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The Effects of Wildfire Smoke on Asthma and Allergy

Terry L. Noah[1,3] · Cameron P. Worden[2,3] · Meghan E. Rebuli[1,3] · Ilona Jaspers[1,3]

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Abstract

Purpose of Review To review the recent literature on the effects of wildfire smoke (WFS) exposure on asthma and allergic disease, and on potential mechanisms of disease.

Recent Findings Spatiotemporal modeling and increased ground-level monitoring data are allowing a more detailed picture of the health effects of WFS exposure to emerge, especially with regard to asthma. There is also epidemiologic and some experimental evidence to suggest that WFS exposure increases allergic predisposition and upper airway or sinonasal disease, though much of the literature in this area is focused more generally on $PM_{2.5}$ and is not specific for WFS. Experimental evidence for mechanisms includes disruption of epithelial integrity with downstream effects on inflammatory or immune pathways, but experimental models to date have not consistently reflected human disease in this area.

Summary Exposure to WFS has an acute detrimental effect on asthma. Potential mechanisms are suggested by in vitro and animal studies.

Keywords Wildfire smoke · Wood smoke · Asthma · Allergy

Introduction

Abundant epidemiologic evidence now strongly links exposure to particulate air pollution with human respiratory diseases and mortality, and experimental evidence suggests this is linked to oxidative effects on cellular function and inflammation [reviewed in 1]. Although some studies link air pollution with risk for non-respiratory conditions such as cancer and diabetes, the most consistent and concerning findings are for increased risk of cardiopulmonary disease and mortality with exposure to fine particulate matter ($PM_{2.5}$). Studies have applied increasingly sophisticated and detailed exposure assessment methods to gain knowledge of risk factors, dose–response, and clues as to mechanisms of disease. Recent examples include the use of zip code-level air pollution assessments in New York City to estimate reductions in mortality and asthma morbidity resulting from specific air quality improvements [2], and the use of land-use regression models for air pollutant exposure in a large prospective longitudinal cohort in the United Kingdom, to estimate risk of developing chronic lung disease in a healthy adult population [3].

$PM_{2.5}$ is chemically heterogeneous depending on its sources, which include traffic, industry, and biomass burning; health effects thus vary by source. While $PM_{2.5}$ levels have decreased overall in the USA in the decades following the Clean Air Act, exposure from biomass fuel burning and wildfires is a major global problem and is also increasing regionally in the USA in association with climate change [4–6]. As a result, wildfire smoke (WFS) is a specific subtype of $PM_{2.5}$ that has received more attention in recent years in terms of health effects, especially in relation to respiratory illness [7–9]. WFS is composed of a complex mixture of particulate matter, carbon oxides, nitrogen oxides, hazardous air pollutants, water vapor, and trace levels of thousands of other compounds [8]. A 2019 workshop convened by the American Thoracic Society concluded that WFS causes acute respiratory effects, particularly for those with underlying chronic respiratory disorders, and that research is needed regarding longer-term effects of exposures, especially in

✉ Terry L. Noah
terry_noah@med.unc.edu

1 Department of Pediatrics, University of North Carolina at Chapel Hill, 260 Macnider Building, 333 S. Columbia St., Chapel Hill, NC 27599, USA

2 Department of Otolaryngology/Head & Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, USA

3 Center for Environmental Medicine, Asthma and Lung Biology, University of North Carolina at Chapel Hill, Chapel Hill, USA

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susceptible subgroups like children, asthmatics, or occupationally exposed groups [10•]. A systematic review published in 2021 found that for 5 pre-post and 11 cross-sectional studies of sites from the USA and several other countries, there was a significant increase in emergency department (ED) visits and hospitalizations for respiratory illnesses after WFS exposure, particularly in children < 5 years old [11]. Techniques have advanced to estimate the $PM_{2.5}$ health effects specific for WFS in large populations, using combinations of ground-level monitoring and satellite imaging with chemical analysis of aerosols; in California, such studies have demonstrated exposure dose-related increases in respiratory hospitalizations in the presence of WFS [12] and health disparities in $PM_{2.5}$ exposures [13].

Wildfires are increasing in both prevalence and intensity worldwide as a result of global climate change [14–16]. Wildfires impact the lives of hundreds of thousands of individuals in the USA alone. According to the National Interagency Fire Center, as of October 3, 2022, in the USA, there had been 54,184 fires, covering almost 7 million acres, thus far during that year [17]. Of particular concern, there has been rapid growth in the prevalence of homes located within the wildland-urban interface (WUI), representing homes that reside within 0.5 miles of wildlands [18•, 19]. Fires at this interface are likely to produce smoke that differs chemically from WFS in wilderness areas, with complex mixtures of combustion emissions from both biogenic and anthropogenic sources, including plastics, metals, insulation material, and other sources with known toxic combustion products.

