Inhalation Toxicology, 20:25–29, 2008

ISSN: 0895-8378 print / 1091-7691 online
DOI: 10.1080/08958370701758759

informa
healthcare

Ambient Air Pollution Particles and the Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Thaw Sint and James F. Donohue
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

Andrew J. Ghio
National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA

Investigation has repeatedly demonstrated an association between exposure to ambient air pollution particles and numerous indices of human morbidity and mortality. Individuals with chronic obstructive pulmonary disease (COPD) are among those with an increased sensitivity to air pollution particles. Current and ex-smokers account for 80 to 85% of all those with COPD. The human breathing in an urban site with a significant level of particulate matter (PM) may be exposed to 720 μg daily. A single cigarette introduces 15,000 to 40,000 μg particle into the respiratory tract of the smoker. It is subsequently confounding why such a relatively small mass of airborne PM should have any biological effect in the patient with COPD, as these individuals are repeatedly exposed to particles (with a similar size and composition) at perhaps a thousandfold the mass of ambient PM. Regarding this increased sensitivity of COPD patients to air pollution particles, there are several possible explanations for this seeming contradiction, including correlations of PM levels with other components of air pollution, an accumulation of multiple independent risk factors in a patient, changes in individual activity patterns, disparities in dosimetry between healthy subjects and COPD patients, and some unique characteristic of an ambient air pollution PM. Regardless of the underlying mechanism for the increased sensitivity of COPD patients, exposures of these individuals to elevated levels of PM should be discouraged. To provide a greater awareness of PM levels, the U.S. Environmental Protection Agency now includes levels of air pollution particles in an air quality index.

Suspended particulate matter (PM) has presented a challenge to the human respiratory tract for as long as our species has survived. This was initially of crustal and plant origin but later included particles generated from the burning of biomass for purposes of heating and food preparation (Pabst & Hofer, 1998). Only recently, in the past few hundred years, have humans been exposed to PM emanating from industrial processes and the combustion of coal, gas, and oil.

Received 10 May 2007; accepted 14 September 2007.
This report has been reviewed by the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the agency; nor does mention of trade names or commercial products constitute endorsement or recommendation for use.
Address correspondence to Andrew J. Ghio, Campus Box 7315, Human Studies Division, U.S. EPA, 104 Mason Farm Road, Chapel Hill, NC 27599, USA. E-mail: ghio.andy@epa.gov

During the past century, episodes of extremely high PM levels in both Europe and the United States increased human morbidity and mortality (Bell & Davis, 2001; Helfand et al., 2001; Nemery et al., 2001). These air pollution debacles were instrumental in bringing about widespread monitoring and regulation of air quality in the United States, beginning about 1970. However, in the past two decades, epidemiologic studies delineated an association between exposures to ambient air pollution particles (at levels lower than those currently observed in many cities worldwide) and numerous indices of human morbidity and mortality (Dockery et al., 1993). These findings were met with some skepticism (Gamble & Lewis, 1996), but both reevaluation of the initial studies (Krewski et al., 2000) and a plethora of new investigations providing substantially concordant results (Samet et al., 2000) confirmed the validity of these observations.

Individuals with chronic obstructive pulmonary disease (COPD) are among those with an increased sensitivity to PM. Scrutiny of deaths that occurred during the London fog of 1952 revealed that patients with bronchitis comprised the majority

TABLE 1
Association of PM exposure with indices of morbidity for COPD patients

Study location	Time of study	Measure of PM	Index of morbidity	Reference
Barcelona, Spain	1985–1989	Black smoke	Emergency room visits	Sunyer et al., 1993
Detroit, Michigan	1986–1989	PM_{10}	Hospital admissions	Schwartz, 1994
Ontario, Canada	1983–1988	Particulate sulfates	Hospital admissions	Burnette et al., 1995
Spokane, Washington		PM_{10}	Hospital admissions	Schwartz, 1996
European cities		Black smoke and total PM	Hospital admissions	Anderson et al., 1997
Sydney, Australia	1990–1994	PM_{10}	Hospital admissions	Morgan & Wlodarczyk, 1998
Reno, Nevada	1990–1994	PM_{10}	Hospital admissions	Chen et al., 2000
European cities	1993	PM_{10}	Hospital admissions	Atkinson et al., 2001
Vancouver, Canada	1995–1999	$PM_{2.5}$ and PM_{10}	Hospital admissions	Chen et al., 2004
Atlanta, Georgia	1993–2000	PM_{10}	Emergency room visits	Peel et al., 2005
Vancouver, Canada	1994–1998	PM_{10}	Hospital admissions	Yang et al., 2005
US counties	1992–2002	$PM_{2.5}$	Hospital admissions	Dominici et al., 2006
US cities	1986–1999	PM_{10}	Hospital admissions	Medina-Ramon et al., 2006

