Rouadi et al. World Allergy Organization Journal (2020) 13:100467
http://doi.org/10.1016/j.waojou.2020.100467

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Immunopathological features of air pollution and its impact on inflammatory airway diseases (IAD)

Philip W. Rouadi[a]*, Samar A. Idriss[a]**, Robert M. Naclerio[b], David B. Peden[c], Ignacio J. Ansotegui[d], Giorgio Walter Canonica[e], Sandra Nora Gonzalez-Diaz[f], Nelson A. Rosario Filho[g], Juan Carlos Ivancevich[h], Peter W. Hellings[i,j], Margarita Murrieta-Aguttes[k], Fares H. Zaitoun[l], Carla Irani[m], Marilyn R. Karam[n] and Jean Bousquet[o,p,q]

ABSTRACT

Air pollution causes significant morbidity and mortality in patients with inflammatory airway diseases (IAD) such as allergic rhinitis (AR), chronic rhinosinusitis (CRS), asthma, and chronic obstructive pulmonary disease (COPD). Oxidative stress in patients with IAD can induce eosinophilic inflammation in the airways, augment atopic allergic sensitization, and increase susceptibility to infection. We reviewed emerging data depicting the involvement of oxidative stress in IAD patients. We evaluated biomarkers, outcome measures and immunopathological alterations across the airway mucosal barrier following exposure, particularly when accentuated by an infectious insult.

Keywords: Inflammatory airway disease, Air pollution, Oxidative stress biomarkers, Tobacco smoke, Antioxidant

INTRODUCTION

The presence in the air of one or more natural or anthropogenic substances at a concentration, or location, for a duration, above their natural levels with the potential to cause an adverse health effect defines air pollution.[1] Indoor air pollution refers to chemical, biological, and physical exposure of air pollutants in homes, schools, and workplaces. Similar to indoor air pollution, ambient (outdoor) air pollution can result from chemical substances or biologically derived contaminants modified by climate change or human activity such as bioaerosols and aeroallergens. Air quality guidelines endorsed by the World Health Organization (WHO) aim to provide clean air in and around the home.[2] Air pollution reduced life expectancy in 2017 by 1 year and 8 months on average worldwide.[3] WHO has linked 4.3 million deaths globally in 2012 to household cooking using coal, wood and biomass stoves. Outdoor air pollution in the same year caused an estimated 3.7 million deaths.[4] In inflammatory airway disease (IAD) patients an estimated 7–11% increased risk in asthma-related mortality was commensurate with a rise in ambient pollutant concentrations such as NO2, PM2.5, or ozone when computed few days prior to asthma death.[5] Similar but smaller increments in chronic

*Corresponding author. Department of Otolaryngology-Head and Neck Surgery, Eye and Ear University Hospital, Beirut, Lebanon. E-mail: rouadipws@gmail.com
**Corresponding author. Department of Otolaryngology-Head and Neck Surgery, Eye and Ear University Hospital, Beirut, Lebanon E-mail: samar.a.idriss@hotmail.com
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2020.100467
Received 11 May 2020; Received in revised from 31 August 2020; Accepted 11 September 2020
Online publication date xxx

obstructive pulmonary disease (COPD)-related mortality were attributed to pollution and ranged from 0.78% to 1.78%.[6]

In the respiratory tract, air pollution can impact wellness in healthy people and patients with IAD, irrespective of their atopic status. Hence, the airway mucosal barrier may be disrupted by immunopathological mechanisms resulting from effects of pollution and IAD. The co-occurrence of IAD phenotypes (allergic rhinitis, and chronic rhinosinusitis, COPD and asthma) within an individual increases the likelihood of pollutant induced exacerbation of disease or infection.

We reviewed the following IADs in relation to air pollution. Allergic rhinitis (AR), is an IgE mediated inflammatory disease generated by a spectrum of outdoor aeroallergens like pollens or indoor aeroallergens such as dust mites, cockroaches, cat allergens, or molds. CRS represents multiple overlapping rhinosinusitis phenotypes with different endotypes.[7] Asthma is characterized by chronic atopic or non-atopic inflammation of the airway with superimposed episodes of acute exacerbations. The majority of exacerbations are triggered by respiratory viral infections, most commonly human rhinovirus.[8,9] Other triggers include allergens and atmospheric pollutants.[10,11] COPD, another chronic inflammatory airway disease, is characterized by airflow limitation and cough. Acute exacerbation of COPD, like in the upper airway, can be triggered by infection and inhalation of irritants.[12,13]

CHARACTERISTICS OF AIR POLLUTANTS

Chemical pollutants are health-damaging atmospheric aerosol and non-aerosol particles originating from a variety of natural (eg, volcanic eruptions) or anthropogenic sources (eg, biomass burning, fossil fuel combustion, or traffic related particles). Primary pollutants such as particulate matter (PM) and volatile organic compounds are aerosol particles directly emitted as solid or liquid droplets in the air. In the atmosphere, natural gas-to-particle conversion can culminate in secondary chemical pollutant particles like are ozone and PM.[14]

Particular matter and nanoparticles

Particularte matter (PM) is a mixture of solid and liquid particles suspended in indoor and outdoor air. Their source, size, classification, and airway distribution patterns are well described.[15–17] Various human indoor activities cause resuspension and deposition of particles in indoor air, a process governed primarily by the effective size of the particle. This can range from hours for PM_{10} to several months for 2-μm particulate pollutants.[18] $PM_{2.5}$ broadly represents around 50% of the total mass of PM_{10} and can be inhaled more deeply into the lungs, with a portion depositing in the alveoli and entering the pulmonary and systemic circulation.[17] The submicron PM family, ultrafine particles and nanoparticles, due to their small size, have a relatively large surface area allowing a greater proportion of compounds to be displayed at the surface such as metals and organic compounds.[19,20] They cannot be taken by macrophages and can escape phagocytosis. When retained in the lungs, the ensuing inflammation can result in asthma and lung fibrosis;[20,21] yet they can allocate to distant organs through systemic circulation resulting in different toxicological phenotypes such as diabetes and heart disease.[22–24] The adverse health effects of PM are not uniform since PM is not a single entity; rather its constituents and their proportion in ambient air can change from one geographical location to another depending on the type of emissions inherent to each area.[25]

Volatile organic compounds (VOCs) and formaldehyde

VOCs are primary pollutants located mainly indoors and include benzene, toluene, xylenes, terpenes, and polycyclic aromatic hydrocarbons. They produce a secondary pollutant, formaldehyde, by an indoor chemical reaction between ozone or nitrogen oxide and terpene.[26] Formaldehyde appears to be associated with a higher risk of nasopharyngeal carcinoma[27] and leukemia.[28] The primary domestic,[29–31] microbial,[32] and socio-cultural sources of VOCs[33,34] are well elaborated.

Diesel exhaust particles (DEP)

Diesel exhaust represents the most important local contributor to ambient air pollution and has been classified by WHO as carcinogenic to humans.[35] It is a complex mixture of chemicals and metals stratified into 3 fractions: a solid fraction (made of a soot of carbon core, metals, and their oxides),[36] a gaseous fraction (made of nitrogen, oxygen, and polycyclic aromatic hydrocarbons - PAHs), and a liquid fraction[37] where PAHs can adsorb into soot or water droplets.[38,39] Ultrafine particles, nitrogen oxide, and PM (in the range of 2.5 μm) can be produced also by internal combustion of diesel engines. Metal elements include Chromium, Magnesium, Zinc, and Lead and are associated with engine emissions and abrasion of tires and brake pads. Vanadium and Nickel are tracers of long-range transport from the use of heavy fuel oil.[40] The relatively large surface area of diesel exhaust particles (DEPs) permits many of these chemicals and metals to attach to its core. Thus, most of the deleterious effects of DEPs are due to chemicals that are adsorbed onto their surface.[41]

Ozone and nitrogen oxide (NOx)

To date, ozone is considered the most damaging air pollutant in terms of adverse effects on human health, vegetation, and crops.[42–47] It produces short- and long-term effects on cardiorespiratory function.[45] Recent evidence suggests there is no threshold concentration below which there are no effects on health. Ground-level ozone is formed in the atmosphere by a complex reaction of its precursors, nitrogen oxide (NOx), carbon monoxide, and volatile organic compounds in the presence of sunlight.[48] Background ozone concentrations are strongly correlated with the increased global NOx emissions derived from human-generated fossil fuel combustion and biomass burning.[49]

Tobacco smoke (TBS)

Tobaco smoke (TBS) emits a wide range of gases, aerosolized liquids, and fine particulate matter including VOC and formaldehyde, nitrogen oxide, PM2.5, and nicotine.[50,51] TBS is estimated to cause approximately 480,000 excess deaths per year,[52] and it can contribute to 30% of all cancer deaths.[53] Among other actions, TBS can induce DNA damage,[51] change in sputum (mucin) quality, and depressed antioxidant and antimicrobial activity in smokers and among COPD patients.[54,55]

Household dust

Household dust represents a convenient means to sample respiratory exposure to pollutants. In one study, the respirable fraction of dust constituted less than 1% of the total weight of dust surrounding us, and on scan electron microscopy consisted of large flakes (>20 μm diameter) to which are adherent smaller particles.[56] The median aerodynamic diameter of respirable dust particles allows their deposition both in the nose and lungs. The chemical composition of these flakes suggests household dust might be an important carrier vehicle of organic pollutants into the airways in addition to its intrinsic risk of oxidative stress.[56]

TYPES AND AERODYNAMICS PROPERTIES OF ALLERGENS

Allergens can pollute indoor and outdoor air and exacerbate AR and asthma. Indoor allergenic pollutants can be derived from skin scales of pets (eg, cats, dogs), urine of rodents (eg, mice), molds, or from fecal material of arthropods such as house dust mites and cockroaches. Outdoor allergens are aeroallergens originating from grasses, trees, weeds, or molds. Outdoor pollen also modulates indoor aeroallergen concentration. The concentration of aeroallergens in the indoor environment is governed by complex bioaerosol dynamics.[57] For example, airborne cat allergen (Fel d1) is mostly associated with large particles (>9 μm), but around 1/4 of Fel d1 are carried on particles less than 4 micra in diameter. Thus Fel d1 can be deposited in the alveoli but most importantly suspended for several days in the air favoring distribution of the allergen in the environment.[58–60] Also, the 33 groups of mite allergens listed in the WHO nomenclature of allergens are composed of particles ranging in diameter from 10 to 40 μm.[61] Hence, they can become airborne upon disturbance and can be carried on house dust that becomes a vector for exposure. How dust mite allergen particles can induce and

trigger asthma in lower airways remains to be determined.[62]

INFECTIOUS PARTICLES

The diversity and functioning of the normal microbiome are crucial for maintaining the health of the host. While the effects of PM on human health are well established, the impact of infectious particles on bacterial ecosystems has been overlooked.

In vitro studies suggest black carbon, a major component of PM, is strongly implicated in predisposition to respiratory infectious diseases,[25,63] and induces structural and functional changes in the biofilms of both *Streptococcus pneumonia* and *Staphylococcus aureus*.[64] This is manifested by increase in biofilm thickness and tolerance to degradation by proteolytic enzymes, thereby promoting colonization of the respiratory tract. Similarly, evidence suggests indoor and outdoor dust modifies microbial growth, virulence, and biofilm formation of opportunistic pathogens. By exposing 3 opportunistic bacteria (*Pseudomonas aeruginosa, Escherichia coli, and Enterococcus faecalis*) to progressively increasing concentrations of indoor and outdoor dust, a differential growth pattern of pathogens was noted. This was commensurate with increased biofilm formation and sensitivity to oxidative stress following hydrogen peroxide challenge.[65] Consequently, the detrimental impact of particulate pollutants on human health is not only due to direct effects on the host but also may involve the effect on bacterial behavior in the host.

COMPARATIVE ANALYSIS OF OXIDATIVE STRESS-MEDIATED IMMUNOPATHOLOGICAL ALTERATIONS IN CLINICAL MODELS OF IAD

Oxidative stress is a disproportionate generation of free radicals beyond the body antioxidant capacity. It translates into a non-IgE mediated Th2 airway inflammation following exposure to a pollutant. In brief, reactive oxygen species (ROS), generated naturally as by-product of cell growth and metabolism, can be produced following pollutant exposure.[66,67] ROS include oxygen radicals (eg, superoxide, hydroxyl, hydroperoxyl) and certain non-radicals (eg, H_2O_2, ozone, singlet oxygen) that are easily converted into radicals.[68] ROS have a pivotal role in cell signaling in the oxidation/reduction cascades following exposure and ultimately generation of anti-oxidant mechanisms thru nrf-2, activator protein 1, and nuclear factor-kappa B.[69–72] Antioxidants are scavengers of ROS and can be enzymatic or non-enzymatic systems, constitutive or *de novo* synthesized by activated gene expression, according to ROS load. The inflammatory phase of oxidative stress involves cytokines- and chemokines-mediated activation and recruitment of inflammatory cells secondary to direct effect of pollutants on airway epithelial cells.[67] This can propagate oxidative stress further and augment the inflammatory response and tissue damage.[73] Alternatively, ROS can contribute directly to cell injury and apoptosis by disrupting cellular and nuclear membranes in the epithelial barrier wall and altering the function of cellular enzymes.[74,75] A different mechanism by which environmental pollution can trigger disease in the nose is via a neurogenic mechanism.[76] Another component of oxidative pathway is the exposure-driven adjuvant effect on atopy where environmental pollution acts as an exacerbating factor for allergic airway disease by enhancement of allergic airway hypersensitivity in atopic individuals. The evidence emerges from experimental protocols involving inhalation of pollutants and allergen challenge which show pollutants can act synergistically to heighten the allergic response with increased expression of Th2 inflammatory biomarkers.[76,77] This is in contrast to healthy individuals which express either Th1 or a mixed Th1/Th2 profile in controlled exposure studies.[78]

Epidemiological studies suggest pollution modulates AR,[79–85] rhinosinusitis,[86] and asthma.[85,87] Other studies suggest a positive association between exposure and prevalence of AR and asthma[83,88–91] in children and adults predominately in reports on short-term exposure[88] and residential proximity studies to sources of traffic pollution.[87,92] However, other long-term exposure studies provided evidence to the contrary.[93–95] This could be due to differences in study design, methods of exposure assessment, and complex nature of studied pollutants.[79,80,82,92]

Author /year	Clinical Model	Group under study	Outcome measure/ Biomarkers	Clinical Findings
Elhini A, 2006[112]	Human In-vivo	Perennial AR	Inferior turbinate: - HO-1 and HO-2 isoenzyme antioxidant mRNA expression	Upregulated expression of nasal cytoprotective stress response markers, HO-1, but not HO-2, in perennial allergic diseases.
Gratziou C, 2008[106]	Human In-vivo	SAR/Allergic asthma	Exhaled breath air and condensate variation with pollen season and INS therapy - eNO; Iso-8 (lipid peroxidation marker), LTB_4; Nitrate/Nitrite	Compared to healthy subjects, increased all OS markers in (SAR) patients during natural allergen exposure irrespective of asthma comorbidity; compared to patients with SAR only, eNO and nitrates more pronounced in patients with concomitant asthma. Iso-8 and LTB_4 but not nitrate/nitrite are reduced with nasal steroids suggesting a regulatory role in OS response.
Moon J, 2009[113]	Human In-vivo	AR or CRSwNP	Inferior turbinate and nasal polyps: - NOX1 and NOX4 antioxidant levels and mRNA expression	Increased NOX -1 and −4 levels and mRNA expression in allergic nasal mucosa and nasal polyps mediated by ROS-generating NADPH oxidase suggest their role in pathogenesis of AR and CRSwNP.
Sadowska-Woda I, 2010[114]	Human In-vivo	Perennial AR in children	Blood erythrocytes analysis with desloratadine therapy: - Catalase and superoxide dismutase (antioxidant enzymes), malondialdehyde (lipid peroxidation marker)	Reduction in antioxidant enzyme (catalase and superoxide dismutase) activity and malondialdehyde level and reversal with desloratadine suggest OS is implicated in pathogenesis of PAR and desloratadine can exert an antioxidant effect
Sagdic A, 2011[107]	Human In-vivo	Allergic and non-allergic asthma, AR	Blood erythrocyte analysis: - CuZnSOD and GSH-Px antioxidant enzyme activity; malondialdehyde (lipid peroxidation marker)	Decreased CuZnSOD enzyme activity but not GSH-Px and MDA in allergic and non-allergic asthma and AR suggest OS mediates inflammation in rhinitis and asthma, irrespective of atopic status.
Celik M, 2012[111]	Human In-vivo	Allergic asthma and rhinitis in children	Nasal and oral exhaled breath condensate with topical steroid therapy:	Decrease in GSH antioxidant enzyme level and increase in MDA oxidative biomarker in both

