

Inflammatory health effects of indoor and outdoor particulate matter



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Activity Objectives:

1. To recognize that particulate matter (PM) can have significant pulmonary and cardiovascular effects.
2. To identify some of the inflammatory changes and potential health consequences that can occur with exposure to PM.

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Inflammation is a common and essential event in the pathogenesis of diverse diseases. Decades of research has converged on an understanding that all combustion-derived particulate matter (PM) is inflammatory to some extent in the lungs and also systemically, substantially explaining a significant portion of the massive cardiopulmonary disease burden associated with these exposures. In general, this means that efforts to do the following can all be beneficial: reduce particulates at the source, decrease the inflammatory potential of PM output, and, where PM inhalation is unavoidable, administer anti-inflammatory treatment. A range of research, including basic illumination of inflammatory pathways, assessment of disease burden in large cohorts, tailored treatment trials, and epidemiologic, animal, and *in vitro* studies, is highlighted in this review. However, meaningful translation of this research to decrease the burden

of disease and deliver a clear and cohesive message to guide daily clinical practice remains rudimentary. Ongoing efforts to better understand substantial differences in the concentration and type of PM to which the global community is exposed and then distill how that influences inflammation promises to have real-world benefit. This review addresses this complex topic in 3 sections, including ambient PM (typically associated with ground-level transportation), wildfire-induced PM, and PM from indoor biomass burning. Recognizing the overlap between these domains, we also describe differences and suggest future directions to better inform clinical practice and public health. (*J Allergy Clin Immunol* 2018;141:833-44.)

Key words: Air pollution, inflammation, particulate matter, wildfire, biomass

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Abbreviations used

ALRI:	Acute lower respiratory tract infection
BAL:	Bronchoalveolar lavage
COPD:	Chronic obstructive pulmonary disease
CVD:	Cardiovascular disorder
ED:	Emergency department
ICS:	Inhaled corticosteroid
PAH:	Polycyclic aromatic hydrocarbon
PM:	Particulate matter
TLR:	Toll-like receptor

Air pollution is a mixture of thousands of components. All components of air pollution are harmful to human health, but the most severe effects have been attributed to particulate matter (PM).¹ In 1987, the US Environmental Protection Agency revised the National Ambient Air Quality Standard for PM, forwarding PM with a mean aerodynamic diameter of less than 10 μm (PM_{10}) as a relevant index because this fraction is more representative of the particles that can be inhaled and enter the human lung. It consists of a broad range of particulate components, as well as a plethora of substances bound to the core of the particles, and can be split up further in several size fractions based on the aerodynamic diameter resulting from collection with specific particle matter samplers: coarse (2.5–10 μm [$\text{PM}_{2.5-10}$]), fine (<2.5 μm [$\text{PM}_{2.5}$]), and ultrafine (<0.1 μm [$\text{PM}_{0.1}$]). Coarse PM derives predominantly from crushing and grinding processes and mostly deposits in the extrathoracic and upper tracheobronchial regions. $\text{PM}_{2.5}$ originates mainly from combustion sources, such as vehicle emissions, coal burning, and industrial processes. $\text{PM}_{2.5}$ can be inhaled more deeply into the lungs, with a portion depositing in the alveoli and entering the pulmonary circulation and likely the systemic circulation. Ultrafine particles ($\text{PM}_{0.1}$) derive primarily from vehicle emissions and can translocate from the alveoli to the circulatory system. $\text{PM}_{2.5}$ broadly represents approximately 50% of the total mass of PM_{10} .¹

The composition of PM varies according to the predominant source of particles, season, prevailing weather conditions, and space, and this attributes to PM a highly variable toxicity.^{2,3} PM deposited in the alveoli of the lung can induce local inflammation, which can subsequently elicit a systemic inflammatory state.⁴ The inflammatory response is believed to be a major biologic mechanism underlying PM exposure-related health events.

The primary purpose of this clinical review is to present a concise and nonexhaustive review of the human science connecting particle-rich aerosols (from a variety of combustion sources) with inflammation both in the lungs and in the circulation (Fig 1), with the aim to inform care providers. Accordingly, the review is oriented toward aspects of this vast literature base that can help the clinician understand the underlying evidence for these inflammatory phenomena and how this can inform prevention and treatment. As such, we recognize the wide range of interpretation as to what constitutes inflammation, but we refer generally to the cascade of cellular and biochemical events intended to defend and protect against insults and threats and ultimately usher cells and associated molecules to the site of injury/threat. Here we are focused on the lung as the primary site of inflammation,

although secondarily, we consider systemic phenomena that often ensue.

We put this in the context of inhaled PM from combustion (rather than engineered PM), recognizing that in most instances PM is associated with gaseous components with their own tendency to inflame; we comment on this briefly but do not attempt to parse out what is specifically attributable to the particulate phase because this is a topic for other venues. Similarly, we primarily present clinically applicable aspects of this topic, more so than detailing molecular events, but we do include a basic description of relevant pathways (Fig 2) because these are important when considering anti-inflammatory interventions or other technological methods to mitigate the inflammation associated with PM. Finally, we acknowledge that there are other relevant themes (eg, specific susceptibility factors, such as age or underlying disease) that are important but not our focus.

Understanding the health effects of air PM is a multidisciplinary endeavor, and research approaches include epidemiology, human clinical studies, animal exposure studies, and *in vitro* studies. In each of the 3 main sections of this review, focusing on ambient PM, wildfire-derived PM, and PM from indoor biomass burning, we cover key findings from these approaches (in that order separately for pulmonary and systemic/cardiovascular effects) and then end the section with clinically relevant suggestions and a final summary.

INFLAMMATORY HEALTH EFFECTS OF AMBIENT (TRAFFIC-RELATED) PM EXPOSURE

The evidence linking ambient (outdoor) PM (primarily derived from transit of people and goods) to inflammation includes both direct and indirect lines of support. The direct evidence comes primarily from animal and cellular models, which are informative in spite of legitimate questions of applicability to the intact human context and from rare controlled human exposure studies. The indirect evidence comes largely from observational (epidemiologic) studies, which are very important in spite of being limited in their ability to definitively demonstrate inflammation as a result of PM exposure.

