Advances in Understanding Air Pollution and CVD

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ABSTRACT

The MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution) 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. 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.

Heart disease is the leading cause of death in the United States 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. Previous 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 (Multi-Ethnic Study of Atherosclerosis and Air Pollution) 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 >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) 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—such as heart attacks—in this population, to see whether 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.

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 6 U.S. communities: Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN. MESA participants were aged 45 to 84 years at enrollment between 2000 and 2002, with an approximately equal sex

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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 2 existing MESA clinical centers, MESA Air also recruited new participants in 2 new communities in Los Angeles and 1 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 previous 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 and 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 they are included in those analyses where only residential address is required to estimate outdoor air pollutant levels. Thus, >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, MESA Air analyses include as many as 7,551 participants from these 3 recruitment sources. Additional details regarding participant eligibility, recruitment, and the resulting demographic distributions of the cohort are provided in Kaufman et al. [1].

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, oxides of nitrogen (NO_X), nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), 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 2-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 $PM_{2.5}$, black carbon, trace elements, NO_2, NO_X, and SO_2. A total of 90 participants completed the 2-week personal sampling component of MESA Air [4].

Every MESA Air participant was asked to complete a comprehensive MESA Air questionnaire at recruitment [8]. The questionnaire 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 6 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 whether their patterns were the same in both seasons. For each day of the week, the MESA Air questionnaire included questions documenting hours spent in each of 7 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.

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 United States from 1980 to the present.

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 $PM_{2.5}$, NO_2, NO_X, black carbon (as measured by light absorption coefficient) [9], O_3 [11], and, most recently, 4 $PM_{2.5}$ 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 2-week periods throughout a 4-year period; all available Air Quality System (AQS) monitoring data reported by the U.S. Environmental Protection Agency [13]; and a custom-built, comprehensive database of >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 spatiotemporal exposure model to estimate each participant's predicted residential pollutant concentration for ambient-source $PM_{2.5}$ and gaseous pollutants for every 2-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 spatiotemporal residual. Prediction accuracy was high for most models, with a cross-validation R^2 >0.80 at regulatory and fixed monitoring sites for most regions and pollutants [9,11] Model prediction accuracy for 4 $PM_{2.5}$ 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 spatiotemporal modeling methods for environmental exposures with spatial and spatiotemporal covariates and irregular monitoring data, which are available for R users as the SpatioTemporal package (R Foundation, Vienna, Austria) [14,15].

National models

MESA Air researchers developed regionalized national universal Kriging models for annual average $PM_{2.5}$ and NO_2 across the United States [16,17]. The NO_2 model also incorporated satellite tropospheric data. These models demonstrated very high levels of cross-validated accuracy of prediction with overall R^2 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 4 $PM_{2.5}$ components: elemental carbon, organic carbon, silicon, and sulfur [18]. Our models performed well, with cross-validated R^2 values ranging from 0.62 to 0.95 [18]. Subsequent national models were generated for SO_2, 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 here.

Historical models

In addition to the unified spatiotemporal 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 spatiotemporal historical prediction model was developed using historical geographic predictors and annual average $PM_{2.5}$ data from 1999 through 2012 taken from the U.S. Environmental Protection Agency's FRM (Federal Reference Method) network with supplemental data from the IMPROVE (Interagency Monitoring of Protected Visual Environments) sites located predominantly in rural areas. The model uses a temporal basis function with a spatially varying coefficient to represent smooth spatiotemporal variability. The spatially

