CENTER FOR CLEAN AIR RESEARCH
UNIVERSITY of WASHINGTON
Department of Environmental and Occupational Health Sciences

University of Washington CCAR Year 6 Annual Progress Report

Reporting Period: August 1, 2014 – July 31, 2015

Submission Date of Report: July 31, 2016
EPA Agreement Number: RD-83479601 / EPA-RC2009-STAR-C1
Center Name: UW CCAR, Center for Clean Air Research
Center Director: Sverre Vedal

Collaborating Institutions	Location
University of Washington	Seattle, WA
Washington State University	Pullman, WA
Lovelace Respiratory Research Institute	Albuquerque, NM
University of New Mexico	Albuquerque, NM

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IV. UW CCAR CLARC Program Collaborations

REPORT OVERVIEW

This Annual Progress Report covers the sixth year of funding to date and the first year of a two-year no-cost extension [8/1/2015 – 7/31/2016] for the University of Washington's Clean Air Research Center, termed the "UW CCAR - Center for Clean Air Research."

Each of the four individual EPA Clean Air Research Centers aim to advance understanding of the human health effects of exposures to complex (multipollutant) air pollution mixtures. The UW Center, specifically, is examining how pollution from roadways affects cardiovascular health. The research integrates exposure, epidemiological, toxicological, clinical, and statistical sciences to study the cardiovascular hazards of recent and aged roadway emissions.

The Center consists of two core function groups providing biostatistical analysis support and administrative activities. There are four separate institutions, contributing to five distinct but integrated research projects, with a sixth project being carried out in the Biostatistics Core. The projects and core groups are listed below and will be expanded on in individual summaries. Center investigators and their respective institutions will be listed with their associated research projects.

The individual project summaries review objectives and report on changes or difficulties encountered during the reporting period. Progress and preliminary results, as well as discussion about future activities, are included. The Administrative Core summary serves as the overall Center review. Additionally, there is a separate financial report, which provides a more detailed summary of the Center's financial picture to date.

<u>Research Projects & Core Groups:</u>

- Administrative Core
- Biostatistics Core
- Project 1 - Exposure Mapping – Characterization of Gases and Particles for Exposure Assessment in Health Effects and Laboratory Studies
- Project 2 - Simulated Roadway Exposure Atmospheres for Laboratory Animal & Human Studies
- Project 3 - Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions
- Project 4 - Vascular Response to Traffic-Derived Inhalation in Humans
- Project 5 - Effects of Long-Term Exposure to Traffic-Derived Aerosols and Gases on Subclinical Measures of Cardiovascular Disease and DNA Methylation in a Multi-Ethnic Cohort

ADMINISTRATIVE CORE – CENTER REVIEW

Member	Institution
Sverre Vedal – Center Director	University of Washington
Jacob McDonald – Center Deputy Director	Lovelace Respiratory Research Institute
Timothy Larson – Center Deputy Director	University of Washington
Amanda Gassett – Center Quality Assurance Manager	University of Washington
Elizabeth Spalt – Center Manager	University of Washington

Objective of Research

The UW CCAR is focused on the cardiovascular health effects of near-roadway pollution, a complex mixture of particle, vapor and gas phase components that vary by vehicle emission source, road surface, extent of physical aging and the type and degree of atmospheric processing and photochemical reactions. This exposure scenario is not only known to be of considerable health importance, but also serves as a prototypical case for developing research approaches to dealing with multi-pollutant exposure-effect relationships. Our aim is to integrate exposure, epidemiological, toxicological, clinical, and statistical sciences to study cardiovascular hazards of fresh and aged roadway emissions and significantly advance our understanding of the components and reaction products that cause these effects.

The Center consists of five highly integrated research projects and two facility cores that together are pursuing the following six aims:

1. To characterize real-world near-roadway pollutant concentrations, particle size distributions and chemical composition

2. To simulate realistic contrasting near-roadway multi-pollutant exposure atmospheres for laboratory animal and human studies

3. To identify cardiovascular and immunologic effects and the pathogenic mechanisms of near-roadway exposures using animal models

4. To identify cardiovascular and immunologic effects of near-roadway exposures in human clinical studies

5. To identify effects of long-term exposure to traffic-derived particles and gases on sub-clinical measures of cardiovascular disease and DNA methylation in a multi-ethnic population

6. To develop a statistical and methodological framework for studying health effects of multi-pollutant mixtures

Progress Summary / Accomplishments

Committees and Meetings

- Investigators Committee – The Investigators Committee is comprised of key members from all five research projects, as well as representatives from the Biostatistics and Administrative Cores. This group continues to meet regularly for status reports and to discuss the day to day scientific activities of the Center and its individual projects. As the research and data become more developed and integrated across projects, the presentations from rotating investigators have become more valuable for examining preliminary results and shaping progress and direction.

- Internal Steering Committee – The Internal Steering Committee (ISC) is comprised of the Center Director, Deputy Directors, project and core PI's, the Center Quality Assurance Manager (QAM), and the Center Manager. This group meets to discuss finances, budgets, resource allocation, and collaborations. The ISC also serves as the Cross Collaboration Committee and convened recently to discuss the progress and direction of the inter-Center collaboration projects.

- Scientific Advisory Committee – The Scientific Advisory Committee (SAC) is comprised of ten scientists representing varying specialties and institutions, including the US EPA and members from the other CLARC Centers. A list of the committee members with their associated institutions appears in Table 1. The Year 4 SAC meeting was held on October 6th and 7th 2014. No additional SAC meetings have been held or are planned per mutual agreement among CCAR Investigators, CCAR SAC members, and US EPA.

Table 1 – CCAR Scientific Advisory Committee Members

Expertise	**Member**	**Institution**
Exposure Science	Michael Brauer	University of British Columbia
Exposure Science	Thomas Peters	University of Iowa
Exposure Science	Barbara Turpin	Rutgers University
Epidemiology	Arden Pope	Brigham Young University
Toxicology	Ian Gilmour	US EPA
Toxicology	Jesus Araujo	University of California Los Angeles *(Added as of 7/26/13)*
Toxicology	*Jake Lusis*	*University of California, Los Angeles (Replaced as of 7/26/13)*
Toxicology	Sanjay Rajagopalan	University of Maryland (Michigan State University CLARC Member)
Statistics	Brent Coull	Harvard University (Harvard University CLARC Member)
Clinical Studies	John Balmes	University of California, San Francisco (Committee Chair)
Clinical Studies	Nicholas Mills	University of Edinburgh, UK

Information Technology

- The Center continues to utilize the University of Washington's Department of Environmental and Occupational Health Sciences (DEOHS) server space at no cost to the UW Center. Current hardware provides adequate storage and computing space for the foreseeable future of the Center. This resource continues to be appropriately maintained, secured, and archived by DEOHS IT personnel, with password access for approved Center/project personnel.

- As research has progressed into Year 6, Projects 2 and 3 have utilized their own institution or research group IT resources in collecting, processing, analyzing, and storing their respective raw and "intermediate" data. This is appropriate given the physical separation [Albuquerque, NM] of these two projects from the Seattle-based Center. The remaining CCAR Projects are all making use of the DEOHS server system and its security advantages. The Biostatistics Core performs much of the analysis and modeling on their own IT resources but also relies heavily on the DEOHS server structure for data sharing and review, and for Center integration activities.

- The Center's web site continues to provide information to the investigators and CLARC Program members, as well as to the general public. Content relating to the Center's calendar, researchers, projects, collaborators, and products remains current.

- For file and data exchange, we have utilized an online drop box for non-sensitive external file sharing.

- For regular Investigators Meetings, we have utilized webinar programs including Microsoft Lync (now Skype for Business).

Subawards

- The Center's subawards for Lovelace Respiratory Research Institute (LRRI) and the University of New Mexico were renewed for Year 6. The subaward for Washington State University was extended into Year 5 in order to complete exposure characterization experiments and data analysis but has since concluded. We appreciate their participation and contributions to the Center as the research progresses. Financial information relating to the subawards can be found in the separate Center Annual Financial Report.

Changes in Original Study Goals

None for this reporting period.

Challenges and Delays

- The EPA IRB indicated a preference to explore an alternative to the planned controlled exposure studies for Project 4. Instead of the original plan, Project 4 has utilized a typical commute exposure design, where participants are studied while participating in a heavily-trafficked drive with or without an operational filtration system in place. The original

health outcomes proposed for Project 4 are being measured. The change in protocol resulted in a delay in the start of this project. IRB approval was obtained from University of Washington in April 2014 and from USEPA in May 2014, and the commute exposure drives began in December 2014.

- The University of Washington received a two-year no cost extension from EPA to finish the scope of work for CCAR.

Changes in Key Personnel
None during this project period.

Unexpected Cost Increases
None during this project period. Other relevant financial information is detailed in the individual project summaries contained in the separate Center Annual Financial Report.

Quality Control / Assurance

- As the research progressed and significant data is collected, there has been a heightened effort to promote the expertise of the Biostatistics Core to all of the individual projects. The Biostatistics Core has their respective aims, but was also created and structured to be a Center resource for consultation and review of questions, materials, methods, and processes. It is anticipated, and expected, that project investigators will continue rely on the Biostatistics Core as the data intensive second half of the Center's award period continues.

- With the significant progress of all projects, the CCAR QMP is continuing to undergo a comprehensive review by the Center Manager and Project PI's to confirm the currency of overall goals and objectives, training, procedures and systems, documentation, and data storage and security. This document [QMP Revision 2.0] will be reviewed and approved by the CCAR QAM Amanda Gassett, the CCAR Director Sverre Vedal, and the EPA CLARC Quality Assurance Officer Lisa Doucet. This document has been sent to the EPA CLARC Project Officer and also resides on the CCAR internal server and the CCAR public accessible Web Site.

- Each individual research project's Quality Assurance Officer (QAO) is continually creating and revising Standard Operating Procedures (SOPs), as required, as part of an ongoing process to document all Center and project specific activities.

- The Center's Quality Assurance Manager (QAM) has worked closely with all projects. All projects have submitted Quality Assurance Project Plans (QAPPs) that have been reviewed, revised, and approved by the QAM. When appropriate, the Biostatistics Core will be required to fully document their activities. This documentation will also be reviewed and approved by the Center's QAM.

Planned Activities for the Subsequent Reporting Period
The individual project and Biostatistics Core summaries will address planned and future activities.

Administrative Core

- Quality Management – The Center will continue to follow up with each individual project, and associated QAO, to review, revise, and archive all relevant SOPs, and their respective QAPPs.

- Quality Management – To supplement the formal QAPP for each Project, the Center's Quality Assurance Manager has requested that each project collecting research data create a separate QC Report. This report will need to be "customized" to each individual project and data collection method but should contain such items such as, but not limited to:

    1. Summary of sampler type and use/deployment characteristics
    2. Summary of collection media planning, deployment, capture, and validity results
    3. Criteria for usable data or for flagging or voiding suspect data
    4. Information on comparison to existing or available AQS data
    5. Summary statistics in relation to Data Quality Objectives [DQO's]
    6. Laboratory Analysis QC
    7. Method limit of detection results
    8. Method QC results i.e. duplicate and blank samples, standard curves, etc.

- Quality Management - With the Center well into Year 6 and research activities seeing significant progress across all projects, a comprehensive quality review of all Center projects and activities was completed in July 2016 by the QAM. Because of the substantial distances between institutions, the significant differences in types of data collected, the sheer volume of information involved, and the time and effort this undertaking could require, the design and execution of this review will be a continuing topic of discussion in the investigators meetings, as well as between the QAM, the Center's Director, and the Center's Manager.

- Data Use Requests – As the projects collect, process, and analyze data, discussion has been raised about creating a more formal method for handling data use requests. This idea concerns internal to the Center requests, but also in the longer term, external requests from a variety of interested collaborators. This item will be progressively addressed in upcoming Investigators Meetings as well as among the Internal Steering Committee members.

Human Subjects & IACUC

Below is a current and historical summary of the Human Subjects and Institutional Animal Care and Use Committee (IACUC) status for each individual research project. The Center Manager has confirmed that all projects and personnel have the appropriate certifications and training required for Year 6, and beyond.

Administrative Core - All Human Subjects training and certifications are current and documented with the UW CCAR Manager, as of July 31, 2016. Institutional IACUC approval

for the University of Washington and LRRI are on file with the Center Manager and the CLARC EPA Project Officer.

Biostatistics Core - There are no ongoing or planned Human Subjects or IACUC activities for the Biostatistics Core.

Project 1 - There are no ongoing or planned Human Subjects or IACUC activities for Project 1.

Project 2 - There are no ongoing or planned Human Subjects or IACUC activities for Project 2.

Project 3 – There are no ongoing or planned Human Subjects activities for Project 3.

University of Washington:

IACUC Protocol #2650-08, February 24, 2011

1. IACUC Protocol #2650-08 Annual Approval: March 7, 2016 through March 6, 2017.
2. IACUC Protocol #2650-08 Annual Approval: March 9, 2015 through March 8, 2016.
3. IACUC Protocol #2650-08 Annual Approval: February 18, 2014 through February 17, 2015.
4. IACUC Protocol #2650-08 Annual Approval: February 14, 2013 through February 23, 2014.
5. IACUC Protocol #2650-08 Annual Approval: February 22, 2012 through February 23, 2013.
6. Significant change approval to Protocol #2650-08 for Biological Use Authorization (BUA) to add "Endotracheal Installation of C. Pneumonia to Mice" was submitted February 23, 2012, approved March 12, 2012, and is on file with the Center Manager.

Lovelace Respiratory Research Institute:

Past work performed under **IACUC Protocol #FY11-083, March 18, 2011**

1. Amendment A to Protocol #FY11-083 for adding one laboratory person was submitted for documentation purposes June 20, 2011 and is on file with the Center Manager.
2. Amendment B to Protocol #FY11-083 for adding one new strain, C57B16, and 104 mice was submitted May 11, 2012, approved June 7, 2012, and is on file with the Center Manager.

and under **IACUC protocol #FY12-016, November 30, 2011**

1. Amendment E to protocol FY12-016 was approved 20 Sep 2013 to extend possible euthanasia time points post exposure.
2. Amendment F to protocol FY12-016 was approved 25 Nov 2013 to include additional exposure atmospheres.
3. Amendment G to protocol FY12-016 was approved 13 Jan 2014 to include additional mice for further experiments.
4. Amendment I to protocol FY12-016 was approved 22 Apr 2014 to change the strain of approved mice from C57Bl/6 to ApoE -/- mice.

Recent work performed under FY15-023, titled "Effects of mixtures of causal components of vehicular emissions and other inhalation toxicants on markers of cardiovascular disease and inflammation in rats and mice," approved January 22, 2015

1. Amendment A was approved on February 11, 2015, to request shortened quarantine for some groups of animals
2. Amendment B was approved on March 30, 2015, to request an additional blood sampling method of retro-orbital bleeding
3. Amendment C was approved on June 25, 2015, to request IP injection method for dosing Fasudil and Fluorescein.

Additional recent work performed under IACUC Protocol FY15-133, titled "Effects of mixtures of toxic components of vehicular emissions and other inhalation toxicants on markers of cardiovascular disease and inflammation in mice," approved Oct 14, 2015

Project 4 – There are no ongoing or planned IACUC activities for Project 4.

Project 4 submitted their Human Subjects application to the University of Washington IRB on January 13, 2014 (Committee D), and it was approved by the University of Washington IRB on April 10, 2014 (IRB #46658, annual review March 2016 with approval through 3/20/2017). Five modifications to this application have been approved by University of Washington IRB:

- Modification 1 for amended recruitment scripts and consent was approved 4/10/2014
- Modification 2 for changes to protocol and consent for blood procedures / location change was approved 7/14/2014.
- Modification 3 for amended recruitment materials and consent regarding additional drive and compensation change was approved 12/2/2014.
- Modification 4 – for final approval of the conditional approval of Modification 3.
- Modification 5 for changes to protocol regarding repeat drive for one subject who experienced higher CO2 levels due to recirculation setting in vehicle approved 9/21/2015.

Project 5 – There are no ongoing or planned IACUC activities for Project 5.

The existing IRB approvals at the University of Washington cover activities at both Wake Forest and at UCLA. As described below, IRBs at both Wake Forest University and UCLA fully approved all activities.

Human Subjects / IRB Modification #39

Submitted November 13, 2012; Modification of the MESA Air Human Subjects Application (IRB #26962, Committee E/G). Approved by the University of Washington Human Subjects Division / Internal Review Board on December 31, 2012. As requested by University of Washington Human Subjects also submitted as a separate IRB Application (IRB #44310, Committee EJ). Approved by the University of Washington Human Subjects Division / Internal Review Board on December 28, 2012 with annual reviews approved December 2013, December 2014, and December 2015. Also approved by the Wake Forest University Internal Review Board

on December 20, 2012, as Amendment #11 for IRB study # BG05-006. Also approved by UCLA Institutional Review Board on September 16, 2013 as Amendment #13 for IRB #11-001546.

- Includes the CCAR Project 5 sampling campaigns for 96 MESA Air participants to the main MESA Air IRB application.
- Personal, indoor residential, outdoor residential and in-vehicle air monitoring among a subset of 48 MESA Air participants each in Winston-Salem and Los Angeles (each) in two distinct seasons in each city.
- Location tracking, via time-location diaries, proximity monitors, and GPS units.
- Recruitment brochure, participation tracking logs, contact scripts, eligibility screeners, consent forms, time-location diaries, diary instructions and technician observation forms.

Human Subjects / IRB Modification #40

Submitted April 2, 2013; Modification of the MESA Air Human Subjects Application (IRB #26962, Committee E/G). Approved by the University of Washington Human Subjects Division / Internal Review Board on April 26, 2013. Also approved by the Wake Forest University Internal Review Board on March 28, 2013, as Amendment #13 for Study #BG05-006. Also approved by UCLA Institutional Review Board on September 16, 2013 as Amendment #13 for IRB #11-001546 (submitted with initial package to UCLA).

- Addition of a results letter, to provide participants information on the air pollution levels we measured in their homes and the travel routes we observed.

Human Subjects / IRB Modification #4

Initially Submitted June 4, 2013; Modification of the MESA Air Human Subjects Application (IRB #26962, Committee E/G). Approved by the University of Washington Human Subjects Division / Internal Review Board on June 21, 2013. Also approved by the Wake Forest University Internal Review Board on June 4, 2013, as Amendment #14 for Study #BG05-006. Resubmitted at University of Washington IRB's request as Modification #4 to IRB #44310 and approved on October 17, 2013. Also approved by UCLA Institutional Review Board on September 16, 2013 as Amendment #13 for IRB #11-001546 (submitted with initial package to UCLA).

- Additional materials to be provided to participants during future field campaigns. Photo inserts for the recruitment brochures, a list of "do's and don'ts" regarding the sampling equipment, and a simplified time-location diary and instructions.
- Expand the total number of participants included in this sampling to allow 48 participants to be recruited at each field campaign in each city, rather than 48 total per city.

Publications / Presentations / Posters - Cumulative

The below publications, presentations, and posters are also included in their associated individual project summaries.

