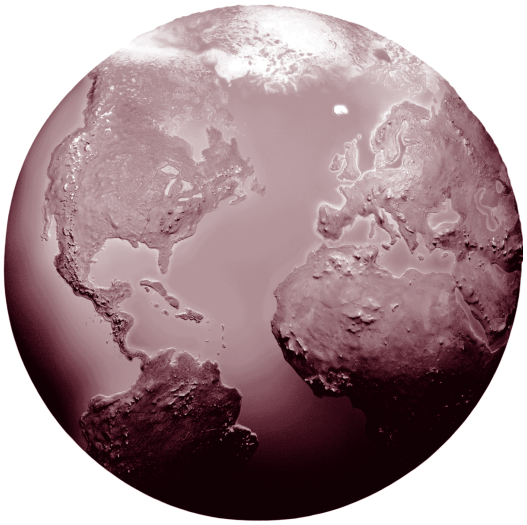

HEALTH EFFECTS INSTITUTE

ANNUAL CONFERENCE 2018

Program and Abstracts

April 29–May 1, 2018

The Drake Hotel

140 E. Walton Place

Chicago, Illinois

1-800-55-DRAKE (37253)

Trusted Science • Cleaner Air • Better Health

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HEALTH EFFECTS INSTITUTE

2018 Annual Conference

April 29–May 1

The Drake Hotel
Chicago, Illinois

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AT A GLANCE

Sunday April 29

9:00 Pre-Conference Workshop

11:30 Lunch

1:00 Ozone: Global Pollutant, Personal Effects

3:55 Presentation of Student and Postdoc Travel Awards

4:15 Poster Session 1

6:00 Opening Reception, Dinner and Keynote Speaker

Monday April 30

7:00 Breakfast

8:30 Health Effects of Traffic-Related Air Pollution: Assessing the Evidence in an Evolving and Complex World

10:45 Air Pollution and Diabetes: What Is the Evidence?

12:30 Lunch

1:30 Poster Session 2

3:15 Can We Rely on Environmental Health Research?

5:30 Adjourn for Free Evening

Tuesday May 1

7:00 Breakfast

8:30 Advancing Air Quality, Global Health, and Energy Science at HEI

11:15 The Power of Place: Pathways to Healthy Urban Living

12:00 Lunch

1:00 The Power of Place (*Continued*)

2:30 Conference Adjourns

HEI Annual Conference 2018 Program

Sunday, April 29, 2018

PRE-CONFERENCE WORKSHOP

9–11:30 AM **Causal Modeling in Air Pollution Research and Policy**

Chairs: *Francesca Dominici*, Harvard T.H. Chan School of Public Health and HEI Research Committee; and *Katherine Walker*, Health Effects Institute

Recent years have seen a growing interest in the application of modeling methods to systematically explore causal relationships between air pollution and health. This session will bring together experts in causal modeling to introduce different methods, provide critical perspectives on their potential contributions and limitations, and discuss their interpretation within the broader context of how to understand whether an exposure is or is not causing effects. Open to all conference attendees.

9:00 Opening Remarks / Objectives
Katherine Walker and *Francesca Dominici*

9:10 The Many Paths to Causality
Richard Scheines, Carnegie Mellon University

9:35 Predicting and Evaluating Changes in Health Risks Caused by Changes in Air Pollution
Tony Cox, Cox Associates

10:00 Approaches to Causal Inference in Observational Studies in Medical Decision Making
Sharon-Lise Normand, Harvard Medical School and Harvard T.H. Chan School of Public Health

10:25 AM Break

10:45 Panel Discussion
Lianne Sheppard, University of Washington and HEI Review Committee, and the speakers

MAIN CONFERENCE

11:30 AM Lunch

1:00 PM **Ozone: Global Pollutant, Personal Effects**

Chairs: *Dan Greenbaum*, Health Effects Institute; and
Jana Milford, University of Colorado–Boulder and HEI Review Committee

Ozone is a secondary pollutant that is regulated through the National Ambient Air Quality Standards (NAAQS), which are reviewed every five years; the next ozone review is due to start soon. This session will discuss challenges in controlling ozone levels, including atmospheric transport across continents and climate change, and the current science-based evidence that will contribute to the ozone health assessment. The session will end with a discussion of challenges facing those who must work to implement the ozone NAAQS.

1:00 Welcome and Introduction
Dan Greenbaum

1:10 Global Dimensions to Regional Air Quality: Transboundary Transport and Climate Change
Arlene Fiore, Columbia University

1:50 Recent Studies That Will Contribute to the Ozone Health Assessment and the Setting of the Standard

- 1:50 Introduction
  Jana Milford
- 2:00 Link Between Ozone and Health: Epidemiological Evidence
  Mike Jerrett, University of California–Los Angeles

2:30 PM Break

2:50 Link Between Ozone and Health: Clinical Studies
Mark Frampton, University of Rochester Medical Center and HEI Review Committee

3:20 Panel Discussion: How Does Scientific Knowledge and Uncertainty Inform Attainment Efforts at Ground Level?
Philip Fine, South Coast Air Quality Management District
David Brymer, Texas Commission on Environmental Quality

3:40 General Discussion

3:55 PM **Presentation of Student and Postdoc Travel Awards**
Dan Greenbaum

4:00 PM Break

4:15 PM **Poster Session 1**

5:30 PM Break

6:00 PM **Opening Reception, Dinner, and Keynote Speaker**

Venkat Sumantran, Chairman, Celeris Technologies, and coauthor of *Faster, Smarter, Greener: The Future of the Car and Urban Mobility*

Monday, April 30

7:00 AM Breakfast

8:30 AM **Health Effects of Traffic-Related Air Pollution: Assessing the Evidence in an Evolving and Complex World**

Chairs: *Francesco Forastiere*, Lazio Regional Health Service, Italy; and *Fred Lurmann*, Sonoma Technology, Inc.

This session will discuss important factors related to the design and interpretation of health studies of traffic-related air pollution. It is intended to aid the scope of a new systematic review to assess health effects of such air pollution, which will update HEI's 2010 literature review. The session will also introduce the Traffic Review Panel, as well as announce new HEI studies that will assess the health effects of traffic-related air pollution while taking into account other factors such as noise, socioeconomic status, and green space.

8:30 Introduction of Panel Members for the New Review of the Traffic and Health Literature
Bob O'Keefe, Health Effects Institute

8:40 Traffic-Related Air Pollution: A Moving Target
Beth Conlan, Ricardo, United Kingdom

9:10 Important Knowledge Gaps in Studying Health Effects of Traffic Exposure
Francesco Forastiere

9:30 Comments from Stakeholders and General Discussion
Kathryn Sargeant, U.S. Environmental Protection Agency
Kurt Karperos, California Air Resources Board
Matthew Spears, Engine Manufacturers Association

10:10 The New HEI Traffic and Health Studies
Hanna Boogaard, Health Effects Institute

10:15 AM Break

10:45 AM **Air Pollution and Diabetes: What Is the Evidence?**

Chairs: *Barbara Hoffmann*, University of Düsseldorf, Germany, and HEI Research Committee; and *Ivan Rusyn*, Texas A&M University and HEI Research Committee

Diabetes and obesity, as well as air pollution, are known risk factors in the development of cardiovascular and respiratory diseases. Air pollution is associated with development of diabetes in adults, and there is some evidence that early-life exposure in children may be associated with diabetes later in life. This session will discuss the evidence, who is most susceptible, and what mechanisms are behind these observations.

10:45 Brief Introduction to the Session
Ivan Rusyn

10:50 Overview of Evidence of a Link Between Air Pollution and Diabetes
Barbara Hoffmann

11:10 Mechanistic Insights into Air Pollution and Type 2 Diabetes
Sanjay Rajagopalan, Case Western University

11:30 Long-Term Exposure to Air Pollution and Type 2 Diabetes in Adults
Robin Puett, University of Maryland

11:50 Early-Life Exposure to Air Pollution and Diabetes in Childhood
Abby Fleisch, Maine Medical Center

12:10 General Discussion

12:30 PM Lunch

1:30 PM Poster Session 2

3:00 PM Break

3:15 PM Can We Rely on Environmental Health Research?

Chairs: *Amy Herring*, Duke University and HEI Research Committee; and
Kiros Berhane, University of Southern California and HEI Review Committee

Awareness has grown during the last decade that many scientific studies have not been reproduced and the problem seems to be particularly widespread in certain fields. Environmental standards are health based and there have been long-standing debates about replicability and reproducibility of the studies underpinning regulations (including concerns about data access, quality, and analyses), though arguably the recent debate has given this issue greater visibility. Reproducibility is the focus of several recent debates in scientific journals and also is reflected in congressional efforts at transparency. This session will describe the background on this issue, different perspectives on it, and approaches to addressing it.

3:15 Reproducibility and Replicability: Definitions and What They Imply
Steve Goodman, Codirector of Meta Research Innovation Center, Stanford University

3:45 Choices and Consequences: Study Design, Data Analysis, Reporting, Interpretation
Amy Herring

4:15 Reproducibility and Air Pollution Epidemiology
Rick Burnett, Health Canada

4:45 Panel Discussion
Ila Cote, Formerly of the U.S. Environmental Protection Agency
Richard Smith, University of North Carolina–Chapel Hill

5:30 PM Free Evening

Tuesday, May 1

7:00 AM Breakfast

8:30 AM Advancing Air Quality, Global Health, and Energy Science at HEI

Research Committee Chair *David Eaton*, University of Washington–Seattle, and Review Committee Chair *James Merchant*, University of Iowa, will introduce the two committees and preside over a presentation of HEI's research program, which includes traffic-related air pollution, low levels of exposure, accountability, and mechanisms of effect, as well as the expanding Global Health Program. Energy Research Committee Chair *George Hornberger*, Vanderbilt University, will join them to present HEI's Energy Research Program, focused

on the potential for human exposure and health effects from the development of oil and natural gas from unconventional resources.

Part I: Progress on Air Quality and Global Health Science

Chairs: *David Eaton, Jim Merchant*

8:30 Introduction of New Chair of the Research Committee
Dan Greenbaum, Health Effects Institute

8:40 Introduction to Core Research and Review Committees
Chairs

8:55 Presentation of 2017 Walter A. Rosenblith New Investigator Awards
Annemoon van Erp, Health Effects Institute

9:05 Core Science Program: Traffic-Related Air Pollution, Low Levels of Exposure, Accountability, and Mechanisms
Rashid Shaikh, Health Effects Institute

9:25 Global Health Program: GBD MAPS, Household Air Pollution, and Ports
Katy Walker, Health Effects Institute

Part II: Launching the HEI Energy Research Program and Initial Findings

Chair: *George Hornberger*

9:50 Introduction to the Energy Research Committee and the Program
George Hornberger

10:05 Progress on Systematic Review of the Human Health Literature Related to Unconventional Oil and Natural Gas Development
Anna Rosofsky, Health Effects Institute

10:25 Plans for Exposure Literature Review and Research Planning
Donna Vorhees, Health Effects Institute

10:45 AM Break

11:15 AM The Power of Place: Pathways to Healthy Urban Living

Chairs: *David Foster,* University of Wisconsin–Madison and HEI Research Committee; and *Frank Kelly*, King's College London, United Kingdom, and HEI Review Committee

More than half of the world's population now lives in urban areas, and this number is expected to increase because of continuing population growth and urbanization. Air pollution and noise, along with interrelated factors such as physical inactivity, lack of green space, stress, and socioeconomic deprivation, are associated with adverse health. This session will explore how integrated urban design, transport planning, and new mobility and transportation technologies can improve city residents' health and reshape cities in the future.

11:15 Keynote Speaker: Health of Urban Populations
Sandro Galea, Boston University

12:00 PM Lunch

1:00 Interrelationships Between Urban Green Space, Air Pollution, and Health
Jaime Hart, Harvard T.H. Chan School of Public Health

1:30 Healthy Urban Living: Urban Design, Transport Planning, and Travel Choice
Lawrence Frank, University of British Columbia, Canada

2:15 General Discussion

2:30 PM Conference Adjourns

POSTER SESSION 1

Sunday, April 29, 4:15–5:45 PM

GLOBAL HEALTH AND ENERGY RESEARCH AT HEI

HEI's research portfolio includes the expanding Global Health Program and a new Energy Research Program. Two major initiatives in the Global Health Program will be presented. **Dr. Brauer** will represent the HEI GBD MAPS Working Group, an international group of collaborators that recently completed studies on the major sources of air pollution contributing to disease in China and India. **Dr. Walker** will demonstrate HEI's new website and online tools related to the State of Global Air project. **Dr. Vorhees** and others will describe progress in HEI's Energy Research Program, focused on the potential for human exposure and health effects from the development of oil and natural gas from unconventional resources.

Contributions to Disease Burden from Major Sources of Air Pollution in China and India
Michael Brauer, Aaron Cohen, Katherine Walker, Richard T. Burnett, Joseph Frostad, Qiao Ma, Randall V. Martin, Shuxiao Wang, Chandra Venkataraman, and the HEI GBD MAPS Working Group

State of Global Air 2018
Katherine Walker, Michael Brauer, Hilary Polk, Annemoon van Erp, Kathryn Liziewski, and Aaron Cohen

Progress with HEI's Energy Research Program
Donna Vorhees, Anna Rosofsky (presenter), Kathryn Liziewski, Dan Greenbaum, Robert O'Keefe, and Rashid Shaikh

HEALTH EFFECTS OF AIR POLLUTION

Several ongoing studies at HEI are evaluating different aspects of associations of various neurological and respiratory outcomes in children with air pollution, and the influence of socioeconomic factors and genetic backgrounds on cardiovascular outcomes in adults. **Dr. Clougherty** (RFPA 15-2) is quantifying combined effects of spatial and temporal trends in multiple pollutants and stressors, including socioeconomic position, on cardiovascular events presented in New York City hospitals from 2005 to 2011. **Dr. Guxens**, the 2016 recipient of HEI's Walter A. Rosenblith New Investigator Award, is investigating the association between autism spectrum disorders and prenatal air pollution exposure at different time windows and the association between brain changes in children and prenatal and postnatal air pollution exposure at different time windows. **Dr. Kraus** (RFPA 10-3) has conducted a genome-wide interaction study (GWIS) to examine gene–traffic-exposure interactions associated with coronary atherosclerosis. **Dr. Pedersen**, a 2017 recipient of HEI's Walter A. Rosenblith New Investigator Award, will evaluate whether early-life exposure to air pollution is associated with development of asthma in children and adolescents.

