated (Table 4.3) while the multiple cross-sectional association between PNC and MMSE scores was strengthened slightly (Table 4.2). Furthermore, the positive associations between the PIR and both MMSE and Modified MMSE scores were attenuated and not significant (Table 4.2).

Table 4.2. Multiple cross-sectional associations between an interquartile increase in PNC or PIR and cognitive function (associations with $p < 0.05$ denoted by an asterisk)

	MMSE								Modified MMSE							
	IQR PNC (n = 658)				IQR PIR (n = 643)				IQR PNC (n = 795)				IQR PIR (n = 791)			
	beta	95%L	95%U	p	beta	95%L	95%U	p	beta	95%L	95%U	p	beta	95%L	95%U	p
Main model†	-0.180	-0.407	0.046	0.119	0.199	0.030	0.369	0.021*	-0.085	-0.243	0.073	0.292	0.095	-0.014	0.204	0.089
Adjusted for age, baseline level (for change models), and education	-0.207	-0.435	0.020	0.074	0.206	0.039	0.373	0.016*	-0.102	-0.260	0.056	0.207	0.126	0.018	0.234	0.022*
Parallel main model	-0.156	-0.388	0.076	0.187	0.156	-0.017	0.328	0.078	-0.086	-0.244	0.073	0.290	0.130	0.018	0.243	0.023*
Parallel main model (no sex)	NA				0.188	0.020	0.355	0.028*	NA				Same as main model			
Main model for other MMSE	-0.200	-0.428	0.027	0.084	0.183	0.014	0.351	0.034*	-0.087	-0.245	0.071	0.280	0.103	-0.007	0.213	0.066
Excluding people who died before year 5 (n = 51)	-0.160	-0.393	0.073	0.179	0.187	0.014	0.360	0.034*	-0.080	-0.241	0.081	0.328	0.081	-0.029	0.192	0.150
Excluding people with ≤8th grade education	-0.249	-0.518	0.021	0.071	0.125	-0.083	0.333	0.238	-0.058	-0.225	0.108	0.491	0.070	-0.051	0.191	0.259
Sex																
Male	-0.504	-0.888	-0.119	0.010*	0.124	-0.150	0.398	0.376	-0.184	-0.461	0.093	0.192	0.172	-0.010	0.354	0.065
Female	0.031	-0.245	0.306	0.827	0.233	0.011	0.455	0.039*	-0.041	-0.233	0.152	0.679	0.105	-0.036	0.245	0.144
Cognitive impairment																
Yes	0.098	-0.166	0.362	0.468	0.040	-0.206	0.285	0.752	-0.037	-0.331	0.258	0.808	0.137	-0.117	0.391	0.291
No	-0.230	-0.412	-0.048	0.013*	0.011	-0.134	0.156	0.881	-0.142	-0.260	-0.023	0.020*	-0.061	-0.156	0.035	0.213
Baseline age																
Younger than 65 years of age	-0.253	-0.492	-0.013	0.039*	0.173	-0.003	0.349	0.053	-0.111	-0.272	0.049	0.175	0.069	-0.043	0.181	0.226
At least 65 years of age	0.277	-0.383	0.938	0.411	0.365	-0.251	0.981	0.246	0.160	-0.271	0.592	0.467	0.277	-0.145	0.699	0.199
Depressed																
Yes	-0.259	-0.552	0.035	0.084	0.218	0.002	0.434	0.048*	-0.124	-0.331	0.083	0.239	0.125	-0.013	0.262	0.076
No	-0.095	-0.459	0.269	0.608	0.191	-0.059	0.440	0.134	-0.116	-0.339	0.108	0.311	0.036	-0.128	0.200	0.668
Baseline employment status																
Yes	-0.157	-0.572	0.259	0.460	0.110	-0.174	0.394	0.447	0.143	-0.123	0.409	0.292	0.087	-0.085	0.258	0.324
No	-0.231	-0.516	0.054	0.112	0.121	-0.115	0.357	0.316	-0.178	-0.373	0.017	0.073	0.029	-0.125	0.183	0.711
Smoker status																
Current	-0.079	-0.509	0.351	0.719	0.004	-0.317	0.325	0.980	-0.120	-0.442	0.201	0.463	0.054	-0.183	0.291	0.658
Former	-0.300	-0.668	0.069	0.111	0.267	-0.014	0.547	0.063	-0.230	-0.463	0.004	0.054	0.129	-0.039	0.297	0.133
Never	-0.075	-0.452	0.301	0.695	0.213	-0.060	0.487	0.126	0.061	-0.194	0.316	0.639	0.066	-0.114	0.247	0.473
Hypertension medication use																
Yes	0.021	-0.296	0.338	0.898	0.120	-0.099	0.340	0.284	0.000	-0.222	0.222	0.999	0.041	-0.104	0.186	0.578
No	-0.406	-0.730	-0.081	0.014*	0.264	-0.012	0.540	0.061	-0.249	-0.450	-0.047	0.015*	0.128	-0.041	0.296	0.138
No previous heart attack/stroke	-0.074	-0.315	0.167	0.548	0.256	0.079	0.432	0.004*	-0.021	-0.185	0.142	0.797	0.117	0.002	0.233	0.047*
Family history of diabetes																
Yes	-0.209	-0.605	0.186	0.300	0.352	0.089	0.616	0.009*	-0.188	-0.457	0.081	0.171	0.162	-0.003	0.327	0.054
No	-0.460	-0.890	-0.031	0.036*	-0.267	-0.663	0.129	0.187	-0.264	-0.503	-0.025	0.030*	-0.239	-0.502	0.024	0.075
Diabetic																
Yes	0.111	-0.232	0.454	0.525	0.279	0.057	0.501	0.014*	-0.022	-0.260	0.216	0.855	0.063	-0.089	0.216	0.415
No	-0.377	-0.673	-0.081	0.013*	0.122	-0.119	0.363	0.322	-0.112	-0.322	0.098	0.296	0.124	-0.029	0.277	0.112
Replacing PIR with physical activity (IQR = 5.8)	NA				0.123	-0.032	0.279	0.120	NA				0.057	-0.041	0.156	0.253
Physical activity																
Top 1/3rd (≥ 32.2 points)	-0.343	-0.677	-0.009	0.044*	0.098	-0.127	0.323	0.393	-0.084	-0.315	0.146	0.472	0.096	-0.051	0.243	0.202
Middle 1/3rd	0.154	-0.235	0.543	0.437	0.472	-0.014	0.959	0.057	0.166	-0.111	0.443	0.240	0.305	-0.041	0.651	0.084
Bottom 1/3rd (<28.6 points)	-0.351	-0.822	0.120	0.145	0.617	-0.179	1.414	0.129	-0.283	-0.578	0.011	0.059	0.236	-0.250	0.722	0.342
BMI																
BMI ≥ 30 kg/m²	-0.152	-0.469	0.166	0.349	0.189	-0.026	0.403	0.084	-0.071	-0.303	0.161	0.548	0.103	-0.032	0.238	0.135
18.5 kg/m² ≤ BMI < 25 kg/m²	-0.166	-0.628	0.297	0.483	0.625	0.094	1.156	0.021*	-0.174	-0.513	0.165	0.314	0.325	0.000	0.649	0.050
Covariates†	age, education, sex, marital status, anxiety medications, physical activity				age, education, depression, marital status, anxiety medications, diabetes status				age, education, sex, depression, marital status, psychological acculturation				age, education, depression, marital status, psychological acculturation			

