encourage scientists across the world to participate in a review of our data, methods, and results through the GBD collaborator network.

Ashkan Afshin, M.D., Sc.D.
Marissa B. Reitsma, B.S.
Christopher J.L. Murray, D.Phil., M.D.
Institute for Health Metrics and Evaluation
Seattle, WA
cjlm@uw.edu

Since publication of their article, the authors report no further potential conflict of interest.

1. Di Angelantonio E, Bhupathiraju SN, Wormser D, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388:776-86.
2. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer — viewpoint of the IARC Working Group. N Engl J Med 2016;375:794-8.
3. World Health Organization. Noncommunicable diseases global monitoring framework: indicator definitions and specifications. November 2014 (http://www.who.int/nmh/ncd-tools/indicators/GMF_Indicator_Definitions_Version_NOV2014.pdf).

DOI: 10.1056/NEJMc1710026

Air Pollution and Mortality in the Medicare Population

TO THE EDITOR: Di et al. (June 29 issue)[1] 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.[2-4]

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.[4] To strengthen future arguments for establishing seasonal standards, there should be a clear distinction in meteorologic data between one season and another.

Haris Majeed, M.Sc.
Hamnah Majeed
University of Toronto
Toronto, ON, Canada
haris.majeed@utoronto.ca

No potential conflict of interest relevant to this letter was reported.

1. Di Q, Wang Y, Zanobetti A, et al. Air pollution and mortality in the medicare population. N Engl J Med 2017;376:2513-22.
2. Zhang Y, Wang Y. Climate-driven ground-level ozone extreme in the fall over the Southeast United States. Proc Natl Acad Sci U S A 2016;113:10025-30.
3. Strode SA, Rodriguez JM, Logan JA, et al. Trends and variability in surface ozone over the United States. J Geophys Res 2015;120:9020-42.
4. Bell ML, Dominici F, Samet JM. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiology 2005;16:436-45.

DOI: 10.1056/NEJMc1709849

TO THE EDITOR: As Di et al. report, fine particulate matter (particles with a mass median aerodynamic diameter of less than 2.5 μm [$PM_{2.5}$]) can exert lethal effects even below the National Ambient Air Quality Standard set by the Environmental Protection Agency (EPA).[1] Aung et al.[2] linked cardiac toxic effects, including death, to $PM_{2.5}$ levels that are similarly considered to be acceptable in the United Kingdom.

Some origins of $PM_{2.5}$, such as road dust, elude control, whereas diesel engines generate $PM_{2.5}$ 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.[3,4] Given the lack of a threshold for $PM_{2.5}$ 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.

Lawrence W. Raymond, M.D.
Carolinas HealthCare System
Charlotte, NC
larry.raymond@carolinashealthcare.org

No potential conflict of interest relevant to this letter was reported.

1. Berger RE, Ramaswami R, Solomon CG, Drazen JM. Air pollution still kills. N Engl J Med 2017;376:2591-2.
2. Aung N, Sanghvi MM, Zemrak F, et al. Impact of fine particulate matter air pollutant on cardiac atrial and ventricular structure and function derived from cardiovascular magnetic resonance (CMR) imaging — evidence from the UK Biobank. Presented at EuroCMR 2017, Prague, May 26, 2017. abstract.
3. Kravchenko J, Akushevich I, Abernethy AP, Holman S, Ross WG Jr, Lyerly HK. Long-term dynamics of death rates of emphysema, asthma, and pneumonia and improving air quality. Int J Chron Obstruct Pulmon Dis 2014;9:613-27.
4. Ross WG Jr. The North Carolina Clean Smokestacks Act. N C Med J 2011;72:128-31.

DOI: 10.1056/NEJMc1709849

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]

James E. Enstrom, Ph.D., M.P.H.
University of California, Los Angeles
Los Angeles, CA
jenstrom@ucla.edu

No potential conflict of interest relevant to this letter was reported.

