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Mechanisms linking traffic-related air pollution and atherosclerosis

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Abstract

Purpose of review—Recent discoveries in the field of air pollution toxicology highlight the potential impact of specific sources of air pollution, especially related to roadway emissions, on acute and chronic cardiovascular disease. This review covers potential mechanisms, both in terms of biological pathways and chemical drivers, to explain these observations.

Recent findings—Air pollution is associated with chronic progression of cardiovascular disease. Roadway exposures appear to have a strong correlation to these adverse outcomes. Controlled toxicological studies highlight potential interactions between vehicle-source emissions and adverse vascular outcomes. Mechanistically, a role for both innate and adaptive immune responses is emerging, with important recent findings demonstrating that immunomodulatory pattern-recognition receptors such as Toll-like receptor-4 and lectin-like oxidized LDL receptor-1 may play a role in communicating airway exposures to cardiovascular outcomes.

Summary—An improved understanding of the sources and mechanisms underlying adverse cardiovascular health outcomes of air pollution would enhance our ability to manage vulnerable populations and establish precise, effective regulatory policies.

Keywords

atherosclerosis; diesel; particulate matter; pattern-recognition receptors; traffic

INTRODUCTION

Air pollution is a ubiquitous and complex environmental health concern. Even at levels within the Environmental Protection Agency's allowable limits, trends for increased cardiopulmonary morbidity and mortality due to particulate matter have been routinely demonstrated in large population studies. The WHO estimates that the global impact of air pollution is roughly 800 000 premature deaths per year, the vast majority arising from cardiopulmonary outcomes [1]. More recently, it has been estimated that air pollution in the United States causes an average loss of 7 months of life per person [2]. Particulate matter levels are associated with both acute cardiac events [3■,4] as well as chronic progression of

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atherosclerotic disease [5,6]. These relationships have been firmly established for a singular pollutant, airborne particulate matter, but substantial evidence for other pollutants has been reported as well, especially those associated with traffic sources [5]. Unfortunately, our understanding of the underlying mechanism for exacerbated cardiovascular disease by air pollution is inadequate, which limits our ability to manage vulnerable populations and establish precise, effective regulatory policies.

A major unanswered question relates to the transference of toxicity from pulmonary exposures to systemic vascular outcomes. Growing evidence suggests that inhaled air contaminants evoke a systemic innate immune response that promotes vascular diseases. Recent studies highlight a role for immunomodulatory pattern-recognition receptors, including Toll-like receptors (TLRs) and the lectin-like oxidized low-density lipoprotein (oxLDL) receptor (LOX-1) for driving the extrapulmonary inflammatory manifestations [7■■,8■■]. Expression of LOX-1 is elevated in systemic arteries following exposure to a diverse profile of air pollutants, including diesel emissions, gasoline emissions, and ozone [7■■,9]; blocking LOX-1 abrogates exhaust-induced aortic lipid peroxidation and inflammation. Furthermore, circulating LOX-1 levels are elevated in both mice and humans following acute exposures. Likewise, recent work on airborne particulate matter highlights a similar role for TLR-4, which is thought to mediate similar outcomes [8■■]. The following sections provide a background of relevant research findings and potential.

ATHEROSCLEROTIC OUTCOMES IN CONTROLLED EXPOSURE STUDIES

Over the past 15 years, the investigation into the effects of air pollution exposure on human health has focused on the progression of cardiovascular disease, namely atherosclerosis, as well as onset of clinical cardiovascular events. Although the majority of the published reports of associations between air pollution exposure and its sequelae on the human cardiovascular system are derived from studies involving daily particulate matter and gaseous pollutant levels and corresponding hospital admissions for cardiovascular events and relative mortality [4,6,10–14], there are a subset of human studies that have investigated the effects of air pollution exposure on the cardiovascular system using controlled exposure studies. For example, in a cohort of 60–80-year-old men, exposure to concentrated ambient air pollution particles (CAPs) caused significant decrease in heart rate variability, which was not observed in a similar study with young, healthy volunteers [15]. In a cohort of volunteers with prior myocardial infarction, exposure to diesel exhaust (300 μg particulate matter per m^3) for 1 h during periods of rest and moderate exercise resulted in increased ischemic cardiac burden and decreased release of endothelial tissue plasminogen activator (tPA) [16], a key regulator of endogenous fibrinolysis. Similarly, diesel exhaust exposure decreased release of tPA in healthy individuals exposed to the same levels and time periods [17], an effect that persisted at 6 h postexposure.

