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Outdoor Air Pollution and New-Onset Airway Disease

An Official American Thoracic Society Workshop Report

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Abstract

Although it is well accepted that air pollution exposure exacerbates preexisting airway disease, it has not been firmly established that long-term pollution exposure increases the risk of new-onset asthma or chronic obstruction pulmonary disease (COPD). This Workshop brought together experts on mechanistic, epidemiological, and clinical aspects of airway disease to review current knowledge regarding whether air pollution is a causal factor in the development of asthma and/or COPD. Speakers presented recent evidence in their respective areas of expertise related to air pollution and new airway disease incidence, followed by interactive discussions. A writing committee summarized their collective findings. The Epidemiology Group found that long-term exposure to air pollution, especially metrics of traffic-related air pollution such as nitrogen dioxide and black carbon, is associated with onset of childhood asthma. However, the evidence for a causal role in adult-onset asthma or COPD remains insufficient. The Mechanistic Group concluded that air pollution exposure can cause airway remodeling, which can lead to asthma or COPD, as well as asthma-like phenotypes that worsen with long-term exposure to air pollution, especially fine particulate matter and ozone. The Clinical Group concluded that air pollution is a plausible contributor to the onset of both asthma and COPD. Available evidence indicates that long-term exposure to air pollution is a cause of childhood asthma, but the evidence for a similar determination for adult asthma or COPD remains insufficient. Further research is needed to elucidate the exact biological mechanism underlying incident childhood asthma, and the specific air pollutant that causes it.

Keywords: air pollution; asthma; COPD; new-onset airway disease

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Overview

This workshop was convened to evaluate the evidence regarding outdoor air pollution as a causal factor in the development of new-onset asthma and/or chronic obstructive pulmonary disease (COPD). The available evidence on epidemiological associations, biological mechanisms, and clinical considerations was evaluated. Workshop participants presented the current state of the science in their respective fields, based on their expertise and review of the latest research available. Key conclusions and recommendations included the following:

- The weight of the evidence is consistent with a causal relationship between new onset of childhood asthma and long-term exposure to outdoor air pollution, especially metrics of traffic-related air pollution (TRAP), such as nitrogen dioxide (NO_2) and black carbon (BC).
- It is unclear whether direct effects of NO_2 (the best-studied TRAP component in epidemiologic studies) or other components of TRAP, such as fuel combustion particles (implicated in toxicologic animal studies), explain the causal link with asthma.
- Further studies are needed to determine whether the relationships found in TRAP studies can be generalized to air pollution from other combustion sources, and to assess the impact of air pollution on the development of adult-onset asthma and/or COPD.
- The reduced incidence of new onset of childhood asthma should be included in future assessments of the health and monetary benefits of lessening exposures to air pollution, especially TRAP.

Introduction

Acute exacerbation of existing respiratory diseases by air pollution is well established and is commonly factored into the decision-making process of policymakers. For example, short-term outdoor air pollution exposures, including fine particulate matter (particulate matter less than or equal to 2.5 μm in aerodynamic diameter [$PM_{2.5}$]) (1), ozone (O_3) (2), NO_2 (3), and sulfur dioxide (4) have been accepted by the U.S. Environmental Protection Agency as causally related to acute adverse respiratory health effects. The effects of air pollution on asthma include acute associations with increased symptoms (5), rescue medication use (6), school absences (7, 8), emergency department visits (9, 10), hospitalizations (11, 12), asthma lung function deficits (13–15), and airway hyperresponsiveness (16), Similarly, documented adverse COPD health associations with short-term $PM_{2.5}$ exposures include reduced pulmonary function (17) and increased emergency room visits (18), hospital admissions (19), and mortality (20).

Compared with acute exposures and health effects, it has been more challenging to study and evaluate the effects of long-term exposure on incident disease; thus, less evidence has been available in the published literature. However, there is growing evidence that long-term outdoor air pollution exposures may also cause new onset of airway disease. This Workshop was convened to evaluate the evidence of outdoor air pollution as a causal factor in the development of new-onset asthma and/or COPD.

Methods

At the annual American Thoracic Society (ATS) International Conference in May 2018, a cross-disciplinary group met to evaluate the evidence regarding the potential role of air pollution in the onset of new airway disease. The group included researchers experienced in the mechanistic aspects of airway disease development, air pollution epidemiologists, and clinicians with expertise in airway disease pathology/diagnosis. Participants presented the current state of the science in their respective fields, based on their expertise and a review of latest research available on their specific topics. This is a consensus document, rather than a formal systematic examination of all the evidence. Consensus was reached by majority vote. A writing committee summarized the Workshop findings, which all participants could review for an accurate reflection of the proceedings. Potential conflicts of interest were handled in accordance with the policies and procedures of the ATS.

