Update in Environmental and Occupational Lung Diseases 2013

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In this update, recent publications within the field of environmental and occupational medicine, from this journal and others, are highlighted. Effects of ambient air pollution on a diverse range of airways disease continue to be discovered, reiterating the impressive potency of this near-ubiquitous and largely anthropogenic toxicant. Air pollution is now recognized as the third leading cause of disability-adjusted life years due to chronic respiratory disease globally (1). Studies in the past year have significantly strengthened the link between air pollution exposure and adverse health outcomes including mortality (2–4), lung cancer (4–6), infections (7–9), and obstructive lung disease (including asthma) (10, 11). Important underlying mechanistic details were illuminated in several animal models (12–17). The association between poor indoor air quality and lung diseases is a topic of increasing interest and was investigated in several reports in 2013 (18–21). Controlled human exposure experiments were in the spotlight, in part because of ethical concerns about the justification of this approach. An important position paper by leading researchers and a biomedical ethicist strongly supports the usefulness of controlled exposures, which continue to provide new insights into adverse health effects of different pollutants (22).

Asbestos exposure is a well-recognized risk factor for pleural mesothelioma, and two epidemiology studies were published that explored the interaction between exposure to asbestos, other mineral fibers, and cigarette smoking in mesothelioma, asbestosis, and lung cancer (23, 24). Arsenic is increasingly recognized as a groundwater contaminant, with potential effects on lung development and function. An important paper provided strong evidence that even low levels of arsenic exposure are associated with reduced lung function (25). The adverse health effects of global warming are becoming apparent, and one paper provided a sobering reminder that elevated ambient temperatures are a strong risk factor for respiratory morbidity (26). Unfortunately, the adverse effects of environmental and occupational exposures on lung health occur disproportionately in ethnic minorities and those with lower socioeconomic status, underscoring the urgent need to address these important health disparities (27). Although our understanding of the adverse effects of environmental and occupational exposures on lung health continues to expand, more research is needed to understand mechanisms involved and discover the optimal public health measures to mitigate risk.

Air Pollution

Effects on Mortality

The association between particulate matter (PM) exposure and ischemic cardiovascular events is well established. However, it is not as clear that PM exposure is associated with mortality from chronic obstructive pulmonary disease (COPD), lung cancer, or other pulmonary diseases. Carey and colleagues used a large (835,607 subjects) database to show that PM, nitrogen dioxide (NO_2), and sulfur dioxide were associated with all-cause mortality in England: interestingly, the signal was stronger for respiratory than cardiovascular causes (2). This paper provides a counterpoint to the prevailing view that these pollutants are particularly associated with deaths from cardiovascular causes. Whether this represents something unique to the cohort studied in England requires further study. The association between respiratory mortality and air pollution was underscored by Gan and colleagues, who reported a link between traffic-related elevations in black carbon concentrations and COPD hospitalization and mortality (3). A key strength of this population-based cohort study from Vancouver, Canada was the use of personalized exposure estimates afforded by land use regression. Additionally, exposure to higher levels of wood smoke pollution was also associated with increases in COPD hospitalizations. Although the study by Carey and colleagues argues against ozone as a key mediator of noted effects in England (2), Jerrett and colleagues provide a contrasting perspective using data from the American Cancer Society cohort from an earlier era (4). Exposure to fine PM, ozone, and NO_2 was positively associated with ischemic heart disease mortality, whereas NO_2 (a marker for traffic pollution) and fine PM were also associated with mortality from all causes combined. Taken together, these studies

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firmly establish that even low-level exposure to ambient outdoor air pollution from traffic and other sources is an important risk factor for lung disease and deaths from COPD. A recent American Thoracic Society consensus statement stopped short of linking air pollution exposure with the development of or mortality attributable to COPD (28), but in light of these new studies the causality of these associations should be reassessed.

Chen and colleagues reported on the "Great Smog of 2013" in Beijing, China, when residents were exposed to the worst air quality on record (29). During a 1-week stretch in January 2013, the average concentration of particles less than 2.5 μm in diameter ($PM_{2.5}$) was 231 $\mu g/m^3$, with a peak daily value of 443 $\mu g/m^3$, both substantially higher than maximal recommended exposures. The authors compared hospital visits and admissions during matched periods before, during, and after the event. Although mortality was not specifically investigated, the authors did detect significant increases in hospital visits for both cardiovascular and respiratory diseases (29), underscoring the urgent need to improve air quality in Beijing and other metropolitan areas (30, 31).