Susceptibility to Multiple Air Pollutants in Cardiovascular Disease
Jane E. Clougherty, Jamie L. Humphrey, Ellen J. Kinnee, Laura D. Kubzansky, Colleen E. Reid, and Leslie A. McClure

Air Pollution, Autism Spectrum Disorders, and Brain Imaging Amongst CHildren in Europe — the APACHE Project
Mònica Guxens

Angiopoeitin-2 as a Biomarker for Gene–Environment Interactions in a Cardiovascular Disease Cohort
Jiangda Ou, Janet Huebner, Cavin Ward-Caviness, Robert B. Devlin, Lucas M. Neas, David Diaz-Sanchez, Wayne E. Cascio, Elizabeth R. Hauser, and William E. Kraus

Impact of Exposure to Air Pollution on Asthma: A Multi-Exposure Assessment
Marie Pedersen, Zorana J. Andersen, Anne-Marie N. Andersen, Xavier Basagaña, Hans Bisgaard, Jørgen Brandt, Esben Budtz-Jørgensen, Klaus Bønnelykke, Leslie Stayner, Matthias Ketzel, Bert Brunekreef, and Steffen Loft

In related work (not funded by HEI), **Dr. Rosofsky** assessed the relationships between trends in ambient air pollution in Massachusetts and inequality; **Dr. Keller**, a Postdoc Travel Award recipient, is assessing the relationship between particulate matter exposure and asthma in children; and **Ms. Yan**, a Student Travel Award recipient, is exploring the nonlinear shape of the fine particulate matter concentration-response curve at the high particulate matter levels of Beijing, China.

Prenatal Ambient Air Pollution Exposure: Association with Longitudinal Weight Growth Trajectories in Early Childhood*
Anna Rosofsky, M. Patricia Fabian, Stephanie Ettinger de Cuba, Megan Sandel, Sharon Coleman, Brent Coull, Jonathan Levy, and Antonella Zanobetti

Long-Term Coarse Particulate Matter Exposure and Asthma Among Children in Medicaid*
Joshua P. Keller, Corinne A. Keet, and Roger D. Peng

Fine Particulate Matter Pollution and Human Mortality in Beijing, China: An Investigation of the Shape of the Concentration-Response Association*
Meilin Yan, Michelle Bell, Roger Peng, Ander Wilson, Qinghua Sun, Brooke Anderson, and Tiantian Li

IMPROVING ASSESSMENT OF EXPOSURE TO TRAFFIC-RELATED AIR POLLUTION

HEI has a number of studies underway that evaluate aspects of exposure to traffic-related air pollution, both from tailpipe and non-tailpipe emissions. **Dr. Frey** explored how traffic activity metrics, land-use parameters, and environmental factors influence the near-road concentrations measured at fixed sites and during mobile sampling campaigns. **Dr. Apte**, a 2017 recipient of HEI's Walter A. Rosenblith New Investigator Award, is investigating the potential for mobile monitoring using fleet vehicles to fill current gaps in fine-scale air pollution exposure assessment in the United States and in India. **Dr. Koutrakis** is using a mobile sampling laboratory to collect particle samples in the greater Boston area with the aim of identifying variables that may influence levels of ambient particles released directly (tailpipe and non-tailpipe emissions) and indirectly (resuspended road dust) and their levels. In related work (not funded by HEI), **Dr. Patton** compared performance and predictions for different models that have been proposed for use in exposure assessment near roads; **Mr. Shah**, a Student Travel Award recipient, is using mobile monitoring measurements and source apportionment to measure the levels and composition of particulate matter in the city of Oakland, California, and to identify major sources of air pollution in the city's neighborhoods.

Scalable Multi-Pollutant Exposure Assessment Using Mobile Monitoring Platforms
Joshua S. Apte, Adam A. Szpiro, and Michael Brauer

* Study not funded by HEI.

Characterizing the Determinants of Vehicle Traffic Emissions Exposure: Measurement and Modeling of Land-Use, Traffic, Transformation, and Transport
H. Christopher Frey, Andrew Grieshop, Nagui Rouphail, Joe Guinness, Andrey Khlystov, John Bangs, and Daniel Rodriquez

Chemical and Physical Characterization of Non-Tailpipe and Tailpipe Emissions at 100 Locations Near Major Roads in the Greater Boston Area
Petros Koutrakis, Brent Coull, Marco Martins, Joy Lawrence, and Stephen Ferguson

Comparison of Regression and Dispersion Models of Near-Highway Ultrafine Particle Number Concentrations for Use in Health Studies*
Allison P. Patton, Chad Milando, Prashant Kumar, and John L. Durant

Gradients in Concentration and Composition of Fine Particulates in a Coastal City: Downtown Dominates a Large Area Emission Source in Port of Oakland CA*
Rishabh Shah, Ellis Robinson, Peishi Gu, and Albert Presto

NEW DATABASES AND EMERGING EXPOSURES TO AIR POLLUTION

Research related to particulate matter and ozone is expanding to include additional sources of exposure and new databases. Scientists (not funded by HEI) in this topic area will present ongoing work on understanding and communicating the health impact of exposure to smoke from wildfires, an increasing concern especially in the western United States **(Dr. Baxter)**; describe the world's largest database of ozone health metrics from 9,000 monitoring sites worldwide **(Dr. Cooper)**; and present research on the growing importance of products containing volatile chemicals (e.g., pesticides, paints) to urban air pollution exposures relative to volatile chemicals from mobile source exhaust **(Dr. McDonald)**.

Highlights from EPA's Wildland Fire Research*
Lisa Baxter and Beth Hassett-Sipple

The Tropospheric Ozone Assessment Report (TOAR): Presenting the World's Largest Database of Ozone Health Metrics from 9000 Monitoring Sites Worldwide*
Owen R. Cooper

Volatile Chemical Products Emerging as Largest Petrochemical Source of Urban Organic Emissions*
Brian C. McDonald, Joost A. de Gouw, Jessica B. Gilman, Shantanu H. Jathar, Ali Akherati, Christopher D. Cappa, Jose L. Jimenez, Julia Lee-Taylor, Patrick L. Hayes, Stuart A. McKeen, Yu Yan Cui, Si-Wan Kim, Drew R. Gentner, Gabriel Isaacman-VanWertz, Allen H. Goldstein, Robert A. Harley, Gregory J. Frost, James M. Roberts, Thomas B. Ryerson, and Michael Trainer

* Study not funded by HEI.

POSTER SESSION 2

Monday, April 30, 1:30–3:00 PM

HEALTH EFFECTS AT LOW AMBIENT CONCENTRATIONS

The three studies funded under HEI RFA 14-3, *Assessing Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution,* are investigating health effects in millions of people exposed to low levels of air pollution in North America and Europe. The studies aim to shed light on the observation that some epidemiological studies have reported associations of air pollution with health effects at levels below current air quality standards, raising questions as to whether current standards are protective of the general population. **Dr. Brauer** is investigating mortality effects of low levels of air pollution in Canada using Canadian Census data from about 10 million people. **Dr. Brunekreef** is investigating health effects of low levels of air pollution in Europe using pooled data from 11 ESCAPE cohorts and seven large administrative cohorts, resulting in a study population of about 35 million people. **Drs. Dominici** and **Zanobetti** are examining health effects of low levels of air pollution in the United States using data from ~61 million people enrolled in Medicare and Medicaid and developing new causal modeling methods to characterize the shape of the exposure–response function. Posters of the three substudies of each of these large studies will be presented. In related work (not funded by HEI), **Dr. Suh** investigated confounding in long-term epidemiology studies of large administrative cohorts due to long-term temporal trends in $PM_{2.5}$ and other sources of unmeasured confounding.

Identifying the Shape of the Association Between Long-Term Exposure to Low Levels of Ambient Air Pollution and the Risk of Mortality: An Extension of the Canadian Census Health and Environment Cohort Using Innovative Data Linkage and Exposure Methodology
(PI: Brauer)

Substudies:

MAPLE: Mortality–Air Pollution Associations in Low Exposure Environments
Michael Brauer, Jeffrey R. Brook, Paul Bissonnette, Richard T. Burnett, Tanya Christidis, Daniel L. Crouse, Anders Erickson, Perry Hystad, Chi Li, Lauren Pinault, Randall V. Martin, Michael Tjepkema, Aaron van Donkelaar, Crystal Weagle, and Scott Weichenthal

Exposure Estimation for MAPLE: Mortality–Air Pollution Associations in Low Exposure Environments
Randall V. Martin (Presenter), Paul Bissonnette, Jaqueline Burke, Robyn Latimer, Chi Li, William Russell, Graydon Snider, Emily Stone, Aaron van Donkelaar, Crystal Weagle, Perry Hystad, Jeffrey R. Brook, Alain Robichaud, Richard Menard, Scott Weichenthal, Richard T. Burnett, Daniel L. Crouse, Anders Erickson, Lauren Pinault, Michael Tjepkema, and Michael Brauer

Evaluation of a Method to Indirectly Adjust for Unmeasured Covariates in Large Administrative Data Cohort Analyses: An Analysis of Associations Between Fine Particulate Matter and Mortality in the 2001 Canadian Census Health and Environment Cohort (2001 CanCHEC)
Anders C. Erickson (Presenter), Michael Brauer, Lauren L. Pinault, Daniel L. Crouse, Scott Weichenthal, Randall V. Martin, Perry Hystad, Jeffrey R. Brook, Michael Tjepkema, and Richard T. Burnett

Mortality and Morbidity Effects of Long-Term Exposure to Low-Level $PM_{2.5}$, Black Carbon, NO_2 and O_3: An Analysis of European Cohorts
(PI: Brunekreef)

Substudies:

Mortality, Morbidity and Low-Level Air Pollution in a Pooled Cohort of 485,000 in Europe in the ELAPSE Project
Bert Brunekreef, Maciek Strak (Presenter), Jie Chen, Marjan Tewis, Kees de Hoogh, Sophia Rodopoulou, Evi Samoli, Klea Katsouyanni, and Gerard Hoek, on behalf of the ELAPSE Project Team

Mortality, Morbidity and Low-Level Air Pollution in a Population of 35 Million in Europe: Analysis of Administrative Cohorts in the ELAPSE Project
Bert Brunekreef, Danielle Vienneau (Presenter), Nicole Janssen, Massimo Stafoggia, Mariska Bauwelinck, Klea Katsouyanni, Evi Samoli, Sophia Rodopoulou, Maciek Strak, and Gerard Hoek, on behalf of the ELAPSE Project Team

Development of the Statistical Protocol for the Investigation of the Health Effects of Long-Term Exposure to Low Air Pollutant Concentrations in the ELAPSE Project
Bert Brunekreef, Klea Katsouyanni (Presenter), Evangelia Samoli, Gerard Hoek, Sophia Rodopoulou, and Maciek Strak, on behalf of the ELAPSE Project Statistical Group

Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Pollution
(PI: Dominici)

Substudies:

Sensitivity of the Association of Long-Term $PM_{2.5}$ and Mortality to Modeling Choices
Danielle Braun (Presenter), Marianthi-Anna Kioumourtzoglou (Presenter), Xiao Wu, Christine Choirat, Qian Di, and Francesca Dominici

An Ensemble Model-Based Approach for Spatially and Temporally Resolved NO_2 Exposures in the Continental United States
Qian Di (Presenter), Petros Koutrakis, Christine Choirat, Joel Schwartz, and Francesca Dominici

Nationwide Studies of Short- and Long-Term Effects of $PM_{2.5}$ and O_3 on Mortality
Francesca Dominici (Presenter), Qian Di, Yan Wang, Antonella Zanobetti, Lingzhen Dai, Yun Wang, Petros Koutrakis, Christine Choirat, and Joel Schwartz

Investigation of Confounding in Air Pollution Epidemiology Studies Using a Large Medicare Beneficiary Dataset*
Annette C. Rohr (Presenter), Ki-Do Eum, Fatemeh Karzemiparkouhi, Chit Vivian Pun, and Helen H. Suh

HEALTH EFFECTS OF TRAFFIC-RELATED AIR POLLUTION AND NOISE

Three studies were funded recently under RFA 17-1, *Assessing Adverse Health Effects of Exposure to Traffic-related Air Pollution, Noise, and their Interactions with Socio-Economic Status*. **Drs. Dadvand** and **Sunyer** will recruit pregnant women and assess the effects of in-utero exposure to traffic-related pollution on birth weight, fetal growth trajectories, and placental function for each pregnancy in Barcelona. **Dr. Franklin** will assess the effects of metals from non-tailpipe emissions

* Study not funded by HEI.

on asthma and lung function in the most recent cohort of the Children's Health Study in southern California (recruited during 2002–2012), using available PM filters. **Dr. Raaschou-Nielsen** will assess myocardial infarction, stroke, diabetes, and biomarkers related to cardiovascular disease and diabetes in three large Danish cohorts. All three studies will estimate exposure to several pollutants and transportation noise and evaluate the roles of socioeconomic status, green space, physical activity, diet, and stress.

Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)
Payam Dadvand, Jordi Sunyer, Maria Dolores Gómez-Roig, Gustavo Arévalo, Xavier Basagaña, Maria Foraster, Michael Jerrett (Presenter), Jose Lao, Edurne Mazarico Gallego, Teresa Moreno, Tim Nawrot, Mark J. Nieuwenhuijsen, Xavier Querol, Joel Schwartz, and Cathryn Tonne

Intersections as Hot Spots: Assessing the Contribution of Localized Non-Tailpipe Emissions and Noise on the Association Between Traffic and Children's Health
Meredith Franklin, Scott Fruin, and Rob McConnell

Health Effects of Air Pollution Components, Noise, and Socioeconomic Status ("HERMES")
Ole Raaschou-Nielsen, Theis Lange, Matthias Ketzel, Ulla Hvidtfeldt, Henrik Brønnum-Hansen, Thomas Münzel, Ole Hertel, Jørgen Brandt, and Mette Sørensen

IMPROVED SCIENCE FOR DECISIONS

HEI's Accountability (health outcomes) research program was designed to evaluate whether regulations and other actions taken to improve air quality result in the intended public health benefits. **Dr. Meng** is evaluating the impact of the 2006 Emission Reduction Plan for Ports and Goods Movement issued by the California Air Resources Board to improve air quality in the goods movement corridors. Results from Phase I indicated that policies regulating goods movement are achieving the desired outcomes in improving air quality for the state. In Phase II, Meng and colleagues are examining whether reductions in ambient air pollution due to goods movement actions have led to improvements in health outcomes in California Medicaid fee-for-service beneficiaries with chronic diseases. In related work (not funded by HEI), **Dr. Castillo** will use a case study of the Integrated Air Quality Management Plan for the Aburrá Valley to show how the Clean Air Institute has been mainstreaming health impact assessment, and **Dr. Sacks** will describe a method to consider multipollutant impacts in health impact assessment.

Improvements in Air Quality and Health Outcomes Among California Medicaid Enrollees Due to Goods Movement Actions (Phase II Health Effects Study)
Ying-Ying Meng, Jason G. Su, Michael Jerrett, Xiao Chen, John Molitor, and Dahai Yue

Mainstreaming Health Effects Evaluation into Air Quality Management Planning in Latin America: The Case of the Aburrá Valley*
Juan J. Castillo, Juliana Klakamp, and Sergio Sanchez

A Proof-of-Concept Approach for Quantifying Multi-Pollutant Health Impacts Using the Open-Source BenMAP-CE Software Program*
Jason Sacks, Evan Coffman, Ana Rappold, Jim Anderton, Meredith Amend, Kirk Baker, and Neal Fann

* Study not funded by HEI.