Other studies report a causative role of components of air pollution, such as vehicular emissions, on altered thrombosis or changes in hemostasis. A double-blind randomized crossover study in which 20 healthy volunteers were exposed to either dilute diesel exhaust or filtered air reported that inhalation of diesel engine emissions resulted in increased platelet activation and thrombus formation [18]. Additionally, diesel exhaust exposure has also been reported to induce plasma cytokine production and decrease endothelium-dependent vasodilation in healthy male volunteers [19]. These combined results suggest that air pollution exposure can result in altered cardiac function, blood pressure regulation, and fibrinolysis in humans after an acute exposure, a combination of which likely account for the associations reported in epidemiological studies.

In addition to effects on cardiac function, thrombosis formation and fibrinolysis regulation, acute exposures to traffic-generated air pollution have also been reported to induce expression of factors associated with progression of atherosclerosis and subsequent plaque rupture. In healthy humans, a 2 h exposure to 100 μg particulate matter per m^3 of diesel exhaust during periods of exercise and rest resulted in a significant increase in plasma levels of endothelin-1 (ET-1) and oxides of nitrogen [20], which are associated with atherosclerotic plaque growth [21]. Additionally, diesel-exposed individuals exhibited elevated total and active matrix metalloproteinase-9 (MMP-9), which have been associated with plaque rupture in humans [22]. Results from this same cohort show alterations in plasma lipids and upregulation of the soluble form of the oxLDL receptor, LOX-1, with exposure to diesel exhaust [7▪▪], both of which have been shown in human studies of progression of atheromatous plaque growth and rupture [23,24].

A more in-depth understanding of the mechanisms involved in the observed effects, including progression of atherosclerosis, of exposure to air pollution seen in human studies has been provided through numerous animal studies involving both acute and chronic exposures of components of air pollution. Exposure of Watanabe heritable hyperlipidemic rabbits to PM10 (particulate matter <10 μm) resulted in progression of atherosclerotic lesions, with increased plaque-cell turnover and extracellular lipid pools in coronary and aortic lesions, as well as increased lipids in aortic lesions [25]. In agreement with these findings, Sun *et al.* [26] reported that exposure to CAPS in the hypercholesterolemic apolipoprotein E-null ($ApoE^{-/-}$) mouse resulted in increased plaque lipid content, macrophage infiltration, and induction of vascular reactive oxygen species (ROS). Similar findings have been reported for diesel engine exhaust exposure as well [27▪,28▪]. The size of the particulate matter (which may also reflect compositional differences) may play a significant role in the degree of plaque growth and/or lipid composition with exposure. In a study of the effects of PM 2.5 vs. ultrafine particles (UFPs; mass mean aerodynamic diameter <0.18 μm), it was reported that UFP-exposed $ApoE^{-/-}$ mice developed 25 vs. 55% more aortic atherosclerosis, assessed by the mean lesional area in the aortic root, compared with PM 2.5 or filtered air-exposed mice [29].