Epidemiologic studies have provided strong evidence for associations of PM inhalation with inflammatory lung and cardiovascular diseases. In general, there is sufficient evidence of the adverse effects related to short-term exposure, whereas fewer studies have addressed the longer-term health effects.⁵ Short-term exposure to outdoor PM has been associated with significant increases in hospitalizations, emergency department (ED) visits, or home medical visits, mainly for chronic obstructive pulmonary disease (COPD), asthma, and pneumonia, whereas chronic exposure to increased levels of air PM has been related to the incidence of COPD and chronic bronchitis, asthma, and emphysema.^{6,7} For example, in a very large study in 10 US cities, a 2.5% increase in COPD-related admissions occurs for each 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} .⁸ Another US study shows that a sudden increase in $\text{PM}_{2.5}$ is associated with an increased risk by approximately 0.9% for COPD-related hospitalizations.⁹ Furthermore, a recent population-based cohort study from Canada confirms that ambient air pollution, including traffic-related $\text{PM}_{2.5}$ pollution, is a risk factor for COPD-related hospitalization.¹⁰

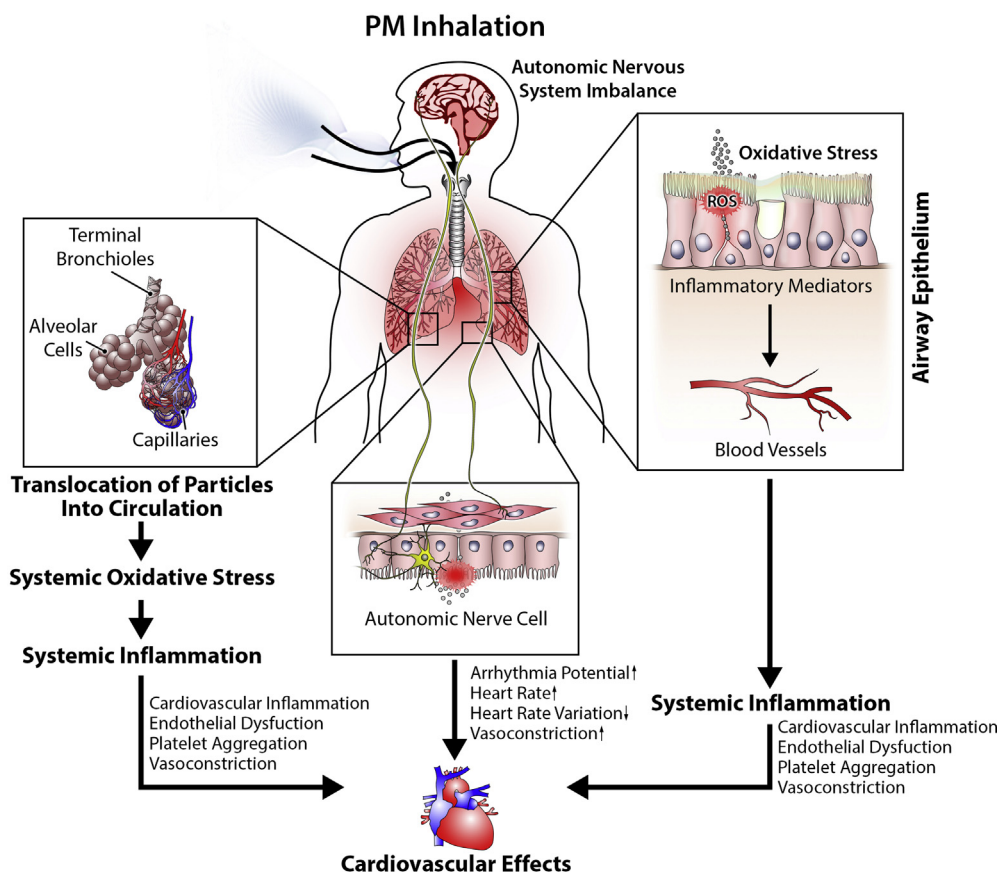


FIG 1. Schematic representation of pathways for the respiratory and systemic effect of PM exposure through inhalation. Inhaled PM from different sources can deposit on different airway segments, some of which can enter the circulation through the air-blood barrier, resulting in oxidative stress and subsequent lung and systemic inflammation.

It is noteworthy that 2 large, consecutive, cross-sectional studies in rural and urban areas of Italy found that prevalence rates of respiratory symptoms, as well as diagnoses of chronic bronchitis, emphysema, asthma, and pleuritis, increased with age and tended to be higher in urban than rural areas, significantly for cough, wheeze, and emphysema in male subjects and for pleuritis in female subjects.¹¹ Another study in Germany showed that women living near a major road, compared with those living farther away, reported more frequent cough and COPD.¹²

Potential inflammatory biomarkers associated with PM-induced respiratory effects have been characterized by using nasal or bronchoalveolar lavage (BAL), sputum induction and exhaled breath analysis.¹³ For example, changes in fraction of exhaled nitric oxide values were associated with increases in ultrafine particles and PM_{2.5}.^{14,15} Another study performed also in China reiterated fraction of exhaled nitric oxide association with ambient PM and added exhaled hydrogen sulfide levels, which were also positively associated with PM, as another marker of airway inflammation.¹⁶ Increased percentages of neutrophils and IL-8 level in nasal lavage fluid were associated with PM_{2.5} exposure in a cohort study.¹⁷