We focused on the development of new-onset asthma or COPD related to outdoor air pollution exposure by addressing several key questions:

- Does the available epidemiologic evidence concerning long-term air pollution exposure support an association with new-onset asthma or COPD?
- Are there biological mechanisms by which air pollution could plausibly cause new asthma or COPD?
- Are the health effects of air pollution identified through epidemiologic and mechanistic studies consistent with the diagnosis of new asthma or COPD in a clinical setting?
- Is there sufficient overall evidence to conclude that long-term exposure to air pollution contributes to the induction of new asthma and/or COPD?

In this Workshop report, we first summarize the epidemiological associations found to date, and then assess whether these associations are biologically and/or clinically plausible.

Epidemiological Evidence

Air Pollution and New-Onset Asthma

Epidemiologic evidence linking exposure to air pollution with the development of new-onset asthma has grown in recent years. Many studies have focused on surrogate metrics of TRAP, as well as individual ambient air pollutants. Commonly studied TRAP components include nitrogen oxides, NO_2, BC, $PM_{2.5}$, and PM less than or equal to 10 μm in aerodynamic diameter (PM_{10}).

Nitrogen Oxides, BC, $PM_{2.5}$, and Other Traffic-related Pollution

TRAP studies in children. TRAP exposures were previously evaluated as a cause of childhood or adult-onset asthma in Health Effects Institute (HEI) Special Report 17 (21). This 2010 publication concluded that living near busy roads is a risk factor for onset of childhood asthma, but the data were insufficient to conclude causality. Several studies on the topic have been published since the release of that report. For example, the Southern California Children's Health Study (CHS) found an increased risk of new-onset childhood asthma from TRAP at home residences (22). Khreis and colleagues subsequently synthesized 41 studies that focused on children's TRAP exposures as a potential cause for asthma development (23), and found associations with TRAP metrics, especially NO_2. (Figure 1). A 2017 meta-analysis of 18 studies of prenatal air pollution exposures and childhood asthma similarly found associations for NO_2 and PM_{10} (24). Findings were null for O_3 and $PM_{2.5}$ mass (perhaps indicating that effects varied by the $PM_{2.5}$ constituent or source). Other primary studies indicated that TRAP, including prenatal exposure, contributes to childhood asthma development (25–33).

In addition, in the United States, Latino and black populations disproportionately live in neighborhoods with higher air pollution levels (34). Puerto Ricans and black individuals have a higher prevalence of asthma than white individuals (35). The largest study of air pollution and incident childhood asthma in U.S. minorities found that early-life NO_2 exposure was associated with childhood asthma in Latinos and African Americans (36). Since this Workshop was convened, a multilevel longitudinal study drawn from three waves of the CHS over a decade of air pollution decline found that decreases in ambient NO_2 and $PM_{2.5}$ between 1993 and 2014 were significantly associated with lower asthma incidence (37). This study is consistent with an inference of causality in the association between air pollution and asthma incidence, as an intervention to reduce exposure was followed by a reduction in disease incidence.

TRAP studies in adults. A review and meta-analysis of cohort studies found a positive association between NO_2 exposure and asthma incidence in adults, but was based on only three studies (38). Another review found that the evidence was insufficient to support a causal role for ambient air pollution, but was qualitatively consistent with a role for TRAP in the development of adult-onset asthma (39). A Canadian study determined that living near a major road was associated with increased odds of new-onset asthma (40). In the U.S. Sister Study (a large cohort of U.S. women), incident asthma was positively associated with $PM_{2.5}$ and NO_2, and both pollutants were significantly positively associated with incident wheeze, the cardinal symptom of asthma (41). The ESCAPE (European Study of Cohorts for Air Pollution Effects) study, a meta-analysis involving six European cohorts, reported positive associations between TRAP and adult-onset asthma (42), with several approaching statistical significance, including NO_2, nitrogen oxides, and traffic intensity on the nearest road. Two meta-analyses of adult-onset asthma reported positive associations with NO_2 (13, 23), but only one reached statistical significance (43). Since then, there have been four studies in adult populations (40, 44, 45). The largest of these adult studies found a significant hazard ratio for NO_2 (45).

Overall, studies of new-onset asthma and TRAP pollutants indicate the most consistent positive relationship with NO_2 exposure among children, but it remains unclear whether NO_2 itself is the causal agent, simply has less measurement error than other TRAP components, and/or is simply a proxy for the combustion component of TRAP (e.g., fossil fuel combustion PM).