Investigations into the pathways that contribute to air pollution-mediated progression of atherosclerosis have reported that both subchronic and acute inhalation exposures to traffic-generated air pollution in $ApoE^{-/-}$ mice lead to increased plasma oxLDL, vascular ROS, ET-1 expression, and MMP expression and activity [20,30]. A role for altered lipid homeostasis and signaling in air pollution-mediated progression of atherosclerosis was noted following exposure of $ApoE^{-/-}$ mice to mixed vehicular emissions (gasoline and diesel combined), which resulted in increased expression of the oxLDL receptor LOX-1 in vascular endothelial cells, which is known to be upregulated in human atherosclerosis and is responsible for mediating increased oxLDL uptake into plaques [31,32]. Although the pathways involved in air pollution-mediated atherosclerosis are beginning to be identified, further research is needed to understand which components of the complex mixture of air pollutants are most toxic, and how genetics, dietary differences, and underlying diseases of susceptible individuals contribute to exposure-related progression of cardiovascular disease.

POTENTIAL PATHWAYS LINKING AIRWAY EXPOSURE TO SYSTEMIC VASCULAR DISEASE

Both innate and adaptive immune response activation may be mechanisms by which exposure to vehicular-source and ambient air pollution contributes to atherosclerosis progression. There is considerable evidence that exposure to a number of components of ambient air pollution stimulates an innate immune response with the expression of cytokines by macrophages, dendritic cells, and epithelial cells within the lungs and that this response

is, in part, mediated by activation of TLR-2 and TLR-4 [33–38]. This can lead to increases in plasma cytokines, both proinflammatory and antiinflammatory. Given that atherosclerosis is a unique type of chronic inflammation, it stands to reason that ambient air pollution-induced increases in proinflammatory cytokines could have an indirect effect of contributing to the on-going inflammation within the atherosclerotic plaque. Cytokines such as tumor necrosis factor-α, interleukin (IL)-6, and IL-12 have all been shown to have proatherogenic effects in hyperlipidemic mouse models of atherosclerosis [39–41]. On the other hand, there is also evidence that engine emissions and ambient pollutants can play an adjuvant role with respiratory allergens and induce an antiinflammatory Th-2 response and a switch of B cells to secretion of IgE [42–44]. Thus, the ultimate effect of exposure to traffic-derived air pollution on atherosclerosis may depend on whether an individual has been sensitized to respiratory allergens. A thorough test of this 'indirect' hypothesis will require exposure of mice with cell type-specific deficiencies in the Toll receptors, the proinflammatory cytokines, or their receptors. In addition to ambient air-pollutant effects on the innate immune response, there is emerging evidence that exposure may also have direct effects on lymphocytes populating the lungs or associated lymph nodes and effects on numbers of circulating lymphocytes [44,45]. One example is recent evidence that air pollutants have inhibitory effects on T regulatory cells [46], which are considered atheroprotective [47,48].

A leading paradigm for how air-pollutant exposure contributes to lung disease and atherosclerosis is the induction of oxidative stress [49]. Increases in ROS generation accompany activation of an innate immune response via engagement of TLRs and scavenger receptors [38]. Pollutant exposure and oxidative stress in the lungs also contributes to increases in markers of systemic oxidative stress such as oxLDL and antibodies to oxLDL [7■■,50,51]. It is also possible that exposure to ambient air particulates stimulates the formation of oxidized phospholipids in the lungs presumably derived from the oxidation of lung surfactant. Oxidized phospholipids are recognized by TLRs and by scavenger receptors such as cluster of differentiation-36 or LOX-1 [7■■,52–54]. Thus, they could have direct effects on activation of an innate immune response in the lungs and, if released from the lungs in association with oxLDL or oxHDL, could have systemic effects on atherosclerosis. There are also circulating antibodies that recognize oxidized phospholipids, although it is still controversial whether these antibodies are proatherogenic or antiatherogenic [55,56].

In all of the cases cited above, the effects on atherosclerosis of pollutant exposure are indirect. However, there is some limited evidence that UFPs may be able to enter the circulation and, thus, could have direct effects on the blood vessels [57,58]. So far, there have not been reports of ambient air-pollutant particulates within atherosclerotic plaques. However, there have been reports of pollutant effects in the brain and central nervous system [59,60] suggesting that components of air pollutants can cross the blood–brain barrier. Thus, air-pollutant exposure could have neurological effects that could in turn affect vascular functions and atherosclerosis. Finally, it is also conceivable that macrophages and dendritic cells that take up the particulates in the lungs could egress from the lungs in transit to lymph nodes for antigen presentation. Additional studies with tracer-labeled particulates are needed to further test this hypothesis.

