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Air Pollution and Cardiovascular Disease in the Multi-Ethnic Study of Atherosclerosis

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Abstract Research to date demonstrates a relationship between exposure to ambient air pollutants and cardiovascular disease (CVD). Many studies have shown associations between short-term exposures to elevated levels of air pollutants and CVD events, and several cohort studies suggest effects of long-term exposure on cardiovascular mortality, coronary heart disease events, and stroke. The biologic mechanisms underlying this long-term exposure relationship are not entirely clear but are hypothesized to include systemic inflammation, autonomic nervous system imbalance, changes in vascular compliance, altered cardiac structure, and development of atherosclerosis. The Multi-Ethnic Study of Atherosclerosis provides an especially well-characterized population in which to investigate the relationship between air pollution and CVD and to explore these biologic pathways. This article reviews findings reported to date within this cohort and summarizes the aims and anticipated contributions of a major ancillary study, the Multi-Ethnic Study of Atherosclerosis and Air Pollution. (Prog Cardiovasc Dis 2011;53:353-360)

Keywords: Air pollution; cardiovascular disease; subclinical atherosclerosis; progression

Research to date suggests a causal relationship between exposure to ambient air pollutants and cardiovascular disease. Although many investigations have focused on documenting the relationship between short-term exposures to elevated levels of air pollutants and the triggering of cardiovascular disease events in susceptible populations, several cohort studies also suggest effects of long-term exposure on cardiovascular disease risk. In particular, 2 landmark studies demonstrated relationships between fine particulate matter (PM) air pollution (particulate matter <2.5 μm in aerodynamic diameter [$PM_{2.5}$]) on risk of mortality when city-wide,[1] and later county-wide,[2] averages of air pollutant levels were assigned based on residential location. Subsequent cohort studies confirmed these initial findings, reporting associations between long-term exposures to $PM_{2.5}$ and cardiovascular disease (CVD) mortality, coronary heart disease events, and stroke.[3-8] It remains unclear exactly which biologic mechanisms underlie this long-term relationship; hypotheses include, among others, systemic inflammation, autonomic nervous system (ANS) imbalance, changes

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Abbreviations and Acronyms

AGTR1 = type 1 angiotensin II receptor

ALOX15 = arachidonate 15-lipoxygenase

ANS = autonomic nervous system

AQS = Air Quality System

CAC = coronary artery calcium

CI = confidence interval

CRP = C-reactive protein

CT = computed tomography

CVD = cardiovascular disease

EPA = Environmental Protection Agency

HRV = heart rate variability

IMT = intima-medial thickness

LVM = left ventricular mass

MESA = Multi-Ethnic Study of Atherosclerosis

MESA Air = Multi-Ethnic Study of Atherosclerosis and Air Pollution

NO_X = oxides of nitrogen

PM = particulate matter

$PM_{2.5}$ = particulate matter less than 2.5 μm in aerodynamic diameter

PM_{10} = particulate matter less than 10 μm in aerodynamic diameter

rMSSD = root mean square of successive differences

RR = relative risk

SBP = systolic blood pressure

in vascular responsiveness and compliance, altered cardiac structure, and development of atherosclerosis.[9]

The Multi-Ethnic Study of Atherosclerosis (MESA) provides a useful cohort in which to investigate the relationship between air pollution and CVD and these potential pathways. The Multi-Ethnic Study of Atherosclerosis was initiated by the National Heart, Lung, and Blood Institute in July 2000 to investigate the prevalence, correlates, and progression of subclinical CVD in a multiethnic cohort of 6814 men and women.[10] Participants of MESA were recruited from 6 US communities: Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County (Winston-Salem), NC; Los Angeles County, CA; New York, NY; and St Paul, MN. Participants were aged 45 to 84 years at enrollment, with an approximately equal sex ratio, and were recruited from 4 ethnic/racial groups. Participants of MESA were free of recognized clinical CVD at baseline.