* **Bold** denotes new entries, post-Year 4 CCAR Annual Report

Current: 7/31/16

Center Publications to Date:

1. **Brower JB, Doyle-Eisele M, Moeller B, Stirdivant S, McDonald JD, Campen MJ. Metabolomic Changes in Murine Serum Following Inhalation Exposure to Gasoline and Diesel Engine Emissions. *Inhalation Toxicology.* 2016, 28(5): 241-250.**
2. **Chi GC, Barr RG, Donohue K, Hensley M, Hou L, Kaufman JD, Liu Y, MacDonald J, McCall C, Siscovick D. Long-term outdoor air pollution and DNA methylation in circulating monocytes: Results from the Multi-ethnic Study of Atherosclerosis (MESA). *Environmental Health*. 2016, Submitted.**
3. **Galaviz VE, Quintana PJE, Yost MG, Sheppard L, Paulsen MH, Camp JE, Simpson CD. Urinary metabolites of 1-nitropyrene in US-Mexico border residents who frequently cross the San Ysidro Port of Entry. *Journal of Exposure Science and Environmental Epidemiology.* 2015, advance online publication.**
4. **Hazlehurst MF, Spalt EW, Curl CL, Davey ME, Vedal S, Burke GL, Kaufman JD. Integrating data from multiple time-location measurement methods for use in exposure assessment: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). Journal of Exposure Science and Environmental Epidemiology. 2016, Submitted.**
5. **Keller JP, Chang HH, Strickland MJ, Szpiro AA. Measurement error correction for predicted spatiotemporal air pollution exposures. *Epidemiology.* 2016, Submitted.**
6. **Kim SY, Olives C, Sheppard L, Sampson PD, Larson TV, Kaufman JD. Historical prediction modeling approach for estimating long-term concentrations of PM2.5 in cohort studies before 1999 implementation of widespread monitoring. *Environmental Health Perspectives*. 2016, advance online publication. DOI:10.1289/EHP131**
7. **Kim SY, Sheppard L, Bergen S, Szpiro AA, Sampson PD, Kaufman JD, Vedal S. Prediction of fine particulate matter chemical components with a spatio-temporal model for the Multi-Ethnic Study of Atherosclerosis cohort. *Journal of Exposure Science and Epidemiology*. 2016, advance online publication.**
8. **Larson T, Gould TR, Riley EA, Austin E, Fintzi J, Sheppard L, Yost MG, Simpson CD. Ambient Air Quality Measurements from a Continuously Moving Mobile Platform: Estimation of Area-Wide, Fuel-Based, Mobile Source Emission Factors Using Absolute Principal Component Scores. *Atmospheric Environment.* 2016, submitted.**
9. **Riley EA, Schaal L, Sasakura M, Crampton R, Gould TR, Hartin K, Sheppard L, Larson T, Simpson CD, Yost MG. Correlations between short-term mobile monitoring and long-term passive sampler measurements of traffic related air pollution. *Atmospheric Environment.* 2016, 132: 229-239.**

10. Riley EA, Gould T, Hartin K, Fruin SA, Simpson CD, Yost MG, Larson T. Ultrafine particle size as a tracer for aircraft turbine emissions. *Atmospheric Environment.* 2016, 139:20-29.
11. Wang M, Keller JP, Adar SD, Kim S-Y, Larson TV, Olives C, Sampson PD, Sheppard L, Szpiro AA, Vedal S: Development of long-term spatiotemporal models for ambient ozone in six metropolitan regions of the United States: The MESA Air study. *Atmospheric Environment.* 2015, 123:79-87.
12. Wang M, Sampson PD, Hu J, Kleeman M, Keller JP, Olives C, Szpiro AA, Vedal S, Kaufman JD. Combining Land-Use Regression and Chemical Transport Modeling in a Spatio-temporal Geostatistical Model for Ozone and $PM_{2.5}$. *Environmental Science and Technology*, 2016, 50(10):5111-5118.
13. Weuve J, Kaufman JD, Szpiro AA, Curl C, Puett RC, Beck T, Evans DA, Mendes de Leon CF. Exposure to Traffic-Related Air Pollution in Relation to Progression in Physical Disability among Older Adults. *Environmental Health Perspectives*. 2016, advance online publication.
14. Yin F, Driscoll WS, Sulaiman D, Ricks R, Ramanathan G, Stewart JA, Mehrabian M, Beaven SW, Lusis AL, Rosenfeld ME, Araujo JA. Diesel Exhaust Alters Lipid Metabolism and Induces Hyperlipidemia in Association with Down-Regulation of PPAR alpha and Changes in Gut Microbiota. *Atherosclerosis, Thrombosis and Vascular Biology (ATVB)*. 2016. Submitted.
15. Aragon MJ, Chrobak I, Brower J, Roldan L, Fredenburgh LE, McDonald JD, Campen MJ: Inflammatory and Vasoactive Effects of Serum Following Inhalation of Varied Complex Mixtures. *Cardiovascular toxicology.* 2016, 16(2): 163-171.
16. Bergen S, Sheppard L, Kaufman JD, Szpiro AA. Multi-pollutant measurement error in air pollution epidemiology studies arising from predicting exposures with penalized regression splines. *Journal of the Royal Statistical Society, Series C.* 2016, advance online publication.
17. Bergen S, Szpiro AA: Mitigating the impact of measurement error when using penalized regression to model exposure in two-stage air pollution epidemiology studies. *Environmental and Ecological Statistics.* 2015, 22(3): 601-631.
18. Bergen S, Sheppard L, Sampson PD, Kim S-Y, Richards M, Vedal S, Kaufman JD, Szpiro AA: A national prediction model for PM2. 5 component exposures and measurement error–corrected health effect inference. *Environmental health perspectives.* 2013, 121(9):1017.
19. Campen M, Robertson S, Lund A, Lucero J, McDonald J: Engine exhaust particulate and gas phase contributions to vascular toxicity. *Inhalation toxicology.* 2014, 26(6):353-360.
20. Campen MJ, Lund A, Rosenfeld M: Mechanisms linking traffic-related air pollution and atherosclerosis. *Current opinion in pulmonary medicine.* 2012, 18(2):155.
21. Chan SH, Van Hee VC, Bergen S, Szpiro AA, DeRoo LA, London SJ, Marshall JD, Kaufman JD, Sandler DP: Long-Term Air Pollution Exposure and Blood Pressure in the Sister Study. *Environ Health Perspect.* 2015, 123(10):951-8.
22. Chi, GC, Hajat A, Bird CE, Cullen MR, Griffin BA, Miller KA, Shih RA, Stefanick ML, Vedal S, Whitsel EA, Kaufman JD. Individual and Neighborhood Socioeconomic Status and the Association Between Air Pollution and Cardiovascular

Disease. Environmental Health Perspectives. *Environmental Health Perspectives.* 2016, advance online publication.
23. Cosselman, KE, Navas-Acien, A, Kaufman, JD. Environmental Factors in Cardiovascular Disease. *Nature Reviews Cardiology*. 2015, 12(11): 627-642
24. Erickson M, Gueneron M, Jobson B: Measuring long chain alkanes in diesel engine exhaust by thermal desorption PTR-MS. *Atmospheric Measurement Techniques.* 2014, 7(1):225-239.
25. Galaviz V, Yost M, Simpson C, Camp J, Paulsen M, Elder J, Hoffman L, Flores D, Quintana P: Traffic pollutant exposures experienced by pedestrians waiting to enter the US at a major US–Mexico border crossing. *Atmospheric Environment.* 2014, 88:362-369.
26. Gueneron M, Erickson MH, VanderSchelden GS, Jobson BT: PTR-MS fragmentation patterns of gasoline hydrocarbons. *International Journal of Mass Spectrometry.* 2015, 379:97-109.
27. Herring CL, Faiola CL, Massoli P, Sueper D, Erickson MH, McDonald JD, Simpson CD, Yost MG, Jobson BT, VanReken TM: New Methodology for Quantifying Polycyclic Aromatic Hydrocarbons (PAHs) Using High-Resolution Aerosol Mass Spectrometry. *Aerosol Science and Technology.* 2015, 49(11):1131-1148.
28. Hudda N, Gould T, Hartin K, Larson TV, Fruin SA: Emissions from an international airport increase particle number concentrations 4-fold at 10 km downwind. *Environmental science & technology.* 2014, 48(12):6628-6635.
29. Jandarov R, Sheppard L, Sampson PD, Szpiro AA. A novel principal component analysis for spatially misaligned air pollution data. *Journal of the Royal Statistical Society, Series C.* 2016, advance online publication.
30. Keller J, Drton M, Larson T, Kaufman JD, Sandler D, Szpiro AA. Covariate-adaptive clustering of exposures for air pollution epidemiology cohorts. *Annals of Applied Statistics*. 2015, Submitted.
31. Keller JP, Olives C, Kim S-Y, Sheppard L, Sampson PD, Szpiro AA, Oron AP, Lindström J, Vedal S, Kaufman JD: A unified spatiotemporal modeling approach for predicting concentrations of multiple air pollutants in the multi-ethnic study of atherosclerosis and air pollution. *Environmental health perspectives.* 2015, 123(4):301-309.
32. Kim S-Y, Dutton SJ, Sheppard L, Hannigan MP, Miller SL, Milford JB, Peel JL, Vedal S. The short-term association of selected components of fine particulate matter and mortality in the Denver Aerosol Sources and Health (DASH) study. *Environmental Health.* 2015, 14(1):49.
33. Kim S-Y, Sheppard L, Larson TV, Kaufman JD, Vedal S. Combining PM2. 5 Component Data from Multiple Sources: Data Consistency and Characteristics Relevant to Epidemiological Analyses of Predicted Long-Term Exposures. *Environmental health perspectives.* 2015, 123(7): 651-8.
34. Kim S-Y, Sheppard L, Kaufman JD, Bergen S, Szpiro AA, Larson TV, Adar SD, Roux AVD, Polak JF, Vedal S. Individual-level concentrations of fine particulate matter chemical components and subclinical atherosclerosis: a cross-sectional analysis based on 2 advanced exposure prediction models in the multi-ethnic study of atherosclerosis. *American journal of epidemiology.* 2014, 180(7):718-728.

35. Lee A, Szpiro A, Kim S, Sheppard L: Impact of preferential sampling on exposure prediction and health effect inference in the context of air pollution epidemiology. *Environmetrics.* 2015, 26(4):255-267.
36. Lund AK, Doyle-Eisele M, Lin Y-H, Arashiro M, Surratt JD, Holmes T, Schilling KA, Seinfeld JH, Rohr AC, Knipping EM: The effects of α-pinene versus toluene-derived secondary organic aerosol exposure on the expression of markers associated with vascular disease. *Inhalation toxicology.* 2013, 25(6):309-324.
37. Mauderly J, Kracko D, Brower J, Doyle-Eisele M, McDonald J, Lund A, Seilkop S: The National Environmental Respiratory Center (NERC) experiment in multi-pollutant air quality health research: IV. Vascular effects of repeated inhalation exposure to a mixture of five inorganic gases. *Inhalation toxicology.* 2014, 26(11):691-696.
38. McDonald JD, Chow JC, Peccia J, Liu Y, Chand R, Hidy GM, Mauderly JL: Influence of collection region and site type on the composition of paved road dust. *Air Quality, Atmosphere & Health.* 2013, 6(3):615-628.
39. Nicholas T. Contribution of the in-vehicle microenvironment to individual ambient source-derived NO2 exposure concentration. M.S. Thesis, University of Washington. 2014.
40. Olives C, Sheppard L, Lindström J, Sampson PD, Kaufman JD, Szpiro AA: Reduced-rank spatio-temporal modeling of air pollution concentrations in the Multi-Ethnic Study of Atherosclerosis and Air Pollution. *The Annals of Applied Statistics.* 2014, 8(4):2509-2537.
41. Oppenheim HA, Lucero J, Guyot A-C, Herbert LM, McDonald JD, Mabondzo A, Lund AK: Exposure to vehicle emissions results in altered blood brain barrier permeability and expression of matrix metalloproteinases and tight junction proteins in mice. *Particle and Fibre Toxicolgy.* 2013, 10(62).
42. Paffett ML, Sheppard L, Robertson S, Weaver J, Lucas SN, Campen M. Ozone inhalation enhances coronary artery constriction and impairs dilation via superoxide-dependent mechanisms. *Toxicology and Applied Pharmacology.* 2015, In Press.
43. Riley EA, Banks L, Fintzi J, Gould TR, Hartin K, Schaal L, Davey M, Sheppard L, Larson T, Yost MG: Multi-pollutant mobile platform measurements of air pollutants adjacent to a major roadway. *Atmospheric Environment.* 2014, 98:492-499.
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51. Vedal S, Kaufman JD: What does multi-pollutant air pollution research mean? *American journal of respiratory and critical care medicine.* 2011, 183(1):4-6.
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Center Presentations to Date:

1. **Keller, J. Covariate-adaptive Clustering of Exposure for Air Pollution Epidemiology Cohorts. Joint Statistical Meetings, Seattle, WA, August 2015.**
2. **Riley E, Gould T, Fruin S, Simpson C, Yost M, and Larson T. Black carbon and ultrafine particle counts downwind of two major airports. International Society of Exposure Science Annual Meeting, Henderson, NV. October 2015.**
3. **Wang, M. Hybrid Spatiotemporal Model Combining Land Use Regression and Chemical Transport Modeling in a Geo-statistical Framework for Ozone and PM2.5 in Los Angeles, California. International Society of Exposure Science Annual Meeting, Henderson, NV. October 2015.**
4. **Wang, M. Long-term exposure to ozone and accelerated emphysema progression and lung function decline: the MESA Air and Lung Studies. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2016.**
5. Austin E. Identifying multi-pollutant spatial patterns in mobile monitoring data from Baltimore, MD using cluster analysis. Annual Symposium on Environmental, Occupational and Population Health, Semiahmoo, WA, January 2014.

6. Austin, E. Identification and Classification of Multipollutant Peak Events in Mobile Monitoring Data. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.
7. Bergen, S. Optimal Penalty Parameter Selection to Minimize the Impact of Exposure Measurement Error in 2-Stage Air Pollution Epidemiology Analyses. ISEE/ISES/ISIAQ. Basel Switzerland, August 2013.
8. Bergen, S. Optimal Penalty Parameter Selection to Minimize the Impact of Exposure Measurement Error in 2-Stage Air Pollution Epidemiology Analyses. Joint Statistical Meetings. Montreal Canada, August 2013.
9. Bergen, S. Multi-pollutant measurement error in air pollution epidemiology studies arising from predicting exposures with penalized regression splines. Joint Statistical Meetings. Boston MA, August 2014.
10. Campen, MJ. Endothelial Cell Pattern Recognition Receptors, CD36 and LOX-1, Contribute to Responses to Pollution-Induced Circulating Factors. Society of Toxicology, Phoenix, Arizona, March 2014.
11. Doyle-Eisele M, Rohr A, Knipping E, Lund A, Brower J, McDonald JD. Secondary Organic Aerosols Generated from α-Pinene-Amine Mixtures: Effects on the Cardiovascular System. Presented (1222/322) at Society of Toxicology, Phoenix, Arizona, 2014.
12. Fuchs M, VanderSchelden GS, Flyckt CL, Jobson BT. Diesel Exhaust Flow Tube Reactor Characterization. 2014 Air & Waste Management Association PNWIS Conference, Spokane, WA, November 5-8.
13. Hazlehurst, M. Integrating Data from Multiple Time-Location Measurement Methods for Use in Exposure Assessment: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). International Society for Environmental Epidemiology. Seattle, WA. August 2014.
14. Holmes T, McDonald JD, Kuehl P, Kracko D. Characterization of the Blu E-Cigarette to Define the Composition of Inhaled Material. Presented (1202/302) at Society of Toxicology, Phoenix, Arizona, 2014.
15. Jandarov, R. A novel dimension reduction approach for spatially-misaligned multivariate air pollution data. Joint Statistical Meetings. Montreal Canada, August 2013.
16. Jandarov R. A novel dimension reduction approach for spatially-misaligned multivariate air pollution data. Work-In-Progress webinar for the Clean Air Research Centers, University of Washington, Seattle, WA, USA, February 2014
17. Jandarov, R. A novel dimension reduction approach for spatially-misaligned multivariate air pollution data. International Society for Environmental Epidemiology. Seattle WA, August 2014.
18. Jobson, BT, MH Erickson, Gueneron, M., VanderSchelden, G., Measuring Small Photoproducts and Big Organics by PTR-MS, Canadian Chemistry Conference, Vancouver, B.C. June 2014.
19. Keller, J. A Unified Spatiotemporal Modeling Approach for Prediction of Multiple Air Pollutants in MESA Air. International Society for Environmental Epidemiology. Seattle WA, August 2014.
20. Keller, J. Covariate-adaptive Clustering of Exposures for Air Pollution Epidemiology Cohorts. Western North American Region of The International Biometric Society (WNAR). Boise, ID. June 2015.

21. Lee, Adel. Impact of Monitoring Network Design on Exposure Prediction and Measurement. Joint Statistical Meetings. Montreal Canada, August 2013.
22. McDonald JD, Influence of Collection Region and Site Type on the Composition of Paved Road Dust: It's Not Just Dirt!!! Presented (2312) at Society of Toxicology, Phoenix, Arizona, 2014.
23. Nicholas, T. Contribution of time in-transit to individual exposure to traffic-related air pollution. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.
24. Olives, C. Reduced-rank spatio-temporal modeling of air pollution concentrations in the Multi-Ethnic Study of Atherosclerosis and Air Pollution. Joint Statistical Meetings. Boston MA, August 2014.
25. Olives, C. Correcting for Spatial Measurement Error in Air Pollution Cohort Studies. International Society for Environmental Epidemiology. Seattle WA, August 2014.
26. Riley EA, Banks L, Fintzi J, Gould TR, Hartin K, Schaal L, Davey M, Sheppard L, Larson T, Yost MG, Simpson CD. Multi-pollutant Mobile Platform Measurements of Traffic-associated Air Pollutants adjacent to the I-40 Corridor in Albuquerque, NM. Canadian Chemistry Conference and Exhibition, Vancouver, B.C., June 2014.
27. Riley, E. Multi-pollutant mixtures identified from a principal component analysis by melding mobile monitoring and integrated passive sampler data. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.
28. Sampson P. A novel dimension reduction approach for spatially-misaligned multivariate air pollution data (work of Roman Jandarov), presented at the Multivariate Spatial Models workshop of the Pan-American Advanced Study Institute on Spatio-Temporal Statistics, Buzios, RJ, Brazil, June 2014.
29. Sampson P. The deformation approach to nonstationary spatial covariance modeling incorporating a partial warp parameterization of thin-plate splines, presented at the Pan-American Advanced Study Institute on Spatio-Temporal Statistics, Buzios, RJ, Brazil, June 2014.
30. Sampson, PD. Spatio-temporal Modeling for Environmental Monitoring Data. International Symposium on Statistics (ISS). St. John's, Newfoundland, Canada, July 2015.
31. Sheppard L. Effects of Classical-Like and Berkson-Like Measurement Error on Inference. International Society for Environmental Epidemiology. Seattle WA, August 2014.
32. Spalt, EW. Patterns in Indoor, Outdoor, In-Vehicle, and Personal Measurements of Volatile Organic Compounds. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.
33. Sullivan, MD. Ambient Transition Metals, Lung Density and Lung Function In The Multi-Ethnic Study of Atherosclerosis (MESA). American Thoracic Society International Conference. Philadelphia, PA, May 2013.
34. Szpiro AA, Paciorek CJ. Model Choice for Spatial Prediction of Multiple Air Pollution Exposures. Joint Statistical Meeting. San Diego, CA, July 2012.
35. Szpiro A. Multipollutant research: challenges and progress (invited panel discussant). Health Effects Institute Annual Meeting. Alexandria VA, May 2014.
36. Szpiro A. Measurement error in air pollution cohort studies. Planning workshop for RFPA on concentration-response function for adverse health effects of long-term air

pollution exposure (invited participant). Health Effects Institute. Boston, MA, June 2014.