OZONE AND PARTICULATE MATTER MECHANISMS

Phase 1 of the Multicenter Ozone Study in oldEr Subjects (MOSES) investigated the effects of controlled exposure to ozone on the cardiovascular system; it was published in 2017 (Research Report 192). In the follow-on study (Phase 2), the MOSES investigators (**Drs. Balmes, Bromberg,** and **Frampton**) are investigating whether personal and ambient ozone and other pollutant exposures impact or modify the pre- to post-chamber ozone exposure changes in the endpoints measured in Phase 1, and whether they impact the baseline (pre-exposure) levels. HEI is also currently funding two experimental studies investigating oxidative responses and chemical cellular changes in response to air pollution. **Dr. Contreras**, the 2014 recipient of HEI's Walter A. Rosenblith New Investigator Award, is investigating potential chemical changes that are induced in different types of RNA molecules in lung cells after exposure to urban air mixtures and will study how these perturbations affect normal patterns of cellular regulation. **Dr. Gowdy**, the 2015 recipient of the Walter A. Rosenblith New Investigator Award, is investigating whether vascular injury after exposure to ozone is mediated through changes in the lung and blood of levels of oxidized phospholipids. In related work (not funded by HEI), **Drs. Hazari** and **Kodavanti** are evaluating the roles that stress hormones and noise play in mediating cardiovascular and cardiometabolic effects of air pollutants.

Multicenter Ozone Study in oldEr Subjects (MOSES), Part 2: Impacts of Personal and Ambient Concentrations of Ozone and Other Pollutants on Biomarkers of Cardiovascular and Pulmonary Function
David Q. Rich (Presenter), Mark Frampton, Sally W. Thurston, Kelly Thevenet-Morrison, Wojciech Zareba, John Balmes, Mehrdad Arjomandi, Peter Ganz, Philip Bromberg, Milan Hazucha, and Neil Alexis

The Role of Air Pollution on RNA Oxidative Stress, Characterization of Stress-Response Enzymes, and Applications Toward RNA-Based Biosensors
Lydia M. Contreras, Juan C. Gonzalez, and Kevin Baldridge

Sex Differences in Pulmonary Eicosanoid Metabolism in Response to Ozone Exposure
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Thinking Outside of the Lungs: Systemic Stress Response as a Pathway and Modifier of Air Pollution Health Effects*
Mehdi S. Hazari (Presenter), Urmila P. Kodavanti, Aimen K. Farraj, and Ian Gilmour

* Study not funded by HEI.

ABSTRACTS

(In Alphabetical Order by Principal Investigator)

Scalable Multi-Pollutant Exposure Assessment Using Mobile Monitoring Platforms

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Background Urban air pollution concentrations can vary sharply over short distances. High spatial resolution surfaces of urban air quality data are needed for a variety of purposes, including exposure assessment for health studies, identification of emissions sources, and characterization of exposure. However, conventional techniques are generally unable to routinely provide data on intraurban exposure gradients.

Objectives This project investigates the potential for mobile monitoring using fleet vehicles to fill current gaps in fine-scale air pollution exposure assessment. The project builds on recent work to develop very large (multi-year, $>10^7$ observations) mobile monitoring datasets using Google Street View cars equipped with fast-response gas and particle analyzers. The emphasis here is on developing, validating, and challenging this method with a view to *scalability:* to addressing persistent air quality data gaps at large scale.

Study Design The following investigations are planned for this three-year study. First, we will externally validate the mobile measurement technique by comparing Google Street View pollution observations against a dense network of 100 fixed-site air pollution monitors in Oakland, California. Second, we will collect a new set of mobile measurements in New Delhi, India, to test the extensibility of this mobile measurement technique to developing-world settings. Third, we will compare and contrast the information provided by the mobile monitoring approach relative to what can be detected by other conventional exposure assessment techniques, including satellite remote sensing, land-use regression, and chemical transport model simulations. Fourth, we will probe mobile measurements with data mining techniques to understand how sources influence population exposures, and compare these understandings with what can be learned by high-resolution receptor modeling. Finally, we plan to evaluate how this monitoring approach could be scaled up to address large scale data gaps in low- and high-income regions of the world.

Highlights from EPA's Wildland Fire Research*

Lisa Baxter and Beth Hassett-Sipple

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Wildland fires are increasing in frequency, size, and intensity in the United States. They emit gases and particles that contribute to the formation of ozone and other pollutants (e.g., particulate matter) that impact public health, visibility, and an array of public welfare metrics including commerce and tourism. Smoke from wildland fires now accounts for approximately 35 percent of the fine particle air pollution ($PM_{2.5}$) in the country. Smoke plumes can extend for hundreds of miles across state and national boundaries, making any given wildland fire, and a season of wildfire events, an issue of nationwide concern.

Given the broad range of ways wildfires can impact human health and the environment, the U.S. Environmental Protection Agency's Office of Research and Development is conducting wildland fire research in an integrated approach and in collaboration with Federal, state, Tribal, and community partners. This work includes advancing innovative measurement methods to improve wildfire emissions inventories; expanding our understanding of wildland fire impacts on air quality; enhancing our knowledge of human health and ecological effects; and providing critical science to minimize public and environmental impacts.

To study the potential health effects of breathing wildfire smoke, EPA researchers have developed a novel combustion and smoke collection system that can mimic the combustion phases of a fire (flaming and smoldering) to develop exposures for toxicological studies. EPA investigators have also conducted a first-of-its-kind study estimating the health and health care cost impacts of wildland fires in the U.S. between 2008-2012.

EPA is supporting research that will improve the ability of air quality managers, health care providers, and others to assess potential health risks from wildland fire smoke and communicate public health information to those who may be impacted by fires. These efforts include the development of a Community Health Vulnerability Index (CHVI) to identify communities at higher health risk to wildland fire smoke exposure. In addition, an ongoing citizen science study utilizes a mobile application — Smoke Sense App — to evaluate the extent to which exposure to wildland fire smoke affects health and productivity, and to inform health risk communication strategies that enhance public health protection during smoke days.

As these initiatives progress, EPA will continue to explore opportunities to improve the integration, translation, and communication of scientific and technical information related to wildland fires.

* Study not funded by HEI.

MAPLE: Mortality–Air Pollution Associations in Low Exposure Environments

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Background Fine particulate matter ($PM_{2.5}$) has been associated with mortality in many studies across the globe. However, the range in concentration for which this association is present is not known. Since nearly the entire population of Canada lives in areas with ambient concentrations below 12 μg/m^3, and studies repeatedly demonstrate associations with mortality in this population, it is an ideal environment to study the mortality impacts of low $PM_{2.5}$ concentrations.

Objectives To apply novel satellite-based estimates of exposure to $PM_{2.5}$ to several large population-based cohorts, and to characterize the shape of the relationship between $PM_{2.5}$ exposure with cause-specific mortality.

Methods We developed annual satellite-based $PM_{2.5}$ exposure estimates at 1 km resolution across Canada for 1998-2016. Estimates were back-casted to 1981 using remote sensing, chemical transport models and historical ground monitoring data. Historical estimates for NO_2 and ozone were also developed for the same period. Further refinements will incorporate new information on the relationship between aerosol optical depth (AOD) and $PM_{2.5}$ based on measurements at five sites across Canada.

Exposure estimates were applied to four large, population-based, cohorts: ~8.5 million subjects who completed the 1991, 1996, and 2001 census long forms, and 389,000 participants of the Canadian Community Health Survey (CCHS) 2001, 2003, 2005, and 2007/2008 panels. All subjects are being linked to annual tax records, to establish residential histories, and mortality until 2016.

We analyzed the 2001 census cohort (CanCHEC 2001) linked to a mortality dataset including all International Classification of Disease (ICD-10) codes listed on the death certificate to evaluate the use of contributing cause of death information in informing cause-specific mortality analyses. In addition, we evaluated the application of indirect adjustment methods using the CCHS for behavioral risk factors not recorded in the census cohorts and compared exposure profiles between the CCHS and the CanCHEC 2001 cohort.

Results and Conclusions Satellite-based $PM_{2.5}$ estimates were highly correlated with ground monitors ($R^2 = 0.82$) across North America. Root-mean-squared-error (1.5 μg/m^3 for the full dataset) decreased slightly when higher $PM_{2.5}$ concentrations were excluded. Initial results from filter analysis indicate variation in $PM_{2.5}$/AOD relationships across sampling sites, suggesting potential for further reductions in RMSE. Mention of diabetes was identified as an important contributing cause of cardiovascular disease mortality linked to $PM_{2.5}$ exposure. In the 2001 CanCHEC, co-mention of diabetes increased magnitude of the association compared to CVD mortality without diabetes, suggesting that restricting analyses to the primary cause of death likely underestimates the role of co-morbidities such as diabetes on air pollution-related mortality.

Contributions to Disease Burden from Major Sources of Air Pollution in China and India

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Background Ambient air pollution is a leading global risk factor – with 7.5% of total deaths (4.1 million) attributable to exposure to fine particles ($PM_{2.5}$) in the 2016 Global Burden of Disease (GBD). A majority of this burden is found in low and middle-income countries in Asia. A variety of sources contribute to ambient $PM_{2.5}$ pollution. The Health Effect Institute's Global Burden of Disease-Major Air Pollution Sources (GBD-MAPS) project, estimated the burden attributable to major air pollution sources in order to support air quality management efforts designed to reduce exposure. In Asia, major sources include the burning of coal for thermal power and industry, household burning of solid fuels, and transportation.

Objectives To estimate the contributions of major source sectors to ambient $PM_{2.5}$ concentrations and disease burden under current conditions and multiple future emissions scenarios for China and India.

Methods GBD-MAPS extended the GBD methodology, using emissions inventories and projections together with chemical transport model (GEOS Chem) simulations to i) estimate source contributions to ambient $PM_{2.5}$, ii) assess the contribution of major sources of $PM_{2.5}$ pollution to current disease burden in China (2013 base year) and India (2015 base year), and iii) predict the impact of different future emissions scenarios on resulting disease burden in 2030 (China) and 2050 (India).

Results Coal-burning, especially industrial, was found to be the most significant contributor to burden from air pollution in China, responsible for 40% (366,000 deaths in 2013) of the disease burden attributable to ambient $PM_{2.5}$. In India, residential biomass combustion was a critical factor, responsible for 25% (268,000 deaths in 2015) of the $PM_{2.5}$ burden. In both countries modeling of future emissions scenarios indicated increases in future attributable deaths for all future scenarios, due to aging and growing populations. However, increasing numbers of deaths were avoided with increasingly stringent emissions scenarios.

Conclusions Heavy industrial and population growth in Asia suggest "business as usual" scenarios to result in severe burden from air pollution, especially that related to coal combustion, for years to come. Aggressive legislation and enforcement of air quality management are required to substantially reduce the future burden of air pollution in Asia.

Evaluation of a Method to Indirectly Adjust for Unmeasured Covariates in Large Administrative Data Cohort Analyses: An Analysis of Associations Between Fine Particulate Matter and Mortality in the 2001 Canadian Census Health and Environment Cohort (2001 CanCHEC)

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Background The method of indirect adjustment for unmeasured confounding variables has become a promising technique in large environmental epidemiological cohort studies. This method has not, however, been formally evaluated or tested for application in non-linear survival models.

Objectives To describe and evaluate the indirect adjustment method using a large national longitudinal cohort, the 2001 Canadian Census Health and Environment Cohort (CanCHEC, N=2.4 million), and several pooled cycles of the Canadian Community Health Survey (CCHS, N=450,000) as the representative matching dataset with detailed risk factor information (e.g. smoking, body mass index, exercise).

Methods First, we assessed the distribution of fine particulate matter ($PM_{2.5}$) among subjects across characteristics (age, sex, etc.) for both the cohort and the health survey to compare for consistency. Next we examined the direction and magnitude of correlations amongst the variables available for both the cohort and health survey. We implemented validation tests to assess the performance of the indirect adjustment method on non-linear Cox proportional hazard models using only the CanCHEC and indirectly adjusting for known variables. To evaluate the application of the CCHS for the indirect adjustment of the CanCHEC, we assessed survival models wherein specific variables available in both datasets were excluded (e.g. education, income), applied indirect adjustment, and then returned to assess the amount of bias correction.

Results Comparisons of the cohorts at baseline (2001) showed very similar $PM_{2.5}$ distribution profiles across population characteristics, although $PM_{2.5}$ levels for CCHS participants tended to be consistently 1.8-2.0 $\mu g/m^3$ lower than in the CanCHEC cohort. This finding is likely due to sampling differences between urban and rural areas for the census and health survey. Applying a sample-weighting scheme to the CCHS largely corrected for this discrepancy in mean $PM_{2.5}$ levels. Correlations among variables within the two cohorts were consistent. Results for validation tests are on-going.

Conclusions A thorough and formal evaluation of the indirect adjustment method for health outcome data using a large longitudinal mortality cohort and representative health survey will help establish protocols that other jurisdictions can use to assess the viability of this method and possibly correct for differences in their own cohort datasets when information on potential confounding variables are not available.

Exposure Estimation for MAPLE: Mortality–Air Pollution Associations in Low Exposure Environments

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Background Uncertainty remains in the association between mortality and long-term exposure to ambient fine particulate matter ($PM_{2.5}$) at low concentrations. A paucity of air quality monitors in regions with low concentrations inhibits exposure assignment from ground-based monitors alone. Reduced ground-based monitoring for historical time periods also poses challenges for exposure assignment in cohort studies.

Objectives To develop $PM_{2.5}$ concentration estimates across Canada by combining satellite remote sensing, chemical transport modeling, and ground-based monitoring.

Methods We developed estimates of $PM_{2.5}$ concentrations at 1km by 1km resolution across North America for each year from 1981 to 2012 (and ongoing out to 2016). The estimates were based on a combination of satellite remote sensing of aerosol optical depth (AOD), relating AOD to $PM_{2.5}$ using the GEOS-Chem chemical transport model, and integrating of these concentrations with ground-based monitoring data through geographically weighted regression. Estimates prior to 1998 included additional PM_{10} and total suspended particles (TSP) ground-based monitoring information.

We deployed targeted ground-based monitoring of the relationship between AOD and $PM_{2.5.}$ This monitoring is being used to evaluate and improve the GEOS-Chem calculation of the relation between AOD and $PM_{2.5}$.

Annual concentration estimates are also developed for O_3 and NO_2 using a combination of ground-based monitoring, chemical transport modeling, and for NO_2 land use information and satellite remote sensing.