Links to Lung Cancer

In 2012, diesel exhaust was officially designated a human carcinogen by the International Agency for Research on Cancer, part of the World Health Organization. This reflected cumulative data on the effects of chronic exposure to diesel exhaust, which was strengthened even further in the past year. Diesel exhaust was tied closely to lung cancer in a study that linked three occupational cohorts from the United States (5). With lifelong exposure, even ambient levels of pollution were associated with lung cancer, suggesting that the concern extends beyond those working in particulate-prone occupations. In the American Cancer Society cohort (*see above*), only NO_2 had significant positive association with lung cancer mortality (4). Raaschou-Nielsen deepened this evidence base further still, using more than 4 million person-years of risk to connect PM specifically with risk of lung adenocarcinoma (6). Consequently, research should now focus on the mechanisms for these sobering associations, so that rational public health measures can be put in place to mitigate risks.

Relationship with Infections

As opposed to the association with mortality and lung cancer, the effects of PM and other air pollutants on infections is less definitive. Stern and colleagues provided an important advance by focusing on infants, using a prospective birth cohort to demonstrate that even current levels of ambient particulates in a very well-developed country (Switzerland) may increase respiratory symptoms and—particularly in those with preexisting lung function deficits—duration of respiratory tract infections (7). In adults, increased risk for infection is one explanation posed for the novel finding that acute exacerbations of idiopathic pulmonary fibrosis are linked to ozone and NO_2 exposure, recently noted by Johannson and colleagues (8). In a mouse model, early-life exposure to combustion-derived PM caused immunosuppression that persisted even to adulthood (12). Separately, exposure to chlorine gas was found to predispose to invasive fungal infection via suppression of antimicrobial myeloid cells (13), but it remains to be seen how these mechanisms extrapolate to less irritating ambient pollutants. In contrast, one "criteria" pollutant (32), namely carbon monoxide, was associated with a nearly 6% *decrease* in hospital admission for respiratory tract infection in Hong Kong, particularly in children and adults (9). In a thoughtful editorial, Goldberg and Holguin speculate on potential mechanisms for this association and touch on the classic "dose is the poison" construct to encourage further investigation of carbon monoxide's therapeutic potential (33).

Association with Asthma, Airway Obstruction, and Allergy

The association between air pollution exposure and risk of asthma in children was highlighted by Nishimura and colleagues. These authors harnessed the GALA II and SAGE II populations, which included Latino (n = 3,343) and African American (n = 977) children with and without asthma from five urban regions in the mainland United States and Puerto Rico (10). The key finding was that exposure to ambient NO_2 during infancy was associated with a small but statistically significant increased risk for asthma during later childhood years (odds ratio [OR] = 1.17). Because this study included only minority children, it is not clear whether minority children are particularly vulnerable in this regard. Although most of the recent literature on air pollution's health effects continues to emphasize long-term effects, Rice and colleagues nicely captured a signal connecting exposure to PM or ozone with only a 1- or 2-day lag with decreases in FEV_1 (11). Remarkably, exposures fell generally within acceptable governmental standards, and the cohort studied was not a particularly vulnerable population (mostly never smoking and middle aged).

Allergic rhinitis is much more common than asthma, but the relationship between ambient pollution and rhinitis pathophysiology is not well understood. Fuertes and colleagues studied the association between traffic-related air pollution exposure and childhood allergic rhinitis in the Traffic, Asthma, and Genetics (TAG) study, a pooled analysis of six birth cohorts (n = 15,299) (34). The authors detected an association between allergic rhinitis and $PM_{2.5}$ mass, which was critically dependent on the inclusion of certain large cohorts, as statistical significance was lost on cohort exclusion. Additionally, there was no evidence for gene-by-environment interactions, because air pollution–associated rhinitis risk was not increased in subjects with common variants in antioxidant (GSTP1) or pattern recognition receptor (TLR2 and TLR4) genes. Although noting that statistically detecting such interactions often requires particularly large sample sizes (even larger than those in Fuertes and colleagues [34]), and recognizing the complexity of oxidative stress pathways, this study does not support the widely held belief that defective antioxidant status is a risk factor for the potentiating effects of air pollution exposure on allergen sensitization.

Mechanistic Insights into Air Pollution and Allergen Sensitization: An Emerging Role for IL17

Several mechanistic studies during the past year provided new insights into how air pollution might potentiate allergen sensitization and the development of asthma. Current thinking is that air pollution acts as an "inhaled adjuvant" in this regard (i.e., that it boosts the development of adaptive immunity by generating mucosal inflammation). Support for this model comes from the observation that pollutants including PM can activate dendritic cells, key antigen-presenting cells

