Ambient Air Pollution and Clinical Implications for Susceptible Populations

Laura G. Hooper[1] and Joel D. Kaufman[2,3,4]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, [2]Department of Environmental and Occupational Health Sciences, [3]Department of Medicine, and [4]Department of Epidemiology, University of Washington, Seattle, Washington

Abstract

Air pollution is associated with a diversity of health effects, and evidence for a causal relationship with specific diseases exists. Exposure to air pollution is ubiquitous and typically beyond the control of the individual; the resulting health burden for the population can be high. Disproportionate effects are seen in individuals who have increased susceptibility to air pollution owing to individual- or community-level characteristics. As studies grow increasingly sophisticated, the understanding of who comprises the susceptible population continuously expands. Characteristics of susceptibility include genetic predisposition; socioeconomic factors; life stage; the presence of preexisting diseases, such as asthma, chronic obstructive pulmonary disease, cystic fibrosis; and the unique population of lung transplant recipients. This review explores how select populations, namely individuals with preexisting pulmonary disease and those living in communities of low socioeconomic status, have an increased susceptibility to the health effects of ambient air pollution. Genetic susceptibility, though a fundamental determinant of risk, is beyond the scope of this review and is not discussed. Strategies designed to mitigate air pollution–related health effects are discussed using a framework that addresses pollution exposure at multiple levels—government, state, community, and the individual. Emission reduction strategies remain the basis for public health protection; however, ancillary harm reduction measures are explored that can be adopted by susceptible communities and individuals.

Keywords: lung diseases; particulate matter; environment and public health

(Received in original form July 19, 2017; accepted in final form November 16, 2017)

Supported by grant P30ES007033 to the Interdisciplinary Center for Exposures, Diseases, Genomics, and Environment (EDGE Center).

Author Contributions: Both authors contributed to content development and manuscript drafting, and approved the final version of the published manuscript.

Correspondence and requests for reprints should be addressed to Joel D. Kaufman, M.D., M.P.H., University of Washington, 1959 NE Pacific Street, Seattle, WA 98195. E-mail: joelk@u.washington.edu.

Ann Am Thorac Soc Vol 15, Supplement 2, pp S64–S68, Apr 2018

DOI: 10.1513/AnnalsATS.201707-574MG
Internet address: www.atsjournals.org

Modern air pollution health effects research began after discrete episodes of extremely high pollution levels when industrialization and urbanization met especially stagnant meteorological conditions. The 1952 London and 1930 Meuse Valley fog tragedies are among the most commonly cited environmental episodes in this category. In 1930 in Belgium's Meuse Valley, more than 60 people died over a 2-day period when stagnant weather and a temperature inversion led to the accumulation of high concentrations of sulfur compounds, including sulfur dioxide (SO_2), fluoride gases, and particulate matter generated from the nearby industrial center of Liege, Belgium. This mortality figure represented a greater than 10-fold increase over the normal mortality rate (1). Despite the public outcry and prescient warnings from the scientific community regarding the public health risk posed by a similar episode in a more populated center, some 20 years later the City of London experienced a lethal smog of historic proportions (2).

A temperature inversion in early December 1952 coupled with London's residential and industrial dependence on coal fires led to a toxic smog that resulted in more than 3,000 excess deaths in the 3 weeks after the episode (3). Although the acute health effects of the extreme pollution exposure were immediately recognized, perhaps the more striking findings came from later analyses showing chronic health effects and persistently elevated mortality for months after the acute episode. In an analysis by Bell and Davis, the true scale of the London fog was likely closer to 12,000 excess deaths in the year after the event (3). The persistent elevation in mortality above background levels in the months after the event suggest that this was not simply a "mortality displacement phenomenon" whereby the most fragile people died a few weeks earlier than they would have without the acute pollution exposure. Instead, the susceptible

population extended beyond those already at the mortality tipping point to include the broader population (3). It is this observation that laid the groundwork for studies that have broadened the understanding that the spectrum of individuals susceptible to the health effects of air pollution encompasses a wider scope of increasingly healthy individuals.

