Gaps and future directions in research on health effects of air pollution

Ruzmyn Vilcassim[a,*] and George D. Thurston[b]

[a]Department of Environmental Health Sciences, The University of Alabama at Birmingham, School of Public Health, USA
[b]Departments of Medicine and Population Health, New York University School of Medicine, USA

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Summary
Despite progress in many countries, air pollution, and especially fine particulate matter air pollution ($PM_{2.5}$) remains a global health threat: over 6 million premature cardiovascular and respiratory deaths/yr. have been attributed to household and outdoor air pollution. In this viewpoint, we identify present gaps in air pollution monitoring and regulation, and how they could be strengthened in future mitigation policies to more optimally reduce health impacts. We conclude that there is a need to move beyond simply regulating $PM_{2.5}$ particulate matter mass concentrations at central site stations. A greater emphasis is needed on: new portable and affordable technologies to measure personal exposures to particle mass; the consideration of a submicron (PM_1) mass air quality standard; and further evaluations of effects by particle composition and source. We emphasize the need to enable further studies on exposure–health relationships in underserved populations that are disproportionately impacted by air pollution, but not sufficiently represented in current studies.

Keywords: **Air pollution; Exposure assessment; Health effects; Gaps; Future directions**

Introduction
Since the early establishment of air quality regulations in the United Kingdom in 1956 and the 1970 Clean Air Act in the United States, followed by similar governmental legislations across Europe and the rest of the world, air pollution levels have decreased considerably in most major cities in high-income countries that used to be primary hubs of industrialization and poor air quality not so long ago. Six 'Criteria' or 'classical' air pollutants were targeted by the United States Environmental Protection Agency (US EPA) and the World Health Organization (WHO): Ground-level ozone (O_3), particulate matter (PM), carbon monoxide (CO), lead, sulfur dioxide (SO_2) and nitrogen dioxide (NO_2). Standards and guidelines were imposed for each pollutant[1,2] initiating mitigatory measures. However, controlling air pollution has been more challenging globally, and levels of air pollutants have worsened in most large cities in low and low-middle income countries,[3] at times leading to historic air pollution episodes in cities such as New Delhi, Beijing, and Karachi.[4,5] In addition, as levels have declined in high income countries, new evidence has documented severe adverse health effects still occur even at their now lowered exposure levels.[6,7] Concentrations previously considered 'healthy' may now exceed the newer more stringent guidelines by the WHO, and frequent short-term excursions are observed even in usually 'low-pollution' cities. Thus, air pollution remains a major global environmental concern impacting human health, particularly among vulnerable groups and socioeconomically disadvantaged communities.[8,9] The Lancet Commission's 2019 report and the WHO have estimated that some 6.7 million premature deaths can be attributed to the combined impact of household and outdoor air pollution, primarily from increased mortality from cardiovascular and respiratory diseases.[10]

Over the past half century, exposure scientists, epidemiologists, and researchers of various related disciplines have made significant contributions in developing methods for monitoring and controlling airborne pollutants and investigating the harmful effects of exposure to air pollution. However, the chemistry of air pollutants, their behavior in the atmosphere/environment, and their interactions with biological systems are complex and, despite major strides in research, many unknowns persist. In 2010, an international specialty conference sponsored by the American Association for Aerosol Research (AAAR) titled "*Air Pollution and Health: Bridging the Gap from Sources to Health Outcomes*"[11] identified key needs to improve our understanding of air pollution related adverse effects: 1) a greater focus on multipollutant science that includes studies on mixtures and pollutant sources, 2) a better understanding of biological mechanism and associations of various health effects with sub-components of PM (e.g., submicron particles, elemental carbon, trace

*Corresponding author. Department of Environmental Medicine, UAB School of Public Health, 1665, University Boulevard, Birmingham, AL, USA.

E-mail address: ruzmyn@uab.edu (R. Vilcassim).

elements, and source-specific mixtures); 3) a further understanding of susceptibility of populations - including the role of genetics/epigenetics, the influence of socioeconomic and other confounding factors, and; 4) the addition of new technologies, such as 'micro-sensors', hybrid air quality modeling, and remote (e.g., satellite) sensing data.[11] While there have been significant improvements in addressing some of these concerns, many gaps identified at that time still persist.