Table 4.3. Associations between an interquartile increase in PNC or PIR and changes in cognitive function (associations with $p < 0.05$ denoted by an asterisk)

	MMSE								Modified MMSE							
	IQR PNC (n = 539)				IQR PIR (n = 544)				IQR PNC (n = 799)				IQR PIR (n = 795)			
	beta	95%L	95%U	p	beta	95%L	95%U	p	beta	95%L	95%U	p	beta	95%L	95%U	p
Main model†	-0.027	-0.169	0.116	0.713	0.051	-0.054	0.155	0.343	-0.097	-0.192	-0.003	0.044*	-0.005	-0.078	0.067	0.884
Adjusted for age, baseline level (for change models), and education	-0.068	-0.211	0.075	0.350	0.052	-0.054	0.158	0.335	-0.100	-0.194	-0.007	0.036*	0.004	-0.069	0.076	0.923
Parallel main model	-0.054	-0.195	0.087	0.454	0.062	-0.044	0.168	0.250	-0.098	-0.192	-0.004	0.041*	0.017	-0.058	0.092	0.660
Main model for other MMSE	-0.063	-0.206	0.081	0.392	0.053	-0.053	0.158	0.329	-0.082	-0.177	0.012	0.086	-0.004	-0.075	0.067	0.915
Excluding people who died before year 5 (n = 51)	-0.038	-0.184	0.107	0.604	0.026	-0.078	0.131	0.622	-0.105	-0.201	-0.009	0.033*	-0.016	-0.090	0.057	0.666
Excluding people with ≤8th grade education	-0.018	-0.194	0.159	0.843	0.058	-0.070	0.186	0.373	-0.099	-0.218	0.020	0.102	0.015	-0.065	0.094	0.718
Sex																
Male	-0.230	-0.454	-0.006	0.044*	-0.028	-0.183	0.128	0.729	-0.260	-0.423	-0.097	0.002*	-0.009	-0.117	0.099	0.868
Female	0.122	-0.046	0.290	0.155	0.097	-0.043	0.237	0.175	-0.031	-0.146	0.085	0.604	0.041	-0.062	0.144	0.431
Cognitive impairment																
Yes	0.187	-0.043	0.418	0.110	0.124	-0.071	0.319	0.213	-0.091	-0.325	0.144	0.448	0.123	-0.085	0.332	0.247
No	-0.093	-0.229	0.043	0.182	-0.024	-0.119	0.072	0.623	-0.092	-0.187	0.004	0.062	-0.060	-0.130	0.009	0.090
Baseline age																
Younger than 65 years of age	-0.010	-0.160	0.141	0.897	0.060	-0.049	0.169	0.282	-0.094	-0.198	0.010	0.075	-0.010	-0.085	0.064	0.787
At least 65 years of age	-0.156	-0.533	0.220	0.416	-0.014	-0.377	0.349	0.940	-0.077	-0.322	0.167	0.534	0.052	-0.233	0.337	0.722
Depressed																
Yes	-0.049	-0.246	0.148	0.625	0.097	-0.048	0.243	0.191	-0.106	-0.232	0.020	0.099	-0.018	-0.117	0.081	0.724
No	-0.023	-0.228	0.183	0.829	-0.030	-0.179	0.119	0.693	-0.082	-0.225	0.062	0.263	-0.028	-0.142	0.086	0.633
Baseline employment status																
Yes	-0.083	-0.352	0.187	0.548	-0.066	-0.229	0.096	0.424	-0.068	-0.233	0.097	0.421	-0.024	-0.124	0.076	0.638
No	-0.064	-0.242	0.114	0.484	0.077	-0.068	0.222	0.297	-0.141	-0.259	-0.022	0.020*	0.013	-0.089	0.116	0.800
Smoker status																
Current	0.177	-0.106	0.460	0.220	0.054	-0.282	0.389	0.753	-0.016	-0.217	0.184	0.874	-0.011	-0.239	0.217	0.925
Former	-0.180	-0.423	0.064	0.148	0.016	-0.131	0.163	0.826	-0.269	-0.435	-0.102	0.002*	0.002	-0.110	0.114	0.971
Never	-0.035	-0.241	0.170	0.736	0.026	-0.108	0.161	0.703	-0.005	-0.136	0.126	0.945	-0.040	-0.141	0.062	0.446
Hypertension medication use																
