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Discussion

Understanding the knowledge gaps between air pollution controls and health impacts including pathogen epidemic

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ABSTRACT

Sustainable development calls for a blue sky with quality air. Encouragingly, the current mass reduction-oriented pollution control is making substantial achievements, as the data from Chinese Environmental Monitoring Stations show a significant drop in the annual average concentrations of particulate matters (i.e., PM_{10} and $PM_{2.5}$) and SO_2. But many challenges and knowledge gaps are still confronted nowadays. On one hand, long-term health impacts of fine air particles have to be closely probed through both epidemiological and laboratory studies, and the toxic effects owing to the interactions between particles and associated chemical pollutants should be differentially teased out. On the other hand, due to sole mass control, there are significant changes of overall pollutant fingerprint, such as the increase of ground-level ozone concentration, which should be taken into account for altered health effects relative to the past. Moreover, the interplays with air pollutants and air-borne pathogens should be scrutinized in more details. In other words, it is worth investigating likely spread of pathogens (even for SARS-CoV-2) with aid of aerosols. Here, we recapitulate the current knowledge gaps between air pollution controls and health impacts including pathogen epidemic, and we also propose future research directions to support policy making in balance mass control and health impacts.

Air pollution poses an outstanding challenge to sustainable development, human health and even pathogen epidemics. According to the report of World Health Organization (WHO) in 2019, air pollution ranked in the first place of top 10 threats to human health (The World Health Organization). Under this setting, air pollution control and according health risks have popularly emerged in both academic research and strategic agendas worldwide. Although significant achievements have been reached due to the efforts in improving air quality in recent decades, there still exist many hurdles with respect to health issues to be addressed, *e.g.*, geographical differences in pathophysiological responses to air pollution, insufficient long-term epidemiological data, uncertainty on the divergent toxicities due to the complicated interactions among versatile environmental factors from different sources, and previously neglected or underestimated adverse effects. Moreover, as the mass of particulate particles (such as fine particulate matter, $PM_{2.5}$) falls, the ground-level O_3 concentration arises (Fig. 1), (Li et al., 2019) which may cause unknown threats to humans. Importantly, mounting data evidence the implications of air pollution in pathogen spread and epidemics (Domingo and Rovira, 2020). Air pollution has been recently found to correlate to increased risk of active tuberculosis (Lai et al., 2016) and influenza (Trinh et al., 2018). Strikingly, the current outbreak of novel coronavirus pneumonia (COVID-19) caused by the 2019 novel coronavirus (SARS-CoV-2) is attracting global attention. However, there is still no insight into the reasons for its outbreak from the eco-environmental and climate aspects. It would be great interest to embark on the role of aerosols, especially in indoor circumstance and airtight space, in enhancing the transport, viability and infection of the SARS-CoV-2 virus (Doremalen et al., 2020; Bashir et al., 2020). Thus, the sole mass decline of total air pollutants may not be able to reflect the full profiles of health impacts (Fig. 2). To this end, here we summarize the current knowledge gaps between air pollution controls and health impacts, and discuss the future development in

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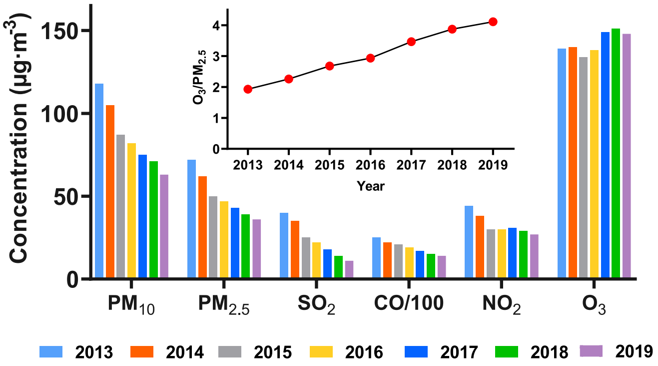

Fig. 1. Annual average concentrations of PM_{10}, $PM_{2.5}$, SO_2, CO, NO_2, O_3 over years in China (2013–2019). The insert shows the ratios of annual average concentrations of O_3 to those of $PM_{2.5}$. (Data collected from *Chinese Bulletin on Environmental Conditions. 2013–2019*).

health impact assessment upon air pollution.

