Pulmonary, Sleep, and Critical Care Updates

Update in Environmental and Occupational Medicine 2010

G. R. Scott Budinger¹ and Gökhan M. Mutlu¹

¹Department of Medicine, Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Large genome-wide association studies in patients with asthma, chronic obstructive pulmonary disease (COPD), and other major lung diseases have provided insight into the genetic determinants of disease (1, 2). However, the relatively small risk attributable to genetic variation observed in those studies has prompted investigators to renew their focus on the role of environmental exposures in the development of lung disease. Indeed, understanding how environmental exposures alter gene expression was identified as a major goal in a National Heart, Lung, and Blood Institute workshop report focused on understanding the link between genes and their function (3). The purpose of this update is to highlight the advances in environmental and occupational medicine published in the *Journal* over the past year in the broader context of the exciting ongoing work in this area.

AIR POLLUTION

Particulate Matter

Exposure to particulate matter (PM) air pollution remains a major cause of morbidity and mortality. The majority of the mortality associated with PM exposure is attributable to an increased incidence of ischemic cardiovascular events including myocardial infarction and stroke. This year, Brook and colleagues published an update summarizing the evidence linking PM exposure with adverse cardiovascular outcomes and the potential mechanisms by which this might occur (4). These authors concluded that the overall evidence is consistent with a causal relationship between PM less than 2.5 μm in diameter ($\text{PM}_{2.5}$) exposure and cardiovascular morbidity and mortality.

In the past decade, investigators have also linked PM exposure with a variety of adverse health outcomes including accelerated atherosclerosis in postmenopausal women, loss of lung function in healthy adults, impaired lung development in children, exacerbations of obstructive lung disease, pneumonia, and an increased risk of venous thromboembolism (5–15). Studies published in the *Journal* and elsewhere contributed to our understanding of the diseases associated with PM exposure and the mechanisms by which they develop.

PM and asthma. Strickland and colleagues examined the association between short-term exposure to ambient air pollution

and the frequency of emergency department (ED) visits in children with asthma (16). They used stationary monitoring data to estimate ambient air pollution exposures in the days before ED visits for 91,386 children. They found that traffic-related particles and ozone were independently associated with increased rates of ED visits. Levels on the day of the visit were most strongly associated with risk, suggesting a lag time between exposure and effect on the order of hours to a day. The effects were seen despite relatively low levels of ambient pollutants. In an accompanying editorial, Gent and Bell noted that despite our uncertainty regarding the constituents of the particles required for their toxicity, the data argue for lower standards for particle exposure than those currently in place (17).

Desert dust is usually considered an inert particle; however, Kanatani and colleagues examined the association of the levels of ambient desert dust, using light detection and ranging, with the risk of asthma hospitalization in children ages 1–15 years in an area of Japan subject to desert dust storms (18). In the 4 years of the study, six heavy dust events were observed with ambient dust concentrations exceeding 100 $\mu\text{g}/\text{m}^3$. After adjustment for other air pollutant levels, pollen, and meteorologic factors, the risk of an asthma-related hospitalization was associated with a heavy dust event in the preceding week. Although not definitive, the relatively modest health effects observed after these high levels of exposure support the prevailing hypothesis that constituents absorbed onto the particles are major contributors to their adverse health effects.

Whereas the studies by Strickland and colleagues and Kanatani and colleagues suggest that PM exposure might worsen already existing asthma, Gehring and colleagues conducted a study to examine the relationship between PM exposure and the development of asthma in the first 8 years of life (19). They examined a cohort monitored yearly from birth until age 8 years. Every year, the families were asked to fill out an asthma-related questionnaire and at age 8 years the majority of the cohort underwent testing for either allergic sensitization or bronchial hyperresponsiveness. The annual incidence of asthma was 6% at age 1 year, and 1 to 2% at later ages. Levels of $\text{PM}_{2.5}$ were associated with a significant increase in incidence of asthma (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.10–1.49), prevalence of asthma (OR, 1.26; 95% CI, 1.04–1.51), and prevalence of asthma symptoms (OR, 1.15; 95% CI, 1.02–1.28) (19). In an accompanying editorial, Ryan and Holguin commented that this study provides significant new evidence that traffic-related pollution is an environmental exposure associated with asthma development, perhaps contributing to the dramatic increase in asthma in urban environments (20).

