

3. Craven LJ, Nair Parvathy S, Tat-Ko J, Burton JP, Silverman MS. Extended screening costs associated with selecting donors for fecal microbiota transplantation for treatment of metabolic syndrome-associated diseases. *Open Forum Infect Dis* 2017;4(4): ofx243.
4. Costello SP, Tucker EC, La Brooy J, Schoeman MN, Andrews JM. Establishing a fecal microbiota transplant service for the

treatment of *Clostridium difficile* infection. *Clin Infect Dis* 2016; 62:908-14.

5. Biedermann L, Zeitz J, Mwinji J, et al. Smoking cessation induces profound changes in the composition of the intestinal microbiota in humans. *PLoS One* 2013;8(3):e59260.

DOI: 10.1056/NEJMc1913670

Ambient Air Pollution and Mortality in 652 Cities

TO THE EDITOR: In response to the article by Liu et al. (Aug. 22 issue)¹: the inhalable fraction of particulate matter with an aerodynamic diameter of 10 μm or less (PM_{10}) in the real world is made up of a mixture of substances probably derived from many sources.² In urban areas, a substan-

tial fraction of PM_{10} is related to combustion emissions (transport, industry, power generation, and the like).³ However, in arid regions, a large fraction of PM_{10} derives from desert dust particles. This kind of PM_{10} , emitted from the soil of deserts and transported by the action of wind, causes dust storms that are common in North Africa, the Middle East, and inner Asia and that occur occasionally in Mediterranean countries and the North Atlantic. The global effect is poor air quality for more than 2 billion people.⁴

The influence of PM_{10} that is derived from combustion on cardiovascular pathophysiology is different from the influence of PM_{10} derived from dust.⁵ This differentiation should be considered in global studies that have included regions affected by desert dust, such as inner Asia (Fig. 1); studies need to be done to determine the causal components in particulate matter.

Daniel Hernandez-Vaquero, M.D., Ph.D.

Instituto de Investigación Sanitaria del Principado de Asturias
Oviedo, Spain
dhvaquero@gmail.com

Sergio Rodriguez, Ph.D.

Estación Experimental de Zonas Áridas
Almería, Spain

Alberto Dominguez-Rodriguez, M.D., Ph.D.

Hospital Universitario de Canarias
Tenerife, Spain

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

1. Liu C, Chen R, Sera F, et al. Ambient particulate air pollution and daily mortality in 652 cities. *N Engl J Med* 2019;381:705-15.
2. Pope CA III, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc* 2006; 56:709-42.
3. Putaud J-P, Van Dingenen R, Alastuey A et al. A European aerosol phenomenology: physical and chemical characteristics of particulate matter from 60 rural, urban, and kerbside sites across Europe. *Atmos Environ* 2010;44:1308-20.

