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Gene–Air Pollution Interaction and Cardiovascular Disease: A Review

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Abstract Genetic susceptibility is likely to play a role in response to air pollution. Hence, gene-environment interaction studies can be a tool for exploring the mechanisms and the importance of the pathway in the association between air pollution and a cardiovascular outcome.

In this article, we present a systematic review of the studies that have examined gene-environment interactions in relation to the cardiovascular health effects of air pollutants.

We identified 16 articles meeting our search criteria. Of these studies, most have focused on individual functional polymorphisms or individual candidate genes. Moreover, they were all based on 3 study populations that have been extensively investigated in relation to air pollution effects: the Normative Aging Study, Air Pollution and Inflammatory Response in Myocardial Infarction Survivors: Gene-Environment Interaction in a High Risk Group, and Multiethnic Study of Atherosclerosis.

In conclusions, the studies differed substantially in both the cardiovascular outcomes examined and the polymorphisms examined, so there is little confirmation of results across cohorts. Gene-environment interaction studies can help explore the mechanisms and the potential pathway in the association between air pollution and a cardiovascular outcome; replication of findings and studies involving multiple cohorts would be needed to draw stronger conclusions. (Prog Cardiovasc Dis 2011;53:344-352)

Keywords: Gene-environment interaction; cardiovascular disease; polymorphism

Epidemiological studies have clearly shown that air pollution is associated with cardiovascular diseases (CVDs).[1-4] However, the mechanisms by which air pollution exerts these effects are not fully understood. Possible biologic mechanisms and pathways include direct effects on the myocardium, disturbances of the cardiac autonomic nervous system, and pulmonary and systemic oxidative stress and inflammatory responses that trigger endothelial dysfunction, atherosclerosis, and coagulation/thrombosis.[5-7]

If a particular pathway is important in the association between air pollution and a cardiovascular outcome, then genetic polymorphisms, which modify the activity of that pathway, may also modify the association of air pollution with the outcome. Hence, gene-environment interactions can be a tool for exploring the relative importance of the pathway containing the genetic polymorphism. Although toxicological studies can also examine pathways of toxicity of air pollutants, they are generally done at concentrations many times (and often orders of magnitude) higher than common environmental exposures. Because the relative importance of a pathway may be dose dependent, this supports a role for such gene-environment studies at the exposure levels of interest. This insight motivates examination of the role of pathway-specific polymorphisms as modifiers of air pollutant effects.

Air pollutant inhalation into the lungs induces local pulmonary oxidative stress and inflammation. Experimental studies have shown that inhaled air pollutants interact with

