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**THE EDITORIALIST REPLIES:** Although the randomized, controlled trial by Cahen et al. did show the clear superiority of surgical drainage over endoscopic therapy for pain associated with chronic pancreatitis, the study was very small — only 39 patients were included. The previous randomized, controlled trial by Dite et al.,<sup>1</sup> which was similar to that of Cahen et al., included 72 patients, and the authors came to a conclusion that was different from that stated by Kleeff and colleagues. In the study by Dite and colleagues, the initial success rate

was similar for surgery and endoscopic treatment, although at the 5-year follow-up, complete absence of pain was more frequent among the surgically treated patients (34%, vs. 15% among the endoscopically treated patients) and the rate of partial relief was similar (52% and 46%). Dite et al. and a recent guideline from the American Society for Gastrointestinal Endoscopy<sup>2</sup> concluded that endoscopic treatment may be preferred because of its lower degree of invasiveness, with surgery reserved as second-line therapy.

I agree with Kleeff and colleagues that we owe patients a summary of available evidence so that they can make informed choices regarding their treatment options. However, a single, small study does not adequately summarize the evidence.

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Since the publication of her editorial, Dr. Elta reports serving on the advisory council for MGI Pharma. No other potential conflict of interest relevant to this letter was reported.

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## Air Pollution and Cardiovascular Events

**TO THE EDITOR:** In the report by Miller and colleagues on long-term exposure to air pollution and the incidence of cardiovascular events in women (Feb. 1 issue),<sup>1</sup> the authors state that their robust findings (hazard ratio for death from cardiovascular disease, 1.76) cannot be explained by acute effects of particulate matter. Although particulate matter might subtly promote atherosclerosis,<sup>2</sup> their findings in no way illustrate synergistic, long-term health consequences of exposure beyond acute effects.

The largest portion of the observed cardiovascular morbidity and mortality is due to particulate matter as a “triggering event” within hours to weeks after exposure. Cohort studies<sup>1</sup> relate long-term levels of particulate matter to events but provide no information regarding the time courses over which exposures actually cause outcomes. The differences between the results of time series (relative risk of death from cardiovascular disease approximately 1.01), which can provide similar data on mortality,<sup>3</sup> and the results reported by Miller

et al. are primarily likely to be due to underestimation of the true risk by time series, for multiple reasons. Moreover, case–crossover studies<sup>4</sup> show that the risks within a single hour after exposure are similar in magnitude to those reported by Miller et al., that lowering pollution dramatically reduces mortality within only months,<sup>5</sup> and that extending exposure lag-times to weeks yields findings similar to those of cohort studies. It is not biologically plausible that long-term exposure would increase mortality by a factor of 76 (or even by a factor of 2) because of cumulative health responses beyond acute effects (hours to weeks in duration).

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**TO THE EDITOR:** Miller et al. overstate the risk of death from cardiovascular disease associated with exposure to particulate matter of less than 2.5  $\mu\text{m}$  in aerodynamic diameter ( $\text{PM}_{2.5}$ ). The exposure increment of 10  $\mu\text{g}$  per cubic meter for  $\text{PM}_{2.5}$  used in the study is not available for most American cities. This exposure increment has been used correctly to describe between-city exposures to  $\text{PM}_{2.5}$ <sup>1</sup> or within-city exposures in Los Angeles,<sup>2</sup> a megalopolis with unusually variable levels of  $\text{PM}_{2.5}$ . The actual increment for  $\text{PM}_{2.5}$  within most cities would be much less. With 62  $\text{PM}_{2.5}$  monitors covering 16 metropolitan areas around New York City,<sup>3</sup> the 10th to 90th percentile exposure increment is 3.23  $\mu\text{g}$  per cubic meter. The 10th to 90th percentile range of within-city deviations reported by Miller et al. is 3.3  $\mu\text{g}$  per cubic meter. The authors also report that the within-city and between-city regression coefficients are different ( $P=0.07$ ), probably because of the variation in  $\text{PM}_{2.5}$  across the United States, which is mostly due to secondary sulfate levels, whereas the variation within cities arises from traffic sources. The toxicity of these mixtures differs,<sup>4</sup> and the exposure increment used for interpreting the hazard ratio should reflect this difference. Using an exposure increment of 3.3  $\mu\text{g}$  per cubic meter on the basis of data for New York City and data from the study by Miller et al. yields a hazard ratio for death from cardiovascular disease of 1.31, not 2.28, as reported, which is consistent with prior research.<sup>1,2</sup>