that instruct T-cell differentiation (35, 36). Although $CD4^+$ Th2 cells are firmly implicated in the pathogenesis of allergic asthma, the role of other lymphocyte subsets is becoming apparent (37). Th17 cells, which secrete IL-17A and promote neutrophil-dominant responses, have attracted attention recently because these cells arise in the lung after mucosal sensitization, tend to be steroid-insensitive, and are associated with severe asthma in some studies (38, 39). Several papers in 2013 uncovered an interesting role for Th17 responses in mediating the effect of air pollution on allergen-driven lung inflammation and airway hyperresponsiveness (AHR). Martin and colleagues capitalized on a mouse model of sensitization to ovalbumin to demonstrate that preexposure to NO_2 promotes an antigen-specific response that requires the IL-1 receptor and caspase-1 to generate Th17 cells (14). Interestingly, dexamethasone blocked Th17 cytokine production in this model but did not affect responses induced by adoptively transferred canonical Th17 cells (40). Thus, Th17 cells that arise in the lung in response to NO_2 priming followed by allergen exposure are different than those that arise *in vitro* under highly polarizing conditions. Surprisingly, however, IL-1R knockout mice developed enhanced AHR compared with wild-type mice, demonstrating the complexity of mucosal immune responses in this context and the need for further work (40). In a separate study, Brandt and colleagues demonstrated that combined exposure to diesel exhaust particles and house dust mites elicited IL17-dependent AHR in mice, although airway inflammation had a mixed Th2/Th17 phenotype (15). These investigators also showed that plasma IL-17A levels were higher in children exposed to higher diesel exhaust particle levels. In another study, the ability of ambient PM to promote Th17 responses was found to depend on the aryl hydrocarbon receptor, implicating a role for polycyclic aromatic hydrocarbons (16). In a study of mice exposed to engineered nanomaterials, Sayers and colleagues observed a mixed Th1/Th2/Th17-dependent phenotype that was dependent on COX-2 (17). Collectively, these studies emphasize the emerging role of IL17-dependent immune responses induced by air pollution and environmental exposures and underscore the importance of coexposure studies in immunotoxicology.

Indoor Air Pollution

Indoor air quality is increasingly linked with exacerbations of asthma and other lung diseases, but the mechanisms remain poorly understood. Matsui and colleagues explored the relationship between indoor NO_2, airborne endotoxin levels, and asthma symptoms in a cohort of children living in Baltimore, Maryland (18). In children living in homes with lower NO_2 concentrations, higher endotoxin was associated with an increase in acute asthma-related medical visits (OR = 1.27). In contrast, in those living in homes with higher NO_2 concentrations, endotoxin was negatively associated with such visits (OR = 0.80). The modifying effect was essentially opposite that observed with airborne nicotine (a proxy for secondhand smoke [SHS]), suggesting complex relationships that bear further study before public health recommendations can be proposed. The accompanying editorial summarized the challenges in assessing multiplicative interactions of different environmental exposures using statistical modeling (41). In another study from this group, Lu and colleagues reported a significant association between being overweight or obese and asthma symptoms in children exposed to indoor $PM_{2.5}$ or NO_2 (19). Interestingly, however, other measures of asthma morbidity (such as lung function or health care use) did not vary by weight. The relationship between SHS exposure and adult-onset asthma was specifically investigated by Lajunen and colleagues (20). These authors reported a strikingly synergistic interaction between parental history of asthma, SHS exposure, and risk of adult-onset asthma in a population-based incident case-control study from Finland. Specifically, the ORs for asthma were 1.97 for SHS exposure, 2.64 for parental asthma, but 12.69 for their joint effect (20). In former smokers with COPD, Hansel and colleagues found that even small increases in indoor $PM_{2.5}$ and NO_2 were associated with increased respiratory symptoms and risk of exacerbation (21). This report underscores the importance of studying vulnerable populations who may be especially susceptible to adverse health effects of poor indoor air quality.

Controlled Human Exposures

The mechanisms by which outdoor and indoor pollutants contribute to respiratory morbidity and mortality require further study, both to provide biological plausibility for observed findings from other disciplines and also to concretely assess the potential for interventions in the (human) species of ultimate concern. Controlled human exposure studies have provided important insights in this regard and occupy a critical position between epidemiological associations and *in vitro* mechanistic research in cells or animal models (Figure 1). Controlled human exposures require specialized approaches and infrastructure and careful attention to safety and are not widely available. In a recent position paper, Rom, Boushey, and Caplan provide important historical and ethical perspectives on these studies and conclude that "(s)tudies in humans in real-time are nonetheless essential to the understanding the adverse health effects of air pollution, and importantly, chamber studies have ethically modeled exposures at levels of pollutants above, at, or below promulgated air quality standards, measured adverse health effects, and performed this with a remarkable safety record" (22). Several studies in 2013 were reported that provided new insights using these approaches. Yamamoto and colleagues conducted a double-blinded, randomized crossover study of filtered air versus diesel exhaust exposure (with or without supplementation with the antioxidant N-acetylcysteine) in 13 subjects with asthma (42). These authors studied gene expression profiles in peripheral blood mononuclear cells before and after exposure, focusing on micro-RNA (mi-RNA) expression. mi-RNAs are small noncoding RNAs that regulate gene expression at the post-transcriptional level and have previously been shown to be regulated by diesel exhaust in human airway epithelium (43). Yamamoto and colleagues found that diesel exhaust exposure induced several mi-RNAs in circulating cells, including those involved in oxidant responses. Interestingly, supplementation with N-acetylcysteine attenuated the effects of diesel exhaust exposure, although there was interindividual variability in this regard (42). Additional support for the role of oxidative stress came from a report by Alexis and colleagues, who built on prior ozone exposure studies showing variability in neutrophilic airway inflammation (44). In a newer analysis, the authors compared