(Logan, 1953). Several epidemiologic studies addressed the issue of increased morbidity and mortality among patients with COPD following exposure to PM at levels currently observed nationally and internationally. These investigations showed significantly increased morbidity rates of individuals with COPD following exposure to air pollution particles (Table 1). Geographic location and time of the study varied between three different continents and the early 1980s to 2002, respectively. Different measures of PM exposure were employed (i.e., black smoke, total mass, PM_{10}, and $PM_{2.5}$), and the health endpoints were either emergency room visits or hospital admissions. They all supported some association between PM exposure and increased COPD morbidity.

Similar to investigation on morbidity indices, several epidemiologic studies confirmed an elevated mortality rate among individuals with COPD following exposure to PM (Table 2). This investigation was carried out between at a wide range of sites between 1973 and 2001. Black smoke, total mass, PM_{10}, and $PM_{2.5}$ were all used as measures of particle mass. Results established a greater relative risk for mortality in those individuals with COPD. In contrast, there was a lack of any association between mortality among those with COPD and PM exposure reported using data collected by the American Cancer Society as part of the Cancer Prevention II study (Pope et al., 2004).

In addition to this epidemiologic investigation, there have been several panel studies that have approached acute worsening of COPD by PM. Pulmonary function in COPD patients decreased significantly with increasing levels of PM_{10} (Pope & Kanner, 1993). A prospective study of COPD patients over a 3-mo period in Christchurch, New Zealand, showed that PM_{10} elevations worsened nighttime chest symptoms (Harre et al., 1997). In Denver, CO, a panel of COPD patients was followed during two winter seasons; PM pollution reduced peak flow and increased rescue bronchodilator use in the second winter (Silkoff et al., 2005).

Finally, one investigation into an association between PM exposure and COPD exacerbations was a controlled human exposure. Healthy subjects and COPD patients were exposed to a high concentration (200 $\mu g/m^3$) of ambient particles that contained predominantly $PM_{2.5}$ (Gong et al., 2005). Small but statistically significant declines in maximal midexpiratory flow and arterial oxygen saturations resulted. These decrements were larger for healthy subjects compared to COPD patients.

TABLE 2
Association of exposure to PM with indices of mortality for COPD patients

Study location	Time of study	Measure of PM	Index of mortality	Reference
Philadelphia	1973–1980	Total suspended particles	COPD mortality	Schwartz & Dockery, 1992 Schwartz et al., 1996
Barcelona	1990–1995	Black smoke	COPD mortality	Garcia-Aymerich et al., 2000 Sunyer et al., 2000
Mexico City	1994	PM_{10}	COPD mortality	Tellez-Rojo et al., 2000
Netherlands	1986–1994	PM_{10} and	COPD mortality among the elderly	Fischer et al., 2003
Shanghai	2001	$PM_{2.5}$	COPD mortality	Kan & Chen, 2003

Though debate about the causal nature of association between particulate air pollution and COPD exacerbations continued, mounting evidence from all these studies supported a revision of U.S. National Ambient Air Quality Standard for PM in 1997. The revision added $PM_{2.5}$ as another indicator of air pollution because available evidence indicated these particles (which comprise about 50% of PM_{10} nationwide) might be more damaging than coarser particles. It was proposed that this reflects a greater capacity of smaller particles to reach terminal bronchioles and alveoli.

The human breathing with a tidal volume of 0.5 L and a respiratory rate of 20 per minute and living in an environment with an ambient PM_{10} concentration of 50 $\mu g/m^3$ (an urban site with significant levels) will be exposed to 720 μg in a single day (not all of which will deposit in the lung). Equating only the particle exposure to that of a cigarette smoker, annually this would approximate 1/10th to 1/40th of a pack-year smoking. The ambient air pollution particle is typically carbonaceous, with size and chemical characteristics comparable to products of combustion such as diesel exhaust, wood stove emissions, the burning of biomass, and cigarette smoke (Ghio et al., 1994, 1996, 2000). Cigarette smoking accounts for 80 to 85% of all COPD in the United States. A single cigarette introduces 15,000 to 40,000 μg PM into the respiratory tract of the smoker (National Research Council, 1986). A large portion of COPD (20% of all disease) that is not associated with cigarette smoking is considered occupational in origin (American Thoracic Society, 2003). These other causes of COPD (e.g., coal mining) similarly follow high particle exposures frequently exceeding 1000 $\mu g/m^3$.