LINKING COMPLEX POLLUTANT MIXTURE WITH COMPLEX DISEASE

Air pollution is a complex chemical mixture made up of both solid (particulates) and gaseous components. Although air quality monitoring networks throughout the United States provide large quantities of highly useful data, they also fail to capture much of the temporal and spatial dynamics that impacts the daily lives of the public. For justifiable reasons, local air quality monitoring stations are located at a reasonable distance from traffic, yet people spend a great deal of time in traffic with very immediate and proximal exposures to

vehicular emissions. Several recent studies have observed a signal from traffic-related emissions, either by assessing health impacts of living close to roadways [5,61] or by source apportionment methods [62]. These studies typically find that fresh vehicular emissions are associated with a stronger negative health impact than other metrics of air pollution.

Owing to the vast number of chemicals in combustion source emissions, sorting out both individual drivers of vascular toxicity as well as potential interactions among pollution components has been a major challenge. The vascular toxicity of a number of gaseous air pollutants has recently been explored to determine whether they might explain the responses to gasoline engine emissions. Multivariate analysis indicated that NO, NO_2, and CO were strong predictors of vascular lipid peroxidation and induction of MMP-9 and ET-1 mRNA. In 7-day exposures, NO and CO could both induce several outcomes, albeit to a lesser degree, of gasoline exhaust exposure, including activation of MMP-9 and upregulation of ET-1 mRNA [63]. NO_2 did not seem to exhibit substantial systemic vascular effects.

Scientists in the field have long hypothesized a potential interaction between specific gases and particles, with the assumption that gases may adhere to or modify the chemistry of particulate matter, thereby altering the toxicity of particulate matter. Earlier studies found that ‘incubating’ diesel particulate matter with ozone would dramatically increase the toxicity of diesel particles [64]. Most recent efforts have focused on filtering particulate matter from whole emissions, ostensibly to compare the relative contribution of particulate matter. In acute human studies, it was found that whole diesel emissions could alter vasoreactivity [17], but this effect could not be replicated by either ambient particulate matter or NO_2 (a major gaseous component of diesel emissions) by themselves [65,66]. Particle traps, however, installed on the diesel exhaust system did have a demonstrable protective effect on vasomotor effects of whole diesel [67■■].

The permutation missing from these valuable human studies is exposure to freshly generated diesel particulate matter in the absence of the copollutant gases. That is, is it really the diesel particulate matter that is so toxic, or is it the fresh diesel particulate matter with volatile/semivolatile adherents from the gas phase the concern? If so, then efforts to filter diesel particulate matter from engines will still be beneficial, but there are a number of other background particles, including road dust, onto which the gas phase components may still adhere. In animal studies of amore chronic nature, filtration of particulate matter from gasoline or diesel engines had minimal impact on biomarkers of vascular disease [27■,30]. When gasoline emissions and diesel emissions were combined, however, an interaction between gases and particles became clear. Vascular oxidative stress in ApoE-null mice exposed to this mixed emissions model was synergistically increased compared with either of the individual emissions [7■■]. Moreover, filtration of the particulate fraction almost completely removed the effect, whereas adding the mixed vehicular gases to secondary particles significantly increased vascular toxicity. The authors proposed that this effect may relate to the complex surface area of diesel particles that acts to carry volatile organic compounds (which are quite high in the gasoline engine emissions, but not in diesel) deeper into the lungs and also afford a longer residence time.

CONCLUSION

It seems clear that a number of components of combustion emissions may exhibit vascular toxicity, but limited experimental evidence exists currently from which to derive a model of interactive or cumulative effects. Much has been learned in the past decade in terms of the breadth of cardiovascular health implications of air pollution, and a number of cogent mechanistic pathways have emerged in recent years. As we continue to elaborate the potential health effects and mechanisms thereof, we will have improved means of

determining susceptibility in individuals in order to better manage risk in the vulnerable patient. Additionally, going forward, greater emphasis on mixtures will be necessary from a research point of view to support incorporating mixtures or concepts of cumulative impacts into the regulatory framework.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 171–172).