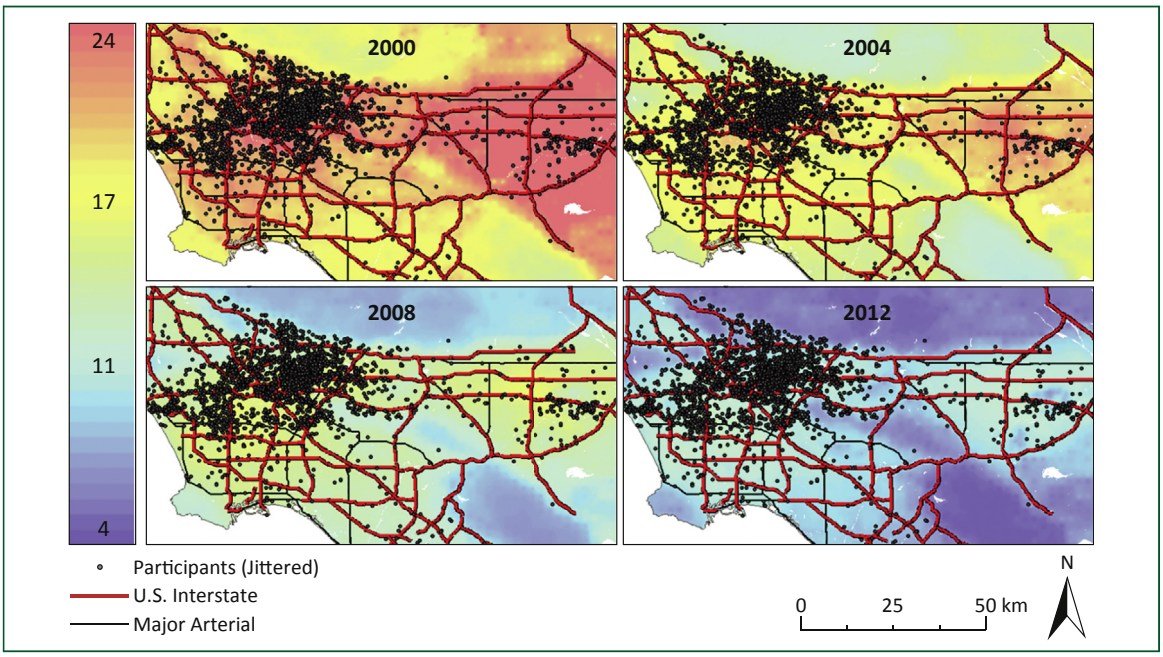

FIGURE 1. Annual average predicted $PM_{2.5}$ concentrations ($\mu g/m^3$) in Los Angeles for the years 2000, 2004, 2008, and 2012. PM, particulate matter.

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 to 2012 in FRM and IMPROVE. The model was validated using external sources of $PM_{2.5}$ data collected before 1999 from IMPROVE for 1990 to 1998 (not used for model fitting), California Air Resources Board dichotomous

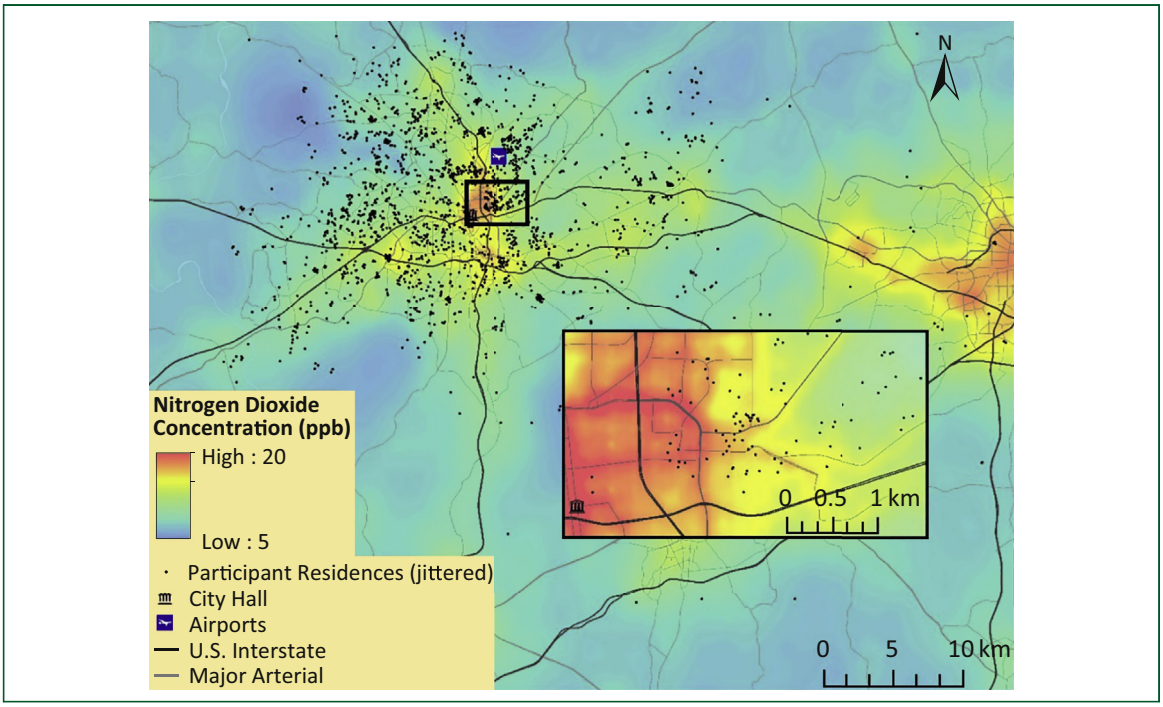

FIGURE 2. Year 2000 annual average predicted NO_2 concentrations in Winston-Salem, NC.

sampler monitoring, the Children's Health Study, and the Inhalable Particulate Network. The historical $PM_{2.5}$ prediction model performed well ($R^2 = 0.85$ to 0.91) in the validation using IMPROVE data for 1990 to 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. Although these models cannot perform with the same effectiveness as the MESA Air models from 1999 to 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 they have begun to be used in collaborative efforts in several cohorts.