The initial MESA examination occurred between 2000 and 2002, and measurements included coronary artery calcium (CAC) using computed tomography (CT); flow-mediated brachial artery endothelial vasodilation, carotid artery intima-medial wall thickness (IMT), and distensibility of the carotid arteries using ultrasonography; peripheral vascular disease using ankle and brachial blood pressures; retinal photography; magnetic resonance imaging; electrocardiography; and assessments of urinary albumin concentration, standard CVD risk factors, sociodemographic factors, life habits, and psychosocial factors. Subsequent examinations, including repetitions of certain baseline measurements as well as new measures, were scheduled at approximately adjacent 2-year intervals, with a fifth MESA examination beginning April 2010. Fig 1 depicts the physiologic pathways that have been proposed to underlie the relationship between air pollution and CVD and includes outcome measurements that may be indicators of activity along these pathways. All outcome measures shown in this figure are available on some or all of the MESA study participants.

As part of a project on effects of PM exposures on subclinical CVD (R830543) funded in 2003 by the US Environmental Protection Agency (EPA), MESA investigators combined information from the Air Quality System (AQS), a national regulatory monitoring network that contains data collected by approximately 5000 EPA, state, local, and tribal monitors, with information on other spatial covariates and recent and 20-year historical information on participants' residential locations to estimate recent and long-term (20-year) exposures to air pollutants. Furthermore, in 2004, the EPA funded a major new study within the MESA cohort, the MESA and Air Pollution (MESA Air, RD831697). This study leverages the National Heart, Lung, and Blood Institute investment in MESA and supplements that study with additional subjects, outcome measurements, and state-of-the-art cohort-specific air pollution exposure assessment for $PM_{2.5}$, oxides of nitrogen (NO_X), and black carbon. Here, we review the findings of initial work conducted as part of these 2 ancillary studies (Table 1). These analyses have ranged from the basic science of gene association to clinical effects on blood pressure and heart rate variability (HRV). This article describes the work to date on air pollution and CVD in MESA, organized by mechanistic pathway, and concludes with a description of MESA Air and its anticipated contributions.

Air pollution and CVD findings in the MESA cohort

Inflammation

As the mechanism of PM-induced cardiovascular events and acceleration of atherosclerosis has been hypothesized to involve generation of an inflammatory state, several studies have evaluated the association of inflammatory makers with PM exposure. In MESA, the association between $PM_{2.5}$ and C-reactive protein (CRP) was examined.[11] Data from the AQS monitoring system were used to estimate $PM_{2.5}$ exposures for the prior day, prior 2 days, prior week, and prior 30 and 60 days. The 30- and 60-day mean exposures showed a weak positive association with CRP, although the confidence intervals (CIs) were wide. After adjusting for appropriate person-level covariates, the relative increase in CRP (mg/L) per 10 $\mu g/m^3$ increase in fine particles was 3% (95% CI, −2 to 10) for 30-day mean and 4% (95% CI, −3 to 11) for a 60-day mean. It was concluded that fine PM had little

