HHS Public Access

Author manuscript

Ann Glob Health. Author manuscript; available in PMC 2016 February 18.

Published in final edited form as:

Ann Glob Health. 2015 ; 81(3): 368–374. doi:10.1016/j.aogh.2015.08.006.

A Systematic Review of Innate Immunomodulatory Effects of Household Air Pollution Secondary to the Burning of Biomass Fuels

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Abstract

BACKGROUND—Household air pollution (HAP)-associated acute lower respiratory infections cause 455,000 deaths and a loss of 39.1 million disability-adjusted life years annually. The immunomodulatory mechanisms of HAP are poorly understood.

OBJECTIVES—The aim of this study was to conduct a systematic review of all studies examining the mechanisms underlying the relationship between HAP secondary to solid fuel exposure and acute lower respiratory tract infection to evaluate current available evidence, identify gaps in knowledge, and propose future research priorities.

METHODS—We conducted and report on studies in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. In all, 133 articles were fully reviewed and main characteristics were detailed, namely study design and outcome, including in vivo versus in vitro and pollutants analyzed. Thirty-six studies were included in a nonexhaustive review of the innate immune system effects of ambient air pollution, traffic-related air pollution, or wood smoke exposure of developed country origin. Seventeen studies investigated the effects of HAP-associated solid fuel (biomass or coal smoke) exposure on airway inflammation and innate immune system function.

RESULTS—Particulate matter may modulate the innate immune system and increase susceptibility to infection through a) alveolar macrophage-driven inflammation, recruitment of neutrophils, and disruption of barrier defenses; b) alterations in alveolar macrophage phagocytosis and intracellular killing; and c) increased susceptibility to infection via upregulation of receptors involved in pathogen invasion.

CONCLUSIONS—HAP secondary to the burning of biomass fuels alters innate immunity, predisposing children to acute lower respiratory tract infections. Data from biomass exposure in developing countries are scarce. Further study is needed to define the inflammatory response, alterations in phagocytic function, and upregulation of receptors important in bacterial and viral

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The authors declare they have no conflicts of interest.

binding. These studies have important public health implications and may lead to the design of interventions to improve the health of billions of people daily.

Keywords

biomass; household air pollution; indoor air pollution; innate immunity; long-term exposure; $PM_{2.5}$

INTRODUCTION

Nearly half the world's population is dependent on the burning of solid fuels, such as coal and biomass, for daily cooking, drying, and heating activities.[1] The combustion efficiency of household stoves used in developing countries may be as low as 80%, leading to large emissions of the 2 most widely measured pollutants, particulate matter (PM) and carbon monoxide (CO).[2] Current World Health Organization (WHO) guidelines recommend a $PM_{2.5}$ annual mean exposure of less than 10 μg/m^3 and a 24-hour mean of less than 25 μg/m^3; however, recent data suggested that there is no safe level of $PM_{2.5}$ exposure.[3,4] Studies in South Asia, Latin America, and Africa demonstrate $PM_{2.5}$ and CO household air pollution (HAP) cooking exposures ranging from 110 to 27,000 μg/m^3 and 9 to 10,769 mg/m^3, respectively, well above regulatory minimums.[5]

HAP secondary to the burning of solid fuels is directly responsible for 3.5 million deaths globally, predominantly in low- and middle-income countries (LMIC).[6] Acute lower respiratory tract infections (ALRI) are a leading cause of childhood morbidity and mortality. HAP, a modifiable ALRI risk factor, has been demonstrated to have an odds ratio (OR) of 1.78 (95% confidence interval [CI] 1.45–2.18) and 3.53 (95% CI, 1.93–6.43) in different summaries.[7,8] A recent estimate of the global burden of disease suggested that HAP-associated ALRI causes 455,000 deaths and a loss of 39.1 million disability-adjusted life years annually, with a population attributable fraction of 52%.[9]

In order for an inhaled pathogen to establish infection in the lower respiratory tract, it must first evade the innate immune system, which is comprised of barrier defenses, antimicrobial molecules, alveolar macrophages (AM), neutrophils, natural killer (NK) cells, and dendritic cells.[10] Airway cells tightly regulate innate immune system function and, along with AMs, sense pathogen-associated molecular patterns (PAMPs) via toll-like receptors (TLRs).[11] Activation of TLRs triggers a cascade of pathogen-induced immune responses, including cytokine release and AM and neutrophil generation of reactive oxygen species (ROS), phagocytosis, and intracellular killing. A tightly regulated response is required, as excessive inflammation can damage epithelial barriers, promote lung injury, and increase susceptibility to future infection.