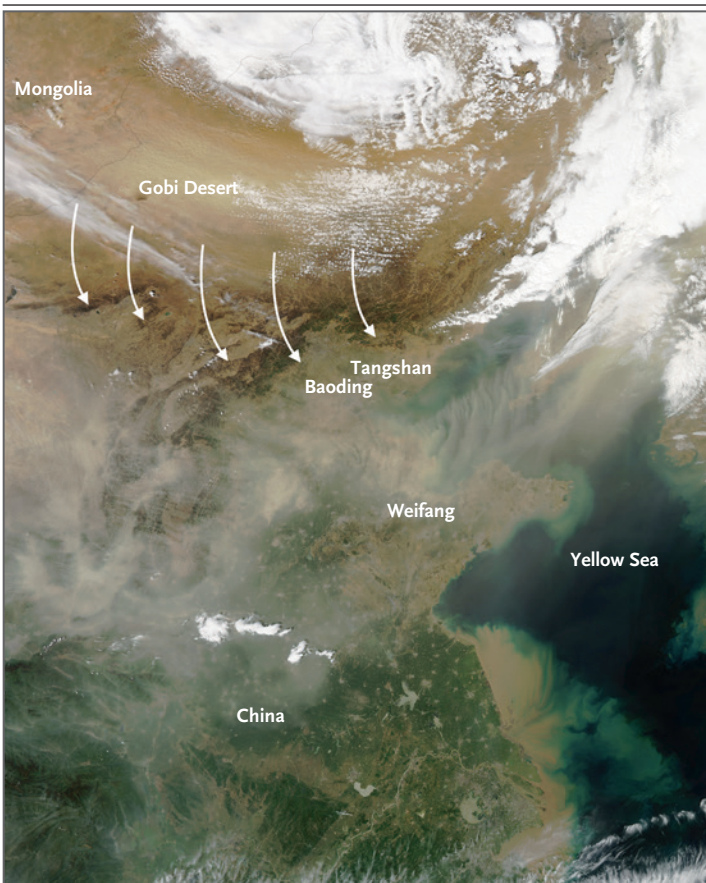


Figure 1. Dust Intrusion from the Gobi Desert into China.

Marked cities were part of the study by Liu et al.¹ Image from the Land, Atmosphere Near real-time Capability for EOS (LANCE) system operated by the NASA Earth Science Data and Information System (ESDIS).

4. Engelstaedter S, Tegen I, Washington R. North African dust emissions and transport. *Earth Sci Rev* 2006;79:73-100.
5. De Longueville F, Hountondji YC, Henry S, Ozer P. What do we know about effects of desert dust on air quality and human health in West Africa compared to other regions? *Sci Total Environ* 2010;409:1-8.

DOI: 10.1056/NEJMc1913285

TO THE EDITOR: Liu et al. claim that poor air quality, due to increased particulate matter, in more than 600 cities across the world can be linked to mortality. We question the reliability of this claim given negative studies^{1,2} and reanalysis of two meta-analytic studies^{3,4} in which the reanalysis attempts to vitiate the conclusion of the source studies that particulate matter causes heart attacks. With respect to Liu et al., 16 P values that we computed from data regarding fine particulate matter with an aerodynamic diameter of 2.5 μm or less ($\text{PM}_{2.5}$) in Table 1 of their article lead to a striking P-value plot: 8 values along a roughly 45-degree line are consistent with the lack of a causal association, whereas 8 are less than 0.05, supporting an association (Fig. 1). In effect, we think that Liu et al. reported data from studies that form a two-component mixture, as observed in two recent reports^{3,4}; we think it makes no sense to report an average based on a mixture having two components.

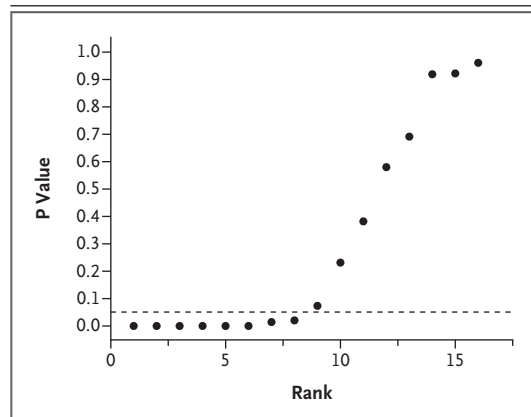


Figure 1. Plot of P Values.

In this plot, P values for the association between fine particulate matter with an aerodynamic diameter of 2.5 μm or less and all-cause mortality are ranked from smallest to largest and plotted against the integers 1 through 16. Each P value corresponds to one country listed in Table 1 of the article by Liu et al. The dashed line at 0.05 represents nominal statistical significance.

S. Stanley Young, Ph.D.

CGStat
Raleigh, NC
genetree@bellsouth.net

Warren Kindzierski, Ph.D.

University of Alberta
Edmonton, AB, Canada

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

1. Milojevic A, Wilkinson P, Armstrong B, Bhaskaran K, Smeeth L, Hajat S. Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality. *Heart* 2014;100:1093-8.

2. Young SS, Smith RL, Lopiano KK. Air quality and acute deaths in California, 2000-2012. *Regul Toxicol Pharmacol* 2017; 88:173-84.

3. Young SS, Acharjee MK, Das K. The reliability of an environmental epidemiology meta-analysis, a case study. *Regul Toxicol Pharmacol* 2019;102:47-52.

4. Young SS, Kindzierski WB. Evaluation of a meta-analysis of air quality and heart attacks, a case study. *Crit Rev Toxicol* 2019; 49:85-94.