For the above reasons, it is critical that we better understand WFS exposures, their complexity, and their resulting impacts on public health. In the current review, we summarize recent epidemiologic literature relevant to effects of WFS exposure on asthma and on allergic or sinonasal disease, as well as emerging mechanistic concepts.

Wildfire Smoke and Asthma

As pointed out in a 2019 review by Reid and Maestas [20], the evidence for an association between WFS and respiratory diseases is clearest for acute effects on asthma, compared to the evidence for long-term effects or for acute respiratory conditions other than asthma, as illustrated by several population-based studies of hospital admission rates [21, 22]. We focused the current review on original research studies referenced in PubMed, for the past 5 years, using search terms "wildfire smoke AND asthma." Studies that did not attempt to estimate WFS-specific exposure (as opposed to particulate matter in general) were not reviewed. Highlights of these studies are shown in Table 1 [references 23••, 24-38, 39•]. A variety of specific methods were used to estimate exposure, but most involved combining data from ground-level, fixed monitoring sites for $PM_{2.5}$ with meteorological data and satellite-based imaging or physicochemical data to model the portion of exposure specific to WFS. Nearly all studies showed a statistically significant, exposure dose-related increase in risk for diagnosis or exacerbation of asthma after exposure to WFS. Many of these studies were conducted in western North America, where seasonal wildfires are common, but it has been pointed out by O'Dell and colleagues [40] that actual asthma morbidity from WFS in the USA may be greater in the east, due to much greater population density.

The information summarized in Table 1 shows that most studies sought to link WFS exposure estimates with health markers for asthma from de-identified population health databases, using billing codes and discrete, easily quantified events such as ED visits or hospital admissions. Periods of active WFS exposure were typically compared with non-exposure periods for the same population; some studies employed a time-stratified case-crossover analysis, which can compare exposure days vs. adjacent non-exposure days at the individual level. Some reports also estimated specific lag times for WFS effects. Reported relative risk or odds ratios for increased short-term WFS effects on asthma were remarkably consistent, most commonly around 1.10 (range 1.07–1.68) per 10 $\mu g/m^3$ increase in WFS $PM_{2.5}$ (range 1–23 $\mu g/m^3$). Increased risk of new onset asthma, as measured by increases in asthma consultation post-fire, was also found in firefighters exposed to the Fort McMurray fire in Alberta, Canada [39•]. Notably, the reported odds ratio was higher in this frequently exposed occupational group than most of the other studies in Table 1 (OR 2.56). Only one of the studies reviewed did not find a significant risk from WFS; uniquely among this series of papers, this study looked at lung function and symptom scores in a relatively small group of asthmatics [27]. Many of the reviewed studies also assessed risk for non-asthma respiratory conditions such as pneumonia or COPD, and non-respiratory conditions such as cardiovascular disease. In general, the evidence for WFS exposure effects was less consistent for these conditions, than for asthma.

Young asthmatic children may be at special risk for WFS-induced exacerbation of symptoms [11, 23••]. Childhood risk was highlighted in a recent review [41], along with the possibility that longer-term effects on lung function could occur, as has been noted in a study of infant rhesus monkeys exposed to ambient WFS [42••]. However, other studies did not find a difference between children and adults in terms of risk for asthma exacerbation from WFS exposure. Increased risk for those with low socioeconomic status was highlighted by Reid et al. [21], and several studies highlighted increased risk for indigenous groups [33–35]. The two studies that specifically commented on sex-specific effects reported stronger WFS effects in women than in men [21, 34].

As noted above, evidence from animal studies suggests there may be long-term impacts of WFS exposure on lung

Table 1 Summary of original studies on asthma and wildfire smoke published in 2018–2023 and indexed in PubMed

