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Advances in Understanding Air Pollution and Cardiovascular Diseases: The Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air)

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Abstract

The Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) leveraged the platform of the MESA cohort into a prospective longitudinal study of relationships between air pollution and cardiovascular health. MESA Air researchers developed fine-scale, state-of-the-art air pollution exposure models for the MESA Air communities, creating individual exposure estimates for each participant. These models combine cohort-specific exposure monitoring, existing monitoring systems, and an extensive database of geographic and meteorological information. Together with extensive phenotyping in MESA—and adding participants and health measurements to the cohort—MESA Air investigated environmental exposures on a wide range of outcomes.

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Advances by the MESA Air team included not only a new approach to exposure modeling but also biostatistical advances in addressing exposure measurement error and temporal confounding. The MESA Air study advanced our understanding of the impact of air pollutants on cardiovascular disease and provided a research platform for advances in environmental epidemiology.

A. Introduction

Heart disease is the leading cause of death in the US and several studies have suggested that, like cigarette smoking or stress, exposure to air pollutants is an important risk factor for cardiovascular morbidity and mortality. Studies in animals have shown relationships between air pollution exposure and cardiovascular effects, such as atherosclerosis. Human cross-sectional, time-series, and cohort studies have found that people living in communities experiencing higher levels of air pollution have more frequent cardiovascular disease events. However, few studies have been able to look at the health effects of air pollution levels on specific individuals over long periods of time. Prior studies of the long-term effects of air pollution on cardiovascular health were built—after the fact—on studies designed to assess either other risk factors or other outcomes. The MESA Air study was uniquely designed to look at the prospective relationship between air pollution exposure and the development of cardiovascular disease and includes intensive individual participant measures of health and subclinical disease processes.¹

MESA Air measured subclinical markers of arteriosclerosis and atherosclerosis -- calcification of the coronary arteries and thickness of artery walls -- in a population of 7,551 older adults who were free of cardiovascular disease at enrollment and estimated the amount of air pollution experienced by these people over the course of more than 10 years. In order to create these air pollution estimates, MESA Air investigators collected thousands of air samples in the places where the study participants lived, including samples at many of their houses. Throughout the course of the study, MESA and MESA Air repeatedly measured coronary artery calcium (CAC) and carotid artery wall thickness (Intima-Media Thickness or IMT) to determine the extent and rate of development of atherosclerosis. MESA Air then examined the relationship between each person's exposure to air pollution and their development of atherosclerosis, while accounting for many other factors about each person including demographics and other health factors. MESA and MESA Air also carefully tracked cardiovascular events -- like heart attacks -- in this population, to see if these events were associated with higher levels of air pollution.

Concentrations of air pollutants are continuing to decrease in the United States,^{2, 3} which is a victory for public health. MESA Air is positioned to understand these concentration differences over time and the resulting impact on health endpoints.

A.1. Study population

MESA Air is an ancillary study to MESA, a long-term study of the progression of cardiovascular disease in adults, which included 6,814 participants from six US communities: Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN. MESA participants were aged 45–84 years at enrollment

between 2000 and 2002, with an approximately equal gender ratio, and were free of recognized cardiovascular disease at baseline. Four ethnic/racial groups were targeted for inclusion: non-Hispanic black, Chinese, non-Hispanic white, and Hispanic, but recruitment of racial/ethnic groups varied by study site. All participants provided informed consent before participation.

In order to capitalize on exposure heterogeneity in the vicinity of two existing MESA clinical centers, MESA Air also recruited new participants in two new communities in Los Angeles and one new community in New York. As with the existing MESA cohort, the recruitment of these participants was community-based. Eligible “New Recruits” for MESA Air were defined as persons living within certain geographic boundaries who, were between the ages of 49 and 88 at recruitment, and were non-Hispanic black, Chinese, non-Hispanic white, or Hispanic and, like MESA participants, had no prior clinically apparent cardiovascular disease at the time of recruitment. New Recruits were selected from Santa Monica/Coastal LA County to represent an upwind, and lower exposure, location relative to the city center. Recruits from Riverside County were selected to represent a downwind location relative to the urban center and as an area with some of the highest pollution levels in the nation. Participants were also recruited from Rockland County, upwind of the New York City region, to have similar regional scale pollution to those participants in North Manhattan and the South Bronx but without the urban contribution to pollutants. In Coastal LA and Riverside, CA, 77 and 80 participants were enrolled, respectively, and 100 participants were enrolled from Rockland County, NY.

The largest portion (n=5,674) of the MESA Air cohort was recruited from the main MESA cohort at a clinical exam, consented to participate in air pollution specific questionnaires and other study-specific components. Another 1,130 MESA participants did not have the opportunity to explicitly consent to the study-specific components of the MESA Air ancillary study, but are included in those analyses where only residential address is required to estimate outdoor air pollutant levels. Thus, more than 99% of the MESA cohort is included in at least some MESA Air analyses. A large MESA ancillary study, MESA Family, was an additional source of consented MESA Air participants. The MESA Family study aimed to recruit 300 siblings of the MESA study participants from each field center, for an investigation of genetic aspects of subclinical cardiovascular disease. MESA Air recruited from this population, limiting recruitment to those residing in the MESA Air communities and who were without cardiovascular disease at study entry, resulting in 490 participants from the MESA Family study recruited to MESA Air.

As described above, MESA Air analyses include as many as 7,551 participants from these three recruitment sources. Additional details regarding participant eligibility, recruitment, and the resulting demographic distributions of the cohort are provided in Kaufman et al. 2012.¹

A.2. Exposure measurements

Intensive community-scale exposure monitoring occurred in the MESA Air regions from July 2005 through July 2009.⁴ All outdoor monitors collected cumulative, time-integrated data over 2-week periods, and samples were analyzed for fine particulate matter (PM_{2.5}),

black carbon (BC), oxides of nitrogen (NO_x), nitrogen dioxide (NO₂), ozone (O₃), sulfur dioxide (SO₂), and trace elements. In ancillary studies, investigators analyzed levels of elemental and organic carbon, endotoxins, and coarse particulate matter (PM_{2.5-10}) at a subset of locations, and extended the analysis of trace metals.^{5, 6} Outdoor monitoring campaigns included fixed monitoring stations, community saturation monitoring, and residential monitoring at participant homes. In addition to predicting air pollutant concentrations outdoors at participants' homes, the MESA Air exposure assessment also estimated the amount of outdoor pollutants infiltrated indoors and encountered by participants. To inform these models, MESA Air collected 526 two-week, paired indoor-outdoor PM_{2.5} filter samples from a subset of study homes.^{4, 7} PM_{2.5} elemental composition was measured by X-ray fluorescence, and infiltration efficiencies were estimated as the indoor/outdoor sulfur ratio in collected fine particles. To evaluate sources of measurement variation and assumptions underlying the MESA Air exposure estimates, a subset of participants was also recruited for personal monitoring. Personal sampling included PM_{2.5}, BC, trace elements, NO₂, NO_x, and SO₂. A total of 90 participants completed the two-week personal sampling component of MESA Air.⁴