It is worth noting that several epidemiologic studies have demonstrated a link between PM and use of anti-inflammatory

medications. For example, fine and ultrafine particle exposure was associated with glucocorticoid use in Germany.¹⁸ In Holland PM₁₀ exposure was associated with inhaled corticosteroid (ICS) use 2 days later,¹⁹ and in another Dutch study black smoke (a marker for PM) was also associated with subsequent ICS use.²⁰ However, considering these studies collectively, there are at least 4 major caveats that compromise their ability to directly support the contention that ambient particulate ambient causes inflammation: (1) it is difficult to separate the effects of PM from those of associated ambient gases because these are typically highly correlated with PM; (2) simply observing use of anti-inflammatory medications after PM exposure does not prove that inflammation was present; (3) another investigation²¹ showed no association between PM and ICS use; and (4) often these studies also showed concomitant increases in bronchodilator use (which might act and benefit independently of anti-inflammatory properties, but might also do potential harm by increasing particle deposition).²²

Many other observations associate PM with symptoms, which can again suggest inflammation but is subject to the same caveats noted above. In fact, a seminal study by Pope et al²³ noted change in medication use even absent changes in airflow or symptoms, which could be interpreted as a change in medication use absent

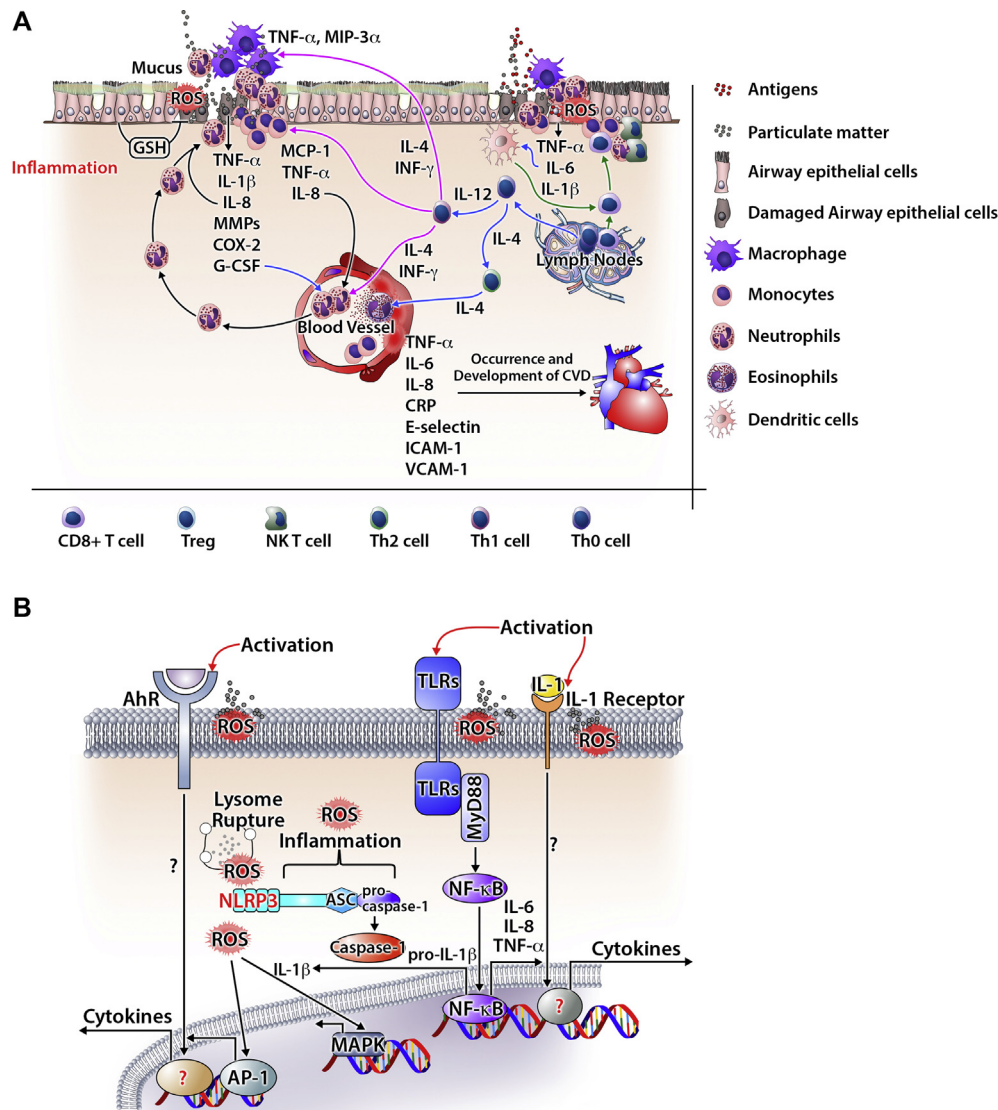


FIG 2. Cellular pathways of inflammatory effects caused by combustion-derived PM exposure. **A**, Potential immunoinflammatory and cellular interactions contribute to PM exposure-induced inflammation. Innate cells are the first line of defense against these particles. PM from various combustion sources causes injury in airway epithelial cells, monocytes, and macrophages accompanied by TNF- α , IL-8, IL-6, IL-1 β , granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein (MIP) 3 α , and monocyte chemoattractant protein (MCP) 1 release, and matrix metalloproteinase (MMP) activation. These mediators can recruit neutrophils, monocytes, and macrophages to the damaged tissue. In addition, IL-4, IFN- γ induction T_H1 cells, and IL-4 from the T_H2 response can recruit pathogenicity of innate immune cells and cause local inflammation. Serum levels of TNF- α , IL-8, IL-6, C-reactive protein (CRP), E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular adhesion molecule 1 (VCAM-1) are known to cause vascular endothelial injury and further participate in CVD development. **B**, TLR-mediated myeloid differentiation response gene-88 (MyD88) signaling, aryl hydrocarbon receptor (AhR), and IL-1 receptor activation are associated with inflammatory cytokines generated from airway epithelial cells after combustion-derived particle exposure. PM is known to cause airway epithelial injury through oxidative stress; endogenous reactive oxygen species (ROS) production induces cytokines release through activating NOD-like receptor-related protein 3 (NLRP3) inflammasome, activator protein 1 (AP-1), and mitogen-activated protein kinase (MAPK) signaling.

significant inflammation. More recently, this “confounding by indication” possibility has been addressed by a randomized trial²⁴ in which results even suggested potential worsening of airway responsiveness (relative hyperresponsiveness) with ICSs, although this was reflective of gaseous rather than PM exposure specifically. However, there are further lines of evidence within

observational studies that more neatly connect ambient PM exposure to lung inflammation. For example, a study from California²⁵ demonstrated that anti-inflammatory medications, more so than direct bronchodilators, attenuated asthmatic symptoms associated with PM (and to a greater extent than was observed with ozone).

