

be addressed in interpreting the outcome of this study.

Fu Lung Luan, M.D.

University of Michigan
Ann Arbor, MI 48109
fluan@med.umich.edu

1. The ACCORD Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.
2. Hollenberg NK. Considerations for management of fluid dynamic issues associated with thiazolidinediones. *Am J Med* 2003; 115:Suppl 8A:111S-115S.
3. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-71. [Erratum, *N Engl J Med* 2007;357: 100.]
4. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007;298: 1189-95.

THE AUTHORS REPLY: In response to Banarer: because of slow recruitment, the VADT received approval to extend its accrual period from 2 to 2.5 years. This extension lengthened the entire study from 7 to 7.5 years. During the 6-month accrual extension, the study exceeded the original goal of 1700 patients and finished recruitment with 1791 patients. The additional 91 patients and the 6-month extension of follow-up counterbalanced a 14% dropout rate. Therefore, the achieved power to detect the originally planned 21% reduction in the primary end point was 88% in the study; this information was not included because of word-count limitations.

Although the long-term findings from the UKPDS are very important, they are based on a study population that was quite different from the VADT study population and that was evaluated over a much longer time. We do not believe that performing a post hoc power analysis of our study based on UKPDS variables would serve a

useful purpose, given these differences. The VADT has begun a long-term centralized follow-up of its patients, with analyses proposed after 4 and 9 years. The power to detect a 20% difference in the two treatment groups, given the observed results to date, will be 98% and 99%, respectively.

In response to Luan: dyspnea was a symptom reported by the subject and recorded by the study coordinator. Cardiovascular end points were adjudicated by an independent end-point committee that was unaware of the assignments to treatment groups. The end-point committee found no significant difference between the standard-therapy group and the intensive-therapy group in any end point. The rate of congestive heart failure was slightly, but not significantly, lower in the intensive-therapy group. The results for other cardiovascular end points, with the exception of stroke and sudden death, also favored the intensive-therapy group. Our data on rosiglitazone were presented at the annual meeting of the American Diabetes Association in June 2008; these data suggest a beneficial effect of this thiazolidinedione. Overinterpretation of reported data is always a risk in any large study, especially when blinded hard data are ignored. We strongly object to the use of our data to support an opinion that is not based on objective trial information.

William C. Duckworth, M.D.

Phoenix Veterans Affairs Health Care System
Phoenix, AZ 85012
william.duckworth@va.gov

Tom Moritz, M.S.

Hines Veterans Affairs Medical Center
Chicago, IL 60141

Carlos Abraira, M.D.

Miami Veterans Affairs Medical Center
Miami, FL 33125

Air Pollution and Life Expectancy

TO THE EDITOR: In their study of the association between fine-particulate air pollution and life expectancy, Pope et al. (Jan. 22 issue)¹ adjusted for changes in the prevalence of smoking in order to determine the contribution of reduced levels of air pollution to an improved life expectancy. As the authors observed previously,² the effects of smoking on mortality dwarf those of air pollution, since being a current smoker increases the risk of lung cancer by 1480%, as compared with an in-

crease of 8% per increase of 10 μg per cubic meter in fine-particulate pollution.

A potential arithmetic problem arises. Small errors in estimating either the extent of the change in the prevalence of smoking or the effect of smoking on life expectancy would greatly alter the calculation of the residual, relatively tiny effect of air pollution. Yet changes in tobacco use result in time-delayed effects on rates of cancer and death from cardiac causes that are difficult to

estimate,^{3,4} with a 20-year lag between a decreased rate of smoking and a decreased rate of lung cancer.³ Thus, although the prevalence of smoking decreased, the proxy markers that were used for smoking (deaths from lung cancer or chronic obstructive pulmonary disease [COPD]) increased during the observation period, making them a curious choice. Similarly, would not health effects of air pollution be delayed by some incalculable time?

Michael R. Bubb, M.D.

University of Florida
Gainesville, FL 32610
bubbmr@medicine.ufl.edu

1. Pope CA III, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. *N Engl J Med* 2009; 360:376-86.
2. Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiovascular mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002;287:1132-41.
3. Thun MJ, Jemal A. How much of the decrease in cancer death rates in the United States is attributable to reductions in tobacco smoking? *Tob Control* 2006;15:345-7. [Erratum, *Tob Control* 2006; 15:488.]
4. Barone-Adesi F, Vizzini L, Merletti F, Richiardi L. Short-term effects of Italian smoking regulation on rates of hospital admission for acute myocardial infarction. *Eur Heart J* 2006;27:2468-72.

TO THE EDITOR: Pope et al. attribute a 5-month gain in life expectancy at birth to improved ambient air quality, as measured during two periods, from 1979 through 1983 and from 1997 through 2001. This inconsistency in time scales for outcomes (over a lifetime) and exposures (over a 20-year period) exaggerates benefits; outcomes are overestimated, relevant changes in exposure are underestimated, or both. Long-term effects of air pollution on health tend to be manifested in middle age,¹ during which the remaining life expectancy is approximately 10 to 20% of that at birth.² The middle-aged subjects in the study were born between about 1900 and 1950; because of previous pollution abatement, their current pollution exposures were only a fraction of their earlier and lifetime exposures.³ Any effects on infant mortality must be evaluated against these earlier exposures.

In addition, this ecologic analysis considers only one pollutant and a surrogate measure of smoking status (concurrent lung cancer), thus neglecting differences in disease latency. It also ignores gradients in advances in medical care that contributed significantly to an improved adult life expectancy in the 1980s and 1990s.⁴ This inadequate treatment of confounders is a likely

source of additional upward bias in the estimates of the effects of air pollution on longevity.⁵

Frederick W. Lipfert, Ph.D.