Yes	0.029	-0.155	0.213	0.760	-0.026	-0.154	0.103	0.695	-0.039	-0.171	0.093	0.561	-0.055	-0.151	0.040	0.257
No	-0.115	-0.348	0.117	0.330	0.160	-0.023	0.343	0.086	-0.183	-0.320	-0.045	0.009*	0.047	-0.065	0.158	0.414
No previous heart attack/stroke	0.011	-0.139	0.161	0.884	0.092	-0.021	0.206	0.111	-0.081	-0.182	0.020	0.117	0.021	-0.058	0.100	0.601
Family history of diabetes																
Yes	-0.167	-0.413	0.080	0.186	0.128	-0.076	0.332	0.219	-0.194	-0.362	-0.026	0.024*	0.042	-0.088	0.171	0.529
No	-0.080	-0.407	0.247	0.632	-0.175	-0.444	0.094	0.202	-0.202	-0.395	-0.008	0.041*	-0.129	-0.330	0.073	0.211
Diabetic																
Yes	-0.004	-0.218	0.210	0.972	0.059	-0.080	0.198	0.403	-0.111	-0.244	0.023	0.103	-0.029	-0.138	0.079	0.598
No	-0.026	-0.223	0.170	0.794	0.057	-0.099	0.214	0.473	-0.038	-0.173	0.096	0.576	0.012	-0.088	0.111	0.819
Replacing PIR with physical activity (IQR = 5.8)	NA				0.054	-0.065	0.173	0.374	NA				0.043	-0.033	0.118	0.268
Physical activity																
Top 1/3rd (≥ 32.2 points)	-0.107	-0.316	0.102	0.315	-0.088	-0.216	0.039	0.174	-0.043	-0.178	0.093	0.538	-0.046	-0.135	0.043	0.310
Middle 1/3rd	0.051	-0.163	0.264	0.642	0.064	-0.223	0.352	0.661	0.042	-0.120	0.205	0.610	0.062	-0.146	0.269	0.560
Bottom 1/3rd (<28.6 points)	-0.001	-0.319	0.316	0.995	0.319	-0.218	0.855	0.245	-0.298	-0.486	-0.109	0.002*	-0.264	-0.579	0.050	0.099
BMI																
BMI ≥ 30 kg/m²	0.032	-0.159	0.224	0.740	0.020	-0.102	0.142	0.749	-0.095	-0.225	0.036	0.156	0.014	-0.077	0.105	0.764
18.5 kg/m² ≤ BMI < 25 kg/m²	-0.221	-0.535	0.094	0.169	0.359	-0.097	0.814	0.123	-0.099	-0.329	0.131	0.399	0.089	-0.168	0.346	0.498
Covariates†	baseline MMSE score, age, education, diabetes status				baseline MMSE score, age, education, statin medications				baseline Modified MMSE score, age, education, sex, marital status, psychological acculturation, perceived stress				baseline Modified MMSE score, age, education, marital status, psychological acculturation, perceived stress			

Discussion

Associations between UFP exposure and cognitive function

In the longitudinal BPRHS, we found that an IQR increase in long-term exposure to PNC was associated, although not significantly, with decreased MMSE scores. To provide context, the effect estimate for an IQR increase in PNC exposure was equivalent to a person aging by approximately four years. The association between PNC and cognitive function was stronger and significant among males and among healthier participants. The same overall trends were observed when examining the association between PNC and scores on the Modified MMSE scale, although the associations were attenuated. Our overall results are consistent with other studies which have examined the association between long-term exposure to other traffic-related air pollutants and cognitive function in adults (Chen & Schwartz, 2009; Power et al., 2011; Weuve J et al., 2012; Ailshire & Crimmins, 2014).