The exact component of HAP that modulates the innate immune response is unknown. PM likely plays a central role, as diminished immunotoxicity has been demonstrated following removal of the PM component of wood smoke.[12] Exposures vary not only in the mixture of toxins involved, but also in the size of particles released. Indeed, studies comparing the immune effects of air pollution originating from developed versus developing countries show different immune responses, and differences in particulate size, such as coarse and

ultrafine, have been shown to induce different innate immune responses.[13,14] Taken together, these findings suggest that the immunomodulatory effects are likely emission-specific and operate through different mechanisms.

Despite the large burden of disease, the mechanism by which HAP secondary to the burning of solid fuels predisposes children to ALRI is unclear. Therefore, we conducted a systematic review of all studies examining the mechanisms underlying the relationship between HAP secondary to solid fuel exposure and ALRI to evaluate current available evidence, identify gaps in knowledge, and propose future research priorities.

MATERIALS AND METHODS

We conducted research and report the study in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We searched PubMed, Ovid Medline, EMBASE, and Web of Science from their inception to November 2014 with an English-language restriction. MeSH terms and keyword search items were used to identify relevant studies. The search process combined exposure, outcome, and mechanism terms. Article titles and abstracts were initially screened for eligibility. Articles were retrieved for full review if they were original studies; used emissions from solid fuel, particularly biomass or coal originating from developing countries; and investigated the mechanism by which these emissions alter the innate immune response and/or predispose to ALRI. We reviewed the reference list of all included studies to identify additional eligible studies. Additionally, we nonexhaustively reviewed studies of innate immune response to ambient or urban air pollution or woodsmoke exposures from developed countries, to draw lessons from this more expansive body of literature.

RESULTS

Seventeen studies investigated the effects of HAP-associated solid fuel (biomass or coal smoke) exposure on airway inflammation and innate immune system function. Thirty-six studies were included in a nonexhaustive review of the innate immune system effects of ambient air pollution, traffic-related air pollution, or woodsmoke exposure of developed country origin.

Alterations in Innate Immune Response to Ambient or Urban Air Pollution or Wood Smoke Exposures Originating From Developed Countries

PM induces a proinflammatory state that may have downstream deleterious effects, resulting in lung injury. AMs phagocytize PM and release cytokines to recruit inflammatory cells[15–18] and produce an array of proinflammatory mediators.[19,20] Once ingested, intraphagocytic PM increases ROS production, biotoxic compounds that are critical to host defense.[21–24] $PM_{2.5}$ constituents upregulate heme-oxygenase-1, a marker of oxidative stress in alveolar type II cell lines, and induces an oxidant imbalance in AMs.[21–25] Primed AM particle-mediated cytokine release may be inhibited by antioxidants,[26] suggesting that PM-induced inflammation is oxidant dependent.[27]

PM reduces M2 cytokines (interleukin [IL]-4, IL-10, and IL-13) while stimulating the release of M1 cytokines (IL-12, interferon-³), thereby attracting neutrophils into the airspaces.[28–30] PM-induced AM apoptosis[31] leads to further inflammation and compromised host resistance, via abruption and fragmentation of alveolar epithelial cells, denuded basement membrane, and increased number of pinocytic vesicles in close proximity with carbon black, demonstrating that PM locally affects barrier defenses.[32]

PM activates TLRs via endotoxin, metals, microbial components, and other organic compounds.[33,11] PAMPs from gram-negative, gram-positive, or fungal elements bind to TLRs to release a number of cytokines including tumor necrosis factor (TNF), IL-1, IL-6, and IL-8 and recruit inflammatory cells to the airways. Polymixin B can partially inhibit this response, suggesting that particle-bound lipopolysaccharide, a component of gram-negative cell walls, is involved in AM activation.[34] TLR2 and TLR4 likely mediate signaling pathways,[35] as these pathways can be blocked by blocking antibodies.[36] Heat-treating ambient $PM_{2.5–10}$[37] inhibited macrophage and monocyte expression of mCD14, CD11b/CR3, and HLA-DR but did not eliminate the neutrophil influx, suggesting that the PM itself, and not the PM-associated microbial products, are important in stimulating neutrophils.

In vitro and animal models of PM-exposed AM demonstrate reduced pathogen phagocytosis and impaired bacterial pulmonary clearance.[38] Interestingly, chronic exposure alters phagocytic activity and superoxide dismutase (SOD) activity even in the absence of lung histopathologic changes or inflammation.[39] The reduction of bacterial clearance was not demonstrated in PM-free smoke and metals, ubiquitous components of most PM emissions, may play a key role in the impairment of phagocytosis and subsequent pathogen killing.[40]