23 Carll Ct.
Northport, NY 11768
flipfert@suffolk.lib.ny.us

1. Lipfert FW, Morris SC. Temporal and spatial relationships between age-specific mortality and ambient air quality in the United States: regression results for counties, 1960-97. *Occup Environ Med* 2002;59:156-74.
2. Anderson RN, DeTurk PB. United States life tables, 1999. *Natl Vital Stat Rep* 2002;50:33.
3. Lipfert FW. Trends in airborne particulate matter in the United States. *Appl Occup Environ Hyg* 1998;13:370-84.
4. Hunink MG, Goldman L, Tosteson AN, et al. The recent decline in mortality from coronary heart disease, 1980-1990: the effect of secular trends in risk factors and treatment. *JAMA* 1997; 277:535-42.
5. Bateson TF, Coull BA, Hubbell B, et al. Panel discussion review: session three — issues involved in interpretation of epidemiologic analyses — statistical modeling. *J Expo Sci Environ Epidemiol* 2007;17:Suppl 2:S90-S96.

THE AUTHORS REPLY: Bubb and Lipfert express their concerns regarding inadequate adjustment for smoking and other potential confounders in our study. Smoking has a substantial effect on life expectancy, but Bubb exaggerates the “potential arithmetic problem.” The excess risk of death from any cause would be approximately 100% for current smokers, as compared with an increase of approximately 6 to 15% for each increase of 10 μg per cubic meter in the concentration of particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($\text{PM}_{2.5}$).¹ In populations ubiquitously exposed to moderately high levels of ambient air pollution ($\text{PM}_{2.5}$, 15 to 30 μg per cubic meter) but in which a fraction of people (15 to 20%) are smokers, the net population-level effects of smoking and pollution on life expectancy may be similar. We observed changes in life expectancy that were associated with changes in both air-pollution levels and proxy variables for smoking, which are independent of each other in multivariate regression models.

Lipfert suggests that inadequate treatment of confounders is a potential source of upward bias in the estimates of the effects of air pollution. Uncontrolled factors can result in upward or downward bias, depending on whether they are positively or negatively associated with air pollution. Direct measures of county-level access to advances in medical care are not available, but confounding by these variables is at least partially controlled by adjustment for socioeconomic and demographic variables. Associations between changes in life expectancy and air-pollution levels

are statistically robust in analyses adjusted for changes in socioeconomic and demographic variables, providing little evidence of significant confounding. Nevertheless, we agree that potential residual confounding is a concern in this and other observational studies.

With regard to time scales of exposure, daily time-series, intervention, and prospective cohort studies provide substantial evidence that the associations between air-pollution levels and mortality have time scales of days to years. The time scale of exposure that captures most of the excess risk of death from any cause is recent exposure (over a period of up to a few years).^{1,2} Disease latency (and thus the relevant time scale) is relatively longer for lung cancer specifically. However, we also controlled for smoking, using rates of death from COPD and survey-based smoking prevalence at the metropolitan level. The estimated increases in life

expectancy associated with declines in air-pollution levels were not highly sensitive to adjustment for any of the smoking-related variables. The data set used for the interactive graphic was redacted to make the presentation manageable. A full data set is available from Dr. Pope on request.

C. Arden Pope III, Ph.D.

Brigham Young University
Provo, UT 84602-2363
cap3@byu.edu

Majid Ezzati, Ph.D.

Douglas W. Dockery, Sc.D.

Harvard School of Public Health
Boston, MA 02115

1. Pope CA III, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc* 2006; 56:709-42.

2. Schwartz J, Coull B, Laden F, Ryan L. The effect of dose and timing of dose on the association between airborne particles and survival. *Environ Health Perspect* 2008;116:64-9.

Blood-Pressure Measurement

TO THE EDITOR: In their Video in Clinical Medicine and accompanying article, Williams et al. (Jan. 29 issue)¹ omit an important step in blood-pressure measurement — the determination of orthostatic (postural) blood pressure. Although guidelines on this procedure are not consistent, it is generally recommended that orthostatic blood pressure be measured while the patient is in the standing position every minute during the first 3 minutes after he or she has been lying supine for 5 minutes.² If the patient cannot stand for this period of time, the lowest systolic blood pressure should be recorded.

Orthostatic hypotension is a physical sign defined as a reduction of at least 20 mm Hg in systolic blood pressure or of at least 10 mm Hg in diastolic blood pressure within 3 minutes after standing.³ Guidelines for the management of hypertension recommend that orthostatic blood pressure be assessed in patients with diabetes, the elderly, patients receiving antihypertensive treatment, and patients with other conditions in which orthostatic hypotension may be common or suspected.^{4,5} The diagnosis of orthostatic hypotension is extremely important, since this condition is responsible for recurrent symptoms such as syncope, dizziness, and light-headedness, as well as serious injuries and deterioration in the quality of life.²

Dimitrios Terentes-Printzios, M.D.

Charalambos Vlachopoulos, M.D.

Christodoulos Stefanadis, M.D.

University of Athens Medical School
11527 Athens, Greece

1. Williams JS, Brown SM, Conlin PR. Videos in clinical medicine: blood-pressure measurement. *N Engl J Med* 2009;360(5):e6 (Web only). (Available at <http://www.nejm.org>.)

2. Brignole M, Alboni P, Benditt DG, et al. Guidelines on management (diagnosis and treatment) of syncope — update 2004. *Europace* 2004;6:467-537.

3. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology* 1996;46:1470.

4. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007;28:1462-536.

5. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206-52.

TO THE EDITOR: In both the article and video on blood-pressure measurement, Williams et al. never mention the measurement of blood pressure in both arms. Blood pressure should initially be recorded in both arms because in a substantial number of patients, particularly the elderly, there are large differences (>10 mm Hg) in blood-pressure readings between the two arms. The arm