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 2-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 sex, age, race/ethnicity, income, education, and employment status [8,21]. These resources can be applied to other similar populations.

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].

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—47]. 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.

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 10 years of repeated CAC measurements. CAC by computed tomography was measured 1 to 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 to 2010 ranged from 9.2 to 22.6 μg $PM_{2.5}/m^3$ and 7.2 to 139.2 parts per billion NO_X. For each additional 5 μg $PM_{2.5}/m^3$, CAC progression was accelerated by 4.1 Agatston units/year (95% confidence interval [CI]: 1.4 to 6.8) and for each 40 parts per billion NO_X, CAC progression was accelerated by 4.8 Agatston units/year (95% CI: 0.9 to 8.7) (Figure4). 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 [41].

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 [48]. 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 among 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 [27,28]. Long-term $PM_{2.5}$ exposure was significantly associated with decreased endothelial function according to brachial ultrasound results [30].

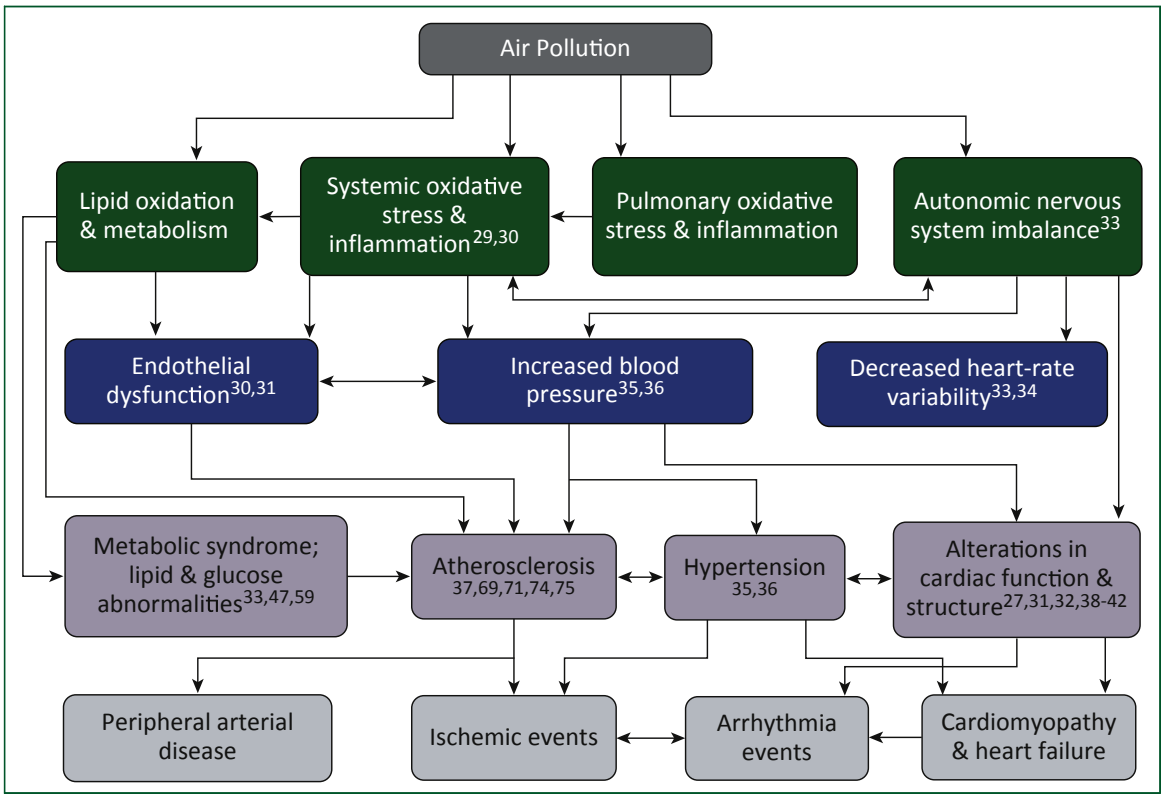

FIGURE 3. Proposed mechanisms of cardiovascular effects from chronic exposure to air pollution. Relevant MESA Air citations are noted. Figure adapted from Cosselman et al. [24].