Results Satellite-based $PM_{2.5}$ estimates were consistent with ground-based monitors ($R^2 = 0.82$, slope=0.97) across North America even when large fractions were withheld for cross-validation (excluding up to 70% of monitors decreased R^2 to 0.78). Root-mean-squared-error decreased slightly with decreasing $PM_{2.5}$ concentrations from 1.5 $\mu g/m^3$ for the full dataset to 1.3 $\mu g/m^3$ for concentrations < 8 $\mu g/m^3$. Historical $PM_{2.5}$ surfaces benefitted from PM_{10} and TSP data.

Initial targeted ground-based monitoring identified the mass scattering efficiency (the relationship between $PM_{2.5}$ and scatter) as a driving factor of the relation between AOD and $PM_{2.5}$. Development of the representation of aerosol size and aerosol hygroscopicity in the GEOS-Chem model improved the simulation of mass scattering efficiency.

Conclusions A combination of satellite remote sensing, chemical transport modeling, and targeted ground-based monitoring offers valuable information about ambient air quality at low concentrations.

Development of the Statistical Protocol for the Investigation of the Health Effects of Long-Term Exposure to Low Air Pollutant Concentrations in the ELAPSE Project

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Background and Objectives ELAPSE investigates the effect of long-term exposure to low levels of $PM_{2.5}$, NO_2, O_3 and black carbon on mortality and morbidity in European cohort studies. We present the statistical analysis protocol in this abstract.

Statistical Methods Data are pooled from 11 cohorts with detailed information at the individual level and analysed as one dataset. Additionally 7 European administrative cohorts are included, analysed individually, with cohort-specific effect estimates consequently pooled by random-effects meta-analysis. Pooling individual data from the 11 cohorts presents a great challenge in terms of variables' availability and harmonization. Further, area-level covariates are different between European countries as they are reported under varying geographical scales and definitions. The main exposure indices are the pollutants' concentrations at the subject's residence estimated by modelling at specific reference years. We assess the latency of effects by using exposures 2, 4 and 6 years prior to each health event. Time-varying exposures and levels derived from the average of back extrapolated estimates and local models are also being assessed.

We apply Cox proportional hazard models with varying control for individual- and area-level covariates that are outcome-specific. In the pooled ESCAPE cohorts analysis we compare different approaches accounting for the clustering of data by cohort including correction of the standard errors, stratification and frailty models with random intercepts. We further apply multiple imputation by chained equations for main covariates such as smoking. In the administrative cohorts' analysis we compare Cox models with and without control for large geographical areas and correction of the standard errors. In all analyses we assess model diagnostics, and heterogeneity between cohorts/areas. We use the pooled database and the UK administrative cohort, which includes information on several individual confounders, to evaluate the impact of missing covariates in the other administrative cohorts and further apply indirect adjustment correction methods previously proposed.

We apply multi-pollutant models and compare risk estimates from single and multi-pollutant models to disentangle interdependencies and pollutant-specific impact on the analysed outcomes. We evaluate effect modification patterns and investigate concentration-response by fitting fractional polynomials, spline and threshold models. Analysis are also being performed by subgroups below certain concentration levels. Finally we assess measurement error by regression calibration and comparison of effects using exposure estimates derived from 80% of the monitors for the LUR models.

Specific codes have been developed for all analyses in the R statistical package.

Discussion Comparison of various models' results demonstrates the robustness of our findings and provides an indirect approach to address the causality of the associations.

Mortality, Morbidity and Low-Level Air Pollution in a Pooled Cohort of 485,000 in Europe in the ELAPSE Project

Bert Brunekreef[1], Maciek Strak[1] (Presenter), Jie Chen[1], Marjan Tewis[1], Kees de Hoogh[2,3], Sophia Rodopoulou[4], Evi Samoli[4], Klea Katsouyanni[4,5]; and Gerard Hoek[1], on behalf of the ELAPSE Project Team

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Background Epidemiological cohort studies have consistently found associations between long-term exposure to outdoor air pollution and morbidity and mortality endpoints. Recent evaluations by the World Health Organization and the Global Burden of Disease study have suggested that these associations may persist at very low concentrations. However, uncertainty about the shape of the concentration response function exists at these low concentrations. Within the multicentre Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), we investigate the association between long-term exposure to low concentrations, defined as less than current EU, EPA and WHO Limit Values or guidelines, of several air pollutants and morbidity and mortality endpoints.

Methods To assess long-term residential exposure, we developed a Europe-wide hybrid land use regression models estimating annual 2010 mean concentrations of $PM_{2.5}$, NO_2, O_3 and BC (including cold and warm season estimates for O_3). The models were based on AirBase routine monitoring data and ESCAPE monitoring data (for BC) and incorporated land use and traffic data supplemented with satellite observations and dispersion model estimates as additional predictor variables. Models were applied to 100*100 m grids across Europe to allow for exposure assignment in all ELAPSE cohorts. We applied multivariate Cox proportional hazard models to investigate the association between long-term air pollution exposure and a number of morbidity and mortality endpoints in a pooled cohort (this abstract) and in several large administrative cohorts (companion abstract).

Results We pooled data, so far, from eight European cohort studies, resulting in a study population of 400,187 subjects. We are adding three more cohorts, increasing the study population with 85,000 subjects. The average follow up time in the pooled cohort was 19 years. Average exposure to air pollution was 15.1 (SD 3.3) $\mu g/m^3$ for $PM_{2.5}$, 25.1 (8.1) $\mu g/m^3$ for NO_2, 1.5 (0.4) $\mu g/m^3$ for BC, and 67.6 (6.9) $\mu g/m^3$ for (annual) O_3. $PM_{2.5}$ was moderately correlated with NO_2 (Pearson's r 0.53) and highly correlated with BC (0.80), whereas NO_2 was moderately correlated with BC (0.69). Ozone had a high negative correlation with NO_2 (-0.81) and low negative correlations with the two other pollutants (-0.23 to -0.26). First results of the associations between exposure and selected endpoints will be presented at the HEI annual meeting.

Conclusions We successfully pooled data and assigned exposure for several European cohorts. Analyses of associations between low-level air pollution and morbidity and mortality endpoints are ongoing. Details regarding statistical analyses can be found in another companion abstract.

Mortality, Morbidity and Low-Level Air Pollution in a Population of 35 Million in Europe— Analysis of Administrative Cohorts in the ELAPSE Project

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Background ELAPSE aims to investigate the adverse health effects of long-term exposure to low levels of ambient air pollution in Europe. To capture a large population and exposure contrast, we exploit large administrative cohorts geographically spread across Europe. Specifically, these are used to explore associations between exposure to NO_2, $PM_{2.5}$, Black Carbon and O_3 and mortality as well as CVD and cancer incidence.

Methods Europe-wide hybrid land use regression models for each pollutant were developed for 2010 (i.e. ELAPSE exposures). These were transferred to each cohort, and linked to participants on the basis of address-level geocodes. To facilitate harmonisation, the cohorts implemented the ELAPSE codebook where possible, including specified definitions for socio-economic status (SES) at different geographic scales. Each cohort further collected local air pollution exposure data, area-level SES data, and health survey data for indirect adjustment. Statistical scripts were centrally developed, on the basis of the study manual, and tested in a selection of cohorts. These apply Cox proportional hazard models with successively more detailed control for individual- and area-level confounders. Data from the administrative cohorts are being analysed locally and combined by meta-analysis.

Results Seven very large administrative cohorts (>35 million participants) are included, with data access granted for 6 cohorts (English pending). Exposure estimates and area-level covariates have been linked to 5 cohorts (Belgian, Danish, Dutch, Rome and Swiss; Norwegian in progress). As an example, the median exposures range from 23, 16, 1.6 and 73 $\mu g/m^3$, respectively for NO_2, $PM_{2.5}$, Black Carbon and O_3, in the Swiss cohort (4.4 mil adults). A series of working group and bilateral meetings have taken place to ensure harmonisation across the cohorts in particular for area-level SES definition and statistical modelling. Statistical scripts have been developed using the Rome cohort, and tested with the larger Swiss cohort. Testing has focused on aspects related to Cox models with time invariant exposure, basic confounder adjustment and the different options to control for potential differences in baseline hazard by region. Epidemiological results for a section of administrative cohorts will be presented at the HEI conference.

Conclusions As more cohorts proceed with the analysis, further harmonisation of geographic areas for SES and model definition will be implemented to ensure the subsequent analyses (i.e., indirect adjustment, dose response modelling) are sufficiently comparable to allow meaningful meta-analyses.

Mainstreaming Health Effects Evaluation into Air Quality Management Planning in Latin America: The Case of the Aburrá Valley*

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Background More than 150 million people live in Latin American cities where WHO Air Quality Guidelines are exceeded. Though health protection should be at the center of policy and decision-making, health evaluation is far from being fully incorporated into air quality management and other related policies at all levels. Mainstreaming health effect considerations into air quality management processes is indispensable for catalyzing abatement efforts towards the achievement of Sustainable Development Objectives. The Clean Air Institute (CAI) works with interested parties to incorporate integrated approaches, methodologies and tools for preparing and implementing comprehensive air quality management instruments. By applying the Integrated Environmental Strategies approach, CAI has been assisting the identification, evaluation and prioritization of interventions to effectively abate air pollution at local and national scales. In this work, CAI describes how it has been mainstreaming health impact assessment, using as an example the case of the Integrated Air Quality Management Plan for the Valley of Aburrá 2017-2030 (PIGECA), officially launched late 2017. Our purpose was dual: first, to evaluate the health benefits of the adoption of plan; and second, to provide a basis for the further institutionalization of health benefit considerations in the overall air quality management process.

Methods The health impact assessment presented here is an essential part of the Integrated Environmental Strategies approach used to prepare the Aburrá Valley's PIGECA. Based on local air quality monitoring data and health incident rates, we applied health impact functions to quantify the number of avoidable deaths due to the reduction on $PM_{2.5}$ concentrations and cumulative benefits for the period 2017– 2030. Information was processed using BenMAP-CE v1.1. Colombia's value of a statistical life was used to perform the economic valuation. The analytical process was enriched by a multi-stakeholder policy dialogue, which helped to advance a common understanding about the importance of air pollution from a health perspective.

Results The implementation of PIGECA is expected to lead to a reduction of 18,344 cases of mortality during 2017-2030. The successful implementation of the plan could reduce attributed health burden on 74% for 2030. Cumulative economic benefits could reach 3.9 USD Billion (which represents around 2% of the regional GDP). Moreover, PIGECA explicitly includes key measures to reinforce health as the core of air quality management in the region for achieving air quality goals.

Conclusions Health considerations can be mainstreamed as a core of the air quality management process in Latin America. Health assessment is crucial to raise awareness and build consensus to address air quality issues at a magnitude consistent to its challenges. Dissemination and replication of this experience provides a great value to assist other cities for developing comprehensive air quality management plans, including sound health assessments and engaging multiple stakeholders. BenMAP-CE provides an excellent platform to support analysis and, furthermore, to bridge gaps for increasing collaboration between health, environment and other authorities and actors.

* Study not funded by HEI.

Susceptibility to Multiple Air Pollutants in Cardiovascular Disease

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Background Cardiovascular disease (CVD), the leading cause of death in the U.S., has been linked to chronic and acute air pollution exposures. Research has identified stronger effects of air pollution in lower-socioeconomic position (SEP) communities, where exposures are also often higher. While specific factors underlying this susceptibility remain unknown, chronic psychosocial stress related to social adversity has been hypothesized as a critical component. The potential interplay between social and environmental exposures is particularly relevant for CVD, as both impact upon several common processes in CVD. More clearly elucidating susceptibility factors will help to better identify at-risk populations, to offer methods for investigating joint effects of multiple exposures, and, ultimately, to develop more cost-effective interventions towards reducing disproportionate CVD burdens and health disparities.

Methods We are quantifying relationships between exposures to multiple pollutants and CVD events in New York City using four unique datasets: [1] Spatial data on citywide community SEP and stressor indicators; [2] Surfaces for fine-scale spatial variation in multiple pollutants from NYC Community Air Survey (NYCCAS) [fine particles ($PM_{2.5}$), nitrogen dioxide (NO_2), summertime ozone (O_3), sulfur dioxide (SO_2)]; [3] Daily ambient pollution concentrations from EPA Air Quality System monitors; [d] Complete data on in- and out-patient unscheduled CVD events presented in NYC emergency departments (EDs) 2005-2011 (n = 1.3 million), from NY State Department of Health Statewide Planning and Research Cooperative System (SPARCS).

Under Aim 1, we used ecologic cross-sectional models to examine spatial relationships among pollutants, stressors, and age-adjusted community CVD rates. For Aim 2, we are examining associations between spatio-temporal pollution exposures and CVD events using case-crossover models, inherently adjusting for non-time-varying individual confounders. In Aim 3, we will test modification in these associations by community SEP and/ or chronic stressor exposures.

Results Results for Aim 1 suggested that, in ecologic models, social stressors generally explained greater variation in CVD than did pollutants. Further, above-median material deprivation (e.g., poor housing) conferred stronger associations between area-level SO_2 and CVD, in the hypothesized direction. Preliminary case-crossover analyses (Aim 2) suggest slightly stronger associations between O_3 and CVD in communities with above-median assault rates.

Discussion Ecologic results from Aim 1 suggested that social stressors may explain more variance in CVD than does ambient air pollution, and that some social stressors may confer stronger associations between pollution and CVD. These observed associations may under-estimate true effects, however, due to the small sample size (n = 34 areas), exposure misclassification for both stressors and pollutants, or complex joint distributions between pollutants and social stressors across NYC. Preliminary results from on-going case-crossover analyses (Aim 2) suggest some potential effect modification by stressors, in case-level relationships between spatio-temporal pollutant exposures and CVD risk.

The Role of Air Pollution on RNA Oxidative Stress, Characterization of Stress-Response Enzymes, and Applications toward RNA-Based Biosensors

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Background We have previously shown that levels of 8-oxoguanosine (8OG) may present a more immediate and consistent measure of cellular stress in air pollution exposure models (Baldridge et al. 2015). However, a mechanistic understanding of the role for RNA oxidation in acute air pollution stress responses has not been investigated. Our main objective in this work is to elucidate underlying biological processes altered in the human lung cell models upon air pollution exposure by functional profiling of stress-induced RNA oxidation transcripts.

Methods We exposed BEAS-2B lung cell cultures ($N = 3$) to different levels of air pollution mixtures (4 ppm ozone, 872 ppb acrolein, 698 ppb methacrolein; 0.4 ppm ozone, 872 ppb acrolein, and 698 ppb methacrolein; and 0.4 ppm ozone, 100 ppb acrolein, and 100 ppb methacrolein) for 90 minutes. We extracted total RNAs and treated samples with an antibody against 8OG, with subsequent RT-qPCR analysis of enriched and un-enriched RNA pools for both pollution-exposed and clean-air-control samples. We isolated proteins from BEAS-2B cultures and performed Western blots for both treatment conditions to analyze relevant protein expression. We measured levels of intracellular cholesterol by a colorimetric assay for both treatment conditions. We conducted functional profiling using gene sets differentially enriched (adjusted p-value < 0.05) using Enrichment Map and Cytoscape. For our work related to developing oxidizing-recognizing proteins, we developed a molecular dynamics-based method that screens a library of ~100 modifications already parametrized in CHARMM (Chemistry at Harvard macromolecular mechanics) in collaboration with Dr. Phanourios Tamamis at Texas A&M. The method was subsequently validated using the protein *E.* PNPase and a set of previously characterized RNA modifications by electrophoretic mobility shift assays (EMSAs). We conducted EMSAs of PNPase with three RNA modifications predicted to improve its binding affinity ($N = 3$) using 25-mers each containing 6 modifications distributed through the oligonucleotide.