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Abbreviations and Acronyms

ACE = *angiotensin-I converting enzyme*

ADRB2 = *β2-adrenergic receptor*

AGT = *angiotensinogen*

AGTR1 = *type 1 angiotensin II receptor*

ALOX15 = *arachidonate 15-lipoxygenase*

APOE = *apolipoprotein E*

BC = black carbon

BP = blood pressure

CRP = C-reactive protein

cSHMT = *cytoplasmic serine hydroxymethyltransferase*

CVD = cardiovascular disease

DGCR8 = *DiGeorge critical region-8*

EDN1 = *endothelin 1*

GRK4 = *G protein–coupled receptor kinase 4*

GSS = genetic susceptibility score

GSTM1 = *glutathione S-transferase μ1*

GSTP1 = *glutathione S-transferase π1*

GSTT1 = *glutathione S-transferase θ1*

GT = guanine thymine

GWAS = genome-wide association study

HFE = *hemocromatosis*

HMOX-1 = *heme oxygenase 1*

HRV = heart rate variability

IL-6 = *interleukin 6*

ITPR2 = *inositol 1,4,5-triphosphate receptor 2*

LPL = *lipoprotein lipase*

LVM = left ventricular mass

MESA = Multiethnic Study of Atherosclerosis

MI = myocardial infarction

miRNA = microRNA

MTHFR = *methylenetetrahydrofolate reductase*

NAS = Normative Aging Study

NQO1 = *NAD(P)H dehydrogenase, quinone 1*

PM = particulate matter

PTGS1 = *prostaglandin-endoperoxide synthase 1*

PTGS2 = *prostaglandin-endoperoxide synthase 2*

ROS = reactive oxygen species

SNP = single-nucleotide polymorphism

TLR4 = *toll-like receptor 4*

VEGF = *vascular endothelial growth factor*

protective secretions at the airway and alveolar surfaces and induce generation of reactive oxygen species (ROS) either directly via Fenton reactions[8] or after activation by cytochrome P450–dependent enzymatic activities.[9,10] Because of their small size, ultrafine particles (ie, particles with aerodynamic diameter <100 nm) may penetrate through the cell membrane and affect intracellular structures related to oxidative stress generation, such as mitochondria.[10] When pulmonary stress responses are insufficient to contain the levels of particulate matter (PM)–induced ROS, oxidative stress can trigger a variety of pulmonary inflammatory processes by activating specific signaling pathways including signal transduction of membrane ligands, pattern recognition receptors, and/or intracellular pathways (eg, mitogen-activated protein kinases) that lead to the activation of proinflammatory transcription factors, cytokines, and chemokines.[6] Recent research has shown that PM-related oxidative stress and inflammation can extend from the lungs to involve cardiovascular structures.[11-13] For example, Gurgueira et al[12] reported that oxidative stress in cardiac tissue increased after adult rats were exposed to concentrated ambient particles. Other studies have demonstrated that particulate air pollution activates the vanilloid receptors on C fibers in the lung, and this plays a role in the generation of systemic changes, including oxidative stress.[14] In human studies, Kim et al[13] showed that levels of urinary 8-hydroxy-2′-deoxyguanosine (a biomarker of oxidative DNA damage and repair) increased in workers after occupational exposure to fine PM, and this has also been reported in a general population study.[15] Recently, Hou et al[16] have shown increased mitochondrial DNA damage, as reflected in increased mitochondrial DNA copy number, in a similar occupational setting of PM exposure. Several human studies have shown that PM exposure increases the levels of circulating inflammatory biomarkers, such as plasma C-reactive protein (CRP) and interleukins.[17-21] Systemic inflammatory responses have been linked to alteration of circulating levels of blood clotting factors,[22,23] increased blood coagulation,[24-26] and atherogenesis.[27]

Understanding the relative roles of such potential pathways has been a major goal of recent air pollution epidemiology. However, human investigations on the molecular and biochemical pathways of air pollution effects have been mostly limited to the use of blood-based biomarkers of oxidative stress, inflammation, and blood clotting. Because target tissues, such as endothelia, arterial walls, and heart tissues, cannot be collected before disease development, the early pathologic processes leading to PM-related CVD cannot be directly investigated in the tissue of concern.

Growing evidence indicates that genetic susceptibility is likely to play a role in response to air pollution. Genetic differences may determine who will have worse health damage from short-term or protracted exposure to air pollution. Because air pollution standards are often based on the effects in sensitive subgroups, identification of these differences will, in addition to providing insight on mechanism, also contribute to understanding the distribution of risk and to setting of air quality standards. In addition, genetic polymorphisms are identical in all the cells of a given individual, including the cardiovascular target tissues. Hence, the investigation of genetic variations in population-based studies of air pollution effects provides a unique opportunity