1. World Health Organization. Geneva, Switzerland: World Health Organization; 2002. World Health Report 2002.
2. Pope CA 3rd, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. N Engl J Med. 2009; 360:376–386. [PubMed: 19164188]
3. Nawrot TS, Perez L, Künzli N, et al. Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet. 2011; 377:732–740. [PubMed: 21353301] A meta-analysis finds that exposure to traffic and air pollution rank very highly as likely triggers of acute coronary events.
4. Peters A, Dockery DW, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. Circulation. 2001; 103:2810–2815. [PubMed: 11401937]
5. Hoffmann B, Moebus S, Möhlenkamp S, et al. Heinz Nixdorf Recall Study Investigative Group. Residential exposure to traffic is associated with coronary atherosclerosis. Circulation. 2007; 116:489–496. [PubMed: 17638927]
6. Kunzli N, Jerrett M, Mack WJ, et al. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect. 2005; 113:201–206. [PubMed: 15687058]
7. Lund AK, Lucero J, Harman M, et al. LOX-1 mediates vascular inflammation and oxidative injury caused by inhaled vehicular emissions. Am J Respir Crit Care Med. 2011; 184:82–91. [PubMed: 21493736] Highlights a potential role of the immunomodulatory pattern-recognition receptor in driving systemic vascular oxidative stress after inhalational exposure to an urban background of vehicular exhausts. Also notes a potential synergy between mixtures from gasoline and diesel combustion sources.
8. Kampfrath T, Maiseyeu A, Ying Z, et al. Chronic fine particulate matter exposure induces systemic vascular dysfunction via NADPH oxidase and TLR4 pathways. Circ Res. 2011; 108:716–726. [PubMed: 21273555] Demonstrates that TLR-4 mediates systemic inflammatory responses of concentrated ambient particulates. Also begins to draw a line between modifications of lung surfactant phospholipids and systemic responses of the innate and possibly adaptive immunity.
9. Kodavanti UP, Thomas R, Ledbetter AD, et al. Vascular and cardiac impairments in rats inhaling ozone and diesel exhaust particles. Environ Health Perspect. 2011; 119:312–318. [PubMed: 20980218]

