

9. Trenk D, Hochholzer W, Fromm MF, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol* 2008;51:1925-34.
10. Frere C, Cuisset T, Morange PE, et al. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. *Am J Cardiol* 2008; 101:1088-93.
11. Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost* 2007;5:2429-36.
12. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) study. *J Am Coll Cardiol* 2008;51:256-60.
13. Simon T, Versuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363-75.
14. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009; 360:354-62.

Copyright © 2009 Massachusetts Medical Society.

## Evaluating the Effects of Ambient Air Pollution on Life Expectancy

Daniel Krewski, Ph.D.

Air pollution is an important determinant of population health. In this issue of the *Journal*, Pope et al.<sup>1</sup> provide data that once again reinforce this fundamental concept. In an analysis that correlates reductions in fine particulate matter (i.e., particles less than 2.5  $\mu\text{m}$  in aerodynamic diameter, or  $\text{PM}_{2.5}$ ) in the air with life expectancies, the investigators found that a decrease in the concentration of  $\text{PM}_{2.5}$  of 10  $\mu\text{g}$  per cubic meter is associated with an increase in life expectancy of 0.77 year. Their analysis is based on correlating reductions in particulate air pollution over the past several decades with increases in life expectancy in 217 counties in 51 metropolitan areas in the United States. Although ecologic in nature (i.e., reflecting associations between air pollution and life expectancy at the county rather than the individual level), these results appear to be robust with respect to adjustment for changes in socioeconomic, demographic, and smoking patterns occurring over the same period.

The finding is comparable with previous predictions of reductions in life expectancy of 1.11 years in the Netherlands,<sup>2</sup> 1.37 years in Finland,<sup>3</sup> and 0.80 year in Canada<sup>4</sup> resulting from increases in ambient  $\text{PM}_{2.5}$  concentrations of 10  $\mu\text{g}$  per cubic meter. However, the strength of the study by Pope et al. resides in its ability to demonstrate an increase in life expectancy resulting from actual reductions in particulate air pollution. This finding provides direct confirmation of the population health benefits of mitigating air pollution and greatly strengthens the foundation of the argument for air-quality management.<sup>5</sup>

This work could be extended to take into account quality of life. For example, Coyle et al.<sup>4</sup>

estimated that an increase of 10  $\mu\text{g}$  per cubic meter in  $\text{PM}_{2.5}$  concentrations would lead to a quality-adjusted reduction in life expectancy of 0.60 year, as compared with the unadjusted reduction of 0.80 year. The work by Pope et al. represents an important contribution to the large and growing body of evidence linking ambient air pollution with adverse health outcomes. At the global level, the World Health Organization<sup>6</sup> estimates that 1.4% of all deaths and 0.8% of disability-adjusted life-years are the result of particulate air pollution.

The short-term health effects of particulate and gaseous air pollutants have been well documented, largely through time-series studies relating short-term elevations in ambient levels of such pollutants to increases in morbidity and mortality from cardiorespiratory conditions. A recent combined analysis of time-series data from 124 of the largest cities in North America and Europe produced an estimated increase in the rate of death from any cause ranging from 0.2 to 0.6% for an increase in ambient  $\text{PM}_{10}$  concentrations of 10  $\mu\text{g}$  per cubic meter,<sup>7</sup> depending on the assumed lag time between exposure to particulate matter and death and on the method used for seasonality control, the form of the temporal smoothing function, and degree of smoothing. Risk estimates for Europe and the United States were similar but were higher in Canada.

The long-term effects of exposure to "criteria" air pollutants (particulate matter, ozone, sulfates, sulfur dioxide, nitrous oxides, and carbon monoxide) have been documented in large-scale cohort studies, including the Harvard Six Cities Study<sup>8</sup> and the American Cancer Society Cancer

**Table 1. Estimates of Increased Mortality Associated with an Increase in PM<sub>2.5</sub> Concentrations of 10 µg per Cubic Meter Based on Extended Follow-up of the American Cancer Society Cancer Prevention Study II.\***