Modern-day air quality standards are motivated by the protection of all people, but particularly of susceptible individuals. In the United States, the National Ambient Air Quality Standards mandated by the Clean Air Act are set with the explicit intent to protect susceptible groups with an "adequate margin of safety" based on the best available evidence (4). In fact, it is data from susceptible subpopulations that show a greater risk of adverse health outcomes resulting from a given exposure that have driven the standards for air pollutants to increasingly lower levels (5). Protection of susceptible groups is the fundamental motivation for the regulation of air pollution.

Defining Susceptibility

The interplay between varying levels and types of air pollution and the dynamic physiologic response is complex. It is generally accepted that there are individuals in the population who, by virtue of preexisting disease or genetic factors, will bear the brunt of health effects resulting from increased pollutant concentrations. Although public health efforts to reduce exposures will protect all members of the population, questions remain about whether additional protections are needed for some individuals.

The concept of susceptibility, at both the individual and population levels, describes the characteristics that increase the risk of experiencing adverse health outcomes in response to air pollution exposure. The terms *susceptibility* and *vulnerability* are often used interchangeably in the literature; however, there is value in understanding their distinct definitions. In this review, we define *vulnerability* as referring to external factors that confer increased risk for an adverse outcome, whereas we use *susceptibility* to refer to intrinsic characteristics that increase risk. These characteristics might include not only the presence of underlying disease, age, and genetic background but also sex, race, ethnicity, epigenetic changes, socioeconomic position, nutritional status, and personal behaviors. Some elements of these susceptibility characteristics are dynamic over an individual's lifetime. Coupled with variability in air pollution exposures, the risk assessment for an individual may be fluid and vary substantially over the course of the individual's life.

Preexisting Disease Increases Susceptibility

Advances in modern epidemiological methods and exposure assessment methods, combined with experimental studies, have increased confidence in the causal effects of air pollution exposures in communities. The literature base convincingly supports the association between short-term acute spikes in air pollution and exacerbations of underlying diseases, including asthma, chronic obstructive pulmonary disease, myocardial infarction, and heart failure.

Asthma is perhaps the most well studied of these, so much so that, regarding traffic-related pollution, the Health Effects Institute concluded that there is sufficient evidence to infer a causal association with childhood asthma exacerbations (6). Asthma exacerbations, characterized by emergency room visits, hospitalizations, and increased medication use, are increased for both children and adults during episodes of peak air pollution (7).

In persons with underlying chronic obstructive pulmonary disease, short-term exposure to particulate matter (particulate matter $\leqslant$2.5 μm in aerodynamic diameter [$PM_{2.5}$] and particulate matter $\leqslant$10 μm in aerodynamic diameter [PM_{10}]), nitrogen dioxide (NO_2), carbon monoxide (CO), SO_2, and ozone are all associated with exacerbation frequency. Among these, particulate matter and NO_2 showing the strongest effect (8).

Persons with cystic fibrosis are a particularly at-risk population because cystic fibrosis is a disease whose clinical course is characterized by chronic and recurrent infections and progressive loss of lung function over time. Particulate matter, specifically $PM_{2.5}$, may facilitate the first acquisition of *Pseudomonas aeruginosa* infection in children (9). Exposure to $PM_{2.5}$, PM_{10}, and ozone appears to be associated with increased frequency of exacerbations and decline in lung function in cystic fibrosis (10).

Lung transplant recipients represent a unique population in their susceptibility to environmental exposures, particularly regarding the direct inhalational contact between air pollutants and allografted lungs. With interstitial lung disease, chronic obstructive pulmonary disease, and cystic fibrosis leading the list of indications for lung transplant, the transplant population is remarkable in its diversity of age, underlying disease, comorbidities, and degree of immunosuppression. The harmful effects of air pollution exposure to lungs is known (11). Extending these implications to the long-term health of lung allografts is a plausible concern (12). Two recent studies have shown associations between air pollution exposures and markers of poor prognosis in post–lung transplant cohorts, specifically lower vital capacity and increased risk of mortality related to chronic lung allograft dysfunction (13, 14). Current data are insufficient to answer whether lung transplant recipients, or transplant recipients in general, are at higher risk from the damaging effects of air pollution. However, transplanted lungs represent an indisputably precious resource that clinicians and recipients alike have a vested interest in protecting from environmental threats.