Table 1
Summary of the selected studies

Author and Years of Study	Population	Characteristics	Genes	Exposure	Health Outcomes	Significant Interactions	Direction*
Schwartz et al[33]	NAS	Boston	*GSTM1*	$PM_{2.5}$	HF	*GSTM1*	↓
2000-2004	n = 497	100% men					
Park et al[31]	NAS	Boston	*HFE* variant	$PM_{2.5}$	SDNN, LF/HF, HF	*HFE*	↓
2000-2004	n = 518	100% men		BC	SDNN, HF, LF/HF		
				Ozone	SDNN, HF, LF/HF		
Chahine et al[29]	NAS	Boston	*HMOX-1*	$PM_{2.5}$	SDNN	*GSTM1*	↓
2000-2005	n = 476	100% men	*GSTM1*		HF	*GSTM1*	↓
	n tot = 638				LF	*GSTM1, HMOX-1*	↓
Baccarelli et al[24]	NAS	Boston	*MTHFR*	$PM_{2.5}$	SDNN	*cSHMT*	↓
2000-2005	n = 549	100% men	*cSHMT*		HF	*cSHMT*	↓
	n tot = 735						
Mordukhovich et al[30]	NAS	Boston	*GSTM1, GSTP1*	BC	Diastolic BP		
1999-2007	n = 461	100% men	*GSTT1*		Systolic BP		
	n tot = 1067		*HMOX-1, NQO1*				
Park et al[37]	NAS	Boston	*HFE, TF C2, HMOX-1*	Tibia lead	QT intervals	*HFE, TF C2, HMOX-1*	↑
1991-1995	n = 613	100% men		Patella lead		*HFE, TF C2, HMOX-1*	↑
				Blood lead		*HFE, TF C2, HMOX-1*	↑
Madrigano et al[36]	NAS	Boston	*GSTM1, HMOX1*	$PM_{2.5}$	sICAM-1	*GSTM1*	↑
1999-2008	n = 809	100% men	*VEGF, LPL, APOE*	BC	sVCAM-1		
	n tot = 1819	white	*HFE, NOS3*				
Wilker et al[38]	NAS	Boston	202 SNPs in 25 genes	$PM_{2.5}$	Δ diastolic BP	*PHF11*	↑
1995-2006	n = 945	100% men			Δ systolic BP	*MMP1, ITPR2*	↑
	n tot = 2098						
Ren et al[32] 1995-2006	NAS	Boston	*HFE, NQO1*	$PM_{2.5}$	Homocysteine	*CAT, HFE*	↑
	n = 1000	100% men	*CAT, GSTM1*			*GSTT1, GSTM1*	↑
	n tot = 2414	Non-Hispanic	*GSTP1, GSTT1*	BC	Homocysteine	*GSTT1, HFE*	↑
		White	*GSTP1, HMOX-1*			*NQO1*	↑
Baja et al[28]	NAS	Boston	*GSS, HFE*	BC	QT intervals	*GSS*	↑
2000-2008	n = 580	100% men	*GSTP1*	CO		*GSS*	↑
	n tot = 926		*HFE*	NO_2		*GSS*	↑
Ren et al[34]	NAS	Boston	*APOE*	$PM_{2.5}$	SDNN	*APOE, LPL, VEGF*	↓
2000-2007	n = 583	100% men	*LPL*		LF	*APOE, LPL, VEGF*	↓
	n tot = 839		*VEGF*		HF	*APOE, LPL, VEGF*	↓
Ren et al[39]	NAS	Boston	20 oxidative stress–related SNPs	Sulfates	8-OHdG	*GSTP1*	↑
2006-2008	n = 320	100% men		OC		*CAT, GSTM1, GC*	↑
				O_3			
Wilker et al[35]	NAS	Boston	SNPs in 19	BC	Diastolic BP	*DICER, GEMIN4*	↑
1995-2008	n = 789	100% Men	miRNA genes		Systolic BP	*GEMIN3, GEMIN4*	↑
	n tot = 2349					*DGCR8*	
Ljungman et al[40]	AIRGENE	Multicity	*IL-6, FGA, FGB,*	*CO*	IL-6	*IL-6*	↑
2003-2004	n = 955	100% men	*FGG*	NO_2	IL-6	*FGB*	↑
	n tot = 5539			$PM_{2.5}$, PM_{10}	IL-6	*FGB*	↑
				CO	IL-6	*FGB*	↑

Peters et al[41]	AIRGENE	Multicity	*FGA, FGB,* and *FGG*	PM_{10}	Fibrinogen	*FGA*	↑
2003-2004	n = 854	100% men				*FGB*	↑
	n tot = 5082						
Van Hee et al[42]	MESA	Multicity	*ACE, ADRB2, AGT,*				
2000-2002	n = 1139	52% women	*TLR4, VEGFA*	Residential	LVM	*AGTR1, ALOX15*	↑
		Balanced ethnic group	*AGTR1, ALOX15, EDN1, GRK4, PTGS1, PTGS2, VEGFB*	Proximity to major roadways			