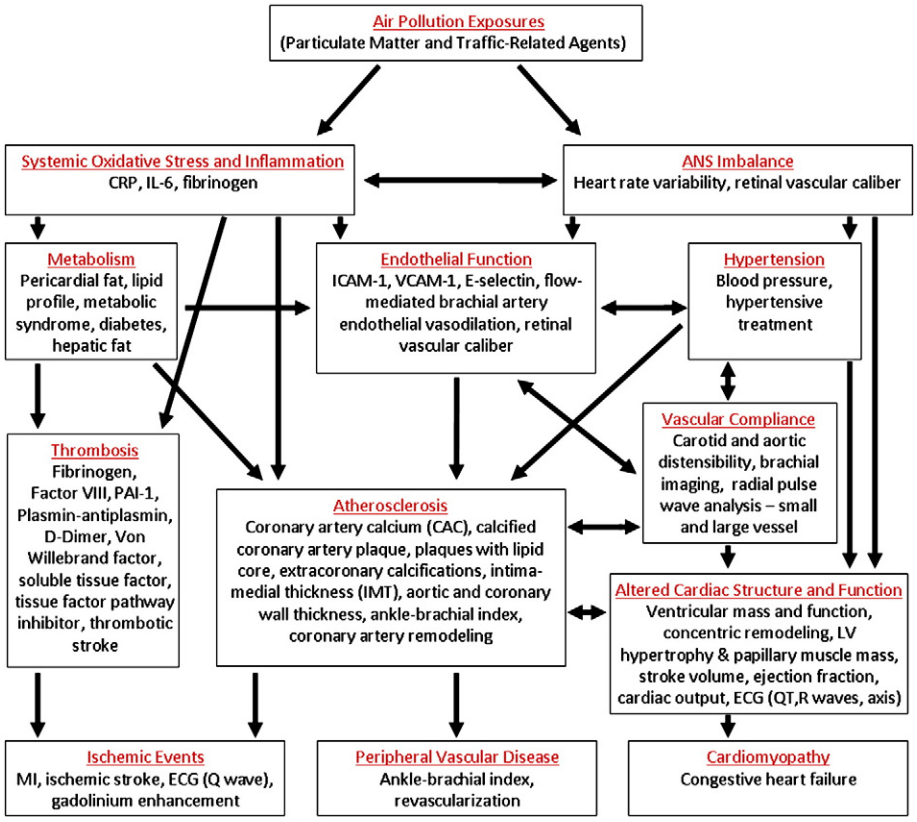

Fig 1. Physiologic pathways by which air pollution may impact CVD. General pathways/mechanisms are listed red, with potential indicators of these pathways listed below. All indicators listed are available as outcome measures in MESA.

demonstrable effect. No association was seen between $PM_{2.5}$ and interleukin 6. The finding of potentially some, albeit small and not statistically significant, increase in CRP is partially concordant with the findings of other investigators.[12-14] Of the studies that have examined this relationship, Peters et al[12] and Seaton et al[13] found more significant increases in CRP, whereas the findings of Pope et al[14] were largely isolated to 1 particular subject in their sampling group.

Autonomic nervous system imbalance

Heart rate variability is a marker of a healthy cardiovascular system. Reduction in HRV is associated with ANS imbalance and is seen in patients with diabetes, metabolic syndrome, and established coronary artery disease.[15] The mechanism for reduction in HRV appears to be related to connections between cardiac myocytes, and hence, connexins and gap junctions have been implicated. Previously, several investigators have shown epidemiological data linking PM exposure to decreased HRV.[16-25] Only a few studies have been conducted in population-based cohorts.[20,22,23] Several of these studies found associations between PM exposure and autonomic dysfunction to be stronger among persons with type 2 diabetes.[20,22,24]

Multi-Ethnic Study of Atherosclerosis investigators evaluated the effects of $PM_{2.5}$ on HRV and effect modification by metabolic syndrome including central obesity, type 2 diabetes, and hypertension.[26] In this study, $PM_{2.5}$ concentrations were obtained from AQS monitor data for the 60 days before the day on which HRV measures were obtained, and average periods were assessed for the 1, 2, 7, 30, and 60 days before HRV measurement. After controlling for confounding variables, $PM_{2.5}$ was associated with a 2.1% decrease in the root mean square of successive differences (rMSSD) (95%CI, −4.2 to 0.0). The association was stronger among individuals with metabolic syndrome compared to those without, with an interquartile range elevation in 2-day $PM_{2.5}$ associated with a 6.2% decrease in the rMSSD (95% CI, −9.4 to −2.9) as compared to almost no change found in those without metabolic syndrome. These findings support the notion that the ANS may well play a role in the mechanism of $PM_{2.5}$-induced cardiovascular complications, especially when accompanied by the metabolic syndrome.

