Medicine and Society article in this issue, reassure us that physicians of the past have successfully taken "off their white coats and wade[d] into the fray in which actions are taken and decisions made."[9] These previous political mobilizations, to address such public health threats as tuberculosis and nuclear war, carry applicable lessons for today.

The timeline for action to avert some of the most catastrophic health outcomes of climate change has been estimated to be a little over a decade.[10] We hope that our interactive feature will serve as a central resource to inform readers about current and projected consequences of the climate crisis and motivate them to act now to minimize these harms. We, as a medical community, have the responsibility and the opportunity to mobilize the urgent, large-scale climate action required to protect health — as well as the ingenuity to develop novel and bold interventions to avert the most catastrophic outcomes.

An audio interview with Dr. Salas is available at NEJM.org

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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Do We Really Need Another Time-Series Study of the $PM_{2.5}$–Mortality Association?

John R. Balmes, M.D.

The link between particulate pollution and mortality was originally recognized in the context of severe episodes of poor air quality in the 20th century, such as the London Fog of 1952.[1] These episodes showed clear evidence that the number of deaths increased in association with high levels of particulate matter (PM). The policy response to the increasing evidence of the effects of air pollution on public health was for governments to develop air-quality regulations. In the United States, the Clean Air Act of 1970 mandated that the Environmental Protection Agency (EPA) develop national ambient air-quality standards (NAAQS) to protect even the most vulnerable members of the general population from adverse health effects.[2] An NAAQS for PM was initially established in 1971.

The current primary NAAQS for PM applies to particles with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) — particles that are small enough to be deposited in the alveoli. A secondary NAAQS applies to particles with an aerodynamic diameter of 10 μm or less (PM_{10}) — particles that can be deposited in large airways. The epidemiologic evidence in support of the adoption of an NAAQS for $PM_{2.5}$ was largely from time-series studies.[3] Time-series analyses include daily measures of health events (e.g., daily mortality), regressed against concentrations of PM (e.g., 24-hour average $PM_{2.5}$) and weather variables (e.g., daily average temperature) for a given geographic area. The population serves as its own control, and confounding by population characteristics is negligible because these are stable over short time frames. Time-series studies can be confounded by time-varying factors such as influenza epidemics and temperature; however, statistical methods to reduce such confounding have been developed.[3]

Many time-series studies have been conducted in cities in various countries around the world. Efforts have been made to include larger regions in time-series analyses to increase the generalizability of the reported associations.[4] A meta-analysis has shown that the $PM_{2.5}$–mortality association remains robust in pooled analyses.[5] Multiple longitudinal cohort studies of the association between long-term $PM_{2.5}$ exposure and mortality, in which individual-level covariates were included in the analyses, have generally shown even stronger associations, providing important support for the evidence from time-series studies.[6] Moreover, experimental data from exposure studies in animals and controlled exposure studies in humans have increasingly provided mechanistic evidence in support of the epidemiologic findings.

Given the abundance of evidence in support of an association between short-term $PM_{2.5}$ exposure and mortality, what is the contribution of the time-series study by Liu et al. in this issue of the *Journal*?[7] First, this study included almost 60 million deaths from 652 cities in 24 countries, thereby greatly increasing the generalizability of the association and decreasing the likelihood that the reported associations are subject to confounding bias. In observations consistent with previous studies, all-cause (nonaccidental), cardiovascular, and respiratory mortality were associated with short-term exposures to both PM_{10} and $PM_{2.5}$. The strength of the associations was reduced but remained significant in two-pollutant models that addressed potential confounding by gaseous pollutants.

Perhaps the most interesting result of the study by Liu et al. is from their concentration–response analysis. On the basis of studies of exposure to multiple combustion sources of $PM_{2.5}$ (outdoor air pollution, secondhand tobacco smoke, and active tobacco smoking) and cardiovascular mortality, Pope et al. proposed that the shape of the concentration–response relation is curvilinear, with a lesser slope at higher exposure levels.[8] Although other studies have reported evidence of such curvilinearity, the current study of PM data from many regions around the world provides the strongest evidence to date that higher levels of exposure may be associated with a lower per-unit risk. Regions that have lower exposures had a higher per-unit risk. This finding has profound policy implications, especially given that no threshold of effect was found. Even high-income countries, such as the United States, with relatively good air quality could still see public health benefits from further reduction of ambient PM concentrations (i.e., below the current NAAQS).