Of the various air pollutants, greater importance has been attributed to the mass concentration of particulate matter (particularly PM with aerodynamic diameters smaller than 10 μm and 2.5 μm; PM_{10} and $PM_{2.5}$), due to studies showing stronger links between fine PM concentration and adverse health effects.[12] While, even to-date, the mass concentration of PM is used as the standard and main exposure metric in many studies, the AAAR conference attendees raised concerns that mass concentration alone does not appear to be a metric sufficient to fully and effectively evaluate the health effects of PM exposure: the size, source, and composition of PM and other physical properties also need to be considered in evaluating health effects. More recently, Nicolaou and Chekley (2021)[13] discussed deficiencies in air quality monitoring including, research on the long-term effects of exposure, lack of knowledge in relative toxicities from different sources and the joint and independent effects of multipollutant exposures, the impacts of ultrafine particulate matter, and importantly, the need for more effort in research in low-and-middle-income countries (LMICs), where exposures are highest, but data are sparse. In addition, attention has been drawn to gaps in our understanding of air pollution control and health, particularly on diseases spread by airborne pathogens.[14] Thus, most knowledge gaps discussed in the past still persist, although insights into some have advanced significantly in recent years, such as studies on epigenetic factors associated with air pollution exposure,[15,16] as well as analyses of source mixtures and metals more strongly associated with health outcomes.[17,18] In addition, improved understanding of the biological mechanisms regarding how air pollutants affect various organ systems, including cardiovascular, neurological, developmental, and metabolic systems, provide vital insights for other aspects of research including identifying susceptibility and possible treatments. For example, recent research has pointed to oxidative stress from fine PM containing both transition metals and acidic sulfates, such as emitted by fossil fuel combustion, as a likely important health impact causal pathway.[19]

Therefore, despite a long history of air pollution research, there is still much to learn about the interactions between air pollutants and human health systems, and the external modifying factors influencing this relationship. New challenges have emerged, in addition to the pre-existing issues and gaps in knowledge. In this viewpoint, we identify critical gaps in air pollution research/knowledge, and discuss future directions and their potential impact on air pollution related health risks along the following key themes: (1) Air pollution monitoring methods and technological limitations e.g. air pollution source and composition, number concentration vs. mass concentration, central vs. personal monitoring; (2) Exposure assessment uncertainties impacting health outcomes assessed and, (3) Regulatory standards and policies.

Gaps in monitoring methods and technological limitations

PM mass, size, composition, and source

While the U.S. EPA recognized the key role of fine particulate matter in the health effects of particles when it changed the U.S. ambient air quality standard from PM_{10} to $PM_{2.5}$ in 1997,[20] further progress has been lagging in its regulation to better monitor and focus regulation on those fine particles that are most toxic, which varies within $PM_{2.5}$ depending on size, composition, and source. The growing evidence that the most toxic particles are among the submicron size (e.g., nanoparticles), and from sources emitting the most toxic mix of constituents (e.g. fossil fuel combustion), is yet to be addressed in regulations, or in most PM air pollution studies.[21] While some have called for the conduct of site-specific epidemiological studies of $PM_{2.5}$ health effects in every locality to address the variation in $PM_{2.5}$ toxicity per unit mass[22], *the development and application of source sector-specific and composition-specific health effect estimates (e.g., for those with the highest risk per $\mu g/m^3$) would more efficiently allow the derivation of more locally appropriate site-specific health effect coefficients, based on local measurements of $PM_{2.5}$ source and composition, sidestepping the need for multiple epidemiological studies in each locality*. Thus, better quantifying source and composition-based air pollution associated health impacts needs to begin with more detailed particulate matter monitoring when evaluating air pollution levels over space and time.

In most countries and cities, air pollution concentrations are obtained via central fixed reference-grade ambient monitors. In the U.S., the EPA has established a large network of central ambient monitors, mainly to measure and meet federal regulatory NAAQ standards, which are based on either hourly, daily and/or annual averages of overall mass concentration. In addition, the U.S. EPA has established a more limited Chemical Speciation Network (CSN) that are useful in evaluating variations in $PM_{2.5}$ composition, as well as useful for the estimation of source-specific exposure levels at those sites and at intervening locales using land use regression methods (e.g., see Rahman and Thurston, 2021).[23] Such data have proved useful in discriminating the varying health effects of different $PM_{2.5}$ components, but more such composition-based analyses of $PM_{2.5}$ samples and their health effects at more sites around the world are needed to enable more location-specific health effects estimation, enabling more health benefit optimized $PM_{2.5}$ mitigation policies. The expansion and maintenance of a worldwide CSN will be financially and technically challenging, added by the complexity of chemical compositions of various PM components. However, the data generated from such methods are key to connect epidemiologic findings with toxicological findings, as demonstrated in the NPACT study in the USA.[18,24] The studies conducted under the NPACT initiative were key in identifying source components of PM which have greater potential to cause harm, as well as to identify the challenges and complexities that need to be addressed to understand the mechanisms of individual component toxicities.