DOI: 10.1056/NEJMc1913285

TO THE EDITOR: Liu et al. found consistent increases in daily all-cause, cardiovascular, and respiratory mortality in association with increasing concentrations of ambient particulate matter in 652 cities worldwide. We caution that future studies should not consider populations of individual cities as a static entity. Cities are increasingly connected, currently with 1.2 billion international arrivals per year.¹ Cities, their residents, their visitors, and their temporary residents do not represent a constant cohort but present dynamic interdependent systems in concert with variable pollution profiles. The health effects that are observed in an individual's usual residence city might be more associated with exposures in a frequent destination city or temporary residence city. Even short-stay international travel to cities with elevated air pollution by healthy adults has now been associated with adverse cardiopulmonary health effects, including decreased lung function and heart-rate variability and an increase in respiratory symptoms.² Future research should consider mobile sectors of the population when studying air pollution-related health outcomes. Municipal authorities should be responsible for the health of their residents and visitors.

M.J. Ruzmyn Vilcassim, Ph.D.

University of Alabama at Birmingham School of Public Health
Birmingham, AL
ruzmyn@uab.edu

David O. Freedman, M.D.

University of Alabama at Birmingham School of Medicine
Birmingham, AL

Annelies Wilder-Smith, M.D., Ph.D.

Heidelberg Institute of Global Health
Heidelberg, Germany

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

1. Glaesser D, Kester J, Paulose H, Alizadeh A, Valentin B. Global travel patterns: an overview. *J Travel Med* 2017;24(4):tax007.
2. Vilcassim MJR, Thurston GD, Chen LC, et al. Exposure to air pollution is associated with adverse cardiopulmonary health effects in international travellers. *J Travel Med* 2019;26(5):taz032.

DOI: 10.1056/NEJMc1913285

TO THE EDITOR: The editorial by Balmes¹ regarding the 652-city study of air pollution by Liu et al. cites an article in *Science*² that states that I want to rely on studies that use a theoretical approach called “manipulative causality” as the basis for regulatory decision making, thereby restricting epidemiologic evidence considered in assessing causality. Neither article correctly paraphrases my views. The Clean Air Scientific Advisory Committee recently asked for a “clearer discussion of causality.”³ My personal view is that the weight-of-evidence approach of the Environmental Protection Agency (EPA) does not offer a clear definition for causality in studies of air pollution. I think that the EPA should specifically characterize the types of harm to human health that are preventable or can be lessened by reducing exposures to particulate matter (manipulative causation), since this is ultimately what could matter most to policymakers.⁴ Balmes opines that this “would set a dangerous precedent for environmental policy.” I seek clarity in the definition of causality in studies of air pollution, not restrictions on the evidence considered.

Louis A. Cox, Jr., Ph.D.

University of Colorado
Denver, CO
tcoxdenver@aol.com

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

1. Balmes JR. Do we really need another time-series study of the PM_{2.5}-mortality association? *N Engl J Med* 2019;381:774-6.

2. Goldman GT, Dominici F. Don't abandon evidence and process on air pollution policy. *Science* 2019;363:1398-400.
3. Cox LA Jr. Letter to Honorable Andrew R. Wheeler regarding CASAC review of the EPA's integrated science assessment for particulate matter (external review draft — October 2018). April 2019 (<https://yosemite.epa.gov/sab/sabproduct.nsf/LookupWebReportsLastMonthCASAC/6CBCBBC3025E13B4852583D90047B352/%24File/EPA-CASAC-19-002+.pdf>).
4. Burns J, Boogaard H, Polus S, et al. Interventions to reduce ambient particulate matter air pollution and their effect on health. *Cochrane Database Syst Rev* 2019;5:CD010919.

DOI: 10.1056/NEJMc1913285

THE AUTHORS REPLY: Hernandez-Vaquero et al. raise a point regarding the identification of the causal components for mortality within inhalable particulate matter. We agree that the toxicity of particulate matter may vary with respect to different sources (such as combustion emissions and desert dust), and the composition of particulate matter is a potential source of heterogeneity in our study. More data are needed to expand our understanding of this link in inner Asia or the Middle East, where desert dust is the main contributor to inhalable particulate matter.