New-Onset Pulmonary Disease Linked to Air Pollution Exposure

Susceptibility to air pollution health effects is not limited to persons at the extremes of age or those with preexisting diseases. Increasingly sophisticated exposure assessments employed in large prospective cohort studies are uncovering evidence that air pollution exposure is linked to new-onset cardiovascular and pulmonary diseases in previously unaffected individuals (15). Lung cancer is a principal example. On the basis of compelling evidence, notably the evidence derived from the landmark ESCAPE (European Study of Cohorts for Air Pollution Effects) analysis, the International Agency for Research on Cancer classified outdoor air pollution, inclusive of particulate matter and diesel exhaust, as a group I carcinogen; air pollution is acknowledged as a cause of lung cancer (16, 17).

A growing literature base supports the link between long-term ambient pollution exposure and incident asthma in both children and adults. In the Southern California Children's Health Study, exposure to traffic-related pollution at home and school is associated with an increased risk of developing asthma in

previously asymptomatic children (18). The association with traffic-related pollution was again demonstrated in a British Columbia cohort which showed that early-life exposure to PM_{10}, SO_2, and black carbon were all associated with significant odds of an incident asthma diagnosis in children under 5 years of age (19). The data on adults are less robust, but at least two large cohort studies suggest associations between NO_2 and $PM_{2.5}$ exposure and adult-onset incident asthma (20, 21).

Linking air pollution exposure with incident disease in previously healthy persons challenges the idea that there is a population at no risk from the health effects of ambient pollution. Susceptibility exists on a spectrum, and there is clearly a concentration–response curve between pollution exposure and health effect risk. The striking feature in several of these cohort studies of incident disease is that the health effects occurred at levels of pollution common in developed countries, if not at or below the regulatory standards (15, 16). It is unknown whether the concentration–response curve exhibits a threshold below which health effects are not seen. Abatement efforts to reduce exposure levels would be sensitive to both the presence of a threshold and the shape of the curve at low levels (22). More precise information on the health effects at low exposure levels is needed to inform regulatory policies.

Socioeconomic Position as an Effect Modifier

Apart from preexisting diseases and intrinsic factors such as age, ethnicity, race, genetic background, and sex, socioeconomic determinants contribute to the effects of air pollution on health. Individuals at the lowest end of the socioeconomic spectrum are burdened by the so-called triple jeopardy of environmental injustice; they are exposed to higher levels of air pollutants, have a susceptibility to poorer baseline health status, and lack access to the resources to cope with pollution threats (23). Socioeconomic status is known to covary with the spatial distribution of air pollution, with poorer communities experiencing higher pollution exposure (23). This is compounded by the higher prevalence of preexisting disease that is linked to food insecurity, psychosocial stressors, built environments not conducive to health-promoting behaviors, educational disadvantage, and reduced access to medical care (24). This confluence of circumstances suggests that low socioeconomic status is best characterized as a state of increased susceptibility and vulnerability.

Recent research suggests that neighborhood-level socioeconomic status may modify the health effects of particulate air pollution exposure. Living in socioeconomically disadvantaged communities appears to interact with $PM_{2.5}$ exposure and synergistically increase the risk of cardiovascular disease (25). This is consistent with earlier findings that living in a disadvantaged neighborhood is an independent risk factor for coronary artery disease, even after controlling for traditional coronary artery disease risk factors and independent markers of socioeconomic status, including income, occupation, and education (26). The mechanisms by which community-level disadvantages may increase susceptibility to particulate air pollution health effects need further study. Theories include food scarcity, leading to reduced antioxidant intake; limited access to medical care, including preventive services; and exposure to copollutants (27). This area of research challenges the traditional view attributing increased susceptibility to specific intrinsic or acquired individual factors and suggests that recognition of exposure to disadvantaged socioeconomic circumstances may identify broader subgroups with elevated susceptibility to air pollution's harmful effects.