Hypertension

Inhaled particles may down-regulate nitric oxide synthase and affect autonomic dysfunction, and both

Table 1
Summary of studies of air pollution and CVD in MESA

Author/Year	Outcome	Result (95% CI)
Diez Roux et al[11]/2006	CRP	3% (−2 to 10) increase for 30-d mean $PM_{2.5}$ 4% (−3 to 11) increase for 60-d mean $PM_{2.5}$
Park et al[26]/ 2010	HRV	2.1% (−4.2 to 0.0) decrease in rMSSD for interquartile range increase in 2-day average $PM_{2.5}$ (stronger in people with metabolic syndrome)
Adar et al[30]/2010	Central retinal arteriolar and venular equivalents	−0.8- (−1.1 to −0.5) and −0.4-μm (−0.8 to 0.1) decreases in central retinal arteriolar equivalents and 0.9- (0.4 to −1.4) and 0.4-μm (0.3-1.1) increases in central retinal venular equivalents per interquartile increases in long- and short-term $PM_{2.5}$ levels
Auchincloss et al[28]/2008	SBP, pulse pressure	SBP, 0.99-mm Hg (0.15-2.13) increase for 30-d mean $PM_{2.5}$ Pulse pressure, 1.12-mm Hg (0.28-1.97) increase for 30-d mean $PM_{2.5}$
O'Neill et al[31]/in press	Arterial stiffness	No significant associations; for example, large and small artery vessel compliance values were 0.0 (−0.8 to 0.8) and 0.2 (−0.6 to 1.0), respectively, for annual average nearest monitor $PM_{2.5}$
O'Neill et al[34]/ 2008	Urinary albumin excretion	No significant associations; mean difference in log of urinary albumin/creatinine ratio of −0.02 (−0.07 to 0.03) long-term PM_{10} exposure
Van Hee et al[35]/2009	LVM	1.4 g/m^2 increase in LVM for participants living closer to a major roadway
Van Hee et al[37]/2010	LVM (gene-environment interactions)	Tag SNPs in the AGTR1 and ALOX15 genes were each significantly ($q < 0.2$) associated with 9%-10% differences in the association between LVM and proximity to major roadways
Diez Roux et al[40]/2008	CAC, IMT	RR of 1.04 (1.01-1.07) for carotid IMT for participants' exposure to PM_{10} with coronary risk factors No significant effect for CAC
Allen et al[41]/2009	Aortic calcification	RR of 1.06 (0.96-1.16) for abdominal aortic calcification with a 10 μg/m^3 increase in $PM_{2.5}$

Abbreviation: Tag SNP indicates tagged single-nucleotide polymorphisms.

mechanisms could increase blood pressure. Because nitric oxide is a vasodilator, reduced bioavailability would increase blood pressure, as would increased autonomic tone—particularly sympathetic tone—resulting in vascular vasoconstriction. Previously, a repeated measures study showed an association between particle inhalation and increasing blood pressure among cardiac patients.[27]

In the MESA cohort, investigators used AQS monitors to estimate $PM_{2.5}$ exposures for the preceding 1, 2, 7, 30, and 60 days, and roadway location data were used to estimate local exposures to traffic-related pollutants.[28] Both systolic blood pressure (SBP) and pulse pressure were positively associated with exposure to $PM_{2.5}$. The observed long-term associations were more dramatic than the short-term. A 10 μg/m^3 increase in $PM_{2.5}$ 30-day mean was associated with a 1.12-mm Hg higher pulse pressure (95% CI, 0.28-1.97) and a 0.99-mm Hg higher SBP (95% CI, −0.15 to 2.13). This difference in SBP was roughly equivalent to a 1.5- to 3.5-year aging affect seen in the cohort. The results were generally not statistically significant for mean arterial blood pressure and diastolic blood pressure.