10. Pope CA III, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation. 2004; 109:71–77. [PubMed: 14676145]
11. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA. 2006; 295:1127–1134. [PubMed: 16522832]
12. Peng RD, Chang HH, Bell ML, et al. Coarse particulate air pollution and hospital admissions for cardiovascular and respiratory diseases among medicare patients. JAMA. 2008; 299:2172–2179. [PubMed: 18477784]
13. Van Hee VC, Adar SD, Szpiro AA, et al. Exposure to traffic and left ventricular mass and function: the multi-ethnic study of atherosclerosis. Am J Respir Crit Care Med. 2009; 179:827–834. [PubMed: 19164703]
14. Wellenius GA, Schwartz J, Mittleman MA. Particular air pollution and hospital admissions for congestive heart failure in seven United States cities. Am J Cardiol. 2006; 97:404–408. [PubMed: 16442405]
15. Devlin RB, Ghio AJ, Kehrl H, et al. Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. Eur Respir J Suppl. 2003; 40:76s–80s. [PubMed: 12762579]
16. Mills NL, Törnqvist H, Gonzales MC, et al. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. N Engl J Med. 2007; 357:1075–1082. [PubMed: 17855668]
17. Mills NL, Törnqvist H, Robinson SD, et al. Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. Circulation. 2005; 112:3930–3936. [PubMed: 16365212]
18. Lucking AJ, Lundback M, Mills NL, et al. Diesel exhaust inhalation increases thrombus formation in man. Eur Heart J. 2008; 29:3043–3051. [PubMed: 18952612]
19. Törnqvist H, Mills NL, Gonzales M, et al. Persistent endothelial dysfunction in humans after diesel exhaust inhalation. Am J Respir Crit Care Med. 2007; 176:395–400. [PubMed: 17446340]
20. Lund AK, Lucero J, Lucas S, et al. Vehicular emissions induce vascular MMP-9 expression and activity associated with endothelin-1 mediated pathways. Arterioscler Thromb Vasc Biol. 2009; 29:511–517. [PubMed: 19150882]
21. Ihling C, Szombathy T, Bohrmann B, et al. Coexpression of endothelin-converting enzyme-1 and endothelin-1 in different stages of human atherosclerosis. Circulation. 2001; 104:864–869. [PubMed: 11514370]
22. Newby AC. Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture. Physiol Rev. 2005; 85:1–31. [PubMed: 15618476]
23. Hayashida K, Kume N, Murase T, et al. Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 levels are elevated in acute coronary syndrome. A novel marker for early diagnosis. Circulation. 2005; 112:812–818. [PubMed: 16061745]
24. Ishino S, Mukai T, Kume N, et al. Lectin-like oxidized LDL receptor-1 (LOX-1) expression is associated with atherosclerotic plaque instability: analysis in hypercholesterolemic rabbits. Atherosclerosis. 2007; 95:48–56. [PubMed: 17239887]
25. Suwa T, Hogg JC, Quinlan KB, et al. Particulate air pollution induces progression of atherosclerosis. J Am Coll Cardiol. 2002; 39:935–942. [PubMed: 11897432]
26. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA. 2005; 21:3003–3010. [PubMed: 16414948]
27. Campen MJ, Lund AK, Knuckles TL, et al. Inhaled diesel emissions alter atherosclerotic plaque composition in ApoE$^{-/-}$ mice. Toxicol Appl Pharmacol. 2010; 242:310–317. [PubMed: 19891982] In this study, chronic diesel exhaust inhalation causes changes in plaque inflammation and vascular oxidative stress in a concentration-dependent manner.
28. Bai N, Kido T, Suzuki H, et al. Changes in atherosclerotic plaques induced by inhalation of diesel exhaust. Atherosclerosis. 2011; 216:299–306. [PubMed: 21435644] Diesel exhaust inhalation promotes the growth of plaques as well as the complexity.
29. Araujo JA, Barajas B, Kleinman M, et al. Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. Circ Res. 2008; 102:589–596. [PubMed: 18202315]