Interventions

Abundant evidence supports the relationship between reductions in air pollution and improved health outcomes, including reductions in mortality (28–30). Regulations that target emission reductions are the mainstay of current efforts to curb the health effects of air pollution. The singular importance of government-level policies to limit emissions and reduce exposures for the population at large is indisputable. However, given the broad spectrum of susceptible subgroups with ubiquitous ambient pollution exposure, a framework is needed that incorporates individual- and community-level strategies for harm reduction. Such a framework would acknowledge the primary role of government-level regulatory policies with community and individual measures seen as complementary but not sufficient.

Government-Level Policies

With the passage of the Clean Air Act and the subsequent implementation of National Ambient Air Quality Standards, aggregate emission of and population exposure to criteria pollutants in the United States have declined dramatically despite population and economic growth over the same period (31). Current emission reduction policies regulate existing energy production processes while promoting cleaner fuel sources and energy technologies.

Efforts to address climate change represent an important opportunity for simultaneously reducing key sources of air pollution. Measures to reduce air pollution and limit climate change exist in overlapping spheres (32). Fossil fuel combustion is the primary source of both greenhouse gas emissions and the air pollutants most strongly linked to adverse health outcomes, particulates, oxides of nitrogen, and SO_2. Action to slow climate change will have ancillary public health benefits derived from reductions in air pollution, with the reverse also being true: two sides of the same coin. For many, the future benefits of reducing climate impacts may resonate less than the near-term personal health gains that will be achieved with air pollution reduction. Opinion leaders and policymakers need to understand the short- and long-term public health cobenefits associated with policies designed to reduce emissions from fossil fuel combustion, both to address the public's concerns and to achieve improved public health.

Community-Level Interventions

Concurrent with broader efforts to reduce emissions, rethinking land use could reduce air pollution exposures for particularly susceptible populations. Typical urban design tends to locate residential developments and key community resources (i.e., schools, hospitals) along transit corridors. This has the net effect of collocating the primary sources of traffic-related air pollution and the populations with increased susceptibility to air pollution health effects (33). The State of California, a national leader in air quality initiatives, has made formal distance recommendations for the siting of sensitive land uses such as healthcare facilities, daycare centers, schools, and playgrounds (34). Forethought in city planning exercises that incorporate

knowledge of exposure sources (i.e., transit corridors and railway yards) and community susceptibility profiles might promote physical separation of susceptible subpopulations from pollution sources.

Smarter urban planning relies on balancing the relative benefits and hazards of active travel (e.g., walking, cycling) with increased urban density and traffic-related pollution exposure. Minimizing sprawl to decrease vehicle travel dependence must be evaluated in the context of increasing urban density whereby active travel tends to locate in close proximity to high-traffic streets (33, 35). Physical activity remains a mainstay of the recommendations to improve public health. For the general population, except in the most extreme circumstances of high levels of ambient pollution, the benefits of physical activity seem to outweigh the health risks related to pollution exposure (36). It is unknown where the risk–benefit balance lies for the most susceptible subgroups; however, urban planning efforts that increase walkability and endeavor to reduce traffic-related pollution through improved public transportation will undoubtedly benefit communities as a whole.

Individual Measures

Individual interventions are not the primary solution, but certain highly susceptible subgroups may benefit from short-term personal risk reduction measures. In China, where average pollution levels routinely exceed the World Health Organization's recommendations, members of the general populace routinely turn to face masks to filter the polluted air (37). Particulate respirators designed to filter 95% of particulates may reduce the health effects of urban pollution (38). However, ineffective and flimsy surgical-style masks are perhaps the most widely used as a result of availability, knowledge gaps, and cost (39). This highlights a key challenge of shifting responsibility to the individual; personal harm reduction measures that require knowledge and resources may have reduced efficacy when implemented in the most vulnerable populations.