Ozone

There is extensive evidence that O_3 exposure acutely exacerbates asthma, but less support for the hypothesis that long-term exposure causes incident asthma. In a study of long-term exposures, O_3 was associated with new-onset asthma in adult male Seventh-day Adventists (46). A study in Taiwan indicated an association between O_3 exposure and risk of childhood asthma (47). Also, the California CHS found that in communities with high O_3 concentrations, the relative risk of developing asthma was increased in children who played three or more sports as compared with children who played no sports (48). However, prenatal exposure to O_3 has not been associated with subsequent childhood asthma (24). Still, the ambient quenching of O_3 by traffic-emitted nitric oxide (49) can cause a negative correlation between O_3 and NO_2, potentially confounding the relationships between O_3 and respiratory outcomes in epidemiologic models.

Potential PM Composition Influences

Exposure to PM air pollution has been associated with chronic airway diseases, including asthma (23, 30, 41). In a study of TRAP and new-onset asthma in a high-risk cohort, Carlsten and colleagues found that, among the TRAP pollutants considered, $PM_{2.5}$ was the air pollutant most strongly associated with new-onset childhood asthma (50). PM, however, varies greatly in chemical composition as a function of its size and source (1). Also, traffic-related PM (indicated by BC) was found to be significantly related to an increased risk of new-onset asthma in children (23) (Figure 2). Although the investigators of the PIAMA (Prevention and

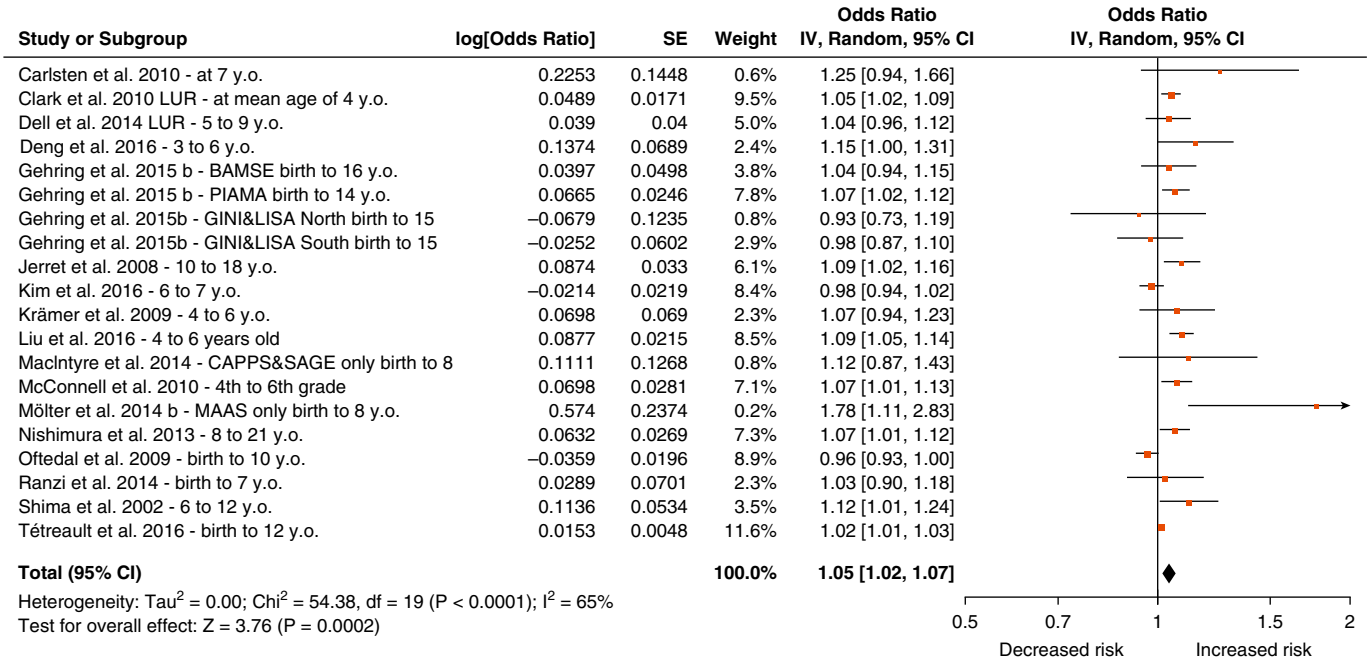

Figure 1. Meta-analysis of studies of nitrogen dioxide and new-onset asthma in children. Reprinted by permission from Reference 23. CI = confidence interval; I^2 = percentage of variation across studies due to heterogeneity; IV = instrumental variable; SE = standard error.

Incidence of Asthma and Mite Allergy) birth cohort identified traffic as the major contributing factor in their study area, $PM_{2.5}$ sulfur, a marker for fossil fuel combustion, generally had the largest relative risk for incident asthma among several PM constituents examined (51), so the $PM_{2.5}$ and BC associations reported may not be specific to TRAP only.