Every MESA Air participant was asked to complete a comprehensive MESA Air Questionnaire (MAQ) at recruitment.⁸ The MAQ was the primary data collection tool for gathering information on home characteristics relevant to pollutant infiltration efficiencies and about behaviors related to individual exposures and was repeated up to six times during follow up-phone calls and a later clinic exam. Repeated administration was triggered for participants who indicated a major change in lifestyle (change in residence, work or school status, caregiver status, or in household members). Questions asked about home characteristics related to building type, building age, the presence of an attached garage, and other factors relevant to infiltration. Participants were also asked specific questions about their typical time-location patterns in winter and summer and could designate if their patterns were the same in both seasons. For each day of the week, the MAQ included questions documenting hours spent in each of seven locations: home indoors, home outdoors, work/volunteer/school indoors, work/volunteer/school outdoors, in transit (e.g., car, bike), other indoors, and other outdoors. Participants also designated which days of the week they considered weekends and weekdays. The amount of time by transit mode (e.g., walking/biking, car/taxi, bus, train/subway), road types travelled (e.g., freeways, residential streets), and traffic conditions experienced (e.g., light traffic/moving at the speed limit) were also documented.

B. Exposure assessment / Air pollution modeling

MESA Air developed state-of-the-art air pollution prediction models for each of the MESA Air communities. In so doing, models provided very precise and finely-resolved exposure estimates at each participant's residence, in a manner especially well-suited for the study of long-term health effects. In the process of developing modern and efficient statistical approaches for the MESA Air communities, MESA Air researchers developed novel modeling approaches, which could then estimate exposures at other locations and in other time periods. Even without the specialized information available on the MESA cohort during

the period of the cohort's follow-up, they represent advances in the ability to predict individual-level air pollution concentrations throughout the US from 1980 to the present.

B.1. Models for MESA Air cities

Individual-level exposure to outdoor ambient-source air pollutants was estimated for 7,551 MESA and MESA Air study participants.⁹⁻¹¹ MESA Air researchers developed a unified modeling approach for predicting PM_{2.5}, NO₂, NO_X, BC (as measured by light absorption coefficient),⁹ O₃,¹¹ and most recently four PM_{2.5} components: elemental carbon, organic carbon, sulfur, and silicon.¹² These exposure estimates incorporated data from several sources including: extensive, project-specific air monitoring programs within the study communities and at participants' homes, involving the deployment of over 7,400 monitors collecting cumulative, time-integrated data over two-week periods throughout a four-year period; all available Air Quality System (AQS) monitoring data reported by the US EPA¹³; and a custom-built, comprehensive database of more than 800 geographic and traffic-related variables providing information such as subject residential proximity to potential exposure sources. These data sources were integrated via a unified spatio-temporal exposure model to estimate each participant's predicted residential pollutant concentration for ambient-source PM_{2.5} and gaseous pollutants for every two-week period from the year prior to recruitment (1999), over the entire study period (year 2012, at the time of writing).

Region-specific models included a long-term spatial mean, temporal trends with spatially-varying coefficients, and a spatio-temporal residual. Prediction accuracy was high for most models, with a cross-validation R² greater than 0.80 at regulatory and fixed monitoring sites for most regions and pollutants.^{9, 11} Model prediction accuracy for four PM_{2.5} components (sulfur, silicon, elemental carbon, and organic carbon) was reasonably high for all except silicon.¹² These complex models capture both spatial and temporal variability in these pollutants. Figure 1 shows annual average predictions of PM_{2.5} for Los Angeles for the years 2000, 2004, 2008, and 2012, demonstrating changes in fine particulate concentrations over time. Figure 2 shows the fine scale spatial variability these models are able to capture for a single year. An important outcome of the MESA Air modeling effort is the development of flexible spatio-temporal modeling methods for environmental exposures with spatial and spatio-temporal covariates and irregular monitoring data, which is available for R users as the SpatioTemporal package.^{14, 15}

B.2. National Models

MESA Air researchers developed regionalized national universal kriging models for annual average PM_{2.5} and NO₂ across the U.S.^{16, 17} The NO₂ model also incorporated satellite tropospheric data. These models demonstrated very high levels of cross-validated accuracy of prediction with overall R² of 0.85 or more and well-calibrated prediction intervals. MESA Air investigators have also developed national spatial exposure models that used partial least squares and universal kriging to estimate annual average concentrations of four PM_{2.5} components: elemental carbon (EC), organic carbon (OC), silicon (Si), and sulfur (S).¹⁸ Our models performed well, with cross-validated R² values ranging from 0.62 to 0.95.¹⁸ Subsequent national models were generated for SO₂, sulfate, nitrate, nickel, vanadium, copper, arsenic and chromium.⁵ This new generation of highly accurate modeling

approaches, enabled by the MESA Air project, can be used to predict ambient air pollution concentrations for other study populations, with a few of the collaborations to date described below.