Results Initial RT-qPCR profiling and Western blotting analysis demonstrate differential expression and oxidation enrichment of RNAs that encode for specific proteins within the cholesterol pathway when exposed to differential levels of pollution mixtures compared to cells exposed to clean air. Moreover, the functional profiling of oxidation transcripts reveals that critical cellular processes such as mRNA splicing, histone modifications, rRNA and tRNA processing, and cell cycle are potentially altered by stress-induced RNA oxidation. Lastly, our efforts to characterize protein binding to modified RNAs have led to a validated high-throughput computational method that has, so far, identified 10 modifications that can increase the binding affinity of PNPase. This model predicts that the sites that interact with the modified RNAs (via H-bonds, salt bridges and van der Walls forces) are localized near the putative binding site of the widely conserved RNA-binding domains in PNPase. These predictions agree with experimental shift assays of PNPase mutants suggesting that binding site multiplicity is involved on the specific interactions of PNPase and modified RNAs.

The Tropospheric Ozone Assessment Report (TOAR): Presenting the World's Largest Database of Ozone Health Metrics from 9000 Monitoring Sites Worldwide*

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Tropospheric ozone is a greenhouse gas and pollutant detrimental to human health and crop and ecosystem productivity. Since 1990 a large portion of the anthropogenic emissions that react in the atmosphere to produce ozone has shifted from North America and Europe to Asia. This rapid shift, coupled with limited ozone monitoring in developing nations, left scientists unable to answer the most basic questions: Which regions of the world have the greatest human and plant exposure to ozone pollution? Is ozone continuing to decline in nations with strong emissions controls? To what extent is ozone increasing in the developing world? How can the atmospheric sciences community facilitate access to the ozone metrics necessary for quantifying ozone's impact on human health and crop/ecosystem productivity?

To answer these questions the International Global Atmospheric Chemistry Project (IGAC) initiated the Tropospheric Ozone Assessment Report (TOAR). With over 230 member scientists and air quality specialists from 36 nations, TOAR's mission is to provide the research community with an up-to-date scientific assessment of tropospheric ozone's global distribution and trends from the surface to the tropopause. TOAR has also built the world's largest database of surface ozone observations and generated ozone exposure metrics at thousands of measurement sites around the world, freely accessible for research on the global-scale impact of ozone on human health, crop/ecosystem productivity and climate. This presentation will provide an overview of TOAR's unique database with an emphasis on its utility for epidemiological research.

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Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)

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Background A substantial body of evidence has associated air pollution to impaired fetal growth; however, there are still substantial limitations in terms of applied exposure assessment methods, disentangling role of co-exposure such as noise, and evaluating the modifiers, mediators, and mitigators of this association. FRONTIER aims to provide a robust and comprehensive evaluation of the impact of maternal exposure to traffic-related air pollution on fetal growth. Towards this aim, it will (i) disentangle the effects of noise; (ii) identify the relevant window(s) of exposure; (iii) evaluate its modification by socioeconomic status, stress, and physical activity; (iv) elucidate the role of placental function as an underlying mechanism; and (v) explore the potential of green spaces to mitigate it.

Methods FRONTIER will establish a new pregnancy cohort of 800 women in Barcelona, Spain. Fetal growth will be characterized by anthropometric measures at birth together with ultrasound-based trajectories of fetal development. Placental function will be evaluated using state-of-the-art Doppler ultrasound indicators. Hair cortisol levels at the third trimester will be used as an indicator of maternal stress during pregnancy. Time-activity patterns will be objectively characterized using a combination of smartphones and personal physical activity monitors. We will develop and validate an innovative exposure assessment framework integrating data on time-activity patterns with a hybrid modeling framework combining dispersion and land use regression models and campaigns of personal and home-outdoor air pollution monitoring to estimate maternal exposure level as well as inhaled dose of NO_2, $PM_{2.5}$, $PM_{2.5}$ light absorption (a marker of tailpipe emissions), and $PM_{2.5}$ Cu, Fe, and Zn contents (markers of non-tailpipe emissions) at the main microenvironments for pregnant women (home, workplace, and the commuting routes). We will assess maternal exposure to noise by integrating measurements at participants' bedroom window using noise monitors together with modeled microenvironmental levels of noise and data on noise sensitivity, annoyance, and protections against noise. We will apply detailed information on different characteristics of each tree canopy in our study region together with a high-resolution remote-sensing map of greenness to separately characterize the canopy and greenness surrounding maternal residential address. We will develop single- and multi-pollutant models to evaluate the impact of air pollution exposure and inhaled dose on fetal growth.

Results and Conclusions FRONTIER will generate vigorous evidence base as well as practical information for implementing finely-targeted regulations and mitigation actions to tackle effects of air pollution on fetal growth.

Sensitivity of the Association of Long-Term $PM_{2.5}$ and Mortality to Modeling Choices

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Background To date, multiple studies have used spatio-temporal prediction models to assign long-term fine particle ($PM_{2.5}$) exposure to study participants and investigate the association with mortality. All these studies, nonetheless, have used different exposure models, ways to assign exposure, health models, and confounding adjustment approaches. To our knowledge, few studies have rigorously assessed the sensitivity of the reported results to the above modeling choices.

Methods We used data from Medicare enrollees from six New England states between 2003 and 2012 (N > 3 million), for whom residential information is available at zip-code level. There is spatial-misalignment between outcomes that are available at the zip-code level, confounders that are measured at the grid cell-, zip code- or ZCTA-level, and $PM_{2.5}$ concentrations that are predicted at 1 km $\times$ 1 km grid cells. Previous work has assigned exposures by estimating zip-code level $PM_{2.5}$ exposure using the average of the four grid points nearest to the zip-code centroid. With the assistance of GIS experts, we extend this approach to develop novel methodology and software that uses as inputs gridded air pollution predictions and aggregates those in pre-defined spatial polygons, e.g. zip-codes at which the Medicare data are available. The new method uses zonal statistics by performing a spatial merge to aggregate the data at the zip-code level with the option of either area- or population-weighted weights. We conducted health analyses using: (1) three different validated and widely-used exposure models, (2) two different ways to assign zip-code-level exposures (the average of the four grids nearest to the zip-code centroid vs. using zonal statistics and area weights), (3) two different health model parameterizations (Cox vs. log-linear models), (4) use of categorical vs. continuous exposures, and (5) confounding adjustment by inclusion of potential confounders in the health model vs. using generalized propensity scores (GPS).

Results Overall, we estimated significantly harmful $PM_{2.5}$ effects on mortality under all scenarios. However, the estimated effects varied across the different exposure models, with significant effect modification by population density observed for only one model. We additionally observed higher effect estimates for area-weighted zip-code averaged exposures, but no significant differences between Cox vs. log-linear models. Finally, when using categorical exposures (defined by policy-relevant cut-offs) we obtained slightly different health effect estimates adjusting for confounding using GPS vs. simply including the potential confounders in the health model.

Conclusions Although the overall conclusion would not change depending on the modeling choices in this very large study, these differences might be important for smaller sample sizes. Moreover, obtaining accurate estimates would greatly inform risk assessments and cost-benefit analyses, thus impacting regulatory actions.

An Ensemble Model-Based Approach for Spatially and Temporally Resolved NO_2 Exposures in the Continental United States

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Background Nitrogen dioxide (NO_2) is a criteria pollutant, commonly used as a traffic emissions tracer, and has been linked to multiple adverse health effects. Unlike particulate matter and ozone, NO_2 modeling has received less attention. Previous studies used satellite data and kriging methods to estimate annual NO_2. However, few studies attempted to model NO_2 with both high spatial and temporal resolutions.

Methods We used multiple predictor variables and several machine learning algorithms to model daily NO_2. More specifically, we used satellite data, chemical transport model outputs, land-use variables, and meteorological variables as predictors to train the model using ground-level NO_2 measurements from EPA monitoring stations. We used machine learning models including a neural network, gradient boosting, and random forests as three separate approaches to model NO_2. We then used an ensemble model to aggregate these machine learning algorithms, since they are complementary to each other. We used the ensemble model to predict daily NO_2 at 1 km $\times$ 1 km grids in the continental United States from 2000 to 2016. We validated the model using ten-fold cross-validation.

Results Ten-fold cross-validation indicated a good performance of our ensemble model-based predictions with daily $R^2 = 0.78$ and MSE = 2.74 ppb. The model predicted high NO_2 concentrations in urban areas, as expected.

Conclusions We developed a new machine learning ensemble model to predict daily NO_2 concentrations with high accuracy. We are able to predict daily NO_2 even at locations without ground monitoring stations. These predictions will allow for the estimation of health effects of both short-term and long-term NO_2 exposure across the United States.

Nationwide Studies of Short- and Long-term Effects of $PM_{2.5}$ and O_3 on Mortality

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Background Although strong links for both short- and long-term fine particle ($PM_{2.5}$) and ozone (O_3) exposures and mortality have been reported, evidence is limited for air pollution levels below the National Ambient Air Quality Standards. Furthermore, previous studies have predominantly focused on urban populations, due to lack of exposure information availability and statistical power at rural areas. We present our findings on two nationwide studies investigating the impacts of short- and long-term $PM_{2.5}$ and O_3 exposure on mortality, and assess if effect estimates differ among populations living below the national standards.

Methods We used data from Medicare beneficiaries in the continental United States between 2000 and 2012. We used validated prediction models that are highly resolved in time and space to estimate zip-code level daily (for short-term) and annual (for long-term) $PM_{2.5}$ and O_3 exposures. For short-term effects, we employed a time-stratified bidirectional case-crossover design and examined the association between mortality and the average $PM_{2.5}$ and O_3 exposures at the day of the event and the previous day. For the short-term O_3 effects we assessed warm-season (April-September) exposures. For long-term effects, we used Cox proportional hazards models with time-varying exposures and adjusted for demographic characteristics, Medicaid eligibility, and area-level covariates. For both short- and long-term analyses we assessed exposure to $PM_{2.5}$ and O_3 simultaneously in the model, to account for potential co-pollutant confounding.

Results We estimated highly statistically harmful effects in all cases. Specifically, for short-term effects, we observed a 1.05% (95%CI: 0.95-1.15%) and 0.51% (95%CI: 0.41-0.61%) increase in mortality per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and 10 ppb increase in warm-season O_3 respectively. There was no evidence of a threshold in either exposure-response relationships. For long-term effects, we observed a 7.3% (95%CI: 7.1-7.5%) and 1.1% (95%CI: 1.0-1.2%) increase in mortality per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and 10 ppb increase in O_3 respectively. When the analysis was restricted to person-years with exposure to $PM_{2.5}$ of less than 12 $\mu g/m^3$ and O_3 of less than 50 ppb, the same increases in $PM_{2.5}$ and O_3 were associated with increases in the risk of death of 13.6% (95%CI: 13.1-14.1) and 1.0% (95%CI: 0.9-1.1), respectively.

Conclusions In the entire Medicare population there was significant evidence of adverse effects related both to short- and long-term exposure to $PM_{2.5}$ and O_3. These effects persisted even at concentrations below the current national standards. Our findings suggest that these standards may need to be re-evaluated.

Multicenter Ozone Study in oldEr Subjects (MOSES). Part 2: Impacts of Personal and Ambient Concentrations of Ozone and Other Pollutants on Cardiopulmonary Biomarkers

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Background The Multicenter Ozone Study in oldEr Subjects (MOSES) was a multicenter study evaluating whether short-term controlled exposure of older, healthy individuals to low levels of ozone induced acute changes in cardiovascular biomarkers. In MOSES Part 1, ozone exposure caused concentration-related reductions in lung function with evidence for airway inflammation and injury, without convincing evidence for effects on cardiovascular function. However, pollutant exposures before the study may have independently impacted the study biomarkers, and/or modified biomarker responses to controlled ozone exposures.

Study Design In MOSES Part 2, we used a longitudinal panel study design, cardiopulmonary biomarker data from MOSES Part 1, and passively collected personal exposure samples (PES) of ozone and NO_2, and ambient air pollution and weather measurements in the 96 hours before the pre-exposure visit. Using mixed effects linear regression, we evaluated whether PES concentrations and ambient pollutant concentrations in the previous 96 hours were associated with pre- to post-exposure biomarker changes, independent of the controlled ozone exposures **(Aim 1)**; modified biomarker responses to the MOSES controlled ozone exposures **(Aim 2)**; and were associated with changes in biomarkers measured at the pre-exposure visit **(Aim 3)**.

Results As hypothesized for Aim 3, increased ambient ozone concentrations were associated with decreased pre-exposure heart rate variability (HRV). For example, High Frequency (HF) HRV decreased in association with increased ambient ozone concentrations in the previous 96 hours (-0.460 ln of ms^2; 95% CI, -0.743, to -0.177 for each 10.35 ppb increase in ozone; p=0.002). However, these increases in ambient ozone were also associated with increases in HF and LF from pre- to post-exposure (Aim 1), likely reflecting a "recovery" of HRV during the MOSES ozone exposure sessions. Similar patterns were observed for FEV1 and FVC and increased ambient $PM_{2.5}$, CO, and NO_2 in the previous 96 hours. However, increased pollutant concentrations were not associated with adverse changes in other cardiopulmonary biomarkers. In Aim 2, effects of MOSES controlled ozone exposures on FEV1 and FVC (but not other biomarkers) were modified by ambient NO_2 and CO, and PES NO_2, with reductions in FEV1 and FVC observed only when these concentrations were "High" in the 72 hours before the pre-exposure visit.

Conclusions Increased ambient ozone concentrations were associated with reduced HRV, with "recovery" during exposure visits. Increased ambient $PM_{2.5}$, NO_2, and CO (markers of traffic pollution), were associated with reduced pulmonary function, independent of the MOSES controlled ozone exposures. Pulmonary responses to the experimental ozone exposures were modified by ambient NO_2 and CO concentrations, and PES NO_2 concentrations, with adverse changes in FEV1 occurring only when ambient and PES pollutant levels were high.

Intersections as Hot Spots: Assessing the Contribution of Localized Non-Tailpipe Emissions and Noise on the Association Between Traffic and Children's Health

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Traffic emissions are comprised of a complex mixture of components including tailpipe emissions, non-tailpipe emissions, and noise. While regulations have resulted in drastic reductions in tailpipe emissions, growing vehicle fleets and miles traveled have contributed to increased noise and non-tailpipe emissions such as brake wear, tire wear, and associated resuspended road dust. It is critical to assess effects of these lesser-studied non-tailpipe exposures that are high in toxic transition metals, and of noise, which can also amplify the detrimental health effects associated with near-roadway exposure.