PM and COPD. In an official American Thoracic Society (ATS) public policy statement entitled “Novel risk factors and the global burden of chronic obstructive pulmonary disease,” Eisner and colleagues summarized the evidence linking exposure with outdoor pollutants and the development of COPD in adulthood (21). The authors cited the large body of data suggesting that air pollution exposure is associated with impaired lung development in children and accelerated loss of lung function in adults. In addition, they cited the biological plausibility

(Received in original form March 14, 2011; accepted in final form April 13, 2011)

Supported by ES015024 (G.M.M.), ES013995 (G.R.S.B.), and HL071643 (G.M.M. and G.R.S.B.); and by a Northwestern University Clinical and Translational Sciences Institute (NUCATS) CTI Pilot Award (UL1 RR025741 (NCCR) (G.M.M.).

Author contributions: G.R.S.B. and G.M.M. were both involved in the search for papers and in the organization and writing of the manuscript.

Correspondence and requests for reprints should be addressed to G. R. Scott Budinger, M.D., Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, 240 E. Huron Street, McGaw M-300, Chicago, IL 60611. E-mail: s-budinger@northwestern.edu

Am J Respir Crit Care Med Vol 183, pp 1614–1619, 2011

DOI: 10.1164/rccm.201103-0467UP

Internet address: www.atsjournals.org

of an association between PM exposure and COPD in human and animal exposure studies. However, as an association between outdoor pollutants and objectively defined COPD by spirometry is lacking, the authors concluded that there is limited evidence suggesting a relationship between outdoor air pollution and COPD. Addressing this question, Andersen and colleagues provided new evidence supporting an association between long-term PM exposure and COPD in 57,053 participants in the Danish Diet, Cancer, and Health cohort (22). They estimated air pollution exposure from the residential addresses of these subjects. They found that COPD incidence was associated with the 35-year mean NO₂ level, with stronger associations in subjects with diabetes and asthma.

PM and pneumonia. To examine the contribution of air pollution exposure to the risk of developing community-acquired pneumonia, Neupane and colleagues conducted a population-based, case-control study in Ontario, Canada examining 345 hospitalized patients with community-acquired pneumonia and 494 control participants, all of whom were over 65 years of age (12). They obtained data on nitrogen dioxide, sulfur dioxide, and PM_{2.5} before the study period from the residential addresses of participants. They found that long-term exposure to higher levels of nitrogen dioxide and PM_{2.5} was significantly associated with hospitalization for community-acquired pneumonia with odds ratios of 2.30 (95% CI, 1.25 to 4.21) and 2.26 (95% CI, 1.20 to 4.24), respectively. These results were discussed in an accompanying editorial (17) and associated correspondence (23, 24).

PM and obstructive sleep apnea. Zanobetti and colleagues examined the association between the severity of obstructive sleep apnea and the levels of particulate matter air pollution less than 10 µm in diameter (PM₁₀), using data from the Sleep Health Heart Study (25). During the summer months, they observed an association between the levels of PM₁₀ and the Respiratory Disturbance Index, sleep time at less than 90% O₂ saturation, and sleep efficiency. These results suggest that reducing exposure to PM may lead to a reduction in cardiac risk by decreasing the severity of obstructive sleep apnea and associated hypoxemia.

PM and cardiovascular disease. Investigators continued to examine the potential mechanisms by which PM might induce cardiovascular disease. Adar and colleagues evaluated the relationship between air pollution and retinal vessel diameter, using data obtained from subjects enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) study between 2002 and 2003 (26). Among the 4,607 participants with complete data, retinal arterial diameters were narrower among persons residing in regions with increased long- and short-term levels of PM_{2.5} and in individuals living near a major road. These findings suggest that even small increases in short- and long-term exposure to PM are associated with detectable changes in the microvasculature and support measures to reduce pollution exposure to levels lower than are common even in the developed world. In populations exposed to PM, investigators have consistently observed an increase in plasma markers of inflammation as well as a reduction in heart rate variability, a marker of enhanced sympathetic tone (4). In 25 elderly subjects, Luttmann-Gibson and colleagues reported an interesting link between these observations (27). PM-induced alterations in heart rate variability occurred only in those patients with systemic inflammation evaluated by changes in C-reactive protein. Consistent with these findings, Schneider and colleagues reported that short-term ambient PM_{2.5} exposure increased markers of systemic inflammation (IL-6 and tumor necrosis factor-α levels) and caused changes in ventricular repolarization in 22 adults with type 2 diabetes mellitus (28). O'Toole and colleagues found that young men acutely exposed to PM_{2.5} had fewer circulating endothelial progenitor cells (29). In that study, PM_{2.5} exposure was also associated with increased levels of platelet-

monocyte aggregates, high-density lipoprotein, and nonalbumin protein, suggesting that PM exposure might induce direct endothelial injury (29). Xu and colleagues found that long-term exposure of mice to inhaled PM worsened insulin resistance vascular function and visceral inflammation through a mechanism that requires p47^{phox}, a component of NAD(P)H oxidase (30).