Study [reference]	Population and location	Exposure assessment	Asthma outcome	Asthma risk estimate	Comment
Hutchinson JA, et al. *PLoS Med.* 2018;15:e1002601. [23••]	San Diego County, Oct. 2007 fire complex, Medi-Cal beneficiaries	Spatiotemporal model using wildland fire emission system and atmospheric dispersion	Hospital admissions, outpatient visits	RR 1.08 (1.04, 1.13) per 10 μg/m^3 ↑ in $PM_{2.5}$ for ED visit for asthma during early post-exposure period	243% increase in asthma diagnosis for children age 0–1 yr during exposure period
DeFlorio-Barker S, et al. *Environ Health Perspect.* 2019;127:37,006. [24]	Hospitalized adults ≥ 65 yr, all US counties within 200 km of large wildfires 2008–2010 (asthma admissions, Medicare database)	Fixed monitor data, adjusted for "smoke" days from wildfires (CMAQ framework)	Hospital admissions	$PM_{2.5}$ attributable increase in asthma admissions 7% for "smoke" days, 2% for "nonsmoke" days	Increased risk for asthma, unlike for other cardiopulmonary conditions
Stowell JD, et al. *Environ Int.* 2019;133(Pt A):105,151. [25]	Colorado 2011–2014 fire seasons (May-Aug.)	Ground $PM_{2.5}$ from EPA monitors, plus high-res satellite optical density data for WFS	ED and hospital admissions	OR 1.08 (1.06, 1.11) per 1 μg/m^3 ↑ in WFS $PM_{2.5}$	Similar results for adults and children with asthma
Reid CE, et al. *Environ Int.* 2019;129:291–298. [26]	Northern California, Zip codes exposed to Jun-Jul 2008 fires	Spatiotemporal model, fixed monitors, machine learning algorithm	ED visits and hospital admissions	RR 1.11 (1.09, 1.14) per 10 μg/m^3 ↑ in $PM_{2.5}$	Unlike $PM_{2.5}$ O3 effect was not significant in the multivariate model
Lipner EM, et al. *Geohealth.* 2019;3(6):146–159 [27]	Pediatric asthma patients at National Jewish Health (Western U.S.) 2012–2015	Retrospective; assessed local WFS-related $PM_{2.5}$ during clinic visits	Asthma symptom score, PFT during routine (not sick) clinic visits	No association of symptoms with WFS; FEV_1 ↓ next day in older kids (12–21 yrs)	Assessed nonurgent visits, unlike all other studies
Gan RW, et al. *J Expo Sci Environ Epidemiol.* 2020;30:618–628 [28]	2013 Oregon wildfire season; asthma claims Time-stratified, case-crossover design	Blended model of in situ monitoring, chemical transport models, and satellite-based data	Asthma healthcare utilization (insurance claims)	ED visits: OR 1.09 (1.04, 1.13) per 10 μg/m^3 increase in WFS $PM_{2.5}$	Similar results for office visits, and refills of rescue inhalers
Kiser D, et al. *Environ Health.* 2020;19:92. [29]	Reno, NV 2013–2018; data from a regional health system	Local fixed monitors for $PM_{2.5}$, with dates when WFS was present	ED or urgent care visits	Presence of WFS increased the 5 μg/m^3 ↑ in $PM_{2.5}$-associated asthma effect by 6.1% (2.1, 12.0)	Similar outcome as DeFlorio-Barker 2019
Magzamen S, et al. *Geohealth.* 2021;5:e2020GH000330 [30]	Colorado Front Range area, 2012 and 2015 Time-stratified case-crossover analysis	Surface monitors for Western US, plus satellite-based smoke plume estimates	Hospital admissions	OR 1.46 (1.09, 1.94) for asthma admissions, for each 10 μg/m^3 ↑ in WFS $PM_{2.5}$	This relationship was seen for "long-range transport" WFS events, but not local wildfires
Tornevi A, et al. *Int J Environ Res Public Health.* 2021;18:6987. [31]	Sweden, 2018 wildfire events in Jamtland Harjedalen region	Modeled WFS $PM_{2.5}$ exposures using MATCH model (complex meteorological and atmospheric chemical data)	Clinic visits	RR 1.68 (1.09, 2.57) for "smoke days" (daily maximum 1-h mean $PM_{2.5} > 20$ μg/m^3)	
Malig BJ, et al. *Sci Total Environ.* 2021;787:147,507 [32]	San Francisco Bay area, Oct. 2017 wildfires	County-level monitoring avg $PM_{2.5}$ during wildfire period compared to adjacent periods	ED visits and hospital admissions	ED asthma visits: RR 1.46 (1.38, 1.55) per 23 μg/m^3 ↑ in $PM_{2.5}$ during fire period, vs 0.77 (0.55, 1.08) in non-fire period	

Table 1 (continued)