Although the generally coherent link between ambient PM and pulmonary disease is perhaps not surprising, it is remarkable to note how the association between PM and inflammation-related cardiovascular diseases, such as ischemic heart disease, cardiac dysrhythmias, congestive heart failure, cerebrovascular disease, and stroke, has emerged very strongly. This notion is supported by a number of studies showing that each 10 to 20 $\mu\text{g}/\text{m}^3$ increase in PM levels is associated with an increase of 0.5% to 2% in cardiovascular mortality.²⁶ A retrospective cohort study in Boston found that subjects with an acute myocardial infarction were 3 times more likely to have been exposed to traffic in the hour before symptom onset, suggesting a causal link between high levels of acute exposure to combustion-derived particulate air pollution and onset of myocardial infarction.²⁷

Systemic responses are the main pathways through which PM is thought to influence cardiovascular health, which can be induced either directly by the movement of proinflammatory, procoagulatory, and pro-oxidant components of PM to the circulation, indirectly as a consequence of the pulmonary changes induced by PM, or through PM-mediated changes in the autonomic nervous system.^{28,29} Increased cellular and inflammatory mediators, including IL-1 β , IL-6, IL-8, IFN- γ , C-reactive protein, TNF- α , fibrinogen, and increased white blood cells in circulating blood have been observed after acute and long-term exposure to PM.²⁹

Characteristics of PM that have been held responsible for the adverse effects described earlier include transitory metal content (eg, Fe, Ni, Cu, Co, and Cr) and iron mobilization, particle size and surface area, endotoxin contamination, and organic compounds, such as polycyclic aromatic hydrocarbons (PAHs).⁷ Additionally, it should be noted that epidemiologic studies suggest that certain subgroups are more susceptible than the general population to effects associated with PM exposure, perhaps because of inflammation-prone “substrate.” For example, susceptibility factors include age, comorbidity, and genetic variation in antioxidant genes,^{30–32} all of which can be associated with less anti-inflammatory reserve. For example, the obese, the elderly, and patients with diseases, such as COPD, previous myocardial infarction, or diabetes, have a higher risk of experiencing an acute exacerbation of their disease at the same air pollution concentration.²⁸

Toxicological studies with animal and cellular models have provided experimental support for the associations found in epidemiologic studies between PM exposure and adverse cardiopulmonary effects. In spite of being at least 1 step removed from the real-world clinical scenarios that justifiably matter most to clinicians, such models are highly instructive because of their ability to precisely control variables and manipulate interventions convincingly. For example, an important contribution of *in vitro* models has been linking oxidative stress to inflammation and assessing dose-response relationships.³³ A particular advantage of animal studies is to dissect novel pathophysiologic pathways at a level of detail otherwise impossible. For example, a guinea pig model has been instrumental in describing the role of respiratory reflexes in mediating cough-related phenomena in response to PM from diesel exhaust.³⁴

Most of the animal studies have focused on respiratory effects, but there is strong evidence that systemic effects can be induced. For example, intratracheal instillation of diesel exhaust particles caused mouse lung inflammation characterized by influx of inflammatory cells, increase of total proteins, and releases of

IL-6 in BAL fluid.^{35,36} Exposure to PM triggers IL-6 production by alveolar macrophages, resulting in reduced clotting times, intravascular thrombin formation, and accelerated carotid artery thrombosis.³⁷ *In vitro* studies showed that PM and diesel exhaust particles activated macrophages and human airway epithelial cells to produce inflammatory cytokines, including TNF- α , IL-1 β , GM-CSF, IL-6, and IL-8.^{38,39} Inflammation and oxidative stress are intimately linked phenomena. Inhaled PM can induce interactive pulmonary oxidative stress and inflammation that contribute to a systemic inflammatory state, which in turn results in cardiovascular disease.⁴⁰

Controlled human exposures, being both in the model organism of primary concern and capable of virtually eliminating relevant confounding, serve as a powerful link between human observational studies and preclinical model experiments. The ability to provide evidence that supports (or, alternatively, calls into question) epidemiology and animal-based evidence within such a directly relevant setting is highly advantageous. However, significant limitations include being confined to shorter (acute) exposures and subacute (days) observation periods and being limited in terms of the number of study subjects (sample size) because of cost and practical demands.

Crossover human exposure studies to real-world conditions have contributed to understanding pollutant-induced health effects.⁴¹ For example, 20 volunteers with mild allergic asthma were exposed inside a car for 30 minutes in a traffic tunnel. The results showed that exposure to air pollution in traffic tunnels might significantly enhance asthmatic reactions to subsequently inhaled allergens.⁴² Another study of short-term exposure to traffic-related pollution in patients with asthma demonstrated consistent reductions in FEV₁ and forced vital capacity accompanied by increases in biomarkers of neutrophilic inflammation and airway acidification.⁴³ Healthy volunteers exposed to air from a heavy-traffic street showed no effects on tests of pulmonary function, lung permeability, or plasma markers of inflammation.^{44,45}

Directly controlled human studies allow even more precise and consistent exposure conditions and have yielded further insight. That said, controlled human exposure studies have generally supported the link between PM and airway inflammation.⁴⁶ Inhalation of diesel exhaust increased numbers of airway inflammatory cells (neutrophils, mast cells, and lymphocytes) and levels of upregulated inflammatory mediators (adhesion molecules, IL-8, IL-13, and growth-related oncogene), even in healthy subjects.^{46,47} Another study has also elucidated the particular role of adaptive immunity in the setting of coexposures⁴⁸ and have further buttressed the role of oxidative stress—metabolizing genes (and their variants) as important mediators of this relationship.^{49,50} Furthermore, underappreciated inflammatory mechanisms, such as neurogenic⁵¹ or adipokine-related⁵² mechanisms, have been illuminated as another reminder of why a narrow focus on traditional inflammation might miss important pathways. Collectively, these studies demonstrate how specific yet common combinations of conditions can result in greatest risk through direct observation of proinflammatory pathways. Importantly, these data buttress epidemiologic findings, suggesting that air pollution effects, although detectable in healthy subjects, are most prominent in susceptible populations.