Based on the mass of particles only:

- Smoking 1/10th to 1/40th of one cigarette a day can expose the lungs of an individual to more particles than a day of living in an urban site.
- Smoking one cigarette can be equivalent to 14–56 days of exposure to air pollution particles in an urban site.
- Smoking one pack of cigarettes can be equivalent to ¾–3 yr of exposure to air pollution particles in an urban site.
- Spending an hour in either a restaurant or bar that allows smoking can approximate a full day of exposure to air pollution particles in an urban site.
- Working a shift in a one of numerous occupations in which the environment exceeds 1000 $\mu g/m^3$ can be analogous to a week of exposure to air pollution particles in an urban site.

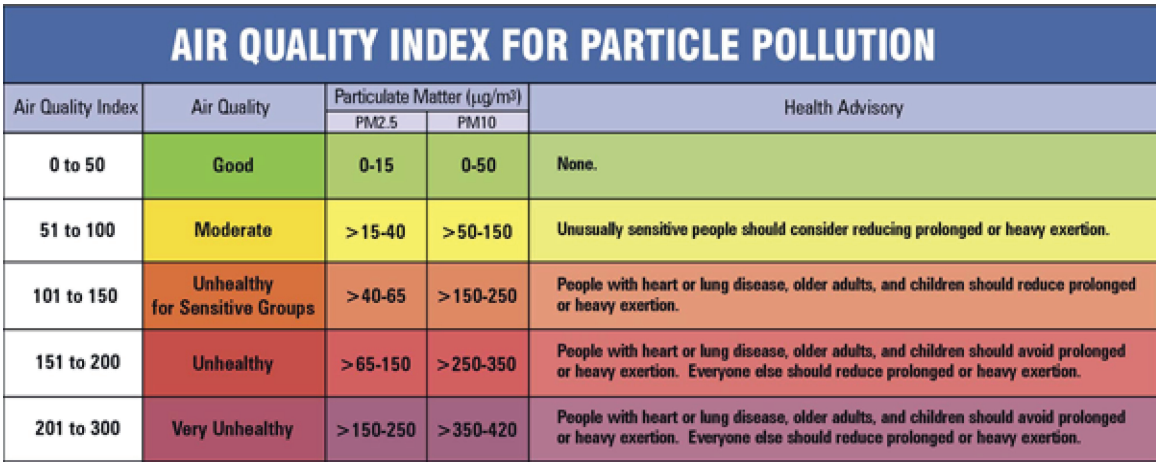
In an individual repeatedly exposed to particles (with what is a comparable size and composition) at perhaps a thousandfold the mass of ambient PM (e.g., a heavy cigarette smoker), it is confounding why such a relatively small mass of air pollution particles should have any biological effects in patients with COPD. Alternatively, it can be asked how individuals who smoke cigarettes are able to survive such a particle challenge. We focus on possible reasons for discrepancies in health effects observed between exposures to cigarette smoking, which have failed to demonstrate changes in acute endpoints (e.g., human mortality) at massive doses, and air pollution particles, which have shown a biological effect at relatively small exposure levels.

MECHANISM UNDERLYING A BIOLOGICAL EFFECT OF PM ON COPD EXACERBATION

Regarding this disparate response to inhaled particles and an increased sensitivity of COPD patients to air pollution particles, there are several possible explanations. First, acute exacerbations of COPD after exposures to air pollution particles may reflect correlations of PM levels with other components of air pollution that may truly be responsible for the observed health effects (Kan & Chen, 2003). Worsening of COPD could potentially result after interaction between the air pollution particle and one or more of these components. Alternatively, the sensitivity of COPD patients to air pollution particles may reflect the accumulation of multiple independent risk factors (e.g., age and comorbidities such as coronary artery disease and diabetes) and not the obstructive lung disease itself. Third, COPD may require changes in individual activity patterns for the patient, with greater durations of time spent at home where, in specific individuals, exposures to PM can be different (Leech & Smith-Doiron, 2006). Therefore, they may receive a greater exposure to PM relative to other populations. Fourth, compared to healthy subjects, COPD patients have increased particle deposition rates compared with healthy subjects (Brown et al., 2002). This could contribute to a greater effect on the health of this population. Finally, there is the possibility of some unique characteristic of ambient air pollution PM. While the human lung could have developed some adaptation to carbonaceous products of wood (and other vegetation) combustion over thousands of years of repeated exposures, there has been an inadequate interval of time for such a response to products of gas, coal, and oil burning. Therefore, relative to particles emitted from combustion of wood (and other vegetation), air pollution PM may display a greater biological effect. Additionally, at the level of the individual, the patient with COPD may demonstrate a tolerance for a specific particle (e.g., that associated with either cigarette smoking or an occupational setting) after a prolonged duration of exposure but not to air pollution PM. Certainly, the repeated use of cigarettes demands some development of tolerance to components of the smoke. This is evidenced by the fact that almost every person who smokes provides a history of illness with the first cigarette (Eissenberg & Balster, 2000). This tolerance, while allowing repeated exposures to over a gram of cigarette-related particle per day, may not convey any protective effect in exposures to air pollution particles.

