encourage scientists across the world to participate in a review of our data, methods, and results through the GBD collaborator network.
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Since publication of their article, the authors report no further potential conflict of interest.

Air Pollution and Mortality in the Medicare Population

TO THE EDITOR: Di et al. (June 29 issue) provide a sophisticated examination of the association between exposure to ozone concentrations and mortality among the Medicare cohort population. They frame the warm season in the years 2000 through 2012 to encompass the months of April through September. However, April through September is too long a period to be described as solely a warm season. The authors combine average ozone levels in three different seasons: spring (April through May), summer (June through August), and fall (September). In general, ozone concentrations over the United States are usually higher in the summer than in the spring, since the chemical reactions that form ozone are temperature-dependent.

In addition, the long warm season reported could lead to ambiguity in the mortality results, since ozone has a dominant effect on mortality during particular times of the year, rather than during a longer period of 6 months. To strengthen future arguments for establishing seasonal standards, there should be a clear distinction in meteorologic data between one season and another.

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TO THE EDITOR: As Di et al. report, fine particulate matter (particles with a mass median aerodynamic diameter of less than 2.5 μm [PM2.5]) can exert lethal effects even below the National Ambient Air Quality Standard set by the Environmental Protection Agency (EPA). Aung et al. linked cardiac toxic effects, including death, to PM2.5 levels that are similarly considered to be acceptable in the United Kingdom.

Some origins of PM2.5, such as road dust, elude control, whereas diesel engines generate PM2.5 even when idling, in the form of tailpipe emissions from fuel combustion and from particulate precursors such as oxides of nitrogen and volatile organic compounds. Therefore, most states have mandated idling limits ranging from seconds to 2 hours; 19 states specify 5-minute limits. Unfortunately, 15 states, including Florida and North Carolina, have no such limits. North Carolina recently repealed existing restrictions, despite the reduction in deaths from respiratory illnesses in that state after passage of the Clean Smokestacks Act. Given the lack of a threshold for PM2.5 in the mortality association reported by Di et al., prudence favors the institution of diesel idling restrictions in states that currently have none. Their air quality would surely benefit.

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To the Editor: The article by Di et al. contains weak noncausal evidence that PM$_{2.5}$ is related to total mortality in the Medicare population. It does not cite the previous evidence reported by Zeger et al.$^1$ of a large, unexplained geographic variation in the risk of death associated with PM$_{2.5}$ and of no risk of death associated with PM$_{2.5}$ if the risk is based on a local regression coefficient that indicates the association between location-specific trends in pollution and mortality, as described in the detailed statistical analysis reported by Greven et al.$^2$

The article by Di and colleagues also does not cite recent data showing no risk of death associated with PM$_{2.5}$ in the National Institutes of Health–American Association of Retired Persons Diet and Health Study cohort$^3$ and the Cancer Prevention Study cohort.$^4$ We think that before the findings of the federally funded study by Di et al. are accepted as valid, the underlying Medicare data should be analyzed independently in accordance with the HONEST (Honest and Open New EPA Science Treatment) Act.$^5$

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The authors reply: In response to Majeed and Majeed: our definition of warm-season ozone is consistent with that in the study by Jerrett et al., the results of which were also published in the Journal.$^1$ Although ozone levels peak over the summer, in recent decades, summer ozone levels have decreased, but spring and autumn ozone levels have increased. Using a statistical approach for causal inference, we have previously shown that exposure to high levels of ozone in the spring, summer, and fall is associated with an increased risk of death.$^2$

In response to Raymond: given that there is no threshold for the relationship between PM$_{2.5}$ and mortality, any reduction in air pollution is beneficial. Establishing a restriction on diesel idling would reduce air pollution without cost.

Enstrom points to some studies with null findings that we did not cite. Our conclusions would not have changed on the basis of which of the hundreds of studies of air pollution we might have cited. This is because our study is not a meta-analysis. It is an analysis of new nationwide data and an assessment of exposure with high spatial resolution (i.e., daily PM$_{2.5}$ and ozone concentrations for nationwide grids that were 1 km by 1 km), and we reported strong, not weak associations. Sensitivity analyses showed that smoking and socioeconomic status are unlikely to confound the association, and we controlled for spatial variation (see the Supplementary Appendix, available with the full text of our article at NEJM.org). Moreover, meta-analyses of all published cohort studies show strong, robust associations of PM$_{2.5}$ with mortality,$^3$ and two recent studies have shown similar associations with the use of causal modeling techniques.$^4$ The Medicare beneficiary denominator file from the Centers for Medicare and Medicaid Services is a publicly available data source, and therefore this study can be independently replicated.

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Since publication of their article, the authors report no further potential conflict of interest.
CD55 Deficiency and Protein-Losing Enteropathy

TO THE EDITOR: Ozen et al. (July 6 issue) describe 11 study participants with loss-of-function variants in CD55 and complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy (the CHAPLE syndrome). CD55-deficient mice recapitulate some of the clinical characteristics of this newly identified syndrome and have a predisposition to glomerular injury, which is consistent with the presence of proteinuria in 2 of the 11 patients. Therefore, urinary protein loss may represent a feature of the CHAPLE syndrome (since CD55 is expressed in human glomeruli) and may lead to hypoalbuminemia, hypogammaglobulinemia, and edema. A comparison of the clinical symptoms among the 11 patients described by Ozen et al. showed that the 2 patients with proteinuria (Patients 4.1 and 6.1) also had pronounced hypoalbuminemia and hypogammaglobulinemia. Additional data regarding renal function and proteinuria among the series of patients could enable a better understanding of the degree of renal involvement in this rare condition and the role of CD55 in human glomerular physiology. Similarly, we wonder about the effects of eculizumab (which inhibits the complement component C5) on renal function and proteinuria in the 3 patients with the CHAPLE syndrome who are described in the letter by Kurolap et al. in the same issue of the Journal.

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DR. OZEN AND COLLEAGUES REPLY: Angeletti and colleagues raise the interesting possibility that the CHAPLE syndrome may also involve kidney disease. As they correctly point out, 2 of the 11 patients who are described in our article (Patients 4.1 and 6.1) presented with proteinuria. Patient 4.1 had moderate proteinuria (15 to 26 mg of protein per square meter per hour) that lasted for 2 weeks. (A urine dipstick test was negative for protein before and after this 2-week period.) Patient 6.1 had a history of transient proteinuria earlier in his disease course (20 mg per square meter per hour at 2 years of age, followed by normal results a year later), as well as unilateral kidney agenesis, with his single kidney showing increased parenchymal echogenicity and hypertrophy on some examinations. However, during clinical follow-up of both patients, no proteinuria was detected on urine examinations (on 24-hour urine collection, protein-to-creatinine ratio in spot urine testing, or both), and the patients had normal kidney function as assessed on creatinine clearance tests. Thus, neither patient had persistent proteinuria that could account for the degree of ongoing hypoalbuminemia or hypogammaglobulinemia observed in the CHAPLE syndrome. In addition, Patients 4.1 and 1.1 were evaluated for microalbumin and beta-2