Investigators explored genetic factors that may enhance the susceptibility to PM. In a cross-sectional study of 1,376 genotyped participants in the Multi-Ethnic Study of Atherosclerosis, Van Hee and colleagues found that single nucleotide polymorphisms (SNPs) in genes responsible for oxidative stress, inflammation, and vascular function (e.g., angiotensin II receptor and arachidonate 15-lipoxygenase) modified the association between the residential proximity to major roadways and left ventricular mass, a strong predictor of negative cardiovascular outcomes (31). In 320 aging men, Ren and colleagues showed that SNPs in several oxidative stress-related genes modified the association between pollutant exposure and the levels of urinary 8-hydroxy-2'-deoxyguanosine, a biomarker of oxidative stress (32). A better understanding of how air pollution affects these genes that modify the risk for cardiovascular disease may help researchers focus their efforts on specific mechanistic pathways.

Biomass

In some regions of the world, women cook using open fire stoves. The fuel used in these stoves is collectively known as biomass, which includes wood, animal dung, and crop residues. In the ATS policy statement identifying novel risk factors for COPD, the authors concluded that there is sufficient evidence to support an association between burning of biomass fuel and the development of COPD in women (21). Sood and colleagues examined the relationship between self-reported wood smoke exposure and COPD outcomes adjusted for other variables in U.S. women (33). They found that wood smoke exposure was associated with a lower FEV₁ and a higher prevalence of airflow obstruction and chronic bronchitis. Furthermore, wood smoke exposure, when combined with aberrant promoter methylation of the p16 or GATA4 gene, was strongly predictive of a lower FEV₁.

In a hospital-based case-control study of women with a confirmed diagnosis of tuberculosis, Pokhrel and colleagues observed an increased risk of developing tuberculosis in women who used a biomass fuel stove compared with using a clean-burning fuel stove (liquefied petroleum gas, biogas). Even higher risks were observed in women who used kerosene stoves or lamps for lighting or who used biomass fuel for heating (34). In contrast, another study failed to show an association between using solid fuel for cooking and tuberculosis (35).

Ozone

The association between ozone and all-cause mortality is weaker than the association observed with PM; however, ozone remains an important contributor to the morbidity associated with lung disease (36). Stafoggia and colleagues sought to determine which groups of the population are most susceptible to the adverse health outcomes associated with ozone exposure (37). They employed a case-crossover analysis of 127,860 deaths in 10 cities in Italy and used fixed environmental data to estimate ozone exposure. They found that a 10-µg/m³ increase in ozone was associated with a 1.5% increase in total mortality, which persisted for several days with a lag time between 0 and 5 days for most conditions. Older patients, women, and diabetics were at increased risk, suggesting that ozone may exacerbate existing conditions to increase mortality. These findings were discussed in an associated editorial (17). The ATS Environmental Health Policy Committee reviewed data

documenting the adverse health consequences of ozone exposure and urged the U.S. Environmental Protection Agency to consider reducing the acceptable levels of ozone exposure (38).

To determine how ozone exposure might worsen asthma, Garantziotis and colleagues explored the mechanisms by which ozone induces airway hyperresponsiveness (AHR) in mice (39). They found that ozone increased levels of the extracellular matrix protein hyaluronan in the lungs. Ozone and hyaluronan induced a similar pattern of lung inflammation in mice and ozone increased the expression of Toll-like receptor-4 (TLR4) on macrophages. Mice deficient in TLR4 were resistant to the increase in AHR induced by the administration of ozone or hyaluronan. The authors conclude that the increases in AHR are mediated by changes in the extracellular levels of hyaluronan and TLR4-dependent inflammation. It is thought that ozone exposure induces oxidant stress in the lung.

Carbon Monoxide

Epidemiologic studies associate atmospheric carbon monoxide (CO) pollution with adverse cardiovascular outcomes and increased cardiac mortality risk. Andre and colleagues exposed Wistar rats to either filtered air (CO < 1 ppm) or air enriched with CO (30 ppm with five peaks of 100 ppm per 24-h period) for 4 weeks and evaluated the myocardial function by echocardiography and EKG and *in vitro* by measuring the excitation-contraction coupling of single left ventricular cardiomyocytes (40). They found that CO caused fibrosis in the left ventricle and a small reduction in cardiac function and increased the number of arrhythmias *in vivo*. Both contraction and relaxation of single cardiomyocytes were altered *in vitro*.