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**THE AUTHORS REPLY:** The correspondents comment on the magnitude of the risk estimate in our study, emphasizing the mortality results. Our primary hypothesis concerned the effect of fine particulate matter on all incident cardiovascular events, for which the hazard ratio was 1.24 (95% confidence interval, 1.09 to 1.41). Beyond exposure considerations, there are important differences between prior studies and our research regarding the population under study and the outcomes assessed.

Brook and Rajagopalan suggest that the effects on mortality we reported can be ascribed entirely to short-term exposure. Indeed, acute effects of air pollution are important and warrant additional study. Cohort studies cannot easily distinguish between acute and long-term effects, since such studies reflect both different time courses of the underlying exposure distribution and different exposure–risk relationships.<sup>1,2</sup> The cohort design suggests that long-term exposure is important, and the toxicologic database<sup>3,4</sup> suggests that air pollution may promote atherosclerosis. Additional research is needed to determine whether different time scales of exposure share pathophysiological underpinnings.

Jerrett and Burnett are concerned that our use of an exposure increment of 10  $\mu\text{g}$  per cubic meter for  $\text{PM}_{2.5}$  provides an exaggerated estimate of the effect of particulate matter. For ease of comparison with published results from studies of previous national cohorts,<sup>5</sup> we reported estimates using the exposure increment conventionally used in those studies. The increment of 10  $\mu\text{g}$  per cubic meter lies well within the range of the individual exposure increments (3.4 to 28.3  $\mu\text{g}$  per cubic meter; 10th to 90th percentile, 9.1 to 18.3) among participants in the Women's Health Initiative Observational Study. Since we found no reason to doubt a linear relationship between pollutants and effects, readers can and should scale the exposure increment to their own scientific context.

We agree with Jerrett and Burnett that the sources and components of particulate matter are likely to be important for determining toxicity and that much variation within cities is attributable to traffic sources. Our study, like prior work, does not provide specific guidance on sources and components.

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## Inhaled Insulin for Diabetes Mellitus

**TO THE EDITOR:** An important uncertainty about treatment with inhaled insulin is the potentially increased risk of lung cancer. In their *Clinical Therapeutics* article on inhaled insulin for diabetes mellitus, McMahon and Arky (Feb. 1 issue)<sup>1</sup> report that short-term studies in animals have not shown a substantial effect on cell-proliferation indexes in the alveolar or bronchiolar areas of the lung. This is not quite correct. One of the short-term studies reports an increased rate of mitosis induced by inhaled insulin in rats.<sup>2</sup>

Presumably in response to this finding, Pfizer, the manufacturer of a dry-powder formulation of human insulin, proposed to conduct a 12-year prospective study “to compare lung cancer mortality between INH [inhaled insulin]–treated and non–INH-treated patients.”<sup>3</sup> However, the rate of lung cancer depends on the rate of smoking 20 years earlier. It is therefore highly unlikely that we can expect a reliable result within 12 years.

McMahon and Arky report that “insulin acts as a weak growth factor when it binds to the type 1 insulin-like growth factor receptor.”<sup>1</sup> It also can have a mitogenic effect mediated by its own receptors, especially if — like the insulin used for inhalation — it has a long average residence time at the receptor.<sup>4</sup> Only 25% of the dose deposited in the lung is absorbed.<sup>1</sup> This necessarily leads to high insulin concentrations in the alveolar and bronchiolar tissue. Studies of human bronchial epithelial cells suggest that insulin-receptor activation is in itself insufficient for malignant transformation. The insulin-receptor pathway, however, is thought to promote malignant progression of these cells

once malignant transformation has been induced by other agents.<sup>5</sup>

Informing patients about the “unknown long-term adverse effects of this form of therapy”<sup>1</sup> is not sufficient. One should point out that lung cancer has not been ruled out as one of the possible side effects. Only with this information do patients have the opportunity to make an informed choice of treatment.

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**TO THE EDITOR:** McMahon and Arky do not recommend inhaled insulin in patients with asthma