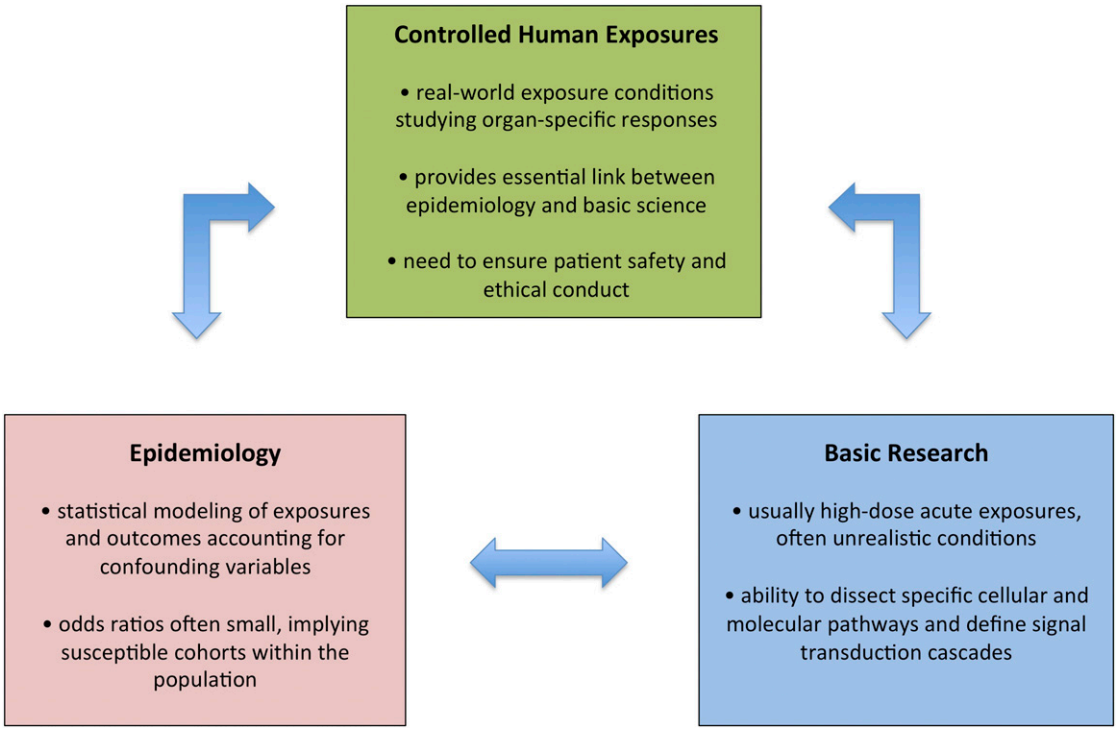

Figure 1. Controlled human exposures provide a critical link between epidemiology and basic research.

ozone-induced sputum neutrophilia in subjects with and without the GSTM1 null genotype, a common variant in an antioxidant gene. The authors concluded that subjects with increased neutrophilic response to low-level ozone (0.06 ppm for 6 h) were 13 times more likely to have the GSTM1 null genotype than nonresponders. Sava and colleagues exposed eighteen subjects with asthma to filtered air or diesel exhaust (300 $\mu g/m^3$ $PM_{2.5}$), and 18 hours later nasal lavage fluids were collected and methacholine bronchoprovocation was investigated (45). The authors detected a small but statistically significant increase in nasal lavage substance P (but not calcitonin gene-related peptide) after diesel exhaust exposure. Although methacholine reactivity did not increase after diesel exposure versus filtered air, these authors did detect a significant association between changes in substance P and the methacholine dose–response slope. This study suggests that neurogenic inflammation may contribute to adverse health effects of diesel exposure in susceptible patients with asthma (45). Taken together, these studies suggest that controlled human exposures will continue to provide new insights into the adverse health effects of air pollution in the future.