Tobacco Smoke

Low-level tobacco smoke exposure is a significant, widespread public health concern. Individuals exposed to low levels of tobacco smoke have decrements in lung function and higher risk for lung disease compared with unexposed individuals. In a study of 121 human subjects (40 nonsmokers, 45 smokers, and 36 individuals with low-level tobacco smoke exposure) evaluating the biological correlates of this risk, Strulovici-Barel and colleagues found that the small airway epithelium responds to low levels of tobacco smoke with transcriptome modifications (41). The investigators established a dose-dependent relationship between the changes in the small airway epithelial transcriptome and the levels of urine nicotine and cotinine.

OCCUPATIONAL LUNG DISEASE

Metal smelting requires heat and carbon from such sources as coke, coal, or wood to reduce mineral ores to smelted metals (42). Dusts are released into the workplace during metal smelting. Johnsen and colleagues investigated the relationship between the annual change in lung function and occupational dust exposure among workers in 15 Norwegian smelting facilities (43). They found that for all smelters, the annual decline in FEV₁ was negatively associated with increasing dust exposure, suggesting that metal smelting may increase the risk of developing COPD.

Shi and colleagues performed a prospective cohort study in 447 cotton textile workers exposed to cotton dust and 472 unexposed silk textile workers (44). Cessation of textile work was positively associated with an improvement in FEV₁ that was greater in cotton (11.3 ml/yr) than silk (5.6 ml/yr) workers. Smoking seemed to exacerbate the spirometric changes, and the risk of symptoms of chronic bronchitis and byssinosis, associated with cotton work.

Tossa and colleagues examined the utility of exhaled nitric oxide (NO) measurements in predicting the development of AHR in apprentice bakers, pastry makers, and hairdressers during their 2 years of training (45). They found that an increase in the fractional concentration of exhaled nitric oxide during the training was associated with an increased incidence of AHR in atopic and nonatopic subjects. The development of atopy in bakers/pastry makers and the sensitization of hairdressers to alkaline persulfates were also independently associated with the incidence of AHR.

Rodríguez-Trigo and colleagues compared lung function, respiratory symptoms, and a variety of biomarkers in local fisherman who were involved or uninvolved in the cleanup of oil resulting from the crash of the oil tanker *Prestige*, which spilled more than 67,000 tons of bunker oil off the coast of northwestern Spain (46). Whereas lung function was similar in the two groups, fisherman exposed to oil were at increased risk for lower respiratory tract symptoms; had higher exhaled breath levels of 8-isoprostane, vascular endothelial growth factor, and basic fibroblast growth factor; and had more structural chromosomal abnormalities. These findings indicate that even brief periods of exposure to oil sediments may have important health effects. Appropriate precautions should be taken to protect workers in oil clean-up activities.

Ameille and colleagues sought to determine whether occupational exposure to asbestos is associated with the development of airway obstruction (47). They examined the association between asbestos exposure in 3,660 subjects and pulmonary function and high-resolution computed tomographic abnormalities. They were unable to find an association between the cumulative exposure to asbestos and pulmonary function parameters. Although this study may suggest that some individuals are resistant to the adverse consequences of asbestos, the difficulties in examining even these very large cohorts are discussed in an accompanying editorial (48).

Cummings and colleagues reported two cases of pulmonary alveolar proteinosis, including one death, in workers at a facility producing indium-tin oxide (ITO), a compound used to make flat panel displays (49). Both workers were exposed to airborne ITO dust and had indium in lung tissue specimens. One worker was tested for autoantibodies to granulocyte-macrophage colony-stimulating factor and was found to have an elevated level. These cases suggest that inhalational exposure to ITO causes pulmonary alveolar proteinosis, which may occur via an autoimmune mechanism. The mechanism of this toxicity was discussed in an accompanying editorial (50, 51).

Mack and colleagues evaluated the role of regulatory T cells in chronic beryllium disease, which is a CD4⁺ T cell-mediated disorder characterized by persistent lung inflammation (52). The bronchoalveolar lavage fluid from patients with chronic beryllium disease showed a reduction in the number of regulatory T cells, which were also dysfunctional. Furthermore, the percentage of regulatory T cells in bronchoalveolar lavage fluid was inversely correlated with disease severity.