(continued)

Author /year	Clinical Model	Group under study	Outcome measure/ Biomarkers	Clinical Findings
			- MDA (lipid peroxidation marker) and GSH (antioxidant) enzyme level	allergic asthma and rhinitis, separately or combined. Also co-existence of allergic asthma and rhinitis does not augment OS, and no apparent regulatory role of topical steroid on OS response.
Cho DY, 2012[96]	Human In-vivo	CRSwNP and CRSsNP	Nasal polyp, tissue and lavage: - Cytokines (Eotaxin, monokine-induced by IFN-γ -MIG, TNF-α, and IL-8) and H_2O_2 (released into mucosal fluid layer); DUOX1 and DUOX2 (NADPH oxidase) mRNA expression and protein level	Increased level of DUOX1 and DUOX2 in nasal polyps positively correlate with cytokine levels of eotaxin, MIG and TNF-α; also increased level of DUOX2 but not DUOX1 in nasal tissue of CRSsNP positively correlate with H_2O_2. Findings suggest OS can differentially modulate different CRS phenotypes in terms of DUOX -1 and −2 antioxidant enzyme level and expression.
Emin O, 2012[108]	Human In-vivo	Perennial AR in children	Blood analysis: - Plasma total oxidant status (TOS); total antioxidant status (TAS); total serum IgE levels; skin sensitization	Increased TOS and decreased TAS is independent of total IgE levels and allergic sensitization in children with PAR.
Guibas G, 2013[126]	Rat In- vivo	Ova-sensitized rats	Sinonasal tissue and blood with NAC and Ova challenge: - Tissue eosinophil and mast cells; iNOS and COX2 mucosal expression; and serum TNF-α	Following Ova challenge, upregulated count of eosinophils and mast cells, mucosal expression of iNOS, COX-2, and TNF-α level and their downregulation by NAC (except for COX2 expression) suggest important antioxidant property of NAC in allergic reactions and a diverse role of COX2 in redox sensitive reactions.
Ozkaya E, 2013[109]	Human In-vivo	Perennial AR in children	Blood analysis: - Plasma PON1 (antioxidant enzyme activity) and TOS; total serum IgE level; Nasal symptoms score	Nasal symptom scores correlate negatively with serum PON1 and positively with TOS levels and hence serve as predictors of disease severity in children with AR, independently of total IgE levels.

(continued)

Author /year	Clinical Model	Group under study	Outcome measure/ Biomarkers	Clinical Findings
Yu Z, 2015[97]	Human In-vivo	Eosinophilic and non-eosinophilic CRS with nasal polyps	Nasal Polyp (NP): - HO-1 and HO-2 (antioxidant) enzymes mRNA expression and protein level.	Increased HO-1 and HO-2 expression in nasal polyps, more so for HO-1 expression in non-ECRS compared to ECRS; their induction by cytokines and inhibition by TGF-β1 suggest a differential role of HO-1 in different endotypes of nasal polyps.
Chan TK, 2016[75]	Mice and human In-vivo	Asthmatic HDM-sensitized mice	Mice BAL +/or LT following HDM challenge; or BEAS or asthmatic patients: - Neutrophil, Eosinophil, Mφ, Total T cell counts; 8-IP, 3- NT, 8-OG (markers of oxidative damage to lipids, proteins and nucleic acids, respectively); γ H2AX [DNA DS breaks marker-DSB] positive cells, Rad51, Ku70, PARP-1 and PAR (DNA repair pathway marker); NU7441 (DNA DSB repair inhibitor); IL-4, IL-5, IL-13, IL-33 production; Apoptosis in situ and in vitro	HDM challenge triggered an ROS-mediated induction of DNA damage (γ H2AX) in healthy or asthmatic humans and mice; in challenged mice recruitment of inflammatory cells and upregulation of markers involved in oxidative damage to lipids, proteins and nucleic acids (8-IP, 3-NT, 8-OG); in all three groups induction of DNA repair proteins. HDM challenge and administration of DNA repair inhibitor (NU7441) induces DNA repair markers (Rad51, Ku70, PARP-1 and PAR) in asthmatic patients and HDM-challenged mice concomitant with increased cytokines (IL-4, IL-5, IL-13, IL-33) and Annexin V/P staining in BEAS; all suggesting the importance of DNA repair in protection against HDM exposure-induced cell apoptosis and in suppressing airway inflammation in-vitro.
Ulusoy S, 2016[110]	Human In-vivo	SAR	Blood analysis with pollen season: Thiol-SH (antioxidant marker) level, disulfide-SS (oxidative stress marker) level, and total SH (TT) level	Decreased levels of thiol-SH and increased levels of disulfide-SS during exacerbations of SAR compared to asymptomatic period suggests natural allergen exposure reverses oxidative and anti-oxidative status in SAR, which are not completely abolished even outside pollination season

(continued)

Author /year	Clinical Model	Group under study	Outcome measure/ Biomarkers	Clinical Findings
Hong Z, 2016[98]	Human In-vitro	PM2.5	NEC with pollutant exposure and NAC administration: Cell viability, Reactive oxygen species (ROS); Antioxidant enzyme activity of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px); nuclear translocation of NF-E2-related factor-2 (Nrf2) (protector from oxidative stress); Levels of cytokines and respective mRNA expression of GM-CSF, TNF-α, IL-13, eotaxin, IL-6 and IL-8	Pollutant exposure decreased cell viability and antioxidant enzymes levels in parallel with increased ROS levels, cytokines expression and important Nrf2 protective activity; overall effect reversed by NAC treatment.

Table 1. (Continued) Outcome findings in clinical exposure models of IAD with reference to biomarkers. ***3-NT*** *(3-Nitrotyrosine);* ***8-IP*** *(8-Isoprostane);* ***8-OG*** *(8-Oxoguanine);* ***AR*** *(Allergic rhinitis);* ***BEAS*** *(human bronchial epithelial cell);* ***CAT*** *(Catalase);* ***COX*** *(cyclooxygenase);* ***CRS*** *(chronic rhinosinusitis);* ***CRSsNP*** *(chronic rhinosinusitis without nasal polyps);* ***CRSwNP*** *(chronic rhinosinusitis with nasal polyps);* ***DNA-DS*** *(double stranded DNA);* ***DSB*** *(Double-strand break);* ***DUOX*** *(Duol oxidase);* ***ECRS*** *(Eosinophilic chronic rhinosinusitis);* ***eNO*** *(exhaled nitric oxide);* ***GM-CSF*** *(Granulocyte Macrophage Colony-Stimulating Factor);* ***GSH*** *(Glutathione);* ***GSH-Px*** *(Glutathione peroxidase); H2AX (histone family member X);* ***HDM*** *(house dust mite);* ***HO*** *(heme oxygenase);* ***IFN*** *(interferon);* ***IgE*** *(immunoglobin);* ***IL*** *(interleukin);* ***iNOS*** *(inducible Nitric oxide oxygenase);* ***INS*** *(intranasal steroid);* ***Iso-8*** *(8-iso-prostaglandin);* ***LTB4*** *(leukotriene B4);* ***MDA*** *(malondialdehyde);* ***MIG*** *(Monokine-induced by interferon γ);* ***mRNA*** *(Messenger RNA);* ***Mφ*** *(Macrophages);* ***NAC*** *(N-acetylcysteine);* ***NADPH*** *(Nicotinamide adenine dinucleotide phosphate);* ***NEC*** *(Nasal epithelial cell);* ***NOX*** *(nitrogen oxide);* ***NP*** *(nasal polyps);* ***Nrf2*** *(Nuclear factor erythroid 2-related factor 2);* ***OS*** *(oxidative stress);* ***Ova*** *(ovalbumine);* ***PAR*** *(perennial allergic rhinitis);* ***PARP*** *(poly ADP ribose polymerase);* ***PM*** *(particulate matter);* ***PON*** *(paraoxonase);* ***ROS*** *(reactive oxygen species);* ***SAR*** *(seasonal allergic rhinitis);* ***SOD*** *(Superoxide dismutase);* ***TAS*** *(total antioxidant stress);* ***TGF*** *(transforming growth factor);* ***TNF*** *(tumor necrosis factor);* ***TOS*** *(total oxidant status)*

In*In-* vivo*vivo* studies in both human and animal models suggest pollutant exposure induces inflammatory changes in normal, chronically diseased and allergic nasal and sinonasal tissues (Table 1). The cytokine profile of affected tissues suggests activation of the oxidative inflammatory pathways.[96–98] Moreover, there is compelling evidence for involvement of oxidative stress inflammatory pathways following pollutant exposure in the pathogenesis of rhinitis, CRS, and asthma irrespective of atopic status. This stems from an abundance of literature on oxidative stress biomarkers studied under natural or experimental allergen exposure both in seasonal and perennial AR described in Table 1. In fact, dust mite or ragweed allergic patients exposed to diesel exhaust particlesDEPs in climate chamber expressed higher nasal symptom scores following dust mite or ragweed challenge, respectively, when compared to non-exposed but allergen-challenged patients.[99,100] Also in the lower airways, short-term natural increase in ambient air ozone was associated with deteriorating lungh function tests in atopic asthmatics despite use of proper asthma controller therapy.[101] Similarly, an ozone exposure protocol revealed atopic asthmatics expressed depressed spirometry testing results compared to healthy volunteers.[102] Along with this, climate chamber studies revealed (ozone) exposure of healthy or allergic asthmatics induces a neutrophilic[103] or a mixed neutrophilic and eosinophilic[104] inflammatory profile in the lower airways, respectively. Furthermore, gene expression profiles of sputum cells recovered from healthy volunteers and allergic asthmatic patients also confirmed significant difference in inflammatory response to ozone exposure.[105]

Analysis of biomarkers activity greatly improved our understanding of cascade and signal pathways involved in atopic and non-atopic phenotypes of airway disease following exposure. Although most oxidative stress biomarkers require tissue specimen collection, some studies suggest an analysis of biomarkers can be determined non-invasively in

exhaled breath condensates or blood.[106–111] Natural allergen exposure reverses oxidative and antioxidative status compared to asymptomatic period, with a persistent oxidative state outside pollination season in allergic patients when compared to healthy controls. AR and asthma comorbidity in children does not seem to augment oxidative stress markers compared to AR alone,[111] although adult patients with seasonal AR and asthma manifest an exaggerated stress response during natural allergen exposure compared to AR alone.[106] Clinically, oxidative stress correlates with nasal symptom scores in children with perennial AR and can predict AR severity independent of total IgE.[109] Additionally, ROS status does not correlate with atopic skin sensitization in children with perennial AR.[108] Furthermore, dust mite challenge in asthmatics or sensitized mice resulted in oxidative damage to nucleic acids as well as lipids and proteins and subsequently triggered DNA repair pathways. Further blockage of DNA repair proteins resulted in increased production of DNA double-strand breaks and cell apoptotic enzymes suggesting importance of DNA repair in suppressing airway inflammation.[75]

Endogenous antioxidant response in atopic respiratory diseases is complex and oxidative stress response to anti-inflammatory drugs isare poorly understood. Antioxidant enzymes mostly studied in atopic respiratory diseases include heme oxygenase 1 and 2,[112], NADPH oxidases,[113] catalase,[98,114] superoxide dismutase,[98,107,114] dual oxidases 1 and 2 (in CRS patients),[96] paraoxonase,[109] and glutathione peroxidase.[98,111] Antioxidant activity can also be measured by serum thiol-SH and total antioxidant status (Table 1). In this respect, evidence suggests oxidative stress decreases antioxidant enzyme activity or total antioxidant status in atopic children[108,109,111] or in human *in vitro* controlled exposure studies,[98] whereas other studies present evidence to the contrary. For example, heme oxygenase antioxidant (iso)enzyme-1 activity was preferentially increased in a human *in vitro* model of perennial AR,[112] and upregulated in a human exposure model of COPD aggravated by infection;[115]; also dual oxidase antioxidant (iso) enzymes showed preferential upregulation in different phenotypes and endotypes of CRS.[96,97] Contrary to this, antioxidant enzymes can be downregulated in asthma and rhinitis irrespective of atopic status,[107] and *in vitro* animal exposure models challenged by an infectious insult.[72] Importantly, genetic polymorphism in antioxidant/detoxifying genes like GSTM1 and GSTP1 can alter oxidative stress response in patients with COPD and those with AR following exposure.[116,117]

Exogenous (dietary) antioxidants are scavengers of oxygen free radicals and can act on different levels of defensive antioxidation pathways.[118,119] Epidemiologic,[120] *in vivo*[121,122] and *in vitro*[123] studies suggest a beneficial role of exogenous antioxidants in patients with IAD or in controlled exposure studies of healthy sinonasal epithelial cells. However, lack of clinical trials data clearly supporting their efficacy, in addition to their potential role in skewing Th1/Th2 balance towards a Th2-type immunity as suggested *in vitro*,[124] renders their indication restricted to special situations such as over exposure to environmental pollutants, among others.[125] N-acetylcysteine maintains a potent antioxidant effect in *in vitro* studies[98] or in ovalbumin-sensitized rats by downregulating tumor necrosis factor-alpha in recruited inflammatory cells.[126] Along these lines, intranasal steroids can exhibit an exogenous antioxidant regulatory role in seasonal AR by decreasing exhaled breath condensates of leukotriene B4 and 8-Isoprostane, although no effect was seen on exhaled carbon monoxide and nitrogen oxide.[106] In another study involving children with AR and asthma, no effect of topical nasal steroid therapy was noted on measured lipid peroxidation oxidative stress biomarkers and antioxidant enzymes.[111] Data on potential antioxidant effect of inhaled steroids in adult asthmatics is scarce. Epidemiological studies suggested prior intake of oral[127] or inhaled steroids[128] in adult asthmatic patients had no effect on asthma control, as measured by clinical symptoms and FEV1 testing, with PM and ozone exposure. Other similar studies noted increased consumption of asthma controller therapy (bronchodilators, inhaled corticosteroids, or both) with PM10[129] or NO_2 exposure[130] in adults. Moreover, in children inhaled steroid therapy downregulated induced expression of heme oxygenase-1 in non-smoking patients with

bronchiectasis but had no effect on exhaled carbon monoxide.[131] Furthermore, desloratadine can exert an antioxidant effect in children with perennial AR by increasing antioxidant enzyme activities (catalase and superoxide dismutase) and decreasing lipid peroxidation marker (malonaldehyde) although no effect was seen on total antioxidant status.[114] When compared to placebo, fexofenadine improved nasal symptom scores in ragweed AR patients following ragweed challenge and DEP controlled exposure.[100]