Conclusions Regarding the Epidemiology of New-Onset Asthma

- Overall, long-term exposure to air pollution, especially as represented by common metrics of TRAP exposure, is associated with onset of childhood asthma.
- The strongest epidemiologic evidence for a causal relationship with new-onset childhood asthma comes from studies that used NO_2 as the TRAP metric.
- Evidence suggests that TRAP plays a role in adult-onset asthma, but it is not yet compelling.
- Greater effects likely occur in subgroups (e.g., genetically susceptible individuals and minorities).
- NO_2 may be acting as a marker for PM secondary to combustion of fossil fuels, other reactive gases, or other nontailpipe TRAP pollutants.

Air Pollution and New-Onset COPD

The potential role of air pollution in COPD onset was addressed in a 2010 ATS review (52) and an HEI report (21). The ATS review concluded that there was limited/suggestive evidence, and the HEI report concluded that there was insufficient evidence of a causal association between TRAP and COPD.

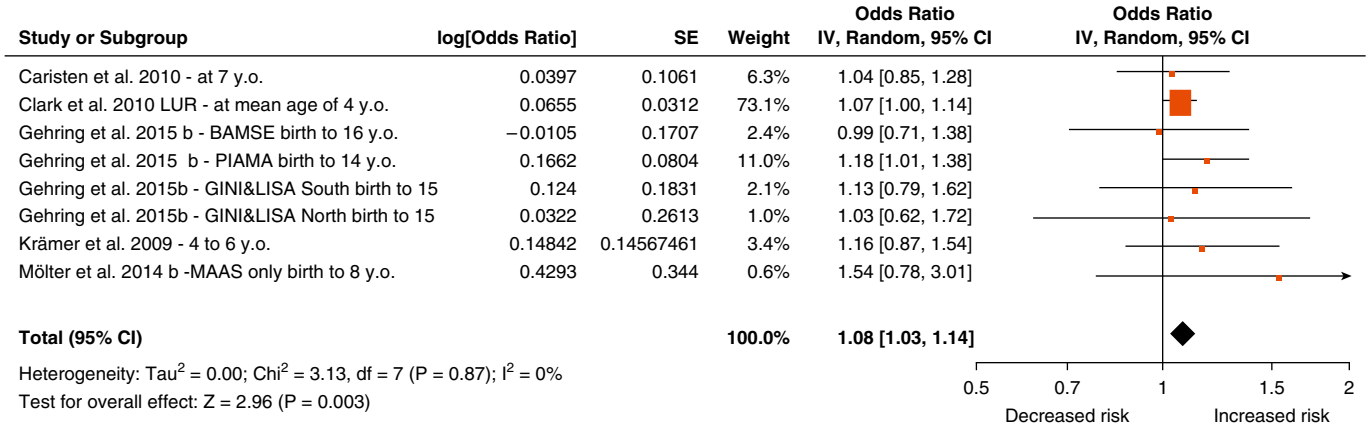

Figure 2. Meta-analysis of black carbon soot associations with new-onset asthma. Reprinted by permission from Reference 23. CI = confidence interval; I^2 = percentage of variation across studies due to heterogeneity; IV = instrumental variable; SE = standard error.

Since the publication of those reviews, a few new COPD studies have emerged. Some included new onset of chronic bronchitis symptoms and/or emphysema as COPD surrogates, and found positive (but not statistically significant) associations with air pollution (53, 54). An analysis of the European Community Respiratory Health Cohort yielded significant associations between NO_2 and chronic bronchitis (55). The ESCAPE study found significant associations between COPD incidence and TRAP among females (56). Most studies that assessed COPD using spirometry revealed positive associations with NO_2 and/or $PM_{2.5}$ (45, 57–60). One study investigated the development of asthma and COPD overlap syndrome (ACOS) in patients with asthma, and found a significant association between long-term $PM_{2.5}$ exposure and ACOS development (60). Associations found between indoor exposures to biomass pollution and increased risk of COPD, albeit at much higher than usual ambient $PM_{2.5}$ levels, are consistent with an association between fine PM and the development of COPD (61).

Only a limited number of studies have examined the associations between O_3 and COPD. A study of adults ⩾40 years of age found no association between COPD development and O_3 (58). A survey-based study of 6,040 adults found that O_3 exposure was associated with the development of ACOS in adults with asthma (60), but the association was nonsignificant after adjustment for $PM_{2.5}$. However, because the large hospital databases or survey cohorts used in these studies lacked important individual risk factors, the results should be interpreted with caution. Overall, there is little firm evidence that O_3 causes new-onset COPD.