The comments by Young and Kindziersky are based on a biased summary of the literature and a misunderstanding of the study design that we used. First, the link between exposure to particulate matter and a short-term increase in mortality is firmly established from dozens of large-scale, multicenter epidemiologic investigations and reports worldwide.¹⁻³ This evidence cannot be dismissed by two small studies that assessed only cardiovascular events or were conducted in limited locations. More important, the authors did not acknowledge that our study is not a meta-analysis, but a multilocation study with direct data collection in 652 cities. The risks that we report in Table 1 of our article therefore do not represent previously published estimates, but country-specific effects pooled from multiple cities directly measured with the use of a two-stage design. Thus, none of their arguments related to publication bias, “P-hacking,” and subpopulations actually applies. Finally, the fact that some P values are above the significance threshold is expected, given the uncertainty of single estimates inherent in multicenter studies or related to the small data sets available from some regions. Our pooled estimates, however, indicate strong evidence of an association, with values that are consistent with those of most previous studies.

Vilcassim et al. raise an issue of uncertainty from traveling or migration and proposed to pay attention to the health effects of air pollution among the mobile sector of the population. However, few natural deaths are expected to occur among active travelers; we cannot account for in-migration or out-migration, but the numbers are probably small compared with deaths in the resident population.

Cong Liu, M.S.

School of Public Health, Fudan University
Shanghai, China

Antonio Gasparini, Ph.D.

London School of Hygiene and Tropical Medicine
London, United Kingdom

Haidong Kan, Ph.D.

School of Public Health, Fudan University
Shanghai, China
kanh@fudan.edu.cn

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

1. Romieu I, Gouveia N, Cifuentes LA, et al. Multicity study of air pollution and mortality in Latin America (the ESCALA study). *Res Rep Health Eff Inst* 2012;171:5-86.
2. Samoli E, Peng R, Ramsay T, et al. Acute effects of ambient particulate matter on mortality in Europe and North America: results from the APHENA study. *Environ Health Perspect* 2008; 116:1480-6.
3. Samet JM, Zeger SL, Dominici F, et al. The National Morbidity, Mortality, and Air Pollution Study. II. Morbidity and mortality from air pollution in the United States. *Res Rep Health Eff Inst* 2000;94:5-79.

DOI: 10.1056/NEJMc1913285

THE EDITORIALIST REPLIES: Cox expounds that the weight-of-evidence approach of the EPA does not offer a clear definition for causality; I disagree. The previously established approach of the EPA combines evidence from epidemiologic studies, human experimental studies, and toxicologic studies in animals to causally link exposure to an

environmental hazard and a health outcome. Although Cox favors studies that involve manipulative causation, these are not feasible in large-scale, multi-city studies of air pollution. In such settings, the Bradford Hill guidelines for inference of causation from observational studies are standard.¹ These guidelines include strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence, and analogy. Although the evidence for the PM_{2.5}-mortality association meets all of these guidelines, Cox does not accept them.^{2,3} The proven weight-of-evidence approach of the EPA is explicitly based on the Bradford Hill guidelines, which were used to establish the link between smoking and lung cancer, and is endorsed by the American Thoracic and European Respiratory Societies and the National Research Council.^{4,5} We should not discard this time-tested approach to abet Cox's efforts to obfuscate our knowledge that PM_{2.5} can cause death.

John R. Balmes, M.D.

University of California, San Francisco
San Francisco, CA

Since publication of his editorial, the author reports no further potential conflict of interest.

1. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300.
2. Integrated Science Assessment (ISA) for Particulate Matter (external review draft). Research Triangle Park, NC: Environmental Protection Agency, October 2018 (<https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=341593>).
3. Goldman GT, Dominici F. Don't abandon evidence and process on air pollution policy. *Science* 2019;363:1398-400.
4. Thurston GD, Kipen H, Annesi-Maesano I, et al. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. *Eur Respir J* 2017;49:1600419.
5. Evidence integration for hazard identification. In: Committee to Review the IRIS Process, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies. Review of EPA's Integrated Risk Information System (IRIS) process. Washington, DC: National Academies Press, 2014.

DOI: 10.1056/NEJMc1913285

Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes

TO THE EDITOR: Preventive strategies for cardiovascular complications in type 2 diabetes mellitus are essential. Subcutaneous glucagon-like peptide-1 (GLP-1) receptor agonists have signifi-

cantly reduced cardiovascular risk in four of six published outcome trials.^{1,2} In the Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 trial (Aug. 29 issue),³ the first oral GLP-1 receptor