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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