Conclusions Regarding the Epidemiology of New-Onset COPD

- Studies indicated that exposure to traffic has adverse effects on COPD, but were not conclusive. The strongest evidence comes from meta-analyses of COPD, and few longitudinal studies have been conducted.
- Overall, the available epidemiological evidence regarding an association between air pollution and new-onset COPD remains insufficient to indicate a causal relationship.

Mechanistic Evidence

A key factor that should be considered in evaluating the causality of the above-discussed epidemiological associations is their biological plausibility (62, 63). The mechanistic literature regarding air pollution and asthma includes animal models and exposure paradigms, but only a few such studies have focused on COPD. Several mechanisms can plausibly explain how air pollution can induce new-onset airway disease with implications for both asthma and COPD, including *1*) structural remodeling of lung components, predisposing to respiratory disease; *2*) induced immune changes, promoting allergic sensitization or prolonged inflammation; *3*) changes in innate cells (e.g., group 2 innate lymphoid cells [ILC2]) in nonatopic asthma; and *4*) other modifiers of exposure, including genetics and stress.

Repeated inflammation and long-term air pollution exposure leads to airway remodeling. Early-life changes, including airway remodeling and oxidant stress, can be related to the onset of COPD or asthma, which may further progress to COPD (64). The conducting airways are an epithelial mesenchymal trophic unit (65) composed of airway epithelium, extracellular matrix, and fibroblasts, which interacts with nerves, smooth muscle, and immune cells. These elements grow interactively in a progressive fashion that may be disturbed by air pollution exposure. Alveolar growth and septation occur through young adulthood (66, 67), providing a substantial window of opportunity for air pollution–induced disruption.

Asthma Development

Animal studies have demonstrated that early-life air pollution exposures alter conducting airway and alveolar growth (68–70). Air pollutants impact alveolar growth by pre- and postnatal exposures in mice (71), as well as by postnatal exposures in primates (72). Evidence strongly suggests that the cellular mechanism underlying this altered growth involves decreased cellular proliferation (73). In nonhuman primates, which have a postnatal maturation pattern and lung anatomy similar to those of humans, O_3 (70) and O_3 plus allergic sensitization to allergen induce substantial airway (74) and alveolar (75) remodeling during the early postnatal period. These changes include alterations in smooth muscle, innervation, mucous cell abundance, and allergic sensitization linked to airway hyperresponsiveness (76). The most oxidizing particles, similarly to traffic combustion particles, change airway and/or lung size (68, 69). Thus, oxidant stress may be a common link with reduction in lung growth.

Numerous studies have demonstrated pulmonary responses to oxidant stress after exposure to air pollution. These responses occur in mice and rats with long-term exposure to particulate air pollution (77, 78), diesel exhaust (79–81), iron soot (82), and ambient PM (83), with changes in the antioxidant enzymes 8-hydroxydeoxyguanine (8-OHdG) and glutathione/oxidised glutathione (GSH/GSSG), and oxidation of lipids. Increases in tissue expression of antioxidant genes and proteins are a common response to long-term exposure. Treatment with antioxidants blunts the oxidant effects of particles (84, 85), but early-life responses to oxidant stress may differ from those observed in adults (86). In neonatal rats exposed to polycyclic aromatic hydrocarbon–laden ultrafine PM, which is similar to traffic PM, antioxidant gene and protein expression was not upregulated to levels similar to those observed in adults (87–89). There may be critical windows of time during postnatal lung development when antioxidant defenses are less able to upregulate.

Early-Life Exposure Causes Immune Changes, Including Type 1/Type 2 Skewing

Early-life air pollution exposure promotes allergic sensitization. PM components, such as diesel emission particles (DEP) (90–93), ultrafine particles (94–96), and $PM_{2.5}$ (97–99), can act as allergen-like adjuvants. Such particles have redox-active metals, can induce inflammation and oxidative stress, shift immune function from a T-helper cell type 1 (Th1) to a Th2 response, and drive lymphocyte proliferation and IgE production.

Particle chemical composition is important to biologic potency (99, 100). Simultaneous intranasal administration of ultrafine carbon black particles (CBP)