Since particulate matter derived from sources most often associated with the adverse health effects of $PM_{2.5}$ (e.g., fossil fuel combustion particles) are found in the submicron part of $PM_{2.5}$ mass, we also recommend another, simpler, approach to focus mitigation on the most toxic particle sources: switch from monitoring and regulating $PM_{2.5}$ to PM_1 (particles less than 1 μm in aerodynamic diameter) mass. This is consistent with the past progression in particle mass regulation from Total Suspended Particulate Matter (TSP), to inhalable particulate matter (PM_{10}) to fine particulate matter ($PM_{2.5}$). While this concept has been in discussion among air pollution scientists in recent years, perhaps the main challenge for implementation of a PM_1 standard was the lack of evidence of associated health benefits in the past. PM_1 is not monitored in the U.S. and many other major cities, limiting the number of studies that investigate associations between PM_1 levels and health outcomes. However, in recent years there has been a growing body of epidemiology results finding stronger health associations with PM_1 mass than with $PM_{2.5}$. For example, Yang et al. (2020) recently found that "Associations with lower lung function were consistently larger for PM_1 than for $PM_{2.5}$.[25] Guo and colleagues (2022) evaluated the varying associations of the incidence rate of female lung cancer with PM_1, $PM_{2.5}$, and PM_{10} in 436 Chinese cancer registries and demonstrated that the association with the incidence rate of female lung cancer was stronger for PM_1 than for $PM_{2.5}$ or PM_{10}.[26] Similarly Hu et al. concluded that their mortality studies found greater PM_1 effects per $\mu g/m^3$, and that "To effectively reduce the adverse health effects of PMs, more attention should be paid to fine and very fine particles".[27] Clearly, further air pollution monitoring of PM_1, and epidemiological studies comparing $PM_{2.5}$ vs. PM_1 associations with adverse health are needed in order to confirm the case for PM_1 based air pollution control and regulations.

Monitoring of personal exposures

While central monitors provide a very useful estimate of a region's typical pollution levels, they are of limited use in providing estimates of personal-level exposures.

- First, the number of residents represented by a central monitor can vary significantly within a country and between countries. In Europe and North America, the estimates are about one monitor per 100,000–600,000 residents, while in contrast, across sub-Saharan Africa one ground-level monitor represents about 15.9 million residents.[28–30]
- Second, central site monitors do not represent concentrations in varying microenvironments and occupational settings, which may be higher. For example, it has been found that street level NO_2 exposures in a city can be significantly higher than measured at a regulation air monitoring site located just a few stories above.[31]
- Third, when the interest is to study the health effects of smaller targeted populations, including vulnerable communities that may live in areas that do not have central monitors, they provide little information on personal exposure levels in populations that may be more strongly linked to health outcomes.

However, it is important to note that, despite these limitations of stationary monitoring, consistent associations have still been found in epidemiological studies over large populations using central monitoring data in different geographical regions. More focused exposures are needed to consider more sensitive subpopulations.

Advanced modeling of higher spatial resolution exposures using central monitor data as inputs have provided more spatially detailed estimates, such as via Land Use Regression (LUR) models, and satellite estimates of surface PM concentrations.[23,32] However, LUR and air quality models require extensive monitoring, meteorological data, and built environment information,[33,34], and may not be broadly applicable to other locations. Similarly, satellite estimates of PM, while more spatially comprehensive, may have errors in the range of 22–85% if they are not cross-validated by ground level monitoring data, and are also impacted by other atmospheric conditions and particles in the atmosphere.[28] Due to such limitations, accurately estimating air pollution exposures for epidemiological studies still remains a challenge, contributing to variations in the estimations of health effects per amount of exposure, particularly in LMICs and rural areas in high-income countries, where central monitor coverage is more sparse.