RECOMMENDATIONS FOR COPD PATIENTS

Regardless of the underlying mechanism for the increased sensitivity of COPD patients to the health consequences of air pollution particles, exposures to elevated levels of PM must be avoided by these individuals.



AIR QUALITY INDEX FOR PARTICLE POLLUTION				
Air Quality Index	Air Quality	Particulate Matter (μg/m³)		Health Advisory
		PM2.5	PM10	
0 to 50	Good	0-15	0-50	None.
51 to 100	Moderate	>15-40	>50-150	Unusually sensitive people should consider reducing prolonged or heavy exertion.
101 to 150	Unhealthy for Sensitive Groups	>40-65	>150-250	People with heart or lung disease, older adults, and children should reduce prolonged or heavy exertion.
151 to 200	Unhealthy	>65-150	>250-350	People with heart or lung disease, older adults, and children should avoid prolonged or heavy exertion. Everyone else should reduce prolonged or heavy exertion.
201 to 300	Very Unhealthy	>150-250	>350-420	People with heart or lung disease, older adults, and children should avoid prolonged or heavy exertion. Everyone else should reduce prolonged or heavy exertion.

FIG. 1. Air quality index for particle pollution.

To provide a greater awareness of PM levels, the U.S. Environmental Protection Agency now includes levels of air pollution particles in an air quality index (Figure 1). An Internet site now forecasts PM levels, as well as ozone concentrations, in locations around the United States on a daily basis (see http://epa.gov/airnow). Along with patients with diabetes and cardiovascular disease, individuals diagnosed to have COPD are among those who are likely to benefit by following recommendations included in this air quality index. A reduction of exposure to particles appears to be of significance in this population, and attempts at such reduction would include:

- First and foremost, smoking cessation must be realized.
- A change in employment should be addressed if occupational exposures to particles exist.
- Residence in areas with frequent exceedences in air pollution PM levels (either PM_{10} or $PM_{2.5}$) is discouraged among these patients.
- Living within 200 m of a highway might be discouraged.
- Activities requiring exertion on days of exceedence for air pollution PM levels are advised against.
- Exposure to environmental tobacco smoke is to be avoided (e.g., bars and restaurants permitting cigarette smoking).
- Woodburning stoves, fireplaces, and kerosene heaters should not be used in the house.
- Specific household activities involving particle exposure may not be possible (e.g., use of household cleansers and mulching).
- The AIRNOW Internet site should be consulted prior to travel to areas within the United States.
- Travel to certain international locations may have to be limited (numerous sites around the world have air pollution PM levels measured in hundreds and even thousands of micrograms per cubic meter).
- Further investigation into the health effects of air pollution PM on COPD patients is absolutely essential.

CONCLUSIONS

The increased sensitivity of patients with COPD to PM is difficult to understand based on the history of particle exposure among these individuals. Regardless of the mechanism, COPD patients should reduce particle exposures when possible.

REFERENCES

American Thoracic Society. 2003. American Thoracic Society statement: Occupational contribution to the burden of airway disease. *Am. J. Respir. Crit. Care Med.* 167:787–797.

Anderson, H. R., Spix, C., Medina, S., Schouten, J. P., Castellsague, J., Rossi, G., Zmirou, D., Touloumi, G., Wojtyniak, B., Ponka, A., Bacharova, L., Schwartz, J., and Katsouyanni, K. 1997. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: Results from the APHEA project. *Eur. Respir. J.* 10:1064–1071.