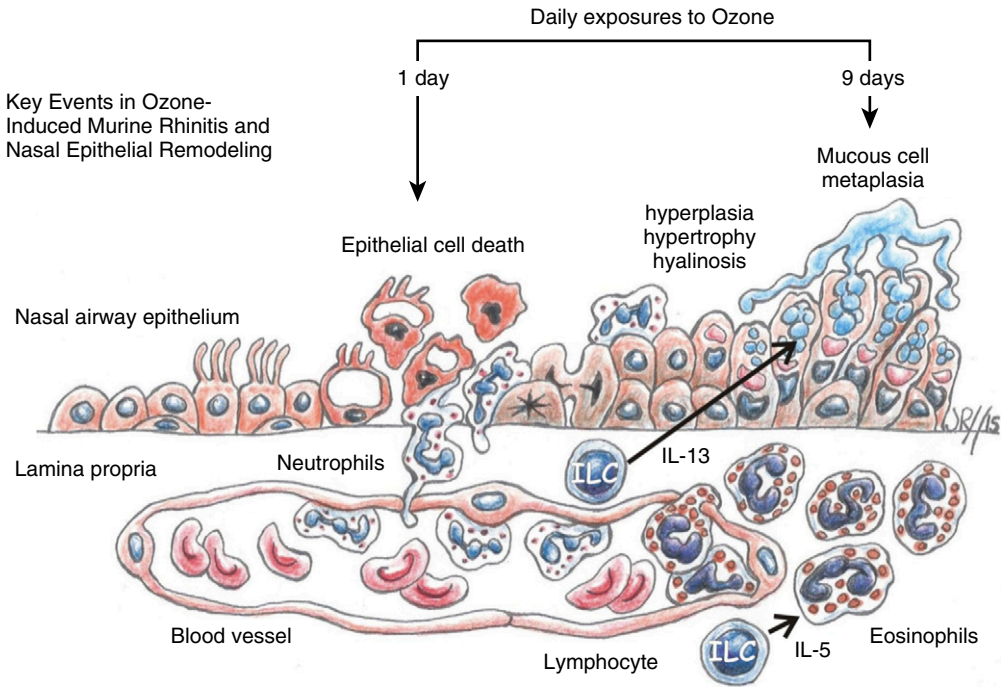

Figure 3. Long-term ozone exposure effects consistent with a role for air pollution in airway inflammation and remodeling leading to asthma development. IL-5 = interleukin-5; IL-13 = interleukin-13; ILC = innate lymphoid cells. Image by Jack R. Harkema.

and allergen (95), has demonstrated increased adjuvant activity. Thus, CBP can directly stimulate dendritic cell maturation (94). DEP and residual oil fly ash (ROFA) can act as adjuvants to increase IgE, bronchoalveolar lavage eosinophilia, lymphocyte reactivity, Th2 cytokine (interleukin-5 and tumor necrosis factor) production, cholinergic airway responses, and allergen-induced bronchoconstriction (95), as can hydrocarbons and soluble transition metals present in DEP and residual oil fly ash, respectively. Thus, DEP and ultrafine particles (UFP) can act as adjuvants in the initial events of allergen sensitization, increasing cytokine production, inflammation, airway hyperresponsiveness (AHR), and airways obstruction.

The role of oxidant stress as a link between air pollution and asthma onset is also supported by studies showing susceptibility based on functional genetic variants in pathways predicted by mechanistic toxicology. For example, Salam and colleagues found that epoxide hydrolase 1 and glutathione-S-transferase variants contribute to the occurrence of childhood asthma and increase asthma susceptibility to pollution exposures from major roads (101). The roles of these enzymes in asthma stem from their function in important xenobiotic metabolic pathways and the subsequent oxidant stress–mediated tissue damage that can contribute to the pathogenesis of asthma.

A Mechanism for Nonatopic Asthma

Consistent with air pollution–induced nonatopic asthma, mice repeatedly exposed to O_3, without allergen exposure, were found to develop nasal type 2 immunity and eosinophilic rhinitis with mucous cell metaplasia (Figure 3) (102). These O_3-induced airway alterations are mediated by ILC2s, rather than by the more classical T and B lymphoid cells that are important in adaptive immune responses typically associated with allergic rhinitis and allergic asthma (103). Furthermore, repeated exposure to O_3 induces ILC2-mediated airway type 2 immunity, eosinophilic inflammation, and mucous cell metaplasia in the pulmonary airways (104, 105). Thus, repeated O_3 exposures may induce a nonatopic asthma phenotype characterized by innate type 2 immunity, eosinophilic inflammation, and mucous cell metaplasia. These findings provide plausible paradigms for biological mechanisms underlying the epidemiologically identified associations between airway eosinophilic inflammation and new onset of nonatopic asthma (106, 107). In addition, after this Workshop was conducted in May 2018, another study evaluated the current scientific evidence of a causal link between DEP and asthma, and found consistent evidence of physiological mechanisms by which DEPs can cause new asthma (108).

COPD Development

Relatively few toxicological studies have focused on COPD and air pollution, as most animal models replicate only a few COPD features, and are expensive, technologically challenging, and time-consuming (109, 110). One recent development is spontaneously hypertensive rats that require less time (14 wk vs. 6 mo) to induce COPD-like changes (111). A ferret model developed airway obstruction characteristic of bronchitis and bronchiolitis (112). Short-term PM exposures caused increased pulmonary injuries and attenuated lung antioxidant responses in spontaneously hypertensive rats, providing further evidence of this model's sensitivity to respiratory changes (113). Long-term exposures to O_3 or diesel exhaust are known to induce

remodeling in distal airway regions, which are key to COPD airway obstruction (114–116).