Asbestos Exposure, Mesothelioma, and Lung Cancer

Lacourt and colleagues reported a case-control study investigating associations between pleural mesothelioma and occupational exposure to asbestos, mineral wool, and silica (23). A total of 1,199 cases and 2,379 control subjects were identified from different sources in France from 1987 to 1996 and 1998 to 2006. Although occupational exposure to asbestos is a well-known risk factor for pleural mesothelioma, the risks associated with mineral wool (which is used in insulation) and silica dust are less clear. The main finding was that occupational exposure to mineral wool was associated with a significantly increased OR for mesothelioma when adjusting for asbestos exposure (e.g., OR = 2.5 for highest exposure group). No such associations were found for silica exposure in adjusted analyses, although a significantly higher OR was observed for silica exposure in the unadjusted subgroup analysis. These seemingly contradictory results could be the result of misclassification, the inability to independently separate exposures to the different compounds, or other factors, which were discussed in subsequent correspondence (46, 47). Coexposure to all three particles seemed to enhance the risk of pleural mesothelioma even further. Although previous cohort studies did not suggest an association between mineral wool exposure and mesothelioma, two previous smaller case-control studies did (48, 49). Taken together, these data suggest that more research is needed to understand how mineral wool and other fibers interact to increase risk of mesothelioma over time.

Markowitz and colleagues studied the association between asbestos exposure, asbestosis, cigarette smoking, and lung cancer in 2,377 male North American insulators (24). Chest X-ray, spirometric, occupational, and smoking data were collected in 1981 to 1983, and lung cancer mortality was monitored from 1981 to 2008. The comparison group was 54,243 non–asbestos-exposed blue-collar male workers for whom occupational and smoking data were available during the same period. This study confirmed the strong association between radiographic evidence of asbestosis and lung cancer mortality, with a striking synergistic effect of concomitant cigarette smoking (rate ratio of 7.40 vs. 36.8 for asbestosis in

the absence or presence of smoking, respectively). A smaller but statistically significant increase in lung cancer mortality was also observed for asbestos exposure even in the absence of radiographic evidence of asbestosis at time of enrollment (RR = 3.6 among nonsmokers). This study has important medicolegal implications, because occupational exposure to lower levels of asbestosis occurs in other professions where it is often not accompanied by overt asbestosis. However, this study did not explicitly determine whether asbestosis was present at the time lung cancer was diagnosed and therefore might have overestimated the effect of asbestos exposure in the absence of asbestosis (50–52). Reassuringly, smoking cessation significantly decreased lung cancer risk in all subgroups, as pointed out in the accompanying editorial (53).

Arsenic

Chronic arsenic exposure is a major public health problem worldwide, affecting hundreds of millions of people (54). The relationship between arsenic toxicity and lung disease has long been recognized, included studies from Chile showing that early life arsenic poisoning resulted in severe and sometimes fatal lung fibrosis in children. In 2013, Parvez and colleagues reported the results of a prospective cohort study in Bangladesh, where low-level arsenic exposure occurs via contaminated well water (25). This study has several strengths, including a large sample size (950 individuals who presented with respiratory symptoms to a local chest clinic), simultaneous analysis of urinary and water arsenic, together with pre- and post-bronchodilator spirometry. The main observation was that increasing levels of urinary and water arsenic were associated with a dose-related decrease in lung function (both FEV_1 and FVC). These associations remained significant in multivariate logistic regression analyses controlling for age, cigarette smoking, socioeconomic status, and other potential confounders (25). Previous experiments using mouse models and cell culture suggest that epithelial cells are one potential target of arsenic in the lung. Sherwood and colleagues reported that arsenic disrupted airway epithelial barrier function using *in vitro* cell culture models (55). Epithelial barrier dysfunction is increasingly associated with lung diseases and can lead to epithelial activation and airway inflammation (56). Using mouse and human airway epithelial cells, these authors and found that arsenic exposure reduced transepithelial electrical resistance, a sign of barrier dysfunction (55). Further research will be needed to determine the mechanisms for this effect and whether it translates into enhanced macromolecular permeability. Taken together, these studies indicate that even low-level arsenic exposure compromises lung function, and the challenges now are to define the relevant mechanisms involved and implement preventive public health measures.

Coal Mine Dust Lung Disease

Petsonk, Rose, and Cohen wrote a timely update summarizing "new lessons from an old exposure" (57). Although pneumoconioses are widely believed to be only of historical interest, the authors summarize recent data indicating an ongoing increase in both the prevalence and severity of coal mine dust lung disease. Particularly concerning are hot spots of exposure, with miners developing rapidly progressive fibrosis and loss of lung function in certain parts of the country. The authors provide recommendations for screening, diagnosis, and management of the broad spectrum of these disorders, including medicolegal implications of establishing the degree of impairment (57).