Abbreviations: n tot, total number of observations including the repeated measurements; HF, high frequency; LF, low frequency; SDNN, standard deviation of normal-to-normal intervals; TF C2, transferrin C2; sICAM-1, soluble intercellular adhesion molecule-1; VCAM-1, Vascular cell adhesion protein 1; PHF11, PHD Finger Protein 11; MMP1, matrix metalloproteinase-1; FGA, Fibrinogen A; FGB, Fibrinogen B; FGG, Fibrinogen G.

* Direction of term for interaction between the exposure and the "at-risk" genotype.

to evaluate mechanisms that operate systemically and/or at the target tissue. In this article, we present a systematic review of the studies, which have examined gene-environment interactions in relation to the cardiovascular health effects of air pollutants.

Methods

To identify all the studies, which examined gene–air pollution interactions in the cardiovascular health effects of air pollutants, we selected published literature meeting the following criteria:

- population-based,
- ambient exposures of any air pollutants,
- health outcomes related to CVD,
- peer-reviewed, and
- written in English.

Studies were identified in PubMed with the following keywords:

- "gene environment," "gene" or "gene environment interaction," or "single-nucleotide polymorphisms (SNPs)" or "polymorphism;"
- "effect modification" or "modify;"
- "air pollution;" and
- "cardiac" or "cardiovascular," "myocardial infarction (MI)" or "inflammatory," or "heart rate variability (HRV)" or "heart rate."

Results

We identified 16 articles meeting our search criteria (Table 1). Most of these studies focused on individual functional polymorphisms or individual candidate genes. Moreover, they were all based on 3 study populations that have been extensively investigated in relation to air pollution effects: the Normative Aging Study (NAS),[24,28-39] Air Pollution and Inflammatory Response in Myocardial Infarction Survivors: Gene-Environment Interaction in a High Risk Group (AIRGENE),[40,41] and the Multiethnic Study of Atherosclerosis (MESA).[42]

The genes examined were *glutathione S-transferaseμ1 (GSTM1)*; *glutathione S-transferaseπ1 (GSTP1)*; *glutathione S-transferase θ1 (GSTT1)*; *heme oxygenase 1 (HMOX-1)*; *NAD(P)H dehydrogenase, quinone 1 (NQO1)*; *catalase (CAT)*; *methylenetetrahydrofolate reductase* (*MTHFR*); *cytoplasmic serine hydroxymethyltransferase (cSHMT)*; *hemocromatosis (HFE)*; genetic susceptibility score (GSS); *interleukin 6 (IL-6)*; *fibrinogen* and its α, β, and γ *subunits*; *angiotensin-converting enzyme (ACE)*; *inositol 1,4,5-triphosphate receptor 2 (ITPR2)*; *β2-adrenergic receptor (ADRB2)*; *angiotensinogen (AGT)*; *type 1 angiotensin II receptor (AGTR1)*; *arachidonate 15-lipoxygenase (ALOX15)*; *endothelin 1 (EDN1)*; *G protein–coupled receptor*

kinase 4 (GRK4); *prostaglandin-endoperoxide synthase 1 (PTGS1)*; *prostaglandin-endoperoxide synthase 2 (PTGS2)*; *toll-like receptor 4 (TLR4)*; *vascular endothelial growth factor (VEGF) A* and *VEGFB; apolipoprotein E (APOE)*; and *lipoprotein lipase (LPL)*.