Nevertheless, our finding of a significant interaction between long-term exposure to air pollution and sex has not been observed previously in a longitudinal study. Specifically, the U.S. Department of Veterans Affairs Normative Aging Study (males) and the Nurses' Health Study Cognitive Cohort (females) found similar effect estimates for traffic-related air pollutants in males and females, respectively (Power et al., 2011; Weuve J et al., 2012). However, neither study considered PNC and neither study directly compared men and women. UFP may act through different physiological mechanisms than other size fractions of PM, especially since UFP can cross the blood-brain barrier (Oberdörster et al., 2004). Additionally, the interaction by sex does not seem to be well-explained by selection bias even though males were slightly more likely to be lost to follow up between the first and the third study visit (risk ratio = 1.13, 95% CI = 0.99 – 1.30). Restricting the models to only those participants who completed all three study visits did not change the results for either men or women. Furthermore, the difference is not

likely to be due to differences in educational attainment as education was controlled for in the models and there are not significant differences in educational attainment by sex in our study population. However, there could be participation bias if men were less likely to participate.

In addition to the significant interaction between sex and PNC exposure, we also observed effect modification by health status. In particular, there were stronger associations between PNC exposure and MMSE scores among younger participants, individuals who were not cognitively impaired, individuals who were more physically active, individuals without diabetes, and individuals not taking medications for hypertension. Our finding that generally healthier individuals may be more susceptible to cognitive effects of long-term exposure to PNC is consistent with our finding that the association between UFP exposure and cardiovascular disease biomarkers is stronger among healthier individuals (Chapter 3). However, cerebrovascular disease has been associated with cognitive impairment and dementia incidence (O'Brien et al., 2003), potentially due to oxidative stress mechanisms which may underlie both cardiovascular disease and vascular dementia (Coyle & Puttfarcken, 1993; Giasson et al., 2000; Berr, Balansard, Arnaud, Roussel, & Alpérovitch, 2000). Thus we may have expected to see stronger associations among individuals who already had vascular problems. It is possible that the declines in cognitive function we observed are not related to vascular dementia, though we did not evaluate data on the association between PNC and specific cognitive deficits so we do not know whether the participants' cognitive profiles are consistent with vascular dementia. Conversely, the associations we observed may reflect differences in vascular dementia if people who were not on medications that improve vascular function were more susceptible to changes in cognitive function with increasing PNC exposure because any potential effect of PNC on vascular health would not have been compensated for by use of the medications.

In contrast to the inverse associations we found between PNC exposure and MMSE scores, we found that the PIR was positively and significantly associated with cognitive function. While this positive association between the PIR and MMSE scores may be counter-intuitive and may be a spurious result due to the multiple comparisons we considered, it was a robust finding since most of the stratified analyses and models with different sets of covariates had positive point estimates. Assuming that the association is real, it may driven more by physical activity or by sex rather than by UFP exposure. Physical activity was more highly correlated with the PIR than was PNC and strong evidence exists from both prospective cohort studies and from randomized trials that increased physical activity is associated with better cognitive function (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Weuve et al., 2004; Lautenschlager et al., 2008; Sofi et al., 2011). Consistent with the possibility that the positive association may be due more to increased physical activity than to increased PNC exposure among participants with high PIRs, we found that when we restricted the main PNC/multiple cross-sectional model to only those participants with physical activity scores in the second and third quartiles, PNC was not associated with MMSE scores whereas when we restricted the model to only those participants in the second and third quartiles of PNC exposure, physical activity was still positively associated with MMSE scores. This suggests that the trends associated with physical activity may be more robust than the trends associated with PNC in the PIR models.

Furthermore, since males had significantly higher PIR scores and they had significantly higher MMSE scores (though not Modified MMSE scores), it is possible that the positive associations between the PIR and MMSE scores could be due, in part, to the sex differences in the severity and age-of-onset of cognitive impairment. Among adults aged 65 and older, women

are at greater risk of developing Alzheimer's and the sex difference increases with age. By the time individuals are in their 80s, women are twice as likely to develop Alzheimer's. However, males over the age of 65 are slightly more likely than females to develop vascular dementia (K. Andersen et al., 1999) and not all studies have found sex-specific differences in incidence rates for cognitive impairment among middle-age and older adults (Katz et al., 2012; Singh-Manoux et al., 2012). Additionally, the differing trends observed for PNC and the PIR may reflect differences in how these metrics assess exposure to UFP since the ambient concentration and the amount of pollutant inhaled could have different physiological consequences. Further assessment of the PIR as an exposure metric would help clarify these questions.