In a study that evaluated the mechanisms by which zinc oxide (ZnO) nanoparticles cause metal fume fever, Kim and colleagues found that ZnO nanoparticles caused dose- and time-dependent injury in lung epithelial cells via mitochondrial dysfunction, and increased intracellular reactive oxygen species (53).

OCCUPATIONAL AND ENVIRONMENTAL ASTHMA

Support for an important environmental contribution to asthma was provided by Ege and colleagues, who compared microbial exposure and asthma development in children living on a farm with those living in other environments (54). In support of the

“hygiene hypothesis” of asthma development, microbial exposure was broader and asthma prevalence was lower in children who lived on a farm.

To determine whether occupational exposure to asthmagens influenced the risk of having atopic or nonatopic asthma, Wang and colleagues recruited 504 adults with current asthma, 504 community-based control subjects, and 504 hospital-based control subjects in southern Taiwan (55). Atopic asthma was defined as having asthma in combination with an increase in total IgE or a positive Phadiatop test result. They found that exposure to high molecular weight asthmagens was associated with an increased risk of atopic asthma, whereas exposure to low molecular weight asthmagens, including industrial cleaning agents and metal sensitizers, was associated with nonatopic asthma. In contrast to the association between living on a farm and the prevalence of asthma in children (54), adults who were agricultural workers had an increased risk for both atopic and nonatopic asthma (55).

Wu and colleagues examined the interaction between environmental fungal exposure and the increased risk of severe asthma observed in patients with SNPs in genes encoding chitinases (56). These enzymes cleave chitin, which is present in the cell wall of fungi. In 395 subjects with asthma, they found that high mold exposure significantly modified the relation between three SNPs in CHIT1 and severe exacerbations requiring emergency department visits. In a related article, Schütze and colleagues sought to determine whether and how mycotoxins, secondary metabolites of mold, might exacerbate asthma (57). They found that the administration of mycotoxins to the lung or colon enhanced the severity of the asthma-like phenotype of mice after ovalbumin sensitization and challenge. Their data suggest that this is secondary to the inhibition of IL-12 release from dendritic cells through an oxidant-dependent mechanism.

To determine how house dust mites might exacerbate asthma, Gregory and colleagues used an adenovirus to overexpress Smad2 in the airway epithelium before exposure to house dust mite antigen (58). In the Smad2-overexpressing mice, they found increased subepithelial collagen deposition and smooth muscle hyperplasia with thickening of the airway smooth muscle layer. These changes were associated with increased levels of IL-25 and activin A and could be prevented by blocking activin A, suggesting that activin A-mediated induction of IL-25 plays an important role in this response.

Environmental stress is thought to worsen preexisting asthma. Wright and colleagues prospectively examined the association between prenatal maternal stress and cord blood mononuclear cell cytokine responses in data obtained from children and mothers enrolled in the Urban Environment and Childhood Asthma Study (59). Mothers with high levels of stress including financial hardship, difficult life circumstances, community violence, and neighborhood/block and housing conditions were older and more likely to have asthma and to deliver lower birth weight infants. Monocytes from the cord blood of stressed mothers showed increased IL-8 and tumor necrosis factor- α release in response to microbial stimulants, increased IL-13 release after dust mite stimulation, and reduced IFN- γ release after phytohemagglutinin administration.

CONCLUSIONS

The increasing number of associations between environmental and occupational exposures and the development of lung disease highlights the importance of the lung in responding to environmental stimuli and its susceptibility to airborne toxins. Continued challenges persist in understanding the mechanisms by which the various cells of the lung sense and respond to environmental contaminants and the differential susceptibility of individuals in the population to airborne exposures.