B.3. Historical Models

In addition to the unified spatio-temporal model that was used to generate predictions covering the main period of MESA and MESA Air follow up (1999-2012), a new exposure model has been recently developed and validated that is capable of estimating PM_{2.5} exposures from 1980 through 2012.^{19, 20} This spatio-temporal historical prediction model was developed using historical geographic predictors and annual average PM_{2.5} data from 1999 through 2012 taken from the EPA Federal Reference Method (FRM) network with supplemental data from the Interagency Monitoring of Protected Visual Environments (IMPROVE) sites located predominantly in rural areas. The model uses a temporal basis function with a spatially varying coefficient to represent smooth spatio-temporal variability. The spatially varying coefficients are modeled in universal kriging frameworks using geographic predictors. The temporal trend in annual averages of PM_{2.5} before 1999 was estimated using extrapolation based on PM_{2.5} data for 1999-2012 in FRM and IMPROVE. The model was validated using external sources of PM_{2.5} data collected before 1999 from IMPROVE for 1990-1998 (not used for model fitting), California Air Resources Board dichotomous sampler monitoring, the Children's Health Study, and the Inhalable Particulate Network. The historical PM_{2.5} prediction model performed well ($R^2 = 0.85-0.91$) in the validation using IMPROVE data for 1990-1998 when a relatively large number of sites were available. This historical prediction modeling approach allows us to assess health effects associated with long-term exposures to PM_{2.5} over extended time periods, capitalizing on the extensive residential history data available in MESA and MESA Air. While these models cannot perform with the same effectiveness as the MESA Air models from 1999-2013, these new historical models will permit meaningful assessment of long-term concentrations to an unprecedented extent for epidemiological analyses. As with our other exposure models, these approaches can be used to predict historical ambient air pollution concentrations for other study populations throughout the contiguous United States, and have begun to be used in collaborative efforts in several cohorts.

B.4. Infiltration and time-location patterns

In addition to estimating outdoor concentrations, the MESA Air group successfully employed individual-level, questionnaire-derived data on residential characteristics in order to calculate infiltration efficiencies for all of the residences in which each participant lived during the MESA Air study.⁷ These infiltration models predicted 60% of the variance in two-week residential infiltration efficiency estimates. This allowed the estimation of concentrations of ambient-source pollution in indoor environments. MESA Air researchers also investigated the time-location patterns of the MESA cohort and found that the time spent in home, work, vehicle, and other locations varied by gender, age, race/ethnicity, income, education, and employment status.^{8, 21} These resources can be applied to other similar populations.

B.5. Exposure relationships

The MESA Air research platform has allowed investigators to explore how exposures to other environmental stressors interact or correlate with exposures to air pollution. Examples include investigations into the relationships between air pollution exposures and biomarkers (e.g., metals in urine) and related exposures (e.g., noise). MESA Air investigators found a positive association of PM_{2.5} levels with urinary tungsten and also some evidence of an association with urinary uranium but did not see any relationship to urinary cadmium or antimony.²² MESA Air researchers also found a moderate correlation between air pollution and noise.²³

C. Health effects analyses

Using state-of-the-art exposure assessment methods, MESA Air has examined the relationship between exposure to ambient air pollution and cardiovascular, pulmonary, and other health effects with a focus on the development of cardiovascular disease (Figure 3).²⁴⁻²⁶ The prospective nature of MESA Air allowed investigations into a large number of health and physiological measures, and in so doing developed a more comprehensive view of the impact of pollution exposure on the interconnected pathways that result in cardiovascular disease events.

C.1. Cardiovascular health effects

A major aim of MESA Air was to investigate the relationship between air pollution exposures and progression of subclinical cardiovascular disease, and MESA Air researchers recently reported the findings with ten years of repeated CAC measurements. CAC by computed tomography was measured 1-4 times (mean: 2.5) over 10 years in 6,795 MESA Air participants. Estimated residence-specific concentrations of PM_{2.5} and NO_x were averaged between participants' examinations. Relationships between CAC progression and these concentrations were assessed, adjusting for baseline age, sex, race/ethnicity, socioeconomic characteristics, cardiovascular risk factors, site, and computed tomography scanner technology. In this population, mean crude CAC increase was 24 Agatston units/year. Participant-specific pollutant concentrations averaged over the years 2000-2010 ranged from 9.2–22.6 µg PM_{2.5}/m³ and 7.2–139.2 ppb NO_x. For each additional 5 µg PM_{2.5}/m³, CAC progression was accelerated by 4.1 units/yr [95% confidence interval: 1.4, 6.8] and for each 40 ppb NO_x, CAC progression was accelerated by 4.8 units/yr [CI: 0.9, 8.7]. These findings indicate that increased concentrations of fine particulate matter and traffic-related air pollution within metropolitan areas, in ranges commonly encountered worldwide, are associated with progression in coronary artery calcification, consistent with acceleration of atherosclerosis.²⁷

Although not explicitly related to air pollution, MESA Air researchers also examined the relationship between CAC progression and other cardiovascular disease risk factors, using an innovative application of mixed-effects models to adjust for modeled baseline and time-varying risk factors, and making use of the 10 year follow-up CAC information provided by MESA Air support.²⁸ Positive associations were observed between CAC progression and

anticipated predictors of atherosclerosis progression such as age, male sex, hypertension, and diabetes.

Other key cardiovascular health findings—MESA Air researchers and collaborating investigators have examined relationships between air pollution exposures and numerous cardiovascular disease endpoints. Positive associations were found between long-term air pollution and markers of inflammation and coagulation including C-reactive protein, interleukin-6, and d-dimer and between short-term exposures and E-selectin, a marker of endothelial activation.^{29, 30} Long-term PM_{2.5} exposure was significantly associated with decreased endothelial function according to brachial ultrasound results.³¹ MESA Air researchers investigated the association between air pollution and the microvasculature via retinal photography and found that both long-term and short-term increased residential concentrations of air pollution were each associated with narrower retinal arteriolar diameters.³² Acute exposures to particulate air pollution were associated with lower heart rate variability, and this relationship was stronger in individuals with metabolic syndrome.³³ There was only a weak relationship between coarse PM exposure and heart rate variability.³⁴ Short- and long-term exposure to air pollutants were found to be positively associated with increases in systolic blood and pulse pressure.^{35, 36}

An elevated but non-significant relationship was found between PM_{2.5} and aortic calcification.³⁷ Higher levels of NO₂ exposure were associated with greater right ventricle mass and larger right ventricle enddiastolic volume.³⁸ Long-term particle mass exposure did not appear to be associated with greater arterial stiffness in the MESA Air cohort.³⁹ Living in close proximity to major roadways is associated with higher left ventricular mass, suggesting chronic vascular end-organ damage from a traffic-related environmental exposure.^{40, 41} Using measurements of QT interval and QRS duration from 12-lead ECGs, MESA Air researchers demonstrated an association between long-term exposure to air pollution and ventricular repolarization and conduction abnormalities in adults without clinical cardiovascular disease, independent of subclinical coronary arterial calcification.⁴² A cross-sectional analysis of circulating adhesion molecules demonstrated evidence of an association between air pollution and several markers of adhesion, including Chemokine (C-C motif) ligand 21 (CCL21).⁴³