Study [reference]	Population and location	Exposure assessment	Asthma outcome	Asthma risk estimate	Comment
Hahn MB, et al. *Geohealth.* 2021;5:e2020GH000349. [33]	Alaska (3 cities) during 2015–2019 wildfire seasons	Ground-based monitors and satellite-based smoke plume estimates	ED visits	Increased asthma-related ED visits among 15–65 yr olds (OR = 1.12, 95% CI = 1.08, 1.16) on day of WFS exposure	Similar for > 65 yr olds, Native Alaskans
Howard C, et al. *BMJ Open.* 2021;11:e037029 [34]	Northwest Territories (Canada), summer 2014 prolonged, severe wildfire period	Compared WFS period to before and after periods	Hospital admissions, ED visits; SABA prescriptions	ED visits: 1.11 (1.07, 1.14) per 10 μg/m^3 ↑ in $PM_{2.5}$ Also, 48% increase in SABA prescriptions	Median 24-h mean $PM_{2.5}$ fivefold higher in the summer of 2014 compared with 2012, 2013 and 2015 (median = 30.8 μg/m^3), with mean peaking at 320.3 μg/m^3. Inuit more affected
Beyene T, et al. *Int J Environ Res Public Health.* 2022;19:7419. [35]	Eastern Australia asthma registry, 2019–2020 bushfires	24-h avg $PM_{2.5}$ at fixed monitoring stations; satellite imagery for bushfire component	Self-reported symptoms	44% had oral steroids during exposure, 65% had persistent symptoms after fires	Mean $PM_{2.5}$ exposure 32.5 μg/m^3 on bushfire days
Heaney A, et al. *Geohealth.* 2022;6:e2021GH000578. [36]	California, 2004–2009 wildfire seasons	Goddard Earth-Observing System (GEOS-Chem), all-source vs without wildfire-specific $PM_{2.5}$	Unscheduled hospital visits for asthma and other conditions	Smoke event days associated with 10.3% (2.3, 19.0) ↑ in asthma visits	Largest effect for children 0–5 yrs
Moore LE, et al. *Int J Environ Res Public Health.* 2023;20(3):1937 [37]	Calgary, Canada 2010–2021	Ground-level monitors with WFS dates estimated from satellite images	Health insurance claims for asthma exacerbation in children	WFS days associated with ↑ asthma exacerbation, RR 1.13 (1.02, 1.24)	Exacerbations significantly reduced during periods of COVID-19 healthcare precautions
Blando J, et al. 2022. *Int J Envir Res Pub Health.* 2022;19(3):1241 [38]	Northeastern North Carolina, patients at allergy clinic, studied before, during and after Dismal Swap peat bog fires in 2008 and 2011	Wind blowing from fire area towards community as proxy for exposure	Peak flow	Reduced peak flow rates associated with past WFS exposure	Study conducted 1 year after exposures
Cherry N, et al. *J Occup Environ Med.* 2021;63(9):779–786 [39•]	Fort McMurray fire in Alberta, Canada 2016, firefighters and controls	Exposure to fire-related $PM_{2.5}$ from Alberta Environment monitoring stations and satellite imagery	Spirometry and asthma consultation	↑ asthma consultation post-fire (OR 2.56; 95% CI 1.75–3.74), ↓ FEV_1 and FVC with increasing exposure	Individuals with ongoing fire symptoms also had a higher occurrence of positive methacholine challenge and bronchial wall thickening (OR 4.35; 95% CI 1.11–17.12. Lower diffusion capacity also related to increased exposure

WFS wildfire smoke, *$PM_{2.5}$* particulate matter ≤ 2.5 μm in diameter, *ED* emergency department, *RR* relative risk, *OR* odds ratio, *SABA* short-acting beta-adrenergic agonist, *COPD* chronic obstructive pulmonary disease, *PFT* pulmonary function tests, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity

function or disease [42••]. However, there are few published data as to longer-term effects of WFS exposures on humans with or without asthma. An observational cohort study in 842 patients at an allergy clinic assessed peak flow rates 1 year after the 2008 and 2011 Dismal Swamp peat bog fires in northeastern North Carolina and estimated a decrease in peak flow rates related to past smoke exposure, based on records of winds blowing in the direction of the community from the fires [38]. In a report currently under review for publication [43], our group conducted a retrospective study assessing the link between developmental exposure to wildfire smoke and evidence for childhood upper and lower respiratory diseases; this study demonstrated that wildfire smoke exposure during the first 6 months of life was associated with increased use of medications for respiratory symptoms. In the study of Alberta firefighters, clinical assessments up to 46 months post-fire were completed. When analyzing those who complained of pulmonary symptoms related to the fire, there was increased incidence of positive methacholine challenge test (28.6% in those with ongoing symptoms and 8.9 without) as well as combined positive MCT and bronchiole wall thickening, both of which were also associated with higher estimated exposure during the fire (10.4 ± 1.4 log$PM_{2.5}$ $\mu g/m^3$*h) [39•]. These studies together suggest potential for long-term impacts of WFS exposure, which should be studied further.

Wildfire Smoke and Upper Respiratory Illness, Allergy, or Rhinitis

Older epidemiologic studies have associated an increase in the incidence of sinonasal symptoms with wildfire or wood smoke exposure, especially among children and first responders [44, 45]. These include a study from the Southern California wildfires of October 2003, during which a 1.98 OR was reported for sneezing or runny nose [46]. More recently, a 3.11 OR (1.62, 5.97) for itchy/watery eyes was reported among children exposed to a large wildfire in Spain, especially among asthmatics [47]. Several studies have been published recently assessing a specific link between WFS and rhinitis or allergy symptoms, but with mixed results. Among the previously discussed asthma epidemiological studies, several included an assessment of the association between WFS and acute upper respiratory illnesses (URI), with some showing no significant WFS effect [25, 31], one showing a positive association with RR 1.77 [23••], and one showing less impact of WFS compared to non-wildfire $PM_{2.5}$ on URI risk [32]. Fadadu et al. [48] found a RR of 1.49 (1.07, 2.07) for children and 1.15 (1.02, 1.31) for adults for clinic visits for atopic dermatitis symptoms, during exposure to WFS from the 2018 Camp Fire in the San Francisco area. While not specific for WFS exposure, several reports are of interest for suggesting that $PM_{2.5}$ exposure can serve as a risk factor for worsening chronic rhinosinusitis (CRS) disease severity, with histological evidence of type 2 eosinophilic inflammation [49–52].