Vascular function

On a variety of scales, changes in vascular function can be assessed and hypothesized to play a role in air pollution's effects, including the observed blood pressure findings. Animal studies have suggested that the microvasculature may be particularly important.[29] In a recent study of the relationship between fine PM exposures and the microvasculature in MESA, Adar et al[30] evaluated central retinal arteriolar and venular equivalents, as measured by digital retinal photography. Outdoor concentrations of $PM_{2.5}$ were estimated at each participant's home for the 2 years preceding the clinical examination using an early MESA Air exposure model, and short-term concentrations were assigned using AQS measurements on the day preceding the clinical examination. After adjusting for appropriate confounders, central retinal arteriolar equivalents were found to be narrower among persons residing in regions with increased long-term levels of $PM_{2.5}$ and on days with high short-term levels of $PM_{2.5}$. In joint exposure models, −0.8- (95% CI, −1.1 to −0.5) and −0.4-μm (95% CI, −0.8 to 0.1) decreases in central retinal arteriolar equivalents per interquartile increases in long- and short-term $PM_{2.5}$ levels were observed.

Vascular compliance

Increased vascular stiffness may also lie on the mechanistic pathway between air pollution exposures and cardiovascular risk, and stiffer arteries are associated

with both higher pulse pressure and adverse ventricular remodeling. Multi-Ethnic Study of Atherosclerosis investigators assessed the relationship between long-term (20-year) exposure to $PM_{2.5}$ and PM less than 10 μm in aerodynamic diameter (PM_{10}) and arterial stiffness as measured by Young's modulus from carotid artery ultrasound and large and small artery vessel compliance from radial artery pulse wave.[31] Twenty-year exposures were estimated based on a space-time model that combined historical AQS and residential history information with other spatial covariates to impute PM exposures for each month over the 20 years before outcome measurement.[32] However, the authors did not find an association between PM exposure and any of these measures of arterial stiffness.

Urinary albumin excretion

Urinary albumin levels are used as a screening tool to evaluate renal function, especially in the setting of risk factors for microvascular impairment as in diabetes. Higher levels of urinary albumin result from glomerular changes, and albumin levels are well correlated with microvascular dysfunction.[33] O'Neill et al[34] investigated the relationship between exposure to PM and urinary albumin excretion. Concentrations of $PM_{2.5}$ and PM_{10} were estimated based on measurements at AQS monitors 1 month, 2 months, and 20 years before urine collection. Creatinine-adjusted albumin excretion was not found to be significantly associated with PM exposures; per 10 $\mu g/m^3$ increment of long-term PM_{10} exposure, the mean difference in the log of the urinary albumin/creatinine ratio was −0.02 (95% CI, −0.07 to 0.03), adjusted for person-level covariates.

Altered cardiac structure and function

Given the association between PM and hypertension, the next step is to take this further and look at the actual effect on heart muscle. To this end, attention turned to studying the association of left ventricular mass (LVM) measured by cardiac magnetic resonance imaging with air pollution.[35] In this study, investigators compared MESA participants living within 50 m of a major roadway to those further than 150 m away. Participants living very near to major roadways were observed to have a 1.4 g/m^2 (95% CI, 0.3-2.5) higher LVM index compared to those with residences rather away. This magnitude of increase in LVM is equivalent to the association with a 5.6-mm Hg increase in SBP in this cohort. Left ventricular systolic function, as estimated by ejection fraction, was not different comparing the 2 groups. Despite the effect of LVM being possibly equated to a 5.6-mm Hg greater SBP, there was no interaction between roadway proximity and hypertension (P = .69 for interaction) or use of any antihypertensive medications (P = .89 for an interaction). Although no association was found with estimated $PM_{2.5}$ concentrations, the linkage between LVM and traffic-related air pollution is important because increased LVM is strongly associated with both heart failure and heart failure severity in patients with heart failure.[36]

After establishing that proximity to traffic-related air pollution was associated with increased LVM, investigators evaluated 12 potential candidate genes that may play in a role of the ventricular hypertrophy.[37] The genes selected (*ACE*, *ADRB2*, *AGT*, *AGTR1*, *ALOX15*, *EDN1*, *GRK4*, *PTGS1*, *PTGS2*, *TLR4*, *VEGFA* and *VEGFB*) were so chosen based on hypothesized role of their products on the mechanism for increased LVM. In this study, 2 genes with potentially compelling mechanisms stood out. Tagged single-nucleotide polymorphisms in the *AGTR1 (rs680136)* and *ALOX15 (rs2664593)* genes were each significantly ($q < 0.2$) associated with 9% to 10% differences in the association between LVM and residential proximity to major roadways. *AGTR1* is particularly compelling because of well-established impacts on inflammation and vasoconstriction.[38] Likewise, *ALOX15* is felt to play a role in vascular inflammation and, particularly, in oxidative stress, the latter frequently implicated in the mechanism of PM-induced cardiovascular complications.[39]