In terms of clinical guidance in this setting, there are 2 main considerations: prevention (of new cardiopulmonary disease or of

exacerbation and/or progression of pre-existing disease) and treatment (eg, therapy in the setting of exacerbation of pre-existing disease). Complete coverage of this topic is beyond the scope of this review, but key points will be emphasized in the following paragraph.

Prevention is clearly preferable because it is more cost-effective, especially considering the broad effects of pollution-related disorders, including quality of life compromised inherent to cardiopulmonary morbidity. Primary prevention (preventing incident disease) is most desirable; although difficult to directly prove in this setting, a reduction of new-onset cases by avoiding air pollution is inferred by the multitude of studies that show significant *de novo* heart and lung disease associated with exposure to PM-rich pollution.^{49,50} Additionally, “natural experiments” and “accountability studies” suggest collectively significant benefit of pollution avoidance. Accordingly, although a randomized controlled trial of traffic avoidance to prevent such disease has not been performed (and would likely be unethical), there is strong reason to believe that such avoidance is beneficial, and direct evidence from the cigarette smoking literature⁵³ lends further credence to this. Secondary prevention is better documented, although most concretely for lung function⁵⁴ and symptoms⁵⁵ than for inflammation specifically (although an inflammatory component can be reasonably inferred therein). For some conditions, such as myocardial infarction (in which inflammation is believed to be a significant trigger), moving toward greater traffic confers risk⁵⁶; thankfully (although perhaps inconveniently), moving away from traffic intensity can be beneficial.⁵⁷ Treatment of pollution-induced inflammation, as noted earlier in this review and elsewhere, can be effective, although it is difficult to determine what fraction of the benefits are through remediation of particulate-versus gaseous-induced inflammation, in the context of common traffic-related mixtures.

In summary, inflammatory health effects of ambient PM exposure are supported by several layers of evidence: an observational link between PM and use of anti-inflammatory medications, an association between PM and biomarkers of inflammation, direct experimental evidence for induction of inflammation by PM, and modification of effects by variants in inflammation-related genes and pathways (Fig 2). Prevention of new or exacerbated disease is probably most effectively achieved through avoidance of PM, whereas anti-inflammatory medications appear effective in attenuating exacerbations.

INFLAMMATORY HEALTH EFFECT ASSOCIATED WITH WILDFIRE PM

Changes in temperature and precipitation patterns from climate change are increasing wildfire prevalence and severity worldwide.⁵⁸ Wildfires, in the form of bush, vegetation, forest, peat, heath, and grass fires, can release large amounts of PM and toxic gases that adversely affect air quality and health. Of the various pollutants released from wildfires, PM is considered to be the most harmful to public health because it is present at higher concentrations than other hazardous substances and can travel great distances away from the fire site.⁵⁹

Wildfire PM is directly emitted from fires and formed through secondary processes.⁶⁰ About 80% to 90% of mass PM produced by wildfires is within the PM_{2.5} range.⁶¹ Compared to ambient

PM, the chemical composition of wildfire PM is mostly carbonaceous and typically composed of at least 50% organic carbon by weight.⁶² Carbonaceous particles and PM_{0.1} of wildfire PM offer a large surface area to initiate production of free radicals and therefore have a greater potential to cause inflammation.^{63,64}

Wildfire PM exposure is typically experienced at the community/general public level and occupationally among wildland firefighters. Virtually all the health studies of wildfire PM have focused on the health effects of acute exposures on the general public. Only a very limited number of health studies have been carried out among wildland firefighters.⁶² Of the health outcomes examined, respiratory morbidity predominates, but cardiovascular, ophthalmic, and psychiatric problems can also result.⁶⁵

Consistent evidence documents associations between wildfire PM exposure and general inflammation-related respiratory health effects (asthma, COPD, acute bronchitis, pneumonia, and upper respiratory tract infections), specifically exacerbations of asthma and COPD.⁶⁶ For example, associations of asthma hospital admissions or ED visits with PM exposure were observed during peat forest fires in North Carolina,⁶⁷ bush fires in Australia,⁶⁸ forest fires in British Columbia,⁶⁹ and forest fires in California.⁷⁰ In addition, an increase of 3.8% in hospital admissions for COPD in Sydney, Australia, was associated with a 10 µg/m³ increase in PM₁₀ from a bushfire,⁶⁸ and a 6.9 % increase in COPD-related hospital admission was related to a 10 µg/m³ increase in forest fire PM_{2.5} in southern California.⁷⁰ ED visits for COPD were also associated with PM_{2.5} during the wildfire.⁶⁶ There seems to be an association between wildfire PM exposure and acute bronchitis and pneumonia. It has been reported that for every 10 µg/m³ increase in wildfire PM_{2.5}, admission for acute bronchitis increased by 9.6% and admission for pneumonia increased by 6.4%.⁷⁰ The findings of increased reliever medication dispensing during wildfire smoke exposure in British Columbia can indicate increases in COPD- or asthma-related exacerbations.^{71,72} In addition, it was reported in preliminary format that wildfire smog exposure was associated with loss of forced vital capacity, slow vital capacity, FEV₁, and peak expiratory flow rate.⁷²