Author Disclosure: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

- Pillai SG, Kong X, Edwards LD, Cho MH, Anderson WH, Coxson HO, Lomas DA, Silverman EK; ECLIPSE and ICGN Investigators. Loci identified by genome-wide association studies influence different disease-related phenotypes in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;182:1498–1505.
- Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, von Mutius E, Farrall M, Lathrop M, Cookson WOCM. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010;363:1211–1221.
- Ober C, Butte AJ, Elias JA, Lusk AJ, Gan W, Banks-Schlegel S, Schwartz D. Getting from genes to function in lung disease: a National Heart, Lung, and Blood Institute workshop report. *Am J Respir Crit Care Med* 2010;182:732–737.
- Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, et al.; American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010;121:2331–2378.
- Downs SH, Schindler C, Liu LJ, Keidel D, Bayer-Oglesby L, Brutsche MH, Gerbase MW, Keller R, Kunzli N, Leuenberger P, et al. Reduced exposure to PM₁₀ and attenuated age-related decline in lung function. *N Engl J Med* 2007;357:2338–2347.
- Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057–1067.
- Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Abrahamowicz M, White WH. Validation of the Harvard Six Cities Study of particulate air pollution and mortality. *N Engl J Med* 2004;350:198–199.
- McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, Harrington R, Svartengren M, Han IK, Ohman-Strickland P, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med* 2007;357:2348–2358.
- Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007;356:447–458.
- Mills NL, Tornqvist H, Gonzalez MC, Vink E, Robinson SD, Soderberg S, Boon NA, Donaldson K, Sandstrom T, Blomberg A, et al. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *N Engl J Med* 2007;357:1075–1082.
- Pope CA III, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. *N Engl J Med* 2009;360:376–386.
- Neupane B, Jerrett M, Burnett RT, Marrie T, Arain A, Loeb M. Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. *Am J Respir Crit Care Med* 2010;181:47–53.
- Baccarelli A, Martinelli I, Zanobetti A, Grillo P, Hou L-F, Bertazzi PA, Mannucci PM, Schwartz J. Exposure to particulate air pollution and risk of deep vein thrombosis. *Arch Intern Med* 2008;168:920–927.
- Baccarelli A, Martinelli I, Pegoraro V, Melly S, Grillo P, Zanobetti A, Hou L, Bertazzi PA, Mannucci PM, Schwartz J. Living near major traffic roads and risk of deep vein thrombosis. *Circulation* 2009;119:3118–3124.
- Dales RE, Cakmak S, Vidal CB. Air pollution and hospitalization for venous thromboembolic disease in Chile. *J Thromb Haemost* 2010;8:669–674.
- Strickland MJ, Darrow LA, Klein M, Flanders WD, Sarnat JA, Waller LA, Sarnat SE, Mulholland JA, Tolbert PE. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. *Am J Respir Crit Care Med* 2010;182:307–316.
- Gent JF, Bell ML. Air pollution, population vulnerability, and standards for ambient air quality. *Am J Respir Crit Care Med* 2010;182:296–297.
- Kanatani KT, Ito I, Al-Delaimy WK, Adachi Y, Mathews WC, Ramsdell JW; Toyama Asian Desert Dust and Asthma Study Team.