Cause of Death	Krewski et al., 2000 <sup>†</sup>	Pope et al., 2002 <sup>‡</sup>		Krewski et al., 2008 <sup>§</sup>	
	PM <sub>2.5</sub> Monitoring 1979–1983, Follow-up 1989	PM <sub>2.5</sub> Monitoring 1979–1983, Follow-up 1998	PM <sub>2.5</sub> Monitoring 1999–2000, Follow-up 1998	PM <sub>2.5</sub> Monitoring 1979–1983, Follow-up 2000	PM <sub>2.5</sub> Monitoring, 1999–2000, Follow-up 2000
	<i>percent increase in mortality (95% CI)</i>				
All causes	4.8 (2.2 to 7.6)	3.1 (1.5 to 4.7)	3.2 (1.2 to 5.3)	2.8 (1.4 to 4.3)	3.6 (1.7 to 5.4)
Cardiopulmonary disease	10.1 (6.1 to 14.3)	7.1 (4.8 to 9.5)	9.2 (6.3 to 12.3)	7.0 (4.9 to 9.2)	10.0 (7.3 to 12.9)
Ischemic heart disease	12.2 (6.6 to 18.1)	13.0 (9.4 to 16.6)	14.3 (9.9 to 19.0)	13.3 (10.0 to 16.7)	15.5 (11.3 to 19.9)
Lung cancer	5.3 (–3.7 to 15.0)	8.9 (3.1 to 15.1)	11.6 (4.1 to 19.7)	7.5 (2.1 to 13.2)	10.9 (3.9 to 18.5)
All other causes	–0.2 (–4.2 to 4.0)	–1.9 (–4.3 to 0.5)	–4.7 (–7.6 to 1.8)	–2.1 (–4.3 to 0.0)	–4.7 (–7.3 to 2.0)

\* Estimates are based on a Cox regression analysis stratifying the baseline hazard function by age (1-year groupings), sex, and race. All analyses of PM<sub>2.5</sub> (particulate matter with an aerodynamic diameter less than 2.5 µm) for the years 1979 through 1983 were conducted using the same 342,521 study subjects. Follow-up year is the most recent year of follow-up for the American Cancer Society (ACS) study cohort available at the time of analysis. PM<sub>2.5</sub> monitoring data were compiled from publicly available data sources independently of the ACS study. All analyses of PM<sub>2.5</sub> for the years 1999 through 2000 were conducted using the same 488,370 subjects. Adapted from Krewski et al.<sup>9</sup>

<sup>†</sup> Data are from Krewski et al.<sup>10</sup>

<sup>‡</sup> Data are from Pope et al.<sup>11</sup>

<sup>§</sup> Data are from Krewski et al.<sup>9</sup>

Prevention Study II.<sup>9</sup> The American Cancer Society cohort, which includes more than 1.1 million people followed since the time of enrollment in 1980, has provided consistent evidence of an association between increased mortality and ambient air pollution in follow-up analyses through 1989,<sup>10</sup> 1998,<sup>11</sup> and 2000<sup>9</sup> (Table 1). Further analyses of the data, using refined estimates of exposure to ambient PM<sub>2.5</sub> and follow-up through 2004, are under way.

The effects of ambient air pollution on population health can be addressed within the broader context of risk assessment and management. Population-health risk assessment involves the systematic assessment of genetic, environmental, and social determinants of health; identified health risks can be addressed using a combination of regulatory, economic, advisory, community-based, and technological risk-management interventions.<sup>12</sup> Craig et al.<sup>5</sup> recently produced a document on how scientific evidence on the effects of ambient air pollution on population health can be used in developing strategies for air-quality management.

Research priorities for airborne particulate matter have been identified by the National Research Council, and progress toward their achievement was monitored from 1998 through 2004.<sup>13</sup> The goal of the research was to increase scien-

tific understanding of the health effects of particulate air pollution, including the biologic mechanisms by which particulate matter in ambient air can lead to increased mortality in the general population. Recent scientific evidence suggests that increased mortality from cardiopulmonary disease is due to increased formation of atherosclerotic plaque, which in turn is due to the induction of systemic inflammation and oxidative stress mediated by cytokines after inhalation of PM<sub>2.5</sub>.<sup>14</sup>

The National Research Council also provided a framework for evaluating the benefits of air-quality regulations.<sup>15</sup> Whereas analyses of regulatory benefits are based on predictions of the health benefits resulting from air-pollution control, Pope et al. provide documented evidence of such benefits as a consequence of actual reductions in air-pollution concentrations occurring over the past several decades in the United States. Hedley et al.<sup>16</sup> have attempted to document improvements in population health resulting from reductions in exposure to airborne particulate matter in Hong Kong.