Systemic inflammation-driven cardiovascular morbidity has been linked to exposure to ambient PM, but among PM_{2.5} and PM₁₀ from wildfires, results have been less consistent, with some studies showing a positive relationship, some showing negative relationships, and some showing no relationship.⁷³ Intriguingly, despite the inconsistent association for cardiovascular morbidities globally, the association was mostly consistent in North America, where the prevalence of cardiovascular diseases is greater than in many other study areas.⁷⁴ All these studies assessed cardiovascular disease based on hospital admissions or ED visits. Overall, there are both fewer wildfire studies examining cardiovascular morbidity and fewer that found a positive relationship between cardiovascular morbidity and wildfire PM than respiratory morbidity, and the majority of studies focused on PM₁₀ rather than PM_{2.5}.⁷⁴ These studies suggest that wildfire smoke can have a selective effect on respiratory outcome (Fig 1).⁷³

Firefighters are at particular risk of inhalation of wildfire smoke particles. Because of work responsibilities, firefighters can encounter higher levels of fire PM. Increased levels of inflammatory biomarkers, including eosinophilic cationic protein

and myeloperoxidase in nasal lavage fluid, were observed among wildfire firefighters (Fig 2).⁷⁵ Another study showed increases in the percentages of granulocytes, mostly neutrophils, in induced sputum, and significant changes in circulating band cells and serum concentrations of the proinflammatory cytokines IL-6 and IL-8 were detected among wildland firefighters (Fig 2).⁷⁶ A similar finding was observed among wildland firefighters in the southeastern United States,⁷⁷ which showed that postshift concentrations of IL-8 in dried blood spot samples were 1.7 times higher than preshift levels.

Air pollution research has revealed population characteristics that are associated with greater biological susceptibility or sociodemographic vulnerability. However, for wildfire PM exposure, few studies on potentially vulnerable/susceptible subpopulations were performed.⁷⁴ There was some indication of increased vulnerability to adverse health effects of wildfire smoke among certain subpopulations: young children, older adults, and subjects of lower socioeconomic status.⁶⁷ It is envisioned that subjects with pre-existing respiratory morbidities are more susceptible to the respiratory effects of wildfire PM, possibly because of weaker immune systems. Pre-existing morbidities, such as asthma, that cannot be fully controlled by medication might lead to greater susceptibility to adverse health effects of wildfire smoke.⁶⁶

Wildfire PM-induced inflammatory effects were also observed in animal studies. A study with a mouse bioassay analyzed the toxicity of PM_{10-2.5} and PM_{2.5} obtained during wildfire and normal conditions in the same region.⁷⁸ Toxicities were manifested as increased neutrophil counts and protein levels in lung lavage fluid and by histologic indicators of increased cell influx and edema in the lung. It was shown that both coarse and fine PM collected from the wildfires had significantly greater inflammatory effects on the mouse lung than PM collected from normal ambient air and that these particles were particularly toxic to lung macrophages, which might be attributable to oxidative stress arising from interactions of PM components with lung macrophages (Fig 2).⁷⁸ Furthermore, the same group observed that wildfire PM could cause major increases in oxidative stress in mouse lungs as measured by decreased antioxidant content of the lung lavage supernatants. Intriguingly, they found that the wildfire coarse PM fraction was more active (proinflammatory activity and oxidative stress) on an equal-dose basis than the fine PM, despite its lower content of PAHs.⁷⁹

In accordance with results from animal studies, *in vitro* studies showed that exposure of rat alveolar macrophages or human dendritic cells to newly formed wood-fire PM_{2.5} resulted in far greater TNF- α production compared with rural ambient urban indoor and outdoor PM_{2.5}.⁸⁰ In a study of human bronchial epithelial cells exposed to PM, it was revealed that urban ambient PM_{2.5} consisted of biological, trace metal, and PAH components, which elicited traditional proinflammatory gene responses along with biomarkers of oxidative stress. In contrast, wildfire PM_{2.5} is likely trace metals and PAHs, which also induce proinflammatory gene (*GMCSF*, *IL1A*, and *IL1B*) responses but elicit a more robust xenobiotic profile (*CYP 1B1*) and oxidative stress induction (*DUOX1*, *SOD2*, and *PTGS2*).⁸¹ Interestingly, there was one study that demonstrated that wildfire coarse PM is about 4 times more toxic to macrophages on an equal-weight basis than the same-sized PM collected from normal ambient air (no wildfires) from the

same region and season, which implicates nuclear factor κ B signaling in the response of macrophages to wildfire PM and suggests that most, if not all, of the cytotoxicity of wildfire PM to lung macrophages is the result of oxidative stress.⁸² Although existing toxicological evidence supports potential respiratory and cardiovascular health effects of wildfire smoke exposure, the body of evidence is relatively small compared with toxicological studies of general PM.⁶⁸

To further toxicological studies, controlled human studies have demonstrated increased inflammatory responses, specifically increased band neutrophil counts in peripheral blood⁸³ and increased cytokine levels⁸⁴ associated with the wildfires (Fig 2). In addition, exposure of healthy volunteers to wood smoke particles demonstrated an increased percentage of blood neutrophils, and bronchial lavage and BAL revealed a neutrophilic influx, indicating involvement of both systemic and pulmonary inflammation.⁸⁵

As stated above, we identified the main health protection issues to be considered in the event of wildfire. These lead to evidence-based actions in response to acute events and ways to prepare for a potential increase in wildfires caused by climate change. Respiratory health effects should be considered in formulating plans to mitigate against risk to health from wildfires. Those with chronic respiratory illness might experience a worsening in their respiratory symptoms. There could be an increased incidence of mild respiratory symptoms among previously healthy subjects, which might require some medical treatment. For some patients with chronic disease, increased doses of anti-inflammatory and bronchodilator medication might be required. Stocks of drugs should be sufficient to accommodate for this.⁶⁷ Other recommendations, which apply specifically to persons who live near combustion sources, include staying indoors and closing the windows or limiting physical activities outdoors.

