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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 interactions 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 which have examined gene-environment interactions in relation to the cardiovascular health effects of air pollutants. We identified 16 papers meeting our search criteria. Of these studies, most have focused on individual functional polymorphisms or individual candidate genes. Moreover they were all based on three study populations that have been extensively investigated in relation to air pollution effects: the Normative Aging Study (NAS), AIRGENE and Multiethnic Study of Atherosclerosis (MESA) study.

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 interactions 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.

Introduction

Epidemiologic studies have clearly shown that air pollution is associated with cardiovascular diseases (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. While 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. Since the

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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 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 (i.e. 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 particulate matter, and this has also been reported in a general population study (15). Recently, Hou et al. have shown increased mitochondrial DNA damage, as reflected in increased mitochondrial DNA copy number, in a similar occupational setting of PM exposure (16). A number of 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 pathological processes leading to PM-related cardiovascular disease 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. Since air pollution standards are often based on 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. Also, 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 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 cardiovascular disease
- Peer-reviewed.
- Written in English.

Studies were identified in PubMed with the following keywords:

- “gene environment”, or “gene” or “gene environment interaction”, or “SNPs” or “polymorphism”
- “effect modification” or “modify”
- “air pollution”
- “cardiac” or “cardiovascular” or “myocardial infarction” or “inflammatory” or “heart rate variability” or “heart rate”.

Results

We identified 16 papers meeting our search criteria (Table). Most of these studies focused on individual functional polymorphisms or individual candidate genes. Moreover, they were all based on three study populations that have been extensively investigated in relation to air pollution effects: the Normative Aging Study (NAS)(24,28-39), AIRGENE (40,41) and the MESA study (42).

The genes examined were: Glutathione S-transferase mu 1 (GSTM1), Glutathione S-transferase pi 1 (GSTP1), Glutathione S-transferase theta 1 (GSTT1), Heme oxygenase-1 (HMOX-1), NQO1, Catalase (CAT), *MTHFR*, cSHMT, hemochromatosis (HFE), genetic susceptibility score (GSS), IL6, fibrinogen and its α , β , and γ subunits, ACE, ITPR2, ADRB2, AGT, AGTR1, ALOX15, EDN1, GRK4, PTGS1, PTGS2, TLR4, vascular endothelial growth factor (VEGF)A, and VEGFB, apolipoprotein E (APOE), and lipoprotein lipase (LPL).

Results from the Normative Aging Study

The NAS is a longitudinal aging study established by the Veterans Administration (VA) 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 four of the gene-environment articles based on the NAS, Heart Rate Variability (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 $<2.5 \mu\text{mol/L}$ in aerodynamic diameter ($\text{PM}_{2.5}$) (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). PM_{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 three-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, two genes in the one-carbon metabolism pathway that participates in glutathione synthesis (24). Another study from Ren and co-authors (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 since Ghio (8) has 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. While 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 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, GC) modified the association of air pollution with 8-OHdG (39). Baja et al (28) showed that BC exposure was positively associated with the duration of the heart-rate-corrected QT interval, and that effect was stronger among subjects with a higher genetic susceptibility score, 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 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 blood pressure was modified by single nucleotide polymorphisms in genes

involved in processing of microRNAs (miRNAs) from pre/primi-miRNA to maturity (35). MiRNAs 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, GEMIN4, and DiGeorge critical region-8 (DGCR8) genes, and in GEMIN3 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 (ICAM-1 and VCAM-1), 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 blood pressure.

Results from AIRGENE

AIRGENE is a multicenter epidemiological study, designed to study the role of air pollution in eliciting inflammation in MI survivors in six European cities, Helsinki, Stockholm, Augsburg, Rome, Barcelona, and Athens. Outcomes of interest were plasma concentrations of the proinflammatory cytokine interleukin 6 (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 six 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 intra-individual variability was observed for IL-6, fibrinogen and CRP.

Liungman et al. (40) investigated whether IL6 and fibrinogen gene variants affected plasma IL-6 responses to air pollution in the AIRGENE patients. Two specific variants in IL6 and fibrinogen genes modified IL6 responses after exposure to carbon monoxide (24-hr average). Non-significant interactions were found for nitrogen dioxide.

Peters and colleagues (41) found that measures of ambient particulate matter with aerodynamic diameter 10 µm or less (PM₁₀) from monitoring stations in the five 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 single nucleotide polymorphisms in the three fibrinogen genes coding for the α,β and γ subunits. The fibrinogen response to PM₁₀ 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

MESA is a prospective cohort study designed to examine the progression of subclinical CVD; it enrolled 6,814 men and women 44–85 years of age who were free of clinical CVD at entry. The participants were recruited from six U.S. communities: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan, New York; and St. Paul, Minnesota. A subcohort of 2,880 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 single-nucleotide polymorphisms 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 type 1 angiotensin II receptor (AGTR1, rs6801836) and arachidonate 15-lipoxygenase (ALOX15, rs2664593) genes were found to be associated with a 9-10% 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 three study populations that have been extensively investigated in relation to air pollution effects: the NAS, AIRGENE, and MESA study. 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 SAPALDIA study that second hand smoke, a pollutant with similarities to urban particulate air pollution, also reduced heart rate variability, and that this association was also modified by polymorphisms in GSTs (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 single 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 multi-cohort 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. GWAS 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 cardiovascular disease. 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 interactions 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.