An important component of environmental-health risk management is the evaluation of the effect of a particular intervention.<sup>17</sup> Although ambient air-pollution concentrations in the United States and other developed countries have been

declining in recent decades, reflecting efforts to reduce emissions from both point (e.g., smokestacks) and mobile (e.g., cars and trucks) sources, few studies have documented an improvement in population health as a consequence of reductions in exposure to air pollution. The Health Effects Institute has emphasized the need for such evaluations by proposing an accountability framework for air-quality management.<sup>18</sup> This framework tracks the effects of interventions to enhance air quality in terms of emissions reductions, improvements in air quality, reductions in human exposure, and, ultimately, improvements in population health. Because long-term exposure to particulate air pollution has a much greater effect on population health than short-term exposure, the results of the study by Pope et al. are of particular importance within the accountability framework established by the Health Effects Institute.

Pope et al. note that although decreases in fine particulate air pollution (PM<sub>2.5</sub>) could account for as much as 18% of the increase in life expectancy of approximately 2.74 years occurring in the United States between 1980 and 1999, other factors may also be partly responsible. Further analyses of this association, adjusting for changes in individual-level variables such as tobacco use, socioeconomic status, dietary patterns, body-mass index, physical activity, and access to health services, would be of value both in identifying other factors contributing to the increased life expectancy observed over this period and in confirming the ecologic findings of Pope et al. Consideration of the joint effects of copollutants would also be of interest.<sup>9</sup> In the interim, these investigators have made an important contribution to air-quality management through their pioneering attempts to document the population health benefits of reducing ambient air pollution by correlating past reductions in ambient PM<sub>2.5</sub> concentrations with increased life expectancy.

Dr. Krewski reports serving as Natural Sciences and Engineering Research Council of Canada Industrial Research Chair in Risk Sciences, a university–industry partnership program, at the University of Ottawa, and as chief executive officer and chief risk scientist for Risk Sciences International (<http://demo.risksciencesint.com>). No other potential conflict of interest relevant to this article was reported.

From the McLaughlin Center for Population Health Risk Assessment, University of Ottawa, Ottawa.

1. Pope CA III, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. *N Engl J Med* 2009;360:376-86.
2. Brunekreef B. Air pollution and life expectancy: is there a relation? *Occup Environ Med* 1997;54:781-4.
3. Nevalainen J, Pekkanen J. The effect of particulate air pollution on life expectancy. *Sci Total Environ* 1998;217:137-41.
4. Coyle D, Stieb D, Burnett RT, et al. Impact of particulate air pollution on quality-adjusted life expectancy in Canada. *J Toxicol Environ Health A* 2003;66:1847-63.
5. Craig L, Brook JR, Chiotti Q, et al. Air pollution and public health: a guidance document for risk managers. *J Toxicol Environ Health A* 2008;71:588-698.
6. The world health report 2002 — reducing risks, promoting healthy life. Geneva: World Health Organization, 2002. (Accessed January 5, 2009, at <http://www.who.int/whr/2002/en/>.)
7. Samoli E, Peng R, Ramsay T, et al. Acute effects of ambient particulate matter on mortality in Europe and North America: results from the APHENA study. *Environ Health Perspect* 2008;116:1480-6.
8. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities Study. *Am J Respir Crit Care Med* 2006;173:667-72.
9. Krewski D, Jerrett M, Burnett RT, et al. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality: special report. Cambridge, MA: Health Effects Institute, 2009.
10. Krewski D, Burnett RT, Goldberg MS, et al. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of particulate air pollution and mortality: special report. Cambridge, MA: Health Effects Institute, 2000.
11. Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002;287:1132-41.
12. Krewski D, Hogan V, Turner MC, et al. An integrated framework for risk management and population health. *Hum Ecol Risk Assess* 2007;13:1288-312.
13. National Research Council. Research priorities for airborne particulate matter: IV. Continuing research progress. Washington, DC: National Academies Press, 2004.
14. Brook RD. Cardiovascular effects of air pollution. *Clin Sci (Lond)* 2008;115:175-87.
15. National Research Council. Estimating the public health benefits of proposed air pollution regulations. Washington, DC: National Academies Press, 2002.
16. Hedley AJ, McGhee SM, Barron B, et al. Air pollution: costs and paths to a solution in Hong Kong — understanding the connections among visibility, air pollution, and health costs in pursuit of accountability, environmental justice, and health protection. *J Toxicol Environ Health A* 2008;71:544-54.
17. Presidential/Congressional Commission on Risk Assessment and Risk Management. Framework for environmental health risk management — final report, vol. 1 and 2. Washington, DC: The White House, 1997.
18. Assessing health impact of air quality regulations: concepts and methods for accountability research. Communication 11. Boston: Health Effects Institute, 2003. (Accessed January 5, 2009, at <http://pubs.healtheffects.org/getfile.php?u=261>.)

Copyright © 2009 Massachusetts Medical Society.