Results from the NAS

The NAS is a longitudinal aging study established by the veterans administration in 1961 of 2280 men from the greater Boston area, then, free of known chronic medical conditions. Participants underwent detailed examination every 3 to 5 years, including routine physical examination, laboratory tests, collection of medical history, social status information, and administration of questionnaires on smoking history, food intake, and other factors that may influence health. Between January 1995 and December 2006, all 1035 participants still appearing for examination were evaluated for homocysteine, gene polymorphisms, and other covariates one or more times; 1000 (96.6%) of these men were non-Hispanic white. In 4 of the gene-environment articles based on the NAS, HRV was investigated as an outcome. Reduced HRV is a noninvasive measure of cardiac autonomic dysfunction that independently predicts cardiovascular mortality and has been consistently related to short-term PM exposure, particularly to fine particulate air pollution of less than 2.5 μmol/L in aerodynamic diameter ($PM_{2.5}$).[43-45] In the first study, Schwartz et al[33] investigated whether the negative association between $PM_{2.5}$ and HRV was modified by existence or absence of the allele for *GSTM1*, a gene involved in ROS clearance. Exposure to $PM_{2.5}$ during the 48 hours before HRV measurement was associated with a significant decrease in HRV in individuals with deleted *GSTM1* present but had no effect in subject with *GSTM1*. In a subsequent study,[29] these findings were extended to include examination of the guanine thymine (GT) short tandem repeat polymorphism in the *HMOX-1* promoter, a second gene participating on responses against oxidative stress. A high number of microsatellite (GT)n dinucleotide repeats in 5′-flanking region may reduce *HMOX-1* inducibility by ROS and has been associated with increased risk of coronary artery disease in high-risk groups with hyperlipidemia, diabetes, or current smoking.[46,47] Particulate matter$_{2.5}$ effects on HRV were found among carriers of the long GT repeats and not among those individuals carrying the short GT repeats. In addition, a significant 3-way interaction of $PM_{2.5}$ with *GSTM1* and *HMOX-1* was found in relation to HRV. Three other NAS investigations on the negative association between $PM_{2.5}$ and HRV showed that the $PM_{2.5}$ effects were stronger among subjects with wild-type *HFE* gene,[31] encoding for a protein product that modulates uptake of iron and divalent cations from pulmonary sources and reduces their toxicity and in carriers of the (CT/TT) C677T *MTHFR* or (CC) C1420T *cSHMT*, 2 genes in the 1-carbon metabolism pathway that participates in glutathione synthesis.[24]

Another study from Ren et al[34] found that the associations between $PM_{2.5}$ and HRV were modified by gene polymorphisms of *APOE, LPL,* and *VEGF*, examining whether exposures to ambient particles act on autonomic function via the lipid/endothelial metabolism pathway.

Taken together, these findings pinpoint the different roles of genes related to oxidative pathways in determining cardiovascular responses to PM exposure, as reflected in reduced HRV. Even the *HFE* results are indirectly associated with oxidative stress because Ghio and Cohen[8] have shown that increased uptake of the iron into cells in the lung results in reduced oxidative stress and inflammation. In a related finding, Park et al[37] reported that iron metabolism genes, including *HFE*, modified the association of lead with QT interval. Although the exposure used was bone lead, most of the lead in people originates from gasoline emissions.

Consistent with these results, interactions with genes in oxidative pathways have been found in the NAS also in relation with other cardiovascular outcomes, such as homocysteine and QT interval. Ren et al[32] showed that the association of $PM_{2.5}$ exposure with increased plasma homocysteinemia was modified by polymorphisms in *HFE* and *CAT* genes. Borderline significant effect modifications were found for *GSTM1* deletions and *GSTT1* polymorphism. In this study, the association between black carbon (BC), a tracer of particles from vehicular traffic, and plasma homocysteine showed statistically significant effect modifications by *GSTT1* and *HFE* polymorphisms and a borderline effect modification by *NQO1* genotypes. In another study, Ren et al[39] took a pathway approach and examined 20 different polymorphisms in 9 genes along the oxidative defense pathway. After adjustment for multiple comparisons, they reported that polymorphisms in 4 genes (GSTP1, GSTM1, *CAT*, and *group-specific component [GC]*) modified the association of air pollution with *urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG)*. Baja et al[28] showed that BC exposure was positively associated with the duration of the heart rate–corrected QT interval and that the effect was stronger among subjects with a higher GSS, a combined score built to reflect functional effects from the HFE C282Y, *GSTP1* A114V, and HFE H63D genotypes. However, a study evaluating effect modifications on the association between BC and increased blood pressure (BP) did not find any significant interactions with *GSTM1, GSTP1, GSTT1, HMOX-1,* or *NQO1* polymorphisms.[30]