Evidence suggests that indoor particulate matter concentrations, from both indoor and outdoor sources, can be decreased by the use of high-efficiency air cleaners and confer potential health benefits (33, 40, 41). It is premature to recommend air cleaners as a strategy to reduce air pollution health effects in the general population, and the cost-to-benefit ratio is unlikely to be favorable in this broad context. However, for the most susceptible subgroups and the most polluted areas, it is reasonable to conclude that the potential benefit of this low-risk and relatively low-cost intervention favors early adoption rather than waiting for definitive data.

Borne out of the mechanistic literature, dietary and pharmacologic interventions to modify the health effects of air pollution exposure are intriguing but inconclusive. Inhalation of air pollutants triggers a local and systemic inflammatory cascade (42). Statins have been investigated in animal models and may attenuate the inflammatory effects of particulates, but evidence in humans is limited (43). Similarly, supplementation with dietary antioxidants has shown mixed results in attenuating the vascular effects of $PM_{2.5}$ and diesel exhaust exposure (44–46).

Although outdoor exercise is overwhelmingly encouraged because of its known health benefits, short-term episodes of high pollution can challenge the clinician to provide evidence-based guidance on limiting outdoor activity. The Air Quality Index is a standardized measure of air quality based on the Environmental Protection Agency's National Ambient Air Quality Standards. As a tool, the index is imperfect but clinically useful because it takes into account the potential health effects of daily pollution levels on increasingly vulnerable subgroups in the general population. More data are needed to risk stratify various susceptible subgroups and tailor their appropriate response to peak pollution days.

Recommendations and Future Directions

The data for individual-level interventions provide insufficient evidence to support guideline-quality recommendations. However, for certain susceptible subgroups, the question for the scientific community is what degree of certainty is required before reasonable exposure mitigation strategies should be endorsed? The lung transplant population provides an instructive example. The societal investment in prolonging survival in this population is substantial. Lung transplant recipients are susceptible to environmental pollutants, and the current state of the science would suggest that in-home air purifiers reduce pollutant concentrations, but data supporting this intervention in this population do not exist. In this unique population, an intervention with a favorable risk–reward relationship is a prudent recommendation even in the absence of trial-supported care guidelines (12). More widely prevalent lung diseases may also benefit from similar recommendations based on imperfect but suggestive evidence. However, recommending interventions on the basis of imperfect evidence must be approached with caution if applied more broadly to increasingly less susceptible populations who may experience diminishing benefits relative to the personal burden of adopting the intervention.

Successful national efforts to reduce air pollution levels are generating important public health gains. However, it is unknown how deleterious to the lungs are the lower concentrations of pollutants now typical in North America: Is there a threshold level below which respiratory health effects will not occur? For the most vulnerable groups, it is conceivable that such a threshold—if present—is below the current level of regulatory concern. As the evidence builds for a causal relationship between air pollution exposure and harmful respiratory health effects, data supporting specific intervention strategies are still needed, particularly for the most susceptible groups. Identifying and prioritizing these susceptible communities to guide clinician and public health practitioner recommendations should be a focus of future research. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Nemery B, Hoet PHM, Nemmar A. The Meuse Valley fog of 1930: an air pollution disaster. *Lancet* 2001;357:704–708.

2 Firket J. Fog along the Meuse Valley. *Trans Faraday Soc* 1936;32: 1192–1196.

3 Bell ML, Davis DL. Reassessment of the lethal London fog of 1952: novel indicators of acute and chronic consequences of acute