This brings us to a more accurate approach for the estimation of individual level exposures to air pollutants-personal monitoring. Personal monitor sampling at breathing level provides the most accurate time-integrated exposures and variations of an individual's exposure.[35] For example, van Nunen et al. (2021) successfully employed 24-h personal monitoring of $PM_{2.5}$, ultrafine particles, and soot concentrations to study their associations with blood pressure and lung function changes.[36] Xie et al. (2021) simultaneously obtained PM measurements from personal monitors and regulatory monitors to study exposures in individuals with asthma, and demonstrated that the portable monitors were better able to capture personalized air quality information compared to the traditional method.[37] However, despite these advantages, the wide use of personal monitors for exposure studies is limited for several reasons. Personal monitors and methods that have been validated and are of research grade have been expensive and require initial training to use, particularly for monitoring of gases and volatile organic compounds (VOCs). Examples for PM personal monitoring methods and devices include gravimetric analysis using portable pumps and filters, as well as light scattering-based nephelometric devices, which can cost in the range of $7000 - $8000 per unit. Therefore, monitoring exposure concentrations of a group/population has been limited by the number and cost of research-grade personal monitors available. Thus, although personal monitoring can provide more accurate estimates of individual and sensitive subpopulation exposures, these limitations have prevented them from significantly advancing the field of air pollution and health studies, as compared to the contribution from studies that have used central-site monitoring data.

In recent years, however, the goal of higher spatial and time resolution individual level air pollution monitoring has been made more attainable by the introduction and rapid advancement of **low-cost sensors**. Low-cost sensors (LCS) are expected to be an important development in the future direction of more democratized, high resolution, and inter-connected air (and health) monitoring, generating 'big data' for complex, but more inclusive, research. In addition to being inexpensive, mobile, and light weight, currently available LCS are smartphone compatible, which has greatly increased their appeal among concerned citizens and environmental non-profits, allowing monitoring among those who could not previously afford the traditionally more expensive personal monitoring equipment. LCS are also typically linked via GPS, and are used for crowdsourcing and identifying air pollution 'hotspots' in cities.[38] Recognizing this, the U.S. EPA has developed a comprehensive program to test and validate currently available low-cost air monitoring devices against reference grade and/or more advanced instruments, which is a major step in testing their capabilities for research.[39,40] A significant body of research has now been done to test and use LCS for personal exposure monitoring, demonstrating their potential for use in research, with proper quality control.[38,39,41,42] Importantly, their advantages make low-cost sensors a strong candidate for studies in LMIC, where resources for environmental monitoring are more scarce.

Despite the numerous advantages of low-cost air monitoring sensors, their accuracy may be limited as measurements can be biased by variations in the ambient environment, inter-instrument variability, limitations in the range of concentrations that can be measured, and concentration plateauing due to signal saturation above certain levels - typically above 100 μg/m^3.[41,43] They have also been found to underperform in lower pollution settings, demonstrating poor agreement with more advance instruments below 40 μg/m^3.[44] Therefore, they are most accurate and have high agreement with reference instruments only within a particular range.[42,43] Sensor 'aging' drift is also a concern.[41] In very high concentration situation LCS may also become saturated, and fail to accurately assess extreme concentrations. Therefore, scientists and the U.S. EPA have recommended periodic calibration of low-cost devices with more advanced or reference instruments to achieve data quality and accuracy.[39,43,45,46] In addition, prior to use in studies, they require continuous development and evaluation of calibration protocols and algorithms, which, if not done, can lead to uncertainties in obtaining reliable and timely air quality data.[42] Indeed, monitoring data quality has been found to improve LCS performance significantly after calibration.[46] Another challenge in LCSs is the lack of a physical size 'cut-point' that are designed into advanced instruments. Sensors estimate particle size using an internal algorithm, which at times have been found to be different from reference instruments.[41] However, overall, LCS present a great potential to be a powerful tool for augmenting central site air quality monitoring data with higher resolution, particularly for research in communities in LMIC and other areas that are unable to afford central site reference monitors.

Other developments in methods and technologies for personal monitoring that have seen progress in recent years and have future potential include, low-cost wearable sensors to measure health biometrics,[47,48] and non-invasive health biomarker analysis methods, such as breath biopsies.[49,50] These methods, combined with low-cost air monitoring devices, could be used to generate high resolution exposure-health metrics for scientists and medical professionals in studying and mitigating the health impacts of air pollution.

Exposure assessment uncertainties and exposure misclassification due to movement between environments with varying conditions

Advancements in monitoring instrument technologies, statistical and modeling methods, and high-resolution geographical mapping have improved our ability to better estimate exposure concentrations of populations in regions of interest, such as in communities living close to a powerplant, or children exposed to vehicle emissions when they live near highways. Recent research indicates that epidemiological effect estimates of $PM_{2.5}$ health effects are robust to the choice of $PM_{2.5}$ exposure assessment spatial resolution.[51–53] However, individuals move between 'microenvironments' with varying sources and concentrations, and failing to incorporate these variations may still lead to exposure misclassification and/or exposure estimation errors. Exposure estimation errors may be exacerbated among those living outside an urban core, or when time is spent in microenvironments with higher than average air pollution within the urban core.[54] More epidemiological studies that incorporate study participant mobility into exposure assessments are needed, which may now be more practical, given the improvements and cost reductions in personal particulate matter monitoring equipment, and the common availability of cell phones for data storage and transmission.