Conversely, a recent analysis of the NAS study showed that the association between BC and increased BP was modified by SNPs in genes involved in processing of microRNAs (miRNAs) from pre-/primi-miRNA to maturity.[35] MicroRNAs are emerging as key regulators of gene expression and might be participating in the regulation of the coordinated changes in gene expression that accompany the responses to air pollution exposures. In particular, interactions modifying BC associations

were observed with SNPs in the *DICER*, gem-associated protein 4 (GEMIN 4), and *DiGeorge critical region 8* (*DGCR8*) genes and in gem-associated protein 3 (GEMIN 3) and *GEMIN4*, predicting diastolic and systolic BP, respectively. The BC-miRNA gene interactions found in the NAS are consistent with recent findings showing that exposure to particulate pollutants modified the expression of selected miRNAs in airway epithelial cells in vitro[48] and in peripheral blood leukocytes in exposed individuals.[49]

Madrigano et al[36] reported that both $PM_{2.5}$ and BC were associated with increases in intracellular and vascular cellular adhesion molecules, which are markers of endothelial activation, and that those associations were modified by *GSTM1*.

Finally, Wilker et al[38] reported that polymorphisms in *ITPR2*, a gene that is in the angiotensin II pathway (immediately downstream from the angiotensin II receptor) modified the association of particle air pollution with postural change in BP.

Results from AIRGENE

AIRGENE is a multicenter epidemiological study, designed to study the role of air pollution in eliciting inflammation in MI survivors in 6 European cities, Helsinki, Stockholm, Augsburg, Rome, Barcelona, and Athens. Outcomes of interest were plasma concentrations of the proinflammatory cytokine IL-6 and the acute phase proteins CRP and fibrinogen. In addition, the study was designed to assess the role of candidate gene polymorphisms hypothesized to lead to a modification of the short-term effects of ambient air pollution. In total, 1003 MI survivors were recruited and assessed with at least 2 repeated clinic visits without any signs of infections; in total, 5813 blood samples were collected. Subjects across the 6 cities varied with respect to risk factor profiles. Most of the subjects were nonsmokers, but light smokers were included in Rome, Barcelona, and Athens. Substantial inter- and intraindividual variability was observed for IL-6, fibrinogen, and CRP.

Ljungman et al[40] investigated whether *IL-6* and *fibrinogen* gene variants affected plasma IL-6 responses to air pollution in the AIRGENE patients. Two specific variants in *IL-6* and *fibrinogen* genes modified IL-6 responses after exposure to carbon monoxide (24-hour average). Nonsignificant interactions were found for nitrogen dioxide.

Peters et al[41] found that measures of ambient PM with aerodynamic diameter 10 μm or less (PM_{10}) from monitoring stations in the 5 cities during the 5 days before the examinations were positively associated with plasma fibrinogen levels and that this effect was modified by genetic variation in the fibrinogen genes. This study examined 21 SNPs in the 3 *fibrinogen* genes coding for the α, β, and γ subunits. The fibrinogen response to PM_{10} exposure was 8- to 11-fold greater among individuals with homozygous minor alleles in the *fibrinogen* gene, compared with carriers of homozygous major alleles.

Results from MESA

Multiethnic Study of Atherosclerosis is a prospective cohort study designed to examine the progression of subclinical CVD; it enrolled 6814 men and women 44 to 85 years old who were free of clinical CVD at entry. The participants were recruited from 6 US communities: Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St Paul, MN. A subcohort of 2880 subjects was selected for genetic studies.