C.2. Other air pollution health effects in MESA

In addition to cardiovascular effects, MESA Air investigators have also investigated the relationship between air pollution and pulmonary health effects, diabetes, and other health effects in the MESA Air cohort. Cross-sectional analyses did not demonstrate a relationship between air pollution exposure and percent emphysema,⁴⁴ but MESA Air researchers found that long-term PM_{2.5} exposure may contribute to subclinical pulmonary vascular differences.⁴⁵ A recent study found a cross-sectional association between several urinary catecholamines and long-term residential concentrations of PM_{2.5} and NO_x, and these novel findings support the hypothesis that air pollutant exposures are related to sympathetic nervous system activation.⁴⁶ MESA Air researchers found that exposure to air pollution (PM_{2.5} and NO₂) was associated with prevalent type-2 diabetes at baseline but not with incident diabetes after nine years of follow-up.⁴⁷ Exposure to higher levels of PM_{2.5} over a

three-month period was associated with reduced HDL cholesterol particle concentration.⁴⁸ In analyses of long term air pollution exposure and “global” DNA methylation, there was little association between PM_{2.5} and long interspersed nucleotide elements (LINE-1) methylation or Alu methylation.⁴⁹ In our analyses thus far, no relationship has been established between air pollution exposure and erectile dysfunction⁵⁰ or non-alcoholic fatty liver disease.⁵¹

C.3. Air pollution health effects using MESA Air exposure models in other populations

Using exposure models which leveraged the MESA Air work, researchers have conducted investigations in a number of other cohorts including the Sister Study, the Parkinson's, Genes and Environment (PAGE) study, the Women's Health Initiative, and the Chicago Healthy Aging Project (CHAP). In a study of adult asthma in women, researchers found that PM_{2.5} exposure increases the risk of developing asthma and that PM_{2.5} and NO₂ increase the risk of developing wheeze, the cardinal symptom of asthma.⁵² A study of aging found a relationship between long-term NO_x exposure and declines in age-related physical disability.⁵³ In the Women's Health Initiative, an increase in PM_{2.5} exposure was associated with an increased risk of a cardiovascular disease event.⁵⁴ Although there was not strong evidence for an association between exposures to ambient PM₁₀, PM_{2.5}, or NO₂ concentrations and risk of Parkinson's disease in older adults, subgroup analyses suggested that female nonsmokers exposed to higher concentrations of PM₁₀ or PM_{2.5} may have a higher risk for Parkinson's disease.⁵⁵

Air pollution and socioeconomic status—MESA Air researchers examined associations between air pollutant concentrations (outdoor PM_{2.5} and NO_x) and both individual and neighborhood socioeconomic status.^{54, 56} One of the important features of this work was the determination that neighborhood SES was more strongly associated with air pollution concentrations than was SES at the individual level. Since neighborhood SES has been associated with cardiovascular health outcomes, this finding has influenced subsequent air pollution health effects analyses to include a neighborhood SES index as a covariate in statistical models, thus reducing potential confounding. Furthermore, research also suggested that low SES communities are exposed to higher concentrations of air pollution, but interestingly there is some heterogeneity by site. In New York City specifically, high SES individuals were exposed to higher concentrations of air pollution, a result only rarely reported in the US environmental justice literature.

The MESA Air group also investigated the association between air pollution and racial residential segregation.⁵⁷ Some theoretical work has suggested that residential segregation is one factor which produces and maintains differential levels of air pollution across the population, but little empirical work was available to support this notion. Ours was one of the first analyses to examine this association empirically and found that neighborhoods where Hispanics were overrepresented were indeed experiencing higher outdoor concentrations of both PM_{2.5} and NO_x.

Additionally, MESA Air has examined the role of sociodemographic and psychosocial characteristics in modifying associations between air pollution exposure and cardiovascular

outcomes. MESA Air research has examined the modifying effect of race/ethnicity, racial residential segregation, low socioeconomic status and psychosocial stress on the association between three air pollutants ($PM_{2.5}$, NO_2 , and NO_X) and two markers of cardiovascular health, left-ventricular mass index and left-ventricular ejection fraction.⁵⁸ Compared with White participants, Black participants showed a stronger adjusted association between air pollution and left-ventricular mass index. There was no evidence for a modifying role of any of the other social factors or of left-ventricular ejection fraction. The modifying role of social and psychosocial factors on associations between exposure to $PM_{2.5}$, and blood pressure measures was also examined.⁵⁹ There was no evidence of synergistic effects of higher $PM_{2.5}$ and adverse social/psychosocial factors on blood pressure. In contrast, there was some evidence of stronger associations of $PM_{2.5}$ with blood pressure in higher socioeconomic status groups.

D. Biostatistical method advancements

MESA Air investigators have made significant and important contributions to the field of measurement error in two-stage air pollution epidemiology studies.^{18, 60-66} This work specifically contributes to our broader understanding of the sources and impacts of measurement error on estimation of health effects in air pollution cohort studies, and, more importantly, how to design exposure models to minimize the impact of this error and correct for it using post-hoc bootstrap and asymptotic calculations.

Additional work examining appropriate methods to adjust for unmeasured temporal confounding in estimating acute air pollution health effects in cohort studies has also been developed and published by MESA Air investigators.⁶⁷ This work provides conditions under which traditional time series methods for semi-parametric regression may validly be utilized in cohort studies and also develops a more efficient pre-adjustment method that utilizes all available exposure data, including monitoring data available on days when health outcomes are not measured. Taken together, the methodological work produced by MESA Air investigators represents a major contribution to the field of air pollution epidemiology at the national, community, and individual levels.

MESA Air biostatistics researchers have also published on methods for selecting and combining data from multiple sources,⁶⁸ exposure estimation,^{69, 70} choice of exposure prediction models,^{6, 71-73} and reduced-rank spatio-temporal modeling.

E. Conclusions

MESA Air was designed to provide the most advanced approach possible to define the relation between air pollution exposure and cardiovascular disease.¹ With the first fully prospective cohort study of this relationship, MESA Air effectively merges state-of-the-art cardiovascular epidemiology with cutting edge exposure assessment, including comprehensive, study-specific air pollution monitoring and novel spatio-temporal exposure modeling. MESA Air's research contributions include the development of city-specific and national exposure models of air pollutants, extensive exposure monitoring, innovative health outcomes assessments (e.g., CAC progression), analyses of relationships between air

pollution and a wide variety of outcomes with a focus on cardiovascular health, and biostatistical method development.