Mechanistic and Experimental Studies

The mechanisms of WFS effects on the lower airways and lungs, under asthmatic or healthy conditions, are likely complex and are an area of active investigation. As reviewed by Tuazon et al. [53], potential mechanisms for which there is supporting evidence include alteration of Th1/Th2 immune balance, epigenetic modifications, oxidative stress, alterations in responses to infectious agents, disrupted epithelial barrier function in the respiratory tract, and coincident increases in wildfires and allergen exposure due to global warming. Additional recent literature in these areas is summarized below and in Table 2 [references [54-75]. While WFS-specific data are only starting to emerge, some recent experimental data from $PM_{2.5}$ exposure are also relevant to mechanistic hypotheses.

Altered Immune or Inflammatory Responses

Studies using lung cell lines or cultured primary cells have allowed exploration of cellular mechanisms for the generally pro-inflammatory effects of direct wood smoke exposure (a commonly used model of wildfire or biomass smoke) in vitro, including activation of NFkB and caspase-1 signaling pathways [54–58]. Exactly how these pathways impact manifestations of asthma and allergy is not yet clear. In terms of acute inflammatory responses to WFS or to wood smoke, interesting data are emerging from experimental studies in animal models. Some recent reports indicate that wood smoke induces a pro-inflammatory response in the respiratory tract in rodents, as evidenced by increased cytokines or inflammatory cells in lavage fluid [58, 61]. A study in a guinea pig model found increased BALF cytokines after smoke exposure, but an actual decrease in neutrophils [60]. Sun and colleagues showed that treatment with ursolic acid, an antioxidant, following $PM_{2.5}$ exposure helped to alleviate symptoms of sneezes and nasal rubs in rats, and reduced serum IL-4, IL-5, IL-13, and eotaxin-1 while reducing nasal mucosal eosinophilia [61]. In contrast, exposure of HDM-allergic mice to smoldering eucalyptus or oak led to reduced minute volume and peak inspiratory flow rates, but actually suppressed markers of inflammation (IL-4, IL-5, in BALF; mixed inflammatory cells in lung) [59]. Thus, the lung wood smoke response in experimental animal models appears to be variable and model dependent.

Limited data are available from controlled exposures of human volunteers to wood smoke and those studies since 2020 have been reviewed in Schwartz et al. [76]. In one study of healthy adult subjects, increasing levels of IL-8, IL-1β, and 8-epi-PGF2α in nasal lavage fluid was

Table 2 Summary of experimental studies 2018–2023 relevant to wildfire smoke effects in asthma and allergy/rhinitis