In a cross-sectional study of the role of noise on the association between NO_x and children's lung function in the Southern California Children's Health Study (CHS), we found that a 14.5 mL (95 % CI: -40.0, 11.0 mL) decrease in forced vital capacity (FVC) per interquartile range (13.6 ppb) in NO_x was strengthened to a 34.6 mL decrease (95% CI: -66.3, -2.78 mL) after adjusting for noise. Noise was clearly an important factor and without taking it into account we would have underestimated the detrimental effects of exposure to traffic-related pollution.

Following this important finding, our current work focuses on intersections and on/off ramps where non-tailpipe and noise contributions are suspected to possibly disproportionately impact health. We will characterize exposure to non-tailpipe emissions with chemically speciated particulate matter concentrations in three size fractions from a spatially dense sampling campaign. Noise estimates from the Traffic Noise Model will be supplemented with noise contributions measured at intersections and on/off ramps. We will examine these as well as other important factors including greenspace and GIS-derived variables to study the effects this multipollutant mixture on respiratory outcomes in a longitudinal cohort of children from the CHS.

Characterizing the Determinants of Vehicle Traffic Emissions Exposure: Measurement and Modeling of Land-Use, Traffic, Transformation, and Transport

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Background The objective is to determine key sources of spatial and temporal variance of near road traffic-related pollutant concentrations, taking into account built environment; road infrastructure and traffic; transport and transformation of traffic generated pollutants; and concentrations in the near road environment.

Methods We conducted measurements at a freeway site and urban site. Metrics for land use, traffic activity, emissions source strength, meteorology, and near road air quality were used to calibrate spatiotemporal models of near road air quality for both sites. Traffic was monitored using a detector at the I-40 site and video at the Durham site, supplemented with on-road measurements of vehicle trajectories. Summer and winter field measurements were made at the freeway and urban sites. At the freeway site, aerosol size distributions, NO/NO_2, black carbon (BC) and aerosol mass concentration and volatility were measured. Measurements of NO/NO_2, BC and aerosol size distribution were collected at a background site. Aerosol size distributions, NO/NO_2, black carbon (BC), and aerosol volatility were measured at locations perpendicular to the freeway. Measurements at the urban site included pedestrian transects for UFP, $PM_{2.5}$, and ozone, and daily $PM_{2.5}$, NO_x, and O_3 measurements at the four quadrants surrounding the intersection.

Results For the freeway site, near road NO_x concentrations were found to be significantly influenced by upwind background concentration, season, wind direction, wind speed, and the interaction between predicted dispersion from R-LINE and heavy duty vehicle index. For UFP at the freeway site, the significant predictors include background concentration, temperature, season, wind direction, and interaction between predicted dispersion and vehicle density index. At the urban site, daily average NO_x concentrations were significantly influenced by distance-adjusted traffic, season, rain, temperature, and the interaction between distance adjusted traffic and season. The urban site UFP concentrations were significantly influenced by distance from the nearest bus stop, traffic counts, tailpipe CO emissions from the nearest 0.05 mile road segment, wind speed, temperature, and relative humidity. We applied the freeway site NO_x concentration model to a different site to gain insight regarding model validity and generalizability.

Conclusions In general, air pollutant concentrations decrease with distance from the roadway and are affected by atmospheric stability, mixing height, wind speed, wind direction, and physico-chemical interactions. Some species, such as NO_x and BC, are relatively unreactive and are useful tracers of vehicle emission dispersion, with the latter being a marker for diesel emissions. UFP number concentrations are strongly influenced by ambient temperature/season. Indices based on traffic count and proximity to the receptor are useful predictors of road side concentrations. Spatial variability in near road concentrations is influenced by spatial variability in vehicle emissions, which are not uniformly distributed along a road. Predicted dispersion is helpful in predicting near road concentration gradients. Relatively simple statistical models can explain a substantial amount of variability in near road concentrations. Implications for future work include further assessment and selection of averaging times, spatial resolution, and study locations for further data collection and model development.

Sex Differences in Pulmonary Eicosanoid Metabolism in Response to Ozone Exposure

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Rationale Epidemiological studies demonstrate that sex impacts the development and progression of several lung diseases. Ozone (O_3) is a criteria air pollutant that can trigger sex-biased pulmonary inflammation. Eicosanoids, potent bioactive lipid mediators, play an important role in regulating a diverse set of homeostatic and inflammatory processes. Accumulating evidence suggests there are sex dimorphisms in eicosanoid biology. However, the impact of O_3 exposure on sex-based pulmonary eicosanoid metabolism has not been investigated.

Methods 8-week-old C57BL/6J mice were exposed to filtered air (FA) or 1 ppm O_3 for 3h. Bronchoalveolar lavage (BAL) and lung tissue were collected 6h or 24h post exposure. Cell counts and protein were measured in BAL. Eicosanoid levels in the lung tissue were measured by LC-MS/MS. Cytokines, chemokines, and eicosanoid biosynthesis enzyme levels in the lungs were measured by RT-PCR.

Results Sex differences in BAL cell counts were observed post O_3 exposure as evidenced by significant increased BAL neutrophils in female 24h after exposure. BAL protein was significantly higher 24h post O_3 exposure in male and female compared to FA exposure with no sex differences observed. The pulmonary levels of prostaglandins (PGD2, PGE2, PGF2a, and PGI2), thromboxanes (TXA2 and TXB2), hydroxyeicosatetraenoic acid (5S-HETE, 8S-HETE, 12S-HETE, 15S-HETE), and leukotriene 4 (LTE4) were significantly increased in females 24h post O_3 exposure compared to males. Males displayed significantly higher levels of 11(12)-epoxyeicosatrienoic acid (EET) at 24h post O_3 exposure compared to females. The mRNA expression of cyclooxygenase (COX1 and COX2) enzymes in lung tissue showed trends of decreasing post O_3 exposure independent of sex.

Conclusion This study is the first to report that O_3 exposure reveals sex differences in pulmonary eicosanoid production. In females, pro-inflammatory eicosanoid (PGs, TXs, etc.) production was increased but not in anti-inflammatory eicosanoid (EETs) production. Our findings reveal that the inflammatory pathologies triggered by O_3 exposure are more pronounced in females and associated with increased levels of pro-inflammatory eicosanoids.

Air Pollution, Autism Spectrum Disorders, and Brain Imaging Among CHildren in Europe — the APACHE Project

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Background We aim to investigate i) the association between prenatal air pollution exposure at different time windows and the development of autism spectrum disorders (ASD) and ii) the association between prenatal and postnatal air pollution exposure at different time windows and brain structural and functional changes in children.

Methods We use data from 2 epidemiological studies: i) a population-based case-cohort study of ASD in Catalunya (Spain), where children diagnosed with ASD identified through the Catalan mental health network are linked to the Catalan birth registry and ii) a population-based birth cohort study, the Generation R (the Netherlands), with existing longitudinal data on brain imaging in children at 6-10 years and at 8-12 years. For both study regions we compile existing land use regression models for a large number of pollutants. For the study of Catalunya, we also combine land use variables and satellite data remote sensing of aerosol optical depth to develop new $PM_{2.5}$ and PM_{10} models. We estimate air pollution levels at participants' home addresses at different time-windows during pregnancy (entire pregnancy, monthly, and weekly) and childhood (entire childhood, yearly, and monthly). We apply methods for measurement error and multi-pollutant models. We assess the association between air pollution exposure at different time windows during pregnancy and the development of ASD. We also assess the association between air pollution exposure at different time windows during pregnancy and childhood and structural and functional brain changes at 6-10 years old and at 8-12 years old.

Results We are setting up the case-cohort study on ASD and developing new air pollution models for Catalunya. There are no results from that study yet. Regarding the imaging study, in the preliminary analysis we found that prenatal $PM_{2.5}$ exposure was associated with a thinner cortex in several brain regions in 6-10 years old children and these alterations partially mediated the association between prenatal $PM_{2.5}$ exposure and impaired child inhibitory control. We are currently working on the association between prenatal and postnatal exposure to several traffic-related air pollutants and white matter microstructure in 8-12 years old children. In single pollutant analysis, higher prenatal and postnatal exposure to several air pollutants was associated with a decrease in fractional anisotropy and an increase in mean diffusivity. When we mutually-adjusted those pollutants that showed an association in the single pollutant analysis, higher postnatal levels of zinc content in $PM_{2.5}$, which reflects tire wear and brake linings, were associated with an increase in mean diffusivity (0.03 increase in mean diffusivity [95%CI 0.01; 0.04] for each 10 ng/m^3 increase of airborne zinc). Further steps will include measurement error correction methods and advanced multipollutant modeling.

Thinking Outside of the Lungs: Systemic Stress Response as a Pathway and Modifier of Air Pollution Health Effects*

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Decades of research have led to the realization that the health effects of inhaled air pollution are not restricted to the respiratory system, and even though the airways remain the primary target, it has become increasingly clear that the response involves far more systemic components than originally thought. As such, fundamental air pollution toxicology evolved to recognize that in addition to the airways, the cardiovascular system is negatively impacted by air pollution, particularly in individuals with underlying disease. In the last few years, this paradigm has broadened even further to include other organ systems like the nervous system, the endocrine system, the gastrointestinal system and others. Furthermore, the cascade of effects that result from air pollution-induced "activation" of these systems, especially those with homeostatic functions, is not thought to be localized but rather disseminated throughout the body. Indeed, the deleterious health effects observed in the lungs and/or heart are a consequence of some of these systemic signals.

Recent work by our group establishes a connection between stress hormones released after ozone exposure and hyperglycemia/glucose intolerance in rats. Moreover, release of adrenergic and glucocorticoid hormones, which represent the sympathetic-adrenal-medullary (SAM) and hypothalamus-pituitary-adrenal (HPA) axes, respectively, modulate pulmonary injury and inflammatory effects. These findings clearly point to a neuroendocrine stress pathway which appears to mediate the response to air pollution and potentially prolong the window of susceptibility after exposure. By extension, the degree of responsiveness to air pollution depends on systemic (homeostatic) balance. The body is constantly exposed to non-chemical stressors, which modulate these internal controls that maintain equilibrium and increase the likelihood of an adverse response to a subsequent challenge.

Our studies with intermittent noise stress demonstrate that rodents develop cardiovascular dysfunction after only one week of exposure. These deleterious effects include a desensitization of the baroreflex, which is a homeostatic control mechanism that utilizes the autonomic nervous system to not only maintain normal blood pressure and cardiac function, but also the body's ability to respond to stress. Thus, there is a latent shift in baseline physiology such that the body is at greater risk of experiencing an adverse effect with a subsequent challenge. In this case, we show that the cardiovascular responses to ozone are worsened by noise, this includes dysregulation of blood pressure, arrhythmogenesis, and cardiac mechanical changes. Once again, this points to the activation of systemic stress pathways which not only mediate injury in distal organs but render the body susceptible by impairing its ability to compensate. In conclusion, in order to better protect public health, air pollution studies need to account for generalized stress responses which are altered by numerous everyday factors and also mediate toxicological effects across the body.

This abstract does not reflect US EPA policy.

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Long-Term Coarse Particulate Matter Exposure and Asthma Among Children in Medicaid*

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Background Short and long-term fine particulate matter ($PM_{2.5}$) pollution is associated with asthma development and morbidity, but there is little data on the effects of long-term exposure to coarse PM ($PM_{10–2.5}$) on respiratory health. We investigated the relationship between long-term outdoor fine and coarse PM exposure and asthma prevalence and morbidity among United States children.

Methods We predicted two-year average $PM_{2.5}$ and $PM_{10\text{-}2.5}$ concentrations during the period 2009-2010 at the zip-code tabulation area level across the contiguous United States using $PM_{2.5}$ and PM_{10} monitor data and geographic characteristics. We obtained data from 7,810,025 children aged 5–20 years enrolled in Medicaid from 2009-2010 and linked them to predicted PM levels via zip code. Using a log-linear regression model, we estimated the association between PM exposure and asthma prevalence and morbidity, adjusting for race/ethnicity, sex, age, area-level urbanicity, area-level poverty, area-level education, and unmeasured spatial confounding.

Results Exposure to coarse PM was associated with increased asthma diagnosis prevalence (relative risk [RR] for 1 $\mu g/m^3$ increase in coarse PM level: 1.006, 95% CI: 1.001-1.011), hospitalizations (RR: 1.023, 95% CI: 1.003-1.042), and emergency department (ED) visits (RR: 1.017, 95% CI: 1.001-1.033) when adjusting for fine PM. Fine PM exposure was more strongly associated with increased asthma prevalence and morbidity than coarse PM. The estimates remained elevated across different levels of spatial confounding adjustment.

Conclusions Among children enrolled in Medicaid, exposure to higher average coarse PM levels is associated with increased asthma prevalence and morbidity. These results suggest the need for direct monitoring of coarse PM and reconsideration of limits on long-term average coarse PM pollution levels.

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Chemical and Physical Characterization of Non-Tailpipe and Tailpipe Emissions at 100 Locations Near Major Roads in the Greater Boston Area

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Background The purpose of the proposed research is to develop sampling and statistical analysis methods to improve assessment of exposure to traffic particles and pollutants for health effects studies, characterize direct (tailpipe and non-tailpipe) and indirect contributions, and identify parameters which influence them.

Methods Using a mobile sampling platform equipped with coarse and fine particulate matter (PM) concentrators we are collecting ambient ultrafine, fine minus ultrafine (accumulation mode), and coarse particle samples near roads in the Greater Boston. In addition, we are collecting $PM_{2.5}$ and PM_{10} samples of aerosolized surface road dust *in situ*, using a Road Dust Aerosolization sampler. We are collecting these road dust and ambient PM samples at three distance ranges (including background) from each of the 100 major (A1, A2, and busy A3) road sites included in this study. The sampling time for ambient particles for each position is one hour, and the road dust sampling duration is 5 min. Each day of sampling, we also collect continuous particle count, particle mass, traffic, and weather data at all 3 locations simultaneously, to assess temporal variability at sites. Potential sites are identified using Google Earth/Google Maps and then evaluated during a site visit. To address temporal variability, a subset of sites will be visited multiple times in different seasons.

Results Following completion of the mobile platform assembly with fine and coarse concentrators, we did several days of performance validation. We found an excellent agreement between concentration and composition of duplicate samples collected using both the fine and coarse particle concentrators. During validation, an average enrichment factor of 10.9 times was observed for the fine particle concentrator and 80.2 times for the coarse particle concentrator.

We started the field measurements, and have completed a small number of sites. As the measurements have recently begun and are ongoing, our data are limited. However, we observed an average enrichment factor for fine concentrated particles in Framingham was 8.8 times ambient and 9.8 times for Marlborough. So far, enrichments have been highest at the Road site as compared to background or intermediate sites. All filters had enough loading for XRF and EC/OC analysis.