In recent decades, China has been suffering serious air pollution, especially the high loading $PM_{2.5}$. Challenged by diverse serious problems caused by air pollution, the Chinese government has largely increased investment in basic research on air pollution formation and control. These studies greatly expand the understanding of the formation mechanism and fundamental principles of air pollution. It is now recognized that air pollution in China is a new type of haze chemical smog, different from London smog and Los Angeles photochemical smog (Chu et al., 2020). The complexity of air pollution resides in its versatile sources, including coal combustion emissions, vehicle emissions, agricultural emissions, industrial emissions and high concentration of natural dust aerosol (He et al., 2014). In the meanwhile, the numerical model for early warning and forecast of air pollution has been greatly upgraded, and the prediction accuracy has also been significantly improved, providing an important scientific support for taking effective pollution control measures and the health assessment of air pollution. On the basis of these scientific understandings, Chinese government has strengthened the furious regulations on the control of these critical source emission in recent decades (Zhang et al., 2019). In fact, over a long-term timescale, the reduction of SO_2 emission has been the major target of air pollution control in China, as the first enactment of the Law of the People's Republic of China on the Prevention and Control of Atmospheric Pollution in 1987. In the early stage, China strengthened the control of SO_2 emissions from coal combustion by dividing acid rain and SO_2 control areas (two-control areas) and implementing total control measures. Through a series of economic and technical means, the rising trend of SO_2 emission was successfully curbed, and the acid rain pollution has been effectively controlled. Then, in order to reduce $PM_{2.5}$ and haze, more stringent measures to reduce SO_2 emissions began to be implemented since the promulgation of the toughest-ever Air Pollution Prevention and Control Action Plan (Action Plan) in 2013. Up to now, most coal-fired power plants, steel-sintering machines and cement kilns in China have been equipped with flue gas desulfurization (FGD). As a consequence, in 2019, the annual average concentration of SO_2 in China dropped to 11 $\mu g \cdot m^{-3}$ (Fig. 1), reaching the first grade of the National ambient air quality standards (i.e., 20 $\mu g \cdot m^{-3}$). Meanwhile, selective catalytic reduction (SCR) or selective non-catalytic reduction (SNCR) systems have also been applied to control NO_x from vehicles, coal-fired power plants, steel-sintering machines, and cement kilns. As a result, the annual average concentrations of SO_2 and NO_2 in 338 cities has been reduced by 72.5% and 38.6% in 2019 relative to 2013, respectively (Fig. 1). (Chinese Bulletin on Environmental Conditions, 2013) Since both SO_2 and NO_2 are the critical precursors of secondary aerosol in the atmosphere, the reduction of their emission is a chief reason for $PM_{2.5}$ decline. Notably, although the national annual mean $PM_{2.5}$ concentrations has dropped from 72 in 2013 to 36 $\mu g \cdot m^{-3}$ in 2019 in China (Fig. 1), it still requires a long-timescale battle to reach the WHO standard (i.e., 10 $\mu g \cdot m^{-3}$). Frankly speaking, the situation of PM pollution varies from place to place and from time to time in China, in that numerous industrialized cities undergo heavier pollution than western countries, giving rise to greater challenges in pollution control and health impact evaluation.

Nonetheless, recent epidemiological studies indicate that PM pollution would increase the occurrence of incident stroke, ischemic heart