The majority of controlled human exposure studies to ambient pollutants have been conducted in climate chambers on healthy individuals.[132-135] For example, relative to clean air, mixtures of VOCs increased ratings of nasal irritation, odor intensity[136] and cognitive symptoms (memory loss, dizziness), and a two-fold increase in polymorphonuclear cells in nasal lavage immediately following exposure.[137] Similar studies using different pollutants showed no detectable effects on nasal symptom scores or markers of nasal inflammation.[134,138] Additionally, healthy subjects exposed to room air, nanoparticles, or O_3/terpene showed no significant changes in inflammatory biomarkers in blood, sputum or nasal secretions and pulmonary function tests. However, only nanoparticles exposure increased significantly high frequency variability in heart rate, thereby indicating a shift in autonomic balance to a more parasympathetic tone.[133] Low level ozone exposure in healthy subjects resulted in increased sputum production of airway inflammatory cells such as neutrophils, monocytes, and dendritic cells, and modification of cell surface phenotypes of antigen presenting cells.[139] Using a similar protocol the reported decrement in lung spirometry testing (FEV1) of healthy subjects was associated with increased neutrophilic airway inflammation following exposure;[140] the latter likely being more pronounced in healthy individuals with GSTM1 null genotype.[141] More importantly, comparing healthy controls to atopic asthmatics, exposure to high levels of ultrafine particles in a climate chamber was associated with a small but significant fall in arterial oxygen saturation, a fall in forced expired volume over 1 s (FEV1) the morning after exposure, and a transient slight decrease in low frequency (sympathetic) power during quiet rest.[142] These controversial results can be related partly to the nature and concentration of the investigated pollutant or its experimental duration of exposure keeping in mind brief exposure to a single pollutant in a climate chamber does not reflect chronic exposure to multiple pollutants in real life. Controlled exposure studies in atopic patients involving allergen challenge revealed more consistent results. For example, dust mite allergic patients reported worsening nasal symptom scores following intranasal dust mite challenge and DEP exposure commensurate with increased histamine levels in nasal washes, all suggestive of induced mast-cell degranulation.[143] Similarly, controlled exposure studies in ragweed allergic patients challenged with DEP and ragweed outside their pollen season reported higher total nasal symptoms scores[100] or increased levels of specific IgE and expression of Th2 inflammatory cytokines, when compared to ragweed challenged alone.[77]

Taken together, controlled airway exposure studies to ambient pollutants in healthy individuals show small but significant negative health effects whereas exposure studies in allergic patients support the role of pollutants in increasing atopic airway hypersensitivity. Large scale translational studies are needed to correlate the bio-cellular toxic effects of pollution with epidemiological studies.

COMPARATIVE ANALYSIS OF IMMUNOPATHOLOGICAL ALTERATIONS IN CLINICAL EXPOSURE MODELS OF IAD ACCENTUATED BY INFECTION

Signal and cascade pathways triggered across the airway mucosal barrier at first encounter of pollutants are complex (see Fig. 1). Airway mucosal cells can recognize pollutants through an epithelial toll-like receptors (TLR)-mediated mechanism either directly or indirectly by the intermediary of pattern recognition receptors (see below). More precisely, pollutants such as PM, cigarette smoke, and ozone can present themselves directly to subclasses of surface TLRs, namely TLR2 and TLR4, which can serve as ligands for these pollutants. Alternatively, pollutants can be bound to pattern recognition receptors, a

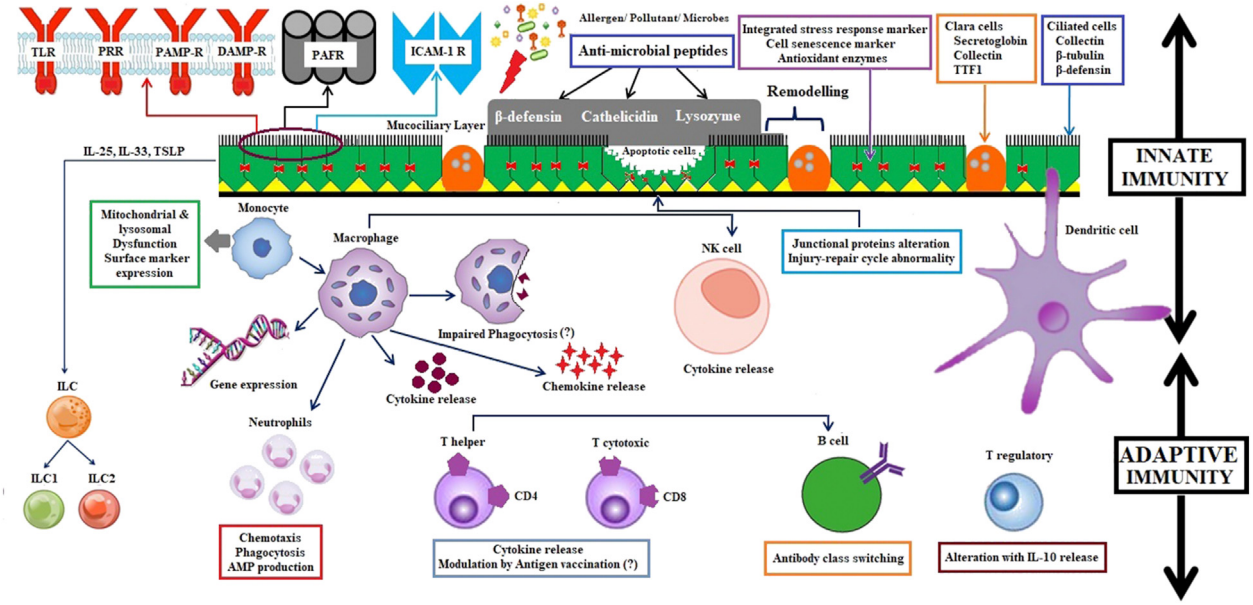

Fig. 1 Immunopathological alterations in innate and adaptive immune system in patients with IAD following pollutant exposure and infection. DAMP-R (Damage-associated molecular pattern receptor); ICAM-1 R (Intracellular adhesion molecule receptor); IL (Interleukin); ILC (Innate lymphoid cell); NK (Natural killer); PAFR (Platelet-activating factor receptor); PAMP-R (Pathogen associated molecular pattern receptor); PRR (Pattern recognition receptor); TLR (Toll like receptor); TSLP (Thymic stromal lymphopoietin); TTF1 (Thyroid transcription factor-1)

collective conglomerate of receptors which encompasses TLRs and normally can recognize conserved molecular structures derived from microbial agents or released by damaged non-microbial cells. Once triggered, pattern recognition receptors and TLRs attract antigen presenting cells and leukocytes to the site of inflammation resulting in priming of the airway to subsequent mucosal infectious insults.[144] Afterwards, when eventuated by an infectious challenge, alveolar macrophages mount a heightened inflammatory response aimed at containing and clearing bacteria while producing minimal collateral tissue damage.[145,146] The immunological "storm" resulting from co-exposure and infection is studied in different clinical models of respiratory cells and also in patients with IAD such as COPD (Table 2). Another signal pathway is mediated by submucosal innate lymphoid cells (ILCs) which can differentiate into adaptive subsets. ILC1s relates to immune reactions in CRS without nasal polyps, COPD, and some viral and bacterial infections; whereas ILC2s becomes important in regulating type 2 immunity and some helminthic and viral infections.[147,148] Other immunologic and antimicrobial responses to pollutant exposure modulate expression of host defense peptides and antiviral mechanisms, impair mucus production crucial for capturing pollutants or weaken tight junctions essential for the epithelial airway defense barrier.[149,150]

Epidemiological studies suggest indoor and outdoor air pollution increase the risk of respiratory tract infections in both pediatric[151–154] and adult populations.[80,151,152,155] For example, morbidity of the recent COVID-19 pandemic disease has been linked partly to air pollution.[156–159] Also, air pollution can aggravate the severity of asthma caused by respiratory viral infections.[160] Moreover, *in vitro* studies suggest air pollution may suppress innate and adaptive immunity and increases susceptibility to bacterial and viral respiratory infections in both human and animal clinical models, following short- or long-term exposure (see Table 2). For example, in the *upper airways* diesel exhaust exposure increased the number of human nasal epithelial cells infected by Influenza A virus *in vitro* The proposed mechanism was enhancement of virus attachment and entry into respiratory cells mediated by radical oxygen species, despite increased antiviral interferon-dependent signaling and interferon-stimulated gene expression by DEP exposure.[161] Also, *in vitro* Rrhinovirus (RV) 16 infectivity following nitrogen oxide and ozone exposure in human respiratory epithelial cells

Author, year	Clinical Model	Sample under study	Pollutant	Infectious agent	Outcome measure	Clinical Findings
Yang H, 2001[168]	Rats In-vivo & In-vitro	LT & BALF	DEP	LM	LT and BALF, Mϕ following exposure and infection: - ROS formation; NO level; CD4 and CD8, $CD4^+/CD8^+$ T cells & Mϕ	DEP exposure in rats increases susceptibility to LM infection by attenuating Mϕ function (ROS and NO production) and T cell (CD4 and CD8) mediated immunity.
Spannhake W, 2002[71]	Human In-vitro	NEC & BEC	NO_2 & O_3	RV16	BEC, following infection and exposure: - IL-8 release (neutrophil chemotactic factor, phagocytosis stimulant); ICAM-1 (receptor for human RV 16- Epithelial surface inflammatory binding protein) mRNA expression	Pollutant-induced exaggerated RV16 infectivity manifested by upregulation of ICAM-1 and increased binding to airway epithelial cells and mediated by induction of proinflammatory IL-8 cytokines production and oxidative stress pathway
Yin X, 2004[171]	Rats In-vivo	LT & BALF	DEP	LM	BALF and LT, following exposure and infection: - LPS-assisted AM IL-1β (acts on NK cell), TNF-α (acts on NK cell), IL-12 (initiator of cell mediated immunity), IL-10 (immunosuppressive cytokine and prolongs intracellular pathogens survival- e.g. LM), IL-2, IFN-γ (released by NK), and IL-6 (induction of cytotoxic T lymphocyte development from murine thymocytes); Lung draining lymph node $CD4^+/CD8^+$ T cells	LM-mediated suppression of innate (i.e. Mϕ, IL-1β, TNF-α, IL-12, IL-2 and IFN-γ) and adaptive (i.e. CD4 and CD8 T cell) immune response upon repeated low dose DEP exposure and downregulation of protective bacteria-induced T cell cytokines (IL-10 and IL-6) and upregulation of macrophage bactericidal cytokines
Jaspers I, 2005[161]	Human In-vitro	NEC & BEC	DEas	IVA	NEC/BEC cells, following exposure and infection: - IVA m-RNA transcription level, viral proteins; IVA-induced IFN-β-mRNA level, ISRE promoter reporter activity (IFN-stimulated	Increased oxidative stress-mediated (DCF-DA) susceptibility to viral infections is manifested by increase in IVA RNA transcription activity and viral proteins in NEC cells. Increased susceptibility is likely unrelated to IFN-β

					genes); DCF-DA (oxidative marker); BEC-attached IVA RNA level	production (IFN-β-mRNA level, ISRE promoter reporter activity not decreased) and expressed by increasing number of infected cells and enhancement of virus attachment and entry into BEC (measured by BEC-attached IVA RNA level)
Harrod K, 2005[163]	Mice In-vivo	BEC	DEE	PAE	BEC, following exposure and infection: - Histopathology severity scores; tissue bacterial count of PAE - Tissue β tubulin (BEC ciliary) marker, epithelial SCGB1A1 (non-ciliated BEC cell marker i.e. Clara cell) marker, and tissue TTF-1 (lung-specific host defense gene expression/transcription regulator)	Impaired bacterial clearance in BEC following PAE infection and short-term DEP exposure (1 week), partly by airway remodeling as manifested by decrease in ciliated (tissue β tubulin) and non-ciliated airway epithelial cell markers (SCGB1A1) and concordant with decrease in lung-specific host defense gene expression in Clara cells (TTF-1)
HongweiZhou, 2007[179]	Mice In-vitro	BALF	PM $<$ 2.5 μm	SP	BALF Mϕ, following exposure and infection: - Tissue count of total SP uptake, ingestion, and killing	Impairment of SP clearance and phagocytosis following PM exposure likely due to decreased internalization but not decreased killing rate nor increased binding of bacteria to macrophages.
Sigaud S, 2007[174]	Mice In-vivo & In-vitro	BALF	PM $<$ 2.5 μm	SP	BALF Mϕ and PMN, following IFN-γ priming and exposure: - PMN count, DCF-DA (OS marker); lung expressed pro-inflammatory cytokine mRNA BALF Mϕ and PMN, following IFN-γ priming, exposure, and infection: - Remaining viable count of SP in-vitro and in-vivo; histopathology	PM $<$ 2.5 μm exposure in addition to viral infection exemplified by IFN-γ priming trigger a neutrophilic inflammation as suggested by activation of genes encoding PMN-recruiting chemokines or their receptors. This can predispose to an SP-induced ROS-mediated severe pneumonia in mice, likely secondary to a neutrophilic (and to a lesser extent Mϕ-mediated) impaired bacterial clearance and phagocytosis.

(continued)

Author, year	Clinical Model	Sample under study	Pollutant	Infectious agent	Outcome measure	Clinical Findings
Mushtaq N, 2011[165]	Human In-vitro	BEC	PM < 10 μm	SP	BEC, following exposure and infection: - Adhesion of SP to PM-exposed BEC in-vitro and in-vivo; and glutathione (oxidative stress marker) level reversal by NAC - PAFR (putative receptor for PM-stimulated pneumococcal adhesion to airway cells) mRNA transcript level, receptor expression, and blocking	PM-enhanced vulnerability to human SP infection in vitro, manifested by increased bacterial adhesion and penetration into BEC, mediated by oxidative stress and PAFR, and reversed by NAC and PAFR blockage
Chaudhuri N, 2012[177]	Human In-vitro	Serum MDMϕ	DEP	E-Coli (LPS endotoxin)	Serum MDMϕ, following exposure: - Cell count of DEP-incorporating MDMϕ in COPD and healthy volunteers; MDMϕ mitochondrial membrane electrical potential and lysosomal fluorescence in healthy volunteers Serum MDMϕ, following exposure, TLR agonist, and LPS endotoxin: - CXCL8 (Mϕ produced IL-8) cytokine responses following TLR4, TLR7 agonists or heat killed *E. coli* in both COPD and healthy volunteers; MDMϕ CD14 (co-receptor to TLR4 for LPS recognition), CD11b (Mϕ differentiation marker) surface marker expression in healthy volunteers	Loss of low-level DEP-exposed MDMϕ along their differentiation into macrophages likely due to dysfunctional (loss of mitochondrial membrane electrical potential and lysosomal function) and phenotypic (TLR-mediated reduction in CD14 and CD11 surface marker expression) structural changes in MDMϕ of healthy exposed individuals. This can likely contribute to inflammation in COPD by decreased MDMϕ pro-inflammatory cytokines (CXCL8) production.