For the road dust samples, Framingham showed higher loading on filters for both $PM_{2.5}$ and PM_{10}, compared to Marlborough. All Road Dust filters also had enough collected material in 5 min sampling to perform XRF analysis.

Conclusions The validation testing and preliminary results from our two sites show that the mobile platform is functioning as intended, resulting in short duration ambient samples which can be analyzed for trace elemental composition, elemental carbon, and organic carbon.

Angiopoeitin-2 as a Biomarker for Gene-Environment Interactions in a Cardiovascular Disease Cohort

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Background We are investigating the effects of acute and chronic air pollution exposure on cardiovascular disease using the 9323-member Duke CATHGEN cohort of individuals undergoing coronary artery catheterization (collected 2001-2011) — CATHGEN includes individuals with and without coronary atherosclerosis. We have shown that air quality, including distance-to-roadway (DTR), $PM_{2.5}$, and ozone are associated with presence of chronic cardiovascular disease and acute cardiovascular events; in addition, specific genetic variants mediate some of these associations. We are continuing to evaluate these relationships using specific disease biomarkers, peripheral blood gene expression, and circulating metabolic intermediates. Previous studies in CATHGEN identified an association between peripheral vascular disease (PVD) and distance-to-roadway (DTR), along with a genome-wide significant interaction with SNP rs755249 in the *BMP8a* gene. We hypothesized that these relationships would also be apparent as associations with angiopoietin-2 (Ang2), a biomarker associated with PVD and other cardiovascular diseases.

Methods Concentrations of Ang2 in human plasma samples (n=2,226) from the CATHGEN cohort were quantified using a sandwich immunoassay (MesoScale Discovery Cat #K151KCD-1; Gaithersburg, MD). Genotyping was performed in CATHGEN participants using the Illumina HumanOmni 1-Quad_v1-0_C array. Geocoded primary residential address information was obtained for CATHGEN participants residing in North Carolina. The perpendicular distance between each primary residence and the nearest primary or secondary roadway was used as the distance to the nearest roadway measure (DTR) of traffic exposure. Race stratified linear regression models were fit to Ang2 plasma concentrations, DTR, genotype and the interaction between DTR and genotype, with adjustment for age, sex, genetic principal components and clinical covariates.

Results A total of 1876 CATHGEN individuals lived in NC with both DTR and Ang2 measures. Consistent with previous analyses in CATHGEN, there was a trend for individuals with PVD to live closer on average to primary or secondary roadways (0.97 km versus 1.09 km, p=0.07). Mean Ang2 plasma concentrations were statistically significantly greater in individuals with PVD when compared with those without PVD (5817 pg/mL versus 4961 pg/mL, p=0.02 unadjusted and p=0.02 adjusted). There was no significant association of Ang2 with DTR (p=0.60). In the subset of 696 individuals with complete DTR, Ang2 and genotype data, the regression coefficient for the interaction between the rs755249 SNP in *BMP8a* and DTR on ANG2 was significantly different from 0 (p=0.014 unadjusted, p=0.049 adjusted, whites only).

Conclusions Consistent with our previous findings in a PVD genome-wide interaction study, Ang2 plasma concentrations are associated with an interaction between DTR and rs755249 genotype. Ang2 may be a good biomarker for the impact of air quality and genotype on cardiovascular health in a high-risk population. However larger sample sizes will be required to untangle these complex relationships.

This abstract does not necessarily represent EPA policy.

Volatile Chemical Products Emerging as Largest Petrochemical Source of Urban Organic Emissions*

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Background A gap in emission inventories of urban volatile organic compound (VOC) sources, which contribute to regional ozone and aerosol burdens, has increased as transportation emissions in the United States and Europe have declined rapidly.

Methods A detailed mass balance demonstrates that the use of volatile chemical products (VCPs)—including pesticides, coatings, printing inks, adhesives, cleaning agents, and personal care products—now constitutes half of fossil fuel VOC emissions in industrialized cities. The high fraction of VCP emissions is consistent with observed urban outdoor and indoor air measurements.

Results We show that human exposure to carbonaceous aerosols of fossil origin is transitioning away from transportation-related sources and toward VCPs. Existing U.S. regulations on VCPs emphasize mitigating ozone and air toxics, but they currently exempt many chemicals that lead to secondary organic aerosols.

Conclusions As transportation emissions decline, chemical products are emerging as major contributors to ozone, aerosols, and air toxics.

* Study not funded by HEI.

Improvements in Air Quality and Health Outcomes Among California Medicaid Enrollees Due to Goods Movement Actions

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Background and Objectives This two-phased project aims to examine reductions in ambient air pollution after the implementation of the "Emissions Reduction Plan for Ports and Goods Movement" by the California Air Resources Board (CARB) in 2006 and subsequent improvements in health outcomes of Medicaid fee-for-service (FFS) beneficiaries in 10 counties in California. Specifically, we examined whether air pollution reductions resulted in reductions in emergency department (ED) visits and hospitalizations among enrollees with chronic conditions.

Methods We created annual air pollution surfaces across California at a spatial resolution of 30m. The study areas were grouped into goods movement corridors (GMCs) as locations within 500 m of truck-permitted freeways and ports; non-goods movement corridors (NGMCs) as locations within 500 m of truck-prohibited freeways or 300 m of a connecting roadway, and control areas (CTRLs). In Phase II, exposures were assigned to enrollees' home addresses. We used a retrospective cohort of 23,000 adult with six years of continuous enrollment (September 1, 2004 to August 31, 2010). Multilevel negative binomial regression models with random intercept for controlling within individual correlation were used to examine temporal changes of ED visits or hospitalizations by comparing GMCs with CTRLs. Based on the parallel assumption, difference in difference (DD) analyses have been conducted for assessing the causal impact of policy on reduction of air pollution, as well as for the causal impact of the reduction of air pollution on improvements in health outcomes.

Results We observed significant reductions in pollutant exposures for enrollees living in 10 counties with the enrollees in GMCs experienced the greatest reduction from the pre- to the post-policy periods for NO_2 and $PM_{2.5}$ using the annual air pollution surfaces. We also observed that the number of ED visits among those with asthma living in GMCs were significantly lower (DD=-0.16, $p<0.05$) compared with those living in CTRLs. The ED visits for those with COPD had similar patterns of reductions; the DD estimate was approximately -0.13 in post years and statistically significant. We also observed signs of reductions in ED visits and hospitalizations for those with heart disease, but they were not statistically significant.

Conclusions Our study results add to empirical evidence that air pollution control actions benefit people with chronic conditions through pollution exposure reductions and health outcome improvements. Our investigation also contributes to scientific knowledge regarding how to assess the health effects of longer-term, large scale, and complex regulatory actions with routinely collected medical claims data.

Comparison of Regression and Dispersion Models of Near-Highway Ultrafine Particle Number Concentrations for Use in Health Studies*

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Background Concentrations of ultrafine particles and other air pollutants are elevated near highways. Health studies on the effects of traffic-related air pollution require estimates of human exposures. Regression and dispersion models are commonly used methods to assess exposure. We compared the ability of regression and dispersion models to predict ultrafine particle number concentrations (PNC) in urban neighborhoods near highways in and around Boston, Massachusetts, for use in health studies.

Methods We measured PNC by mobile monitoring on 34-46 days over the course of one year in two near-highway neighborhoods. For each neighborhood, we built hourly spatial-temporal regression models of PNC predicted by meteorology, traffic, and location. We compared the predictions of the regression models to each other and also to readily-available dispersion models (CALINE4, AERMOD, R-LINE, and QUIC) for four typical meteorological and traffic conditions. Each model's performance was assessed by the fraction of predictions within a factor of 2 or 1.5 of measurements, R^2, normalized mean square error, and fractional bias.

Results In the first neighborhood where the main local source of air pollution was a highway, the models all performed similarly (e.g., overall R^2 between model pairs ≥0.82) and predicted high levels of PNC extending ~100 m from the highway. In the second neighborhood, non-highway sources and street canyons formed by rows of tall buildings were more important in predicting PNC than proximity to highways. In the second neighborhood, the regression model performed better than dispersion models that did not account for building locations, but it performed worse than a dispersion model with buildings included.

Conclusions Our observations support the use of regression models outside of urban centers and demonstrate the importance of area-specific PNC models that align with study area characteristics, including dominant sources and building geometry. Additional work is needed to determine how differences in model predictions affect the usefulness and potential biases when these models are used for exposure assessment in health studies.

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Impact of Exposure to Air Pollution on Asthma: A Multi-Exposure Assessment

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Asthma is the most common chronic disease in children. There is evidence that exposure to ambient air pollution from motor vehicle emissions not only exacerbates existing asthma, but also contributes to the development of asthma. Asthma has a multifactorial etiology, which is still not well understood, as multiple factors starting from fetal life may be involved. Some of these factors may be correlated, share sources and pathways resulting in joint effects that are greater than additive. Thus, the potential for confounding and effect modification of the ambient air pollution exposure effects on asthma is very high. The role of early-life exposure to ambient air pollution on the asthma pandemic remains poorly understood due to the lack of large birth cohort studies with sufficient long follow-up and assessment of multiple exposures.

Our aim is to test the hypothesis that early-life exposure to air pollution from multiple sources have individual and joint effects on risk of development of asthma in children and adolescents. Furthermore, we seek to determine the mechanistic basis for these effects by studying changes in lung function, inflammation, immunological markers and airway DNA methylation.

Unique material on individual health, home, neighborhood and personal characteristics from National registers will be used for prospective studies of all children and adolescents born in Denmark since 1997 (N≈1,150,000) together with detailed questionnaire data from the Danish National Birth Cohort (N≈90,000) and measurements of lung function and biomarkers from the COPenhagen Prospective Studies on Asthma in Childhood (N≈1,000). Nitrogen dioxide, nitrogen dioxides, particulate matter (PM_{10} and $PM_{2.5}$ from all sources and from wood stoves), carbon monoxide, elemental carbon, black carbon, organic carbon, ozone, sulphur dioxide and ammonium will be estimated at home addresses by applying air pollution dispersion models.

Register and questionnaire data on asthma incidence (i.e., hospitalization, medicine prescriptions, and doctor-diagnosis), home characteristics and neighborhood will be evaluated. Confounding and effect modification by personal characteristics and exposures will be considered. Traditional and advanced statistical methods will be used. These complementary studies offer unique opportunities to better understand the role of specific sources of air pollution on asthma development and the mechanisms of asthma causation. This information will be useful to better target strategies for protection of health, to understand and to reduce the risk associated with different sources of air pollution. The findings may have profound implications for public health, given the large burden associated with asthma and the ubiquity of air pollution exposure worldwide.

Health Effects of Air Pollution Components, Noise, and Socioeconomic Status ("HERMES")

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Background Traffic-related air pollution (TRAP), traffic noise and low socioeconomic status (SES) impair health, including CVD and diabetes. However, knowledge gaps still remain including identification of the causal agent(s) in the complex TRAP, the most relevant timing of exposure, the degree of confounding or possible interaction between TRAP and traffic noise, and how SES and individual susceptibility interplay in this equation. HEI has funded the HERMES study to address these questions.

Objectives To identify the specific TRAPs strongest associated with myocardial infarction (MI), stroke and diabetes. To disentangle how TRAP and road traffic noise interact in relation to these endpoints. To investigate how socioeconomic status (SES), green spaces, co-morbidity and stress confound/interact with the associations between TRAP and road traffic noise and risk of MI, stroke and diabetes. To investigate effects of TRAP and road traffic noise in relation to a cardiovascular and metabolic biomarkers.

Experimental Design We will take advantage of an "administrative" cohort covering the entire Danish population (DKPOP) (n=5.5 million), the Diet, Cancer & Health (DCH) cohort (n=57,053), and the DCH Next Generations (DCH-NG) cohort (n=50,000). We will link each individual to the unique and reliable nationwide Danish registries with information on residential address history, prevalent and incident MI, stroke and diabetes, vital status, indicators of stress and SES. Both DCH and DCH-NG have information on individual lifestyle, and DCH-NG furthermore has measurements of cardiovascular and metabolic biomarkers. We will use state-of-the-science models to calculate TRAPs (NO_2, NO_x, black carbon, ultrafine particles, $PM_{2.5}$, PM_{coarse} and PM_{10}) and road traffic noise for all present and past residential addresses for each cohort participant at the exact time of living there.

We will develop new statistical methods for multipollutant analyses based on random forest methodology and apply these to identify the TRAPs strongest related to MI, stroke and diabetes. The statistical analyses will estimate associations expressed both as relative and absolute risk. We will strive to separate effects of long- (years, decades) and short-term (days, weeks) exposure to TRAP by including both measures in the same statistical model. We will focus on effects of recent exposures (health endpoints from 2005 onwards) and we will assess the source-specific contributions to exposure (traffic/non-traffic; tail pipe/non-tail pipe TRAP). Further, we will develop an index for SES at neighborhood level and describe spatial associations between TRAP, noise, SES, co-morbidity and stress-markers. We will investigate how these factors interact with associations between TRAP/noise and the health endpoints.

Discussion It has been a challenge for previous studies to separate effects of single TRAPs on health. We will address that challenge by 1) development and application of new statistical tools based on random forest methodology and 2) use data for the entire Danish population providing excellent statistical power. It has also been a challenge to investigate separate health effects of and interactions between air pollution and noise, which we will address by using large populations and applying state-of-the-science exposure models at similar geographical level and with similarly precise input data.

Prenatal and Postnatal Ambient Air Pollution Exposure and Weight Growth Trajectories in Early Childhood*

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Background Air pollution exposure during pregnancy has been positively associated with impaired fetal growth, low birth weight and higher body mass index later in life. However, there are few studies of longitudinal weight growth trajectories in early childhood to determine the time course of weight gain as a function of air pollution exposures, and the interaction with birth weight.

Methods We combined electronic medical record (EMR) with survey data collected from caregiver-child dyads enrolled in the ethnically diverse Boston-based Children's HealthWatch cohort (n=4,797) to obtain longitudinal weight and covariate information. Geocoded residential addresses at each EMR entry were linked to daily 1km^2 $PM_{2.5}$ predictions. We examined the association between prenatal and postnatal (12-month average preceding each weight measurement) $PM_{2.5}$ exposure and weight (kg) growth trajectories from birth to age six, stratified by sex, using piecewise linear and polynomial mixed models.