Atherosclerosis

Although PM has consistently been associated with cardiovascular clinical events that are hallmarks of atherosclerotic disease, the proposed association with the development of atherosclerosis has not been confirmed. Multi-Ethnic Study of Atherosclerosis is particularly well suited to study the extent of subclinical atherosclerosis. There has been a significant effort over the last decade to develop methods of detecting subclinical atherosclerosis using imaging techniques. Carotid intima-medial thickness and CAC scoring are 2 such measures that have been deemed promising, and these 2 measures are primary outcomes of interest within the MESA study. Multi-Ethnic Study of Atherosclerosis investigators have evaluated the association of 20-year exposure to PM with IMT, CAC, and ankle-brachial artery indices measured later in adulthood at the end of the 20-year period.[40] The authors found that there was a small measurable effect on IMT but not coronary calcium or ankle-brachial artery index. Even the effect on carotid IMT was small, with the greatest relative difference between the 90th and 10th percentiles risk being 1.04 (95% CI, 1.01-1.07) for residentially stable subjects exposed to PM_{10} after control for coronary risk factors.

In addition to CAC, Allen et al[41] conducted a cross-sectional analysis of abdominal aortic calcification, as measured by CT within the MESA cohort. The authors observed a slightly elevated, but nonsignificant, increased

risk of aortic calcification (relative risk [RR], 1.06; 95% CI, 0.96-1.16) with a 10 $\mu g/m^3$ contrast in $PM_{2.5}$. Greater effects were observed among participants with less exposure misclassification, such as those with long-term residence near a $PM_{2.5}$ monitor (RR, 1.11; 95% CI, 1.00-1.22).

Next steps: MESA Air

Multi-Ethnic Study of Atherosclerosis is well positioned to answer many of the outstanding questions about the biologic mechanisms by which air pollution exposures result in cardiovascular risk. Myriad study outcomes are available at numerous points along the potential pathways, and additional data are available to ensure appropriate confounder control. The research conducted to date has informed our understanding of the relationship between air pollution and CVD and has contributed to the available literature on the potential mechanisms underlying this relationship. However, the analyses to date have been cross-sectional in design, and all have been limited by significant uncertainty in the air pollutant exposure estimates used.

Large uncertainty in estimates of air pollution exposure is by no means restricted to studies occurring in the MESA cohort. In general, the collective research on long-term exposure to air pollution and CVD is affected by measurement error and potential misclassification in exposure assessment. Furthermore, no long-term air pollution epidemiology studies to date have been able to account for potentially important individual-level factors, such as the amount of time spent indoors or the infiltration efficiencies of outdoor pollutants into indoor environments.[42]

In 2003, the EPA developed a competitive application process to engage researchers in the design and implementation of a study, specifically to reduce the uncertainty in understanding the relationship between air pollution exposure and CVD.[43] This process resulted in the investment of substantial new resources for MESA Air, initiated in 2004. Multi-Ethnic Study of Atherosclerosis and Air Pollution is using this unusual dedication of resources to combine state-of-the-art epidemiology inherent in the parent MESA study with state-of-the-art exposure estimation. Multi-Ethnic Study of Atherosclerosis and Air Pollution can prospectively assess the relation between individual-level assessment of long-term air pollution exposures and both the *progression* of subclinical atherosclerosis and the incidence of CVD *events*. Recognizing the importance of characterizing fine-scale variation in pollutant concentrations within metropolitan areas, MESA Air assigns an individual-level, temporally resolved estimate of exposure to ambient pollution to each study participant.