37. Szpiro, A. Dimension reduction for spatially misaligned multivariate air pollution data. Joint Statistical Meetings. Boston MA, August 2014.
38. Szpiro, A. Does more accurate exposure prediction necessarily improve health effect estimates? International Society for Environmental Epidemiology. Seattle WA, August 2014.
39. Szpiro, A. Dimension Reduction for Spatially Misaligned Multivariate Air Pollution Data. Society for Epidemiologic Research (SER). Denver, CO. June 2015.
40. VanderSchelden GS, Fuchs M, Bartoshevich R, Wen M, Jobson BT, Measurements of Diesel Exhaust and its Photoproducts using a PTR-MS and a Photochamber. 2014 Air & Waste Management Association PNWIS Conference, Spokane, WA, November 5-8.
41. Vedal S, Szpiro AA. Methods for Estimating Health Effects of Multipollutant Mixtures in Cohort Studies. ISEE Annual Meeting, Barcelona, Spain, September 2011.
42. Vedal S. Multipollutant Data and a Multivariate Modeling Approach for Comparing Cardiovascular Health Effects of Contrasting Air Pollution Mixtures. Symposium (Multipollutant Exposure Metrics and Their Application to Air Pollution Epidemiological Studies). ISES Annual Meeting, Seattle, WA, October 2012.
43. Vedal, S. Estimating Exposure and Health Effects of PM2.5 Components. Fudan School of Public Health. Shanghai, China. June 2013.

Center Posters to Date:

1. **Campen M, Heine L, Liu J, Brower J, Herbert G, Sanchez B, Zychowski K, Topper L, Doyle-Eisele M, and McDonald J. Woodsmoke Exposure Alters Serum Composition That Induces Inflammatory Gene Expression and Impairs Ex Vivo Wound Healing. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
2. **Fitch MN, Lucero J, Campen MJ, Lund A, and McDonald JD. Exposure to Inhaled Air Pollutants Results in Altered Barrier Structure in the Duodenal Epithelium of ApoE KO Mice. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
3. **Keller J, Chang HH, Strickland MJ. Measurement Error Correction for Predicted Fine Particulate Matter and Low Birth Weight. University of Washington DEOHS Student Research Day. Seattle, WA. May 2016.**
4. **Kuehl PJ, Kracko D, Irshad H, Yates E, and McDonald J. Evaluation of Different Particle Size Quantification Instruments - Strengths/ Weaknesses and Characteristics for Consideration in Determining the Appropriate Technique. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
5. **Liu J, Brower J, Doyle-Eisele M, Herbert G, Heine L, Sanchez B, Zychowski K, Topper L, McDonald J, and Campen M. Serum-Borne Vascular Toxicity Following Inhalation of Mixed Engine Emissions and Treated Particles. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
6. **Ramanathan G, Zhao Y, Yin F, Rosenfeld ME, Yang X, and Araujo JA. Liver Transcriptomic and Metabolic Reprogramming After Exposure to Diesel Exhaust. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**

7. **Sampson, P. A partial warp parameterization for the spatial deformation model for non stationary covariance. 'STATMOS' Statistics in the Atmospheric Sciences — Invited Poster Presentations, Joint Statistical Meetings. Seattle, WA. August 2015.**
8. **Schneider L, Lucero J, McDonald JD, and Lund A. Inhalation Exposure to Traffic-Generated Air Pollutants Increases Renal Oxidative Stress, Matrix Metalloproteinase-9 Expression, and Fibrosis, Which Are Mediated Through an Angiotensin II-Dependent Pathway. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
9. **Mota RI, Norenberg JP, Daniels T, Lucas S, Campen M. Competitive receptor-binding assays of 111In-DANBIRT targeting of Luekocyte-function associated antigen-1 in a systemic inflammation rat model to inhaled ozone exposure. Society of Nuclear Medicine and Molecular Imagine Annual Meeting. June 2016.**
10. Austin E, Larson T, Sheppard L, Yost M. (2014). Pollutant variability and correlations in mobile monitoring data as compared to central site monitoring. EPA Air Sensors Workshop, Research Triangle Park, NC, June 2014.
11. Banks LE, Simpson CD, Larson TV, Yost MG. Characterization of Traffic-Related Air Pollutants Near a Major Roadway in Albuquerque Using a Mobile Monitoring Approach. American Industrial Hygiene Conference and Exposition. Montreal, QC, Canada, May 2013.
12. Bergen S, Chan SH, Kaufman JD, Sandler D, Sheppard L, Szpiro AA. Multipollutant measurement error in air pollution epidemiology. ISEE Seattle WA, August 2014.
13. Brower J, Moeller B, Doyle-Eisele M, Stirdivant S, McDonald JD, Campen M. Acute Inhalation Exposure to Mixed Vehicle Emissions Induces Serum Metabolite Changes Related to Oxidative Stress, Lipid Peroxidation, and Energy Metabolism. Society of Toxicology, Phoenix, Arizona, 2014.
14. Campen MJ, McDonald JM, Rosenfeld ME, Lund AK. Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.
15. Fintzi, J. Identification and Description of On-Road Emission Sources: Results from Seattle. University of Washington DEOHS Student Research Day. Seattle, WA. May 2014.
16. Fintzi, J, Sheppard L. Detecting On-Road Emission Sources in Mobile Monitoring Data: A Novel Approach to Thinking about Air Pollution. University of Washington DEOHS Student Research Day, Seattle, WA. May 2013.
17. Hazlehurst, M. Time‐location measurement methods for use in exposure assessment: the Multi‐Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015. ***Winner of a Student Poster Award.***
18. Herring, C, Erickson, M, Gueneron, M, Faiola, C, McDonald, J, Jobson, T, VanReken, T, Hartin, K, Yost, M, and Larson, T, "Characterization of Mixed Diesel and Gasoline Exhaust by HR-ToF-AMS under Varied Engine Load and Dilution Conditions. AAAR 32nd Annual Conference, October 2013. ***Winner of a Student Poster Award.***
19. Jandarov, RA. Novel Principal Component Analysis for Spatially-Misaligned Multivariate Air Pollution Data. ISEE/ISES/ISIAQ. Basel Switzerland, August 2013.
20. Keller J. Covariate-adaptive Clustering of Exposures for Air Pollution Epidemiology Cohorts. University of Washington DEOHS Student Research Day. Seattle, WA. May

2015.

21. Keller JP, Sheppard L, Szpiro AA, Sampson PD. Spatial Analysis of a Marker of Roadway Emission Aging. Clean Air Research Centers Annual Meeting, Boston, MA, June 2012.
22. Riley E. Black Carbon and Ultrafine Particle Counts Downwind of Two Major Airports. University of Washington DEOHS Student Research Day. Seattle, WA. May 2015.
23. Riley E, Austin E, Fintzi J, Larson TV, Yost MG, Sheppard L, Sampson P, Simpson CD. Decoupling Regional and Local Sources in Mobile Monitoring of Air Pollutants. Student Research Day, Department of Environmental and Occupational Health, University of Washington, Seattle, May 29, 2014.
24. Riley EA, Hartin K, Gould T, Larson TV, Yost MG, Simpson CD. Mobile measurements of near-highway air pollutant gradients. Annual Symposium on Environmental, Occupational and Population Health, Semiahmoo, WA, January 2014.
25. Riley EA, Sasakura MD, Hartin K, Crampton R, Gould TR, Larson TV, Yost MG, Simpson CD. Principal Component Analysis of Snap-Shot Air Pollutant Measurements In Baltimore, MD. EPA annual Clean Air Research Center Annual Meeting, Seattle, WA July, 2013.
26. VanReken T, Jobson T. Chemical Characterization of the LRRI Exhaust Exposure Chambers by PTR-MS and HR-ToF-AMS: Early Results. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.
27. Xu W. Use of Mobile and Passive Badge Air Monitoring Data for NO_X and Ozone Air Pollution Spatial Exposure Prediction Models. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.

Relevant Web Sites

http://depts.washington.edu/uwccar/

INDIVIDUAL PROJECT/CORE SUMMARIES

Biostatistics Core

Individual Project Title: Biostatistics Core

Investigator	Institution
Elizabeth A. (Lianne) Sheppard	University of Washington
Paul D. Sampson	University of Washington
Adam A. Szpiro	University of Washington

Objective of Research
The overall objective is to support the statistical needs of all Center projects. This will be achieved through five specific objectives. These are:
1. Advise Center projects on data management and compilation
2. Ensure quality statistical design and analysis of Center research

Implement novel statistical methods that are required for Center projects: Develop an analytical framework for quantifying the health effects of different mixtures of air pollution com

Research Performed - Progress Summary/Accomplishments
We summarize the activities to date of the Biostatistics Core by specific aim:

1. Advise Center projects on data management and compilation

The bulk of this aim focused on support to Project 1, which is now complete. However, this Core continues to serve as a resource in this area and will provide support as needed, particularly to Project 4, which is just completing data collection.

2. Ensure quality statistical design and analysis of Center research

Project 4. The Biostatistics Core has supported the redesign of Project 4 and plans to support data analysis as needed in the remaining no-cost extension period.

Project 5.
This project and related statistical methods research has continued to be an important thrust of activities for the Core in the first no-cost extension year. We have started implementing the following approach:

a. We use k-means clustering to conduct a preliminary identification of clusters in multipollutant datasets comprised of both summaries of mobile monitoring data and badge data, all indexed by fuzzy point locations and season (heating vs. non-heating). (We temporally adjust the mobile monitoring data to prepare it for a purely spatial analysis.)
b. We then use multivariate logistic regression classification algorithm with selected geographic covariates to predict cluster membership at MESA subject locations. We will also explore using support vector machines (SVM) as an alternative classifier, which would enable us to include a larger suite of geographic covariates.

c. In preliminary analyses we used cluster membership as an effect modifier of NO_x, for the role of air pollution on the rate of change of coronary artery calcium (CAC) over time. Details about each step follow.

a. Cluster Analysis

As described in last year's report, we applied traditional k-means cluster analysis methods to the CCAR monitoring data with the goal of identifying spatial differences in the multipollutant sources. We performed the analysis separately within each sampling season for each city, since we have ample reason to believe that source profiles change by season and by city. The four cities studied were Baltimore, Los Angeles, St. Paul and Winston-Salem. All pollutant data in this analysis were normalized by the concentration of NO_X measured at each location. Although we have completed k-mean cluster analyses in all four cities, our health analyses have focused thus far on Baltimore.

The data sources and clustering method are described in more detail in last year's report. Briefly, the data sources included passive badges (VOCs, NO_X, NO_2, ozone) and real-time monitoring data for carbon monoxide, black carbon and size-fractioned PM count (25 nm- 400nm, <1 μm, 1-2.5 μm). We performed k-means clustering, with Eulerian distance measures, separately by city and season over the 43 different monitoring locations. We selected the number of clusters using 3 criteria: 1) Minimizing the number of clusters with fewer than 5 members; 2) Maximizing the separation between the first 2 principal components describing each cluster; and 3) Maximizing the agreement between different validated indices for selecting *k*. Cluster results were presented in last year's report.

In related work (see our description of novel statistical methods developed by the Biostatistics Core below), we have developed *predictive k-means* clustering as an alternative to k-means clustering. The advantage of predictive k-means is that it will identify cluster centers from the monitoring data such that we can more accurately predict cluster membership at subject locations. We have applied predictive k-means as an enhancement to the exposure modeling and health analysis of Project 5 data described above. We selected the best models by minimizing prediction error using cross-validation. In both the heating and non-heating seasons, the best models grouped the data into three clusters using two principal component scores as covariates. In both seasons, the cross-validation prediction error was smaller for predictive k-means than for k-means.

b. *Estimating health effects*:

Predicted cluster memberships at cohort locations partition the subjects by the type of pollution to which they are exposed. As such, we have used cluster membership as an effect modifier of the association between NO_x exposure and measurements of coronary artery calcium (CAC) to determine whether or not the association varies by multi-pollutant profile (as identified by cluster). The NO_x exposure estimates were derived from the spatiotemporal exposure prediction models developed for MESA Air. Predicted cluster membership for Baltimore participants in heating and non-heating are provided in the Project 5 summary.

Following the approach of the MESA Air study, CAC progression was analyzed using a mixed model that allows for estimation of cross-sectional and longitudinal (progression) associations

with NO_x exposure. The mixed-model includes random-intercepts and random-slopes for all time-varying adjustments, each of which varies by participant, and also allows for a fixed effect adjustment for transient confounders. By including cluster membership as an effect modifier in both the cross-sectional and longitudinal terms, we will estimate separate longitudinal associations between CAC and NO_x for each cluster, and thus each multi-pollutant mixture profile.

Following the approach of the MESA Air study, we estimated the association between CAC progression and NO_x by cluster using a staged modeling approach. A staged approach to covariate adjustment considers known relationships between participant characteristics and heart disease, observed relationships between these characteristics and air pollution, and scientific judgment about potential mediators. Our primary model adjusts for age, sex, race/ethnicity, site, scanner type, adiposity, physical activity, smoking and second-hand smoke exposure, employment outside the home, total cholesterol, high density lipoprotein (HDL), triglycerides, statin use (time-varying), neighborhood SES index, education, and income. Simpler models and more fully adjusted models including potential mediators (diabetes, blood pressure and hypertension), and additional potential confounders (C-reactive protein, fibrinogen, creatinine, alcohol use, and family history of premature CVD) are also evaluated. Measurements from participants after coronary revascularization procedures will be excluded from the analysis. In the Project 5 summary, we present preliminary results for the heating and non-heating seasons in Baltimore.

3. *Implement novel statistical methods that are required for Center projects: Develop an analytical framework for quantifying the health effects of different mixtures of air pollution components in a cohort study (Project 1 and Project 5)*

Our goal is to develop a statistical framework for assessing health effects of long-term exposure to multi-pollutant mixtures when health data and monitoring data are spatially misaligned. This entails three primary steps:

3.1. Dimension reduction of the multi-pollutant exposure surface
3.2. Spatial prediction of the (reduced dimension) multi-pollutant exposure surface
3.3. Health effect inference that accounts for uncertainty from prediction (and possibly dimension reduction) in the first two steps

In previous years we have focused on dimension reduction using sparse PCA and predictive sparse PCA, summarized below. Our activities in the past year focused on predictive k-means clustering.

<u>Dimension reduction and spatial misalignment (3.1 and 3.2)</u>: Dimension reduction is often essential for estimating and interpreting associations between a health endpoint and a multivariate exposure, such as a mixture of air pollutants. Principal component analysis (PCA) and sparse PCA are commonly used dimension reduction methods that explain as much variability in the data as possible with linear combinations of a relatively small number of loading vectors (sparseness is desirable to make components more interpretable). The

coefficients in this linear representation are known as principal component scores, and they can be used as low-dimensional representations in a health model.

Spatial misalignment occurs when we do not observe exposure data at locations of interest for a health analysis. We demonstrated the utility of predictive (sparse) PCA in simulated data and in an application to annual averages of particulate matter speciation data from national Environmental Protection Agency (EPA) regulatory monitors (CSN and IMPROVE monitors). A manuscript based on this work is now published in the *Journal of the Royal Statistical Society, Series C* (Jandarov 2016).

In a complementary project we have developed methods for predictive k-means clustering. Predictive *k*-means incorporates geographic covariates (e.g. spatial basis functions or land use covariates) to identify clusters in multi-dimensional measurements and predict cluster membership at cohort locations. This procedure can be derived as a mixture of normal distributions and is solved using a version of the expectation-maximization (EM) algorithm. We have compared this approach to k-means clustering followed by spatial prediction. In simulations, we have demonstrated that predictive *k*-means can reduce prediction error by over 40% compared to k-means, with minimal loss in cluster representativeness. The improved prediction accuracy resulted in large gains of 30% or more in power for detecting effect modification by cluster in a simulated health analysis. In a manuscript submitted to *Annals of Applied Statistics*, we applied this approach to the association between systolic blood pressure and long-term fine particulate matter ($PM_{2.5}$) exposure in the NIEHS Sister Study.

For the Project 5 analysis we have compared the *k*-means clusters to clusters found by the novel predictive *k*-means procedure. They are distinct. We have predicted cluster membership at the cohort locations within each city via multinomial logistic regression using one or more (up to six) principal component analysis (PCA) scores, derived from GIS variables, as the prediction covariates. We will explore alternative prediction models such as neural networks and support vector machines, which would allow for more PCA scores or spatial basis functions to be used in the prediction model.

Measurement error correction (3.3): We have developed a method for measurement error correction with spatially misaligned data, for the general setting where spatial prediction is done by a low-rank penalized regression model. We have applied our multipollutant measurement error correction to an analysis of $PM_{2.5}$ and SBP in the Sisters Study (Bergen et al. 2016).

4. Identify additional statistical methodological research that will advance Center projects

The process of identifying additional methodological research is most effective when it happens organically. Many fresh ideas are generated during discussions at our weekly Environmental (Bio)statistics Working Group meetings, often while we are critiquing progress and results from ongoing projects. In this report we have included our progress related to this aim in the summaries provided above.

5. Communicate and disseminate Center findings

The Core has been supporting and leading efforts to publish and otherwise disseminate UW CCAR research. Titles of specific publications and presentations are given below.