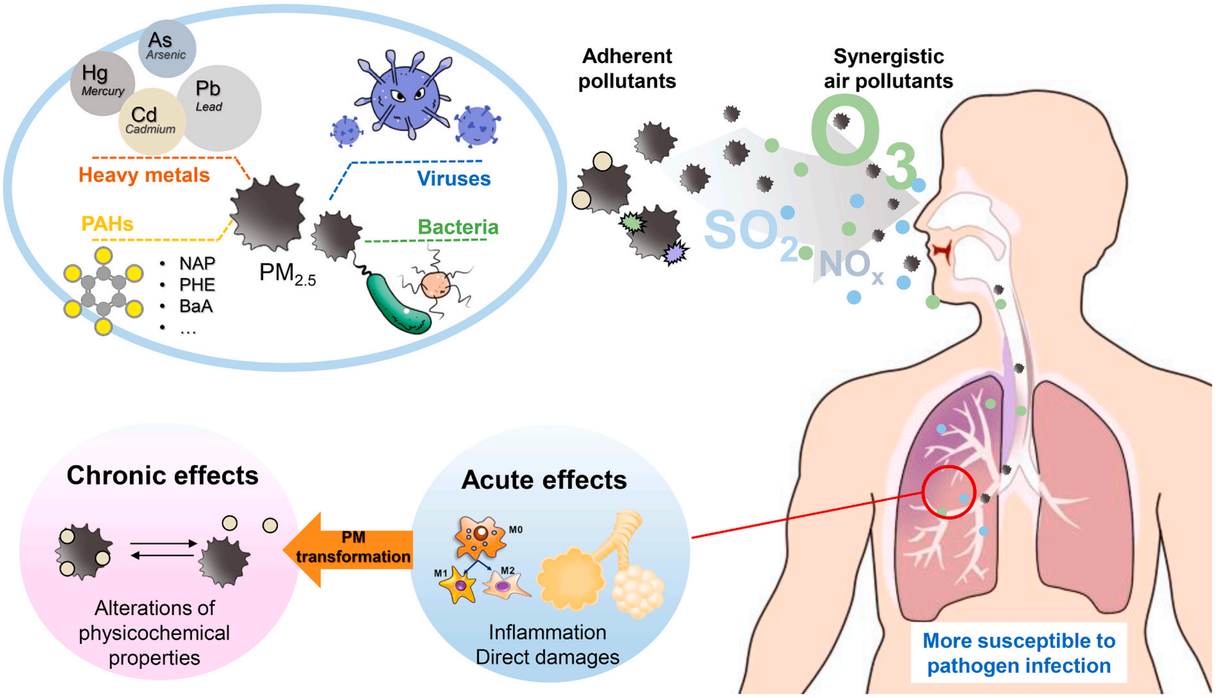

Fig. 2. Proposed schematic delineating the health risks of PMs plus active interplays with entangled pollutants and invading pathogens towards the respiratory system.

diseases and even impaired fetal growth (Huang et al., 2019; Guo et al., 2020). Moreover, many *in vitro* models have been developed for the investigation of detrimental biological effects of PM pollution for the purpose of searching molecular toxicological mechanisms (Valavanidis et al., 2013; Xia et al., 2016; Li et al., 2008). However, the current understandings on the health impacts and potential risks are still far behind the air pollution prevention and control in China, and there are many scientific knowledge gaps to be filled in this regard (Fig. 2). First, the current experimental systems for PM health impact evaluation are implemented without considering their realistic exposure doses and periods. For example, most *in vitro* and animal models bear a pronounced limitation of magnitude higher exposure concentrations of PMs than what could possibly be present in realistic atmosphere. Moreover, a portion of studies were carried out by employing suspensions of particulates for *in vitro* or *in vivo* exposure, which greatly differ from real exposure scenarios. These results therefore may pinpoint the mechanisms responsible for observed toxic effects for PMs but cannot predict their long-term effects under environmental exposure scenarios. Under this setting, future work should aim to illustrate the bio-risk of PMs under more realistic environment conditions. Second, research regarding toxic effects of pollutants that are adhered on PMs has also been a highly active topic. The high-risk components in PMs exhibit significant temporal-spatial variation (Tian et al., 2015; Han et al., 2019). Therefore, it has been argued that the infrastructure of PMs and laden pollutants (*e.g.*, polycyclic aromatic hydrocarbons (PAHs) and heavy metals) on PMs together account for the overall net toxicity (Fig. 2). PAHs and toxic heavy metals are often integrated into PMs through anthropogenic atmospheric emissions. Studies actually suggest that PAHs and heavy metals on PMs are deemed to be the determining causes of a range of diseases, ranging from asthma, emphysema to lung cancers (Betha et al., 2013; Franklin et al., 2008). However, the bio-availability of such pollutants once integrated on PMs, namely their release from particles in biological system, as well as their individual toxic effects, still remain elusive (Fig. 2). In addition, due to complex interplay of chemicals and unknown surface properties on PMs, the desorption mechanism of chemicals from PMs in biological settings and likely "Trojan Horse" (i.e. vehicle-conduced delivery) effects are intertwined and could not be readily differentiated (Liu et al., 2019a). Third, little is known about the potential bio-transformation of PMs in biological systems. Due to the large surface area and ample active functional groups, PMs would react with bio-molecules (*e.g.*, surfactants, enzymes and lipids) (Hu et al., 2017a; Qi et al., 2018), and PMs may catalyze the formation of reactive oxygen species (ROS) undermined cellular oxidative potential, leading to oxidative stress and even cell death (Jiang et al., 2019; Liu et al., 2019b). This process might also induce bio-transformation of PMs, which may alter their physicochemical properties, such as aggregation state, enzyme-mediated changes of functional groups and even degradation by biomolecules (Fig. 2). (Hu et al., 2017a, 2017b; Kotchey et al., 2011) The bio-transformation would consequently alter the bio-reactivity and bio-safety profiles of particles (Qi et al., 2018). Thus far, future work should aim to interrogate the toxicity mechanisms underlying PMs *per se* and their transformation under biological conditions.