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References

1. Kaufman JD, Adar SD, Allen RW, Barr RG, Budoff MJ, Burke GL, Casillas AM, Cohen MA, Curl CL, Daviglus ML, Diez Roux AV, Jacobs DR Jr, Kronmal RA, Larson TV, Liu SL, Lumley T, Navas-Acien A, O'Leary DH, Rotter JJ, Sampson PD, Sheppard L, Siscovick DS, Stein JH, Szpiro AA, Tracy RP. Prospective study of particulate air pollution exposures, subclinical atherosclerosis, and clinical cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). *American Journal of Epidemiology*. 2012; 176(9):825–837. [PubMed: 23043127]
2. USEPA. Air Quality Trends. U.S. Environmental Protection Agency; 2015.
3. USEPA. Our Nation's Air - Status and Trends though 2010. Standards, OoAQPa, editor. U.S. Environmental Protection Agency; Research Triangle Park, NC: 2012.
4. Cohen MA, Adar SD, Allen RW, Avol E, Curl CL, Gould T, Hardie D, Ho A, Kinney P, Larson TV. Approach to estimating participant pollutant exposures in the Multi-Ethnic Study of Atherosclerosis and air pollution (MESA air). *Environmental Science & Technology*. 2009; 43(13):4687–4693. [PubMed: 19673252]
5. Vedal, S.; Kim, S.; Miller, K.; Fox, J.; Bergen, S.; Gould, T. Research Report 178). Health Effects Institute; Boston, MA: 2013. NPACT epidemiologic study of components of fine particulate matter and cardiovascular disease in the MESA and WHI-OS cohorts..
6. Zhang K, Larson TV, Gasset A, Szpiro AA, Daviglus M, Burke GL, Kaufman JD, Adar SD. Characterizing Spatial Patterns of Airborne Coarse Particulate (PM10–2.5) Mass and Chemical Components in Three Cities: The Multi-Ethnic Study of Atherosclerosis. *Environmental health perspectives*. 2014; 122(8):823. [PubMed: 24642481]
7. Allen RW, Adar SD, Avol E, Cohen M, Curl CL, Larson T, Sally Liu L, Sheppard L, Kaufman JD. Modeling the residential infiltration of outdoor PM2. 5 in the multi-ethnic study of atherosclerosis and air pollution (MESA Air). *Environmental health perspectives*. 2012; 120(6):824. [PubMed: 22534026]
8. Spalt EW, Curl CL, Allen RW, Cohen M, Adar SD, Stukovsky KH, Avol E, Castro-Diehl C, Nunn C, Mancera-Cuevas K. Time–location patterns of a diverse population of older adults: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). *Journal of Exposure Science and Environmental Epidemiology*. 2015; 26(4):349–355. [PubMed: 25921083]
9. Keller JP, Olives C, Kim S-Y, Sheppard L, Sampson PD, Szpiro AA, Oron AP, Lindström J, Vedal S, Kaufman JD. A Unified Spatiotemporal Modeling Approach for Predicting Concentrations of Multiple Air Pollutants in the Multi-Ethnic Study of Atherosclerosis and Air Pollution. *Environmental health perspectives*. 2014; 123(4):301–309. [PubMed: 25398188]
10. Sampson PD, Szpiro AA, Sheppard L, Lindström J, Kaufman JD. Pragmatic estimation of a spatio-temporal air quality model with irregular monitoring data. *Atmospheric Environment*. 2011; 45(36):6593–6606.

11. Wang M, Keller JP, Adar SD, Kim S-Y, Larson TV, Olives C, Sampson PD, Sheppard L, Szpiro AA, Vedal S. Development of Long-term Spatiotemporal Models for Ambient Ozone in Six Metropolitan regions of the United States: The MESA Air Study. *Atmospheric Environment*. 2015
12. Kim S-Y, Sheppard L, Bergen S, Szpiro AA, Sampson P, Kaufman JD, Vedal S. Prediction of fine particulate matter chemical components with a spatio-temporal model for the Multi-Ethnic Study of Atherosclerosis cohort. *Journal of Exposure Science and Environmental Epidemiology*. 2016 Advance online publication.
13. Air Quality System (AQS). [<https://www.epa.gov/aqs>]
14. Lindström J, Szpiro AA, Sampson P, Bergen S, Oron AP. SpatioTemporal: Spatio-Temporal Model Estimation. R package version 1.1. 2012
15. Lindström J, Szpiro AA, Sampson PD, Oron AP, Richards M, Larson TV, Sheppard L. A flexible spatio-temporal model for air pollution with spatial and spatio-temporal covariates. *Environmental and ecological statistics*. 2014; 21(3):411–433. [PubMed: 25264424]
16. Sampson PD, Richards M, Szpiro AA, Bergen S, Sheppard L, Larson TV, Kaufman JD. A regionalized national universal kriging model using partial least squares regression for estimating annual PM 2.5 concentrations in epidemiology. *Atmospheric Environment*. 2013; 75:383–392. [PubMed: 24015108]
17. Young MT, Bechle MJ, Sampson PD, Szpiro AA, Marshall JD, Sheppard L, Kaufman JD. Satellite-Based NO₂ and Model Validation in a National Prediction Model Based on Universal Kriging and Land-Use Regression. *Environmental Science & Technology*. 2016
18. Bergen S, Sheppard L, Sampson PD, Kim S-Y, Richards M, Vedal S, Kaufman JD, Szpiro AA. A national prediction model for PM_{2.5} component exposures and measurement error–corrected health effect inference. *Environmental health perspectives*. 2013; 121(9):1017. [PubMed: 23757600]
19. Kim, S-Y.; Olives, C.; Fann, N.; Kaufman, JD.; Vedal, S.; Sheppard, L. International Society for Environmental Epidemiology. Vol. 2015. *Environmental Health Perspectives*; Sao Paulo, Brazil: 2015. Estimation Of Long-Term County-Average PM_{2.5} Concentrations For Area-Level Health Analyses.. Abstract 1129
20. Kim S-Y, Olives C, Sheppard L, Sampson P, Larson TV, Keller JP, Kaufman JD. Historical prediction modeling approach for estimating long-term concentrations of PM_{2.5} in cohort studies before the 1999 implementation of widespread monitoring. *Environmental health perspectives*. 2016 Provisionally Accepted.
21. Spalt EW, Curl CL, Allen RW, Cohen M, Williams K, Hirsch JA, Adar SD, Kaufman JD. Factors influencing time-location patterns and their impact on estimates of exposure: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). *Journal of Exposure Science and Environmental Epidemiology*. 2015; 26(4):341–348. [PubMed: 25921081]
22. Pang Y, Jones MR, Tellez-Plaza M, Guallar E, Vaidya D, Post WS, Kaufman JD, Delaney JA, Navas-Acien A. Association of Geography and Ambient Air Pollution with Urine Metal Concentrations in Six US Cities: The Multi-Ethnic Study of Atherosclerosis. *International Journal of Environmental Research and Public Health*. 2016; 13(3):324.
23. Allen RW, Davies H, Cohen MA, Mallach G, Kaufman JD, Adar SD. The spatial relationship between traffic-generated air pollution and noise in 2 US cities. *Environmental research*. 2009; 109(3):334–342. [PubMed: 19193368]
24. Cosselman KN-A, Ana, Kaufman Joel. Environmental Factors in Cardiovascular Disease. *Nature Reviews Cardiology*. 2015; 12(11):627–642. [PubMed: 26461967]
25. Adar S, Kaufman J. Cardiovascular disease and air pollutants: evaluating and improving epidemiological data implicating traffic exposure. *Inhalation Toxicology*. 2007; 19(S1):135–149. [PubMed: 17886061]
26. Gill EA, Curl CL, Adar SD, Allen RW, Auchincloss AH, O'Neill MS, Park SK, Van Hee VC, Roux AVD, Kaufman JD. Air pollution and cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. *Progress in cardiovascular diseases*. 2011; 53(5):353–360. [PubMed: 21414470]
27. Kaufman JD, SD A, Barr RG, Budoff MJ, Burke G, Curl CL, Daviglus M, Diez Roux AV, Gasset A, Jacobs DR Jr, Kronmal R, Larson TV, Navas-Acien A, Olives C, Sampson P, Sheppard L, Siscovick DS, Stein JH, Szpiro AA, Watson KE. Air Pollution and Coronary Artery Calcification