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 [42]. Acute exposures to particulate air pollution were associated with lower heart rate variability, and this relationship was stronger in individuals with metabolic syndrome [29]. There was only a weak relationship between coarse PM exposure and heart rate variability [33]. Short-term and long-term exposure to air pollutants were found to be positively associated with increases in systolic blood and pulse pressure [31,32].

An elevated but nonsignificant relationship was found between $PM_{2.5}$ and aortic calcification [36]. Higher levels of NO_2 exposure were associated with greater right ventricle mass and larger right ventricle end-diastolic volume [43]. Long-term particle mass exposure did not appear to be associated with greater arterial stiffness in the MESA Air cohort [44]. 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 [45,46]. Using measurements of QT interval and QRS duration from 12-lead electrocardiograms, 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 [47]. A cross-sectional analysis of circulating adhesion molecules demonstrated evidence of an association between air pollution and several markers of adhesion, including chemokine ligand 21 [49].

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 percentage of emphysema [50], but MESA Air researchers found that long-term $PM_{2.5}$ exposure may contribute to subclinical pulmonary vascular differences [51]. 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 [52]. MESA Air researchers found that exposure to air pollution ($PM_{2.5}$ and NO_2) was associated with prevalent type 2 diabetes at baseline but not with incident diabetes after 9 years of follow-up [34]. Exposure to higher levels of $PM_{2.5}$ over a 3-month period was