We particularly note two venues of air pollution related health exposures that impact a large number of individuals, but have lacked sufficient attention and need further exposure - health effects investigations. They are: *(a) when traveling to polluted cities abroad (particularly international travel) and, (b) when using major transit systems, especially in underground subway systems.*

Air pollution health risks when travelling

Until the coronavirus disease (COVID-19) pandemic, international tourist arrivals had been steadily increasing with approximately 1.4 billion worldwide arrivals in 2019.[55,56] After a significant drop in 2020 and 2021, recent estimates show an increasing trend, and international tourism climbed to nearly 60% of pre-pandemic levels in January–July 2022.[56] During travel, a large population of individuals may be exposed to air pollution concentrations and compositions that significantly vary from their home city/country, especially when they travel to popular destinations in Asia, Africa and South America. Megacities in these regions have poor air quality which are known to exceed local and WHO guidelines by several levels of magnitude.[4,5,57] However, although billions of individuals travel internationally, there is very limited research addressing the impact of air pollution on travelers' health.[58]

Travelers may experience a large differential in ambient exposure concentrations and composition within a short time of air travel, increasing their risk of air pollution related injury compared to residents who are more likely to be adapted to local conditions and knowledge. Although limited in number, existing studies have indicated that exposure to elevated levels of $PM_{2.5}$ in cities abroad can be associated with adverse cardiopulmonary health impacts, including a reduction in lung function, increase in respiratory symptoms and, and impacting quality of life.[58–60] Importantly, most study participants recovered from symptoms after returning to home cities. Other studies provide evidence of systemic pro-oxidative and proinflammatory effects associated with travel-related exposure to air pollution, where the elevated levels of biomarkers were interestingly reversed after the participants returned to their home city.[61] In this study, exposure to Polycyclic Aromatic Hydrocarbons (PAHs) in cities traveled to altered oxidative metabolism, which can be attributable to ambient air pollution exposure.

In addition to air pollutant exposure related health risks, travelers may be unpredictably impacted significantly by climate-related events, which are expected to particularly affect vulnerable urban areas in South Asia, East Asia and the Pacific.[62] Rising global temperatures can increase the frequency of 'extreme events' such as floods, heatwaves, dust storms and wildfires, and increases in air or water pollution, thereby elevating health risks, and causing population displacement in affected regions. Thus, global warming is expected to contribute to human mobility, leading to increased migration and travel to regions that are perceived to be 'safer'.[63] While studies on migrant health are emerging, there is a need for more studies linking previous and 'new' exposures of migrant populations to cardiovascular and respiratory health outcomes.[58,63]

Despite these concerns faced by travelers and migrants, insufficient studies have further explored short and long-term health outcomes associated with visiting or temporarily migrating to polluted cities for work, safety, education, leisure etc., especially among vulnerable groups such as older, pregnant, and other susceptible travelers.[58] Adding to the difficulty of conducting such studies is the need to adjust for many confounders, such as stress, temperature changes, changes in diet and water intake, alterations in sleep and sleep patterns, effects of changing altitude, and infectious/transmissible diseases. Studies on physiological outcomes and biomarkers that can detect early cardiovascular effects due to air pollution exposure during international travel will be important to warn elderly and susceptible travelers of risks of traveling to polluted destination cities, prior to travel. Given that cities are increasingly connected via travel, their residents and visitors present dynamic interdependent systems in concert with variable air pollution profiles. Therefore, we suggest that future epidemiological studies that explore ambient PM associated all-cause, cardiovascular, and respiratory mortality not consider populations in individual cities as a static entity, but also strive to consider travel related exposures as a potentially significant component of disease risk when evaluating such outcomes.[64]