exposure to air pollution. *Environ Health Perspect* 2001;109: 389–394.
4 U.S. Environmental Protection Agency. Clean Air Act Title I – Air Pollution Prevention and Control, Parts A through D [accessed 2017 Aug 31]. Available from: https://www.epa.gov/clean-air-act-overview/clean-air-act-title-i-air-pollution-prevention-and-control-parts-through-d.
5 U.S. Environmental Protection Agency (EPA). 2015 National Ambient Air Quality Standards (NAAQS) for ozone. Washington, DC: EPA.
6 Health Effects Institute. Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects. Special report 17. Boston: Health Effects Institute; 2010.
7 Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014;383:1581–1592.
8 Li J, Sun S, Tang R, Qiu H, Huang Q, Mason TG, *et al*. Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2016;11:3079–3091.
9 Psoter KJ, De Roos AJ, Mayer JD, Kaufman JD, Wakefield J, Rosenfeld M. Fine particulate matter exposure and initial *Pseudomonas aeruginosa* acquisition in cystic fibrosis. *Ann Am Thorac Soc* 2015;12:385–391.
10 Goss CH, Newsom SA, Schildcrout JS, Sheppard L, Kaufman JD. Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. *Am J Respir Crit Care Med* 2004;169:816–821.
11 Churg A, Brauer M, del Carmen Avila-Casado M, Fortoul TI, Wright JL. Chronic exposure to high levels of particulate air pollution and small airway remodeling. *Environ Health Perspect* 2003;111:714–718.
12 Kaufman JD, Raghu G. Should we be concerned about air quality as a contributor to poor outcomes in lung transplant recipients? *Eur Respir J* 2017;49:1602369.
13 Benmerad M, Slama R, Botturi K, Claustre J, Roux A, Sage E, *et al*.; SysCLAD consortium. Chronic effects of air pollution on lung function after lung transplantation in the Systems prediction of Chronic Lung Allograft Dysfunction (SysCLAD) study. *Eur Respir J* 2017;49:1600206.
14 Ruttens D, Verleden SE, Bijnens EM, Winckelmans E, Gottlieb J, Warnecke G, *et al*. An association of particulate air pollution and traffic exposure with mortality after lung transplantation in Europe. *Eur Respir J* 2017;49:1600484.
15 Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, *et al*. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. *Lancet* 2016;388:696–704.
16 Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, *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.
17 Straif K, Cohen A, Samet J, editors; International Agency for Research on Cancer (IARC). Air pollution and cancer. IARC Scientific Publication No. 161. Lyon, France: IARC Press; 2013.
18 McConnell R, Islam T, Shankardass K, Jerrett M, Lurmann F, Gilliland F, *et al*. Childhood incident asthma and traffic-related air pollution at home and school. *Environ Health Perspect* 2010;118:1021–1026.
19 Clark NA, Demers PA, Karr CJ, Koehoorn M, Lencar C, Tamburic L, *et al*. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 2010;118:284–290.
20 Jacquemin B, Siroux V, Sanchez M, Carsin AE, Schikowski T, Adam M, *et al*. Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). *Environ Health Perspect* 2015;123:613–621.
21 Young MT, Sandler DP, DeRoo LA, Vedal S, Kaufman JD, London SJ. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of U.S. women. *Am J Respir Crit Care Med* 2014;190:914–921.
22 Goodkind AL, Coggins JS, Marshall JD. A spatial model of air pollution: the impact of the concentration-response function. *J Assoc Environ Resour Econ* 2014;1:451–479.
23 Hajat A, Hsia C, O'Neill MS. Socioeconomic disparities and air pollution exposure: a global review. *Curr Environ Health Rep* 2015;2:440–450.
24 Adler NE, Stewart J. Health disparities across the lifespan: meaning, methods, and mechanisms. *Ann N Y Acad Sci* 2010;1186:5–23.
25 Chi GC, Hajat A, Bird CE, Cullen MR, Griffin BA, Miller KA, *et al*. Individual and neighborhood socioeconomic status and the association between air pollution and cardiovascular disease. *Environ Health Perspect* 2016;124:1840–1847.