Study [reference]	Experimental model	WFS effect domain	Result
Gonzalez DH et al. *Chem Res Toxicol.* 2020;33(4):999–1009. [54]	BEAS-2B exposed to cigarette smoke or wood smoke particles	Altered immune or inflammatory responses	A fulvic acid-like substance in WS particles induces iron deficiency and production of IL-8, IL-6
Wang B et al. *Chemosphere*. 2021;272:129,616 [55]	Human bronchial epithelial cells exposed to traffic-related or WS particles	Altered immune or inflammatory responses	Both TRAP and WS-induced inflammatory responses, but WS-induced IL-6 to greater degree
Gupta A et al. *J Biol Chem.* 2021;297(4):101,147 [56]	BEAS-2B cell line exposed to WS from white oak	Altered immune or inflammatory responses	Links identified between aryl hydrocarbon receptor (AHR) and NFκB in WS-induced inflammatory response
Fu X et al. *Chemosphere*. 2022;307(Pt 2):135,726. [57]	16-HBE cell line exposed to WS particles from burning China fir	Altered immune or inflammatory responses	WS particle-induced pyroptosis, increased ATP secretion, and activation of the caspase-1/IL-1β/IL-18 signaling pathway and downstream cytokines
Ihantola T et al. *Part Fibre Toxicol.* 2020;17(1):27. [58]	Human alveolar epithelial (A549) and murine macrophage (RAW264.7) cell lines, and C57Bl6 mice, exposed to pine and spruce combustion particles	Altered immune or inflammatory responses	Genotoxicity (DNA damage) and inflammatory responses (increased cytokines) noted, though specific responses differed among models
Hargrove MM et al. *Inhal Toxicol* 2019;31(6):236–247 [59]	Control and HDM-allergic mice exposed to smoldering peat, eucalyptus or oak	Altered immune or inflammatory responses	Reduced resp rate and suppressed lung inflammation (eosinophils, IL-4, IL-5)
Ramos C et al. *Toxics*. 2021;9(9):227. [60]	Guinea pigs exposed to pine wood smoke	Altered immune or inflammatory responses	WS exposure increased BALF cytokines and macrophages, but decreased neutrophils
Sun N et al. *Am J Rhinol Allergy.* 2020;34(5):587–596 [61]	Rats with ovalbumin-induced allergic rhinitis exposed to $PM_{2.5}$	Altered immune or inflammatory responses	Antioxidant alleviated $PM_{2.5}$-enhanced AR symptoms and reduced serum type 2 cytokines
Alexis NE et al. *Inhal Toxicol*. 2022;34(11–12):329–339 [62]	Human volunteers exposed to WS (smoldering oak, 2 h, 500 μg/m^3); induced sputum at 4 h and 24 h after exposure	Altered immune or inflammatory responses	Underlying mild asthma history a risk factor for WS-induced increase in % PMN and IL-8 in sputum
Sada-Ovalle I et al. *Front Med (Lausanne).* 2018 13;5:309. [63]	Macrophage cell lines (THP-1) exposed to PAH from WS; infected with *M. tuberculosis*	Altered response to infectious agents	Exposure to wood smoke derived PAH activate THP-1 and reduced mitochondrial function, enhancing growth of *M. tuberculosis*
Brocke SA e al. Am J Physiol Lung Cell Mol Physiol. 2022;322:L479-L94 [64]	Human nasal epithelial cells in air–liquid interface culture, exposed to WS	Altered response to infectious agents	Cells from female donors had greater downregulation of gene expression following SARS-CoV-2 infection than male cells
Vose A et al. *Toxicol Appl Pharmacol*. 2021 Sep 1;426:115,645 [65]	C57Bl6 mice exposed to WS particles then infected with influenza HINI-PR8	Altered response to infectious agents	Prior subacute WSP exposure was *protective* against influenza-induced lung inflammation
Rebuli ME et al. *Am J Respir Crit Care Med.* 2019;199(8):996–1007 [66]	Healthy human volunteers exposed to WS (smoldering oak, 2 h, 500 μg/m^3) then inoculated with attenuated influenza	Altered response to infectious agents	WS-induced sex-specific inflammatory expression profiles in nasal mucosa
Pardo M et al. *Chem Res Toxicol*. 2021 Jun 21;34(6):1588–1603 [67]	A549 and BEAS-2B cells exposed to fractions of wood tar from burning pine pellets	Oxidative stress	Both water- and organic-soluble fractions of wood tar induced increased superoxide anion and total reactive oxygen species, leading to cell death and apoptosis

Table 2 (continued)

Study [reference]	Experimental model	WFS effect domain	Result
Deering-Rice CE et al. *Chem Res Toxicol*. 2018 May 21;31(5):291–301. [68]	Human airway epithelial cells lines and mice exposed to wood smoke particulate matter (WSPM) from pine	Epithelial integrity	Specific chemical constituents of WSPM induced expression of the transient receptor potential vanilloid-3 (TRPV3) ion channel. Exposed mice had increased methacholine sensitivity
Burrell K et al. *Mol Pharmacol*. 2021 Sep;100(3):295–307. [69]	Human bronchial epithelial cells exposed to WS particulate matter (PM)	Epithelial integrity	WS PM induced expression of the transient receptor potential vanilloid-3 (TRPV3) ion channel, which helps coordinate epithelial repair
Li X et al. *Biosci Rep*. 2018 Sep 12;38(5):BSR20171577 [70]	Human bronchial epithelial cells exposed to traffic associated (TA) and wood smoke (WS) particulate matter	Epithelial integrity	Both TA and WS particles induced altered long noncoding RNA and mRNA profile changes, apoptosis, and autophagy; in a dose- and p53-dependent manner
Zeglinski MR et al. *Sci Rep*. 2019 Jul 11;9(1):10,027. [71]	A549 cells (human alveolar epithelial) exposed to birch wood smoke (WS) particles	Epithelial integrity	WS dose-dependent loss of epithelial integrity, reduced E-cadherin expression, via p44/42 MAPK-dependent pathway
Memon TA et al. *Toxicol Sci*. 2020 Apr 1;174(2):278–290. [72]	Mice, primary human airway epithelial cells exposed to wood smoke (WS)	Mucin expression	WS particles induced increased expression of MUC5AC
Tassew D et al. *Environ Health Perspect*. 2022 Jan;130(1):17,010 [73]	Mice, primary human airway epithelial cells exposed to wood smoke (WS)	Mucin expression	WS (oxalate component) induced increased expression of MUC5AC; p53 pathway-dependent
Singh D et al. *J Hazard Mater*. 2023 Jan 5;441:129,874. [74]	Human embryonic kidney 293 (HEK-293 T) cells exposed to WS from mesquite, cherry or oak	Mucin expression	WS-induced promoter activity for mucin-expression genes
Koval LE et al. *Environ Sci Technol*. 2022 Dec 6;56(23):17,131–17,142. [75]	Mice exposed to variety of Wood smoke sources	Other	Flaming peat, flaming eucalyptus, smoldering eucalyptus result in lung transcriptomic changes similar to endotoxin