1. Zeger SL, Dominici F, McDermott A, Samet JM. Mortality in the Medicare population and chronic exposure to fine particulate air pollution in urban centers (2000-2005). Environ Health Perspect 2008;116:1614-9.
2. Greven S, Dominici F, Zeger S. An approach to the estimation of chronic air pollution effects using spatio-temporal information. J Am Stat Assoc 2011;106:396-406.
3. Thurston GD, Ahn J, Cromar KR, et al. Ambient particulate matter air pollution exposure and mortality in the NIH-AARP Diet and Health cohort. Environ Health Perspect 2016;124:484-90.
4. Enstrom JE. Fine particulate matter and total mortality in cancer prevention study cohort reanalysis. Dose Response 2017;15:1559325817693345.
5. H.R. 1430, Honest and Open New EPA Science Treatment (HONEST) Act of 2017 (http://www.govtrack.us/congress/bills/115/hr1430/text).

DOI: 10.1056/NEJMc1709849

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.[4,5] 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.

Qian Di, M.S.
Francesca Dominici, Ph.D.
Joel D. Schwartz, Ph.D.
Harvard T.H. Chan School of Public Health
Boston, MA
fdominic@hsph.harvard.edu

Since publication of their article, the authors report no further potential conflict of interest.

1. Jerrett M, Burnett RT, Pope CA III, et al. Long-term ozone exposure and mortality. N Engl J Med 2009;360:1085-95.
2. Zanobetti A, Schwartz J. Ozone and survival in four cohorts with potentially predisposing diseases. Am J Respir Crit Care Med 2011;184:836-41.
3. Hoek G, Krishnan RM, Beelen R, et al. Long-term air pollution exposure and cardio-respiratory mortality: a review. Environ Health 2013;12:43.
4. Wang Y, Lee M, Liu P, et al. Doubly robust additive hazards models to estimate effects of a continuous exposure on survival. Epidemiology 2017 August 19 (Epub ahead of print).
5. Wang Y, Kloog I, Coull BA, Kosheleva A, Zanobetti A, Schwartz JD. Estimating causal effects of long-term PM2.5 exposure on mortality in New Jersey. Environ Health Perspect 2016;124:1182-8.
DOI: 10.1056/NEJMc1709849

CD55 Deficiency and Protein-Losing Enteropathy

TO THE EDITOR: Ozen et al. (July 6 issue)[1] 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[2,3] and have a predisposition to glomerular injury,[4] 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.[5] in the same issue of the *Journal*.

Andrea Angeletti, M.D.
University of Bologna
Bologna, Italy

Maddalena Marasà, M.D.
Columbia University Medical Center
New York, NY

Paolo Cravedi, M.D., Ph.D.
Icahn School of Medicine at Mount Sinai
New York, NY
paolo.cravedi@mssm.edu

No potential conflict of interest relevant to this letter was reported.

1. Ozen A, Comrie WA, Ardy RC, et al. CD55 deficiency, early-onset protein-losing enteropathy, and thrombosis. N Engl J Med 2017;377:52-61.
2. Bani-Ahmad M, El-Amouri IS, Ko CM, Lin F, Tang-Feldman Y, Oakley OR. The role of decay accelerating factor in the immunopathogenesis of cytomegalovirus infection. Clin Exp Immunol 2011;163:199-206.
3. Lin F, Spencer D, Hatala DA, Levine AD, Medof ME. Decay-accelerating factor deficiency increases susceptibility to dextran sulfate sodium-induced colitis: role for complement in inflammatory bowel disease. J Immunol 2004;172:3836-41.
4. Lin F, Emancipator SN, Salant DJ, Medof ME. Decay-accelerating factor confers protection against complement-mediated podocyte injury in acute nephrotoxic nephritis. Lab Invest 2002;82:563-9.
5. Kurolap A, Eshach-Adiv O, Hershkovitz T, et al. Loss of CD55 in eculizumab-responsive protein-losing enteropathy. N Engl J Med 2017;377:87-9.
DOI: 10.1056/NEJMc1710011

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 of body-surface area 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