The Clean Air Act requires a periodic review of the weight of evidence of adverse health effects of regulated air pollutants by an external body of scientists, called the Clean Air Scientific Advisory Committee (CASAC). Controlled exposure studies in humans, toxicologic studies in animals, and epidemiologic studies are included in the weight-of-evidence reviews by CASAC. In the context of the current review of the NAAQS for PM and the Trump Administration's view of inconvenient scientific evidence as anathema,[9] Anthony Cox, the current chair of CASAC, has characterized the abundant observational epidemiologic evidence from time-series and cohort studies of the $PM_{2.5}$–mortality association as not proving causality. Rather than relying on the weight-of-the-evidence approach that the EPA has traditionally used to infer causation, Cox wants to rely on studies that use a theoretical approach called "manipulative causality."[10] This theory restricts epidemiologic evidence that may be considered acceptable to assess causality to results from intervention studies or studies that have been analyzed with the use of causal inference statistical methods. The effort to exclude all observational epidemiologic data that have not been analyzed in a manipulative causality framework not only makes no sense, it would set a dangerous precedent for environmental policy.

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Why Are Physicians So Confused about Acute Heart Failure?

Milton Packer, M.D.

For most of the past 3000 years, physicians believed that all patients with heart failure had acute heart failure. Heart failure was viewed as an episodic disorder — that is, patients were considered to have heart failure when they presented with fluid retention, and they no longer had heart failure after diuresis.[1] The chronicity of heart failure was recognized only when invasive and noninvasive measurements showed severe ongoing structural and functional abnormalities between episodes.[2]

To develop approaches to preventing hospitalizations and minimizing the functional and prognostic consequences of heart failure, clinical investigators needed to focus on the underlying disease process. Extensive research beginning in the 1980s established that combination therapy with neurohormonal antagonists reverses ventricular remodeling, improves functional capacity, and reduces the risk of disease progression and death. However, use of these drugs in primary care has been distinctly suboptimal, possibly because physicians have been inclined to discount the importance of intensive treatment for a disease whose progression is typically clinically silent.[3]

Instead, practitioners have focused on the treatment of worsening episodes that require hospitalization. Forty years ago, in an era when rheumatic heart disease was common, these events were often dramatic and life-threatening. When patients presented with acute pulmonary edema, physicians took swift steps to abruptly redistribute blood volume away from the pulmonary circulation, with the use not only of diuretics but also of nitrates to increase systemic venous capacitance. The response in patients was dramatic, and it often occurred within minutes; therapy was immediately lifesaving.[1]

Acute pulmonary edema still occurs in clinical practice, and it is often related to a drug-induced or endogenous catecholamine surge. However, most patients who are hospitalized with worsening heart failure do not have a new, acute disorder. Instead, they present with decompensation of chronic underlying ventricular dysfunction as a consequence of gradual but progressive increases in cardiac filling pressures in the preceding weeks.[4] Sometimes the deterioration is triggered by cardiac arrhythmia or pulmonary infection, but typically the deterioration is not sudden or immediately life-threatening.

Are these episodes of worsening heart failure a medical emergency akin to acute pulmonary edema decades ago? Most patients recover within a few days after intensification of medical therapy. However, these events are often accompanied by the early release of troponin, indicating a small degree of myocardial injury[5] that is possibly related to acute ventricular distention. Could emergency interventions to reduce volume overload salvage a few cardiomyocytes, which might (in turn) have benefits for long-term prognosis? We know that each hospitalization accelerates the rate of progression of heart failure.[6] So, is decompensated heart failure similar to an acute coronary syndrome, for which it is critical to perform an emergency intervention to minimize irreversible cardiac injury?

The hypothesis that exceptionally early short-term therapy during a hospitalization for heart failure might yield long-term benefits was sup-