Results Mean prenatal $PM_{2.5}$ concentrations were similar between males (9.6 (SD:1.2, range: 6.5-14.0) μg/m^3) and females (9.5 (SD:1.2, range: 6.3-14.1) μg/m^3). Male and female postnatal concentrations were 7.9 μg/m^3 (SD: 0.9, range: 5.8-12.6) and 7.9 μg/m^3 (SD:1.0, range: 4.3–21.2), respectively. Females with residential prenatal $PM_{2.5}$ above the median (9.5 μg/m^3) had significantly ($p<0.05$) higher weights compared to females with prenatal $PM_{2.5}$ below the median from 0-6 years of age (e.g. 0.16 kg higher at 24 months, 0.62 kg higher at 60 months). The association was similar among low birth weight (LBW) (< 2500 g) females (13.3% LBW). Conversely, males with prenatal $PM_{2.5}$ above the median had lower weights (-0.17 kg at 24 months, -0.72 kg at 60 months) than males with prenatal $PM_{2.5}$ below the median, with differences increasing with age. Male weight trajectories did not differ by birth weight strata (14.1% LBW males). Weight trajectories were not associated with postnatal $PM_{2.5}$.

Conclusions Studying growth trajectories, rather than attained weight measures, provide an opportunity to understand the life course impact of pre- and postnatal air pollution exposure. Our findings demonstrate the complex association between environmental exposures and childhood weight trajectories and emphasize the importance of sex-stratified analyses.

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A Proof-of-Concept Approach for Quantifying Multi-Pollutant Health Impacts Using the Open-Source BenMAP-CE Software Program*

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Disclaimer: The views expressed are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.

Background Air pollution risk assessments often employ effect coefficients from epidemiologic studies to quantify the public health impact of changes in air quality. Partly due to data and methodological limitations, epidemiologic studies have traditionally characterized the health risk of exposure to individual pollutants. Such single-pollutant approaches may: not fully account for the fact that populations are exposed to mixtures of pollutants; not account for synergistic or antagonistic health effects among populations exposed to multiple pollutants; yield biased estimates of individual pollutant effects due to collinearity with other pollutants when applied in a risk assessment. Multipollutant statistical approaches take into consideration collinearity by identifying mixtures of air pollutants that are often commonly emitted from specific sources. Applying a new proof-of-concept version of the environmental Benefits Mapping and Analysis Program—Community Edition (BenMAP-CE) we aim to answer two questions: (1) can effect coefficients from epidemiologic studies employing multipollutant statistical approaches, specifically joint effect models, be employed in air pollution risk assessments? And, (2) how does the procedure for quantifying population health impacts differ between the single and multipollutant context?

Methods Two recent studies employ joint effect models with and without first-order pollutant interactions to estimate the risk of air pollutant-attributable asthma emergency department visits in Atlanta (Winquist et al. 2014) and the state of Georgia (Xiao et al. 2016). Within these studies, associations are examined in relation to short-term exposures to the criteria pollutants: ozone, fine particulate matter, carbon monoxide, nitrogen dioxide, and sulfur dioxide, along with particulate matter components, which collectively represent predefined source groupings (i.e., oxidant gases, secondary pollutants, traffic, power plant, and criteria pollutants). We use the effect coefficients and variance/co-variance matrices from these two studies along with daily air quality predictions from a photochemical transport model in the BenMAP-CE software program to perform an illustrative case study for the city of Atlanta and the state of Georgia.

Results We find that: (1) the interaction models yield larger estimates of pollutant-attributable asthma emergency department visits, irrespective of pollutant group; (2) warm season impacts are greater than cold season impacts, irrespective of pollutant group; (3) certain groups, including the power plant and secondary pollutant groups, yield a negative number of cases. The BenMAP-CE software runtime for each multi-pollutant model was commensurate with the runtime for single pollutant models.

Conclusions This proof-of-concept analysis suggests that air pollutant risk assessments of multipollutant exposures are indeed feasible, but are data-intensive. Future risk assessments that consider both single and multipollutant approaches have the potential to provide a more comprehensive evaluation that can inform air quality management strategies.

* Study not funded by HEI.

Gradients in Concentration and Composition of Fine Particulates in a Coastal City: Downtown Dominates a Large Area Emission Source in Port of Oakland, CA*

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Background Organic aerosol (OA) contributes a significant fraction of atmospheric fine (< 2.5 μm) particulate matter (PM) mass, which is of concern for its detrimental effects on human health. Owing to the presence of congested, diverse emission sources ("hotspots"), populous areas have large spatial gradients in OA concentration and composition.[1] As of 2014, more than half of the world's population lives in urban areas.[2] Hotspots in such densely populated areas must be identified for addressing socio-economic disparity in exposure to pollution.

The city of Oakland, California is one such densely populated (~ 2900 km^{-2}) urban area with a poverty rate roughly twice as much as that of the San Francisco (SF) Bay area.[3] Further, Oakland has a 1 km^2 downtown, a 6 km^2 residential district as well as one of the largest US shipping ports (5 km^2) all within a short spatial transect of 4 km. Four interstate highways closely flank this domain. Dominant wind directions are westerly from SF.

Methods In July 2017, we conducted mobile air quality measurement for 20 days on the streets of Oakland. On-board was a high-resolution aerosol mass spectrometer along with other gas and particulate measurement instruments. We varied the sampling route daily so that certain areas were not systematically sampled in morning versus afternoon.

Results The overall mass-based composition of PM was 50% organic, 23% sulfate, 10% nitrate, 3% black carbon, with other species making up the balance. We find that OA in downtown Oakland is consistently higher and spatially variable (5.8 ± 2.4 μgm^{-3}) compared to the larger area source, the port of Oakland (5.0 ± 1.6 μgm^{-3}) as well as the largely residential West Oakland neighborhood (4.4 ± 1.14 μgm^{-3}). Further, organic signals of cooking and vehicular emission are influenced by time of day: while vehicular OA dominates during morning rush hour, it is overwhelmed by cooking OA after 10 AM. Lastly, through source-apportionment, we identify the dominant fraction of OA to be "semi-fresh" i.e., organic emissions that have undergone a few hours of atmospheric processing. When winds are blowing from SF, we find elevated amounts of semi-fresh OA, suggesting that Oakland experiences elevated OA carried downwind from SF.

Conclusions We measured gradients in concentration and composition of OA in Oakland. Our results show that this relatively low-income city is exposed to processed emissions carried downwind from urban SF, in addition to intra-city cooking and vehicular emission congestion in downtown. These findings have important environmental justice and human exposure implications.

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Investigation of Confounding in Air Pollution Epidemiology Studies Using a Large Medicare Beneficiary Dataset*

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Background Confounding of air pollution impacts on health has been a long-standing concern for epidemiological studies, especially long-term studies where risk factors may vary substantially over time. Studies and methods examining the potential for confounding are thus a high priority. Methodology to address confounding was developed by Greven et al. (2011), who parsed the association between chronic exposure to fine particulate matter ($PM_{2.5}$) and life expectancy into that for "global" (temporal) and "local" (spatio-temporal) $PM_{2.5}$, with unequal coefficients evidence of unmeasured confounding. The goal of our study was to investigate these findings and their robustness in more detail by expanding the database and including additional analyses.

Methods We developed a database of over 20 million Medicare beneficiaries over the period 2000-2012, with each beneficiary linked to $PM_{2.5}$, ozone, and NO_2 monitoring data. Log-linear models adjusted for age, gender, and race were fit to assess the association of 1-year $PM_{2.5}$ exposures and monthly mortality rates. Potential confounding by long-term time trends in $PM_{2.5}$ was examined and adjusted for by (1) calculating residuals of $PM_{2.5}$ on calendar year; and (2) addition of either a spline for time or temporal $PM_{2.5}$ into health models. For cause-specific analyses, beneficiary data from 2000-2008 were used and adjustment was made for neighborhood-level covariates. Cause-specific mortality rate ratios (MRRs) were calculated per 10 $\mu g/m^3$ $PM_{2.5}$ and per 10 ppb ozone and NO_2. For all analyses, exposure measures were decomposed into temporal and spatio-temporal components.

Results For the analysis incorporating temporal trends in $PM_{2.5}$, we found a 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure to be associated with a 1.20 times (95% CI:1.20, 1.21) higher risk of mortality across the 13-year study period, with the magnitude of the association decreasing with shorter study periods. MRRs remained statistically significant but were attenuated when models were adjusted for long-term time trends in $PM_{2.5}$. The residual-based, time-adjusted MRR equaled 1.12 (95% CI:1.11, 1.12) per 10 $\mu g/m^3$ for the 13-year study period and was uniform across study period length. Spline- and decomposition-based approaches produced lower but less stable MRRs (1.03 [95% CI: 1.02, 1.04] and 1.06 [95% CI: 1.06, 1.07], respectively). Cause-specific analyses revealed significant, positive associations between $PM_{2.5}$ and NO_2 and both respiratory- and cardiovascular-related deaths; however, unmeasured confounding remained. Ozone results were dependent on the exposure metric, with warm season 1-hr daily maximum ozone significantly associated with a number of causes of death, 8-hr daily maximum exposures showing mixed results, and 24-hour average metrics not statistically significant.

Conclusions This large dataset of Medicare beneficiaries serves as a valuable tool to investigate confounding in long-term air pollution epidemiology studies. Our findings to date suggest significant associations of long-term air pollutant exposures and mortality; however, controlling for long-term temporal trends in $PM_{2.5}$ reduced MRRs by 40-85%, depending on the method used. Other sources of unmeasured confounding also remained.

* Study not funded by HEI.

Progress with HEI's Energy Research Program

Donna Vorhees, Anna Rosofsky (Presenter), Kathryn Liziewski, Daniel Greenbaum, Robert O'Keefe, and Rashid Shaikh

Health Effects Institute, Boston, MA, USA

Purpose of the Energy Research Program Sound energy policy depends on reliable and credible information about the risks and benefits of our energy source choices. HEI's vision for the Energy Research Program (the "Program") is to provide this critical information, starting with an improved understanding of the potential human exposure and health effects from the onshore development of oil and natural gas from shale and other unconventional resources ("UOGD"). The Program is designed to answer a subset of the research questions defined in a 2015 Strategic Research Agenda prepared by HEI's Special Committee on Unconventional Oil and Gas Development. The Program represents an expansion of HEI's model to address questions involving not only oil- and gas-related emissions to air, but also releases to water and other potential points of exposure that might have health effects.

Year 1 Progress and Products During the first year of the program, HEI's new Initial Energy Research Committee (the "Committee") is publishing impartial, critical reviews of the relevant human health and exposure literature. The critical reviews will explore potential human exposures and health effects associated with oil and natural gas development from unconventional resources. The Committee is reviewing hundreds of reports and peer-reviewed scientific papers related to all UOGD phases that might affect nearby communities. The phases include exploration, well pad construction, drilling and completion, production, well closure, and site reclamation as well as all ancillary facilities (e.g., compressor stations, processing facilities, and gathering pipelines) and waste management (e.g., deep well injection, landfilling, and recycling of wastewater). The literature reviews will summarize what is known and what knowledge gaps remain. Findings from the critical reviews will help to facilitate HEI's planning for population-level exposure research in multiple U.S. regions, beginning in Year 2 of the Program.

These reviews will benefit those in society who are trying to navigate the growing and sometimes conflicting body of information on this topic. Those benefiting might include governmental authorities, including regulators, people living in communities affected by oil and gas, industry, environmental and public health NGOs, and academics.

HEI kicked off its new Energy Research Program with a public meeting on January 17, 2018. Hosted by the Committee, the meeting brought together a wide range of stakeholders to discuss recommendations for Year 1 of the program. Throughout program implementation, HEI will continue to engage with stakeholders at important programmatic intervals.

Vision for Year 2 and Beyond HEI expects to fund population-level exposure research in 2 or 3 major oil- and natural gas-producing regions of the United States starting in Year 2 of the Program. We will present highlights from the Energy Research Committee's planning efforts to date.

State of Global Air 2018

Katherine Walker[1], Michael Brauer[2,3], Hilary Polk[1], Annemoon van Erp[1], Kathryn Liziewski[1], and Aaron Cohen[1,3]

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HEI has just released its second edition of the State of Global Air report and interactive website (*www.stateofglobalair.com*). We have plans to expand the data, metrics, and other information provided on the site every year.

We invite you to stop by and take a look. Let us know how you have used the data from the site, share your views on what information, graphics, or technical capabilities would make the site more informative or useful. We welcome ideas for collaboration on future additions to the site.

What is the State of Global Air?

The State of Global Air report brings into one place the most recent data available from the latest IHME Global Burden of Disease study (2016) on the levels and trends in air quality and health for countries around the globe. This year we focus not only on ambient $PM_{2.5}$ and ozone but also, for the first time, on *household air pollution* from the burning of solid fuels for cooking and heating, a major contributor to pollution both inside and outside the home.

Who is it for?

The report is designed to introduce citizens, journalists, policy makers, and scientists to efforts to estimate and track human exposure to outdoor and household air pollution and their impacts on health as part of the comprehensive Global Burden of Disease project.

How can I explore the data?

This report has a companion interactive website (*www.stateofglobalair.com*), which provides the tools to explore, compare, and download data tables and graphics with the latest ambient and household air exposures and associated burden of disease, including associated estimates of uncertainty. This year's site also provides data on the combined burden from ambient and household exposures. Health burden estimates include deaths, disability adjusted life years (DALYs) and their respective age-standardized rates. These data are available for individual countries and geographic and economic regions, as well as for highlighting trends from 1990 to 2016.

Fine Particulate Matter Pollution and Human Mortality in Beijing, China: An Investigation of the Shape of the Concentration–Response Association*

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Background The short-term association between particulate matter (PM) and mortality has been well-studied in the U.S. and Europe, where the concentration–response association has been found to be approximately linear. However, PM concentrations in typical Chinese mega-cities extend well beyond typical levels in western communities, and limited investigations of the concentration–response shape in Chinese cities have resulted in conflicting findings. Incorrect specification of this association could have important implications in health risk assessments of PM in China.

Methods We investigated the shape of the short-term associations between $PM_{2.5}$ and deaths (all non-accidental, circulatory, and respiratory) in Beijing, China, 2009-2012. First, we fit generalized linear models of mortality risk as either a linear or smooth function of $PM_{2.5}$, controlling for season, weather, and day of week, and compared models using QAIC and cross-validation. Further, we tested a model with separate slopes and intercepts within subsets of $PM_{2.5}$ concentrations. Finally, to determine the sensitivity of health impact assessment to the assumed association shape, we estimated deaths attributable to $PM_{2.5}$ in Beijing using both linear and non-linear concentration–response associations.

Results For non-accidental and circulatory mortality, concentration–response associations were consistent with a linear function of $PM_{2.5}$, even at the high $PM_{2.5}$ concentrations experienced in Beijing. However, for respiratory mortality, results suggest an association that levels off at $PM_{2.5}$ above approximately 100 $\mu g/m^3$. Estimated health impacts for $PM_{2.5}$ were somewhat lower for non-accidental and circulatory deaths when using a non-linear concentration–response association compared to a linear association, but higher for respiratory deaths.

Conclusions Consistency of concentration–response associations for mortality and $PM_{2.5}$ based on linear and smooth functions varied for different outcomes. These findings suggest that non-linear concentration–response associations may be important to consider for health impact assessments of PM in China, particularly for respiratory deaths.

* Study not funded by HEI.

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