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Table

summary of the selected studies

Author and years of study	Population**	Characteristics	Genes	Exposure	Health outcomes	Significant Interactions	Direction*
Schwartz (33) 2000-2004	NAS n=497	Boston 100% Men	GSTM1	PM2.5	HF	GSTM1	↓
Park (31) 2000-2004	NAS n=518	Boston 100% Men	HFE variant	PM2.5	SDNN LF/HF		
				BC ozone	HF SDNN, HF, LF/HF SDNN, HF, LF/HF	HFE	↓
Chahine (29) 2000-2005	NAS n=476 n tot=638	Boston 100% Men	HMOX-1 GSTM1	PM2.5	SDNN HF	GSTM1 GSTM1	↓ ↓
Baccarelli (24) 2000-2005	NAS n=549 n tot=735	Boston 100% Men	MTHFR cSHMT	PM2.5	LF SDNN HF	GSTM1, HMOX-1 cSHMT cSHMT	↓ ↓ ↓
Mordukhovich (30) 1999-2007	NAS n=461 n tot=1067	Boston 100% Men	GSTM1, GSTP1 GSTT1 HMOX-1, NQO1	BC	Diastolic BP Systolic BP		
Park (37) 1991-1995	NAS n=613	Boston 100% Men	HFE, TF C2, HMOX-1	tibia lead patella lead blood lead	QT intervals	HFE, TF C2, HMOX-1 HFE, TF C2, HMOX-1 HFE, TF C2, HMOX-1	↑ ↑ ↑
Mdrigano (36) 1999-2008	NAS n=809 n tot=1819	Boston 100% Men white	GSTM1, HMOX1 VEGF, LPL, APOE HFE, NOS3	PM2.5 BC	sICAM-1 sVCAM-1	GSTM1	↑
Wilker (38) 1995-2006	NAS n=945 n tot=2098	Boston 100% Men	202 SNPs in 25 genes	PM2.5	Δ Diastolic BP Δ Systolic BP	PHF11 MMP1, ITPR2	↑ ↑
Ren (32) 1995-2006	NAS n=1000 n tot=2414	Boston 100% Men Non-hispanic white	HFE, NQO1 CAT, GSTM1, GSTP1, GSTT1	PM2.5 BC	Homocysteine Homocysteine	CAT, HFE GSTT1, GSTM1 GSTT1, HFE	↑ ↑ ↑

Author and years of study	Population**	Characteristics	Genes	Exposure	Health outcomes	Significant Interactions	Direction*
Bajaj (28) 2000-2008	NAS n=580 n tot=926	Boston 100% Men	GSTP1 HMOX-1 GSS,HFE C282Y, GSTP1 A114V, HFE H63D	BC CO NO2	QT intervals	NQO1 GSS GSS GSS	↑ ↑ ↑ ↑
Ren (34) 2000-2007	NAS n=583 n tot=839	Boston 100% Men	APOE LPL VEGF	PM2.5	SDNN LF HF	APOE, LPL, VEGF APOE, LPL, VEGF APOE, LPL, VEGF	↓ ↓ ↓
Ren (39) 2006-2008	NAS n=320	Boston 100% Men	20 oxidative stress-related SNPs	Sulfates	8-OHdG	GSTP1	↑
Wilker (35) 1995-2008	NAS n=789 n tot=2349	Boston 100% Men	SNPs in 19 miRNA genes	OC O3 BC	Diastolic BP Systolic BP	CAT,GSTM1,GC DICER, GEMIN4, GEMIN3, GEMIN4 DGCR8	↑ ↑ ↑
Ljungman (40) 2003-2004	AIRGENE n=955 n tot=5539	Multi city 100% Men	IL6, FGA, FGB, FGG	CO NO2 PM25,PM10 CO	IL6 IL6 IL6 IL6	IL6 FGB FGB FGB	↑ ↑ ↑ ↑
Peters (41) 2003-2004	AIRGENE n=854 n tot=5082	Multi city 100% Men	FGA, FGB, and FGG	PM10	Fibrinogen	FGA FGB	↑ ↑
Van Hee (42) 2000-2002	MESA n=1139	Multi city 52% female	ACE, ADRB2, AGT, TLR4, VEGFA,	residential	Left ventricular mass (LVM)	AGTR1, ALOX15	↑

** n is the total number of subjects, n tot is the total number of observations including the repeated measurements

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