WS wood smoke, $PM_{2.5}$ particulate matter ≤ 2.5 μm in diameter; *PAH* polycyclic aromatic hydrocarbons, *TRAP* traffic-related air pollution

correlated to rising levels of ambient exposure to $PM_{2.5}$ [77]. Our group has recently reported that a history of underlying mild asthma was associated with increased risk for sputum inflammation (neutrophils, IL-8), 24 h after exposure of healthy young adult volunteers to moderate concentrations of wood smoke (smoldering oak) for 2 h [62]. These studies thus suggest that altered inflammation or immunity might be associated with increased risk for WFS-induced asthma effects, but the mechanisms are not yet clear.

Altered Response to Infectious Agents

Another potential pathway for WFS to affect asthma symptoms is by increasing risk of respiratory infection [78]. WFS exposure was linked to an increased risk of SARS-CoV2 infection during the COVID-19 pandemic [79, 80]. An experimental study suggested that exposure to wood smoke might increase risk for mycobacterial infection, by inhibiting macrophage mitochondrial function [63]. In another study, human nasal epithelial cells (hNECs) cultured at air–liquid interface (ALI) exposure to condensates from biomass smoke emissions prior to infection with SARS-CoV-2 reduced expression of antiviral mediators, interferon, and chemokines; cells from female donors displayed a greater downregulation of gene expression following SARS-CoV-2 infection than male cells [64]. In C57BL/6 mice, however, wood smoke particle exposure appeared to be protective against subsequent influenza infection [65]. In our recent controlled wood smoke exposure study, healthy young adults that were exposed to 2 h of either filtered air or wood smoke particles, then nasally inoculated with live-attenuated influenza virus vaccine, displayed a sex-based difference in inflammatory gene expression patterns in the nasal mucosa [66]. Thus, the role of WFS exposures in altering susceptibility or responses to respiratory infection, and its effect on asthma and allergy, appears to be complex and not consistently mimicked by experimental models to date.

Oxidative Stress

Many forms of particulate matter contain redox active chemical components and thus have the ability to generate reactive oxidative species leading to inflammation [81]. In in vitro studies of primary human nasal epithelial cells (hNEC) in culture, $PM_{2.5}$ exposure has been shown to induce endogenous oxidative stress and increase the release of inflammatory cytokine mediators such as IL-6, IL-8, IL-13, TNF-α, and eotaxin [82, 83]. Oxidative stress was recently reported for human lung cells lines exposed in vitro to products of wood burning [67].

Respiratory Epithelial Integrity

In the respiratory tract, adjacent epithelial cells are bound together on the apical mucosal surface primarily via tight junction complexes that serve to limit paracellular flux and help to establish distinct apical and basolateral membrane domains [84]. Disruption of this epithelial barrier can permit penetration of pathogens, allergens, and other toxins into the underlying submucosal tissues leading to inflammation and disease. Multiple experimental studies have shown that long-term particulate matter exposure can lead to downregulation of the nuclear erythroid 2–related factor 2 (Nrf2) pathway which can negatively affect epithelial barrier permeability and can predispose to chronic rhinosinusitis and type 2 inflammation [85–88]. Zeglinski et al. [71] assessed the effects of a wood smoke-infused solution on alveolar epithelial barrier function, cell migration, and survival, and found reduction in barrier function. They also noted that wood smoke exposure activated the p44/42, MAPK signaling pathway, and inhibition of p44/42 phosphorylation prevented loss of barrier. Other recent reports confirm specific effects of wood smoke particles on epithelial barrier factors in vitro [68–70]. Thus, it is possible that WFS has its initial impact on the airways via direct impact on epithelial integrity.

Allergen Exposure

It has been speculated that increased allergen exposure associated with global warming and climate change is driving increased WFS-linked asthma or allergy effects; similar interactions between allergens and air pollutants have been recently demonstrated [89, 90]. However, two recent studies do not appear to support this concept. Bagheri et al. [91] found that pollen counts and $PM_{2.5}$ were each associated with increased respiratory hospital admissions, but pollen was not an independently significant risk factor in multivariate analysis. Paudel et al. [92], using time-series regression models for the period 2002–2019, also did not find significant association between pollen concentrations and wildfire smoke exposure.