26 Diez-Roux AV, Nieto FJ, Muntaner C, Tyroler HA, Comstock GW, Shahar E, *et al*. Neighborhood environments and coronary heart disease: a multilevel analysis. *Am J Epidemiol* 1997;146:48–63.
27 O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N, *et al*.; Workshop on Air Pollution and Socioeconomic Conditions. Health, wealth, and air pollution: advancing theory and methods. *Environ Health Perspect* 2003;111:1861–1870.
28 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.
29 Berhane K, Chang CC, McConnell R, Gauderman WJ, Avol E, Rapapport E, *et al*. Association of changes in air quality with bronchitic symptoms in children in California, 1993-2012. *JAMA* 2016;315:1491–1501.
30 Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med* 2006;173:667–672.
31 U.S. Environmental Protection Agency. Progress cleaning the air and improving people's health [accessed 2017 Jun 27]. Available from: https://www.epa.gov/clean-air-act-overview/progress-cleaning-air-and-improving-peoples-health.
32 World Health Organization (WHO). Reducing global health risks through mitigation of short-lived climate pollutants: scoping report for policymakers. Geneva: WHO; 2015.
33 Giles LV, Barn P, Künzli N, Romieu I, Mittleman MA, van Eeden S, *et al*. From good intentions to proven interventions: effectiveness of actions to reduce the health impacts of air pollution. *Environ Health Perspect* 2011;119:29–36.
34 California Environmental Protection Agency, California Air Resources Board. Air quality and land use handbook: a community health perspective. Sacramento, CA: Author; 2005.
35 Hankey S, Lindsey G, Marshall JD. Population-level exposure to particulate air pollution during active travel: planning for low-exposure, health-promoting cities. *Environ Health Perspect* 2017;125:527–534.
36 Tainio M, de Nazelle AJ, Götschi T, Kahlmeier S, Rojas-Rueda D, Nieuwenhuijsen MJ, *et al*. Can air pollution negate the health benefits of cycling and walking? *Prev Med* 2016;87:233–236.
37 Ma Z, Hu X, Sayer AM, Levy R, Zhang Q, Xue Y, *et al*. Satellite-based spatiotemporal trends in $PM_{2.5}$ concentrations: China, 2004–2013. *Environ Health Perspect* 2016;124:184–192.
38 Shi J, Lin Z, Chen R, Wang C, Yang C, Cai J, *et al*. Cardiovascular benefits of wearing particulate-filtering respirators: a randomized crossover trial. *Environ Health Perspect* 2017;125:175–180.
39 Seltenrich N. The forest and the trees: how population-level health protections sometimes fail the individual. *Environ Health Perspect* 2017;125:A65–A70.
40 Chen R, Zhao A, Chen H, Zhao Z, Cai J, Wang C, *et al*. Cardiopulmonary benefits of reducing indoor particles of outdoor origin: a randomized, double-blind crossover trial of air purifiers. *J Am Coll Cardiol* 2015;65: 2279–2287.
41 Weichenthal S, Mallach G, Kulka R, Black A, Wheeler A, You H, *et al*. A randomized double-blind crossover study of indoor air filtration and acute changes in cardiorespiratory health in a First Nations community. *Indoor Air* 2013;23:175–184.
42 Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol* 2015;12:627–642.
43 Miyata R, Bai N, Vincent R, Sin DD, Van Eeden SF. Statins reduce ambient particulate matter-induced lung inflammation by promoting the clearance of particulate matter < 10 μm from lung tissues. *Chest* 2013;143:452–460.
44 Baccarelli A, Cassano PA, Litonjua A, Park SK, Suh H, Sparrow D, *et al*. Cardiac autonomic dysfunction: effects from particulate air pollution and protection by dietary methyl nutrients and metabolic polymorphisms. *Circulation* 2008;117:1802–1809.
45 Sack CS, Jansen KL, Cosselman KE, Trenga CA, Stapleton PL, Allen J, *et al*. Pretreatment with antioxidants augments the acute arterial vasoconstriction caused by diesel exhaust inhalation. *Am J Respir Crit Care Med* 2016;193:1000–1007.
46 Carlsten C, MacNutt MJ, Zhang Z, Sava F, Pui MM. Anti-oxidant N-acetylcysteine diminishes diesel exhaust-induced increased airway responsiveness in person with airway hyper-reactivity. *Toxicol Sci* 2014;139:479–487.