30. Lund AK, Knuckles TL, Obat Akata C, et al. Exposure to gasoline exhaust results in alterations of pathways involved in atherosclerosis. Toxicol Sci. 2007; 95:485–494. [PubMed: 17065432]
31. Kataoka H, Kume N, Miyamoto S, et al. Expression of lectin-like oxidized low-density lipoprotein receptor-1 in human atherosclerotic lesions. Circulation. 1999; 99:3110–3117. [PubMed: 10377073]
32. Mehta JL, Chen J, Hermonat PL, et al. Lectin-like oxidized low-density lipoprotein receptor (LOX-1): a critical player in the development of atherosclerosis and related disorders. Cardiovasc Res. 2006; 69:36–45. [PubMed: 16324688]
33. Gowdy K, Krantz QT, Daniels M, et al. Modulation of pulmonary inflammatory responses and antimicrobial defenses in mice exposed to diesel exhaust. Toxicol Appl Pharmacol. 2008; 229:310–319. [PubMed: 18343473]
34. Hiramatsu K, Azuma A, Kudoh S, et al. Inhalation of diesel exhaust for three months affects major cytokine expression and induces bronchus-associated lymphoid tissue formation in murine lungs. Exp Lung Res. 2003; 29:607–622. [PubMed: 14594659]
35. Porter M, Karp M, Killedar S, et al. Diesel-enriched particulate matter functionally activates human dendritic cells. Am J Respir Cell Mol Biol. 2007; 37:706–719. [PubMed: 17630318]
36. Salvi SS, Nordenhall C, Blomberg A, et al. Acute exposure to diesel exhaust increases IL-8 and GRO-alpha production in healthy human airways. Am J Respir Crit Care Med. 2000; 161:550–557. [PubMed: 10673199]
37. Shoenfelt J, Mitkus RJ, Zeisler R, et al. Involvement of TLR2 and TLR4 in inflammatory immune responses induced by fine and coarse ambient air particulate matter. J Leukoc Biol. 2009; 86:303–312. [PubMed: 19406832]
38. Miyata R, van Eeden SF. The innate and adaptive immune response induced by alveolar macrophages exposed to ambient particulate matter. Toxicol Appl Pharmacol. 2011; 257:209–226. [PubMed: 21951342]
39. Xiao N, Yin M, Zhang L, et al. Tumor necrosis factor-alpha deficiency retards early fatty-streak lesion by influencing the expression of inflammatory factors in apoE-null mice. Mol Genet Metab. 2009; 96:239–244. [PubMed: 19157944]
40. Huber SA, Sakkinen P, Conze D, et al. Interleukin-6 exacerbates early atherosclerosis in mice. Arterioscler Thromb Vasc Biol. 1999; 19:2364–2367. [PubMed: 10521365]
41. Davenport P, Tipping PG. The role of interleukin-4 and interleukin-12 in the progression of atherosclerosis in apolipoprotein E-deficient mice. Am J Pathol. 2003; 163:1117–1125. [PubMed: 12937153]
42. Diaz-Sanchez D, Tsien A, Fleming J, Saxon A. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. J Immunol. 1997; 158:2406–2413. [PubMed: 9036991]
43. Samuelsen M, Nygaard UC, Lovik M. Allergy adjuvant effect of particles from wood smoke and road traffic. Toxicology. 2008; 246:124–131. [PubMed: 18289765]
44. Bezemer GF, Bauer SM, Oberdorster G, et al. Activation of pulmonary dendritic cells and Th2-type inflammatory responses on instillation of engineered, environmental diesel emission source or ambient air pollutant particles *in vivo*. J Innate Immun. 2011; 3:150–166. [PubMed: 21099199]
45. Leonardi GS, Houthuijs D, Steerenberg PA, et al. Immune biomarkers in relation to exposure to particulate matter: a cross-sectional survey in 17 cities of Central Europe. Inhal Toxicol. 2000; 12(Suppl 4):1–14. [PubMed: 12881884]
46. Nadeau K, McDonald-Hyman C, Noth EM, et al. Ambient air pollution impairs regulatory T-cell function in asthma. J Allergy Clin Immunol. 2010; 126:845–852. [PubMed: 20920773]
47. Gotsman I, Gupta R, Lichtman AH. The influence of the regulatory T lymphocytes on atherosclerosis. Arterioscler Thromb Vasc Biol. 2007; 27:2493–2495. [PubMed: 17901372]
48. Gotsman I, Grabie N, Gupta R, et al. Impaired regulatory T-cell response and enhanced atherosclerosis in the absence of inducible costimulatory molecule. Circulation. 2006; 114:2047–2055. [PubMed: 17060381]