PM may also increase host susceptibility to infection.[41,42] Oxidative stress, involved in host defense against viral and bacterial infections, is believed to upregulate intercellular adhesion molecule-1, low-density lipoprotein, and platelet-activating factor receptors (PAFR), allowing bacterial invasion.[43–45] PM_{10}-induced increased *Streptococcus pneumoniae* adherence to human type II pneumocytes and human primary bronchial epithelial cells may be reversed with the addition of an antioxidant, *N*-acetylcysteine, or a PAFR-blocker, again underscoring the importance of these pathways in PM-associated bacterial invasion.[46]

In summary, ambient or urban air pollution and woodsmoke (originating from developed countries) exposure data suggest that inhalation of PM may modulate the innate immune system and increase susceptibility to infection through a) AM-driven inflammation, recruitment of neutrophils, and disruption of barrier defenses; b) alterations in AM phagocytosis and intracellular killing; and c) increased susceptibility to infection via upregulation of receptors involved in pathogen invasion.

Alterations to Innate Immune Response to HAP Secondary to the Burning of Biomass Fuels

Macrophages appear central to the inflammatory properties of biomass smoke. Two studies[47,48] demonstrated carbon loading of AMs in both adults and children naturally exposed to biomass smoke.[47,48] Marked heterogeneity in AM carbon loading was noted in participants naturally exposed to biomass smoke (human alveolar macrophages [HAM]).[14]

Exposure of HAM and monocyte-derived macrophages exposed in vitro to Malawian or Norwegian woodsmoke showed a dose-dependent increase in macrophage carbon content and reduction of in vitro phagocytosis of fluorescent beads and *S pneumoniae*, with a negative linear correlation between macrophage particulate content and phagocytosis.[14] Malawian woodsmoke had a larger inhibitory effect than Norwegian woodsmoke, despite having a lower cytoplasmic particulate load at each dose. Oxidative burst analysis in AMs derived from bronchoalveolar lavage (BAL) samples of Malawian participants naturally exposed to biomass smoke, demonstrated reduced burst with higher PM loads (analysis of variance, $P < 0.01$). These results suggested that both exposure composition and intensity determine the extent of carbon loading and support the hypothesis that the immunomodulatory effects of PM are likely emission-specific.

In vivo animal and in vitro human cell biomass smoke exposure appears to induce an oxidant imbalance. Animals exposed to biomass smoke demonstrate increased activity of glutathione-*S*-transferase and malondialdehyde (MDA) with concurrent decreased activity of total antioxidant capacity (TAOC) in lung, suggestive of an oxidant imbalance.[49] Cow dung-derived biomass smoke from a traditional Indian cook stove and PM sampled from biomass burning in Kathmandu Valley, Nepal, incubated with respiratory tract lining fluid (RTLF) and glutathione (GSH)[50,51] both demonstrated a dose-dependent depletion of ascorbate (AA) and GSH. Co-incubation of RTLF with PM and diethylenetriaminepentaacetate, a metal chelator, inhibited the AA and GSH changes, implicating PM-associated redox active metals. Coincubation of RTLF with antioxidants, SOD, and catalase provided limited protection from antioxidant loses.

Studies investigating peripheral blood markers of oxidative stress in human participants exposed naturally to biomass smoke, however, show conflicting results. Similar to RTLF experiments, peripheral AA is reduced by biomass exposure.[52] Three studies demonstrated a significant elevation in plasma MDA,[53–55] whereas one failed to demonstrated any difference from control.[56] Antioxidant SOD has been found to be elevated,[55] decreased,[52] or normal[57] in response to natural biomass smoke exposure. Antioxidants vitamin C and E also have been demonstrated to be within the reference range.[57] The ratio of GSH to glutathione disulfide has been found to be decreased[52]; however, a separate study found no significant differences in glutathione peroxidase, glutathione-S-transferase, or glutathione reductase as compared to controls.[55] Differences between studies could be reflective of heterogeneity in exposure composition and intensity, with activation of different pathways or variable dose–response relationships.

Acute biomass-associated PM exposure appears to induce an inflammatory response, including neutrophil influx and cytokine (IL-6, IL-8, IL-17, IL-1², keratinocyte-derived chemokine, granulocyte colony-stimulating factor; granulocyte macrophage colony-stimulating factor) production.[49,58,59] BAL fluid (BALF) from mice acutely exposed to dung or wood PM from India demonstrate a neutrophilic chemokine profile, with higher levels consistently found in the dung-exposed group.[60] Subchronic exposure (3 times a week for 8 weeks) to cow dung PM continued to produce a neutrophilic cytokine profile, whereas subchronic wood PM exposure produced an eosinophilic cytokine profile. Therefore, the type and duration of exposure may explain differences in inflammatory profiles.