Migliaccio C, 2013[170]	Mice In-vivo & In-vitro	AM & BMdM	WS derived PM or IWS	SP	BALF, following high level IWS and SP infection: - Bacterial load; AM Phagocytosis; IFN-γ production; leucocytes class II^{+}MHC (marker of MO activation), AF (marker of phagocytosis); RelB activation and translocation (NF-κβ pathway activity), Cyp1A1 activation (AhR pathway activity)	Impaired antimicrobial defense system with inhalation of high level WS and infection with SP secondary to decrease in IFN-γ production and macrophage number and activation (leucocytes class II^{+}MHC) but not in phagocytic activity (unchanged AF marker), likely mediated via NF-κβ pathway activation and AhR pathway. Unchanged phagocytic activity and no increase in neutrophils or TNF-α (data not shown).
Zhao H, 2014[167]	Rats In-vitro	BALF	PM 2.5 μm	SA	BALF, following exposure: - AM, neutrophils, lymphocytes, and total cells; IL-6 and TNF-α level Following exposure and infection: - Histopathological scoring, rats growth rate, bacterial burden, response of natural killer (NK) cells; and phagocytosis index of SA by AM	PM exposure triggers recruitment of inflammatory cells, secretions of key inflammatory cytokines (IL-6, TNF-α) in BALF and increases susceptibility to SA infection through depressed phagocytosis and abnormal NK cell response, both restored by adoptive transfer of NK cells.
Roos A, 2015[173]	Mice In-vitro	BALF	CS	NTHi	BALF, following CS exposure and NTHi infection in $IL\text{-}17^{+}$ and/or $IL\text{-}17^{-}$ (knock out) or $IL\text{-}1R1^{-}$mice: - Neutrophils, total cells, neutrophils count following anti-IL-17A therapy; IL-17 (Th17 pathway) level, CXCL1, and CXCL5	Following exposure and infection in BALF of $IL\text{-}17^{+}$ mice, an increased cell counts of neutrophils, total lymphocytes and IL-17 noted; Important role of IL-17 in inducing NTHi exacerbated neutrophilia of exposed mice stems from attenuation of IL-17 and cell counts in IL-17 "knock out" mice or with suppression of neutrophilia in NTHi infected mice pre-treated with anti-IL-17A antibody; Important role of IL-1 signaling in exacerbating IL-17A-mediated neutrophilia stems

(continued)

Author, year	Clinical Model	Sample under study	Pollutant	Infectious agent	Outcome measure	Clinical Findings
						from concomitant absence of CXCL1 and CXCL5 induction with decreased IL-17 level in IL-17 "knock out" mice, and from decreased induction of IL-17A-mediated airway neutrophilia in IL-1R1^{-} mice compared with wild-type control animals.
	Human In-vivo	Sputum & Serum Stable COPD & NTHi-AECOPD	*Not applicable*	NTHi	Sputum, before, during or after NTHi AECOPD and stable COPD: - IL-17A, IL-17F, IL-8 (neutrophil chemo attractant)	During NTHi-associated AECOPD a concomitant increased levels of sputum IL-8 and IL-17A noted, with IL-17 expression normalized after resolution of the exacerbation, but no correlation seen among them during AECOPD caused by other microorganisms suggesting IL-17 is a critical mediator of CS-exacerbated pulmonary neutrophilia associated with NTHi in AECOPD Overall, there is an important role of IL-17, and potentially anti-IL-17 therapy, in CS-exacerbated pulmonary neutrophilia mediated by IL-1 signaling and associated with NTHi in AECOPD
Rylance J, 2015[169]	Human In-vivo & In-vitro	BALF & Serum	WS PM $<$ 4 μm HAP	E-Coli (LPS endotoxin)	BALF, following natural (household) or experimental (WS) PM exposure or LPS infection and glutathione depletion: - AM phagocytosis, proteolysis (LDH), and oxidative burst; Glutathione (antioxidant marker) response to buthionine sulfoximine (BSO-	Natural (chronic) PM exposure of human BALF decreases AM cytokine (CXCL8) release, downregulates induced phagosomal oxidative burst but does not impair redox potential, proteolysis or phagocytosis. LPS priming following PM ex vivo exposure increased all cytokine (CXCL8, IL-6, TNF-α, CCL2) levels; however, reduction of

					oxidant); Cytokines (CXCL8, IL-6 and TNF-α, CCL2) release	CCL2, but not CXCL8, response to glutathione depletion upon LPS stimulation and natural exposure suggests CCL2 may have a role in preventing excessive inflammation
Buonfiglio L, 2017[162]	Pig & Human In-vitro	NEC, BEC ASL/AMP	βPM (CFA)	SA	Pig NEC, ASL/AMP and human BEC, following exposure and infection; and human lysozyme following exposure: - Live bacterial tissue count; HBD-3 (human β defensin-3), LL-37 (Cathelicidin), and lysozyme (cationic) level (all 3 are components of ASL/AMP); CFA adsorption to Lysozyme; Zeta potential (electrostatic interaction between CFA and lysozyme)	In human and animal model PM-induced impairment of airway antimicrobial activity against SA manifests as decreased levels of HBD-3, LL-37, and free lysozyme level, all components of epithelial air surface liquid antimicrobial proteins, and results from adsorption and electrostatic interactions between pollutants (CFA) or bacteria with ASL AMPs, leading to depletion of the latter thereby increasing the chance of bacterial proliferation.
Jaligama S, 2017[172]	Neonatal Mice In-vivo	LT	DCB (combustion derived PM with EPFR)	IVA	Neonatal LT and Treg following exposure, or exposure and infection, or Treg depletion, or Treg adoptive transfer, or recombinant IL10 (rIL-10) treatment: - IL-10; Treg; IL-10-anti CD25; weight change and pulmonary viral load.	Following IVA infection in neonatal mice, a PM-induced suppression of adaptive immune system is mediated by increase in Treg and IL-10, reversed by Treg depletion and recapitulated by Treg adoptive transfer or rIL-10 treatment
Ma J, 2017[178]	Mouse In-vivo	BALF	PM2.5	IVA	BALF following exposure and infection, in normal or in Kdm6a (IFN-β and I L-6 gene expression regulator through respective activation by histone demethylation) knockdown mice: - Mice survival rate; IFN-β and IL-6 levels, OAS1 (IFN-β stimulating gene) expression; Mϕ Kdm6a	Short-term (1 day) exposure to PM-inhalation followed by IVA infection results in early phase robust upregulation of IL-6 level and IFN-β level and expression (OAS1), whereas long-term (starting day 3) exposure downregulates innate immune response to IVA infection, likely mediated by macrophage cytokine expression gene regulator, Kdm6a.

(continued)

Author, year	Clinical Model	Sample under study	Pollutant	Infectious agent	Outcome measure	Clinical Findings
Zarcone M, 2017[115]	Human In-vitro	PBEC	DEP	NTHi	PBEC following exposure and infection in healthy and COPD patients: - Epithelial barrier activity; LDH (cytotoxicity) release; Epithelial gene expression of OS response markers (heme oxygenase - HO), HSPA5 binding protein (endoplasmic reticulum chaperone), CHOP (marker for ER-stress induced apoptosis)	DEP- and NTHi-mediated acute attacks in COPD patients results in no epithelial barrier dysfunction nor cytotoxicity. It can be induced by increased expression of HO epithelial antioxidant marker and by alterations in epithelial innate immunity undertaken at the level of endoplasmic reticulum and manifested by depressed gene expression, but not apoptosis (CHOP), of integrated stress response markers HSPA5.
Bhat T, 2018[175]	Mice Ex-vivo	BALF, LT, &serum	SHS	NTHi	LT, BALF, serum, bone marrow and splenocytes following exposure and infection, and/or P6 vaccination: - Lymphocytic inflammation around broncho-alveolar bundles; DC, neutrophils, and Mϕ; $CD4^+$ $CD8^+$ B and T cells, RORγt+ Th17, IL-6, IL-1β, and TNF-α; Anti-P6 (NTHi-derived outer membrane lipoprotein DNA binding protein) total antibodies; Antibodies subclasses IgG1, IgG2a, IgG2b, IgA and Antibody-secreting specific B cells; P6-specific producing Th17 cells, IL-4 and IFN-γ producing T cells, IgG1 and IgG2a subclasses of Anti P6 -secreting B cells; IL-4 and IFN-γ secreting P6-specific T cells; Bacterial clearance, albumin level	SHS exposure and infection impaired bacterial clearance manifested as increase in immune cell infiltrate (Neutrophils, DC, B cells, T cells) except for macrophages, and impeded induction of a robust adaptive immune response manifested as decreased IFN-γ despite increased IL-17, IL-6, IL-1β, TNF-α and RORγt+ Th17; also, prolonged depression in B cell adaptive immune response manifested as reduced total anti-P6 antibodies and Antibody subclasses (IgA, IgG1, IgG2a IgG2b) Following exposure and (P6-) specific T cell stimulation (vaccination), a decrease in IL-4 and IFN-γ in lung and spleen, both required for Antibody class switching to IgG1 and IgG2a, concomitant with decreased frequency of anti-P6 Ig-secreting B cells for both IgG1 and IgG2

						sub-classes suggest depressed T cell adaptive immune system essential for inducing robust antibody responses to NTHi infection. P6 Immunization and SHS exposure impaired induction of robust T and B cell mediated immune response when compared to air exposure, increased influx of neutrophils but not bacterial clearance thereby suggesting significant impairment of neutrophils phagocytic function. Consequently, depressed B and T cell adaptive immune response can be mitigated by P6 antigen vaccination
Chen X, 2018[164]	Human In-vitro	BEC	PM	PAE	BEC, following exposure and infection: - Invasion by PA; Oxidation-sensitive fluorescent probe (DCFH-DA) for ROS formation; SA-β-gal biomarker (cell senescence); hBD-2 (epithelial antimicrobial peptide) level; mRNA expression of hBD-2, lactoferrin, IL-8, and IL-13	PM followed by PAE infection increases epithelial cell senescence biomarker (SA-β-gal) in an ROS-mediated and a concentration-dependent manner and interferes with innate bactericidal response of airway epithelium by suppressing induction of hBD-2 level and mRNA expression, but not lactoferrin, IL-8, or IL-13
Gotts J, 2018[176]	Mice Ex-vivo	LT, BALF, blood and spleen	CS	SP	BALF, LT and blood following exposure and infection, and/or antibiotic therapy: - Mice lung injury (survival rate, lung weight loss, hypothermia, arterial oxygen saturation, excess extra-vascular lung water) with brief or severe CS exposure; Neutrophils, lymphocytes, Mϕ and monocytes; Chemokines for neutrophils	CS improved mice survival on severe exposure but no other parameters of bacterial pneumonia; contributed to confinement of the infection to the lung manifested by a decreased number of neutrophils, increase in Mϕ and monocytes but no change in lymphocytes; and caused a differential elevation of neutrophils antimicrobial peptides MPO, but

(continued)

Author, year	Clinical Model	Sample under study	Pollutant	Infectious agent	Outcome measure	Clinical Findings
					(KC-murine homolog of IL-8), lymphocytes (CXCL9), and monocytes (MIP-1α); MPO (antimicrobial enzyme in neutrophilic granules), and lymphocytes granzyme B (serine protease contained in the cytotoxic granules of lymphocytes); IL-1α, IL-17, TNF-α; SP-D and Ang-2 (alveolar and endothelial cell injury markers, respectively)	not NE or granzyme B. On supplemental antibiotic therapy benefit in survival rate was lost manifested by increased pulmonary edema concomitant with increased numbers of BAL monocytes, upregulated neutrophil, lymphocyte, and monocyte chemokines (KC, CXCL9, and MIP-1α), induced alveolar and endothelial cell injury markers (SP-D Ang- 2), and downregulated Th1 and Th17 inflammatory cytokines (IL-1α, IL-17).
Wang W, 2018[72]	Chicken Ex-vivo	LT	H_2S	LPS	Lung tissue following exposure & infection: - Histopathology; m-RNA level of IL-4, IL-6 (secreted by Th_2), TNF-α, IL-1β, IFN-γ (secreted by Th_1), and HO-1 (antioxidant enzyme); m-RNA expression of oxidative stress NF-κB pathway genes (I- κB and I- κα), TNF-α, and PPAR-γ (peroxisome proliferator nuclear receptor)	H_2S exposure aggravated LPS-induced inflammatory changes in the lungs through Th_1/Th_2 imbalance manifested by increased mRNA expression of IL-4, IL-6, IL-1 β, and TNF-α expression and a concordant decrease in IFN-γ expression; also by depressed antioxidant mechanisms such as antioxidant enzyme (HO-1) levels and PPAR-γ expression, and by activation of NF- κB pathway-related genes (I-κB and I- κα).

Table 2. (Continued) Outcome findings in IAD clinical models challenged by exposure and infection with reference to biomarkers. ***AECOPD*** *(Acute exacerbation of chronic obstructive pulmonary disease);* ***AF*** *(Autofluorescence);* ***AhR*** *(Aryl hydrocarbon receptor);* ***AM*** *(Alveolar macrophages);* ***AMPS*** *(Antimicrobial proteins and peptides);* ***ASL*** *(Airway surface liquid);* ***BALF*** *(Bronchoalveolar lavage fluid);* ***BEC*** *(Bronchial epithelial cells);* ***BMdM*** *(Bone marrow derived Macrophages);* ***BSO*** *(Buthionine sulfoximine);* ***CCL2*** *(Chemokine Ligand);* ***CAP*** *(Concentrated ambient particles);* ***CD*** *(Cluster of differentiation);* ***CFA*** *(Coal fly ash);* ***COPD*** *(Chronic obstructive pulmonary disease);* ***CS*** *(Cigarette Smoke);* ***CYP1A1*** *(Cytochrome P450 Family 1 Subfamily A Member 1);* ***DC*** *(Dendritic cells);* ***DCB*** *(Combustion derived PM with chemisorbed EPFR);* ***DCF-DA*** *(Dichlorofluorescein diacetate);* ***DEas*** *(Aqueous-trapped solution of Diesel exhaust);* ***DEE*** *(Diesel engine emissions);* ***DEP*** *(Diesel exhaust particles);* ***E. Coli*** *(Escherichia coli);* ***EPFR*** *(Environmentally persistent free radicals);* ***H_2S*** *(Hydrogen sulfide);* ***HAP*** *(Household Air Pollution);* ***HBD*** *(Human β defensin);* ***HO*** *(Heme oxygenase);* ***HSPA5*** *(Heat Shock Protein Family A (Hsp70) Member 5);* ***ICAM-1*** *(Intercellular adhesion molecule 1);* ***IFN*** *(Interferon);* ***Ig*** *(Immunoglobulin);* ***IL*** *(Interleukin);* ***IL-1R*** *(Interleukin 1 receptor);* ***ISRE*** *(Interferon specific element);* ***IVA*** *(Influenza A virus);* ***IWS*** *(Inhaled wood smoke);* ***LDH*** *(Lactate dehydrogenase);* ***LM*** *(Listeria Monocytogenes);* ***LPS*** *(Lipopolysaccharide);* ***LT*** *(Lung tissue);* ***MDMϕ*** *(Monocyte-Derived Macrophages);* ***MHC*** *(Major histocompatibility complex);* ***MIP-1alpha***; ***MO*** *(monocytes);* ***MPO*** *(Myeloperoxidase);* ***mRNA*** *(messenger RNA);* ***Mϕ*** *(Macrophages);* ***NAC*** *(N-acetylcysteine);* ***NEC*** *(Nasal epithelial cells);* ***NF-κβ*** *(Nuclear factor kappa beta);* ***NK*** *(Natural killer);* ***NO*** *(Nitric oxide);* ***NO_2*** *(Nitrogen Dioxide);* ***NTHi*** *(Nontypeable Haemophilus influenzae);* ***O_3*** *(Ozone); OAS (Oligoadenylate synthetase);* ***OS*** *(oxidative stress);* ***P6*** *(Protein 6);* ***PAE*** *(Pseudomonas Aeruginosa);* ***PAFR*** *(Receptor for platelet-activating factor);* ***PBEC*** *(Primary bronchial epithelial cells);* ***PM*** *(Particulate matter);* ***PMN*** *(Polymorphonuclear leukocyte);* ***PPAR (****Peroxisome proliferator-activated receptor);* ***rIL-10*** *(Recombinant IL-10);* ***ROR-γ*** *(reactive oxygen radicals);* ***ROS*** *(Reactive oxygen species);* ***RV16 (****Rhinovirus 16);* ***SA*** *(Staphylococcus aureus);* ***SA-γ-gal*** *(Senescence-associated β-galactosidase assay);* ***SCGB1A1*** *(Secretoglobin);* ***SHS*** *(Secondhand smoke);* ***SP*** *(Streptococcus Pneumonia);* ***TLRs*** *(Toll-like receptors);* ***TNF*** *(Tumour Necrosis Factor);* ***Treg*** *(Regulatory T cells);* ***TTF1*** *(Thyroid transcription factor 1);* ***WS*** *(Wood smoke)*

resulted in increased ICAM 1 receptor expression (receptor for RV16) and pro-inflammatory IL-8 cytokine production.[71] In another combined human and animal model, activated nasal airway microbial proteins at the surface mucosal liquid, which include lysozyme, human cathelicidin antimicrobial peptide, and human β defensins, were attenuated following (PM) exposure and *Staphylococcus aureus* infection. The ensuing impaired bacterial killing resulted from adsorption and electrostatic interactions between either pollutant or bacteria with activated microbial proteins leading to the depletion of the latter.[162]

The literature on the *lower airways* exceeds that on the upper airways. In this respect, susceptibility to infections following exposure was examined at several stages of immunological alterations triggered in host cells.

