

## EDITORIALS



## Cardiovascular Risks from Fine Particulate Air Pollution

Douglas W. Dockery, Sc.D., and Peter H. Stone, M.D.

More than a decade ago, prospective epidemiologic studies showed that mortality was increased among people living in communities with elevated concentrations of fine particulate air pollution.<sup>1,2</sup> Subsequent research has shown that particulate air pollution is statistically and mechanistically linked to increased cardiovascular disease.<sup>3</sup> New data are beginning to shed light on which persons are at heightened risk.

In this issue of the *Journal*, Miller et al.<sup>4</sup> report on data from the Women's Health Initiative (WHI) observational study, which greatly expands our understanding of how fine particulate pollution affects health. Earlier long-term prospective cohort studies showed an association between levels of air pollution consisting of particulate matter of less than 2.5  $\mu\text{m}$  in aerodynamic diameter ( $\text{PM}_{2.5}$ ) and an elevated risk of death from all causes and from cardiovascular disease.<sup>1,2,5</sup> The WHI study broadens the scope by finding that nonfatal cardiovascular events are also strongly associated with fine particulate concentrations in the community. Earlier work relied solely on death certificates to define the rate of death from cardiovascular disease. In the WHI study, cardiovascular events and mortality were defined by objective review of medical records. The earlier studies were designed to identify risk factors for respiratory disease<sup>1</sup> and cancer<sup>2</sup> and therefore had limited ability to adjust for cardiovascular risk factors. The WHI observational study was designed to assess the risk of cardiovascular events and therefore could exclude cardiovascular risk factors as explanations for the observed associations with air pollution.

Earlier studies did not include data on the full range of regulated community air pollutants — that is,  $\text{PM}_{2.5}$  (and the larger particle fraction,

$\text{PM}_{10}$ ), sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone. The WHI study considered all of these community air pollutants and found cardiovascular risk associated only with  $\text{PM}_{2.5}$  concentrations. Whereas earlier work compared levels of air pollution and rates of death between various cities, the WHI investigators were also able to compare areas within individual cities. Their analysis demonstrated a relationship between increased levels of fine particulate pollution and higher rates of death and complications from cardiovascular and cerebrovascular disease, depending not only on which city a person lived in but also on where in that city she lived.

Perhaps most important, the WHI study established a stronger statistical association between fine particulate air pollution and death from coronary heart disease than that found in earlier studies. In the WHI study, Miller et al. found an increased relative risk of 1.76 for death from cardiovascular disease for every increase of 10  $\mu\text{g}$  per cubic meter in the mean concentration of  $\text{PM}_{2.5}$ .<sup>4</sup> By comparison, a study by the American Cancer Society showed that each increase of 10  $\mu\text{g}$  per cubic meter in the mean  $\text{PM}_{2.5}$  concentration was associated with an increased relative risk of 1.12 for death from cardiovascular disease, 1.18 for death from ischemic heart disease (the largest proportion of deaths), and 1.13 for death from arrhythmia, heart failure, or cardiac arrest.<sup>5</sup>

Samples in previous studies consisted of subjects from the entire population of the cities being investigated. The WHI analysis was restricted to postmenopausal women with no history of cardiovascular health problems. A 22-year follow-up of a cohort of nonsmoking white adults in California showed an increased risk of death from coronary heart disease with rising levels of

fine particulate air pollution in women but not in men.<sup>6</sup> Does this suggest that the WHI population, or women in general, are more sensitive to the cardiovascular effects of particulate air pollution?

Women have a distinctly different profile of coronary disease. In the Women's Ischemia Syndrome Evaluation study, the cluster of conditions that increase the risk of vascular disease (e.g., hypertension, diabetes, obesity, and inactivity) was seen more frequently in postmenopausal women than in men.<sup>7</sup> Women's coronary arteries are smaller in size and tend to harbor more diffuse atherosclerosis than do men's arteries, and women's microvessels appear to be more frequently dysfunctional than those of men.<sup>7</sup> Indeed, in the Euro Heart Survey, although women were less likely than men to have fixed atherosclerotic obstructive disease, among patients undergoing elective diagnostic angiography for angina, women with confirmed coronary disease had twice the risk of death or myocardial infarction as that of men.<sup>8</sup> These findings suggest that sex may not define susceptibility to air pollution but, rather, may be an indicator of an underlying cardiac substrate that puts women at increased risk.

Characteristics that define increased cardiovascular susceptibility to particulate air pollution have also been identified in men. Stronger associations between fine particulate concentrations and abnormal variability in heart rate were reported in asymptomatic men with higher Framingham cardiovascular risk scores.<sup>9</sup> PM<sub>2.5</sub> was more strongly associated with impaired autonomic cardiovascular function in men with genotypic and phenotypic indicators of increased systemic inflammation and oxidative stress than in those without these markers.<sup>10</sup> However, the increased susceptibility was not found among men taking statins, which both improve lipid profiles and reduce systemic inflammation.