Other Mechanistic Studies

Experimental studies have been published recently using animal or cell culture models. Koval and colleagues [75] assessed lung transcriptomic signatures in female mice exposed to biomass smoke condensates produced from a variety of biogenic sources relevant to wildfires. While exposure to emission condensates from smoldering red oak and smoldering peat caused moderate transcriptomic changes, exposures from flaming peat, flaming eucalyptus, and smoldering eucalyptus induced the greatest

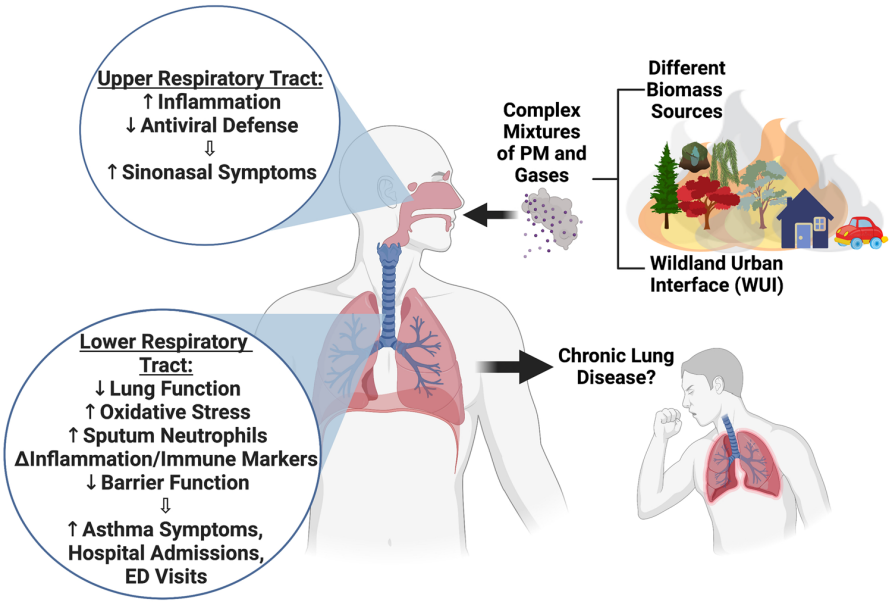

Fig. 1 Potential mechanisms for WFS effects, such as disruption of epithelial integrity with downstream effects on type 2 inflammatory or immune pathways, are emerging from in vitro and animal studies

transcriptomic responses, with similarity to the pro-inflammatory agent lipopolysaccharide. These data suggest that smoke resulting from combustion of these biomass sources induces responses similar to those caused by inhaling endotoxin and that combustion source and temperature affect respiratory outcomes. Carberry et al. [93] found that post-exposure, lung (and heart) extracellular vesicle (EV) microRNA showed differential expression profiles enriched for hypoxia and cell stress-related pathways, and postulated that wildfire exposures induce cardiopulmonary responses mediated by circulating plasma EVs. Interestingly, Xu et al. [94] studied female Australian twin pairs and found that long-term exposure to wildfire-related PM2.5 was associated with distinct blood DNA methylation signatures compared to non-wildfire PM2.5 exposures, supporting the concept of epigenetic effects of WFS.

Conclusions and Areas of Further Research

In summary, there is abundant and fairly consistent epidemiologic evidence suggesting that exposure to WFS has an acute detrimental effect on asthma and that WFS may be more problematic in this regard than other forms of $PM_{2.5}$. Research in this area has been limited historically by the inability to accurately assess exposure at either the population or individual level, but recent advances in spatiotemporal modeling, increased availability of ground-level monitoring data, in combination with access to large health effects databases, are allowing a more detailed picture of the health effects of WFS exposure to emerge, especially with regard to asthma. There is also epidemiologic and some experimental evidence to suggest that WFS exposure increases allergic predisposition and upper airway or sinonasal disease, though much of the literature in this area is focused more generally on $PM_{2.5}$ and is not specific for WFS. Potential mechanisms for these effects, such as disruption of epithelial integrity with downstream effects on type 2 inflammatory or immune pathways, are emerging from in vitro and animal studies (Fig. 1), but experimental models to date have not consistently reflected human disease in this area.

Since WFS exposures are expected to increase in the coming decades, this is a major public health and equity concern, but major gaps remain in our understanding of these complex interactions, and therefore in our ability to formulate effective preventive strategies. For example, there are currently very few data directly addressing the longer-term effects of repeated or chronic WFS exposures on established asthma and/or allergic disease, the specific WFS chemical toxicities of greatest impact on human health, strategies to protect high-risk and vulnerable populations, or the feasibility of large-scale application of monitoring technologies to guide individual actions. The complexity inherent in WFS exposures and how they relate to biological systems will ultimately require the application of new data analysis approaches such as the one described recently by Kim et al. [95]. These approaches may be able to uncover hazardous chemical components/groups within complex WFS mixtures driving respiratory toxicity and its manifestations in asthma and allergic disease.

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Declarations

Conflict of Interest No authors have any financial conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments involving human or animal subjects performed by the authors were in accordance with the ethical standards of institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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- • Of importance
- •• Of major importance

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