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Surviving With Smog and Smoke
Precision Interventions?

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Despite continuous efforts of regional governmental agencies, air pollution remains a major threat to public health worldwide. In January 2017, a severe episode of smog similar to the Great Smog of 1952 occurred in London. The longest episode of Chinese haze also developed in Beijing, during which levels of particulate matter < 2.5 μm rose to 500 μg/m^3. European smog and Chinese haze are associated with large numbers of premature deaths each year, at 400,000 and 1.2 million, respectively, primarily from respiratory diseases, cerebrovascular diseases, and ischemic heart diseases. In addition to air pollution, some are exposed to other harmful environmental factors, such as secondhand smoke. For countries with large populations of smokers, such as China, India, the United States, and Russia, surviving both smog and smoke is a serious problem. With novel genomic and epigenomic studies revealing air pollution- and smoking-induced mutational signatures and epigenetic editing in diseases such as lung cancer, it has become feasible to develop precision strategies for early intervention in the disease-causing pathways driven by the specific mutations or epigenetic regulations, or both. New therapies guided by gene-drug interactions and genomic biomarkers may also be developed. We discuss both perspectives regarding the urgent need to manage the toxic effects of smog and smoke for the benefit of global health and the novel concept of precision intervention to protect the exposed individuals when exposure to smog and secondhand smoke cannot be voluntarily avoided or easily modified. CHEST 2017; 152(5):925-929

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Despite continuous efforts of regional governmental agencies, air pollution remains a major threat to public health worldwide.[1] Notably, the damage from the London fog (or the Great Smog of 1952) is still in effect,[2] after causing 12,000 deaths in 1 week.[3] Mortality rates for the smog episode from December 1952 to February 1953 were 50% to 300% higher than in the previous year.[3] The latest data indicate that exposure to the Great Smog in the first year of life increased the likelihood of childhood and

ABBREVIATIONS: GWAS = genome-wide association studies; $PM_{2.5}$ = particulate matter < 2.5 μm; PM_{10} = particulate matter < 10 μm; ROS = reactive oxygen species; SNP = single nucleotide polymorphism; WHO = World Health Organization

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adulthood asthma by 19.9% and 9.5%, respectively.[2] It is telling that earlier in January of 2017, a severe smog episode similar to the Great Smog of 1952, occurred in London.[4] The air pollution in London is at present causing approximately 10,000 deaths each year.[5] This episode was considered a consequence of a push for diesel fuel and increased open use of wood-burning fires in the winter months.[5] For the whole of Europe, it is estimated that exposure to excessive particulate matter < 2.5 μm ($PM_{2.5}$) causes more than 400,000 premature deaths per year.[6]

In China, air pollution has become increasingly worse in recent years, and it has gained a new term as Chinese haze.[7-9] A haze event is defined by the China Meteorological Administration as a pollution phenomenon that cuts atmospheric visibility to < 10 km. For 8 days beginning December 30, 2016, residents of Beijing and surrounding cities suffered from the longest haze episode on record.[10] The $PM_{2.5}$ concentrations were at approximately 500 $\mu g/m^3$.[10] Of note, the World Health Organization (WHO) guideline for a healthy index of $PM_{2.5}$ is < 10 $\mu g/m^3$ for an annual mean, or < 25 $\mu g/m^3$ for a 24-hour mean (http://www.who.int/mediacentre/factsheets/fs313/en/). For particulate matter < 10 μm (PM_{10}), the WHO guideline requires a level < 20 $\mu g/m^3$ for an annual mean or 50 $\mu g/m^3$ for a 24-hour mean. In the United States, the real-time $PM_{2.5}$ reporting system indicates that the levels of $PM_{2.5}$ in most of US cities monitored are $<$ 50-100 $\mu g/m^3$ (https://airnow.gov/index.cfm?action=airnow.pollutant_summary&pollutant=pm25).

The development of haze in Beijing is affected by climate factors such as humidity and airflow.[11] Of note, it has been shown that excessive $PM_{2.5}$ caused more than 1.2 million premature deaths in China in 2010, 42% higher than the level in 2000.[12] Recent evidence has indicated that outdoor air pollution directly affects lung function in both children and adults, and triggers exacerbations of COPD symptoms.[13] The Chinese Ministry of Environmental Protection has recently started to tackle these problems by using a robust approach for extensive data collection and analyses and making the information publicly available.[14] In the United States, the government started to publish $PM_{2.5}$ levels in 1997 (United States Environmental Protection Agency; https://www.epa.gov/green-book/green-book-pm-25-1997-area-information) following the Air Pollution Control Act of 1955 that marked the first action by the federal government to address air pollution problems (https://www.epa.gov/clean-air-act-overview/evolution-clean-air-act). The overall efforts in China now include satellite collection of pollution data, drone monitoring of pollution discharges and air quality and effectiveness of protection programs, and use of chemical modeling for early warning of potentially severe haze episodes.[14]

