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EDITORIAL COMMENT

Does Air Pollution Accelerate Progression of Atherosclerosis?*

Joel D. Kaufman, MD, MPH
Seattle, Washington

It is an accepted biological premise that development of clinical cardiovascular disease is the result of gene–environment interactions: gene expression that leads to disease is the result of environmental influences in the setting of a susceptible genetic framework. Intensive efforts have gone into exploring the nature of the genetic susceptibility. Meanwhile, investigations of the "environmental" factors underlying cardiovascular diseases have principally focused on factors that are modifiable at the individual level, such as diet, exercise patterns, and medications. However, emerging published data now support the notion that another set of environmental factors—including air pollution, over which individuals have less control—are also influential in the development of clinically important cardiovascular disease. Work published in the current issue of the *Journal* and recently appearing in other venues highlights the potential role of ambient air pollution exposures in the development of atherosclerotic disease.

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The idea that ambient air pollutants—primarily the result of fossil fuel combustion—might contribute to occurrence of cardiovascular diseases has been the subject of increasingly intensive study, and the evidence has rapidly mounted over the last several years (1). Much of that attention has historically focused on whether short-term excursions in air pollutant concentrations were triggering the occurrence of clinical events in susceptible people—as was vividly observed when thousands died in the wake of the London Smog episode of 1952 (2). Scientific attention has now turned to the risk of longer-term air pollution exposures, occurring over the course of 1 year or longer and primarily predicted by the location in which people live, in the development of chronic vascular processes including atherosclerosis. Several cohort studies have now reported an effect of long-term exposure to fine particulate matter air pollution (particles <2.5 μm in diameter [$PM_{2.5}$]) on risk of coronary heart disease events and stroke (3–10).

These findings have led to the question, "Could living in areas with higher $PM_{2.5}$ exposure lead to an increased burden of atherosclerotic disease?" To assess this question, investigators have looked at whether residential pollutant concentrations are associated with established measures of the extent of subclinical atherosclerosis.

The study by Bauer et al. (11) in this issue of the *Journal* reports on the cross-sectional association between residential air pollution concentration estimates and carotid wall intima-medial thickness (IMT) measurements from a population-based cohort set in the Ruhr Valley of Germany. They found a positive association between air pollution and IMT. This group has previously reported on air pollutant exposures and other outcomes in this cohort (12–14). The magnitude of effect observed for a 4.2-$\mu g/m^3$ increase in estimated $PM_{2.5}$ concentration at the home of the subject over the year before the exam was equivalent to a 3- to 4-year age increase in this cohort. This air pollution concentration difference represents an increase equivalent to the difference between county-wide 2008 $PM_{2.5}$ annual average exposures in San Francisco (9.1 $\mu g/m^3$) and San Diego (13.4 $\mu g/m^3$) or between Fairfield, Connecticut (12.8 $\mu g/m^3$) and Baltimore, Maryland (17.0 $\mu g/m^3$) (15).

Exposure assessment in this report is good for an observational study without the benefit of specialized air monitoring data and used both an aerosol chemical transport model (taking into account sources of exposure and meteorological information, on a 1-km grid scale) and calculated distances to high traffic roadways. The authors were able to adjust for major potentially confounding factors. The major limitations of the study are the cross-sectional nature of the design, the potential for misclassification of exposure, and the relatively small amount of variation in exposure in this cohort. It should be noted that other investigators have found cardiovascular impacts of living very near (e.g., <100 m) a major roadway, which is interesting, because concentrations of certain components of fresh traffic-derived emissions decrease exponentially as distances from roads increase. In the current study, Bauer et al. (11) did not find a consistent association for near-road exposures.

Other groups have looked at extent of atherosclerosis, and most although not all have found a positive association with fine particulate matter (16–19). A recently published report by Künzli et al. (20) represented the first attempt to look at progression of IMT and air pollution exposures, which on its surface is an improvement over the cross-sectional design of the Bauer et al. (11) study. However, the study by Künzli et al. (20), set in a series of clinical trials in the Los Angeles area, had important limitations, including the small sample

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From the Departments of Medicine, Environmental and Occupational Health Sciences, and Epidemiology, University of Washington, Seattle, Washington. This work has been supported by National Institutes of Health Grants K24ES013195 and P50ES015915. Dr. Kaufman has reported that he has no relationships to disclose.

size, lack of a population-based set of subjects, and the short period of follow-up; they found an effect of air pollution and residing near roadways on progression of IMT, but the effect was primarily (and surprisingly) in the treatment arms (which included vitamins, hormones, and lipid-lowering agents) of these trials.

Several other lines of evidence support the importance of air pollution exposures in development of heart disease. Some experimental studies in animal models demonstrate that particulate exposure can initiate or accelerate atherosclerosis (21–24). And the reduction of long-term exposure to pollution—something we have witnessed in North America but have yet to see across the industrializing world—has been associated with improvements in life expectancy in a pattern suggesting a role for the pollutants in mortality (25).

This is not the final word on the relationship between air pollutants and atherosclerosis. Because clinical trial approaches in humans will never be able to directly examine this question, we must rely on epidemiological approaches. One challenge of these studies is showing that the exposure of concern occurs at the correct period before the health outcome under study. In the Bauer study (11), exposures estimated over the year before the examination were used to assess relationship with common carotid IMT, a measure likely impacted by a period of accumulated risk factors much greater than 1 year. An improved but more difficult study design would demonstrate that environmental exposures during a specific period of follow-up are associated with a change in extent of atherosclerosis during that same period. Better studies are also made difficult by the need to be able to tease apart the factors that are associated with living in more polluted areas from the pollution itself. Finally, there are several things we would like to know about the participants in this and other studies. How much time do they spend at home? And how much of that time is indoors or outdoors? How much of the pollution is getting into their homes? These factors are important predictors of actual pollution exposure. Studies specifically aimed at this issue will address this more definitively. Research now ongoing in the MESA (Multi-Ethnic Study of Atherosclerosis), combining state-of-the-art assessment of air pollution exposures (26) with state-of-the-art epidemiological methods for study of cardiovascular diseases (27), will eventually provide unprecedented insight into this topic.

Gene–environment interactions underlie the occurrence of cardiovascular disease events. We and our patients do not have too much control over the genes dealt to us, but the environment has proven modifiable. The report by Bauer et al. (11) in this issue, together with other work available, suggests that exposure to particulate matter promotes acceleration of atherosclerosis; further research to elucidate this relationship is underway. Reducing exposure to this potential risk factor presents a challenge to improve public health. On the basis of the currently available evidence it is difficult to recommend individual-level interventions to reduce exposures. Efforts to reduce this environmental impact on health are best undertaken at the population level through initiatives to improve air quality for everyone.

Reprint requests and correspondence: Dr. Joel D. Kaufman, Departments of Medicine, Environmental and Occupational Health Sciences, and Epidemiology, University of Washington, 4225 Roosevelt Way NE, Suite 100, Seattle, Washington 98105-6099. E-mail: joelk@uw.edu.

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