Climate Change Will Impact Pulmonary Disease Burden

The impact of global warming on respiratory health is only now beginning to be understood. Rom, Evans, and Uppal reported on how Superstorm Sandy affected Bellevue Hospital, which can be viewed as a sentinel event of climate change (58). Although warm temperatures are known to increase rates of respiratory mortality, the relationship between heat and respiratory morbidity has not been as well characterized. Previous studies from other countries have provided conflicting results, with some studies reporting slight decreases in hospitalizations during hot weather (e.g., in Athens, Greece). Anderson and colleagues used a dataset that contained daily hospitalization rates from 1999 to 2008 for 221 U.S. counties and studied the relationship between outdoor heat and hospitalization for COPD and respiratory infections using International Classification of Diseases, ninth revision codes (26). The final data set covered approximately 12.5 million Medicare beneficiaries across the United States (more than 30% of the U.S. population $\geq$65 yr of age). The main finding was that respiratory hospitalizations increased 4.3% for each 10°F increase in daily mean summer temperature. These results were similar across demographic groups and were slightly more pronounced in cooler counties. These sobering results suggest that the collision of an aging population with warming global temperatures will result in increased respiratory morbidity in the future. ■

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References

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, *et al*. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224–2260.
2. Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med* 2013;187:1226–1233.
3. Gan WQ, FitzGerald JM, Carlsten C, Sadatsafavi M, Brauer M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. *Am J Respir Crit Care Med* 2013;187:721–727.

4. Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, Martin RV, van Donkelaar A, Hughes E, Shi Y, *et al*. Spatial analysis of air pollution and mortality in California. *Am J Respir Crit Care Med* 2013;188:593–599.
5. Vermeulen R, *et al*. Exposure-response estimates for diesel engine exhaust and lung cancer mortality based on data from three occupational cohorts. *Environ Health Perspect* 2014;122: 172–177.
6. Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, Hoffmann B, Fischer P, Nieuwenhuijsen MJ, Brunekreef B, *et al*. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol* 2013;14: 813–822.
7. Stern G, Latzin P, Röösli M, Fuchs O, Proietti E, Kuehni C, Frey U. A prospective study of the impact of air pollution on respiratory symptoms and infections in infants. *Am J Respir Crit Care Med* 2013; 187:1341–1348.
8. Johannson KA, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, Kim DS, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur Respir J* 2014;43: 1124–1131.
9. Tian L, Qiu H, Pun VC, Lin H, Ge E, Chan JC, Louie PK, Ho KF, Yu IT. Ambient carbon monoxide associated with reduced risk of hospital admissions for respiratory tract infections. *Am J Respir Crit Care Med* 2013;188:1240–1245.
10. Nishimura KK, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA, Thyne S, Farber HJ, Serebrisky D, Kumar R, *et al*. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. *Am J Respir Crit Care Med* 2013;188:309–318.
11. Rice MB, Ljungman PL, Wilker EH, Gold DR, Schwartz JD, Koutrakis P, Washko GR, O'Connor GT, Mittleman MA. Short-term exposure to air pollution and lung function in the Framingham Heart Study. *Am J Respir Crit Care Med* 2013;188:1351–1357.
12. Saravia J, You D, Thevenot P, Lee GI, Shrestha B, Lomnicki S, Cormier SA. Early-life exposure to combustion-derived particulate matter causes pulmonary immunosuppression. *Mucosal Immunol* (In press)
13. Gessner MA, Doran SF, Yu Z, Dunaway CW, Matalon S, Steele C. Chlorine gas exposure increases susceptibility to invasive lung fungal infection. *Am J Physiol Lung Cell Mol Physiol* 2013;304: L765–L773.
14. Martin RA, Ather JL, Lundblad LK, Suratt BT, Boyson JE, Budd RC, Alcorn JF, Flavell RA, Eisenbarth SC, Poynter ME. Interleukin-1 receptor and caspase-1 are required for the Th17 response in nitrogen dioxide-promoted allergic airway disease. *Am J Respir Cell Mol Biol* 2013;48:655–664.
15. Brandt EB, Kovacic MB, Lee GB, Gibson AM, Acciani TH, Le Cras TD, Ryan PH, Budelsky AL, Khurana Hershey GK. Diesel exhaust particle induction of IL-17A contributes to severe asthma. *J Allergy Clin Immunol* 2013;132:1194–1204.e2.
16. van Voorhis M, Knopp S, Julliard W, Fechner JH, Zhang X, Schauer JJ, Mezrich JD. Exposure to atmospheric particulate matter enhances Th17 polarization through the aryl hydrocarbon receptor. *PLoS ONE* 2013;8:e82545.
17. Sayers BC, Taylor AJ, Glista-Baker EE, Shipley-Phillips JK, Dackor RT, Edin ML, Lih FB, Tomer KB, Zeldin DC, Langenbach R, *et al*. Role of cyclooxygenase-2 in exacerbation of allergen-induced airway remodeling by multiwalled carbon nanotubes. *Am J Respir Cell Mol Biol* 2013;49:525–535.
18. Matsui EC, Hansel NN, Aloe C, Schiltz AM, Peng RD, Rabinovitch N, Ong MJ, Williams DL, Breysse PN, Diette GB, *et al*. Indoor pollutant exposures modify the effect of airborne endotoxin on asthma in urban children. *Am J Respir Crit Care Med* 2013;188:1210–1215.
19. Lu KD, Breysse PN, Diette GB, Curtin-Brosnan J, Aloe C, Williams DL, Peng RD, McCormack MC, Matsui EC. Being overweight increases susceptibility to indoor pollutants among urban children with asthma. *J Allergy Clin Immunol* 2013;131:1017–1023.e1–e3.
20. Lajunen TK, Jaakkola JJ, Jaakkola MS. The synergistic effect of heredity and exposure to second-hand smoke on adult-onset asthma. *Am J Respir Crit Care Med* 2013;188:776–782.
21. Hansel NN, McCormack MC, Belli AJ, Matsui EC, Peng RD, Aloe C, Paulin L, Williams DL, Diette GB, Breysse PN. In-home air pollution is linked to respiratory morbidity in former smokers with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187:1085–1090.
22. Rom WN, Boushey H, Caplan A. Experimental human exposure to air pollutants is essential to understand adverse health effects. *Am J Respir Cell Mol Biol* 2013;49:691–696.
23. Lacourt A, Gramond C, Audignon S, Ducamp S, Févotte J, Soit Ilg AG, Goldberg M, Imbernon E, Brochard P. Pleural mesothelioma and occupational coexposure to asbestos, mineral wool, and silica. *Am J Respir Crit Care Med* 2013;187:977–982.
24. Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer: new findings from the North American insulator cohort. *Am J Respir Crit Care Med* 2013;188:90–96.
25. Parvez F, Chen Y, Yunus M, Olopade C, Segers S, Slavkovich V, Argos M, Hasan R, Ahmed A, Islam T, *et al*. Arsenic exposure and impaired lung function. Findings from a large population-based prospective cohort study. *Am J Respir Crit Care Med* 2013;188: 813–819.
26. Anderson GB, Dominici F, Wang Y, McCormack MC, Bell ML, Peng RD. Heat-related emergency hospitalizations for respiratory diseases in the Medicare population. *Am J Respir Crit Care Med* 2013;187: 1098–1103.
27. Schraufnagel DE, Blasi F, Kraft M, Gaga M, Finn PW, Rabe KF; ATS/ERS Committee on Disparities in Respiratory Health. An official American Thoracic Society/European Respiratory Society policy statement: disparities in respiratory health. *Am J Respir Crit Care Med* 2013;188:865–871.
28. 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.
29. Chen R, Zhao Z, Kan H. Heavy smog and hospital visits in Beijing, China. *Am J Respir Crit Care Med* 2013;188:1170–1171.
30. Huang W, Wang G, Lu SE, Kipen H, Wang Y, Hu M, Lin W, Rich D, Ohman-Strickland P, Diehl SR, *et al*. Inflammatory and oxidative stress responses of healthy young adults to changes in air quality during the Beijing Olympics. *Am J Respir Crit Care Med* 2012;186: 1150–1159.
31. Rich DQ, Kipen HM, Huang W, Wang G, Wang Y, Zhu P, Ohman-Strickland P, Hu M, Philipp C, Diehl SR, *et al*. Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. *JAMA* 2012;307:2068–2078.
32. United States Environmental Protection Agency. Six common air pollutants. 2012 [accessed 2014 Jan 1]. Available from: http://www.epa.gov/air/urbanair/
33. Goldberg HJ, Holguin F. Carbon monoxide in small doses—a good thing? *Am J Respir Crit Care Med* 2013;188:1187–1188.
34. Fuertes E, Brauer M, MacIntyre E, Bauer M, Bellander T, von Berg A, Berdel D, Brunekreef B, Chan-Yeung M, Gehring U, *et al*. Childhood allergic rhinitis, traffic-related air pollution, and variability in the GSTP1, TNF, TLR2, and TLR4 genes: results from the TAG Study. *J Allergy Clin Immunol* 2013;132:342–352.e2.
35. Williams MA, Porter M, Horton M, Guo J, Roman J, Williams D, Breysse P, Georas SN. Ambient particulate matter directs nonclassic dendritic cell activation and a mixed TH1/TH2-like cytokine response by naive CD4+ T cells. *J Allergy Clin Immunol* 2007;119:488–497.
36. Bezemer GF, Bauer SM, Oberdörster G, Breysse PN, Pieters RH, Georas SN, Williams MA. Activation of pulmonary dendritic cells and Th2-type inflammatory responses on instillation of engineered, environmental diesel emission source or ambient air pollutant particles in vivo. *J Innate Immun* 2011;3:150–166.
37. Lloyd CM, Saglani S. T cells in asthma: influences of genetics, environment, and T-cell plasticity. *J Allergy Clin Immunol* 2013;131: 1267–1274, quiz 1275.