Associations between UFP exposure and cognitive decline

We did not observe significant associations between either PNC or the PIR with cognitive decline as measured by the MMSE. This may be due to the high prevalence (15.3 percent) of cognitive impairment observed among our participants at baseline in conjunction with the fact that any participant with a MMSE score less than or equal to 10 at baseline was excluded from the study. Since we excluded the participants most likely to show substantial decline over time, it may have been difficult to observe associations between UFP exposure and cognitive decline. Alternatively, and in perhaps direct disagreement with the observed prevalence of cognitive impairment in our sample, it may have also been unlikely to observe substantial cognitive decline due to the relatively young age of our cohort in relation to the typical age of onset of cognitive impairment. Most measures of cognitive function begin to decline beginning between 55 and 60 years of age (Hedden & Gabrieli, 2004) and in our sample, the median age at baseline was 56 years. However, even among adults over 65 years of age in

our sample, there were no significant associations between PNC or the PIR with cognitive decline as measured by the MMSE.

Nevertheless, PNC was significantly associated with cognitive decline as measured by the Modified MMSE scale and PNC was significantly associated with cognitive decline among males as measured by both the MMSE scale and the Modified MMSE scale. Although the trends by sex were consistent with the multiple cross-sectional models, the effect estimates for PNC were about half as strong in the change models as they were in the multiple cross-sectional models. These associations are still potentially clinically important, however, since each IQR increase in exposure is associated with a one percent decline in cognitive function score over the study period. Furthermore, given that the association between PNC and cognitive decline was stronger for the Modified MMSE scale, it is possible that PNC more directly affects attention and calculation skills than other components of cognitive function measured by the MMSE. In our future work, we will assess this idea by examining the association between UFP exposure and various components of cognitive function separately. In particular, we will consider attention, memory, and executive function.

Future work will also carefully consider whether restricting the analysis to only those participants who contributed data at all three study visits changes the results. This was suggested because only participants who were present at the third study visit have data on family history of diabetes and when we included family history of diabetes in the model, the effect estimates nearly doubled for PNC. This could be due to a genetic or health status difference among the participants that makes them more susceptible to any potential cognitive effects of UFP exposure as several studies have shown that diabetes modifies the effect of traffic-related pollution in relation to other health outcomes (Zanobetti & Schwartz, 2001; O'Neill et al., 2005; Dubowsky,

Suh, Schwartz, Coull, & Gold, 2006; Baja et al., 2010; Z. J. Andersen et al., 2011). It is also possible that participants who were able to remain in the study for the full three study visits differed from other participants in ways that could bias our results. Nevertheless, preliminary work addressing this question shows no differences in the overall trends when the models for change only include participants present for all three study visits.

Sensitivity analyses

We conducted two primary sensitivity analyses. First, in a sensitivity analysis excluding participants who died prior to their third study visit, none of the main trends differed. Second, we considered whether the results would differ if we excluded participants with low educational attainment because the MMSE has been validated primarily in more highly educated populations and false positives are more likely among people with lower educational attainment (Tombaugh & McIntyre, 1992). In this restricted analysis, the previously observed positive associations between the PIR and both MMSE and Modified MMSE scores were not significant. Thus, it is possible that the somewhat counter-intuitive result that the PIR is positively associated with MMSE scores is based on an invalid assumption that we can use the MMSE in a population with low educational attainment.

Limitations and next steps

As discussed in Chapter 4, there were a number of limitations in the exposure assessment methodology that could have affected our results. In particular, the lack of PNC monitoring data prior to 2011 forced us to make several assumptions in the PNC model. The most critical of these assumptions was that the spatial variability of PNC was constant with time. While this may not

be true in our study area due to major construction projects, evidence suggests that similar models are stable across many years (Wang, Henderson, Sbihi, Allen, & Brauer, 2013). Additionally, we are assuming that participants' residential annual average exposure was representative of their true exposure despite the fact that people do not spend all of their time at home and ambient exposure measures are only crude proxies for true exposure. Furthermore, we do not have respiratory volume data on the participants with which to validate our PIR algorithm. Each of these limitations, along with the others discussed in Chapter 4 could have resulted in exposure misclassification. While it is likely that the misclassification due to most sources of error was random and thus biased the results towards the null, the inability to adjust exposure values for participants' time-activity may have resulted in non-random misclassification (K. J. Lane et al., 2013).

Beyond the sources of error that may have led to exposure misclassification, there were several limitations in our analysis. First, there was substantial attrition in our study as only 45 percent of the 812 participants completed all three study visits. However, neither baseline MMSE scores nor baseline Modified MMSE scores were associated with the number of study visits that participants attended ($p = 0.954$ and $p = 0.346$, respectively). Additionally, neither mean baseline PNC exposure nor mean baseline PIR was significantly different among participants who attended different numbers of study visits ($p = 0.807$, $p = 0.786$, respectively). The number of visits participants attended was also independent of their educational attainment or age at baseline. Therefore, selection bias caused by attrition seems unlikely. However, we plan to test this assumption by estimating propensity scores for the likelihood that participants would drop out and then conduct a sensitivity analysis weighting observations by the inverse probability of these propensity scores. We will validate our propensity scores by comparing these

scores to the health data for the 82 participants who remained in the BPRHS even though they moved out of Boston before their third study visit.