Air pollution health risks in subways

Underground subway/metro systems move large numbers of people daily, and further growth in such systems are expected.[65,66] Although commuters spend a relatively shorter time on subway platforms, daily exposures to peak levels may significantly impact health. However, despite several studies documenting very high levels of PM exposure in underground systems, especially in North America, Europe,[65,67–70] we are unaware of studies that have yet comprehensively evaluated the health risks of inhalation of high levels of varying compositions in this unique environment. Subway $PM_{2.5}$ levels have shown to be elevated several fold over ambient levels even in busy cities, and contain higher proportions of iron and other metals, such as manganese and chromium.[65,68] High elemental carbon levels have also been reported in subways that utilize diesel-powered maintenance trains.[70] Except for some studies indicating that exposure to subway particles causes inflammation in lung epithelial cells and oxidative stress in exposed workers,[71,72] the health implications of repeated relatively brief, but very high, pollution exposure levels in subways are largely unknown. Further complicating the issue is the ambiguity of classifying the subway environment for regulatory purposes. Should outdoor ambient standards apply, and if so who has the authority to regulate pollution levels in subways? Or is it considered an 'indoor' environment? These legal questions remain unanswered, limiting our ability to evaluate the possible mitigatory options. Pollution mitigation approaches, such as improved ventilation in subway platforms and cars, and the use of electric/battery powered maintenance equipment for system maintenance, are suggested, and may also reduce virus transmission risks at the same time.[73,74] Further research on subway air quality is needed, especially as a large population of commuters around the world is expected to increasingly rely on these systems in the future.

Regulatory standards and policies impacting health

The establishment of ambient air quality standards around the world, particularly in North America and Europe, has greatly improved air quality in many regions compared to levels before they were established, and prompted improvements in air monitoring, technological advancements in emissions control technology, and more environmental friendly practices in industry.[75–77] In the U.S., these gains in air quality reduction benefits were made even as the economy has grown.[77] Legislation in Europe led to the rapid growth in monitoring stations, and progress was made towards improving air quality over time, despite some challenges such as rising O_3 levels in many European cities[76] In recent years, cities such as Beijing, which had extremely poor air quality in the past, has achieved sizable and steady declines in ambient air pollution levels due to stricter control measures on emissions, and particularly on coal burning.[78] Such significant reductions in $PM_{2.5}$ and PM_{10} concentrations in 74 key cities in China (between 2013 and 2016) were shown to be associated with substantial reductions in mortality and years of life lost.[79] Thus, air quality regulations and action plans have overall reduced air pollutant levels and improved the lives of affected populations. However, there is still much to do on improving standards and policies, particularly considering the emerging knowledge on the complexity of particulate air pollutants and recent studies demonstrating inequalities in air pollution exposure and health disparities among historically disadvantaged and vulnerable (due to economic and environmental disasters) populations.

Recent research indicates that there is no known threshold of PM and other pollutants' health effects (e.g., see US EPA, 2019[80]), while reductions will likely become more challenging to implement as regulatory $PM_{2.5}$ mass concentration limits decrease. As a result, the focus on mass without consideration of variations in composition toxicity has the potential drawback that the fine mass constituents that contribute the most mass may become the focus of controls, even if they are not the most toxic constituents. For example, some have recently recommended focusing on controlling gaseous ammonia releases in order to lower $PM_{2.5}$ because it reacts with ambient sulfuric and nitric acid to form particulate matter,[81] but that step would lead to more acidic (less neutralized), and likely much more toxic, particulate matter that remains in the air, likely leading to increased toxicity per unit mass.[82] Therefore, it would likely be more health efficient to consider focus additional PM regulation on the most toxic constituents of $PM_{2.5}$, or on the submicron subcomponent, of the mass PM_1. As discussed above, this concept has been in discussion for many years,[83] but now may well be the time for its implementation.

The issue of varying $PM_{2.5}$ composition and toxicity also has implications to standard and Air Quality Index (AQI) interpretation. In contrast to the setting of a single AQI for individual gaseous pollutants, such as ozone, which is the same compound everywhere, the setting of a single world-wide AQI for particulate matter is less defensible, because $PM_{2.5}$ varies widely in its size distribution, composition, and dominant source, and likely in its toxicity to humans per $\mu g/m^3$, from place to place. Thus, the above discussed need for the assessment of $PM_{2.5}$ exposures and health impacts as a function of size, composition, and source is directly relevant. Such studies would be useful for the setting of locality-specific $PM_{2.5}$ AQI values, For example, a recent study of pollution in Dhaka, Bangladesh found that the hospital admissions and mortality impacts of fossil-fuel combustion $PM_{2.5}$ has a much larger impact per unit mass than biomass related $PM_{2.5}$ in Dhaka.[84] Since biomass burning dominates the $PM_{2.5}$ mass in Dhaka, it may be that the overall health impacts of $PM_{2.5}$ are less per $\mu g/m^3$ than in the developed world cities where the WHO guideline studies were primarily conducted, and so it may well be that a higher AQI guideline would be appropriate in Bangladesh than in the US or Europe. Similarly, windblown sand is a large component of the $PM_{2.5}$ in the Middle East, unlike where $PM_{2.5}$ epidemiological studies have been conducted. Thus, it stands to reason that $PM_{2.5}$ AQI adjustments need to be made, depending on the region and particularly the primary sources of air pollution in that state or nation.