38. Wilson RH, Whitehead GS, Nakano H, Free ME, Kolls JK, Cook DN. Allergic sensitization through the airway primes Th17-dependent neutrophilia and airway hyperresponsiveness. *Am J Respir Crit Care Med* 2009;180:720–730.
39. Newcomb DC, Peebles RS Jr. Th17-mediated inflammation in asthma. *Curr Opin Immunol* 2013;25:755–760.
40. Martin RA, Ather JL, Daggett R, Hoyt L, Alcorn JF, Suratt BT, Weiss DJ, Lundblad LK, Poynter ME. The endogenous Th17 response in NO2-promoted allergic airway disease is dispensable for airway hyperresponsiveness and distinct from Th17 adoptive transfer. *PLoS ONE* 2013;8:e74730.
41. Goss CH, Mayer-Hamblett N. The yin and yang of indoor airborne exposures to endotoxin. *Am J Respir Crit Care Med* 2013;188:1181–1183.
42. Yamamoto M, Singh A, Sava F, Pui M, Tebbutt SJ, Carlsten C. MicroRNA expression in response to controlled exposure to diesel exhaust: attenuation by the antioxidant N-acetylcysteine in a randomized crossover study. *Environ Health Perspect* 2013;121:670–675.
43. Jardim MJ, Fry RC, Jaspers I, Dailey L, Diaz-Sanchez D. Disruption of microRNA expression in human airway cells by diesel exhaust particles is linked to tumorigenesis-associated pathways. *Environ Health Perspect* 2009;117:1745–1751.
44. Alexis NE, Lay JC, Zhou H, Kim CS, Hernandez ML, Kehrl H, Hazucha MJ, Devlin RB, Diaz-Sanchez D, Peden DB. The glutathione-S-transferase mu 1 (GSTM1) null genotype and increased neutrophil response to low-level ozone (0.06 ppm). *J Allergy Clin Immunol* 2013; 131:610–612.
45. Sava F, MacNutt MJ, Carlsten CR. Nasal neurogenic inflammation markers increase after diesel exhaust inhalation in individuals with asthma. *Am J Respir Crit Care Med* 2013;188:759–760.
46. Bonde JP. No indication that mineral wool causes mesothelioma. *Am J Respir Crit Care Med* 2013;188:873.
47. Lacourt A. Reply: no indication that mineral wool causes mesothelioma. *Am J Respir Crit Care Med* 2013;188:873–874.
48. Rödelsperger K, Jöckel KH, Pohlabeln H, Römer W, Woitowitz HJ. Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study. *Am J Ind Med* 2001;39:262–275.
49. Pintos J, Parent ME, Case BW, Rousseau MC, Siemiatycki J. Risk of mesothelioma and occupational exposure to asbestos and man-made vitreous fibers: evidence from two case-control studies in Montreal, Canada. *J Occup Environ Med* 2009;51: 1177–1184.
50. Ross R. Asbestosis, not asbestos exposure, is the primary risk factor for lung cancer. *Am J Respir Crit Care Med* 2014;189: 114–115.
51. Geyer SJ. Asbestos, asbestosis, smoking, and lung cancer: study bias and confounding issues that complicate the interpretation of the results. *Am J Respir Crit Care Med* 2014;189:115–116.
52. Markowitz S, Morabia A, Miller A. Reply: asbestos, asbestosis, smoking, and lung cancer: study bias and confounding issues that complicate the interpretation of the results. *Am J Respir Crit Care Med* 2014;189:116–117.
53. Balmes JR. Asbestos and lung cancer: what we know. *Am J Respir Crit Care Med* 2013;188:8–9.
54. Naujokas MF, Anderson B, Ahsan H, Aposhian HV, Graziano JH, Thompson C, Suk WA. The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem. *Environ Health Perspect* 2013;121: 295–302.
55. Sherwood CL, Liguori AE, Olsen CE, Lantz RC, Burgess JL, Boitano S. Arsenic compromises conducting airway epithelial barrier properties in primary mouse and immortalized human cell cultures. *PLoS ONE* 2013;8:e82970.
56. Rezaee F, Georas SN. Breaking barriers: new insights into airway epithelial barrier function in health and disease. *Am J Respir Cell Mol Biol* (In Press)
57. Petsonk EL, Rose C, Cohen R. Coal mine dust lung disease: new lessons from old exposure. *Am J Respir Crit Care Med* 2013;187: 1178–1185.
58. Rom WN, Evans L, Uppal A. The sentinel event of climate change: Hurricane Sandy and its consequences for pulmonary and critical care medicine. *Am J Respir Crit Care Med* 2013;187: iii–iv.