Additionally, there were limitations in our outcome ascertainment. We used the MMSE which is a validated scale of global cognitive function that is fast and easy to administer in epidemiology studies (Folstein et al., 1975; Tombaugh & McIntyre, 1992). However, the fact that approximately one-third of participants did not answer one question could have introduced bias into the results of the MMSE models. This is suggested by the fact that the trends for the MMSE models and the Modified MMSE models differed in several ways. Another limitation is that potential participants with MMSE scores under 11 were excluded from the study at baseline. This means that we could not assess the associations between UFP and cognitive function among the most severely affected individuals. Additionally, with the MMSE alone, it was not possible to identify specific cognitive deficits. Our future work will consider whether long-term exposure to UFP is associated with scales designed to assess attention, memory, and executive function. If UFP is only associated with changes in certain cognitive processes, this could give insight into the potential mechanisms through which UFP may affect cognitive function.

Furthermore, we may not have been able to adequately account for all relevant confounding and effect modifying variables. Given that exposure to lead in motor vehicle exhaust was common when our study population was young, cumulative exposure to lead may have been a confounding factor since higher bone lead concentrations have been associated with significantly lower cognitive function as measured by the MMSE (Weisskopf et al., 2004). However, we do not have data on participants' bone lead levels or on their exposure to lead at any point so we did not control for lead exposure. Additionally, although moderate alcohol consumption has been associated with less cognitive decline among older adults (Mukamal et al.,

2003; Stampfer, Kang, Chen, Cherry, & Grodstein, 2005; Ganguli, Bilt, Saxton, Shen, & Dodge, 2005), we did not include any measure of alcohol consumption in our models. We also excluded other nutritional factors that could have confounded or modified the association between UFP exposure and cognitive function. In particular, certain B vitamins have been associated with cognitive function among participants in the BPRHS and we did not control for these factors (Moorthy et al., 2012). Moreover, we did not consider the influence of gene-environment interactions despite the fact that we have full genome sequences on every participant in the BPRHS. Future work may consider potential modification of the relationship between UFP exposure and cognitive function by the apolipoprotein E genotype since this genotype has been shown to potentiate the association between cardiovascular disease and cognitive function (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999).

Finally, additional longitudinal studies are needed to assess whether our findings are generalizable to other populations. Our participants were all of Puerto Rican descent, approximately half had less than an eighth grade education, over 15 percent were cognitively impaired at baseline, and the prevalence of a number of chronic physical and mental health conditions was quite high. It is possible that in healthier or more highly educated populations, the associations between UFP and cognitive function would differ.

Conclusion and contributions

In the first longitudinal study to consider the relationship between long-term exposure to UFP and cognitive function, we found that increased PNC exposure was associated with decreased cognitive function and that PNC was significantly associated with cognitive decline as measured by the Modified MMSE. These associations were stronger among males. We also

found that increased PIR was significantly associated with increased cognitive function although this finding was attenuated and non-significant among participants with greater educational attainment and it may have been driven by physical activity patterns. In addition to presenting the first evidence of an association between UFP exposure and cognitive function, we considered a novel exposure assessment metric that may more closely estimate intake dose of traffic-related air pollutants. By comparing this exposure metric to a more traditional ambient concentration metric, we were able to explore the relative strengths and weaknesses of using a measure that is dependent on both ambient concentrations and other parameters, such as physical activity. Although future work is needed to validate our findings, particularly in more highly educated and healthier populations, our analysis has potential policy implications as the EPA considers whether the evidence warrants regulation of UFP on a federal level.

Works Cited

Ailshire, J. A., & Crimmins, E. M. (2014). Fine Particulate Matter Air Pollution and Cognitive Function Among Older US Adults. *American Journal of Epidemiology*, kwu155. http://doi.org/10.1093/aje/kwu155

Andersen, K., Launer, L. J., Dewey, M. E., Letenneur, L., Ott, A., Copeland, J. R. M., … Group, the E. I. R. (1999). Gender differences in the incidence of AD and vascular dementia The EURODEM Studies. *Neurology*, *53*(9), 1992–1992. http://doi.org/10.1212/WNL.53.9.1992

Andersen, Z. J., Hvidberg, M., Jensen, S. S., Ketzel, M., Loft, S., Sørensen, M., … Raaschou-Nielsen, O. (2011). Chronic Obstructive Pulmonary Disease and Long-Term Exposure to Traffic-related Air Pollution. *American Journal of Respiratory and Critical Care Medicine*, *183*(4), 455–461. http://doi.org/10.1164/rccm.201006-0937OC

Anstey, K. J., Sanden, C. von, Salim, A., & O'Kearney, R. (2007). Smoking as a Risk Factor for Dementia and Cognitive Decline: A Meta-Analysis of Prospective Studies. *American Journal of Epidemiology*, *166*(4), 367–378. http://doi.org/10.1093/aje/kwm116