Environmental justice considerations make clear that the environmental health protection improvements suggested here for regulations and policies must most pressingly be applied to address those most affected by air pollution. Growing evidence has established that the burden of air pollution is not equally shared, and socioeconomically disadvantaged populations and certain racial and ethnic groups often face higher exposure to pollutants and greater responses from air pollution.[8,85–87] Thus, future research, education and air pollution control policies should consider their impact on groups most affected, and make an effort to mitigate inequities during the planning and implementation stages. For example, Wang Y et al. (2022) have shown that national inequalities in air pollution exposure can be eliminated with fewer emission reductions if those reductions target the most heavily burdened locations, rather than implementing across the board national standards (Fig. 1).[88]

The exposome and precision environmental health in air pollution research

Recent scientific discussions on the future of the field of environmental health have highlighted the importance of integrating knowledge from various related disciplines. Focus has been drawn to utilizing 'exposomics' which is based on the concept of the 'exposome'-the totality of all exposures in an individual's life course.[89] Although the exposome is not a new concept, the realization that average exposures alone cannot explain disease spread or occurrence has highlighted the importance of considering the variations and complexities of the pollutants, and their interactions with individual and population characteristics over space and time. Thus, the concept is gaining increasing applications in environmental health and toxicology studies. Early prediction and avoidance of diseases has gained greater importance, combined with a push towards more precise individualized treatments for exposure associated diseases.[90]

Precision environmental health, predictive and translational toxicology, social justice, and health disparities have been identified as key areas for future development of environmental health, as well as climate change and innovative computational methods for data analysis. For example, an expert panel from the National Academies sponsored by the National Institutes of Environmental Health Sciences (NIEHS) has identified areas that the biomedical community can use to integrate environmental health science into broader studies of human health.[91] Such integration of exposure data, 'omics' data, and personal health information will greatly improve our ability to predict air pollution related diseases (i.e. using predictively toxicology approaches) and implement more targeted early prevention strategies. However, for precision medicine to be effectively integrated with exposomics and to be utilized for predicting and preventing air pollution related diseases, the focus has to be expanded from genetic or molecular studies alone to also incorporate environmental factors that determine disease progression. Despite the available technologies, researchers have expressed concern that environmental or exposure related issues are rarely considered in current precision medicine programs.[90] Nevertheless, there is huge potential in integrating exposomics and precision medicine methods in future environmental health research, especially when combined with personal wearable monitors, advanced analytical methods, and modern artificial intelligence capabilities.

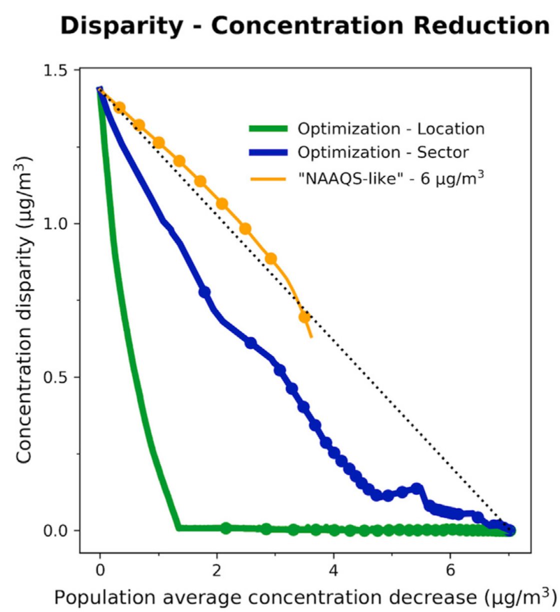

Fig. 1: **$PM_{2.5}$ exposure-disparity and concentration-reduction curves**. Each panel compares three approaches to emission reduction: location (green line), sector (blue line), and NAAQS-like (i.e., employing a concentration standard; here, 6 μg/m^3; orange line). An "equal reduction" approach, where all emissions are reduced proportionately, would be a straight line (black dotted line). The location approach (green line) can eliminate national disparities with modest total emission reductions. Fig. 1 was obtained from [88] with permission from the corresponding author.