- within Six Metropolitan Areas in the USA. The Multi-Ethnic Study of Atherosclerosis and Air Pollution. The Lancet. 2016 Published online May 24, 2016.
28. Gassett AJ, Sheppard L, McClelland RL, Olives C, Kronmal R, Blaha MJ, Budoff M, Kaufman JD. Risk Factors for Long - Term Coronary Artery Calcium Progression in the Multi - Ethnic Study of Atherosclerosis. *Journal of the American Heart Association*. 2015; 4(8):e001726. [PubMed: 26251281]
 29. Adar SD, D'Souza J, Mendelsohn-Victor K, Jacobs DR Jr, Cushman M, Sheppard L, Thorne PS, Burke GL, Daviglius M, Szpiro AA. Markers of Inflammation and Coagulation after Long-Term Exposure to Coarse Particulate Matter: A Cross-Sectional Analysis from the Multi-Ethnic Study of Atherosclerosis. *Environ Health Perspect*. 2015; 123(6):541–548. [PubMed: 25616153]
 30. Hajat A, Allison M, Diez-Roux AV, Jenny NS, Jorgensen NW, Szpiro AA, Vedal S, Kaufman JD. Long-Term Exposure to Air Pollution and Markers of Inflammation, Coagulation, and Endothelial Activation: A Repeat-Measures Analysis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Epidemiology*. 2015; 26(3):310–320. [PubMed: 25710246]
 31. Krishnan RM, Adar SD, Szpiro AA, Jorgensen NW, Van Hee VC, Barr RG, O'Neill MS, Herrington DM, Polak JF, Kaufman JD. Vascular responses to long-and short-term exposure to fine particulate matter: MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution). *Journal of the American College of Cardiology*. 2012; 60(21):2158–2166. [PubMed: 23103035]
 32. Adar SD, Klein R, Klein BE, Szpiro AA, Cotch MF, Wong TY, O'Neill MS, Shrager S, Barr RG, Siscovick DS. Air pollution and the microvasculature: a cross-sectional assessment of in vivo retinal images in the population-based Multi-Ethnic Study of Atherosclerosis (MESA). *PLoS medicine*. 2010; 7(11):e1000372. [PubMed: 21152417]
 33. Park SK, Auchincloss AH, O'Neill MS, Prineas R, Correa JC, Keeler J, Barr RG, Kaufman JD, Diez-Roux AV. Particulate air pollution, metabolic syndrome, and heart rate variability: the multi-ethnic study of atherosclerosis (MESA). *Environmental health perspectives*. 2010; 118(10):1406–1411. [PubMed: 20529761]
 34. Adhikari R, D'Souza J, Solimon EZ, Burke GL, Daviglius M, Jacobs DR Jr, Park SK, Sheppard L, Thorne PS, Kaufman JD. Long-Term Coarse Particulate Matter Exposure and Heart Rate Variability in the Multi-Ethnic Study of Atherosclerosis (MESA). *Epidemiology*. 2016
 35. Auchincloss AH, Diez Roux AV, Dvorchak JT, Brown PL, Barr RG, Daviglius ML, Goff DC Jr, Kaufman JD, O'Neill MS. Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-Ethnic Study of Atherosclerosis. *Environmental health perspectives*. 2008; 116(4):486–491. [PubMed: 18414631]
 36. Chan SH, Van Hee VC, Bergen S, Szpiro AA, DeRoo LA, London SJ, Marshall JD, Kaufman JD, Sandler DP. Long-Term Air Pollution Exposure and Blood Pressure in the Sister Study. *Environ Health Perspect*. 2015; 123(10):951–958. [PubMed: 25748169]
 37. Allen RW, Criqui MH, Roux AV, Allison M, Shea S, Detrano R, Sheppard L, Wong ND, Stukovsky KH, Kaufman JD. Fine particulate matter air pollution, proximity to traffic, and aortic atherosclerosis. *Epidemiology*. 2009; 20(2):254. [PubMed: 19129730]
 38. Leary PJ, Kaufman JD, Barr RG, Bluemke DA, Curl CL, Hough CL, Lima JA, Szpiro AA, Van Hee VC, Kawut SM. Traffic-related air pollution and the right ventricle. the Multi-ethnic Study of Atherosclerosis. *American journal of respiratory and critical care medicine*. 2014; 189(9):1093–1100. [PubMed: 24593877]
 39. O'Neill MS, Diez-Roux AV, Auchincloss AH, Shen M, Lima JA, Polak JF, Barr R, Kaufman J, Jacobs DR. Long-Term Exposure to Airborne Particles and Arterial Stiffness: The Multi-Ethnic Study of Atherosclerosis(MESA). *Environmental health perspectives*. 2011; 119(6):844–851. [PubMed: 21245016]
 40. Van Hee VC, Adar SD, Szpiro AA, Barr RG, Bluemke DA, Diez Roux AV, Gill EA, Sheppard L, Kaufman JD. Exposure to traffic and left ventricular mass and function: the Multi-Ethnic Study of Atherosclerosis. *American journal of respiratory and critical care medicine*. 2009; 179(9):827–834. [PubMed: 19164703]
 41. Van Hee VC, Adar SD, Szpiro AA, Barr RG, Roux AD, Bluemke DA, Sheppard L, Gill EA, Bahrami H, Wassel C. Common genetic variation, residential proximity to traffic exposure, and left ventricular mass: the multi-ethnic study of atherosclerosis. *Environmental health perspectives*. 2010; 962–969. [PubMed: 20308035]