Atkinson, R. W., Anderson, H. R., Sunyer, J., Ayres, J., Baccini, M., Vonk, J. M., Boumghar, A., Forastiere, F., Forsberg, B., Touloumi, G., Schwartz, J., and Katsouyanni, K. 2001. Acute effects of particulate air pollution on respiratory admissions: Results from APHEA 2 Project. *Am. J. Respir. Crit. Care Med.* 164:1860–1866.

Bell, M. L., and Davis, D. L. 2001. Reassessment of the lethal London fog of 1952: Novel indicators of acute and chronic consequences of acute exposure to air pollution. *Environ. Health Perspect.* 109(Suppl. 3):389–394.

Brown, J. S., Zeman, K. L., and Bennett, W. D. 2002. Ultrafine particle deposition and clearance in the healthy and obstructed lung. *Am. J. Respir. Crit. Care Med.* 166:1240–1247.

Burnett, R. T., Dales, R., Krewski, D., Vincent, R., Dann, T., and Brook, J. R. 1995. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. *Am. J. Epidemiol.* 142:15–22.

Chen, L., Yang, W., Jennison, B. L., and Omaye, S. T. 2000. Air particulate pollution and hospital admissions for chronic obstructive pulmonary disease in Reno, Nevada. *Inhal. Toxicol.* 12:281–289.

Chen, Y., Yang, Q., Krewski, D., Shi, Y., Burnett, R. T., and McGrail, K. 2004. Influence of relatively low level of particulate air pollution on hospitalization for COPD in elderly people. *Inhal. Toxicol.* 16:21–25.

Dockery, D. W., Pope, C. A. III, Xu, X., Spengler, J. D., Ware, J. H., Fay, M. E., Ferris, B. G., Jr., and Speizer, F. E. 1993. An association between air pollution and mortality in six U.S. cities. *N. Engl. J. Med.* 329:1753–1759.

Dominici, F., Peng, R. D., Bell, M. L., Pham, L., McDermott, A., Zeger, S. L., and Samet, J. M. 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *J. Am. Med. Assoc.* 295:1127–1134.

Eissenberg, T., and Balster, R. L. 2000. Initial tobacco use episodes in children and adolescents: current knowledge, future directions. *Drug Alcohol Depend.* 59 (Suppl. 1):S41–S60.

Fischer, P., Hoek, G., Brunekreef, B., Verhoeff, A., and van Wijnen, J. 2003. Air pollution and mortality in the Netherlands: Are the elderly more at risk? *Eur. Respir. J.* 21(Suppl. 40):34s–38s.

Gamble, J. F., and Lewis, R. J. 1996. Health and respirable particulate (PM_{10}) air pollution: A causal or statistical association? *Environ. Health Perspect.* 104:838–850.

Garcia-Aymerich, J., Tobias, A., Anto, J. M., and Sunyer, J. 2000. Air pollution and mortality in a cohort of patients with chronic obstructive pulmonary disease: A time series analysis. *J. Epidemiol. Commun. Health* 54:73–74.

Ghio, A. J., Stonehuerner, J., and Quigley, D. R. 1994. Humic-like substances in cigarette condensate and lung tissue of smokers. *Am. J. Physiol.* 266:L382–L388.

Ghio, A. J., Stonehuerner, J., Pritchard, R. J., Piantadosi, C. A., Quigley, D. R., Dreher, K. L., and Costa, D. L. 1996. Humic-like substances in air pollution particulates correlate with concentrations of transition metals and oxidant generation. *Inhal. Toxicol.* 8:4479–494.

Ghio, A. J., Richards, J. H., Carter, J. D., and Madden, M. C. 2000. Accumulation of iron in the rat lung after tracheal instillation of diesel particles. *Toxicol. Pathol.* 28:619–627.

Gong, H., Linn, W. S., Clark, K. W., Anderson, K. R., Geller, M. D., and Sioutas, C. 2005. Respiratory responses to exposures with fine particulates and nitrogen dioxide in the elderly with and without COPD. *Inhal. Toxicol.* 17:123–132.

Harre, E. S. M., Price, P. D., Ayrey, R. B., Toop, L. J., Martin, I. R., and Town, G. I. 1997. Respiratory effects of air pollution in chronic obstructive pulmonary disease: A three month prospective study. *Thorax* 52:1040–1044.

Helfand, W. H., Lazarus, J., and Theerman, P. 2001. Donora, Pennsylvania: an environmental disaster of the 20th century. *Am. J. Public Health* 91:533.

Kan, H., and Chen, B. 2003. A case-crossover analysis of air pollution and daily mortality in Shanghai. *J. Occup. Health* 45:119–124.