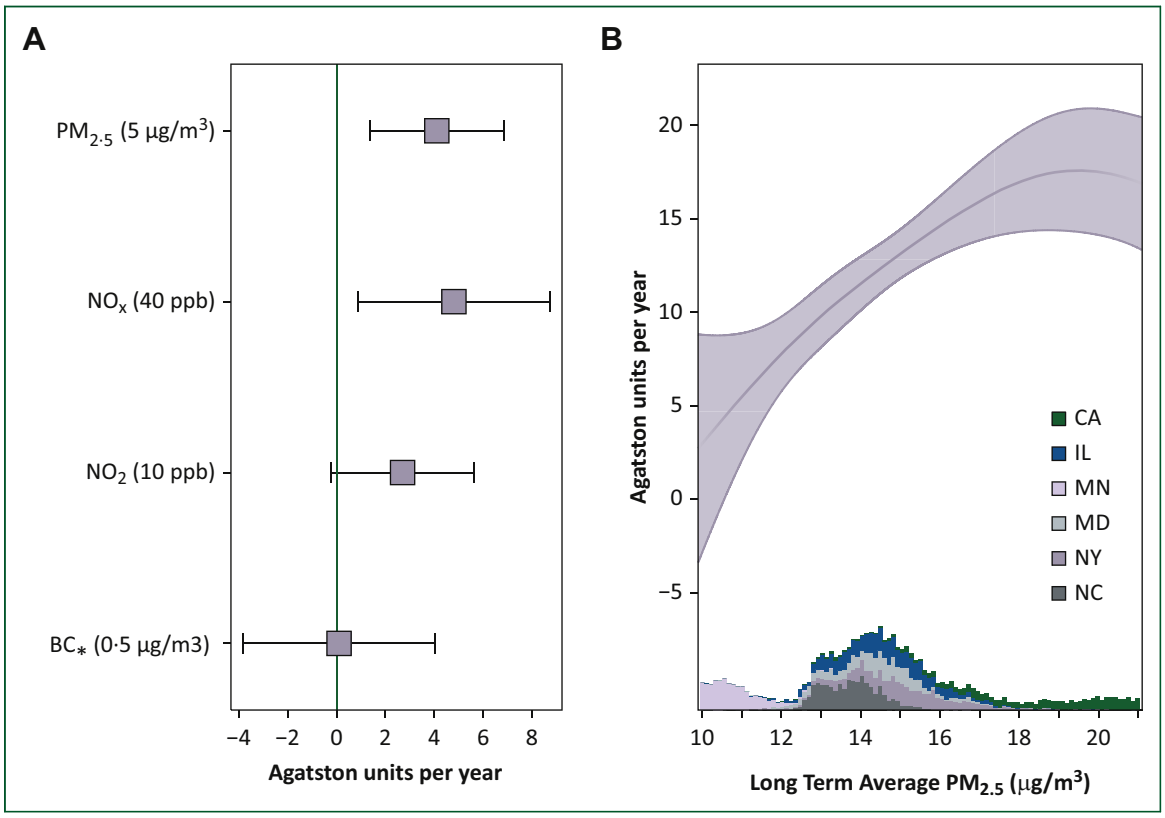

FIGURE 4. Long-term average air pollutant concentrations and coronary artery calcium progression. (A) The linear longitudinal association of fine particulate matter ($PM_{2.5}$), nitrogen oxides (NO_x), nitrogen dioxide (NO_2), and black carbon, with coronary artery calcium progression (Agatston units per year), from linear mixed models adjusted for age, sex, ethnicity, city, income, employment outside the home, smoking status, second-hand smoke exposure, physical activity, adiposity, cholesterol, statin use, neighborhood socioeconomic index, income, education, and scanner type. (B) The concentration-response curve with 95% CIs for the overall change in and coronary artery calcium (progression rate associated with long-term average $PM_{2.5}$ concentrations). The curve is based on a mixed model that includes a thin plate regression spline with 5 degrees of freedom to more flexibly assess the potentially nonlinear association. The relationship at the extremes is less certain and might rely on concentrations that are recorded only in 1 geographical region; the highest and lowest 5% of overall concentrations have been trimmed for visualization. The histogram at the bottom of the right panel shows the relative overall distribution of long-term $PM_{2.5}$ concentrations in the cohort, with different colors representing each clinic location. *Black carbon as measured by light absorption coefficient, where 0.5 $\times$ 10^{-5m-1} is approximately equivalent to 0.5 $\mu g/m^3$. Reproduced with permission from Kaufman et al. [41]. CA, California; IL, Illinois; MD, Maryland; MN, Minnesota; NC, North Carolina; NY, New York.

associated with reduced high-density lipoprotein cholesterol particle concentration [53]. In analyses of long-term air pollution exposure and "global" deoxyribonucleic acid methylation, there was little association between $PM_{2.5}$ and long interspersed nucleotide elements methylation or Alu methylation [54]. In our analyses thus far, no relationship has been established between air pollution exposure and erectile dysfunction [55] or nonalcoholic fatty liver disease [56].

Air pollution health effects using MESA Air exposure models in other populations

Using exposure models that leveraged the MESA Air work, researchers have conducted investigations in a number of other cohorts including the Sister Study, the PAGE (Parkinson's, Genes and Environment) study, the Women's Health Initiative, and the CHAP (Chicago Healthy Aging Project). 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 NO_2 increase the risk of developing wheezing, the cardinal symptom of asthma [57]. A study of aging found a relationship between long-term NO_X exposure and declines in age-related physical disability [58]. In the Women's Health Initiative, an increase in $PM_{2.5}$ exposure was associated with an increased risk of a cardiovascular disease event [59]. Although there was not strong evidence for an association between exposures to ambient PM_{10}, $PM_{2.5}$, or NO_2 concentrations and

risk of Parkinson disease in older adults, subgroup analyses suggested that female nonsmokers exposed to higher concentrations of PM_{10} or $PM_{2.5}$ may have a higher risk for Parkinson disease [60].

Air pollution and socioeconomic status

MESA Air researchers examined associations between air pollutant concentrations (outdoor $PM_{2.5}$ and NO_X) and socioeconomic status (SES) of both individuals and their neighborhoods [59,61]. 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. Because 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 U.S. environmental justice literature.

The MESA Air group also investigated the association between air pollution and racial residential segregation [62]. Some theoretical work has suggested that residential segregation is a factor that produces and maintains differential levels of air pollution across the population, but little empirical work was available to support this notion. Ours was among 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 SES, and psychosocial stress on the association among 3 air pollutants ($PM_{2.5}$, NO_2, and NO_X) and 2 markers of cardiovascular health—left ventricular mass index and left ventricular ejection fraction [63]. 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 [35]. 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.

BIOSTATISTICAL METHOD ADVANCEMENTS

MESA Air investigators have made significant and important contributions to the field of measurement error in 2-stage air pollution epidemiology studies [18,64—70]. 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, of 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 [71]. This work provides conditions under which traditional time series methods for semiparametric regression may validly be used in cohort studies and also develops a more efficient pre-adjustment method that uses 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 [72], exposure estimation [37,73], choice of exposure prediction models [6,38,74,75], and reduced-rank spatiotemporal modeling.

SUMMARY

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 spatiotemporal 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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