42. Van Hee VC, Szpiro AA, Prineas R, Neyer J, Watson K, Siscovick D, Park SK, Kaufman JD. Association of long-term air pollution with ventricular conduction and repolarization abnormalities. *Epidemiology*. 2011; 22(6):773. [PubMed: 21918454]
43. Young, MT.; Rosenfeld, M.; Heckbert, SR.; Sheppard, L.; Bielinski, SJ.; Kaufman, JD. International Society for Environmental Epidemiology. Environmental Health Perspectives; Sao Paulo, Brazil: 2015. Air Pollution And Circulating Adhesion Molecules In The Multi-Ethnic Study Of Atherosclerosis (Mesa).. Abstract 478, 2015
44. Adar SD, Kaufman JD, Diez-Roux AV, Hoffman EA, D'Souza J, Hinckley SK, Rich SS, Rotter JJ, Guo X, Raffel LJ. Air Pollution and Percent Emphysema Identified by Computed Tomography in the Multi-Ethnic Study of Atherosclerosis. *Environmental health perspectives*. 2014; 123(2):144–151. [PubMed: 25302408]
45. Aaron CP, Chervona Y, Kawut SM, Diez Roux A, Shen M, Bluemke DA, Van Hee VC, Kaufman JD, Barr RG. Particulate Matter Exposure and Cardiopulmonary Differences in the Multi-Ethnic Study of Atherosclerosis. *Environ Health Perspect*. 2016
46. Hajat, A.; Diez Roux, AV.; Castro-Diehl, C.; Cosselman, K.; Hill Golden, S.; Szpiro, AA.; Vedal, S.; Kaufman, JD. International Society for Environmental Epidemiology. Environmental Health Perspectives; Sao Paulo, Brazil: 2015. The Association Between Air Pollution And Stress Hormones: Evidence From The Multi-Ethnic Study Of Atherosclerosis.. Abstract 876, 2015
47. Park SK, Adar SD, O'Neill MS, Auchincloss AH, Szpiro A, Bertoni AG, Navas-Acien A, Kaufman JD, Diez-Roux AV. Long-term exposure to air pollution and type 2 diabetes mellitus in a multiethnic cohort. *American Journal of Epidemiology*. 2015; 181(5):327–336. [PubMed: 25693777]
48. Bell, G.; Mora, S.; Greenland, P.; Tsai, M.; Vietllo, A.; Kaufman, JD. Society for Epidemiologic Research Conference. Seattle, WA: 2014. PM2.5 and HDL in the Multi-Ethnic Study of Atherosclerosis (MESA).. 2014
49. Chi, G.; Lui, Y.; MacDonald, J.; Barr, RG.; Donohue, KM.; Hensley, M.; Hou, L.; McCall, C.; Siscovick, DS.; Kaufman, JD. International Society for Environmental Epidemiology. Environmental Health Perspectives; Seattle, WA: 2014. Long-Term Outdoor Air Pollution and Global DNA Methylation in Circulating Monocytes.. Abstract 2680, 2014
50. Bell, G.; Chitaley, K.; Keller, JP. International Society for Environmental Epidemiology. Environmental Health Perspectives; Seattle, WA: 2014. PM2.5 and Erectile Dysfunction in the Multi-Ethnic Study of Atherosclerosis (MESA).. Abstract 1889, 2014
51. Young, MT.; Budoff, MJ.; Temitope, F.; Jingzhong, D.; Kaufman, JD. International Society for Environmental Epidemiology. Environmental Health Perspectives; Basel, Switzerland: 2013. Nonalcoholic Fatty Liver Disease (NAFLD) and Long-Term Ambient Air Pollution Exposure: The Multi-Ethnic Study of Atherosclerosis (MESA).. Abstract 3418, 2013
52. Young MT, Sandler DP, DeRoo LA, Vedal S, Kaufman JD, London SJ. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of US women. *American journal of respiratory and critical care medicine*. 2014; 190(8):914–921. [PubMed: 25172226]
53. Weuve J, Kaufman JD, Szpiro AA, Curl C, Puett RC, Beck T, Evans DA, Mendes de Leon C. Exposure to Traffic-Related Air Pollution in Relation to Progression in Physical Disability among Older Adults. *Environ Health Perspect*. 2016
54. Chi GC, A H, Bird CE, Cullen MR, Griffin BA, Miller K, Shih RA, Stefanick ML, Vedal S, Whitsel EA, Kaufman JD. Individual and Neighborhood Socioeconomic Status and the Association Between Air Pollution and Cardiovascular Disease. *Environmental health perspectives*. 2016 Epub ahead of print.
55. Liu R, Young MT, Chen J-C, Kaufman JD, Chen H. Air pollution exposures and risk of Parkinson disease. *Environmental health perspectives*. 2016 Provisionally Accepted.
56. Hajat A, Diez-Roux AV, Adar SD, Auchincloss AH, Lovasi GS, O'Neill MS, Sheppard L, Kaufman JD. Air pollution and individual and neighborhood socioeconomic status: evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). *Environmental health perspectives*. 2013; 121(11-12): 1325. [PubMed: 24076625]
57. Jones MR, Diez-Roux AV, Hajat A, Kershaw KN, O'Neill MS, Guallar E, Post WS, Kaufman JD, Navas-Acien A. Race/ethnicity, residential segregation, and exposure to ambient air pollution: the