Publications / Presentations / Posters

Publications to Date:

1. **Keller JP, Chang HH, Strickland MJ, Szpiro AA. Measurement error correction for predicted spatiotemporal air pollution exposures. *Epidemiology.* 2016, Submitted.**
2. **Kim SY, Olives C, Sheppard L, Sampson PD, Larson TV, Kaufman JD. Historical prediction modeling approach for estimating long-term concentrations of PM2.5 in cohort studies before 1999 implementation of widespread monitoring. *Environmental Health Perspectives*. 2016, advance online publication. DOI:10.1289/EHP131.**
3. **Kim SY, Sheppard L, Bergen S, Szpiro AA, Sampson PD, Kaufman JD, Vedal S. Prediction of fine particulate matter chemical components for the Multi-Ethnic Study of Atherosclerosis cohort: A comparison of two modeling approaches. *Journal of Exposure Science and Epidemiology*. 2016, advance online publication.**
4. **Wang M, Keller JP, Adar SD, Kim S-Y, Larson TV, Olives C, Sampson PD, Sheppard L, Szpiro AA, Vedal S: Development of long-term spatiotemporal models for ambient ozone in six metropolitan regions of the United States: The MESA Air study. *Atmospheric Environment.* 2015, 123:79-87.**
5. **Wang M, Sampson PD, Hu J, Kleeman M, Keller JP, Olives C, Szpiro AA, Vedal S, Kaufman JD. Combining Land-Use Regression and Chemical Transport Modeling in a Spatio-temporal Geostatistical Model for Ozone and $PM_{2.5}$. *Environmental Science and Technology,* 2016, 50(10):5111-5118.**
6. Bergen S, Sheppard L, Kaufman JD, and Szpiro AA. Multi-pollutant measurement error in air pollution epidemiology studies arising from predicting exposures with penalized regression splines. Journal of the Royal Statistical Society, Series C. 2016, advance online publication.
7. Bergen S and Szpiro AA. Mitigating the impact of measurement error when using penalized regression to model exposure in two-stage air pollution epidemiology studies. Environmental and Ecological Statistics. 2015, 22(3): 601-631.
8. Bergen S, Sheppard L, Sampson PD, Kim S-Y, Richards M, Vedal S, Kaufman JD, Szpiro AA: A national prediction model for PM2. 5 component exposures and measurement error–corrected health effect inference. *Environmental health perspectives.* 2013, 121(9):1017.
9. Jandarov R, Sheppard L, Sampson PD, and Szpiro AA. A novel principal component analysis for spatially misaligned air pollution data. Journal of the Royal Statistical Society, Series C. 2016, advance online publication.
10. Keller JP, Drton M, Larson T, Kaufman JD, Sandler DP, and Szpiro AA. Covariate-adaptive clustering of exposures for air pollution epidemiology cohorts. Annals of Applied Statistics. Submitted.
11. Keller JP, Olives C, Kim SY, Sheppard L, Sampson PD, Szpiro AA, Oron A, Vedal S, Kaufman JD. A unified spatiotemporal modeling approach for prediction of multiple air pollutants in the Multi-Ethnic Study of Atherosclerosis and Air Pollution. Environmental health perspectives 2015, 123(4): 301-309.

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13. Kim S-Y, Sheppard L, Larson TV, Kaufman JD, Vedal S. Combining PM2. 5 Component Data from Multiple Sources: Data Consistency and Characteristics Relevant to Epidemiological Analyses of Predicted Long-Term Exposures. Environmental health perspectives. 2015, 123(7): 651-658.
14. Kim S-Y, Sheppard L, Kaufman JD, Bergen S, Szpiro AA, Larson TV, Adar SD, Diez Roux AV, Polak JF, Vedal S. Individual-level concentrations of fine particulate matter chemical components and subclinical atherosclerosis: A cross-sectional analysis based on two advanced exposure prediction models in the Multi-Ethnic Study of Atherosclerosis. American Journal of Epidemiology. 2014, 180(7):718-28.
15. Lee A, Szpiro AA, Kim S-Y, and Sheppard L. Impact of preferential sampling on exposure prediction and health effect inference in the context of air pollution epidemiology. Environmetrics. 2015, 26(4): 255-267.
16. Olives C, Sheppard L, Lindstrom J, Sampson PD, Kaufman JD, Szpiro AA. Reduced-rank spatio-temporal modeling of air pollution concentrations in the Multi-Ethnic Study of Atherosclerosis and Air Pollution. The Annals of Applied Statistics 8.4 (2014): 2509-2537.
17. Szpiro AA and Paciorek CJ. Measurement error in two-stage analyses, with application to air pollution epidemiology (with invited discussion). Environmetrics, 2013, 24: 501-517.
18. Wang M, Brunekreef B, Gehring U, Szpiro A, Hoek G, Beelen R: A new technique for evaluating land use regression models and their impact on health effect estimates. *Epidemiology.* 2016, 27.1: 51-56.

Presentations to Date:

1. **Keller, J. Covariate-adaptive Clustering of Exposure for Air Pollution Epidemiology Cohorts. Joint Statistical Meetings, Seattle, WA, August 2015.**
2. **Wang, M. Hybrid Spatiotemporal Model Combining Land Use Regression and Chemical Transport Modeling in a Geo-statistical Framework for Ozone and PM2.5 in Los Angeles, California. International Society of Exposure Science Annual Meeting, Henderson, NV. October 2015.**
3. Bergen, S. Multi-pollutant measurement error in air pollution epidemiology studies arising from predicting exposures with penalized regression splines. Joint Statistical Meetings. Boston MA, August 2014.
4. Bergen, S. Optimal Penalty Parameter Selection to Minimize the Impact of Exposure Measurement Error in 2-Stage Air Pollution Epidemiology Analyses. ISEE/ISES/ISIAQ. Basel Switzerland, August 2013.
5. Bergen, S. Optimal Penalty Parameter Selection to Minimize the Impact of Exposure Measurement Error in 2-Stage Air Pollution Epidemiology Analyses. Joint Statistical Meetings. Montreal Canada, August 2013.
6. Jandarov, R. A novel dimension reduction approach for spatially-misaligned multivariate air pollution data. International Society for Environmental Epidemiology. Seattle WA, August 2014.
7. Jandarov R. A novel dimension reduction approach for spatially-misaligned multivariate air pollution data. Work-In-Progress webinar for the Clean Air Research Centers,

University of Washington, Seattle, WA, February 2014.

8. Jandarov, R. A novel dimension reduction approach for spatially-misaligned multivariate air pollution data. Joint Statistical Meetings. Montreal Canada, August 2013.
9. Keller, J. Covariate-adaptive Clustering of Exposures for Air Pollution Epidemiology Cohorts. Western North American Region of The International Biometric Society (WNAR). Boise, ID. June 2015.
10. Keller, J. A Unified Spatiotemporal Modeling Approach for Prediction of Multiple Air Pollutants in MESA Air. International Society for Environmental Epidemiology. Seattle WA, August 2014.
11. Lee, Adel. Impact of Monitoring Network Design on Exposure Prediction and Measurement. Joint Statistical Meetings. Montreal Canada, August 2013.
12. Olives, C. Correcting for Spatial Measurement Error in Air Pollution Cohort Studies. International Society for Environmental Epidemiology. Seattle WA, August 2014.
13. Olives, C. Reduced-rank spatio-temporal modeling of air pollution concentrations in the Multi-Ethnic Study of Atherosclerosis and Air Pollution. Joint Statistical Meetings. Boston MA, August 2014.
14. Sampson, PD. Spatio-temporal Modeling for Environmental Monitoring Data. International Symposium on Statistics (ISS). St. John's, Newfoundland, Canada, July 2015.
15. Sampson P. A novel dimension reduction approach for spatially-misaligned multivariate air pollution data (work of Roman Jandarov), presented at the Multivariate Spatial Models workshop of the Pan-American Advanced Study Institute on Spatio-Temporal Statistics, Buzios, RJ, Brazil, June 2014.
16. Sampson P. The deformation approach to nonstationary spatial covariance modeling incorporating a partial warp parameterization of thin-plate splines, presented at the Pan-American Advanced Study Institute on Spatio-Temporal Statistics, Buzios, RJ, Brazil, June 2014.
17. Sheppard L. Effects of Classical-Like and Berkson-Like Measurement Error on Inference. International Society for Environmental Epidemiology. Seattle WA, August 2014.
18. Szpiro, A. Dimension Reduction for Spatially Misaligned Multivariate Air Pollution Data. Society for Epidemiologic Research (SER). Denver, CO. June 2015.
19. Szpiro, A. Does more accurate exposure prediction necessarily improve health effect estimates? International Society for Environmental Epidemiology. Seattle WA, August 2014.
20. Szpiro, A. Dimension reduction for spatially misaligned multivariate air pollution data. Joint Statistical Meetings. Boston MA, August 2014.
21. Szpiro A. Measurement error in air pollution cohort studies. Planning workshop for RFPA on concentration-response function for adverse health effects of long-term air pollution exposure (invited participant). Health Effects Institute. Boston, MA, June 2014.
22. Szpiro A. Multipollutant research: challenges and progress (invited panel discussant). Health Effects Institute Annual Meeting. Alexandria VA, May 2014.
23. Szpiro AA, Paciorek CJ. Model Choice for Spatial Prediction of Multiple Air Pollution Exposures. Joint Statistical Meeting. San Diego, CA, July 2012.

Posters to Date:

1. **Keller J, Chang HH, Strickland MJ. Measurement Error Correction for Predicted Fine Particulate Matter and Low Birth Weight. University of Washington DEOHS Student Research Day. Seattle, WA. May 2016.**
2. **Sampson, P. A partial warp parameterization for the spatial deformation model for non stationary covariance. 'STATMOS' Statistics in the Atmospheric Sciences — Invited Poster Presentations, Joint Statistical Meetings. Seattle, WA. August 2015.**
3. Austin E, Larson T, Sheppard L, Yost M. (2014). Pollutant variability and correlations in mobile monitoring data as compared to central site monitoring. EPA Air Sensors Workshop, Research Triangle Park, NC, June 2014.
4. Bergen S, Chan SH, Kaufman JD, Sandler D, Sheppard L, Szpiro AA. Multipollutant measurement error in air pollution epidemiology. ISEE Seattle WA, August 2014.
5. Fintzi, J. Identification and Description of On-Road Emission Sources: Results from Seattle. University of Washington DEOHS Student Research Day. Seattle, WA. May 2014.
6. Jandarov, RA. Novel Principal Component Analysis for Spatially-Misaligned Multivariate Air Pollution Data. ISEE/ISES/ISIAQ. Basel Switzerland, August 2013.
7. Keller J. Covariate-adaptive Clustering of Exposures for Air Pollution Epidemiology Cohorts. University of Washington DEOHS Student Research Day. Seattle, WA. May 2015.
8. Riley E, Austin E, Fintzi J, Larson TV, Yost MG, Sheppard L, Sampson P, Simpson CD. Decoupling Regional and Local Sources in Mobile Monitoring of Air Pollutants. Student Research Day, Department of Environmental and Occupational Health, University of Washington, Seattle, May 29, 2014.

Future Activities

Our plans for the remaining funding period include publishing work currently in progress, wrapping up our collaborative projects, and focusing on developing spatial models of the mobile monitoring data for application to Project 5 analyses. We will continue Core activities to support all projects on an as needed basis.

Supplemental Keywords

Environmental Policy, Exposure Modeling, Epidemiologic Inference, Health Effects, Air Pollution Exposure, Multipollutant, Measurement Error

Relevant Web Sites

http://depts.washington.edu/uwccar/

Project 1

Individual Project Title: Exposure Mapping – Characterization of Gases and Particles for Exposure Assessment in Health Effects and Laboratory Studies

Investigator	Institution
Michael Yost (PI)	University of Washington
Timothy Larson	University of Washington
Christopher Simpson	University of Washington
Thomas Jobson	Washington State University
Timothy VanReken	Washington State University

Objective of Research

Roadway-source air pollutants encompass a diversity of chemicals, including both particulate and gas phase components which are transformed by chemical and physical reactions as they age in the environment. Consequently, human exposures to air pollutants can range from relatively un-aged to highly aged components that vary with respect to particle size and the chemical composition of particle and gas phase components. To obtain a more comprehensive understanding of the seasonal and spatial variability in the concentration and composition of air pollutant exposures within MESA-Air cities, we employ mobile and fixed site monitoring to assess both gas and particle components of these pollutants as they age from roadway sources to population areas.

The main project objectives are:

1. Characterize spatial and temporal gradients of selected air pollutants along roadways and within neighborhoods in MESA cities using a mobile platform.

2. Measure spatial variation in concentrations of selected air pollutants at two-week average stationary sites in coordination with the mobile measurements.

3. Characterize aging of air pollutant components as they are transported from roadway sources to neighborhood receptor locations.

4. Provide detailed characterization of laboratory exposure conditions available for toxicology testing, and identify likely conditions that mimic those found in urban settings.

Research Performed - Progress Summary/Accomplishments

The bulk of Project 1 was completed in the first five years of the Center. Work over the last year has focused primarily on data analysis and manuscript preparation. Recent publications include manuscripts on the impacts of air pollution at the US-Mexico border (Galaviz et al. 2015) and near airports (Riley et al. 2016b). We have also recently published a paper investigating the correlations between mobile and passive badge monitoring data (Riley et al. 2016a; Xu et al. 2016). Project 1 researchers have also supported Project 5 and Biostatistics Core researchers with

data preparation and data analysis for the multipollutant exposure analysis piece of that project and Project 4 researchers with data collection for the commute exposures.

Publications / Presentations / Posters

Publications to Date:

1. **Galaviz VE, Quintana PJE, Yost MG, Sheppard L, Paulsen MH, Camp JE, Simpson CD. Urinary metabolites of 1-nitropyrene in US-Mexico border residents who frequently cross the San Ysidro Port of Entry. *Journal of Exposure Science and Environmental Epidemiology.* 2015, advance online publication.**
2. **Larson T, Gould TR, Riley EA, Austin E, Fintzi J, Sheppard L, Yost MG, Simpson CD. Ambient Air Quality Measurements from a Continuously Moving Mobile Platform: Estimation of Area-Wide, Fuel-Based, Mobile Source Emission Factors Using Absolute Principal Component Scores. *Atmospheric Environment.* 2016, submitted.**
3. **Riley EA, Schaal L, Sasakura M, Crampton R, Gould TR, Hartin K, Sheppard L, Larson T, Simpson CD, Yost MG. Correlations between short-term mobile monitoring and long-term passive sampler measurements of traffic related air pollution. *Atmospheric Environment.* 2016a, 132: 229-239.**
4. **Riley EA, Gould T, Hartin K, Fruin SA, Simpson CD, Yost MG, Larson T. Ultrafine particle size as a tracer for aircraft turbine emissions. *Atmospheric Environment.* 2016b, 139:20-29.**
5. Erickson M, Gueneron M, Jobson B: Measuring long chain alkanes in diesel engine exhaust by thermal desorption PTR-MS. *Atmospheric Measurement Techniques.* 2014, 7(1):225-239.
6. Galaviz V, Yost M, Simpson C, Camp J, Paulsen M, Elder J, Hoffman L, Flores D, Quintana P: Traffic pollutant exposures experienced by pedestrians waiting to enter the US at a major US–Mexico border crossing. *Atmospheric Environment.* 2014, 88:362-369.
7. Gueneron M, Erickson MH, VanderSchelden GS, Jobson BT: PTR-MS fragmentation patterns of gasoline hydrocarbons. *International Journal of Mass Spectrometry.* 2015, 379:97-109.
8. Herring CL, Faiola CL, Massoli P, Sueper D, Erickson MH, McDonald JD, Simpson CD, Yost MG, Jobson BT, VanReken TM: New Methodology for Quantifying Polycyclic Aromatic Hydrocarbons (PAHs) Using High-Resolution Aerosol Mass Spectrometry. *Aerosol Science and Technology.* 2015, 49(11):1131-1148.
9. Hudda N, Gould T, Hartin K, Larson TV, Fruin SA: Emissions from an international airport increase particle number concentrations 4-fold at 10 km downwind. *Environmental science & technology.* 2014, 48(12):6628-6635.
10. Riley EA, Banks L, Fintzi J, Gould TR, Hartin K, Schaal L, Davey M, Sheppard L , Larson T, Yost MG, Simpson CD. Multi-pollutant mobile platform measurements of air pollutants adjacent to the I-40 corridor in Albuquerque, NM. *Atmos. Environ*. 2014, 98: 492-499.
11. Xu W, Riley EA, Austin E, Sasakura M, Schaal L, Gould T, Hartin K, Simpson C, Sampson PD, Yost M, Larson T. Use of Mobile and Passive Badge Air Monitoring Data for NOX and Ozone Air Pollution Spatial Exposure Prediction Models. *Journal of Exposure Science and Environmental Epidemiology.* 2016, advance online publication.

Presentations to Date:

1. **Riley E. Gould T, Fruin S, Simpson C, Yost M, and Larson T. Black carbon and ultrafine particle counts downwind of two major airports. International Society of Exposure Science Annual Meeting, Henderson, NV. October 2015.**
2. Austin E. Identification and Classification of Multipollutant Peak Events in Mobile Monitoring Data. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.
3. Austin E. Identifying multi-pollutant spatial patterns in mobile monitoring data from Baltimore, MD using cluster analysis. Annual Symposium on Environmental, Occupational and Population Health, Semiahmoo, WA, January 2014.
4. Fuchs M, VanderSchelden GS, Flyckt CL, Jobson BT. Diesel Exhaust Flow Tube Reactor Characterization. Air & Waste Management Association PNWIS Conference, Spokane, WA, November 2014.
5. Jobson, BT, MH Erickson, Gueneron, M., VanderSchelden, G., Measuring Small Photoproducts and Big Organics by PTR-MS, Canadian Chemistry Conference, Vancouver, B.C. June 2014.
6. Riley E. Multi‐pollutant mixtures identified from a principal component analysis by melding mobile monitoring and integrated passive sampler data. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.
7. Riley EA, Banks L, Fintzi J, Gould TR, Hartin K, Schaal L, Davey M, Sheppard L, Larson T, Yost MG, Simpson CD. Multi-pollutant Mobile Platform Measurements of Traffic-associated Air Pollutants adjacent to the I-40 Corridor in Albuquerque, NM. Canadian Chemistry Conference and Exhibition, Vancouver, B.C., June 2014
8. VanderSchelden GS, Fuchs M, Bartoshevich R, Wen M, Jobson BT, Measurements of Diesel Exhaust and its Photoproducts using a PTR-MS and a Photochamber. 2014 Air & Waste Management Association PNWIS Conference, Spokane, WA, November 5-8.
9. Vedal S. Multipollutant Data and a Multivariate Modeling Approach for Comparing Cardiovascular Health Effects of Contrasting Air Pollution Mixtures. Symposium (Multipollutant Exposure Metrics and Their Application to Air Pollution Epidemiological Studies). ISES Annual Meeting, Seattle, WA, October 2012.
10. Vedal S, Szpiro AA. Methods for Estimating Health Effects of Multipollutant Mixtures in Cohort Studies. ISEE Annual Meeting, Barcelona, Spain, September 2011.

Posters to Date:

1. Banks LE, Simpson CD, Larson TV, Yost MG. Characterization of Traffic-Related Air Pollutants Near a Major Roadway in Albuquerque Using a Mobile Monitoring Approach. American Industrial Hygiene Conference and Exposition. Montreal, QC, Canada, May 2013.
2. Fintzi, J, Sheppard L. Detecting On-Road Emission Sources in Mobile Monitoring Data: A Novel Approach to Thinking about Air Pollution. University of Washington DEOHS Student Research Day, Seattle, WA. May 2013.
3. Herring, C, Erickson, M, Gueneron, M, Faiola, C, McDonald, J, Jobson, T, VanReken, T, Hartin, K, Yost, M, and Larson, T, "Characterization of Mixed Diesel and Gasoline Exhaust by HR-ToF-AMS under Varied Engine Load and Dilution Conditions. *AAAR 32nd Annual Conference*, October 2013. ***Winner of a Student Poster Award.***
4. Keller JP, Sheppard L, Szpiro AA, Sampson PD. Spatial Analysis of a Marker of Roadway Emission Aging. Clean Air Research Centers Annual Meeting, Boston, MA,

June 2012.