Starting with the epithelial barrier level, an initial *in vivo* PM exposure of bronchial epithelial cells in mice followed by experimental infection with *Pseudomonas aeruginosa* resulted in decreased levels of an epithelial ciliary marker (β tubulin) and a non-ciliary epithelial (Clara cells) marker, and their gene expression/transcription regulator, all suggesting airway remodeling is a contributing factor to the impaired bacterial clearance.[163] Furthermore, an initial infection with *Pseudomonas aeruginosa* induced an epithelial antimicrobial peptide human beta defensin 2; but as the model was pre-exposed to PM, induction of human beta defensin 2 was suppressed and a cell senescence biomarker (SA-β-gal) was upregulated in an ROS-dependent process.[164] Also, in an *in vitro* human model, a PM-enhanced susceptibility to *Streptococcus pneumoniae* infection was heightened by increased bacterial adhesion and penetration into bronchial epithelial cells. This was mediated by a receptor for platelet-activating factor, a putative receptor for PM-stimulated pneumococcal adhesion to airway cells.[165]

On a submucosal level, macrophages and monocytes play a central role in phagocytosis. The study of immunopathological alterations in phagocytosis has shown inconsistent results. For example, in an exposure (PM)-infectious animal model, impaired *Streptococcus pneumoniae* clearance and phagocytosis resulted from decreased macrophages internalization of bacteria, although increased binding of microbe to surface of macrophages was reported.[166] In a similar model increased susceptibility to *Staphylococcus aureus* infection resulted from depressed phagocytosis index and abnormal natural killer cell response.[167] Also, in another animal exposure model increased infectivity to *Listeria monocytogenes* resulted from decreased ROS-induced nitric oxide production by alveolar macrophages.[168] In contrast, natural (chronic) PM exposure of human bronchoalveolar lavage fluid decreased macrophage cytokine (CXCL8) release and downregulated induced phagosomal oxidative burst. Per contra, no impairment in macrophage redox potential, proteolysis or phagocytosis was observed likely due to the experimental chronicity of exposure.[169] Additionally, in an analogous model using high levels of the same pollutant (PM), the impaired antimicrobial defense resulted from defective macrophage activation of T cells by class II^+ major histocompatibility complex and subsequent decrease in interferon-γ production, but unaltered phagocytic activity.[170] Interestingly, no increase of neutrophils and TNF-α levels was observed in bronchoalveolar lavage following exposure and infection suggesting acute exposure to relatively high level of PM does not trigger a classic or sustained inflammatory response.[170]

Besides suggesting interference with innate immunity, exposure studies suggest further alterations in adaptive immunity as evidenced by immunopathological relationships between antigen presenting cell cytokines, the corresponding sensitized T cells subsets, and recruited neutrophils (see Table 2). As such, a *Listeria monocytogenes*-mediated suppression of macrophages immune response upon low dose DEP exposure manifested as "dysfunctional" production of macrophages-derived cytokines. This was associated with downregulation of innate protective cytokines (e.g. IL-1β, tumor necrosis factor-α, IL-12, IL-2 and interferon-γ), suppression of adaptive CD4 and CD8 T cell immune response, and upregulation of macrophage bactericidal anti-inflammatory cytokines (IL-10 and IL-6).[171] Other examples of altered cytokine release include the pro-inflammatory

interleukin-8 (IL-8) synergistic release by respiratory cells in an exposure model challenged by viral infection (rhinovirus 16);[71] also a decrease in chemokine ligand 2 level in an experimental PM exposure model involving lipopolysaccharide priming, thereby suggesting an important role of chemokine ligand 2 in preventing excessive inflammation.[169] Besides the role of cytokines in fine tuning extent of inflammation in these models, T cell subsets like T cytotoxic ($CD8^+$) and regulatory T cells (Treg) in addition to neutrophils have been studied. DEP exposure in rats increased susceptibility to *Listeria monocytogenes* infection by attenuating T cell mediated immunity, namely $CD4^+$ T helper lymphocytes and $CD8^+$ T cytotoxic cells;[168] PM exposure in neonatal mice resulted in depression of adaptive response to influenza virus A infection and by an increased expression in Treg cells and IL-10 in lung tissues. Interestingly, the induced immunosuppressive effect was reversed by Treg depletion and restored by either Treg transfer or recombinant IL-10 treatment.[172]

Furthermore, airway neutrophilia, which is instrumental in bacterial clearance, has been studied in in*in*- vitro*vitro* infectious exposure model in relationship to Th1 and Th17 proinflammatory cytokine release. The concomitant increase in bronchoalveolar lavage fluid IL-17 with airway neutrophilia, and their attenuation in IL-17 "knock out" mice following exposure and infection suggested the importance of IL-17 in inducing neutrophil-mediated airway inflammation. Also, decreased induction of IL-17A-mediated airway neutrophilia following exposure and infection in $IL\text{-}1R1^-$ mice compared with wild-type controls also suggests IL-1 signaling is required in IL-17A-exacerbated neutrophilia.[173] Moreover, in an *in vivo* exposure-infectious animal model modulated by interferon-γ priming to mimic viral infection, an impaired PM-mediated bacterial phagocytosis correlated with activation of genes encoding neutrophil-recruiting chemokines and increased histopathology suggestive of severe pneumonia.[174] Still, in an animal *in vivo* model, exposure followed by LPS infection induced cytokine changes in the lung suggestive of a Th1/Th2 imbalance and manifested by increased expression of IL-4 among others, and a concordant decrease in IFN-γ expression.[72]

The infectious-exposure model is an attractive tool to explore immunopathological alterations in COPD patients or in laboratory cells exposed to secondhand smoking. In a mice model, 8 weeks secondhand smoking pre-exposure was followed by infection with non-typeable *Haemophilus influenza* which is a pathogen commonly implicated in acute exacerbation of COPD. The model revealed increased number of immune cell infiltrates except for macrophages, and a suppressed induction of a robust adaptive immune response manifested as decreased IFN-γ. Also, a downregulated T cell adaptive response manifested by decreased bacterial clearance and diminished efficiency of specific antibody subclass switching, both mitigated by anti-viral vaccination.[175] In a similar animal model examining the immunological effect of antibiotic therapy, cigarette smoke exposure followed by *Streptococcus pneumoniae* infection resulted in recruitment of macrophages and monocytes in lung tissue and alveolar fluid reportedly to confine infection to the lung; also a decreased number of neutrophils but a differential increase in neutrophil-mediated antimicrobial peptide, myeloperoxidase. Antibiotic therapy had no effect on mice survival rate but reduced lung injury and induced a differential change of cytokine levels in bronchoalveolar lavage fluid most importantly downregulation of Th1 and Th17 inflammatory cytokines.[176] Human in-vitro pre-exposure and infectious models are designed to mimic acute exacerbations in stable but exposed COPD patients. DEP exposure followed by non-typeable *Haemophilus influenza* infection did not compromise mucosal barrier function in COPD or healthy patients. However, epithelial endoplasmic reticulum activity was markedly disrupted in COPD patients, manifested by depressed gene expression of the integrated stress response markers in an ROS-mediated process.[115] In another model, macrophages differentiating from locally recruited monocytes in lungs of COPD patients were pre-exposed to low level DEP and subsequently challenged with TLR agonists or heat killed *E.coli*. This resulted in structural and functional changes in innate and adaptive immune system consisting of mitochondrial and lysosomal dysfunction in macrophages,

decreased expression of their surface recognition markers, loss of macrophage differentiation, and reduction in proinflammatory cytokine production (e.g.IL-8).[177]

The majority of exposure-infection human and animal models have examined immunological alterations following long-term (weeks) and low-dose pre-exposure periods which best mimics real-life outdoor pollutant exposure or indoor secondhand smoking relevant to COPD. Nevertheless, other models which studied brief and short-term (hours to days) exposure periods have yielded mixed results. For example, one-week diesel exhaust pre-exposure of mice *in vivo* decreased *Pseudomonas aeruginosa* clearance from bronchial epithelial cells, whereas in the same model a six-months pre-exposure did not.[163] Also, in an *in vivo* model, mice were pre-exposed to PM for 1 day (short term) or 2 weeks (long term), later infection with Influenza virus A and survival rate was assessed over the ensuing 10 days following contamination. Short-term exposure improved mice survival rate and triggered a robust immune response whereas long-term exposure did not,[178] reportedly mediated by macrophage cytokine gene expression regulator Kdm6a. To model secondhand smoking exposure or for recent initiation of active smoking, mice were exposed to brief (2 h per day for 2 days) low dose of side stream cigarette smoke or to prolonged (2.5 weeks) high dose cigarette smoke, respectively, and later inoculated with *Streptococcus pneumonia*. Surprisingly, brief exposure did not show significant survival benefit whereas prolonged exposure in mice did, reportedly due to diminished propagation of bacteria into the systemic circulation during chronic exposure.[176] Finally, in a mice model examining only chronic secondhand smoking exposure and its impact on non-typeable *Haemophilus influenza* antimicrobial response, 8 weeks secondhand smoking pre-exposure, theoretically mimicking mainstream smoking, compromised the ability of host T cell-mediated adaptive immune system to mount an effective response against non-typeable *Haemophilus influenza* infection.[175]

Taken together, these models suggest exposure impairs innate and adaptive immunity against airway microbial infections. Limitations inherent to the design of these models compel a careful interpretation of results taking into consideration the response to infectivity of animal host cells, the duration and intensity[64,163,178,179] of pollutant pre-exposure, and the nature of microbial agents used for contamination.

SUMMARY

We reviewed evidence for the involvement of oxidative stress pathways and their nature in healthy individuals and patients with inflammatory airway diseases following exposure to a spectrum of important chemical, allergic and infectious air contaminants. When comparing exposure clinical models in patients with AR, CRS, and allergic asthma, the signal and cascade pathways can generate important oxidative and anti-oxidative markers and induce specific changes in adaptive and innate immune system. Thus, exposure can amplify the inflammatory process in patients with AR, CRS, and allergic asthma supporting evidence that, at least in atopic individuals, exposure can increase airway hypersensitivity. When accentuated by an infectious insult, pre-exposure clinical models in patients with inflammatory airway diseases show specific immunopathological alterations at mucosal and submucosal levels of the airway epithelial barrier and ultimately in the adaptive immune system. The resultant increased susceptibility to infection can be due to either increased infectivity of microbial agents or to a ROS-mediated direct effect of pollutant on host immune defense cells.

FUTURE RESEARCH

The complex nature and composition of chemical air pollutants and their aerodynamic properties is reflected in conflicting epidemiological and experimental results on exposure and its impact on health. Also, the oxidative stress-mediated immunopathological changes have highlighted important antioxidant markers, which can be therapeutically bio-engineered. Since there is no clear consensus on efficacy of natural or synthetic antioxidants,[125,180,181] current research should search for new therapeutic modalities and define the role of currently available ones such as antihistamines, intranasal or inhaled steroids, antibiotics and anti-viral vaccination in patients with inflammatory airway diseases challenged by exposure and at times by an infectious process.

Abbreviations

AR: Allergic rhinitis; **COPD**: Chronic obstructive pulmonary disease; CRS: Chronic rhinosinusitis; **DEP**: Diesel exhaust particles; **IAD**: Inflammatory airway diseases; **IL**: Interleukin; **ILC**: Innate lymphoid cells; **NOx**: Nitrogen oxides; **PAH**: Polycyclic aromatic hydrocarbons; **PM**: Particulate matter; **ROS**: Reactive oxygen species; **TBS**: Tobacco smoke; **TLR**: Toll-like receptors; **Treg**: Regulatory T cell; **VOCs**: Volatile organic compounds

DECLARATIONS

Funding source
Not applicable.

Human and animal research
Not applicable.

Registration of clinical trials
Not applicable.

Availability of data and materials
Not applicable.

Author contributions
We attest that all authors contributed significantly to the creation of this manuscript.

- Philip Rouadi and Samar Idriss initiated the work, contributed substantially to the conception and design of the study, the acquisition, analysis, and interpretation of data.
- Philip Rouadi, Samar Idriss, Robert Naclerio, David Peden, and Ignacio Ansotegui wrote the draft and did a critical review of the article and provided final approval of the version to publish.
- Giorgio Walter Canonica, Sandra N. Gonzalez Diaz, Nelson A. Rosario Filho, Juan Carlos Ivancevich, Peter W. Hellings, Margarita Murrieta-Aguttes, Fares H. Zaitoun, Carla Irani, Marilyn R. Karam, and Jean Bousquet reviewed the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- Philip Rouadi supervised the manuscript.

Ethics committee approval
Not applicable.

Publication consent
All authors agreed to the publication of this work.

Declaration of competing interest
The authors have nothing to declare relative to this paper.

Acknowledgements
This project was initiated by the Rhinitis and Sinusitis Committee of the World Allergy Organization (2018–2019 term).

Author details
[a]Department of Otolaryngology-Head and Neck Surgery, Eye and Ear University Hospital, Beirut, Lebanon. [b]Johns Hopkins University Department of Otolaryngology - Head and Neck Surgery, Baltimore, MD, USA. [c]UNC Center for Environmental Medicine, Asthma, and Lung Biology, Division of Allergy, Immunology and Rheumatology, Department of Pediatrics UNS School of Medicine, USA. [d]Department of Allergy and Immunology, Hospital Quironsalud Bizkaia, Bilbao, Spain. [e]Asthma & Allergy Clinic,Humanitas University & Research Hospital IRCCS, Milano, Italy. [f]University Autonoma de Nuevo Leon Facultad de Medicina y Hospital Universitario U.A.N.L, Monterrey, NL, c.p. 64460, México. [g]Federal University of Parana, Brazil. [h]Faculty of Medicine, Universidad del Salvador, Buenos Aires, Argentina and Head of Allergy and Immunology at the Santa Isabel Clinic, Buenos Aires, Argentina. [i]Department of Otorhinolaryngology, University Hospitals Leuven, Leuven, Belgium. [j]Department of Otorhinolaryngology, Academic Medical Center Amsterdam, The Netherlands - Department Otorhinolaryngology, University Hospital Ghent, Belgium. [k]8 Rue Pierre Poli, Issy Les Moulineaux, 92130, France. [l]LAUMC Rizk Hospital, Otolaryngology-Allergy Department, Beirut, Lebanon. [m]Department of Internal Medicine and Infectious Diseases, St Joseph University, Hotel Dieu de France Hospital, Beirut, Lebanon. [n]Division of Rheumatology, Allergy and Clinical Immunology, Department of Internal Medicine, American University of Beirut, Beirut, Lebanon. [o]INSERM U 1168, VIMA: Ageing and Chronic Diseases Epidemiological and Public Health Approaches, Villejuif, France. [p]University Versailles St-Quentin-en-Yvelines, France. [q]Allergy-Centre-Charité, Charité–Universitätsmedizin Berlin, Berlin, Germany.