Kan, H., and Chen, B. 2003. Air pollution and daily mortality in Shanghai: A time-series study. *Arch. Environ. Health* 58:360–367.

Krewski, D., Burnett, R. T., Goldberg, M. S., Hoover, K., Siemiatycki, J., Jerrett, M., Abrahamowicz, M., and White, W. H. 2000. *Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality. A special report of the Institute's Particle Epidemiology Reanalysis Project*. Cambridge, MA: Health Effects Institute.

Leech, J. A., and Smith-Doiron, M. 2006. Exposure time and place: Do COPD patients differ from the general population? *J. Expos. Sci. Environ. Epidemiol.*16:238–241.

Logan, W. P. D. 1953. Mortality in the London fog incident. *Lancet* 1:336–338.

Medina-Ramon, M., Zanobetti, A., and Schwartz, J. 2006. The effect of ozone and PM_{10} on hospital admissions for pneumonia and chronic obstructive pulmonary disease: A national multicity study. *Am. J. Epidemiol.* 163:579–588.

Morgan, G., and Wlodarczyk, J. 1998. Air pollution and hospital admissions in Sydney, Australia, 1990–1994. *Am. J. Public Health* 88:1761–1766.

National Research Council. 1986. *Environmental tobacco smoke: Measuring exposures and assessing health effects*. Washington, DC: National Academy Press.

Nemery, B., Hoet, P. H., and Nemmar, A. 2001. The Meuse Valley fog of 1930: An air pollution disaster. *Lancet* 357:704–708.

Pabst, M., and Hofer, F. 1998. Deposits of different origin in the lungs of the 5300-year-old Tyrolean Iceman. *Am. J. Phys. Anthropol.* 107:1–12.

Peel, J. L., Tolbert, P. E., Klein, M., Metzger, K. B., Flanders, W. D., Todd, K., Mulholland, J. A., Ryan, P. B., and Frumkin, H. 2005. Ambient air pollution and respiratory emergency department visits. *Epidemiology* 16:164–174.

Pope, C. A. III, Burnett, R. T., Thurston, G. D., Thun, M. J., Calle, E. E., Krewski, D., and Godleski, J. J. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution. Epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 109:71–77.

Pope, C. A. III, and Kanner, R. E. 1993. Acute effects of PM_{10} pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 147:1336–1340.

Samet, J. M., Dominici, F., Curriero, F. C., Coursac, I., and Zeger, S. L. 2000. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. *N. Engl. J. Med.* 343:1742–1749.

Schwartz, J. 1994. Air pollution and hospital admissions for the elderly in Detroit, Michigan. *Am. J. Respir. Crit. Care Med.* 150:648–655.

Schwartz, J. 1996. Air pollution and hospital admissions for respiratory disease. *Epidemiology* 7:20–28.

Schwartz, J., and Dockery, D. W. 1992. Increased mortality in Philadelphia with daily air pollution concentrations. *Am. Rev. Respir. Dis.* 145:600–604.

Schwartz, J., Dockery, D. W., and Neas, L. M. 1996. Is daily mortality associated specifically with fine particles? *J. Air Waste Manage. Association* 46:927–939.

Silkoff, P. E., Zhang, L., Dutton, S., Langmack, E. L., Vedal, S., Murphy, J., and Make, B. 2005. Winter air pollution and disease parameters in advanced chronic obstructive pulmonary disease panels residing in Denver, Colorado. *J. Clin. Immunol.* 115:337–344.

Sunyer, J., Saez, M., Murillo, C., Castellsague, J., Martinez, F., and Anto, J. M. 1993. Air pollution and emergency room admissions for chronic obstructive pulmonary disease: A 5-year study. *Am. J. Epidemiol.* 137:701–705.

Sunyer, J., Schwartz, J., Tobias, A., Macfarlane, D., Garcia, J., and Anto, J. M. 2000. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover analysis. *Am. J. Epidemiol.* 151:50–56.

Tellez-Rojo, M. M., Romieu, I., Ruiz-Velasco, S., Lezana, M.-A., and Hernandez-Avila, M.-M. 2000. Daily respiratory mortality and PM_{10} pollution in Mexico City: Importance of considering place of death. *Eur. Respir. J.* 16:391–396.

Yang, Q., Chen, Y., Krewski, D., Burnett, R.T., Shi, Y., and McGrail, K. M. 2005. Effect of short-term exposure to low levels of gaseous pollutants on chronic obstructive pulmonary disease hospitalizations. *Environ. Res.* 99:99–105.