5. Riley E. Black Carbon and Ultrafine Particle Counts Downwind of Two Major Airports. University of Washington DEOHS Student Research Day. Seattle, WA. May 2015.
6. Riley EA, Hartin K, Gould T, Larson TV, Yost MG, Simpson CD. Mobile measurements of near-highway air pollutant gradients. Annual Symposium on Environmental, Occupational and Population Health, Semiahmoo, WA, January 2014.
7. Riley EA, Sasakura MD, Hartin K, Crampton R, Gould TR, Larson TV, Yost MG, Simpson CD. Principal Component Analysis of Snap-Shot Air Pollutant Measurements in Baltimore, MD. EPA annual Clean Air Research Center Annual Meeting, Seattle, WA July, 2013.
8. Xu W. Use of Mobile and Passive Badge Air Monitoring Data for NO_X and Ozone Air Pollution Spatial Exposure Prediction Models. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.

Future Activities

Activities in the next year will focus on manuscript preparation. Work on publications and dissemination of results is underway and will continue in the remaining no-cost extension period.

Supplemental Keywords

Exposure science, Community Exposures, Chemical Transport, Mobile Monitoring

Relevant Web Sites

http://depts.washington.edu/uwccar/

Project 2

Individual Project Title: Simulated Roadway Exposure Atmospheres for Laboratory Animal and Human Studies

Investigator	Institution
Jacob McDonald (PI)	Lovelace Respiratory Research Institute

Objective of Research

Objectives/Hypothesis: Traffic-related emissions are associated with the incidence and progression of acute and chronic cardiovascular sequelae in human population studies; however, the causal components, subsequent chemical transformation of these components, and their associated toxicity on the cardiovascular system have not yet been determined. Project #2 is in progress to develop atmospheres with the primary objective of simulating environments containing key components of roadway emissions and the products of environmental factors that transform them. Previous, current, and future exposures are designed to determine air contaminants (or components) that cause or potentiate the toxicity of roadway emissions or confound interpretations based on roadway proximity alone.

Approach: This project will generate and characterize multiple complex roadway mixtures for subsequent animal and human exposure-related toxicology studies. In **Aim 1**, we will develop and characterize laboratory-generated exposure atmospheres simulating the key components of near-roadway exposures, including transformed emissions and coexposures. **In Aim 2**, we will conduct inhalation exposures of laboratory animals (as described in Project 3). We had planned to include as **Aim 3**, a study of inhalation exposures of human subjects in an effort to compare significant pathophysiological findings from our animal model exposures to responses in humans. Due to human subjects issues related to Project 4, Aim 3 was dropped.

Expected Results: Results from these studies will identify key components, as well as the most potent combinations, of urban roadway and background copollutants that result in toxicological responses in the cardiovascular system of rodents.

Research Performed - Progress Summary/Accomplishments

Over the past year we have focused on continuing to evaluate the endothelial cell and myography assays with Project 3, and to extend additional endpoints to confirm the cardiovascular response of putative pollutants. These results are described in Project 3. Project 2 developed novel atmospheres that continue to evaluate the role of gas-particle interactions and particle size on the toxicity of inhaled mixtures. This was done by developing novel atmospheres that focus on better understanding the gaseous-particle and size components of motor vehicle exhaust (MVE). Atmospheres included:

	PM (µg/m^3)	NOx (ppm)	CO (100 ppm)

EXPOSURE	Target	Actual	Pre	Post	Pre	Post
Road Dust	300	349	-	-	-	-
Road Dust + MVE	200+100	342	10.2 (2.5)	-	25.6 (8.2)	-
MVE Gases	0	13	28.6 (5.1)	25.6 (6.3)	66.2 (24.4)	58.5 (26.6)
MVE PM	300	328	24.6 (8.0)	4.0 (1.2)	54.6 (9.3)	8.0 (3.1)
Road Dust + 0.33 ppm Ozone	300	344	-	-	-	-
Woodsmoke	300	380	-	-	-	-
MVE (for ApoE-/- mice)	300	349	17.8 (4.8)	-	32.4 (8.2)	-

A major emphasis of our work this year was the development of novel atmospheres that investigated the roles of gases and particle transport into the lung/toxicity as a function of particle size. We developed inhalation atmospheres with ultrafine or fine motor vehicle exhaust particles with or without gases. The ultrafine particles were made with fresh motor vehicle (diesel plus gasoline engine) emissions. The gases were removed by a combination of a parallel plate denuder and a catalytic stripper that enabled removal of both volatile and semivolatile gases. The fine particles were created by resuspension of collected motor vehicle exhaust particles. The resuspended particles were combined with gases obtained from a filtered atmosphere. The figure above showed the concentrations of particulate matter and gases in the four separate atmospheres. The figure below presents the particle size distribution of the atmospheres, illustrating the lack of ultrafine particles in the fine particle group. The fine particle groups showed a size of approximately 1-2 microns. There were no fine particles in the ultrafine particle group. The results of these exposures are provided in the Project 3 summary.

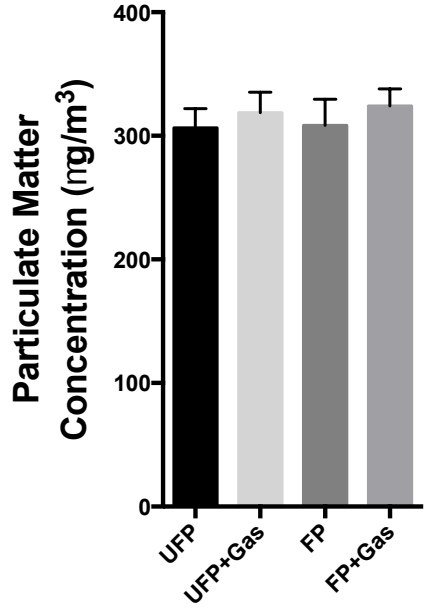


Figure 1. PM concentration by exposure condition

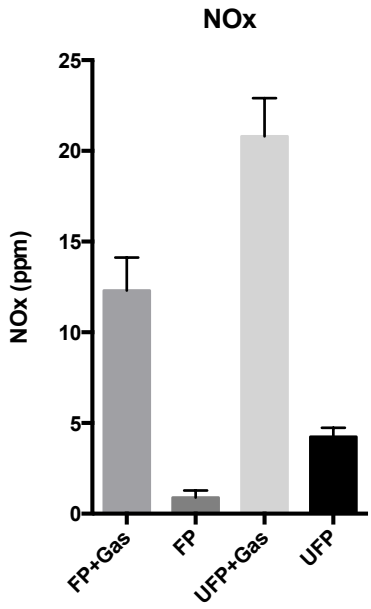


Figure 2. NO_x concentration by exposure condition

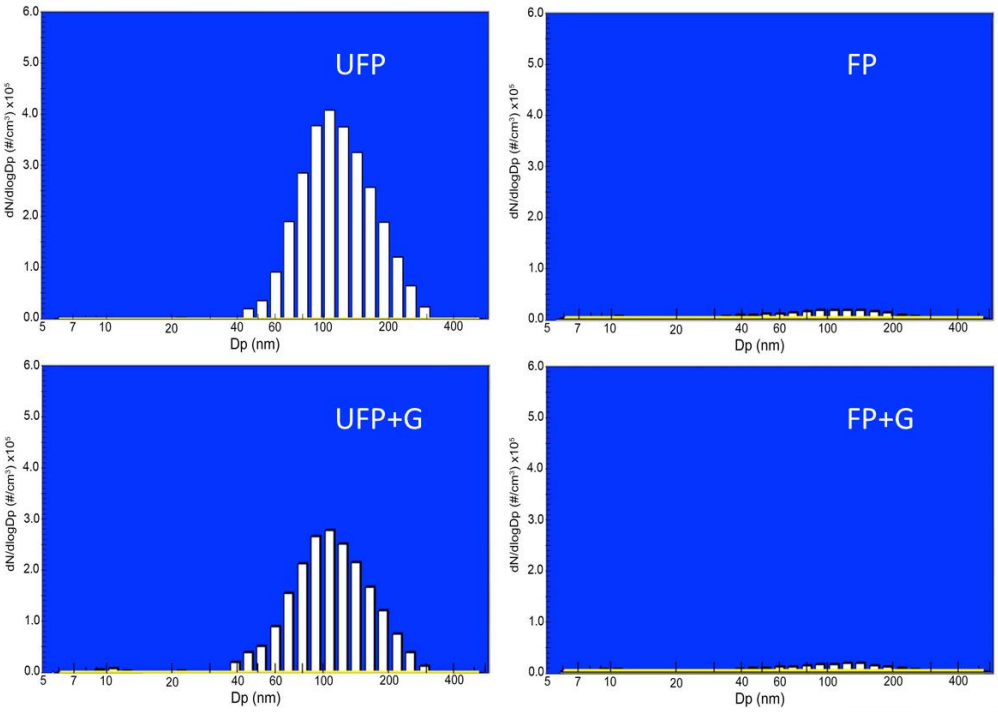


Figure 3. PM concentration and size distribution

Publications / Presentations / Posters

Publications to Date:

1. Lund AK, Doyle-Eisele M, Lin Y-H, Arashiro M, Surratt JD, Holmes T, Schilling KA, Seinfeld JH, Rohr AC, Knipping EM, McDonald, JD. The Effects of α-Pinene- vs. Toluene-Derived Secondary Organic Aerosol Exposure on the Expression of Markers Associated with Vascular Disease. Inhalation Toxicology. 2013, 25(6): 309-324.
2. Mauderly JL, Kracko D, Brower J, Doyle-Eisele M, Lund AK, McDonald JD and Seilkop SK. The National Environmental Respiratory Center (NERC) Experiment in Multi-Pollutant Air Quality Health Research: IV. Vascular Effects of Repeated Inhalation Exposure to a Mixture of Five Inorganic Gases. Inhalation toxicology 2014, 26(11): 691-696.
3. McDonald JD, Chow JC, Peccia J, Liu Y, Chand R, Hidy GM, Mauderly JL. Influence of Collection Region and Site Type on the Composition of Paved Road Dust. Air Qual Atmos Health. 2013, 6(3): 615-628.
4. Oppenheim H, Lucero J, Guyot A, Herbert L, McDonald JD, Mabondzo A and Lund AK. Exposure to vehicle emissions results in altered blood brain barrier permeability and expression of matrix metalloproteinases and tight junction proteins in mice. Particle and Fibre Toxicology. 2013, 10(62).

Presentations to Date:

1. Doyle-Eisele M, Rohr A, Knipping E, Lund A, Brower J, McDonald JD. Secondary Organic Aerosols Generated from α-Pinene-Amine Mixtures: Effects on the Cardiovascular System. Presented (1222/322) at Society of Toxicology, Phoenix, Arizona, 2014.
2. Holmes T, McDonald JD, Kuehl P, Kracko D. Characterization of the Blu E-Cigarette to Define the Composition of Inhaled Material. Presented (1202/302) at Society of Toxicology, Phoenix, Arizona, 2014.
3. McDonald JD, Influence of Collection Region and Site Type on the Composition of Paved Road Dust: It's Not Just Dirt!!! Presented (2312) at Society of Toxicology, Phoenix, Arizona, 2014.

Posters to Date:

1. **Fitch MN, Lucero J, Campen MJ, Lund A, and McDonald JD. Exposure to Inhaled Air Pollutants Results in Altered Barrier Structure in the Duodenal Epithelium of ApoE KO Mice. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
2. **Kuehl PJ, Kracko D, Irshad H, Yates E, and McDonald J. Evaluation of Different Particle Size Quantification Instruments - Strengths/ Weaknesses and Characteristics for Consideration in Determining the Appropriate Technique. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
3. **L. Schneider, J. Lucero, J.D. McDonald, and A. Lund. Inhalation Exposure to Traffic-Generated Air Pollutants Increases Renal Oxidative Stress, Matrix Metalloproteinase-9 Expression, and Fibrosis, Which Are Mediated Through an Angiotensin II-Dependent Pathway. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
4. Brower J, Moeller B, Doyle-Eisele M, Stirdivant S, McDonald JD, Campen M. Acute Inhalation Exposure to Mixed Vehicle Emissions Induces Serum Metabolite Changes

Related to Oxidative Stress, Lipid Peroxidation, and Energy Metabolism. Society of Toxicology, Phoenix, Arizona, 2014.
5. VanReken T, Jobson T. Chemical Characterization of the LRRI Exhaust Exposure Chambers by PTR-MS and HR-ToF-AMS: Early Results. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

Future Activities
Complete analyses and publications of recent studies.

Supplemental Keywords
Inhalation Toxicology, Diesel, Gasoline Engine

Relevant Web Sites

http://depts.washington.edu/envhlth/research_center/center.php

Project 3

Individual Project Title: Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions

Investigator	Institution
Matthew Campen (Co-PI)	University of New Mexico
Michael Rosenfeld (Co-PI)	University of Washington
Jacob McDonald	Lovelace Respiratory Research Institute

Objective of Research

Objectives/Hypothesis: Traffic-related emissions are associated with the incidence and progression of acute and chronic cardiovascular sequelae in human population studies. Such phenomena of near-roadway health effects have yet to be characterized toxicologically. Because of overlapping issues related to noise, socioeconomic status, ethnicity, etc., there is a need to better understand the biological plausibility that fresh mixtures of vehicular emissions have a more potent than expected impact on human health. We hypothesize that the complex mixtures produced by traffic are inherently more toxic due to the combined presence of both particulates and volatile organic emissions. Furthermore, we hypothesize that emissions-induced oxidation of certain endogenous phospholipids, presumably from the pulmonary surfactant, can stimulate the activity of immune cells through such receptors and in turn promote the invasion of existing vascular lesions.

Approach: This project uses complex roadway mixtures as generated and characterized in the laboratory. In **Aim 1**, we will ascertain 1) the potentiating effects of physical and photochemical aging on fresh emissions and 2) interactions of vehicular emissions with pertinent copollutants (ozone, road dust), both in terms of driving systemic vascular oxidative stress**. In Aim 2**, we will examine effects of the emissions-induced oxidative modifications to endogenous phospholipids, in terms of activating immune-modulating receptors such as LOX-1, CD-36, TLR-2, and TLR-4. This Aim will utilize transgenic models to examine the roles of these receptors, as well as characterize the lipidomic alterations in various tissues. Lastly, **in Aim 3**, we will further explore the role of specific immune cell populations as participants in the innate and adaptive responses to emissions-induced phospholipid modifications. In this Aim, we will utilize mouse models of immunodeficiency, including SCID and B-Cell deficient models. Additionally, we will pursue bone-marrow transplants from mice lacking those receptors described in Aim 2 to mechanistically establish the involvement of the oxidatively-modified phospholipids.

Owing to suggestions from the advisory committee, we have focused on the nature and bioactivity of circulating factors induced by pollutant exposures, as these appear to be ligands that interact with the scavenger receptors of interest in Aims 2 and 3. This has been an area of significant progress for the past year.

Expected Results: Findings will 1) indicate the most potent combinations of urban roadway and background copollutants in terms of vascular toxicity and 2) detail the role of the immune system in mechanistically driving the systemic effects of inhaled pollutants.

Research Performed - Progress Summary/Accomplishments

Research this past year has focused on toxicological studies using the exposure atmospheres described in the Project 2 summary. We investigated the impact of particle size on gas-particle interactions in terms of pulmonary and systemic toxicity. As demonstrated in Figure 1, the overall impact of the exposures on inflammation and injury in the lung was minimal for both strains of mice. However, we observed that surface area-dependent gas-particle interaction impacted PM uptake by macrophages (Figures 2 and 3). Similarly, BALF cytokines TNFα and CXCL1 were significantly elevated after UFP+G exposure for both C57BL/6 and ApoE-/- mice (Figure 4). These findings suggest that smaller particles, with a greater surface area, exhibit potentiated pulmonary responses when combined with gaseous copollutants from combustion sources.

Beyond the lung, we also examined neuroinflammatory markers in the hippocampus of exposed mice using qPCR techniques (Figure 5). Especially in ApoE-/- mice, the pattern of increase in IL-6 and TGFb mRNA mirrored the pulmonary findings, again suggesting the most potent effect arose from the UFP+G group.

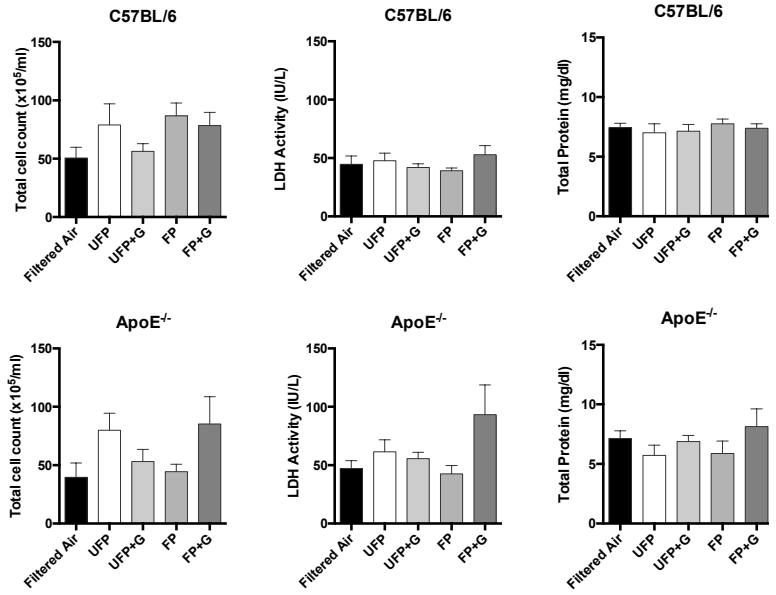


Figure 1. Pulmonary inflammation and injury by exposure condition. The top row shows results for C57BL/6 mice, and the bottom row shows results for ApoE-/- mice. The left, middle, and right plots are total cell count, LDH activity, and total protein, respectively.

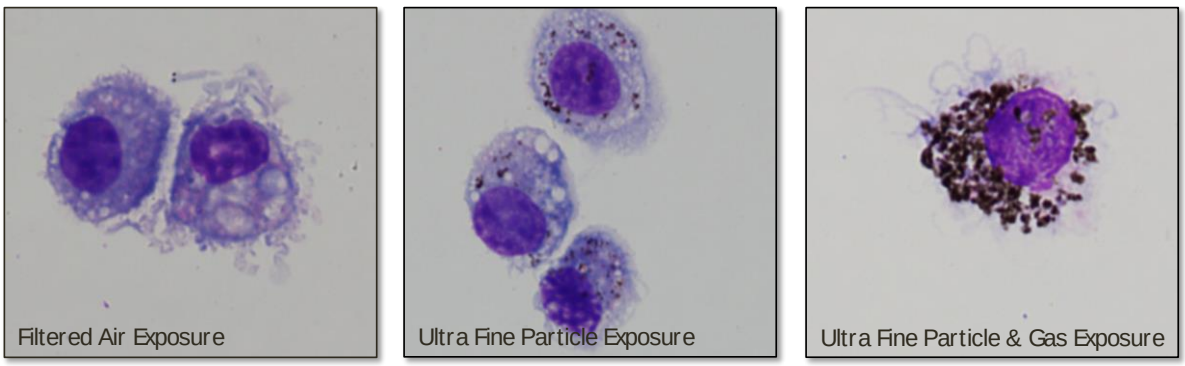


Figure 2. Representative particulate matter uptake by macrophages for FA (left), UFP (center), and UFP+G (right) exposures.