REFERENCES

1. Seinfeld JH, Pandis SN. *Atmospheric Chemistry and Physics: From Air Pollution to Climate Change*. second ed. New York: John Wiley & Sons, Inc.; 2006. https://doi.org/10.1080/00139157.1999.10544295.
2. Bruce N, Adair-Rohani H, Puzzolo E. *WHO Guidelines for Indoor Air Quality: Household Fuel Combustion*. World Health Organization; 2014. http://www.who.int/indoorair/guidelines/hhfc/en/. Accessed January 17, 2020.
3. Health Effects Institute. *State of Global Air 2019*. Special Report.. Boston, MA: Heal Eff Inst; 2019
4. *7 Million Premature Deaths Annually Linked to Air Pollution*. World Health Organization; 2014. https://www.who.int/mediacentre/news/releases/2014/air-pollution/en/. Accessed January 17, 2020.

5. Liu Y, Pan J, Zhang H, et al. Short-term exposure to ambient air pollution and asthma mortality. *Am J Respir Crit Care Med*. 2019;200(1):24–32. https://doi.org/10.1164/rccm.201810-1823OC.
6. Meng X, Wang C, Cao D, Wong CM, Kan H. Short-term effect of ambient air pollution on COPD mortality in four Chinese cities. *Atmos Environ*. 2013;77:149–154. https://doi.org/10.1016/j.atmosenv.2013.05.001.
7. Hamilos DL. Chronic rhinosinusitis: epidemiology and medical management. *J Allergy Clin Immunol*. 2011;128:693–707. https://doi.org/10.1016/j.jaci.2011.08.004.
8. Murray CS, Simpson A, Custovic A. Allergens, viruses, and asthma exacerbations. *Proc Am Thorac Soc*. 2004;1:99–104. https://doi.org/10.1513/pats.2306027.
9. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations: origin, effect, and prevention. *J Allergy Clin Immunol*. 2011;128:1165–1174. https://doi.org/10.1016/j.jaci.2011.10.024.
10. Schwartz J, Slater D, Larson TV, Pierson WE, Koenig JQ. Particulate air pollution and hospital emergency room visits for asthma in Seattle. *Am Rev Respir Dis*. 1993;147:826–831. https://doi.org/10.1164/ajrccm/147.4.826.
11. Spira-Cohen A, Chen LC, Kendall M, Lall R, Thurston GD. Personal exposures to traffic-related air pollution and acute respiratory health among bronx school children with asthma. *Environ Health Perspect*. 2011;119:559–565. https://doi.org/10.1289/ehp.1002653.
12. Jiang XQ, Mei XD, Feng D. Air pollution and chronic airway diseases: what should people know and do? *J Thorac Dis*. 2016;8:31–40. https://doi.org/10.3978/j.issn.2072-1439.2015.11.50.
13. Garmendia J, Morey P, Bengoechea JA. Impact of cigarette smoke exposure on host-bacterial pathogen interactions. *Eur Respir J*. 2012;39:467–477. https://doi.org/10.1183/09031936.00061911.
14. Pöschl U. Atmospheric aerosols: composition, transformation, climate and health effects. *Angew Chem*. 2005;44:7520–7540. https://doi.org/10.1002/anie.200501122.
15. Anderson JO, Thundiyil JG, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. *J Med Toxicol*. 2012;8:166–175. https://doi.org/10.1007/s13181-011-0203-1.
16. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet*. 2014;383:1581–1592. https://doi.org/10.1016/S0140-6736(14)60617-6. Outdoor.
17. Mannucci PM, Harari S, Martinelli I, Franchini M. Effects on health of air pollution: a narrative review. *Intern Emerg Med*. 2015;10:657–662. https://doi.org/10.1007/s11739-015-1276-7.
18. Qian J, Ferro AR, Fowler KR. Estimating the resuspension rate and residence time of indoor particles. *J Air Waste Manag Assoc*. 2008;58:502–516. https://doi.org/10.3155/1047-3289.58.4.502.
19. Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. *Science*. 2006;311:622–627. https://doi.org/10.1126/science.1114397 (80-).
20. Li N, Georas S, Alexis N, Fritz P, Xia T, Williams MS. A work group report on ultrafine particles (AAAAI) why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in humans. *J Allergy Clin Immunol*. 2016;138:386–396. https://doi.org/10.1016/j.jaci.2016.02.023.A.
21. Falcon-Rodriguez CI, Osornio-Vargas AR, Sada-Ovalle I, Segura-Medina P. Aeroparticles, composition, and lung diseases. *Front Immunol*. 2016;7:1–9. https://doi.org/10.3389/fimmu.2016.00003.
22. Song X, Liu Y, Hu Y, Zhao X, Tian J, Ding G. Short-term exposure to air pollution and cardiac arrhythmia: a meta-analysis and systematic review. *Int J Environ Res Publ Health*. 2016;13(642):1–12. https://doi.org/10.3390/ijerph13070642.
23. Du Y, Xu X, Chu M, Guo Y, Wang J. Air particulate matter and cardiovascular disease: the epidemiological , biomedical and clinical evidence. *J Thorac Dis*. 2016;8(1):8–19. https://doi.org/10.3978/j.issn.2072-1439.2015.11.37.
24. Brook RD, Rajagopalan S, Iii CAP, et al. Particulate matter air pollution and cardiovascular disease an update to the scientific statement from the American heart association. *Circulation*. 2010;121:2331–2378. https://doi.org/10.1161/CIR.0b013e3181dbece1.
25. Brugha R, Grigg J. Urban air pollution and respiratory infections. *Paediatr Respir Rev*. 2014;15:194–199. https://doi.org/10.1016/j.prrv.2014.03.001.
26. Korpi A, Järnberg J, Pasanen A. Microbial volatile organic compounds. *Crit Rev Toxicol*. 2009;39:139–193. https://doi.org/10.1080/10408440802291497.
27. Vaughan TL, Stewart PA, Teschke K, et al. Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. *Occup Environ Med*. 2000;57:376–384. https://doi.org/10.1136/oem.57.6.376.
28. Zhang L, Freeman LEB, Nakamura J, et al. Formaldehyde and leukemia: epidemiology, potential mechanisms and implications for risk assessment. *Environ Mol Mutagen*. 2010;51:181–191. https://doi.org/10.1002/em.20534. Formaldehyde.
29. Destaillats H, Maddalena RL, Singer BC, Hodgson AT, Mckone TE. Indoor pollutants emitted by office equipment: a review of reported data and information needs. *Atmos Environ*. 2008;42:1371–1388. https://doi.org/10.1016/j.atmosenv.2007.10.080.
30. Wolkoff P. Volatile organic compounds - sources, measurements, emissions, and the impact on indoor air quality. *Int J indoor air Qual Clim*. 1995;(Suppl 3):9–73.
31. Yu C, Crump D. A review of the emission of VOCs from polymeric materials used in buildings. *Build Environ*. 1998;33:357–374. https://doi.org/10.1016/S0360-1323(97)00055-3.
32. Wady L, Bunte A, Pehrson C, Larsson L. Use of gas chromatography-mass spectrometry/solid phase microextraction for the identification of MVOCs from moldy building materials. *J Microbiol Methods*. 2003;52:325–332. doi:0167-7012/02/$.
33. Su F-C, Mukherjee B, Batterman S. Determinants of personal, indoor and outdoor VOC concentrations: an analysis of the RIOPA data. *Environ Res*. 2013;126:192–203. https://doi.org/10.1016/j.envres.2013.08.005.
34. Lin T, Krishnaswamy G, Chi DS. Incense smoke: clinical, structural and molecular effects on airway disease. *Clin Mol Allergy*. 2008;6:1–9. https://doi.org/10.1186/1476-7961-6-3.

35. Loomis D, Grosse Y, Lauby-secretan B, et al. The carcinogenicity of outdoor air pollution. *Lancet Oncol*. 2013;14:1262–1263. https://doi.org/10.1016/S1470-2045(13)70487-X.

36. Liati A, Eggenschwiler PD. Characterization of particulate matter deposited in diesel particulate filters: visual and analytical approach in macro- , micro- and nano-scales. *Combust Flame*. 2010;157:1658–1670. https://doi.org/10.1016/j.combustflame.2010.02.015.

37. Souza CV De, Correa SM. Polycyclic aromatic hydrocarbons in diesel emission , diesel fuel and lubricant oil. *Fuel*. 2016;185:925–931. https://doi.org/10.1016/j.fuel.2016.08.054.

38. Burtscher H. Physical characterization of particulate emissions from diesel engines: a review. *Aerosol Sci*. 2005;36:896–932. https://doi.org/10.1016/j.jaerosci.2004.12.001.

39. Zielinska B, Sagebiel J, Arnott WP, et al. Phase and size distribution of polycyclic aromatic hydrocarbons in diesel and gasoline vehicle emissions. *Environ Sci Technol*. 2004;38:2557–2567. https://doi.org/10.1021/es030518d.

40. Querol X, Pey J, Minguillón MC, et al. PM speciation and sources in Mexico during the MILAGRO-2006 Campaign. *Atmos Chem Phys*. 2008;8:111–128. https://doi.org/10.5194/acp-8-111-2008.

41. Steiner S, Bisig C, Petri-Fink A, Rothen-Rutishauser B. Diesel exhaust: current knowledge of adverse effects and underlying cellular mechanisms. *Arch Toxicol*. 2016;90:1541–1553. https://doi.org/10.1007/s00204-016-1736-5.

42. Paoletti E. Impact of ozone on Mediterranean forests: a review. *Environ Pollut*. 2006;144:463–474. https://doi.org/10.1016/j.envpol.2005.12.051.

43. Screpanti A, Marco A De. Corrosion on cultural heritage buildings in Italy: a role for ozone? *Environ Pollut*. 2009;157:1513–1520. https://doi.org/10.1016/j.envpol.2008.09.046.

44. Mills G, Hayes F, Simpson D, et al. Evidence of widespread effects of ozone on crops and (semi-) natural vegetation in Europe (1990-2006) in relation to AOT40- and flux-based risk maps. *Global Change Biol*. 2011;17:592–613. https://doi.org/10.1111/j.1365-2486.2010.02217.x.

45. Atkinson R, Barregård L, Bellander T, et al. *Review of Evidence on Health Aspects of Air Pollution – REVIHAAP Project*. 2013. Copenhagen.

46. Ortiz AG, Guerreiro C, Soares J. *Air Quality in Europe – 2019 Report*. 2019. https://doi.org/10.2800/62459. Copenhagen.

47. Sicard P, Augustaitis A, Belyazid S, et al. Global topics and novel approaches in the study of air pollution , climate change and forest ecosystems. *Environ Pollut*. 2016;213:977–987. https://doi.org/10.1016/j.envpol.2016.01.075.

48. Sillman S. The relation between ozone , NO and hydrocarbons in urban and polluted rural environments. *Atmos Environ*. 1999;33:1821–1845. https://doi.org/10.1016/S1352-2310(98)00345-8.

49. Solberg S, Derwent RG, Hov Ø, Langner J, Lindskog A. European abatement of surface ozone in a global perspective. *Ambio*. 2005;34:47–53. https://doi.org/10.1579/0044-7447-34.1.47.

50. Niemann B, Rohrbach S, Miller MR, Newby DE, Fuster V, Kovacic JC. Oxidative stress and obesity, diabetes, smoking, and pollution: Part 3 of a 3-Part Series HHS public access. *J Am Coll Cardiol*. 2017;70(2):230–251. https://doi.org/10.1016/j.jacc.2017.05.043.

51. Fetterman JL, Sammy MJ, Ballinger SW. Mitochondrial toxicity of tobacco smoke and air pollution. *Toxicology*. 2017;391:18–33. https://doi.org/10.1016/j.tox.2017.08.002.

52. Rogers RG, Hummer RA, Kuerger PM, Pampel FC. Mortality Attributable to cigarette smoking in the United States. *Popul Dev Rev*. 2005;31(2):259–292.

53. Ú Martínez, Brandon TH, Sutton SK, Simmons VN. Associations between the smoking-relatedness of a cancer type, cessation attitudes and beliefs, and future abstinence among recent quitters. *Psycho Oncol*. 2018;27:2104–2110. https://doi.org/10.1002/pon.4774.

54. Moore PJ, Sesma J, Alexis NE, Tarran R. Tobacco exposure inhibits SPLUNC1-dependent antimicrobial activity. *Respir Res*. 2019;20:1–11. https://doi.org/10.1186/s12931-019-1066-2.

55. Jiang D, Wenzel SE, Wu Q, Bowler RP, Schnell C, Chu HW. Human neutrophil elastase degrades SPLUNC1 and impairs airway epithelial defense against bacteria. *PloS One*. 2013;8:1–7. https://doi.org/10.1371/journal.pone.0064689.

56. Gustafsson Å, Krais AM, Gorzsás A, Lundh T, Gerde P. Isolation and characterization of a respirable particle fraction from residential house- dust. *Environ Res*. 2018;161:284–290. https://doi.org/10.1016/j.envres.2017.10.049.

57. Nazaroff WW. Indoor particle dynamics. *Indoor Air*. 2004;14:175–183. https://doi.org/10.1111/j.1600-0668.2004.00286.x.

58. Zahradnik E, Raulf M. Animal allergens and their presence in the environment. *Front Immunol*. 2014;5(March):1–21. https://doi.org/10.3389/fimmu.2014.00076.

59. Custovic A, Simpson A, Pahdi H, Green RM, Chapman MD, Woodcock A. Distribution , aerodynamic characteristics , and removal of the major cat allergen Fel d 1 in British homes. *Thorax*. 1998;53:33–38. https://doi.org/10.1136/thx.53.1.33.

60. Chan SK, Leung DYM. Dog and cat allergies: current state of diagnostic approaches and challenges. *Allergy Asthma Immunol Res*. 2018;10:97–105. https://doi.org/10.4168/aair.2018.10.2.97.

61. Pomes A, Chapman MD, Wuschmann S. Indoor allergens and allergic respiratory disease. *Curr Allergy Asthma Rep*. 2016;16:1–17. https://doi.org/10.1007/s11882-016-0622-9. Indoor.

62. Zhang L, Yang L, Zhou Q, et al. Size distribution of particulate polycyclic aromatic hydrocarbons in fresh combustion smoke and ambient air: a review. *J Environ Sci*. 2020;88:370–384. https://doi.org/10.1016/j.jes.2019.09.007.

63. Janssen NAH, Schwartz J, Zanobetti A, Suh HH. Air conditioning and source-specific particles as modifiers of the effect of PM 10 on hospital admissions for heart and lung disease. *Environ Health Perspect*. 2002;110:43–49. https://doi.org/10.1289/ehp.0211043.