Multi-Ethnic Study of Atherosclerosis and Air Pollution also supplements the parent MESA study with additional subjects to increase exposure heterogeneity. From 2005 to 2007, approximately 300 new participants were recruited from 2 geographic areas in the Los Angeles basin (Santa Monica/Coastal LA County and Rubidoux/Riverside County) and 1 in the New York City region (Rockland County). The Coastal LA area represents an upwind location relative to the city center and was selected to represent a lower $PM_{2.5}$ contrast within the Los Angeles basin. Riverside County was 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. Rockland County, NY, is upwind of the New York City region, which allows capture of similar regional scale pollution to those participants in northern Manhattan and the southern Bronx without the urban contribution. With the inclusion of these regions, the MESA Air communities provide a wide range of exposure characteristics across a variety of pollutants.

In addition to these new participants, MESA Air adds new outcome measures to the MESA study. In MESA examination 5, currently scheduled from April 2010 through October 2011, MESA Air is adding 3600 additional CT scans and ultrasounds for CAC and IMT determination to allow measurement of progression of subclinical atherosclerosis for a full 10 years, concurrent with the relevant period of exposure.

Perhaps, most significantly, MESA Air adds state-of-the-art exposure estimation to MESA. Between July 2005 and July 2009, MESA Air deployed 7420 2-week air samples throughout the 6 MESA cities and the 3 additional areas of new recruitment.[44] These samples were analyzed for $PM_{2.5}$, light-absorbing carbon, NO_X, NO_2, NO, O_3, SO_2, and trace elements, and ancillary studies collected samples analyzed for elemental and organic carbon, endotoxin, and PM_{10} and $PM_{2.5}$ at a subset of locations. In addition to the measurements collected directly by the project, MESA Air uses AQS monitoring data, geographic data such as roadway density and land use, and dispersion model outputs in exposure models to identify seasonal and shorter term time trends, to capture key sources of spatial variability, and to account for underlying spatial and spatio-temporal correlation.

Sampson et al[45] describe a first iteration of the hierarchical spatio-temporal model developed as part of MESA Air to estimate outdoor $PM_{2.5}$ concentrations at each participant's residence, using a multistep pragmatic estimation procedure, and Szpiro et al[46] presents a similar model for predicting residential NO_X concentrations, using a unified estimation approach based on efficient maximum likelihood calculations. Ultimately, all of these estimates will incorporate exposure variation due both to pollution infiltration into each participant's residence and participant-specific time-activity patterns.

With 1 exception (Adar et al[30]), the studies previously described have not used pollutant estimates generated through MESA Air, as these "next-generation" estimates

only recently became available. The previous studies have used distance to major roadway as a proxy for exposure to traffic-related air pollution, have used data from the nearest AQS monitors, or have used modeled long-term exposures developed to estimate outdoor concentrations based on AQS data and spatial covariates.[32] Moving forward, estimates developed by MESA Air will be available for all MESA investigators, and the use of these new estimates will substantially reduce the uncertainty associated with estimating air pollution exposures in the cohort. The availability of enhanced pollutant estimates provided by MESA Air, which will be available for the full cohort in 2012 to coincide with conclusion of the fifth MESA clinical examination, will enable more complete assessment of the pathways already examined. It is even possible that some of the early outcomes reported on in this review will be revisited with the new exposure estimates.

Multi-Ethnic Study of Atherosclerosis and Air Pollution is designed to provide the most advanced approach feasible to understanding the relationship between air pollution and CVD. The range of exposures under study is extremely relevant—the annual averages observed are largely at or below regulatory levels.[47-50] Both the clinical and subclinical health measures included in this study are cutting edge and reflect multiple pathways and different levels of severity within the same. The multiethnic study design improves the generalizability of the results. Sufficient populations with key putative risk factors are included, and many outcomes available will illuminate possible mechanistic pathways underlying a relationship that, although generally acknowledged, is still somewhat uncertain.

Statement of Conflict of Interest

All authors declare that there is no conflicts of interest.

Acknowledgments

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