Arvanitakis, Z., Wilson, R. S., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2004). Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Archives of Neurology*, *61*(5), 661–666. http://doi.org/10.1001/archneur.61.5.661

Baja, E. S., Schwartz, J. D., Wellenius, G. A., Coull, B. A., Zanobetti, A., Vokonas, P. S., & Suh, H. H. (2010). Traffic-Related Air Pollution and QT Interval: Modification by Diabetes, Obesity, and Oxidative Stress Gene Polymorphisms in the Normative Aging Study. *Environmental Health Perspectives*, *118*(6), 840–846. http://doi.org/10.1289/ehp.0901396

Berr, C., Balansard, B., Arnaud, J., Roussel, A., & Alpérovitch, A. (2000). Cognitive decline is associated with systemic oxidative stress: the EVA study. Etude du Vieillissement Arteriel. *Journal of the American Geriatrics Society*, *48*(10), 1285–1291.

Block, M. L., & Calderón-Garcidueñas, L. (2009). Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends in Neurosciences*, *32*(9), 506–516. http://doi.org/10.1016/j.tins.2009.05.009

Chen, J.-C., & Schwartz, J. (2009). Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology*, *30*(2), 231–239. http://doi.org/10.1016/j.neuro.2008.12.011

Coyle, J. T., & Puttfarcken, P. (1993). Oxidative stress, glutamate, and neurodegenerative disorders. *Science*, *262*(5134), 689–695. http://doi.org/10.1126/science.7901908

Dubowsky, S. D., Suh, H., Schwartz, J., Coull, B. A., & Gold, D. R. (2006). Diabetes, Obesity, and Hypertension May Enhance Associations between Air Pollution and Markers of Systemic Inflammation. *Environmental Health Perspectives*, *114*(7), 992–998. http://doi.org/10.1289/ehp.8469

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. http://doi.org/10.1016/0022-3956(75)90026-6

Ganguli, M., Bilt, J. V., Saxton, J. A., Shen, C., & Dodge, H. H. (2005). Alcohol consumption and cognitive function in late life A longitudinal community study. *Neurology*, *65*(8), 1210–1217. http://doi.org/10.1212/01.wnl.0000180520.35181.24

Gatto, N. M., Henderson, V. W., Hodis, H. N., St. John, J. A., Lurmann, F., Chen, J.-C., & Mack, W. J. (2014). Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. *NeuroToxicology*, *40*, 1–7. http://doi.org/10.1016/j.neuro.2013.09.004

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., … Winblad, B. (2006). Mild cognitive impairment. *The Lancet*, *367*(9518), 1262–1270. http://doi.org/10.1016/S0140-6736(06)68542-5

Giasson, B. I., Duda, J. E., Murray, I. V. J., Chen, Q., Souza, J. M., Hurtig, H. I., … Lee, V. M.-Y. (2000). Oxidative Damage Linked to Neurodegeneration by Selective α-Synuclein Nitration in Synucleinopathy Lesions. *Science*, *290*(5493), 985–989. http://doi.org/10.1126/science.290.5493.985

Haan, M. N., Shemanski, L., Jagust, W. J., Manolio, T. A., & Kuller, L. (1999). The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA*, *282*(1), 40–46.

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*, *80*(19), 1778–1783. http://doi.org/10.1212/WNL.0b013e31828726f5

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature Reviews Neuroscience*, *5*(2), 87–96. http://doi.org/10.1038/nrn1323

Katz, M. J., Lipton, R. B., Hall, C. B., Zimmerman, M. E., Sanders, A. E., Verghese, J., … Derby, C. A. (2012). Age and Sex Specific Prevalence and Incidence of Mild Cognitive Impairment, Dementia and Alzheimer's dementia in Blacks and Whites: A Report From The Einstein Aging Study. *Alzheimer Disease and Associated Disorders*, *26*(4), 335–343. http://doi.org/10.1097/WAD.0b013e31823dbcfc

Kivipelto, M., Helkala, E.-L., Hänninen, T., Laakso, M. P., Hallikainen, M., Alhainen, K., … Nissinen, A. (2001). Midlife vascular risk factors and late-life mild cognitive impairment A population-based study. *Neurology*, *56*(12), 1683–1689. http://doi.org/10.1212/WNL.56.12.1683

Lane, K. J., Kangsen Scammell, M., Levy, J. I., Fuller, C. H., Parambi, R., Zamore, W., … Brugge, D. (2013). Positional error and time-activity patterns in near-highway proximity studies: an exposure misclassification analysis. *Environmental Health*, *12*, 75. http://doi.org/10.1186/1476-069X-12-75

Laurin, D., Verreault, R., Lindsay, J., MacPherson, K., & Rockwood, K. (2001). Physical activity and risk of cognitive impairment and dementia in elderly persons. *Archives of Neurology*, *58*(3), 498–504.