- Multi-Ethnic Study of Atherosclerosis (MESA). *American journal of public health*. 2014; 104(11): 2130–2137. [PubMed: 25211756]
58. Hicken MTA, Sara, Barr Graham, Diez-Roux Ana, Do Phuong, Hajat Anjum, Kaufman Joel, Kershaw Kerri. Psychosocial adversity and vulnerability to the cardiovascular effects of air pollution: The Multi-Ethnic Study of Atherosclerosis. *Epidemiology*. 2015; 27(1):42–50.
 59. Hicken MT, Adar SD, Roux AVD, O'Neill MS, Magzamen S, Auchincloss AH, Kaufman JD. Do psychosocial stress and social disadvantage modify the association between air pollution and blood pressure? The Multi-Ethnic Study of Atherosclerosis. *American Journal of Epidemiology*. 2013; 178(10):1550–1562. [PubMed: 24064742]
 60. Sheppard L, Burnett RT, Szpiro AA, Kim S-Y, Jerrett M, Pope CA III, Brunekreef B. Confounding and exposure measurement error in air pollution epidemiology. *Air Quality, Atmosphere & Health*. 2012; 5(2):203–216.
 61. Szpiro AA, Paciorek CJ. Measurement error in two - stage analyses, with application to air pollution epidemiology. *Environmetrics*. 2013; 24(8):501–517. [PubMed: 24764691]
 62. Szpiro AA, Sampson PD, Sheppard L, Lumley T, Adar SD, Kaufman JD. Predicting intra - urban variation in air pollution concentrations with complex spatio - temporal dependencies. *Environmetrics*. 2010; 21(6):606–631.
 63. Szpiro AA, Sheppard L, Lumley T. Efficient measurement error correction with spatially misaligned data. *Biostatistics*. 2011; kxq083.
 64. Bergen S, Szpiro AA. Mitigating the impact of measurement error when using penalized regression to model exposure in two-stage air pollution epidemiology studies. *Environmental and Ecological Statistics*. 2015:1–31.
 65. Bergen S, Sheppard L, Kaufman JD, Szpiro AA. Multipollutant measurement error in air pollution epidemiology studies arising from predicting exposures with penalized regression splines. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*. 2016
 66. Olives C, Sheppard L, Lindström J, Sampson PD, Kaufman JD, Szpiro AA. Reduced-rank spatio-temporal modeling of air pollution concentrations in the Multi-Ethnic Study of Atherosclerosis and Air Pollution. *The Annals of Applied Statistics*. 2014; 8(4):2509–2537. [PubMed: 27014398]
 67. Szpiro AA, Sheppard L, Adar SD, Kaufman JD. Estimating Acute Air Pollution Health Effects from Cohort Study Data. *Biometrics*. 2014; 70(1):164–174. [PubMed: 24571570]
 68. Kim S-Y, Sheppard L, Larson TV, Kaufman JD, Vedal S. Combining PM 2.5 Component Data from Multiple Sources: Data Consistency and Characteristics Relevant to Epidemiological Analyses of Predicted Long-Term Exposures. *Environmental Health Perspectives*. 2015; 123(7): 651–658. [PubMed: 25738509]
 69. Sun M, Kaufman JD, Kim S-Y, Larson TV, Gould TR, Polak JF, Budoff MJ, Roux AVD, Vedal S. Particulate matter components and subclinical atherosclerosis: common approaches to estimating exposure in a Multi-Ethnic Study of Atherosclerosis cross-sectional study. *Environ Health*. 2013; 12(1):39–41. [PubMed: 23641873]
 70. Szpiro AA, Paciorek CJ, Sheppard L. Does more accurate exposure prediction necessarily improve health effect estimates? *Epidemiology*. 2011; 22(5):680. [PubMed: 21716114]
 71. Kim S-Y, Sheppard L, Kaufman JD, Bergen S, Szpiro AA, Larson TV, Adar SD, Roux AVD, Polak JF, Vedal S. Individual-level concentrations of fine particulate matter chemical components and subclinical atherosclerosis: a cross-sectional analysis based on 2 advanced exposure prediction models in the Multi-Ethnic Study of Atherosclerosis. *American Journal of Epidemiology*. 2014; 180(7):718–728. [PubMed: 25164422]
 72. Kim S-Y, Sheppard L, Kim H. Health effects of long-term air pollution: influence of exposure prediction methods. *Epidemiology*. 2009; 20(3):442–450. [PubMed: 19289962]
 73. Mercer LD, Szpiro AA, Sheppard L, Lindström J, Adar SD, Allen RW, Avol EL, Oron AP, Larson T, Liu L-JS. Comparing universal kriging and land-use regression for predicting concentrations of gaseous oxides of nitrogen (NO_x) for the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). *Atmospheric Environment*. 2011; 45(26):4412–4420. [PubMed: 21808599]
 74. Adar SD, Sheppard L, Vedal S, Polak JF, Sampson PD, Roux AVD, Budoff M, Jacobs DR Jr, Barr RG, Watson K. Fine particulate air pollution and the progression of carotid intima-medial

thickness: a prospective cohort study from the multi-ethnic study of atherosclerosis and air pollution. PLoS Medicine. 2013; 10(4):e1001430. [PubMed: 23637576]

75. Jones MR, Diez-Roux AV, O'Neill MS, Guallar E, Sharrett AR, Post W, Kaufman JD, Navas-Acien A. Ambient air pollution and racial/ethnic differences in carotid intima-media thickness in the Multi-Ethnic Study of Atherosclerosis (MESA). Journal of Epidemiology and Community Health. 2015

- Research advances achieved by joining modern cardiovascular epidemiology to environmental science.
- MESA Air developed fine-scale, state-of-the-art air pollution exposure assessment.
- MESA Air provides a research platform for advances in environmental epidemiology.

Figure 1.
Annual Average Predicted PM_{2.5} Concentrations (µg/m³) in Los Angeles for the years 2000, 2004, 2008, and 2012.

Figure 2.
Year 2000 Annual Average Predicted NO₂ Concentrations in Winston-Salem, NC.

Figure 3.

Proposed mechanisms of cardiovascular effects from chronic exposure to air pollution.

Relevant MESA Air citations are noted. Note: Figure adapted from Cosselman et al. 2015.²⁴