Of note, smog can be separated into two types: industrial smog and photochemical smog. Industrial smog occurs in foggy cool weather, typical of that in London. Photochemical smog develops in hot dry climates such as Los Angeles and Mexico City.[8] Although ozone is the primary pollutant for photochemical smog,[15] industrial smog (including Chinese haze) contains particulate matter, sulfur dioxide, nitrogen dioxide, and carbon monoxide, and sometimes ozone.[9,16] Nonetheless, for the January 2017 smog in London, it was reported that nitrogen dioxide was the main toxic component.[5]

There is no doubt that exposure to smog or haze can cause respiratory diseases (COPD, asthma, lung cancer, and lower respiratory infections), cerebrovascular diseases, ischemic heart diseases, and other medical conditions.[1] These account for the associated morbidity and mortality. In addition to smog or haze that cannot be easily modified to reduce injuries to individuals exposed to it, some experience additional layers of harmful environmental exposures such as secondhand smoke (also called environmental tobacco smoke). Nonsmokers who breathe in secondhand smoke take in nicotine and toxic chemicals the same way that smokers do (American Cancer Society [https://www.cancer.org/cancer/cancer-causes/tobacco-and-cancer/secondhand-smoke.html]). Although smoking cessation can be championed as an intervention, exposure to secondhand smoke is nonelective and unavoidable, similar to air pollution. It is a major form of indoor air pollution. Of note, China has the largest population of smokers in the world, at 3 of 10 billion people.[17] There are an estimated 7.4 billion people in China who are exposed to secondhand smoke every day, 1.8 billion of whom are children.[18] Therefore, in China, there is a serious condition of surviving smog and smoke at the same time. People living in other countries with large populations of smokers, such as India, the United States, and Russia,[19] face the same problem.

The potential health damage from smog and smoke may be additive or synergistic, resulting in more morbidity and mortality. Smoking shares similarities with smog in generating the same pollutants of particulate matter, sulfur dioxide, nitrogen dioxide, and carbon monoxide.[20-23] Recent studies indicate that both smog and smoke can increase oxidative stress in cells of the airways.[24] Elevated levels of $PM_{2.5}$ induce oxidative

stress and inflammation in cultured macrophages.[25,26] In the Framingham Heart Study, even a short-term exposure to increased $PM_{2.5}$ levels resulted in corresponding increases in oxidative stress biomarkers.[27] Of note, it has been established that smoking induces oxidative stress in vascular endothelial cells.[28] The disease-causing effects of oxidative stress are attributed to elevated levels of reactive oxygen species (ROS) within a certain range and in a dose-dependent manner. Furthermore, initial production of ROS is able to provoke ROS-induced ROS release, resulting in sustained oxidative stress.[29-34] One of the major consequences of oxidative stress is DNA damage and mutations.[35,36] Importantly, the latest studies have revealed mutational signatures and epigenetic footprints in response to air pollution, smoking, and smoking condensates, as discussed further on.

Since both environmental factors of smog and secondhand smoke cannot be voluntarily avoided, perhaps it is time to consider precision interventions to protect affected individuals, for example, through personalized alteration of the disease-causing pathways. Using whole genome and targeted exome sequencing, a recent study by Yu et al[37] reported that somatic mutations in air pollution induced lung cancer (164 patients with non-small cell lung cancer: 79 in highly polluted regions vs 85 in control regions). The subject population was from regions in China where exposure to smoky coal generates high concentrations of $PM_{2.5}$ and PM_{10}. It was previously shown that when $PM_{2.5}$ increases by 5 $\mu g/m^3$, the risk of lung cancer increases by 18%; and when PM_{10} increases by 10 $\mu g/m^3$, the lung cancer risk increases by 22%.[38] In this study, a total of 80 somatic mutations of *TP53* were identified (46 in highly polluted regions vs 34 in control regions), with only nine common mutations.[37] The different 37 mutations of *TP53* can be further validated functionally for oncogenic effects.[37,39] In addition, Alexandrov et al[40] recently identified mutational signatures for 17 types of smoking-induced cancers, one of which is lung cancer. This study also used whole genome and exome sequencing to analyze 3,553 samples (2,490 from tobacco smokers and 1,063 from never smokers). A total of 21 mutational signatures have been identified for lung cancer, including subtypes of small cell lung cancer, lung squamous cell cancer, and lung adenocarcinoma.[40]