In the MESA, living in proximity to major roadways (<50 m compared with >150 m) has been linked with higher left ventricular mass (LVM), a predictor of negative cardiovascular outcomes, such as heart failure, stroke, and sudden cardiac death. Using a tagSNP approach, Van Hee et al[42] investigated whether the association between proximity to major roadways and LVM was modified by SNPs and haplotypes in 12 candidate genes (*ACE, ADRB2, AGT, AGTR1, ALOX15, EDN1, GRK4, PTGS1, PTGS2, TLR4, VEGFA,* and *VEGFB*). In this study, tagSNPs in the *AGTR1* (rs6801836) and *ALOX15* (rs2664593) genes were found to be associated with a 9% to 10% difference in the association between residential proximity to major roadways and LVM.

Discussion

This article presents a systematic review of the studies, which have examined gene-environment interactions in relation to the cardiovascular health effects of air pollutants. The 16 studies that met our search criteria were all based on 3 study populations that have been extensively investigated in relation to air pollution effects: the NAS, AIRGENE, and MESA.

Unfortunately, the studies differed substantially in both the cardiovascular outcomes examined and the polymorphisms examined, so there is little confirmation of results across cohorts. The greatest similarity is that both the NAS and MESA found polymorphisms (but in different genes) in the angiotensin pathway related to cardiovascular outcomes (but different ones). The most consistent finding within a cohort is the multiple findings of modifications by genes in the oxidative stress defense pathway for a variety of outcomes, all within the NAS. This is supported indirectly by a finding in the Swiss study on Air Pollution and Lung Disease in adults study that second-hand smoke, a pollutant with similarities to urban particulate air pollution, also reduced HRV and that this association was also modified by polymorphisms in *glutathione S-transferases*.[50] Supporting evidence also comes from reports from these and other studies that obesity, a pro-oxidative stress state, also tends to modify the same relationships as the genetic polymorphisms.[31,33,36,50-52] Oxidative stress polymorphism have also been reported to

modify the association between air pollution and respiratory outcomes,[53-56] making these findings perhaps the strongest signal to date.

Clearly, to draw stronger conclusions, greater replication will be necessary. One critical issue is whether that replication should be done by SNP or by pathway. Some recent analyses such as Baja et al[28] have used a score system for a pathway and evaluated interactions, a procedure that may have more power than SNP analyses with multiple comparison corrections. Other methods, such as kernel machinery,[39] may be modified to examine interactions by pathway. If the goal was to target a protein, SNP analyses would be more important, but if the goal is to identify mechanistic pathways of toxicity, the pathway approach may make more sense.

With respect to risk assessment, a key feature of these studies is the finding that effect modification was quite large, with the response to air pollution essentially only seen in people with the unfavorable polymorphisms. If the cardiovascular effects of air pollution are restricted to a subset of a third or less of the population, with effect sizes in that subset triple those reported when the entire population is studied, then the inequity in distribution of air pollution–related cardiovascular risk is not trivial and will need to be taken into account in both risk assessments and setting standards.

The cohort studies involved to date have not been large, which limits power to more common polymorphisms if one does not take the pathway approach. Clearly, multicohort studies allowing power to detect rarer genes and for replication is one future direction. With large enough samples, genome-wide association study (GWAS) by environment interactions can be examined, although that will be methodologically challenging.

Most of the studies focused on the interaction of gene polymorphisms with short-term exposure to air pollutant. Only the MESA study examined distance to major roadways, which, instead, reflects long-term exposures to air pollution. All studies conducted, so far, have tested the effect modification associated with selected functional polymorphisms in candidate genes. Genome-wide association study data have been generated in several cohorts that are or might be characterized for their air pollution exposure. Thus, it might be possible in the near future to conduct genome-wide scans of effect modifications of the associations of air pollution exposure with CVD. However, because GWAS studies have been designed to provide sufficient power for testing the main effects of gene polymorphisms on cardiovascular outcomes, even more than in these GWAS studies, genome-wide investigations of effect modifications will need to rely on cooperation and data pooling across multiple cohorts.

Genetic susceptibility is likely to play a role in response to air pollution; therefore, gene-environment interaction studies can be a tool for exploring the mechanisms and the importance of the pathway in the association between air pollution and a cardiovascular outcome; moreover, these studies would contribute to understanding the distribution of risk and to setting of air quality standards. More studies and more collaboration among studies involving multiple cohorts would be needed to draw stronger conclusions.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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