49. Brook RD, Rajagopalan S, Pope CA 3rd, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation. 2010; 121:2331–2378. [PubMed: 20458016]
50. Jacobs L, Emmerechts J, Hoylaerts MF, et al. Traffic air pollution and oxidized LDL. PLoS One. 2011; 6:e16200. [PubMed: 21283820]
51. Soares SR, Carvalho-Oliveira R, Ramos-Sanchez E, et al. Air pollution and antibodies against modified lipoproteins are associated with atherosclerosis and vascular remodeling in hyperlipemic mice. Atherosclerosis. 2009; 207:368–373. [PubMed: 19486979]
52. Walton KA, Hsieh X, Gharavi N, et al. Receptors involved in the oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine-mediated synthesis of interleukin-8. A role for Toll-like receptor 4 and a glycosylphosphatidylinositol-anchored protein. J Biol Chem. 2003; 278:29661–29666. [PubMed: 12777373]
53. Gao D, Ashraf MZ, Kar NS, et al. Structural basis for the recognition of oxidized phospholipids in oxidized low density lipoproteins by class B scavenger receptors CD36 and SR-BI. J Biol Chem. 2010; 285:4447–4454. [PubMed: 19996318]
54. Podrez EA, Hoppe G, O'Neil J, Hoff HF. Phospholipids in oxidized LDL not adducted to apoB are recognized by the CD36 scavenger receptor. Free Radic Biol Med. 2003; 34:356–364. [PubMed: 12543251]
55. Sherer Y, Shoenfeld Y. Antiphospholipid antibodies: are they proatherogenic or an epiphenomenon of atherosclerosis? Immunobiology. 2003; 207:13–16. [PubMed: 12638897]
56. de Faire U, Frostegard J. Natural antibodies against phosphorylcholine in cardiovascular disease. Ann N Y Acad Sci. 2009; 1173:292–300. [PubMed: 19758165]
57. Terzano C, Di Stefano F, Conti V, et al. Air pollution ultrafine particles: toxicity beyond the lung. Eur Rev Med Pharmacol Sci. 2010; 14:809–821. [PubMed: 21222367]
58. Nemmar A, Hoet PH, Vanquickenborne B, et al. Passage of inhaled particles into the blood circulation in humans. Circulation. 2002; 105:411–414. [PubMed: 11815420]
59. Brook RD, Rajagopalan S. Particulate matter, air pollution, and blood pressure. J Am Soc Hypertens. 2009; 3:332–350. [PubMed: 20409976]
60. Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol. 2008; 36:289–310. [PubMed: 18349428]
61. Baccarelli A, Martinelli I, Pegoraro V, et al. Living near major traffic roads and risk of deep vein thrombosis. Circulation. 2009; 119:3118–3124. [PubMed: 19506111]
62. Sarnat JA, Marmur A, Klein M, et al. Fine particle sources and cardiorespiratory morbidity: an application of chemical mass balance and factor analytical source-apportionment methods. Environ Health Perspect. 2008; 116:459–466. [PubMed: 18414627]
63. CampenMJ, Lund AK, Doyle-Eisele ML, et al. A comparison of vascular effects from complex and individual air pollutants indicates a role for monoxide gases and volatile hydrocarbons. Environ Health Perspect. 2010; 118:921–927. [PubMed: 20197249]
64. Madden MC, Richards JH, Dailey LA, et al. Effect of ozone on diesel exhaust particle toxicity in rat lung. Toxicol Appl Pharmacol. 2000; 168:140–148. [PubMed: 11032769]
65. Langrish JP, Lundbäck M, Barath S, et al. Exposure to nitrogen dioxide is not associated with vascular dysfunction in man. Inhal Toxicol. 2010; 22:192–198. [PubMed: 20047363]
66. Mills NL, Robinson SD, Fokkens PH, et al. Exposure to concentrated ambient particles does not affect vascular function in patients with coronary heart disease. Environ Health Perspect. 2008; 116:709–715. [PubMed: 18560524]
67. Lucking AJ, Lundbäck M, Barath SL, et al. Particle traps prevent adverse vascular and prothrombotic effects of diesel engine exhaust inhalation in men. Circulation. 2011; 123:1721–1728. [PubMed: 21482966] This study highlights the likely impact of improved diesel exhaust after treatments, namely the particle traps, on vascular toxicity.

KEY POINTS

- Ambient air pollution has demonstrated effects on both acute risk of cardiac events as well as chronic progression of inflammatory vascular disease.
- New studies have highlighted a likely role for the innate and adaptive immune systems for driving systemic vascular inflammation and oxidative injury after inhalation of air pollutants.
- Mixtures of traffic-related emissions may have greater potential for promoting systemic vascular disease than individual sources.