- Desert dust exposure is associated with increased risk of asthma hospitalization in children. *Am J Respir Crit Care Med* 2010;182:1475–1481.
19. Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M, Oldenwening M, Smit HA, Brunekreef B. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2010;181:596–603.
20. Ryan PH, Holguin F. Traffic pollution as a risk factor for developing asthma: are the issues resolved? *Am J Respir Crit Care Med* 2010;181:530–531.
21. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, Romieu I, Silverman EK, Balmes JR; Committee on Nonsmoking COPD, Environmental and Occupational Health Assembly. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;182:693–718.
22. Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Loft S, Sorensen M, Tjonneland A, Overvad K, Raaschou-Nielsen O. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. *Am J Respir Crit Care Med* 2011;183:455–461.
23. Hnizdo E, Storey E. Occupational exposure to gases, fumes, or chemicals and risk of community-acquired pneumonia. *Am J Respir Crit Care Med* 2010;182:1087–1088.
24. Zanobetti A, Woodhead M. Air pollution and pneumonia: the “old man” has a new “friend.” *Am J Respir Crit Care Med* 2010;181:5–6.
25. Zanobetti A, Redline S, Schwartz J, Rosen D, Patel S, O'Connor GT, Lebowitz M, Coull BA, Gold DR. Associations of PM₁₀ with sleep and sleep-disordered breathing in adults from seven U.S. urban areas. *Am J Respir Crit Care Med* 2010;182:819–825.
26. Adar SD, Klein R, Klein BE, Szpiro AA, Cotch MF, Wong TY, O'Neill MS, Shrager S, Barr RG, Siscovick DS, *et al.* Air pollution and the microvasculature: a cross-sectional assessment of *in vivo* retinal images in the population-based Multi-Ethnic Study of Atherosclerosis (MESA). *PLoS Med* 2010;7:e1000372.
27. Luttmann-Gibson H, Suh HH, Coull BA, Dockery DW, Sarnat SE, Schwartz J, Stone PH, Gold DR. Systemic inflammation, heart rate variability and air pollution in a cohort of senior adults. *Occup Environ Med* 2010;67:625–630.
28. Schneider A, Neas LM, Graff DW, Herbst MC, Cascio WE, Schmitt MT, Buse JB, Peters A, Devlin RB. Association of cardiac and vascular changes with ambient PM_{2.5} in diabetic individuals. *Part Fibre Toxicol* 2010;7:14.
29. O'Toole TE, Hellmann J, Wheat L, Haberzettl P, Lee J, Conklin DJ, Bhatnagar A, Pope CA III. Episodic exposure to fine particulate air pollution decreases circulating levels of endothelial progenitor cells. *Circ Res* 2010;107:200–203.
30. Xu X, Yavar Z, Verdin M, Ying Z, Mihai G, Kampfrath T, Wang A, Zhong M, Lippmann M, Chen L-C, *et al.* Effect of early particulate air pollution exposure on obesity in mice: role of p47^{phox}. *Arterioscler Thromb Vasc Biol* 2010;30:2518–2527.
31. Van Hee VC, Adar SD, Szpiro AA, Barr RG, Roux AD, Bluemke DA, Sheppard L, Gill EA, Bahrami H, Wassel C, *et al.* Common genetic variation, residential proximity to traffic exposure, and left ventricular mass: the Multi-Ethnic Study of Atherosclerosis. *Environ Health Perspect* 2010;118:962–969.
32. Ren C, Vokonas PS, Suh H, Fang S, Christiani DC, Schwartz J. Effect modification of air pollution on urinary 8-hydroxy-2'-deoxyguanosine by genotypes: an application of the multiple testing procedure to identify significant SNP interactions. *Environ Health* 2010;9:78.
33. Sood A, Petersen H, Blanchette CM, Meek P, Picchi MA, Belinsky SA, Tesfaigzi Y. Wood smoke exposure and gene promoter methylation are associated with increased risk for COPD in smokers. *Am J Respir Crit Care Med* 2010;182:1098–1104.
34. Pokhrel AK, Bates MN, Verma SC, Joshi HS, Sreeramareddy CT, Smith KR. Tuberculosis and indoor biomass and kerosene use in Nepal: a case-control study. *Environ Health Perspect* 2010;118:558–564.
35. Gninafon M, Ade G, Ait-Khaled N, Enarson DA, Chiang CY. Exposure to combustion of solid fuel and tuberculosis: a matched case-control study. *Eur Respir J* (In press)
36. Jerrett M, Burnett RT, Pope CA, Ito K, Thurston G, Krewski D, Shi Y, Calle E, Thun M. Long-term ozone exposure and mortality. *N Engl J Med* 2009;360:1085–1095.
37. Stafoggia M, Forastiere F, Faustini A, Biggeri A, Bisanti L, Cadum E, Cernigliaro A, Mallone S, Pandolfi P, Serinelli M, *et al.*; on behalf of the EpiAir Group. Susceptibility factors to ozone-related mortality: a population-based case-crossover analysis. *Am J Respir Crit Care Med* 2010;182:376–384.
38. Dey R, Van Winkle L, Ewart G, Balmes J, Pinkerton K; on behalf of the ATS Environmental Health Policy Committee. A second chance: setting a protective ozone standard. *Am J Respir Crit Care Med* 2010;181:297–299.