Discussion

While acknowledging that the field of air pollution and associated health effects is robust and ever growing, and that scientists throughout the years have greatly contributed to the understanding and betterment of the science, we have identified key gaps and future directions especially needing attention in current and future studies and policies (as summarized in Table 1). Future directions will be influenced by technological developments and more advanced methods of particulate matter air quality

Gaps/limitations identified	Current status	Suggestions/future directions
Air pollution monitoring		
- $PM_{2.5}$ mass concentration determines standards. - Central fixed monitor-based air pollution estimates.	Current standards are based on only mass concentration, not particle characteristics. Air pollution exposure of individuals are calculated/modeled based on fixed location estimates assuming the population within a particular radius is exposed to the calculated concentrations; central monitors are limited and primarily located in urban areas. Air monitoring coverage in LMICs are needed, but very limited.	Monitoring, policy analysis, and regulation needed by particle composition. Source-sector specific health effect estimates are needed, as well as submicron, PM1, mass monitoring. More extensive personal monitoring using low-cost sensors and methods, use of satellite data in combination with sensors for better personal estimates, better air pollution exposure models that integrate data from various sources, improved software and prediction capabilities. Open source databases of air pollution data, including data on LMICs, affordable technology, and collaborations between scientific resource rich and resource deficient countries.
Exposure assessment uncertainties		
Examples of interest: - Exposure during visits to polluted cities. - Exposures in underground transit systems.	Disease risks are often based on exposures estimated from central monitors, not incorporating variations in microenvironments and personal exposure variations. Despite over a billion individuals traveling to international destinations annually, where air pollution levels vary from their home cities, only limited research has explored the health implications of exposure to such varying level and compositions. Although limited, emerging studies have found very high levels of PM in underground systems, particularly high levels of metals; and few studies have explored the health effects/risks.	Personal monitoring with low-cost devices; factoring in study participant mobility; consider the total exposures (Exposome), and apply data for precision medicine to identify and mitigate health outcomes. Further studies and understanding of the physiological changes associated with exposure to varying air pollution during travel, studies on travel health - future travel and migration is expected to increase; early warnings for vulnerable populations. Studies on the health risks commuters and workers face due to being exposed to high levels of subway air pollution, which may be high in iron and black carbon, are warranted.
Regulatory standards and policies		
	Stringent standards and policies in HICs; resources for research and policy implementation have yielded significant improvement in HICs. In-contrast – although exposed to high levels, data, research and standard implementation is very limited in LMICs; increased risk of air pollution related cardiovascular mortality. Current air quality indices (AQIs) are based on considering PM in all regions as equally toxic, despite research to the contrary.	More interest and resource sharing with LMICs needed, as well with underrepresented and socioeconomically disadvantaged communities in HICs; local solutions needed for local problems and increase education and awareness. Considering PM composition and source when setting of locally appropriate AQIs could maximize the health benefits of pollution mitigation measures.

HICs, High-Income Countries; LMICs, Low- and Middle-Income Countries; PM, particulate matter; AQIs, Air Quality Indices.

Table 1: **Summary of gaps and future directions in air pollution research and mitigation.**

measurement, modeling, analysis, and regulation, such as focusing future additional regulation on the most health threatening particles, such as PM_1. On the other hand, other air pollutants, such as volatile organic compounds, nanoparticles, emissions from new technologies and industrial processes, emissions from e-waste disposal and burning also need attention and further investigation as to how more efficiently to mitigate their risks. Occupational exposures, medical exposures, and immune responses to 'new' and more toxic pollutants are other areas of research (among many others) that would also warrant attention and new methodologies for assessment.

Thus, the present and future of environmental health and air pollution research present many challenges, such as changing pollution source mixes and characteristics over space and time, but also new opportunities, as technology opens new exposure measurement possibilities. Strong international cooperation is needed between countries/communities with resources and those that do not, for more extensive and advanced exposure data collection and dissemination, research knowledge, and resource sharing, so that these new methods and technologies become accessible in LMICs and burdened communities, as well. In this way, there is the potential to achieve a world in which scientific collaborations, using more globally accessible methods-such as remote and low-cost sensors, open source data platforms, and capacity building programs, can greatly influence and mitigate air pollution related health risks, enabling better informed, fair, and more equitable environmental health solutions for all.

Contributors
Both authors (RV and GDT) contributed to the conceptualization, preparation of the original draft, and editing of the manuscript. Both authors read and approved the final version of this manuscript.

Data sharing statement
Not applicable.

Declaration of interests
The authors declare no completing interests.

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