64. Hussey SJK, Purves J, Allcock N, et al. Air pollution alters Staphylococcus aureus and Streptococcus pneumoniae biofilms , antibiotic tolerance and colonisation. *Environ Microbiol*. 2017;19:1868–1880. https://doi.org/10.1111/1462-2920.13686.

65. Suraju MO, Lalinde-barnes S, Sanamvenkata S, Esmaeili M, Shishodia S, Rosenzweig JA. Science of the Total

Environment the effects of indoor and outdoor dust exposure on the growth , sensitivity to oxidative-stress , and bio fi lm production of three opportunistic bacterial pathogens. *Sci Total Environ*. 2015;538:949–958. https://doi.org/10.1016/j.scitotenv.2015.08.063.

66. Forrester SJ, Kikuchi DS, Hernandes MS, Xu Q, Griendling KK. Reactive oxygen species in metabolic and inflammatory signaling. *Circ Res*. 2018;122:877–902. https://doi.org/10.1161/CIRCRESAHA.117.311401.

67. Lodovici M, Bigagli E. Oxidative stress and air pollution exposure. *J Toxicol*. 2011:1–9. https://doi.org/10.1155/2011/487074. Review.

68. Dayem AA, Hossain MK, Lee S Bin, et al. The role of reactive oxygen species (ROS) in the biological activities of metallic nanoparticles. *Int J Mol Sci*. 2017;18:1–21. https://doi.org/10.3390/ijms18010120.

69. Cho H, Kleeberger SR. Nrf2 protects against airway disorders. *Toxicol Appl Pharmacol*. 2010;244:43–56. https://doi.org/10.1016/j.taap.2009.07.024.

70. Holguin F. Oxidative stress in airway diseases. *Ann Am Thorac Soc*. 2013;10:150–157. https://doi.org/10.1513/AnnalsATS.201305-116AW.

71. Spannhake EW, Reddy SPM, Jacoby DB, Yu X, Saatian B, Tian J. Synergism between rhinovirus infection and oxidant pollutant exposure enhances airway epithelial cell cytokine production. *Environ Health Perspect*. 2002;110:665–670. https://doi.org/10.1289/ehp.02110665.

72. Wang W, Chen M, Jin X, et al. H2S induces Th1/Th2 imbalance with triggered NF- k B pathway to exacerbate LPS-induce chicken pneumonia response. *Chemosphere*. 2018;208:241–246. https://doi.org/10.1016/j.chemosphere.2018.05.152.

73. Betteridge DJ. What is oxidative stress? *Metabolism*. 2000;49:3–8. https://doi.org/10.1016/S0026-0495(00)80077-3.

74. Nita M, Grzybowski A. The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. *Oxid Med Cell Longev*. 2016:1–23. https://doi.org/10.1155/2016/3164734.

75. Chan TK, Loh Y, Peh Y, et al. House dust mite – induced asthma causes oxidative damage and DNA double-strand breaks in the lungs. *J Allergy Clin Immunol*. 2016;138:84–96. https://doi.org/10.1016/j.jaci.2016.02.017.

76. Naclerio R, Ansotegui IJ, Bousquet J, et al. International expert consensus on the management of allergic rhinitis (AR) aggravated by air pollutants Impact of air pollution on patients with AR: current knowledge and future strategies. *WAO J*. 2020. https://doi.org/10.1016/j.waojou.2020.100106.

77. Diaz-Sanchez D, Albert T, Fleming J, Saxon A. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. *J Immunol*. 1997;158:2406–2413. https://doi.org/10.4049/jimmunol.167.1.98.

78. Schanen BC, Das S, Reilly CM, et al. Immunomodulation and T Helper TH1/TH2 response polarization by CeO2 and TiO2 nanoparticles. *PloS One*. 2013;8:16–26. https://doi.org/10.1371/journal.pone.0062816.

79. Jaakkola MS, Quansah R, Hugg TT, Heikkinen SAM, Jaakkola JJK. Association of indoor dampness and molds with rhinitis risk: a systematic review and meta-analysis. *J Allergy Clin Immunol*. 2012;132:1099–1110. https://doi.org/10.1016/j.jaci.2013.07.028.

80. Wang J, Li B, Yu W, et al. Rhinitis symptoms and asthma among parents of preschool children in relation to the home environment in chongqing , China. *PloS One*. 2014;9:1–12. https://doi.org/10.1371/journal.pone.0094731.

81. Penard-Morand C, Raherison C, Charpine D, et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *Eur Respir J*. 2010;36:33–40. https://doi.org/10.1183/09031936.00116109.

82. Hoek G, Pattenden S, Willers S, et al. PM 10, and children's respiratory symptoms and lung function in the PATY study. *Eur Respir J*. 2012;40:538–547. https://doi.org/10.1183/09031936.00002611.

83. Chen J, Peng L, He S, Li Y, Mu Z. Association between environmental factors and hospital visits among allergic patients: a retrospective study. *Asian Pac J Allergy Immunol*. 2016;34:21–29. https://doi.org/10.12932/AP0639.34.1.2016.

84. Zhang F, Wang W, Lv J, Krafft T, Xu J. Science of the Total Environment Time-series studies on air pollution and daily outpatient visits for allergic rhinitis in. *Sci Total Environ*. 2011;409:2486–2492. https://doi.org/10.1016/j.scitotenv.2011.04.007.

85. Gehring U, Wijga AH, Brauer M, et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 Years of life. *Am J Respir Crit Care Med*. 2010;181:596–603. https://doi.org/10.1164/rccm.200906-0858OC.

86. Bhattacharyya N. Air quality influences the prevalence of hay fever and sinusitis. *Laryngoscope*. 2009;119:429–433. https://doi.org/10.1002/lary.20097.

87. Rosenlund M, Forastiere F, Porta D, Sario M De, Badaloni C, Perucci CA. Traffic-related air pollution in relation to respiratory symptoms , allergic sensitisation and lung function in schoolchildren. *Environ Expo*. 2009;64:573–580. https://doi.org/10.1136/thx.2007.094953.

88. Wouters IM, Hilhorst SKM, Kleppe P, et al. Upper airway inflammation and respiratory symptoms in domestic waste collectors. *Occup Environ Med*. 2002;59:106–112. https://doi.org/10.1136/oem.59.2.106.

89. Norris G, YoungPong SN, Koenig JQ, Larson TV, Sheppard L, Stout JW. An association between fine particles and asthma emergency department visits for children in Seattle. *Environ Health Perspect*. 1999;107:489–493. https://doi.org/10.1289/ehp.99107489.

90. Amâncio CT, Nascimento LFC. Asthma and air pollutants: a time series study. *Rev Assoc Med Bras*. 2012;58:302–307. https://doi.org/10.1590/S0104-42302012000300009.

91. Peden D, Reed CE. Environmental and occupational allergies. *J Allergy Clin Immunol*. 2010;125:150–S160. https://doi.org/10.1016/j.jaci.2009.10.073.

92. Porebski G, Woźniak M, Czarnobilska E. Residential proximity to major roadways is associated with increased prevalence of allergic respiratory symptoms in children. *Ann Agric Environ*

Med. 2014;21:760–766. https://doi.org/10.5604/12321966.1129929.

93. Gruzieva O, Gehring U, Aalberse R, et al. Meta-analysis of air pollution exposure association with allergic sensitization in European birth cohorts. *J Allergy Clin Immunol*. 2014;133:767–776. https://doi.org/10.1016/j.jaci.2013.07.048.
94. Hassoun Y, James C, Bernstein DI. The effects of air pollution on the development of atopic disease. *Clin Rev Allergy Immunol*. 2019;57:403–414. https://doi.org/10.1007/s12016-019-08730-3.
95. Anderson HR, Ruggles R, Pandey KD, et al. Ambient particulate pollution and the world-wide prevalence of asthma, rhinoconjunctivitis and eczema in children: phase One of the International Study of Asthma and Allergies in Childhood (ISAAC). *Occup Environ Med*. 2010;67:293–300. https://doi.org/10.1136/oem.2009.048785.
96. Cho DY, Nayak JV, Bravo DT, et al. Expression of dual oxidases and secreted cytokines in chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2013;3:376–383. https://doi.org/10.1002/alr.21133.
97. Yu Z, Wang Y, Zhang J, et al. Expression of heme oxygenase-1 in eosinophilic and non-eosinophilic chronic rhinosinusitis with nasal polyps: modulation by cytokines. *Int Forum Allergy Rhinol*. 2015;5:734–740. https://doi.org/10.1002/alr.21530.
98. Hong Z, Guo Z, Zhang R, et al. Airborne fine particulate matter induces oxidative stress and inflammation in human nasal epithelial cells. *Tohoku J Exp Med*. 2016;239:117–125. https://doi.org/10.1620/tjem.239.117.Correspondence.
99. Saxon A, Diaz-sanchez D. Diesel exhaust as a model xenobiotic in allergic inflammation. *Immunopharmacology*. 2000;48:325–327. https://doi.org/10.1016/S0162-3109(00)00234-4.
100. Ellis Anne K, Murrieta-Aguettes Margarita, Furey Sandy, Carlsten Christopher. Phase 3, single-center, sequential and parallel group, double-blind, randomized study evaluating the efficacy and safety of Fexofenadine Hydrochloride 180 mg (Allegra/Telfast) versus placebo in subjects suffering from Allergic Rhinitis with symptoms aggravated in presence of pollutants: analysis of individual symptom scores. *World Allergy Organ J*. 2020;13, 100137.
101. Hernandez ML, Dhingra R, Burbank AJ, et al. Low-level ozone has both respiratory & systemic effects in African-American adolescents with asthma despite asthma controller therapy. *J Allergy Clin Immunol*. 2018;142:1974–1977. https://doi.org/10.1016/j.jaci.2018.08.003. Low-level.
102. Hernandez ML, Lay JC, Harris B, et al. Atopic asthmatic subjects but not atopic subjects without asthma have enhanced inflammatory response to ozone. *J Allergy Clin Immunol*. 2010;126:537–545. https://doi.org/10.1016/j.jaci.2010.06.043.
103. Christian DL, Chen LL, Scannell CH, Ferrando RE, Welch BS, Balmes JR. Ozone-induced inflammation is attenuated with multiday exposure. *Am J Respir Crit Care Med*. 1998;158:532–537. https://doi.org/10.1164/ajrccm.158.2.9709023.
104. Peden DB, Boehlecke B, Horstman D, Devlin R. Prolonged acute exposure to 0.16 ppm ozone induces eosinophilic airway inflammation in asthmatic subjects with allergies. *J Allergy Clin Immunol*. 1997;100:802–808. https://doi.org/10.1016/S0091-6749(97)70277-X.
105. Hernandez M, Brickey WJ, Alexis NE, et al. Airway cells from atopic asthmatics exposed to ozone display an enhanced innate immune gene profile. *J Allergy Clin Immunol*. 2012;129:259–261. https://doi.org/10.1016/j.jaci.2011.11.007. Airway.
106. Gratziou C, Rovina N, Makris M, Simoes DCM, Papapetropoulos A, Roussos C. Breath markers of oxidative stress and airway inflammation in seasonal allergic rhinitis. *Int J Immunopathol Pharmacol*. 2008;21:949–957.
107. Sagdic A, Sener O, Bulucu F, et al. Oxidative stress status and plasma trace elements in patients with asthma or allergic rhinitis. *Allergol Immunopathol (Madr)*. 2011;39:200–205. https://doi.org/10.1016/j.aller.2010.07.006.
108. Emin O, Hasan A, Aysegul D, Rusen D. Total antioxidant status and oxidative stress and their relationship to total IgE levels and eosinophil counts in children with allergic rhinitis. *J Investig Allergol Clin Immunol*. 2012;22:188–192. https://doi.org/10.1177/039463200802100419.
109. Ozkaya E, Akduman MDH, Erenberk U, Demir A, Dundaroz MR. Plasma paraoxonase activity and oxidative stress and their relationship to disease severity in children with allergic rhinitis. *Am J Rhinol Allergy*. 2013;27:13–18. https://doi.org/10.2500/ajra.2013.27.3837.
110. Ulusoy S, Ayan NN, Dinc ME, Is A, Bicer C, Erel O. A new oxidative stress marker for thiol-disulphide homeostasis in seasonal allergic rhinitis. *Am J Rhinol Allergy*. 2016;30:53–57. https://doi.org/10.2500/ajra.2016.30.4308.
111. Celik M, Tuncer A, Soyer OU, Sackesen C, Besler HT, Kalayci O. Oxidative stress in the airways of children with asthma and allergic rhinitis. *Pediatr Allergy Immunol*. 2012;23:556–561. https://doi.org/10.1111/j.1399-3038.2012.01294.x.
112. Elhini A, Abdelwahab S, Ikeda K. Heme oxygenase (HO)-1 is upregulated in the nasal mucosa with allergic rhinitis. *Laryngoscope*. 2006;116:446–450. https://doi.org/10.1097/01.mlg.0000194692.51979.d1.
113. Moon JH, Kim TH, Lee HM, et al. Overexpression of the superoxide anion and NADPH oxidase isoforms 1 and 4 (NOX1 and NOX4) in allergic nasal mucosa. *Am J Rhinol Allergy*. 2009;23:370–376. https://doi.org/10.2500/ajra.2009.23.3340.
114. Sadowska-woda I, Bieszczad-bedrejczuk E, Rachel M. Influence of desloratadine on selected oxidative stress markers in patients between 3 and 10 years of age with allergic perennial rhinitis. *Eur J Pharmacol*. 2010;640:197–201. https://doi.org/10.1016/j.ejphar.2010.04.060.
115. Zarcone MC, Schadewijk A Van, Duistermaat E, Hiemstra PS, Kooter IM. Diesel exhaust alters the response of cultured primary bronchial epithelial cells from patients with chronic obstructive pulmonary disease (COPD) to non-typeable Haemophilus influenzae. *Respir Res*. 2017;18:1–11. https://doi.org/10.1186/s12931-017-0510-4.
116. Yang IA, Fong KM, Zimmerman PV, Holgate ST, Holloway JW. Genetic susceptibility to the respiratory effects of air pollution. *Thorax*. 2008;63:555–563. https://doi.org/10.1136/thx.2007.079426.
117. Cao T, Xu N, Wang Z, Liu H. Effects of glutathione S-transferase gene polymorphisms and antioxidant capacity per unit albumin on the pathogenesis of chronic obstructive

pulmonary disease. *Oxid Med Cell Longev*. 2017;2017. https://doi.org/10.1155/2017/6232397.

118. Braskett M, Riedl MA. Novel antioxidant approaches to the treatment of upper airway inflammation. *Curr Opin Allergy Clin Immunol*. 2010;10:34–41. https://doi.org/10.1097/ACI.0b013e328334f613.

119. Decramer M, Mölken MR, Dekhuijzen PNR, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet*. 2005;366:1552–1560. https://doi.org/10.1016/S0140-6736(05)67378-3.

120. Rosenlund H, Magnusson J, Kull I, et al. Antioxidant intake and allergic disease in children. *Clin Exp Allergy*. 2012;42:1491–1500. https://doi.org/10.1111/j.1365-2222.2012.04053.x.

121. Bakhshaee M, Jabbari F, Hoseini S, et al. Effect of silymarin in the treatment of allergic rhinitis. *Otolaryngol Head Neck Surg*. 2011;145:904–909. https://doi.org/10.1177/0194599811423504.

122. Salve VT, Atram JS. N-Acetylcysteine combined with home based physical activity: effect on health related quality of life in stable COPD patients- a randomised controlled trial. *J Clin Diagn Res*. 2016;10:16–19. https://doi.org/10.7860/JCDR/2016/23668.8980.