39. Garantziotis S, Li Z, Potts EN, Lindsey JY, Stober VP, Polosukhin VV, Blackwell TS, Schwartz DA, Foster WM, Hollingsworth JW. TLR4 is necessary for hyaluronan-mediated airway hyperresponsiveness after ozone inhalation. *Am J Respir Crit Care Med* 2010;181:666–675.
40. Andre L, Boissiere J, Reboul C, Perrier R, Zalvidea S, Meyer G, Thireau J, Tanguy S, Bideaux P, Hayot M, *et al.* Carbon monoxide pollution promotes cardiac remodeling and ventricular arrhythmia in healthy rats. *Am J Respir Crit Care Med* 2010;181:587–595.
41. Strulovici-Barel Y, Omberg L, O'Mahony M, Gordon C, Hollmann C, Tilley AE, Salit J, Mezey J, Harvey BG, Crystal RG. Threshold of biologic responses of the small airway epithelium to low levels of tobacco smoke. *Am J Respir Crit Care Med* 2010;182:1524–1532.
42. Hnizdo E. Lung function loss associated with occupational dust exposure in metal smelting. *Am J Respir Crit Care Med* 2010;181:1162–1163.
43. Johnsen HL, Hetland SM, Benth JS, Kongerud J, Soyseth V. Dust exposure assessed by a job exposure matrix is associated with increased annual decline in FEV₁: a 5-year prospective study of employees in Norwegian smelters. *Am J Respir Crit Care Med* 2010;181:1234–1240.
44. Shi J, Hang JQ, Mehta AJ, Zhang HX, Dai HL, Su L, Eisen EA, Christiani DC. Long-term effects of work cessation on respiratory health of textile workers: a 25-year follow-up study. *Am J Respir Crit Care Med* 2010;182:200–206.
45. Tossa P, Paris C, Zmirou-Navier D, Demange V, Acouetey D-S, Michaely J-P, Bohadana A. Increase in exhaled nitric oxide is associated with bronchial hyperresponsiveness among apprentices. *Am J Respir Crit Care Med* 2010;182:738–744.
46. Rodríguez-Trigo G, Zock J-P, Pozo-Rodríguez F, Gómez FP, Monyarch G, Bouso L, Coll MD, Vereia H, Antó JM, Fuster C, *et al.*; SEPAR-Prestige Study Group. Health changes in fishermen 2 years after clean-up of the Prestige oil spill. *Ann Intern Med* 2010;153:489–498.
47. Ameille J, Letourneux M, Paris C, Brochard P, Stofflet A, Schorle E, Gislard A, Laurent F, Conso F, Pairon J-C. Does asbestos exposure cause airway obstruction, in the absence of confirmed asbestosis? *Am J Respir Crit Care Med* 2010;182:526–530.
48. Miller A, Rom WN. Does asbestos exposure (asbestosis) cause (clinical) airway obstruction (small airway disease)? *Am J Respir Crit Care Med* 2010;182:444–445.
49. Cummings KJ, Donat WE, Etensohn DB, Roggli VL, Ingram P, Kreiss K. Pulmonary alveolar proteinosis in workers at an indium processing facility. *Am J Respir Crit Care Med* 2010;181:458–464.
50. Lison D, Delos M. Pulmonary alveolar proteinosis in workers at an indium processing facility. *Am J Respir Crit Care Med* 2010;182:578–579.
51. Costabel U, Nakata K. Pulmonary alveolar proteinosis associated with dust inhalation: not secondary but autoimmune? *Am J Respir Crit Care Med* 2010;181:427–428.
52. Mack DG, Lanham AM, Falta MT, Palmer BE, Maier LA, Fontenot AP. Deficient and dysfunctional regulatory T cells in the lungs of chronic beryllium disease subjects. *Am J Respir Crit Care Med* 2010;181:1241–1249.
53. Kim YH, Fazlollahi F, Kennedy IM, Yacobi NR, Hamm-Alvarez SF, Borok Z, Kim KJ, Crandall ED. Alveolar epithelial cell injury due to zinc oxide nanoparticle exposure. *Am J Respir Crit Care Med* 2010;182:1398–1409.
54. Ege MJ, Mayer M, Normand A-C, Genuneit J, Cookson WOCM, Braun-Fahrlander C, Heederik D, Piarroux R, von Mutius E. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011;364:701–709.
55. Wang T-N, Lin M-C, Wu C-C, Leung S-Y, Huang M-S, Chuang H-Y, Lee C-H, Wu D-C, Ho P-S, Ko AM-S, *et al.* Risks of exposure to

- occupational asthmogens in atopic and nonatopic asthma: a case-control study in Taiwan. *Am J Respir Crit Care Med* 2010;182:1369–1376.
56. Wu AC, Lasky-Su J, Rogers CA, Klanderman BJ, Litonjua AA. Fungal exposure modulates the effect of polymorphisms of chitinases on emergency department visits and hospitalizations. *Am J Respir Crit Care Med* 2010;182:884–889.
57. Schütze N, Lehmann I, Bonisch U, Simon JC, Polte T. Exposure to mycotoxins increases the allergic immune response in a murine asthma model. *Am J Respir Crit Care Med* 2010;181:1188–1199.
58. Gregory LG, Mathie SA, Walker SA, Pegorier S, Jones CP, Lloyd CM. Overexpression of Smad2 drives house dust mite-mediated airway remodeling and airway hyperresponsiveness via activin and IL-25. *Am J Respir Crit Care Med* 2010;182:143–154.
59. Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, Lee-Parritz A, Wood RA, Kattan M, Bloomberg GR, *et al.* Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med* 2010;182:25–33.