Importantly, another previously underestimated issue is the transmission of pathogens through PMs and aerosols in the atmosphere as well as the indoor environments (Fig. 2). So far, only a few studies have looked into the interplay between pathogens (i.e., viruses and bacteria) and air pollution (Trinh et al., 2018; Liu et al., 2018; Sarkar et al., 2019). Although most reports documented that influenza virus dissemination relies on short-distance dispersion of droplets from cough or sneeze, mainly through indoor aerosols, a crucial role of PMs in facilitating virus transport in longer distance has been also proposed (Hammond et al., 1989; Liu et al., 2020). Moreover, mounting evidence suggests that air pollutants, *e.g.*, SO_2 and PMs, positively correlated to clinical influenza-like illness (ILI) in a few places in China, including Beijing, Hong Kong, Jinan and Hefei (Liu et al., 2019c; Su et al., 2019; Feng et al., 2016; Liang et al., 2014; Wong et al., 2009). Nonetheless, there are still controversies on the contributions of air pollutants to viral replication and dissemination based on the epidemiological analysis (Nenna et al., 2017; Zhao et al., 2019; Lee et al., 2019; Croft et al., 2019). It should be noted that both positive and negative correlation for O_3 with ILI has been reported in different population-based studies (Su et al., 2019; Wong et al., 2009), and these discrepancies need to be further examined by laboratory studies. Intriguingly, the current clinical data indicate that males are susceptible to SARS-CoV-2, because its commonly known receptor, ACE2, harbors higher expression in male populations (data collected by *The Human Protein Atlas*, https://www.proteinatlas.org), shedding light on potential pathogenic mechanisms. However, little is known about the impact of environmental factors (including PMs and associated contaminants) on the expression of ACE2. On this regard, it thus is rather important to obtain more data from epidemiological studies with larger population, and to bridge the knowledge gaps between the epidemiological findings and laboratory mechanistic studies.

Besides PMs, the other emerging challenge is the noticeable growth of annual average concentration of O_3 in recent years (Fig. 1). (Li et al., 2019; Chinese Bulletin on Environmental Conditions, 2013) Ozone is the main ingredient in photochemical smog, and is a highly reactive and oxidative gas associated with outstanding adverse health impacts (Zhao et al., 2018; Nuvolone et al., 2018). O_3 is mostly absorbed by the upper respiratory tract because of its low solubility in water (Bush et al., 1996), and inhaled O_3 would consequently react with the thin layer of epithelial lining fluid (ELF) (Nuvolone et al., 2018). The secondary oxidation products induced by O_3 in ELF would further cause cellular injury, inflammatory cascade and impaired immunity (Fig. 2). Moreover, animal studies unraveled that O_3 exposure may induce neuroinflammation and disturbance of neurotransmitter systems, which increases the risk of mental disorders (Zhao et al., 2018). In effect, these understandings mostly come from short-term experimental investigations. For more conclusive evidence on chronic health effects of O_3, such as mortality, length of life expectancy, effects on lung function and atherosclerosis and the onset of asthma, more long-term epidemiological and laboratory studies should be carried out in the future. Meanwhile, the O_3 health effects are supposed to interact with other air pollutants, such as NO_x and PMs, yielding great difficulties in teasing out these confounding variables in incurring toxicity (Fig. 2). To be specific, for even though epidemiological results suggested that acute exposure of PMs and O_3 would similarly cause the exacerbation of asthma (Rosenquist et al., 2020), rather limited studies have actually probed the concurrent effects from O_3 and PMs. Therefore, the synergistic health effect of O_3 and other air pollutants should be scrutinized in the next step of health effect evaluation of air pollution.

Together, the mass reduction oriented-control policy is desirable when the air pollution was serious in the past years. With the great decline in the total mass of air pollutants, more efforts should be devoted to accurate prediction of air pollution, precision control of specific components, and adequate insights into health effects under chronic exposure and upon altered pollutant profiles. Under this setting, many obstacles should be addressed in the future, such as the health risks of PMs and adherent pollutants, the interplays between the spread of airborne pathogens and air pollution, and the synergistic health effects of O_3 and other air pollutants. Hence, the focuses on health risks of air pollution should involve diverse fields, such as molecular biology, toxicology and environmental chemistry, epidemiology and even clinical medicine. The laboratory experimental systems also need to be improved to reach realistic atmosphere standards. Moreover, a more openly shared database for air conditions, toxicological results and epidemic data could be commonly shared and integrated worldwide. Thereby, filling in these fundamental knowledges would be surely beneficial in gaining new insights into health risks, a prerequisite of for policy-making of precision control of air pollution.

Declaration of competing interest

The authors declare no competing financial interest.

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