In summary, consistent evidence of associations between wildfire PM exposure and respiratory morbidity in general, specifically for exacerbations of asthma and COPD, has been identified. More research is needed to determine whether wildfire PM exposure is consistently associated with cardiovascular effects. Research into which populations are most susceptible to health effects from wildfire exposure is also needed to inform public health planning for future wildfires.

INFLAMMATORY HEALTH EFFECTS OF PM FROM INDOOR BIOMASS COMBUSTION

In contrast to outdoor PM pollution, indoor PM pollution is more heterogeneous, with wide variations in pollutants and sources between countries. It is estimated that we spend an average of approximately 90% of our lifetimes indoors.⁸⁶ Therefore household air quality is critical for human health. Currently, indoor PM exposure has developed into a major concern that contributes to adverse cardiopulmonary effects.^{87,88}

Indoor PM pollution is attributed mainly to cooking fumes, outdoor origin of PM, coal and biomass fuel combustion, cigarette smoke, dust mites, microorganisms, and so on.^{86,89} Among these, biomass combustion is the most serious issue, especially in developing countries. About 3 billion persons in the world rely on burning biomass fuels, such as wood, charcoal, dung, or crop residues, in open stoves for cooking, heating, lighting and others.^{90,91} In rural households in developing

countries, where biomass fuels are burning for cooking, the average 24-hour levels of PM₁₀ range from 300 to 3000 $\mu\text{g}/\text{m}^3$ and can even reach 30,000 $\mu\text{g}/\text{m}^3$ or more.⁹² These values are much greater than the US Environmental Protection Agency's national 24-hour standard for PM₁₀ of 150 $\mu\text{g}/\text{m}^3$,⁹³ in comparison with 24-hour average concentrations of PM₁₀ from ambient pollutants and wildfire smog that range from 60 to 350 and 1.6 to 199.2 $\mu\text{g}/\text{m}^3$, respectively.^{94,95} Exposure to incomplete combustion products containing PM, benzene, benzo[a]pyrene, and carbon monoxide from biomass fuels is associated with millions of annual premature deaths caused by lung cancer, ischemic heart disease, acute lower respiratory tract infections (ALRIs), COPD, asthma, and stroke.⁹⁶

Acute and chronic exposure to PM generated by household biomass burning is known to cause a range of inflammation-associated respiratory symptoms.^{89,97,98} Epidemiologic studies have presented convincing evidence that biomass smoke particle exposure increases the risk of infant bronchiolitis, pneumonia in children, and COPD, asthma, and tuberculosis in adults⁹⁸⁻¹⁰⁰ caused by greater abundance of potentially pathogenic bacteria in their lung microstructure.¹⁰¹

Experimental results from cellular and animal models suggest airway inflammatory effects after biomass combustion-derived particle exposure. Oxidative stress and induction of inflammatory mediators (eg, IL-8, TNF- α , and IL-6) through activation of different signaling pathways (eg, mitogen-activated protein kinase, NOD-like receptors, and Toll-like receptors [TLRs]; Fig 2) were observed in human lung cells exposed to biomass smoke particles.¹⁰¹⁻¹⁰³ Consistently, pulmonary inflammatory response was detected in several animal studies. For example, wood or cow dung PM collected from rural Indian homes during cooking leads to pronounced lung inflammatory responses through IL-1 receptor and TLR signaling in mice (Fig 2).¹⁰⁴ It was also reported that biomass smoke exposure alters innate immune responses by initiating cell-surface receptor (TLRs, scavenger receptors, and transient receptor potential channels) signal transduction.¹⁰⁵

Women seem to be a highly exposed population because of daily cooking. High PM₁₀ levels after biomass burning are associated with an increase in inflammatory cell counts and levels of the biomarkers IL-6, IL-8, and TNF- α in the sputum of biomass-using women (Fig 2).¹⁰⁶ Similarly, Guarnieri et al¹⁰⁷ found that women who are continuously exposed to biomass smoke had greater gene expression of TNF- α , IL-8, and matrix metalloproteinase 9 in sputum cells.

There are few controlled human studies of biomass combustion products. Subjects exposed to wood smoke particles exhibit a neutrophilic influx in bronchial lavage and BAL fluid.⁸⁵ However, another study indicated that wood smoke (mean PM_{2.5} concentration, 224 $\mu\text{g}/\text{m}^3$) exposure does not affect airway inflammatory parameters in BAL fluid and bronchial mucosal biopsy specimens and only increases glutathione concentrations in BAL fluid of healthy volunteers (Fig 2).¹⁰⁸

Daily biomass fuel use has been linked to development of cardiovascular disorders (CVDs).¹⁰⁹ Chronic exposure to biomass smoke particles is associated with an increase in levels of biomarkers of endothelial inflammation, including E-selectin, soluble intercellular adhesion molecule 1, and vascular adhesion molecule 1, in the serum of participants,¹¹⁰ which might help us understand accelerated atherosclerosis induced by biomass

smoke particles. Dutta et al¹¹¹ found higher serum levels of IL-6, IL-8, TNF- α , and C-reactive protein in household biomass users, which predisposes them to increased risk of CVD development compared with control subjects (Fig 2). Overall, biomass smoke particle exposure can affect CVD development by evoking systemic inflammatory responses and blood endothelial inflammation (Fig 1).