Of note, another study by Joehanes et al[41] reported epigenetic editing in response to cigarette smoking. A meta-analysis of genome-wide DNA methylation responses, which were assessed using the Illumina BeadChip 450K array on 15,907 blood-derived DNA samples from participants in 16 cohorts, was carried out. A large number of cytosine-phosphate-guanine site annotations were identified in 1,405 genes, which were found to be associated with pulmonary function, cancers, inflammatory diseases, and heart disease.[41] Furthermore, exposure to smoking condensates has been shown to cause DNA damage and injuries to DNA repair mechanisms,[42] although detailed mutational profiling needs to be further elucidated. This shares similarities with previous studies in which 11 different smoking condensates were found to be mutagenic.[43] Collectively, these emerging discovery data will promote subsequent mechanistic investigations of mutation/epigenetic regulation-dependent pathogenic pathways, manipulation of which might be of therapeutic or preventive potential. Besides revealing new therapeutic targets, these novel mutations and epigenetic footprints may also be relevant to specific implementation of pharmacogenomics and biomarker-guided treatments.[44-46] Pharmacogenomics to identify gene-drug interactions would be beneficial in precision intervention using existing or new drugs. Validated oncogenic somatic mutations can also be screened to use as a guide for targeted therapies. In addition, genome-wide association studies (GWAS) are expected to identify germ line polymorphisms that put individuals at higher risk for the development of a specific disease.[47,48] Although the counseling value to patients of these types of genomic biomarkers has been controversial, the latest studies have shown that GWAS-evaluated single nucleotide polymorphisms (SNPs) are functionally important for the development of childhood asthma in response to air pollution exposure.[49] Likewise, SNPs indicative of lung cancer risk have been discovered in coal-exposed populations.[50] These genomic biomarkers are of potential benefit in guiding early interventions in subjects who are genetically predisposed to related diseases. The overall strategies of precision intervention for subjects exposed to smog and smoke are summarized in Figure 1.

With the concept of precision medicine rapidly developing into practice,[51,52] it has become feasible to perform "omics" analyses of individual subjects to generate an integrated genomic and epigenomic atlas that can potentially be instrumental to early intervention in diseases caused by exposure to smog and smoke.[53] This information can be used for precision interventions by promoting individualized application of novel therapies that are developed based on the newly identified therapeutic targets and by promoting individualized application of new therapies that are

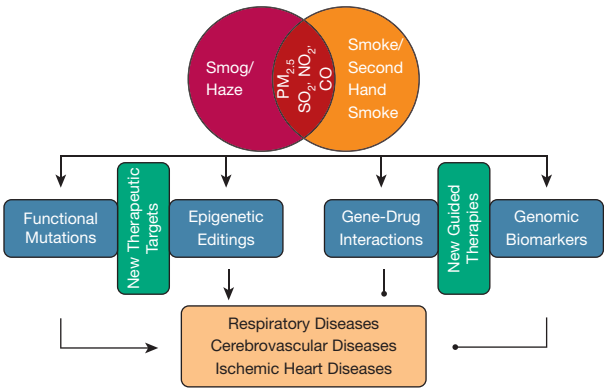

Figure 1 – *Precision interventions for individuals exposed to smog and smoke. Smog/haze and smoke/secondhand smoke are primary causes of air pollution that remain a major threat to public health worldwide. Particulate matter, sulfur dioxide, nitrogen dioxide, and carbon monoxide are common pollutants shared by smog/haze and smoke/secondhand smoke. Elevated levels of particulate matter < 2.5 μm induce oxidative stress, which is known to cause mutations and DNA damage. Recent genomic and epigenomic studies have revealed novel mutational signatures and epigenetic footprints in response to air pollution and smoking exposure. Manipulations of the downstream pathways of these regulatory pathways might be of preventive or therapeutic value. In addition, new information collected on gene-drug interactions and disease-predicting single nucleotide polymorphisms can be used to develop guided therapies, primarily through treating patients more effectively, given the precise genetic background influencing the efficacy of the particular drug, and by treating subjects early when they happen to carry predisposing genomic biomarkers. CO = carbon monoxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.*

guided by newly identified gene-drug interactions and disease-predicting SNPs (as summarized in Fig 1). In addition, some generic approaches to counteract oxidative stress may also prove to be helpful and valuable for immediate use before personalized protection is optimized. For example, a recent study has shown that B vitamins attenuated air pollution-induced epigenetic regulation in healthy subjects, presumably by attenuation of systematic oxidative stress.[54] It is postulated that other antioxidants might have similar effects through epigenomic modulations. These include dietary phytochemicals,[55] the active component of green tea—epigallocatechin gallate,[56] and vitamin C.[57] In the B-vitamin cocktail used, folic acid has been shown to exert potent vascular protective effects in addition to its antioxidative action.[58,59]

Surviving smog and smoke represents a major public health concern that needs urgent attention. Personalized precision intervention may be a feasible approach to achieve rapid progress in effectively protecting exposed individuals from smog- and smoke-induced injuries, while history has shown that it could take decades to half a century to solve the severe air pollution problems such as those currently presented by Chinese haze.

Implementation of precision medicine is evolving quickly worldwide[60,61]; efforts in this direction to control damage to health caused by smog and smoke may prove to be fruitful explorations in generating novel therapies for the prevention and treatment of related diseases.

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