Modifiers of the Impact of Air Pollution on Airway Disease

Interindividual variation has been identified in susceptibility to the pulmonary effects of air pollution, via both extrinsic (environmental) and intrinsic (host) factors (117). Extrinsic factors include socioeconomic status, exposure to other environmental stimuli, nutrition, and coexposures/infections. Intrinsic factors include age, sex, preexisting disease, and genetic background. Other risk factors include host/maternal obesity (118, 119), diabetes and diet (120), childhood rhinovirus and respiratory syncytial virus infections, and psychosocial and maternal stressors (105).

Gaps in the Evidence and Opportunities for Future Research

Various inbred strains and genetic models have been used to investigate susceptibility to respiratory disease; however, these models do not reflect the genetic heterogeneity found in humans. Collaborative Cross and Diversity Outbred models more closely mimic human genetic variability (121). Furthermore, a number of promising animal models of COPD have been developed (111, 112) and used to study factors involved in tobacco smoke–induced COPD, but not air pollution. Because of the structural and immunologic similarities between humans and nonhuman primates, long-term studies in nonhuman primates would be fruitful (122).

Mechanistic Conclusions

- There are asthma-like phenotypes that increase in incidence/severity with long-term exposure to air pollution, especially to PM and O_3, consistent with the biological plausibility of air pollution as a causal factor in asthma development.
- Repeated and intermittent air pollution exposures can cause airway remodeling, which leads to the development of asthma, and may also lead to COPD.
- Sufficient toxicological evidence for air pollution as a cause of COPD is still lacking.
- There remain multiple gaps in our knowledge about airway disease development, including a lack of validated mechanistic models for studies at environmentally relevant exposure levels, and evaluations of epigenetic and genetic influences.

Clinical Considerations

Many of the clinical parameters considered in a diagnosis of asthma or COPD, such as symptoms of wheeze, cough and mucus production, dyspnea, airway hyperresponsiveness, reduced lung function, and airway remodeling, are also caused by long-term air pollution exposure (123). Air pollution is therefore a plausible contributor to the risk of a new clinical diagnosis of asthma or COPD. However, there are