123. London NR, Tharakan A, Rule AM, Lane AP, Biswal S, Ramanathan M. Air pollutant-mediated disruption of sinonasal epithelial cell barrier function is reversed by activation of the Nrf2 pathway. *J Allergy Clin Immunol*. 2016;138:1736–1738. https://doi.org/10.1016/j.jaci.2016.06.027.

124. Zaknun D, Schroecksnadel S, Kurz K, Fuchs D. Potential role of antioxidant food supplements, preservatives and colorants in the pathogenesis of allergy and asthma. *Int Arch Allergy Immunol*. 2012;157:113–124. https://doi.org/10.1159/000329137.

125. Moreno-Macias H, Romieu I. Effects of antioxidant supplements and nutrients on patients with asthma and allergies. *J Allergy Clin Immunol*. 2014;133:1237–1244. https://doi.org/10.1016/j.jaci.2014.03.020.

126. Guibas GV, Spandou E, Meditskou S, Vyzantiadis TA, Priftis KN, Anogianakis G. N-acetylcysteine exerts therapeutic action in a rat model of allergic rhinitis. *Int Forum Allergy Rhinol*. 2013;3:543–550. https://doi.org/10.1002/alr.21145.

127. Desqueyroux H, Pujet JC, Prosper M, Squinazi F, Momas I. Short-term effects of low-level air pollution on respiratory health of adults suffering from moderate to severe asthma. *Environ Res*. 2002;89:29–37. https://doi.org/10.1006/enrs.2002.4357.

128. Jacquemin B, Kauffmann F, Pin I, et al. Air pollution and asthma control in the epidemiological study on the genetics and environment of asthma. *J Epidemiol Community Health*. 2012;66:796–802. https://doi.org/10.1136/jech.2010.130229.

129. Dusseldorp A, Kruize H, Runekreef B, Hofschreuder P, De Meer G, Van Oudvorst AB. Associations of PM10 and airborne iron with respiratory health of adults living near a steel factory. *Am J Respir Crit Care Med*. 1995;152:1932–1939.

130. Von Klot S, Wölke G, Tuch T, et al. Increased asthma medication use in association with ambient fine and ultrafine particles. *Eur Respir J*. 2002;20:691–702. https://doi.org/10.1183/09031936.02.01402001.

131. Horvath I, Loukides S, Wodehouse T, Kharitonov SA, Cole PJ, Barnes PJ. Increased levels of exhaled carbon monoxide in bronchiectasis: a new marker of oxidative stress. *Thorax*. 1998;53:867–870. https://doi.org/10.1136/thx.53.10.867.

132. Isaxon C, Dierschke K, Pagels JH, et al. Realistic indoor nano-aerosols for a human exposure facility. *J Aerosol Sci*. 2013;60:55–66. https://doi.org/10.1016/j.jaerosci.2013.02.003.

133. Hagerman I, Isaxon C, Gudmundsson A, et al. Effects on heart rate variability by artificially generated indoor nano-sized particles in a chamber study. *Atmos Environ*. 2014;88:165–171. https://doi.org/10.1016/j.atmosenv.2014.02.003.

134. Fiedler N, Laumbach R, Kelly-mcneil K, et al. Health effects of a mixture of indoor air volatile organics , their ozone oxidation products , and stress. *Environ Health Perspect*. 2005;113:1542–1549. https://doi.org/10.1289/ehp.8132.

135. Fiedler N, Kipen H, Ohman-strickland P, et al. Sensory and cognitive effects of acute exposure to hydrogen sulfide. *Environ Health Perspect*. 2008;116:78–85. https://doi.org/10.1289/ehp.10531.

136. Prah JD, Case MW, Goldstein GM. 1998 equivalence of sensory responses to single and mixed volatile organic compounds at equimolar concentrations. *Environ Health Perspect*. 1998;106:739–744. https://doi.org/10.1289/ehp.98106739.

137. Koren HS, Graham DE, Devlin RB. Exposure of humans to a volatile organic mixture . III . Inflammatory response. *Arch Environ Health*. 1992;47:39–44. https://doi.org/10.1080/00039896.1992.9935942.

138. Laumbach RJ, Fiedler N, Gardner CR, et al. Nasal effects of a mixture of volatile organic compounds and their ozone oxidation products. *J Occup Environ Med*. 2005;47:1182–1189. https://doi.org/10.1097/01.jom.0000183338.95778.f0.

139. Alexis NE, Lay JC, Hazucha M, et al. Low-level ozone exposure induces airways inflammation and modifies cell surface phenotypes in healthy humans. *Inhal Toxicol*. 2010;22(7):593–600. https://doi.org/10.3109/08958371003596587.Low-level.

140. Kim CS, Alexis NE, Rappold AG, et al. Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours. *Am J Respir Crit Care Med*. 2011;183:1215–1221. https://doi.org/10.1164/rccm.201011-1813OC.

141. Alexis NE, Lay JC, Zhou H, et al. The Glutathione-S-Transferase null genotype and increased neutrophil response to low level ozone (0.06ppm). *J Allergy Clin Immunol*. 2013;131(2):610–612. https://doi.org/10.1016/j.jaci.2012.07.005.

142. Gong H, Linn WS, Clark KW, et al. Exposures of healthy and asthmatic volunteers to concentrated ambient ultrafine particles in los angeles exposures of healthy and asthmatic volunteers to concentrated ambient ultrafine particles in los angeles. *Inhal Toxicol*. 2008;20:533–545. https://doi.org/10.1080/08958370801911340.

143. Diaz-Sanchez D, Penichet-Garcia M, Saxon A. Diesel exhaust particles directly induce activated mast cells to degranulate

and increase histamine levels and symptom severity. *J Allergy Clin Immunol*. 2000;106:1140–1146. https://doi.org/10.1067/mai.2000.111144.

144. Bauer RN, Diaz-Sanchez D, Jaspers I. Effects of air pollutants on innate immunity: the role of Toll-like receptors and nucleotide-binding oligomerization domain – like receptors. *J Allergy Clin Immunol*. 2012;129:14–24. https://doi.org/10.1016/j.jaci.2011.11.004.

145. Aberdein JD, Cole J, Bewley MA, Marriott HM, Dockrell DH. Alveolar macrophages in pulmonary host defence-the unrecognized role of apoptosis as a mechanism of intracellular bacterial killing. *Clin Exp Immunol*. 2013;174:193–202. https://doi.org/10.1111/cei.12170.

146. Morgan DJ, Casulli J, Chew C, et al. Innate immune cell suppression and the link with secondary lung bacterial pneumonia. *Front Immunol*. 2018;9:1–18. https://doi.org/10.3389/fimmu.2018.02943.

147. Mjösberg J, Spits H. Human innate lymphoid cells. *J Allergy Clin Immunol*. 2016;138:1265–1276. https://doi.org/10.1016/j.jaci.2016.09.009.

148. Krohn IK, Bal SM, Golebski K. The role of innate lymphoid cells in airway inflammation: evolving paradigms. *Curr Opin Pulm Med*. 2017;24:11–17. https://doi.org/10.1097/MCP.0000000000000435.

149. Ganesan S, Comstock AT, Sajjan US. Barrier function of airway tract epithelium. *Tissue Barriers*. 2013;1. https://doi.org/10.4161/tisb.24997.

150. Hossain FMA, Choi JY, Uyangaa E, Park SO, Eo SK. The interplay between host immunity and respiratory viral infection in asthma exacerbation. *Immune Netw*. 2019;19:1–21. https://doi.org/10.4110/in.2019.19.e31.

151. Po JYT, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. *Thorax*. 2011;66:232–239. https://doi.org/10.1136/thx.2010.147884.

152. Dherani M, Pope D, Mascarenhas M, Smith KR, Bruce N. Indoor air pollution from unprocessed solid fuel use and pneumonia risk in children aged under five years : a systematic review and meta-analysis. *Bull World Allergy Organ*. 2008;86:390–398. https://doi.org/10.2471/BLT.07.044529.

153. Sih T. Correlation between respiratory alterations and respiratory diseases due to urban pollution. *Int J Pediatr Otorhinolaryngol*. 1999;1:261–267. https://doi.org/10.1016/S0165-5876(99)00174-3.

154. MacIntyre EA, Gehring U, Mölter A, et al. Air pollution and respiratory infections during early childhood: an analysis of 10 European birth cohorts within the ESCAPE project. *Environ Health Perspect*. 2014;122:107–113. https://doi.org/10.1289/ehp.1306755.

155. Neupane B, Jerrett M, Burnett RT, Marrie T, Arain A, Loeb M. Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. *Am J Respir Crit Care Med*. 2010;181:47–53. https://doi.org/10.1164/rccm.200901-0160OC.

156. Travaglio M, Popovic R, Yu Y, Leal N, Martins LM. Links between air pollution and COVID-19 in England. *medRxiv*. 2020. https://doi.org/10.1101/2020.04.16.20067405.

157. Setti L, Passarini F, Gennaro G De, et al. The potential role of particulate matter in the spreading of COVID-19 in northern Italy: first evidence-based research hypotheses. *medRxiv*. 2020. https://doi.org/10.1101/2020.04.11.20061713.

158. Ogen Y. Assessing nitrogen dioxide (NO2) levels as a contributing factor to the coronavirus (COVID-19) fatality rate. *Sci Total Environ*. 2020. https://doi.org/10.1016/j.scitotenv.2020.138605.

159. Setti L, Passarini F, Gennaro G De, et al. SARS-Cov-2 RNA found on particulate matter of Bergamo in Northern Italy: first preliminary evidence. *medRxiv*. 2020. https://doi.org/10.1101/2020.04.15.20065995, 2020.04.15.20065995.

160. Chauhan AJ, Inskip HM, Linaker CH, et al. Personal exposure to nitrogen dioxide (NO2) and the severity of virus-induced asthma in children. *Lancet*. 2003;361:1939–1944. https://doi.org/10.1016/s0140-6736(03)13582-9.

161. Jaspers I, Ciencewicki JM, Zhang W, et al. Diesel exhaust enhances influenza virus infections in respiratory epithelial cells. *Toxicol Sci*. 2005;85:990–1002. https://doi.org/10.1093/toxsci/kfi141.

162. Buonfiglio LGV, Mudunkotuwa IA, Alaiwa MHA, et al. Effects of coal fly ash particulate matter on the antimicrobial activity of airway surface liquid. *Environ Health Perspect*. 2017;125:1–10. https://doi.org/10.1289/EHP876.

163. Harrod KS, Jaramillo RJ, Berger JA, Gigliotti AP, Seilkop SK, Reed MD. Inhaled diesel engine emissions reduce bacterial clearance and exacerbate lung disease to Pseudomonas aeruginosa infection InVivo. *Toxicol Sci*. 2005;83:155–165. https://doi.org/10.1093/toxsci/kfi007.

164. Chen X, Liu J, Zhou J, et al. Urban particulate matter (PM) suppresses airway antibacterial defence. *Respir Res*. 2018;19:1–12. https://doi.org/10.1186/s12931-017-0700-0.

165. Mushtaq N, Ezzati M, Hall L, et al. Adhesion of Streptococcus pneumoniae to human airway epithelial cells exposed to urban particulate matter. *J Allergy Clin Immunol*. 2011;127:1236–1242. https://doi.org/10.1016/j.jaci.2010.11.039.

166. Zhou H, Kobzik L. Effect of concentrated ambient particles on macrophage phagocytosis and killing of Streptococcus pneumoniae. *Am J Respir Cell Mol Biol*. 2007;36:460–465. https://doi.org/10.1165/rcmb.2006-0293OC.

167. Zhao H, Li W, Gao Y, Li J, Wang H. Exposure to particular matter increases susceptibility to respiratory Staphylococcus aureus infection in rats via reducing pulmonary natural killer cells. *Toxicology*. 2014;325:180–188. https://doi.org/10.1016/j.tox.2014.09.006.

168. Yang H, Antonini JM, Barger MW, et al. Diesel exhaust particles suppress macrophage function and slow the pulmonary clearance of Listeria monocytogenes in rats. *Environ Health Perspect*. 2001;109:515–521. https://doi.org/10.1289/ehp.01109515.

169. Rylance J, Chimpini C, Semple S, et al. Chronic household air pollution is associated with impaired alveolar macrophage function in malawian non- Smokers. *PloS One*. 2015;10:1–15. https://doi.org/10.1371/journal.pone.0138762.

170. Migliaccio CT, Kobos E, King QO, Porter V, Jessop F, Ward T. Adverse effects of wood smoke PM2.5 exposure on macrophage functions. *Inhal Toxicol*. 2013;25:67–76. https://doi.org/10.3109/08958378.2012.756086. Adverse.

171. Yin XJ, Dong CC, Ma JYC, et al. Suppression of cell-mediated immune responses to Listeria infection by repeated exposure

to diesel exhaust particles in Brown Norway rats. *Toxicol Sci*. 2004;77:263–271. https://doi.org/10.1093/toxsci/kfh035.

172. Jaligama S, Saravia J, You D, et al. Regulatory T cells and IL10 suppress pulmonary host defense during early-life exposure to radical containing combustion derived ultrafine particulate matter. *Respir Res*. 2017;18:1–14. https://doi.org/10.1186/s12931-016-0487-4.

173. Roos AB, Sethi S, Nikota J, et al. IL-17A and the promotion of neutrophilia in acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;192:428–437. https://doi.org/10.1164/rccm.201409-1689OC.

174. Sigaud S, Goldsmith CW, Zhou H, Yang Z, Imrich A, Kobzik L. Air pollution particles diminish bacterial clearance in the primed lungs of mice. *Toxicol Appl Pharmacol*. 2007;223:1–9. https://doi.org/10.1016/j.taap.2007.04.014.

175. Bhat TA, Kalathil SG, Bogner PN, et al. Secondhand smoke induces inflammation and impairs immunity to respiratory infections. *J Immunol*. 2018;200:2927–2940. https://doi.org/10.4049/jimmunol.1701417. Secondhand.

176. Gotts JE, Chun L, Abbott J, et al. Cigarette smoke exposure worsens acute lung injury in antibiotic-treated bacterial pneumonia in mice. *Am J Physiol Lung Cell Mol Physiol*. 2018;315:25–40. https://doi.org/10.1152/ajplung.00405.2017.

177. Chaudhuri N, Jary H, Lea S, et al. Diesel exhaust particle exposure in vitro alters monocyte differentiation and function. *PloS One*. 2012;7:1–12. https://doi.org/10.1371/journal.pone.0051107.

178. Ma J, Song S, Guo M, et al. Biochemical and Biophysical Research Communications down-regulating pulmonary macrophage Kdm6a and mediates histones modi fi cation in IL-6 and IFN- b promoter regions. *Biochem Biophys Res Commun*. 2017;493:1122–1128. https://doi.org/10.1016/j.bbrc.2017.09.013.

179. Yao H, Edirisinghe I, Rajendrasozhan S, et al. Cigarette smoke-mediated inflammatory and oxidative responses are strain-dependent in mice. *Am J Physiol Lung Cell Mol Physiol*. 2008;294:1174–1186. https://doi.org/10.1152/ajplung.00439.2007.

180. Kurutas EB. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *Nutr J*. 2016;15:1–22. https://doi.org/10.1186/s12937-016-0186-5.

181. Stanner SA, Hughes J, Kelly CNM, Buttriss J. A review of the epidemiological evidence for the ' antioxidant hypothesis. *Publ Health Nutr*. 2003;7:407–422. https://doi.org/10.1079/PHN2003543.