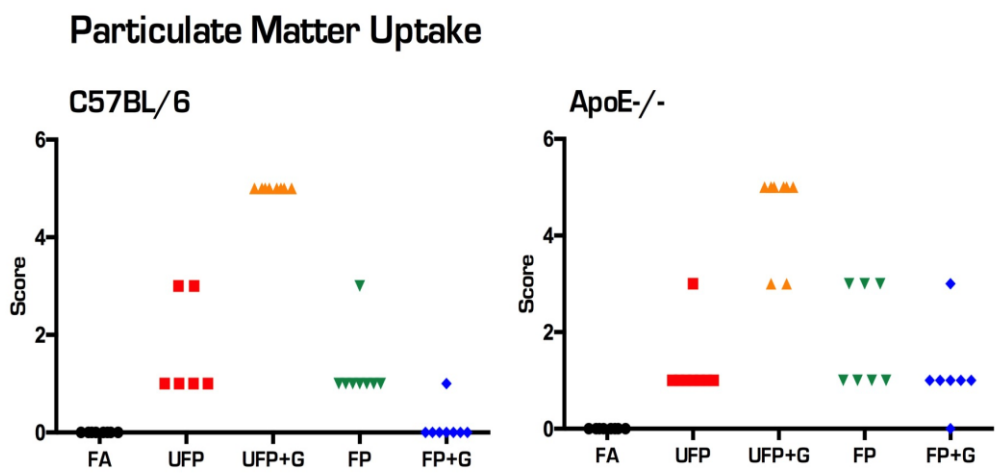
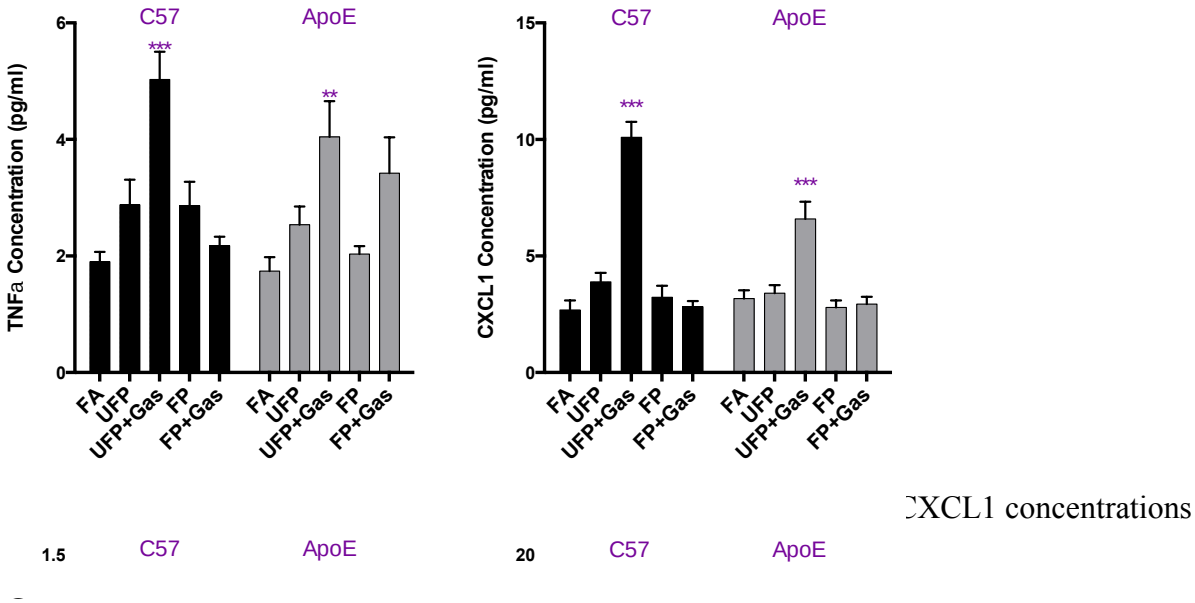


Figure 3. Quantification of macrophage particulate matter uptake in C57BL/6 (left) and ApoE-/- (right) mice. A score of 0 reflects no observable particles present. The middle image in figure 2 reflects a score of 1. The right image in figure 3 reflects a score of 5. Scoring was conducted by a technician blinded to the exposure groupings.



CXCL1 concentrations

Recent studies at the UW (Rosenfeld Lab) have focused on the quantitation of anti-oxidized phospholipid antibodies in blood samples from diesel exhaust exposed humans and from diesel and mixed vehicular emission exposed rodents generated from projects 2, 3 and 4. We had previously shown about a 2 fold increase in these antibodies in plasma from apo E-/- mice exposed to diesel exhaust for 2 weeks as compared to plasma from non-exposed mice (Table).

	Absorbance			
PBS/BSA (Blank)	0.181	0.190	0.191	0.180
Apo E DE Plasma	1.494	0.782	0.514	0.339
Apo E DE Plasma	1.362	0.802	0.496	0.362
Apo E Non DE Plasma	0.580	0.374	0.227	0.249
Apo E Non DE Plasma	0.496	0.376	0.284	0.312
EO6 Positive Control	0.346	0.406	0.448	0.396

We are currently ramping up production (hybridomas) and isolation of the antibody used in the sandwich assay for the plasma content of E06 (anti-phospholipid antibody) and will be measuring the content of E06 in the plasma samples obtained from projects 2, 3, and 4.

Publications / Presentations / Posters

Publications to Date:

1. **Brower JB, Doyle-Eisele M, Moeller B, Stirdivant S, McDonald JD, Campen MJ. Metabolomic Changes in Murine Serum Following Inhalation Exposure to Gasoline and Diesel Engine Emissions. *Inhalation Toxicology*. 2016, 28(5): 241-250.**
2. **Yin F, Driscoll WS, Sulaiman D, Ricks R, Ramanathan G, Stewart JA, Mehrabian M, Beaven SW, Lusis AL, Rosenfeld ME, Araujo JA. Diesel Exhaust Alters Lipid Metabolism and Induces Hyperlipidemia in Association with Down-Regulation of PPAR alpha and Changes in Gut Microbiota. *Atherosclerosis, Thrombosis and Vascular Biology (ATVB)*. 2016. Submitted.**
3. Aragon MJ, Chrobak I, Brower J, Roldan L, Fredenburgh LE, McDonald JD, Campen MJ: Inflammatory and Vasoactive Effects of Serum Following Inhalation of Varied Complex Mixtures. Cardiovascular toxicology. 2016, 16(2): 163-171.
4. Campen M, Robertson S, Lund A, Lucero J, McDonald J: Engine exhaust particulate and gas phase contributions to vascular toxicity. *Inhalation toxicology*. 2014, 26(6):353-360.
5. Campen MJ, Lund A, Rosenfeld M: Mechanisms linking traffic-related air pollution and atherosclerosis. *Current opinion in pulmonary medicine*. 2012, 18(2):155.
6. Paffett ML, Sheppard L, Robertson S, Weaver J, Lucas SN, Campen MJ. Ozone inhalation enhances coronary artery constriction and impairs dilation via superoxide-dependent mechanisms. Toxicol Appl Pharmacol. 2015, In press.
7. Robertson S, Colombo ES, Lucas SN, Hall PR, Febbraio M, Paffett ML, Campen MJ. CD36 Mediates Endothelial Dysfunction Downstream of Circulating Factors Induced by O3 Exposure. Toxicol Sci. 2013, 143(2):304-311.
8. Schisler J, Campen MJ, Madden M, and Willis MS. Transcriptional Endothelial Biosensor Response to Diesel-Induced Plasma Compositional Changes. Inhalation Toxicology. 2015, 27(5): 272–280.
9. Yin F, Lawal A, Ricks J, Fox JR, Larson T, Navab M, Fogelman AM, Rosenfeld ME, Araujo JA. Diesel Exhaust Induces Systemic Lipid Peroxidation and Development of Dysfunctional Pro-Oxidant and Pro-Inflammatory High-Density Lipoprotein. Arterioscler Thromb Vasc Biol. 2013, 33(6):1153-61.

Presentations to Date:

1. Campen, MJ. Endothelial Cell Pattern Recognition Receptors, CD36 and LOX-1, Contribute to Responses to Pollution-Induced Circulating Factors. Society of Toxicology, Phoenix, Arizona, March 2014.

Posters to Date:

1. **Campen M, Heine L, Liu J, Brower J, Herbert G, Sanchez B, Zychowski K, Topper L, Doyle-Eisele M, and McDonald J. Woodsmoke Exposure Alters Serum Composition That Induces Inflammatory Gene Expression and Impairs Ex Vivo Wound Healing. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
2. **Liu J, Brower J, Doyle-Eisele M, Herbert G, Heine L, Sanchez B, Zychowski K, Topper L, McDonald J, and Campen M. Serum-Borne Vascular Toxicity Following Inhalation of Mixed Engine Emissions and Treated Particles. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
3. **Ramanathan G, Zhao Y, Yin F, Rosenfeld ME, Yang X, and Araujo JA. Liver Transcriptomic and Metabolic Reprogramming After Exposure to Diesel Exhaust. Society of Toxicology Annual Meeting, New Orleans, LA. March 2016.**
4. **Mota RI, Norenberg JP, Daniels T, Lucas S, Campen M. Competitive receptor-binding assays of 111In-DANBIRT targeting of Luekocyte-function associated antigen-1 in a systemic inflammation rat model to inhaled ozone exposure. Society of Nuclear Medicine and Molecular Imagine Annual Meeting. June 2016.**
5. Campen MJ, McDonald JM, Rosenfeld ME, Lund AK. Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

Future Activities

Finalize biological assays from the UFP vs FP study and complete publications. Complete collaborative projects.

Supplemental Keywords

Coronary Artery Disease, Oxidized Phospholipids, Atherosclerosis, Particulate Matter, Volatile Organic Compounds, Carbon Monoxide, Ozone

Relevant Web Sites

http://depts.washington.edu/uwccar/

Project 4

Individual Project Title: Effect of Commute Traffic on Vascular Function

Investigator	Institution
Joel Kaufman (PI)	University of Washington
Tim Larson	University of Washington

Objective of Research

Project 4 examines the acute vascular effects of commute traffic exhaust exposures in human subjects, in a multi-pollutant context. This double-blind, randomized, controlled crossover trial will test whether traffic-derived mixed pollution atmospheres of diesel exhaust and gasoline engine exhaust, experienced through travel on roadways in a passenger car, causes an increased vascular response (brachial artery vasoconstriction, increased blood pressure, reduced retinal arteriolar diameter) compared with filtered air (FA) in healthy subjects. Nested aims include: whether specific exhaust-related monocytic gene expression effects are mediated by lipid peroxidation; whether traffic-related pollutants' vasoconstrictive effects are increased in subjects with a common SNP variant in the gene coding for TRPV1; and whether monocyte DNA methylation in specific genes is modified with exposure to typical, roadway-derived exposures. This approach differs from what was proposed in our original grant application—which specified a controlled exposure laboratory experiment—prompted by heightened human subjects concerns at EPA and following discussion with our center's external scientific advisory committee.

Research Performed - Progress Summary/Accomplishments

Project 4 was launched in Year 4 of the Center. In this project, we use a "typical commute" study design and pertinent experience in human exposure studies to advance the Center's research agenda with a double-blind, controlled exposure crossover clinical trial in 16 subjects, randomized to order. Using an innovative approach in which contrasts of in-vehicle exposure and potential participant susceptibility by genotype are nested in the experiment, we can address several hypotheses in this study. Building on our prior work, we are using a typical commute model to confirm or determine whether traffic (e.g., mixed on-road environment with diesel and gasoline engine exhaust components) derived aerosols exert demonstrable and important acute vascular effects in human subjects, and whether traffic-derived aerosols acutely induce increased lipid peroxidation, response to oxidized phospholipids, and result in measurable impacts on gene expression and DNA methylation, in pathways that are related not only to the triggering of acute cardiovascular events, but also to the development and progression of atherosclerosis. Notably, all of the outcomes we measure are completely transient and reversible, and exposures are designed to be those of a typical urban commute path.

Screening

Subjects were screened to determine eligibility. At screening, subjects were required to be in the normal range for BMI, blood sugar, cholesterol and triglyceride levels, lung function, blood pressure, and ECG. Subjects also fill out questionnaires describing past illness, health history, traffic and chemical exposure, smoking history, and occupation. Buccal swab samples were collected in order to achieve a balance of the TRPV1 (SNP I-585V, rs8065080) gene, which our prior work suggests modifies vascular response to traffic-related air pollution.

Eligible subjects complete three monitoring sessions consisting of three 2-hour commutes that travel I-5, extending from North Seattle to roadways in South Seattle (e.g. Duwamish Valley). During each drive, subjects are accompanied by research staff responsible for collecting subject health measurements and monitoring conditions of the drive. Each drive is separated by at least 3 weeks. Two of the monitoring sessions experience an unfiltered pollution exposure, and one is filtered to remove pollutants; the order of the sessions is randomized and the scenario is conducted in a double-blinded manner. During drives, the cabin air and HEPA filters are configured to reflect the randomized exposure conditions (i.e., on-road ambient or filtered air exposure). The cabin ventilation controls are adjusted such that air is entrained and directed to the floor vents, and the temperature inside the vehicle is comfortable for the occupants. Van windows remain closed during the drive and subjects wear N95 masks while transitioning from the lab to the UW van regardless of drive condition.

Enrollment

To date, all 16 subjects have been enrolled with successful genotype-stratification of recruitment. 14 have completed all three drives, and 2 will complete the study by the end of July 2016.

Health Measurements

Subjects complete health measurements at baseline, during the drive, immediately after the drive, 3 hours later, 5 hours later and 24 hours later. These health measurements include: questionnaires, blood markers, Holter ECG, ambulatory blood pressure, 24 hour urine, brachial artery reactivity, retinal photography, and Finometer measurements. The frequency of health measurements are shown in Table 1. All subjects provide a urine sample for a cotinine test and, if female, a pregnancy test.

Table 1. Experimental Session Timeline for CCAR, Project Four

AM/PM	**AM**						**PM**						
Time (hour)	10:00pm-7:00 am	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00		9:00 am (24hr)
Overnight fast	X												X
Urine collection		X	X	X	X	X	X	X	X	X	X	X	X
Vitals BP, PR, RR		X		XX	XXX		X		X		X		X
ABP							X	X	X	X	X	X	X
Holter Monitor 11 min record		XX	X	X	XX	X	XX	X	X	X	XX	X	XX
Blood Draw			X								X		X
BAR Roosevelt			X			X							
Symptom Questions			X		X		X		X		X		X
Commute Drive													
Finometer			X	X	X	X	X		X		X		X
Retinal Photography			X			X							
Lunch							X						

Air Monitoring

This study involves in-vehicle monitoring for 48 drives involving 16 participants in Seattle. Each day of monitoring includes the following suite of monitors in order to collect real-time measurements of the pollutants: $PM_{2.5}$ (Nephelometer, Radiance Research), black carbon (microAethelometer, Aeth Labs), particle count (P-Trak, TSI Inc), PAHs (PAS 2000CE, EcoChem), NO_2 (CAPS, Aerodyne Research Inc), NO_X (UV absorbance Model 410, 2B Technologies), ozone (chemiluminescence 3.02P, Optec), CO (CO T15n, Langan), CO_2 (CO_2 K-30-FS Sensor, CO_2 Meter.com), temp/RH (Precon HS-2000, Kele Precision Mfg), location (GPS BU-353, US GlobalSat). Filters and air monitors inside the car are powered by gel cell batteries connected to power inverters.

Drive Route

A consistent route is used for each subject exposure drive.

Preliminary results for 8 participants (24 drives) are presented in Table 2. As demonstrated here, filtered drives showed an order of magnitude reduction in particles and back carbon compared with unfiltered air drives. As anticipated, reductions in NO_2 and NO_X were more modest. Figures 1 and 2 display the particle number and black carbon results for a single participant.

Table 2. Preliminary comparison between unfiltered and filtered drives (n=8 participants, 24 drives)

	Unfiltered Air Drives		**Filtered Air Drives**	
	Mean	**10th - 90th**	**Mean**	**10th - 90th**
Travel speed (km/hr)	43.4	0.4 - 87	39.5	0.4 - 85
P-Trak count, (pt/cm^3)	29,579	7,612 – 58,360	2,418	372 – 5,242
Neph b-scat (m^-1)	2.5E-05	1.2E-05 - 3.8E-05	1.8E-06	3.1E-07 – 4.5E-06
BC (ng/m^3)	4,017	1,113 – 7,405	302	20 - 693
particle-bound PAH (ng/m^3)	163	38 - 331	148	32 - 335
CO_2 (ppm)	1,434	1,031 – 1,897	1,853	1,074 – 3,825
CO (ppm)	1.4	0.2 - 2.6	1.1	0.5 – 1.9
NO_2 (ppb)	25	12 - 37	16	5 - 30
NO_X (ppb)	135	41 - 245	87	17 - 182

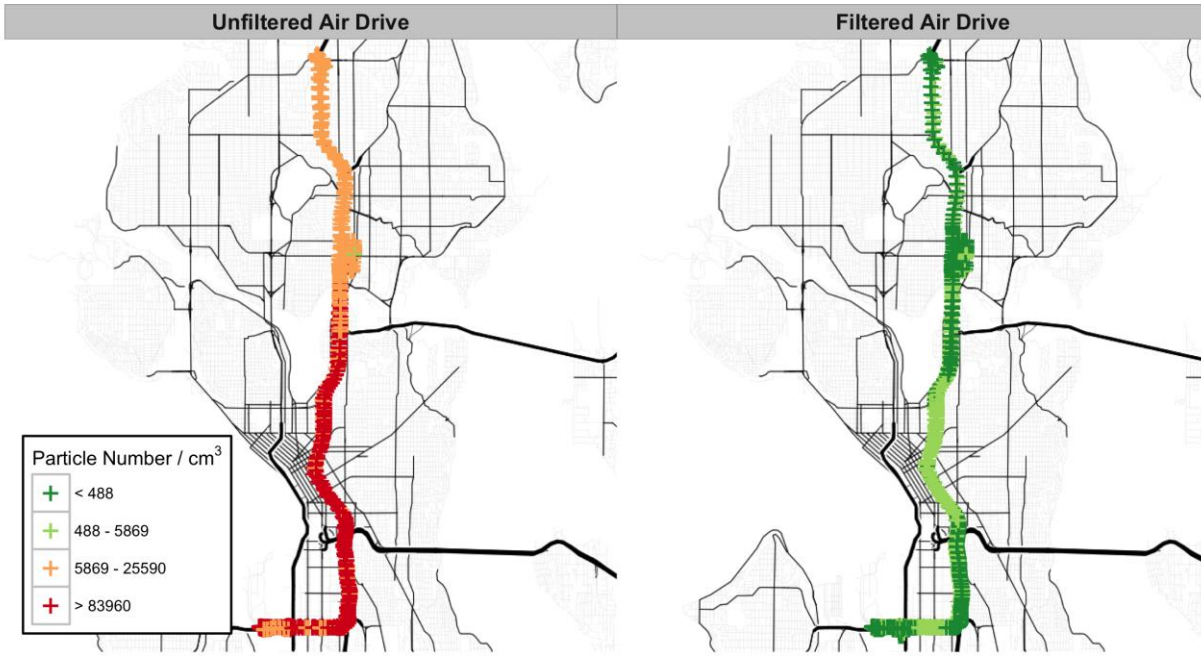


Figure 1. Comparison in measured particle number for unfiltered and filtered drives for a single participant.