Induced sputum, reflective of the lower airways,[61,62] from biomass users demonstrate marked inflammation with significantly more neutrophils, eosinophils, lymphocytes, and AMs per high-power field compared with control liquefied petroleum gas users. Inflammatory markers (TNF-±, IL-6, and IL-8) and markers of oxidant imbalance also have been demonstrated. However, a convenience sample study of women involved in the RESPIRE (Randomized Exposure Study of Pollution Indoors and Respiratory Effects) trial, a cook-stove intervention trial studying the effects of a chimney intervention on ALRI, found no difference in protein levels of IL-8, fibronectin and myeloperoxidase or gene expression of *TNF-±*, *IL-8*, and matrix metallopeptidase 12 (*MMP12*) between the control and intervention groups, despite a significant difference in exposure.[61]

The role of PM-associated endotoxin or microbial components in activating TLRs has not been thoroughly examined. PM-associated endotoxin has been demonstrated to vary based on biomass origin and remains active following combustion.[60] One study evaluated the effect of biomass-associated endotoxin using small airway epithelial cells exposed to biomass smoke generated from dried biomass (India).[59] A dose-dependent decrease in *TIMP-1* and dose-dependent increase in *MMP-1* and *IL-8* were observed. These changes persisted after removal of endotoxin from biomass exposure. A second study, using a mouse AM line, demonstrated that biomass PM-induced inflammation is dependent on *MyD88* signaling and uses TLR2/4 and IL-1R pathways.

Biomass-associated cellular studies are consistently notable for atypical macrophage morphology on BALF with carbon deposition, macronuclei, and numerous small villi-like surface projections suggestive of macrophage activation.[58,59] Carbonaceous material also has been noted in lung epithelial cells. Lung histopathology demonstrates edema, inflammatory infiltrates, and destruction of the epithelial mucosa and the intensity of the abnormalities increased with duration of exposure. Thickened blood vessels have also been described.[60] Animal models of subchronic wood PM exposure demonstrate that, although wood PM is less inflammatory than cow dung PM, wood PM exposure induces more airspace enlargement.[60]

DISCUSSION

Nearly half of the world's population is dependent on the burning of solid fuels, such as coal and biomass, for daily cooking, drying, and heating activities.[1] Despite this incredible burden of disease, little is known about the immunomodulatory effects of HAP. Ambient or traffic-related air pollution studies suggest that PM-induced inflammation is driven by AMs, leading to the recruitment of neutrophils and disruption of barrier defenses. Alterations in AM phagocytosis and intracellular killing are compounded by an upregulation of receptors involved in bacterial and viral pathogen invasion.

To our knowledge, only a handful of studies have explored mechanisms in biomass smoke-induced pulmonary inflammation. These studies demonstrate that biomass smoke exposure likely induces an oxidant imbalance and, acutely, a neutrophilic inflammatory profile. Phagocytosis and intracellular killing may be impaired. The role of PM-associated

endotoxins, metals, microbial components, and other organic compounds in activating TLRs appear important.

There are limitations to the animal and in vitro study approaches widely used to study biomass smoke exposure. Most biomass studies test specific doses of particulate matter and therefore do not take into account real-world differences in combustion. Cow dung, for example, has been shown to produce 23% more $PM_{2.5}$ per kilogram of sample burned and burns faster compared with wood.[60] Animal or in vitro exposure models therefore may under- or overestimate inflammatory profiles or differences in inflammation between biomass sources.

A multitude of hazardous pollutants are produced from biomass combustion, not just PM. Wood smoke may produce 26 hazardous air pollutants, including toxic gases, hydrocarbons, organic alcohols and acids, aldehydes, phenols, quinones, and free radicals.[63] True combustion mixtures may lead to different inflammatory responses. Animal and in vitro models fail to capture the effects of lifelong, chronic exposures. One demonstrated differences in inflammatory profiles following acute and subchronic exposures.[60] It is possible, therefore, that chronic exposures may result in further alterations to inflammatory pathways. Therefore, although animal and in vitro exposure models are helpful to begin to understand biomass-induced immunomodulation, future studies must be designed to overcome these limitations.

A novel study demonstrated feasibility of obtaining BAL samples from naturally exposed adults in a resource-poor setting.[14] Future studies should take advantage of ongoing cook-stove intervention studies to obtain tissues or samples from naturally exposed individuals and controls. As biomass exposure is concentrated in resource-limited settings where bronchoscopy is not always available, techniques such as induced sputum may be considered to obtain lower respiratory samples.

CONCLUSIONS

Epidemiological studies suggest that chronic, in utero and early childhood HAP exposure secondary to the burning of solid fuels alters immune function and predisposes infants to ALRI. Data from developing country biomass exposure are scarce, but suggest that PM may modulate the innate immune system and increase susceptibility to infection similar mechanisms are likely involved but more work is needed. These studies have important public health implications and may lead to the design of interventions to improve the health of billions of people daily.

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