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., … Almeida, O. P. (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*, *300*(9), 1027–1037. http://doi.org/10.1001/jama.300.9.1027

Moorthy, D., Peter, I., Scott, T. M., Parnell, L. D., Lai, C.-Q., Crott, J. W., … Troen, A. M. (2012). Status of Vitamins B-12 and B-6 but Not of Folate, Homocysteine, and the Methylenetetrahydrofolate Reductase C677T Polymorphism Are Associated with Impaired Cognition and Depression in Adults123. *The Journal of Nutrition*, *142*(8), 1554–1560. http://doi.org/10.3945/jn.112.161828

Mukamal, K. J., Kuller, L. H., Fitzpatrick, A. L., Longstreth, W. T., Mittleman, M. A., & Siscovick, D. S. (2003). Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA*, *289*(11), 1405–1413.

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *The Lancet Neurology*, *13*(8), 788–794. http://doi.org/10.1016/S1474-4422(14)70136-X

Oberdörster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Kreyling, W., & Cox, C. (2004). Translocation of Inhaled Ultrafine Particles to the Brain. *Inhalation Toxicology*, *16*(6-7), 437–445. http://doi.org/10.1080/08958370490439597

O'Brien, J. T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., … DeKosky, S. T. (2003). Vascular cognitive impairment. *The Lancet Neurology*, *2*(2), 89–98. http://doi.org/10.1016/S1474-4422(03)00305-3

O'Neill, M. S., Veves, A., Zanobetti, A., Sarnat, J. A., Gold, D. R., Economides, P. A., … Schwartz, J. (2005). Diabetes Enhances Vulnerability to Particulate Air Pollution–Associated Impairment in Vascular Reactivity and Endothelial Function. *Circulation*, *111*(22), 2913–2920. http://doi.org/10.1161/CIRCULATIONAHA.104.517110

Power, M. C., Weisskopf, M. G., Alexeeff, S. E., Coull, B. A., Spiro, A., & Schwartz, J. (2011). Traffic-Related Air Pollution and Cognitive Function in a Cohort of Older Men. *Environmental Health Perspectives*, *119*(5), 682–687. http://doi.org/10.1289/ehp.1002767

Ranft, U., Schikowski, T., Sugiri, D., Krutmann, J., & Krämer, U. (2009). Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environmental Research*, *109*(8), 1004–1011. http://doi.org/10.1016/j.envres.2009.08.003

Singh-Manoux, A., Kivimaki, M., Glymour, M. M., Elbaz, A., Berr, C., Ebmeier, K. P., … Dugravot, A. (2012). Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ*, *344*, d7622. http://doi.org/10.1136/bmj.d7622

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *Journal of Internal Medicine*, *269*(1), 107–117. http://doi.org/10.1111/j.1365-2796.2010.02281.x

Stampfer, M. J., Kang, J. H., Chen, J., Cherry, R., & Grodstein, F. (2005). Effects of Moderate Alcohol Consumption on Cognitive Function in Women. *New England Journal of Medicine*, *352*(3), 245–253. http://doi.org/10.1056/NEJMoa041152

Tombaugh, T. N., & McIntyre, N. J. (1992). The mini-mental state examination: a comprehensive review. *Journal of the American Geriatrics Society*, *40*(9), 922–935.

Wang, R., Henderson, S. B., Sbihi, H., Allen, R. W., & Brauer, M. (2013). Temporal stability of land use regression models for traffic-related air pollution. *Atmospheric Environment*, *64*, 312–319. http://doi.org/10.1016/j.atmosenv.2012.09.056

Weisskopf, M. G., Wright, R. O., Schwartz, J., Spiro, A., Sparrow, D., Aro, A., & Hu, H. (2004). Cumulative Lead Exposure and Prospective Change in Cognition among Elderly Men The VA Normative Aging Study. *American Journal of Epidemiology*, *160*(12), 1184–1193. http://doi.org/10.1093/aje/kwh333

Wellenius, G. A., Boyle, L. D., Coull, B. A., Milberg, W. P., Gryparis, A., Schwartz, J., … Lipsitz, L. A. (2012). Residential Proximity to Nearest Major Roadway and Cognitive Function in Community-Dwelling Seniors: Results from the MOBILIZE Boston Study.

Journal of the American Geriatrics Society, n/a–n/a. http://doi.org/10.1111/j.1532-5415.2012.04195.x

Weuve, J., Kang, J. H., Manson, J. E., Breteler, M. M. B., Ware, J. H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *JAMA*, *292*(12), 1454–1461. http://doi.org/10.1001/jama.292.12.1454

Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, & Grodstein F. (2012). Exposure to particulate air pollution and cognitive decline in older women. *Archives of Internal Medicine*, *172*(3), 219–227. http://doi.org/10.1001/archinternmed.2011.683

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.-O., … Petersen, R. c. (2004). Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, *256*(3), 240–246. http://doi.org/10.1111/j.1365-2796.2004.01380.x

Zanobetti, A., & Schwartz, J. (2001). Are Diabetics More Susceptible to the Health Effects of Airborne Particles? *American Journal of Respiratory and Critical Care Medicine*, *164*(5), 831–833. http://doi.org/10.1164/ajrccm.164.5.2012039