Biomass combustion-derived particles are known to alter innate and adaptive immunity, which might predispose children to ALRIs.¹¹² Exposure to wood smoke particles results in loss of phagocytosis and dose-dependent inflammatory response in human alveolar macrophages obtaining from healthy volunteers' BAL fluid (Fig 2).¹¹³ A study from eastern India suggested that PM₁₀ and PM_{2.5} levels from indoor biomass smoke are positively associated with leukocyte and CD14⁺CD16⁺ monocyte levels in rural women.¹¹⁴

Exposure to biomass smoke particles might be a risk factor of the development of COPD.⁹⁷ Clinical data indicated that patients with biomass smoke-associated COPD have higher numbers of T_H2 cells and IL-4 serum levels than that in patients with tobacco smoking-associated COPD and healthy control subjects (Fig 2). Volunteers exposed to wood incomplete combustion-derived PM₁ with a concentration of 314 $\mu\text{g}/\text{m}^3$ exhibited minor proinflammatory lymphocyte and mast cell recruitment in bronchial biopsy specimens.¹¹⁵ Rural women cooking exclusively with biomass fuels had higher populations of CD8⁺ T cells, CD16⁺CD56⁺ natural killer cells, and regulatory T cells in peripheral blood (Fig 2), whereas total number of CD4⁺ T cells and CD19⁺ B cells was suppressed.¹¹⁶

Taken together, this evidence confirms alterations in innate and adaptive immunity after biomass combustion particle exposure, which can contribute to ALRIs and local and systemic inflammation.

Several intervention studies have been conducted in communities that used biomass cook stoves to reduce the adverse effects of biomass smoke particle exposure. In Malawi and Guatemala studies tested interventions to enhance cleaner-burning biomass-fueled cook stoves, with the goal to reduce pneumonia incidence in young children.^{117,118} However, there is not sufficient evidence to confirm that biomass-burning particle exposure is linked to the increasing risk of pneumonia in children. A better design of stove or fuel interventions producing lower average exposures than current chimney stoves might be needed to substantially reduce pneumonia in populations heavily exposed to biomass fuels.¹¹⁸ To reduce the adverse health effects of biomass smoke particles, an improved biomass stove intervention in rural Mexican women suggested that lower exposure levels of combustion products was associated with low risk of respiratory symptoms and lung function decrease.¹¹⁹ Additionally, air filtration treatment was also reported to evaluate the adverse effects biomass combustion products among asthmatic patients. It is widely acknowledged that air filtration treatment relieves total symptoms and sleep disturbance in asthmatic patients.^{120,121}

In summary, biomass smoke particle exposure is widespread globally, resulting in many adverse health effects through inflammatory responses. In the future, more interventions and effective strategies are needed to protecting residents from biomass combustion emissions by reducing the biomass fuels for daily cooking or warming. Interaction between community-based clinicians and the research community will

be critical to identifying and alleviating biomass fuel combustion-related disorders.

CONCLUSIONS AND FUTURE DIRECTIONS

All particle-rich combustion products appear to be proinflammatory, both in the lung and systemically, although there do appear to be considerable source-specific differences in local and regional inflammatory patterns. For example, wildfire smoke seems particularly toxic to the lung macrophages, perhaps even more so than other combustion-derived PM. If this is confirmed, and future research must prioritize this understanding, there are significant implications to clinicians and public health as we grapple with the scope and burden of pollution-driven morbidity and mortality. How this will inform specific anti-inflammatory strategies, thus far rather generically targeted, will be another area for ongoing investigation and innovation.

More attention will need to be given to particle exposures from indoor biomass burning, which have been historically less appreciated by the biomedical literature in spite of being very common and often at high concentrations in much of the world; associated inflammatory effects appear similar to those seen outdoors, but there are clearly some differences that can have clinical implications. Fuel and engine technology is changing rapidly, and with this, there will likely be changes in associated inflammation and potentially our approach to prevention and treatment. Intersecting with this dynamic, the extent to which inflammation is driven primarily by particulate versus gaseous fractions of combustion-derived aerosols has been difficult to ascertain and also has commercial and clinical implications.

In parallel with technological developments, the world is experiencing very dynamic changes in wildfires, which are bigger and more intense in much of the world; if, as suggested, PM from these fires is less inductive of inflammatory systemic and cardiovascular disease than other PM, this will need to be substantially documented. This is particularly true because the dose-response curve of particle-driven inflammation is little known in the human context; clinical concerns need to be informed by better real-world data across the range of concentrations relevant worldwide.

At the same time, nontraditional forms of inflammation require more attention because therapeutic approaches will likely be very different for these pathways. For example, neurogenic inflammation has been much less studied but might be more important than we know.

Finally, as we assemble and interpret this evolving knowledge base, we need to understand which approaches to prevention and treatment in this context are most feasible and cost-effective. Clearly, the years to come require a concerted effort between biomedical researchers, clinicians, and interdisciplinary colleagues, including engineers and economists, to translate the current understanding of particle-promoted inflammation to practical remediating strategies within a dynamic context that demands practicality and cost-effectiveness.

We appreciate the reviews of this manuscript by Dr Neil Alexis at the Center for Environmental Medicine, Asthma, and Lung Biology, University of North Carolina at Chapel Hill.

What do we know?

- All particle-rich combustion products appear to be proinflammatory, both in the lung and systemically.
- PM inhalation is associated with inflammation-dominated disorders, including COPD, asthma, bronchitis, and cardiovascular disease.
- Exposures to particles from indoor biomass burning, particularly in female subjects, are very common and often at high concentrations in much of the world; associated inflammatory effects appear similar to those seen outdoors.
- Oxidative stress, which is linked to inflammation, is a major mechanism underlying PM-induced cardiovascular and pulmonary health outcomes.

What is still unknown?

- How will emerging changes in fuel and engine technology change PM toxicity and associated inflammation and, consequently, our approach to prevention and treatment?
- Is wildfire-derived PM more inductive of inflammatory systemic and cardiovascular disease than other PM?
- What is the dose-response curve of particle-driven inflammation? How does this effect our approach to treatment?
- What is the role of neurogenic inflammation and other nontraditional pathways in the clinical inflammation associated with particulate-rich air pollution? Will novel treatments of neurogenic inflammation be helpful in this setting?
- To what extent is inflammation and specifically the type of inflammation (eg, $T_H1/T_H2/T_H17$ or neutrophilic versus eosinophilic) driven by particulate versus gaseous fractions of combustion-derived aerosols? How does this relate to the processes of inflammation resolution through removal of exposure and/or introduction of anti-inflammatories?
- In this context, to what extent is personalizing approaches to prevention and treatment feasible and cost-effective?

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