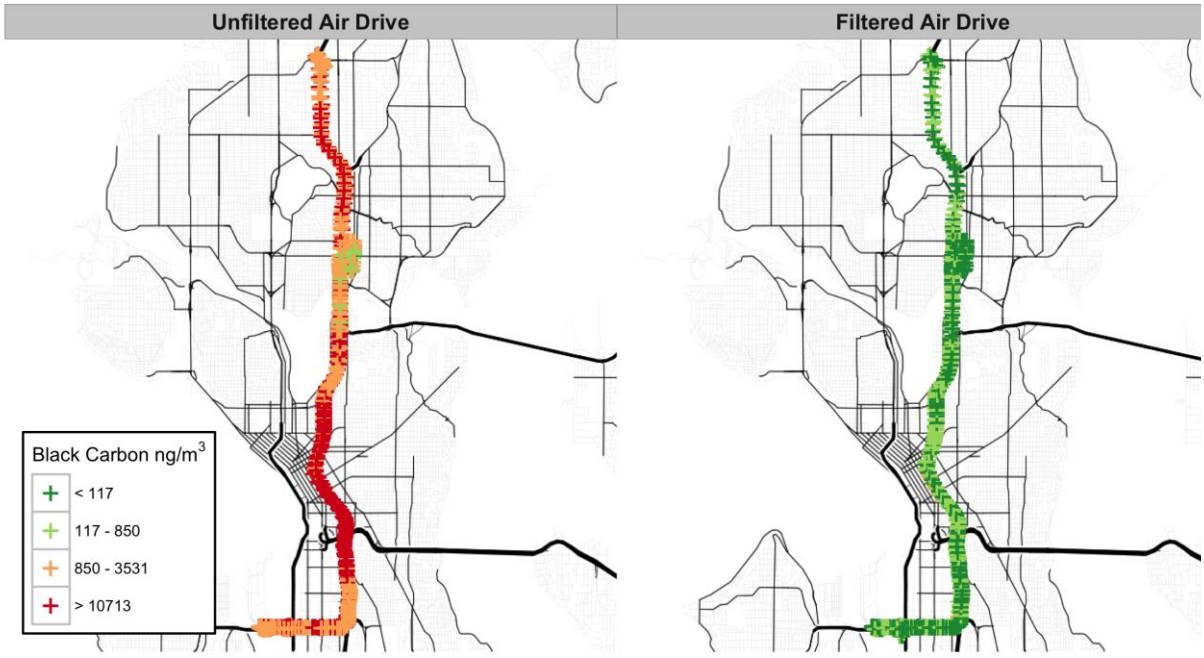


Figure 2. Comparison in black carbon for unfiltered and filtered drives for a single participant.

This same participant's measured particle count and total oxides of nitrogen (NO_X) concentrations are shown as a time series plot for both roadway exposure and filtered air conditions in Figure 3. This variation in levels throughout the exposure period is typical of measured pollutant concentrations which are affected by vehicle operating conditions and the proximity and volume of traffic.

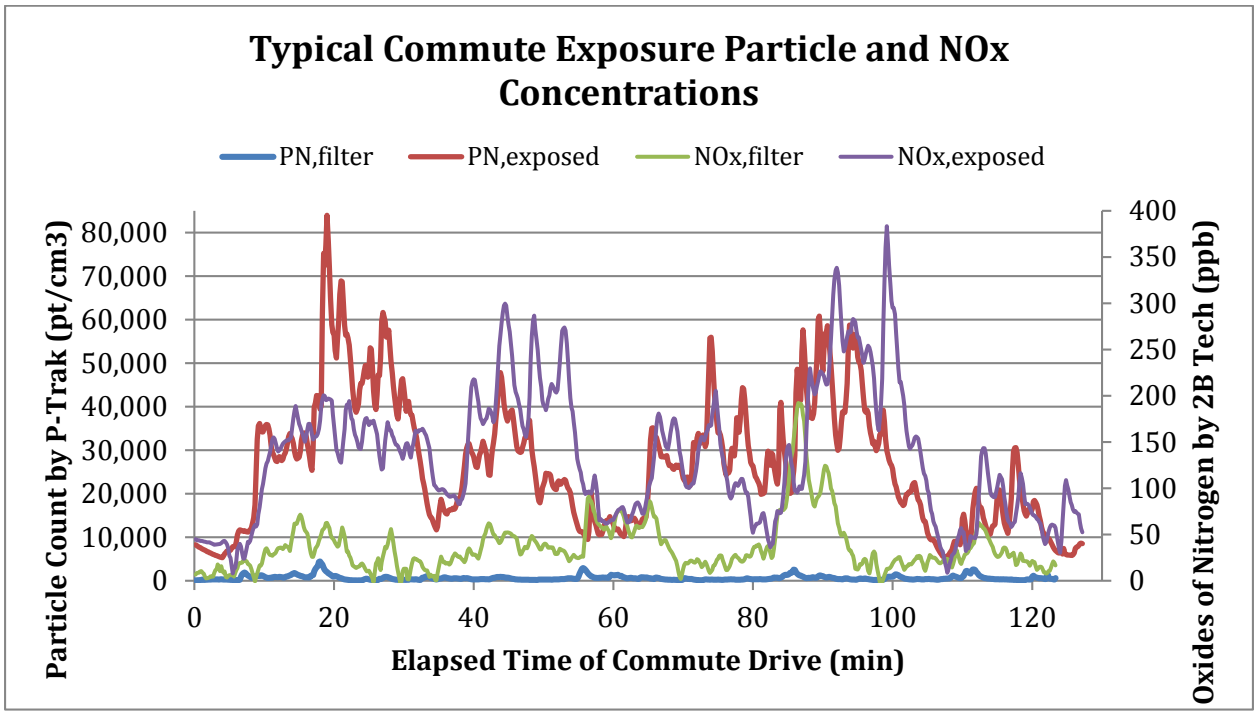


Figure 3. Selected time series variation of particle count (by P-Trak) and NO_X (by 2B Tech analyzer) during an approximate 2-hour exposure drive for both exposure and filtered air.

Publications/Presentations

Publications to Date:

1. Cosselman KE, Navas-Acien A, Kaufman JD. Environmental Factors in Cardiovascular Disease. Nature Reviews Cardiology. 2015, 12(11): 627-642.

Future Activities

We plan to complete the commute exposure study this summer and will move forward with all health analyses starting this fall.

Supplemental Keywords

Relevant Web Sites

http://depts.washington.edu/uwccar/

Project 5

Individual Project Title: Effects of long-term exposure to traffic-derived aerosols and gases on subclinical measures of cardiovascular disease and DNA methylation in a multi-ethnic cohort

Investigator	Institution
Joel Kaufman (PI)	University of Washington
Sverre Vedal	University of Washington
Timothy Larson	University of Washington
Michael Yost	University of Washington
Elizabeth (Lianne) Sheppard	University of Washington
Paul Sampson	University of Washington
Adam Szpiro	University of Washington

Objectives of Research
Project 5 has three primary objectives, which are unchanged from those described previously:

1. Employ the small-scale gradient data acquired as part of the mobile monitoring campaign in Project 1, in conjunction with central fixed site data, regulatory monitoring data, and geographic covariates, to build a multi-pollutant exposure model for traffic-derived air pollutants. This model will incorporate complex spatial information on primary and secondary traffic-derived particles and gases.

2. Develop and validate individual-level exposure estimates for traffic-derived air pollutants, integrating: i) the outdoor residential concentration estimates from the multi-pollutant model; ii) estimates of residential infiltration rates; iii) road class- and traffic condition-specific estimates of on-roadway concentrations; and iv) individual-level questionnaire-derived time-location information. These individual-level exposure estimates will also utilize personal monitoring data designed to clarify the in-transit component of total exposure.

3. Estimate the effect of individual-level exposure to traffic-derived air pollution on subclinical cardiovascular disease using these exposure models. Health outcomes will include left ventricular myocardial mass as ascertained by MRI, arteriolar diameters as measured by retinal photography, coronary artery calcium as ascertained by CT, intima-medial thickness as measured by ultrasound, and DNA methylation.

Research Performed - Progress Summary/Accomplishments
Aim 1: Developing spatial exposure model. For Aim 1 of Project 5, we are working closely with Project 1 and Biostatistics Core personnel to develop approaches to the high-dimensional data which can be applied to epidemiological analyses. Methods for this approach are described in the Biostatistics Core Section above. Results for the cluster analysis were provided in last year's report; here we present the cluster assignments for MESA Air participants in Baltimore. Health analyses are currently underway.

Heating

Membership in clusters identified by *k*-means from the heating season data for monitoring locations and MESA Air participants are presented in Figure 1.

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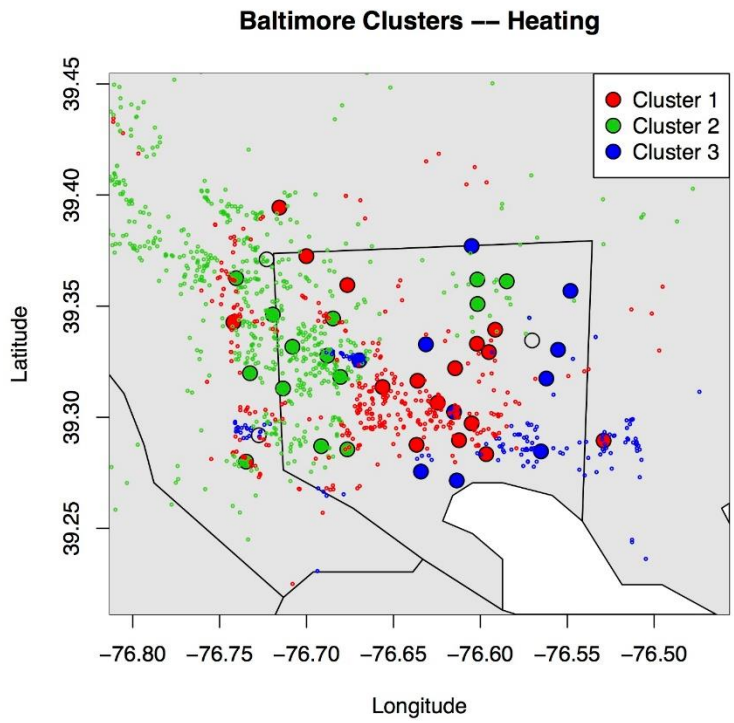

Figure 1. Cluster membership for MESA Air participants in Baltimore during the heating season.

Non-Heating

Membership in clusters identified by *k*-means from the non-heating season data for monitoring locations and for MESA Air participants are presented in Figure 2.

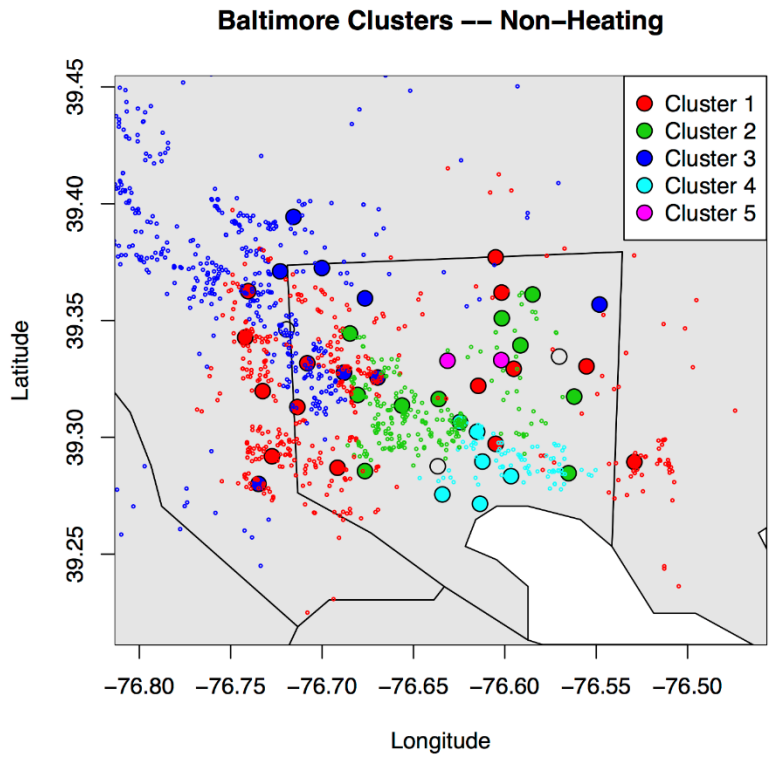

Figure 2. Cluster membership for MESA Air participants in Baltimore during the non-heating season.

Aim 2: Understanding in-vehicle contribution to individual level multi-pollutant exposures. In prior reports, we discussed in detail the field work portion of this project, in which data was collected to address much of the second aim of this project. Through a combination of personal, residential and in-vehicle sampling, paired with intensive location tracking, we are seeking to understand the influence of time spent in transit on personal exposure, which will improve our individual-level exposure estimates and contribute to our epidemiological analysis.

Four exposure campaigns were conducted in two seasons each in Winston-Salem, NC and Los Angeles, CA. Each campaign involved assessment of time-location patterns using multiple methods and individual-level air monitoring in several microenvironments: residential outdoors, residential indoors, in-vehicle, and personal monitoring. A novel in-vehicle passive monitoring device was built specifically for this study to capture exposures while driving. A summary of participant characteristics and measured air pollutant concentrations by sampling location were presented in the last report.

After reviewing the results for all four of the monitoring campaigns, and subsequent to analysis presented previously, we became concerned that the in-vehicle concentrations (e.g. of oxides of nitrogen) calculated based on measurements from the field study were higher than anticipated. We conducted a series of additional assessments to better understand this issue, and to evaluate some hypotheses we developed about sources of potential errors from equipment issues, such as

biases from actual device sampling times or canister leakage. Tests were conducted in the laboratory with known levels of nitrogen dioxide (NO_2) in order to measure the level of NO_2 inside of the sealed in-vehicle monitor at varying time points after it the lid was closed. A decrease in NO_2 levels within the canister over time suggested that the Ogawa badges continued to absorb NO_2 from the air trapped inside of the canister once it was closed. Though these novel samplers were designed to minimize empty space, approximately 350 mL of air was trapped inside the canister upon closure. Failing to account for this led to a bias (correctable) in actual sampling time used in the concentration calculations.

Using the sampling rate or molecular weight and molar volume of air at standard temperature and pressure for each pollutant and assuming a relative humidity of 43%, sampling of the 350mL volume of air would take 10-40 minutes depending on the analyte. Each time a participant opened and closed the canister, this additional time to sample the air inside the canister after it was closed was added to the aggregate sampling time for the Ogawa or 3M badge. Table 1 shows the additional time per opening for each analyte. On average, participants took 38 trips during the two-week sampling period and the average additional sampling time ranged from 6 hours to 25 hours depending upon the parameter. Table 2 shows the median vehicle concentrations before and after the addition of the extra participant-specific sampling time.

Table 1. Additional sampling time per trip and in total for in-vehicle samples.

Analyte	Sampling time per trip (min)	Average total additional sampling time (hrs)
NO_2	40.2	25
NO	22.7	14
O_3	16.1	10
Pentanes	9.9	6
Isoprene	8.7	6
Nonane	14.2	9
Decane	15.2	10
Undecane	15.5	10
Dodecane	16.3	10
Benzene	9.9	6
Toluene	11.1	7
m-Xylene	12.8	8
o-Xylene	12.8	8

Table 2. Revised median in-vehicle concentrations for each of the analytes

Pollutant	Winston-Salem, NC		Los Angeles, CA	
	Winter	*Summer*	*Winter*	*Summer*
NO_2	27	18	33	39
NO_x	51	27	104	24
O_3	18	10	9	18
Pentanes	214	491	204	150
Isoprene	0.02	1.3	1.2	1.1
Nonane	0.6	0.6	0.4	0.3
Decane	1.4	2.4	2.7	2.2
Undecane	2.1	5.6	8.1	6.4
Dodecane	2.5	6.6	6.9	9.5

Benzene	1.1	1.7	1.4	1.8
Toluene	6.1	12.9	5.0	5.4
m-Xylene	3.3	4.1	2.1	2.2
o-Xylene	1.6	21	1.1	1.2

Using these concentrations, we have assessed the relative importance of the in-vehicle microenvironment for individual exposure to NO_2. This work is currently being written up in a manuscript titled "Contribution of the in-vehicle microenvironment to individual ambient source nitrogen dioxide exposure: the Multi-Ethnic Study of Atherosclerosis and Air Pollution" that has been drafted and circulated to co-authors. A third paper is also in progress, and will examine the measured concentrations and comparisons of those concentrations between microenvironments for the entire suite of pollutants measured in this study.

In addition to the air monitoring described above, each of the field campaigns also included intensive methods for time-location measurement. Time-location data during these two-week periods was collected using Global Positioning System (GPS) units and Time-Location Diaries (TLDs) simultaneously. GPS units were customized to allow continuous location tracking for periods up to and exceeding two weeks. In order to analyze the GPS tracking data, an automated rule-based method was developed to process the large quantity of GPS data collected. To produce the single best estimate of time-location patterns during the monitoring periods, the GPS and TLD measurements were integrated in order to capitalize on the strengths of each tool. The GPS measurements of time at home and in other locations was divided into indoors and outdoors based on proportions indoors and outdoors reported in the TLD. On average, during these two-week monitoring periods participants spent 4-5 percent of their time in vehicles, 2-6 percent of their time outdoors, and the remainder (89-94 percent) indoors (Figure 3).