The mechanisms by which fine particulate air pollution influence the risk of cardiovascular disease are still under investigation. There is evidence that inhalation of particulate air pollution creates and exacerbates both pulmonary and systemic inflammation and oxidative stress, leading to direct vascular injury, atherosclerosis, and autonomic dysfunction.<sup>3</sup> Buildup of atherosclerotic plaque, measured by the carotid intima-media thickness, is higher in communities with higher mean PM<sub>2.5</sub> concentrations.<sup>11</sup> Particulate air pol-

lution has been found to lead to rapid and significant increases in fibrinogen, plasma viscosity, platelet activation, and release of endothelins, a family of potent vasoconstrictor molecules.<sup>3</sup>

Taken together, these studies suggest that the status of cardiovascular risk factors has a substantial effect on susceptibility to the adverse effects of particulate air pollution. A particularly appealing aspect of the design of the WHI study is the range of data collected on all subjects, including demographic and lifestyle characteristics, cardiovascular risk factors, medical history, diet, and medications. With this wealth of data, the next generation of analyses should be able to focus risk stratification even further to identify the characteristics of persons who are most susceptible to the adverse effects of air pollution.

A multifaceted approach that encompasses both public health and medical interventions is needed to reduce the burden of cardiovascular disease attributable to air pollution. Comprehensive management of the harmful effects of fine particles must start with intensive efforts to reduce this destructive form of air pollution. Fine particulate air pollution results not only from the combustion of carbonaceous fuels in our vehicles, power plants, and factories but also from secondary particles produced by oxidation of gaseous pollutants emitted by these same sources. The evidence that has accumulated thus far regarding the health threat from PM<sub>2.5</sub> pollution is convincing enough to have prompted the Environmental Protection Agency (EPA) to lower the short-term (24-hour) standard for fine particulate concentration that communities must achieve. Unfortunately for public health, the EPA failed to follow the recommendation of its science advisers and reduce the long-term standard for fine particles.<sup>12</sup> The findings of the WHI study strongly support the recommendation for tighter standards for long-term fine particulate air pollution.

Even with tighter standards, people will continue to be exposed to fine particulate air pollution. Although the public health burden of cardiovascular disease attributable to air pollution is large, the evidence suggests that individual risks are modest. If the WHI and other studies can identify intrinsic and acquired individual factors that lead to increased adverse cardiovascular responses to air pollution, then it should be possible to offer focused interventions to persons who

are at greatest risk and thereby ameliorate at least some of the patient-specific damages of air pollution.

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From the Department of Environmental Health, Harvard School of Public Health (D.W.D.), and the Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School (P.H.S.) — both in Boston.

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## The Healing Power of Listening in the ICU

Craig M. Lilly, M.D., and Barbara J. Daly, Ph.D, R.N.

Critical care services are highly valued because they can often restore function in patients with acute life-threatening illnesses. In this context, advances in medical science have led to increased expectations for favorable outcomes of episodes of critical illness, even when the patient has severe coexisting chronic disease. The growing demand for critical care has led both to increased numbers of patients who survived with desirable functional outcomes and to increased numbers of patients who die in the intensive care unit (ICU). Today, many deaths in the ICU occur after a decision has been made to discontinue or forgo advanced supportive technology.<sup>1</sup> Decisions to shift from apparently ineffective technology to a treatment plan that focuses primarily on the patient's comfort are usually made in discussions between caregivers and family members.<sup>2</sup> These discussions involve complex conversations and are important to families. Communication processes that have been shown to improve the well-being of patients and family members include proactive, multidisciplinary sessions that provide patients (when they are able to communicate) and family members with the opportunity to ask ques-

tions, articulate the patient's values, express painful emotions, discuss concerns, and obtain help with managing feelings of guilt.<sup>3</sup>

A clinical course that runs counter to the family's hopes and expectations is extraordinarily stressful and is an important contributor to ICU-related post-traumatic stress disorder (PTSD) among families.<sup>4</sup> A better understanding of how intensive care clinicians can support families as they make the transition from a goal of cure to one of comfort and acceptance of death is clearly needed. Recognition of the relationship between satisfaction, on the one hand, and expectations, perceptions, and prognosis, on the other hand, can lead to communication processes that synchronize the perceptions of family members with those of providers and close gaps between reality and expectations. Curtis and colleagues have described some of the components of a system of communication that is being increasingly recognized as an effective means of promoting harmony between critical care providers and families.<sup>5</sup> This five-part system, known by the mnemonic VALUE, includes the following elements: valuing and appreciating what the family mem-