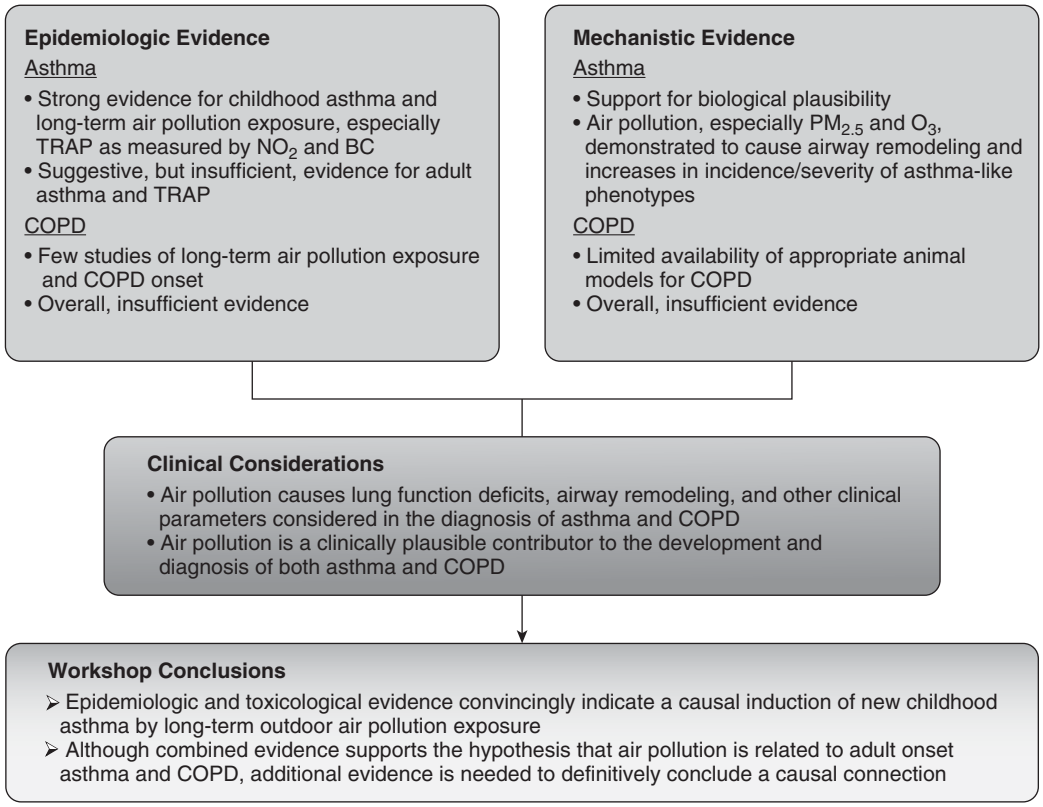

Figure 4. Workshop findings and conclusions. BC = black carbon; COPD = chronic obstructive pulmonary disease; NO_2 = nitrogen dioxide; $PM_{2.5}$ = particulate matter less than or equal to 2.5 μm in aerodynamic diameter; TRAP = traffic-related air pollution.

challenges in translating epidemiological and toxicological findings to the clinical context. Large observational epidemiological studies often do not have the same information that may be incorporated into a clinician's diagnostic decision. Studies of exposures to air pollution and the risk of new-onset asthma or COPD have generally relied on self-reported physician diagnoses. For both asthma and COPD, a self-reported physician diagnosis is relatively specific but not sensitive, and cases may be missed or overreported in epidemiologic studies. Additional medical information, including medical history, response to therapeutic medication, physical examination, and lung function measurements, used for the diagnosis of asthma or COPD, may be lacking in epidemiologic studies. For example, pre- and postbronchodilator spirometry and/or methacholine challenge can contribute to a diagnosis, but may not always be included in large epidemiological studies.

Asthma is clinically defined by a history of intermittent respiratory symptoms (e.g., wheeze, shortness of breath, chest tightness, and cough) with reversible airways obstruction and/or hyperresponsiveness (124). Several phenotypes (e.g., allergic and nonallergic) and endotypes (e.g., with or without biomarkers of enhanced Th2 response) have been described (125), and air pollution may have differential effects on the risk for new-onset asthma depending on genetic susceptibility, the presence of allergy, coexposures, obesity, age, and sex. The etiology of asthma is likely multifactorial, and air pollution alone may rarely be the sole or even primary cause.

COPD is a condition characterized by more persistent respiratory symptoms (e.g., shortness of breath, chronic cough, and sputum production), defined by fixed airways obstruction that does not reverse with bronchodilator administration (126). COPD also has several phenotypes (e.g., chronic bronchitis and emphysema) and endotypes (e.g., sputum with or without eosinophils) (127). Spirometry is required for a COPD diagnosis (112), but many published observational studies of air pollution exposures and COPD have not used spirometry to define the outcome. It is well recognized that COPD is clinically underdiagnosed (128). Another challenge is inadequate data to adjust for possible confounding from smoking, occupational exposures, or household air pollution from combustion of solid fuels for cooking and heating, and the long latency period for COPD development (52). COPD is likely multifactorial, and air pollution is often working in concert with other determinants of disease risk.

Clinical Conclusions

Many of the clinical parameters considered in a diagnosis of asthma or COPD (e.g., lung function deficits and airway remodeling) are also caused by long-term air pollution exposure, as documented above, indicating that air pollution is a clinically plausible contributor to the development and diagnosis of both asthma and COPD.

Workshop Conclusions and Recommendations

A summary of the Workshop findings and conclusions is presented in Figure 4. At the end of the Workshop, votes were taken on each of the overarching questions, and there was unanimous agreement that:

1. There are biological mechanisms by which air pollution could plausibly cause the induction of new asthma and/or COPD.
2. Air pollution's known effects on the lung and airways could plausibly contribute to a diagnosis of asthma or COPD in a clinical setting.
3. Epidemiologic and toxicological evidence convincingly indicates a causal link between long-term exposure to outdoor air pollution (especially TRAP) and new childhood asthma.
4. Based on the above, it is concluded that there is sufficient scientific evidence to conclude that long-term outdoor air pollution exposure causally contributes to the development of new childhood asthma.
5. Although combined toxicological and epidemiological evidence supports the hypothesis that long-term air pollution is related to adult-onset asthma and COPD onset, further investigations are needed to definitively conclude that there is a causal connection.

Future Directions

1. Developing long-term, well-characterized mechanistic air pollution inhalation exposure models for asthma and COPD.
2. Gaining a better understanding of whether the epidemiological associations found for TRAP are due to direct effects of NO_2, or to a component of the $PM_{2.5}$ mass with which NO_2 is commonly associated (e.g., fossil-fuel combustion fine particles).
3. Conducting further investigations of air pollution's impacts on the development of COPD and adult-onset asthma. ■

This official Workshop report was prepared by an *ad hoc* subcommittee of the ATS Assembly on Environmental, Occupational and Population Health.

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