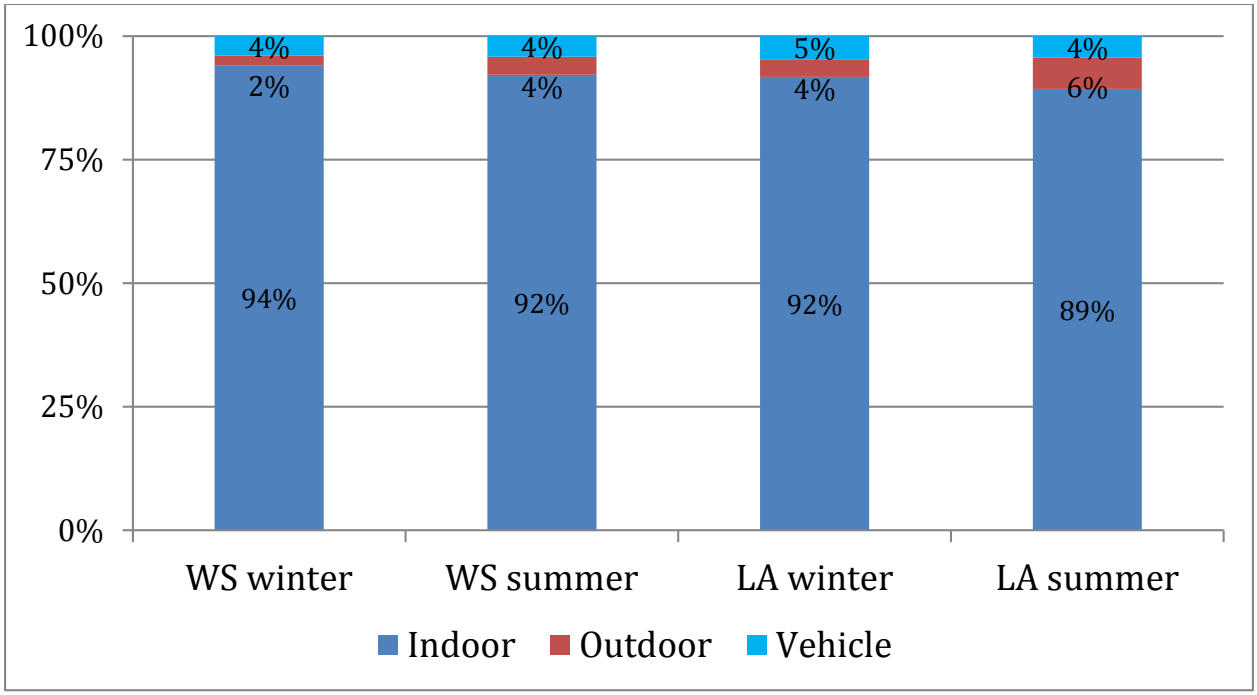

Figure 3. Percent of time spent in vehicle, outdoors, and in-vehicle by sampling campaign.

The percent of time spent indoors, outdoors, and in-vehicle based on this integration of intensive two-week measurement methods was compared to questionnaire data previously collected as part of the MESA Air study. The magnitude of the average amount of time spent in each microenvironment, particularly time spent in-vehicle, is similar across measurement methods at the cohort level but time-location patterns were less well correlated at the individual level. A manuscript describing this work, entitled "Integrating data from multiple time-location measurement methods for use in exposure assessment: the Multi-Ethnic Study of Atherosclerosis and Air Pollution," has been submitted to the Journal of Exposure Science and Environmental Epidemiology.

Aim 3: Epidemiological Analyses. Several analyses relating to Aim 3 of Project 5 are in progress. These include analyses using the following outcomes: arteriolar diameters as measured by retinal photography, coronary artery calcium (CAC) as ascertained by CT, intima-medial thickness as measured by ultrasound, and DNA methylation. As described in the Biostatistics section above, cluster membership is used as an effect modifier of the association between NO_x exposure and measurements of coronary artery calcium (CAC) to determine whether or not the association varies by multi-pollutant profile (as identified by cluster). Preliminary findings from Baltimore indicate that cluster membership seems to modify the relationship between NO_x exposure and CAC progression, especially in the non-heating season, with the cluster close to the Baltimore inner harbor (cluster 4) showing a larger effect (Table 3). This finding needs to be interpreted very cautiously at this point until more definitive analyses are completed.

Table 3. Effect of cluster membership on the association between NO_x exposure and CAC progression in Baltimore by season.

	Cluster	Estimate	Std Error	95% CI
Baltimore total	(none)	25.8	6.01	(14.0, 37.6)
Heating season	1	27.8	8.61	(10.9, 44.7)
	2	27.1	9.15	(9.13, 45.0)
	3	17.7	14.1	(-9.91, 45.2)
Non-heating season	1	19.7	10.0	(0.14, 39.4)
	2	14.9	12.9	(-10.3, 40.1)
	3	36.5	10.7	(15.5, 57.4)
	4	63.9	17.1	(30.5, 97.3)

Much of the completed work for Aim 3 thus far has focused on DNA methylation, some of which was presented in last year's annual report. We did not find evidence that long-term ambient $PM_{2.5}$ and NO_X exposure were associated with global DNA hypo-methylation in monocytes at ALU or LINE-1 loci.

We investigated candidate methylation sites that were previously associated with expression of nearby genes in the same sample of participants that we used in our study and found five methylation sites significantly associated with $PM_{2.5}$ exposure (Table 3). Three of the CpG sites not only had DNA methylation associated with $PM_{2.5}$ which was statistically significant after correction for multiple comparisons, but the cis-gene transcript also had mRNA expression

associated with $PM_{2.5}$ as well. These may be more plausibly involved in the pathogenesis of air pollution-related disease. The following genes were associated in this manner with $PM_{2.5}$.

- ANKHD1 – Ankyrin repeat and KH domain containing 1, and may support proliferation and cell cycle progression of cancer cells
- LGALS2 – Galectin 2 polymorphisms linked to MI and coronary artery disease, and may modulate both pro- and anti-inflammatory molecules.
- ANKRD11 - regulates chromatin modification and was linked to autism. Inflammation is suggested potential common mechanism between air pollution-related CVD and autism.
- BAZ2B - bromodomain containing chromatin remodeling protein that epigenetically regulates transcription and polymorphism associated with sudden cardiac death.
- PPIE - stimulates folding and conformational changes in proteins and may be linked to leukemia, colorectal cancer, and body mass index.

Table 4. Association Between $PM_{2.5}$ (per 2.5 $\mu g/m^3$) and eMS and Gene Expression

		$PM_{2.5}$ and DNA Methylation			**$PM_{2.5}$ and Gene Expression**	
Gene[a]	**Chr**	**CpG**	**β (95% CI)[b]**	**P-value**	**β (95% CI)[b]**	**P-value**
ANKHD1	5	cg20455854	0.139 (0.074, 0.203)	2.77E-05	-0.048 (-0.074, -0.022)	3.71E-04
LGALS2	22	cg07855639	0.081 (0.043, 0.120)	3.28E-05	-0.147 (-0.240, -0.053)	0.002
ANKRD11	16	cg07598385	0.108 (0.056, 0.160)	4.97E-05	-0.075 (-0.142, -0.008)	0.028
BAZ2B	2	cg17360854	0.081 (0.042, 0.120)	5.08E-05	-0.016 (-0.060, 0.027)	0.463
PPIE	1	cg23599683	-0.057 (-0.085, -0.029)	7.17E-05	0.004 (-0.020, 0.028)	0.728

Note: Models adjusted for age, sex, race/ethnicity, site, smoking, socioeconomic status, body mass index, recent infection, residual cell contamination, methylation chip and position

We did not find any CpG sites significantly associated with NOx.

Publications / Presentations / Posters

Publications to Date:

1. **Chi GC, Barr RG, Donohue K, Hensley M, Hou L, Kaufman JD, Liu Y, MacDonald J, McCall C, Siscovick D. Long-term outdoor air pollution and DNA methylation in circulating monocytes: Results from the Multi-ethnic Study of Atherosclerosis (MESA). *Environmental Health*. 2016, Submitted.**
2. **Hazlehurst MF, Spalt EW, Curl CL, Davey ME, Vedal S, Burke GL, Kaufman JD. Integrating data from multiple time-location measurement methods for use in exposure assessment: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). Journal of Exposure Science and Environmental Epidemiology. 2016, Submitted.**
3. **Weuve J, Kaufman JD, Szpiro AA, Curl C, Puett RC, Beck T, Evans DA, Mendes de Leon CF. Exposure to Traffic-Related Air Pollution in Relation to Progression in Physical Disability among Older Adults. *Environmental Health Perspectives*. 2016, advance online publication.**

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11. Vedal S, Kaufman JD: What does multi-pollutant air pollution research mean? *American journal of respiratory and critical care medicine.* 2011, 183(1):4-6.
12. Young, MT, Sandler, DP, DeRoo, LA, Vedal, S, Kaufman, JD, & London, SJ. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of US women. *American journal of respiratory and critical care medicine*. 2014, 190(8), 914-921.

Presentations to Date:

1. **Wang, M. Long-term exposure to ozone and accelerated emphysema progression and lung function decline: the MESA Air and Lung Studies. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2016.**
2. Hazlehurst, M. Integrating Data from Multiple Time-Location Measurement Methods for Use in Exposure Assessment: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). International Society for Environmental Epidemiology. Seattle, WA. August 2014.
3. Nicholas, T. Contribution of time in-transit to individual exposure to traffic-related air pollution. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.
4. Spalt, EW. Patterns in Indoor, Outdoor, In-Vehicle, and Personal Measurements of Volatile Organic Compounds. Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.

5. Sullivan, MD. Ambient Transition Metals, Lung Density and Lung Function In The Multi-Ethnic Study of Atherosclerosis (MESA). American Thoracic Society International Conference. Philadelphia, PA, May 2013.
6. Vedal, S. Estimating Exposure and Health Effects of PM2.5 Components. Fudan School of Public Health. Shanghai, China. June 2013.

Posters to Date

1. Hazlehurst, M. Time‐location measurement methods for use in exposure assessment: the Multi‐Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). Annual Conference on Environmental, Occupational, and Population Health. Semiahmoo, WA. January 2015.

Future Activities

We are in the process of preparing two additional manuscripts related to Aim 2: 1) an analysis of the relative contributions of each microenvironment to overall exposure to ambient-source nitrogen dioxide and 2) a manuscript discussing the results of all of traffic-related air pollutant sampling.

The multipollutant work described in this summary and in the Biostats Core is in progress and will continue with plans for manuscript(s). We will also continue our methylation analyses incorporating additional approaches including more conventional ("epigenome-wide") and more innovative methods of interrogating high-dimensional methylation data (e.g. "bumphunting") and approaches that incorporate a multi-pollutant framework. We anticipate three manuscripts to be submitted related to the DNA methylation work in the upcoming year.

Supplemental Keywords

Cardiovascular Disease, Subclinical

Relevant Web Sites

http://depts.washington.edu/uwccar/

CCAR CLARC Program Collaborations

CCAR is committed to participating in four of the five CLARC collaborative projects that have been proposed. The individual projects, the investigators from the CCAR team and approximate time periods and total budgets are included in the table below. Included as part of our collaborative budget are funds to support the preparation of a collaborative manuscript on commuting study designs. This manuscript is being developed with researchers from the SCAPE CLARC. Additionally, brief summaries for each project are included detailing the progress to date and future planned activities.

UW CCAR Involvement in the CLARC Collaborative Projects				
PROJECTS	**CCAR Investigators**	**Activities**	**Period**	**Estimated total budget**
#1 Circulating Inflammatory Potential of Inhaled Coarse PM	Matt Campen Jake McDonald	• Ex Vivo Endothelial Cell Assays • High Fructose Rat Model in Designed Exposure Atmospheres	10/12-11/16	$100,000
#2 Mobile and Fixed Site Characterization of Vehicle Emission Impacts in Atlanta	Tim Larson Mike Yost	• Mobile and Fixed Site Monitoring Campaign in Atlanta	10/12-11/16	$64,000
#3 Measurement Error for Air Pollution Cohort Studies: Application and Comparison of Several Statistical Methods to Georgia Birth Cohort Data	Adam Szpiro	• Measurement Error Correction Approach to Georgia Birth Cohort	12/12-11/16	$47,000
#4 Inter-comparison of ambient $PM_{2.5}$ estimation models in NC	Paul Sampson	• Satellite PM Metric Addition to the PM Spatio-Temporal Model in North Carolina	12/12-11/16	$24,000
Collaborative Manuscript: Commuting Study Designs	Joel Kaufman Tim Larson Sverre Vedal Adam Szpiro		7/15-11/16	$15,000

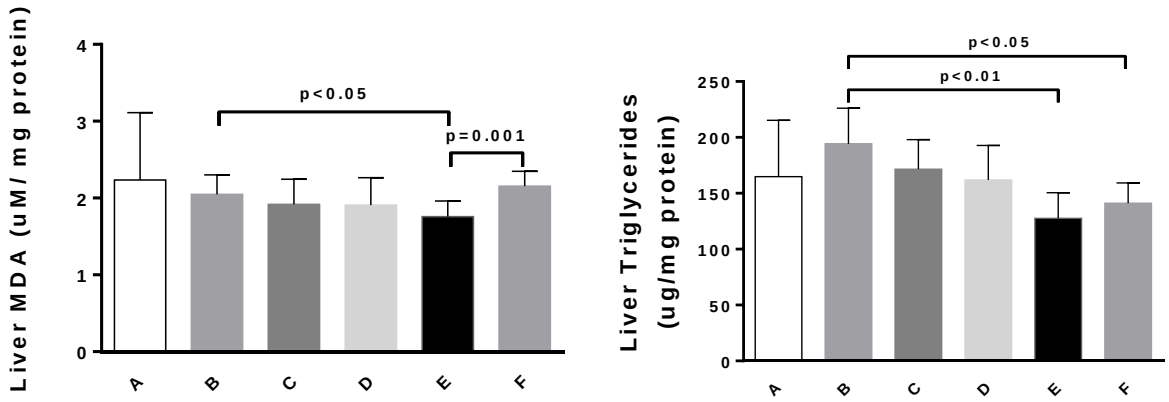
Collaborative Project #1 Summary – Circulating Inflammatory Potential of Inhaled Coarse PM

(Collaborators: GLACIER, Harvard, and CCAR)

Tissues (liver, serum) from a-50 day exposure to complex emissions were sent to Jesus Araujo to examine lipid alterations. Initial data from these assays are unremarkable. ApoE-null mice were exposed to one of the following atmospheres:

A. Filtered Air controls
B. MVE low, at 100 μg/m^3
C. MVE high, at 300 μg/m^3
D. MVE PM with SVOCs removed, at 300 μg/m^3
E. MVE PM with gases denuded, at 300 μg/m^3
F. Woodsmoke, at 450 μg/m^3

Malondialdehyde (left) and triglycerides (right) were unchanged in the exposed livers relative to control.



More assays are being considered, but overall the results are disappointing.

We also have not yet completed analyses on serum samples from Dr. Rob Brook at the University of Michigan, but the final plates are being run this month.

Collaborative Project #2 Summary – Mobile and Fixed Site Characterization of Vehicle Emission Impacts in Atlanta

(Collaborators: SCAPE and CCAR)

Investigators: Timothy Larson,[1,2] Chris Simpson,[1] Timothy Gould[2], Kris Hartin[1], Miyoko Sasakura[1], Michael Yost[1] Departments of (1)Environmental & Occupational Health Sciences, and (2) Civil & Environmental Engineering , University of Washington;

Rodney Weber[3], Vishal Verma[3], Laura King[3], Ted Russell[4], Jim Mulholland[4], Heather Holmes[4], Eric Edgerton[5] Schools of (3) Earth & Atmospheric Sciences and (4) Civil & Environmental Engineering, Georgia Institute of Technology; (5) Atmospheric Research and Analysis Inc.

Project Goals & Progress

The goal of this collaborative project is to compare a limited set of spatially intensive mobile and fixed site measurements of selected pollutant with downscaled CMAQ predictions in Atlanta, Georgia.

We completed mobile platform and fixed-site monitoring in greater Atlanta, GA over a two-week period in September 2013, and final QC of the data is complete. Comparison of the fixed site data with the CMAQ predictions is in progress. We plan to include comparisons of both the measured mobile fuzzy point medians and the measured fixed site means of NO2 with the CMAQ model predictions in a joint paper. We reported the mobile monitoring comparisons in last year's progress report. The final fixed site data set was only recently finalized and therefore comparisons with the CMAQ predictions are still in progress.

Collaborative Project #3 Summary - Measurement Error for Air Pollution Cohort Studies: Application and Comparison of Several Statistical Methods to Georgia Birth Cohort Data

Objective of Research

The objective of this project is to compare and contrast methods for measurement error with spatially misaligned exposure data in air pollution cohort studies. Investigators from the CLARCs at UW, Harvard, and Emory are participating in this project.

Planned Activities

We will utilize Emory's birthweight cohort data as a testbed for applying measurement error correction techniques developed at the three participating centers. The birthweight data will be derived from administrative records for all singleton live births in Georgia from 2001-2006. Exposures to PM2.5 will be predicted from spatio-temporal models based on regulatory monitoring in Georgia and nearby counties in surrounding states. An initial estimate of the association between PM2.5 exposure (by trimester) will be calculated without accounting for measurement error. Four versions of measurement error correction will be applied to this analysis: parameter bootstrap (UW), non-parametric bootstrap (UW), SIMEX (Harvard), and Bayesian (Emory). We will also conduct simulation studies to elucidate any differences in findings between the three correction methods. Note that the scope of this project includes only single pollutant measurement error. Multi-pollutant methods are currently under development at the three centers, and future collaborations will build on the present project to compare and contrast these methods.

Project Deliverables

- Measurement error corrected findings to be incorporated in a substantive paper on the risks of air pollution and low birth weight
- A statistical paper comparing and contrasting correction methods

Groundwork for Future Collaboration

- Review paper for applied readers that summarizes what is known about characterizing and correcting for measurement error in air pollution cohort studies, focusing on use of spatio-temporal model predictions (analogous to the Zeger et al. (EHP, 2000) paper for time series studies)
- Extension to multi-pollutant analyses and nonlinear models such as logistic regression and survival

Research Performed / Progress Summary

Emory investigators have successfully applied UW's spatio-temporal exposure model in the Atlanta area and have used predicted exposures to quantify the association between birthweight and PM2.5 exposure. UW has replicated Emory's analysis and has applied the parameter bootstrap and the non-parametric bootstrap to assess bias and/or inflated standard errors from measurement error. A paper reporting these results is currently under review by *Epidemiology* (Keller at al., 2016).

Collaborative Project #4 Summary - Inter-comparison of ambient PM2.5 estimation models in NC

(Collaborators: SCAPE, Harvard, and CCAR)

The goal of this effort is to summarize the strengths and limitations of current satellite-driven PM2.5 exposure models and CMAQ PM2.5 simulations, and to identify directions for future model development and applications in various population-based health effects studies. There are six candidate models to be evaluated: (1) Koutrakis group's mixed effects model, (2) Schwartz group's multi-level model, (3) Chang's spatial downscaler, (4) Liu group's mixed effects model, (5) UW/CCAR group's spatiotemporal model, and (6) Russell group's CMAQ PM2.5 simulation.

Research Performed / Progress Summary

Although the project resulted in a successful collaboration across institutions, investigators have elected not to pursue further research on this project. The approach taken, using a 10 km grid, was no longer considered state-of-the-art and unlikely to result in a publication.