Indoor Air Pollution and Respiratory Health

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Synopsis:

Worldwide, over four million deaths annually are attributed to indoor air pollution. This largely preventable exposure represents a key target for reducing morbidity and mortality worldwide. Across settings, significant respiratory health effects are observed, ranging from attenuated lung growth and development in childhood to accelerated lung function decline and chronic obstructive pulmonary disease later in life. Numerous factors influence personal exposure to household air pollutants, including household characteristics, combustion of solid fuels, cooking practices, and allergens from household pests. This review outlines important sources of indoor air pollution, their respiratory health effects, and strategies to reduce household pollution and improve lung health across the globe.

Introduction: Why Indoor Air Pollution is important

The World Health Organization estimates that Household air pollution (HAP) accounts for an estimated 4.3 million premature deaths annually and 110 million disability-adjusted life years lost[1]. This largely preventable exposure has been listed by the Comparative Risk Assessment for the 2010 Global Burden of Diseases the third leading risk factor for morbidity and mortality worldwide, representing about 4.5% of global burden of disease[2]. Even in industrialized settings the home represents a critical source of pollutant exposure, with individuals spending approximately 90% of their time indoors, the majority of that being in the home[3–5]. While a significant source of morbidity related to household air pollution is from cardiovascular disease, HAP has a wide range of respiratory sequela across

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the lifespan, adversely affecting lung development early in life to potentially increasing the risk of chronic obstructive pulmonary disease (COPD) in adulthood. The impact on respiratory health has been observed across a variety of settings and disease processes, in both low-middle income and high-income countries. Today, organizations including the WHO, United Nations, American Thoracic Society, and European Respiratory Society have begun to invest in developing strategies to reduce the global respiratory health effects of HAP[6,7]. This article outlines sources of indoor air pollution, the respiratory effects of indoor air pollution in low-middle income and high-income countries, as well as strategies to reduce pollutant exposure in both settings (Figure 1).

Indoor air pollution in Low-Middle Income Countries

In Low-Middle Income Countries (LMICS), nearly 3 billion people rely on biomass fuels for cooking and heating daily[8]. Biomass fuels, often referred to as solid fuels, include wood, dung, agricultural crop waste, and coal. Biomass is the main domestic energy source for ~40% of all households and ~90% of rural households in LMICs. Solid fuels are often burned in inefficient and poorly vented combustion devices (i.e., open fires, traditional stoves). Multiple respiratory health outcomes have been associated with HAP in LMICs, including preterm birth; low birth weight and attenuated lung function; childhood respiratory infection; as well as increased risk for development of asthma, chronic obstructive pulmonary disease (COPD), lung cancer and exacerbations of existing diseases[9,10].

Indoor air pollution in High Income Countries

While respiratory health effects of pollution are most prominent in low-middle income countries, significant mortality has been observed at lower pollutant concentrations typical of high-income countries, including the US and Canada. In 2016, the WHO estimated that nearly 400,000 deaths in high-income countries were attributable to HAP, due to ongoing use of solid fuels, as well as other sources of pollution relevant to high-income countries. Currently 6.5 million people in the US still rely on solid fuels for heating, particularly those living in rural areas. Moreover, urbanization and the expanding built environment predispose individuals in high-income settings to other pollutants indoors, including indoor particulate matter (PM), environmental tobacco smoke, gases such as nitrogen dioxide (NO_2) from cooking and heating, allergens from indoor pests, toxic cleaning chemicals, and molds related to increased indoor humidity and dampness. These important sources of Indoor air pollution are outlined in the following section.

Sources of Indoor Air Pollution

Indoor air includes pollutants that penetrate from the outdoors, as well as sources that are unique to the indoor environment. Thus, indoor pollution differs from outdoor pollution in source, composition, and concentration, and as a result the effects of indoor air pollution cannot be easily extrapolated from studies of outdoor air pollution[11]. The burning of solid fuels represents a significant source of household pollution across the globe, while numerous household activities more common in urban environments have also been associated with the generation of pollutants[12,13]. Environmental tobacco smoke (ETS) from primary and secondhand smoke remains an important source of household air pollution. In this review we

primarily discuss non-tobacco sources of pollution that are often overlooked. However, initiatives to reduce smoking and environment tobacco smoke remain imperative and a continued high priority. We will focus on household behaviors and practices associated with increased production of pollutants (solid fuel combustion, cooking and heating practice, cleaning, and indoor smoking) in both LMICs and High-Income countries. Other sources of interest include general housing characteristics which directly influence (dampness, humidity, pests and allergens) and modify exposures (ventilation).

Household Behaviors and Practices: Smoking, Solid Fuel Combustion, Cooking & Heating, Cleaning,

Smoking.—Tobacco smoke is a major source of indoor particulate matter, accounting for 50–90% of indoor PM concentrations in high income countries[14,15]. Indoor tobacco smoke is a critical driver of environmental health disparities with as many as half of all children and up to 70% of African American children exposed to second hand smoke in the United States[16].

Solid Fuel Combustion.—A significant body of evidence related to HAP and respiratory health has been generated from studies concerning the combustion of solid fuels, used for cooking and heating. The combustion products include gases (i.e NO_2 and Carbon Monoxide (CO)) and particulate matter, including particles with median diameter $<10_{um}$ (PM_{10}) and those with median diameter $<2.5_{um}$ ($PM_{2.5}$). Additionally, formaldehyde, airborne endotoxins, and a number of toxic organic compounds (eg, benzene; 1,3 butadiene; benzo[a] pyrene, and other polycyclic aromatic hydrocarbons) are present in biomass smoke. While household pollution from the burning of biomass and solid fuels has been thought to mostly affect individuals from low-middle income countries, data from the US Census Bureau's American Community Survey has indicated that 6.5 million people in the US live in homes heated primarily by wood or coal[17]. The burden of household pollution from solid fuels in the US has been shown to disproportionately affect those living in poor communities, with 53–65% of homes that primarily heat with wood or coal also facing household $PM_{2.5}$ concentrations that exceed the WHO 24-hour particulate matter guidelines[17–20].

Cooking and Heating.—Even in homes that do not use solid fuels, other common heating and cooking practices can increase household pollutant concentrations. Combustion of fuels used for cooking and heating can produce NO_2, Volatile Organic Compounds (VOCs), Sulfur Dioxide (SO_2), CO_2, CO, and particulate matter. Exposure concentrations are driven by factors that include ventilation, duration of use of the cooking or heating equipment, and individual proximity to the source of pollutants. NO_2 is of particular interest for homes that use gas stoves for cooking[13]. One study indicated that each hour of gas stove or furnace use was associated with an 18 ppb increase in 24-hour NO_2 concentrations[21]. NO_2 levels are even greater in poorly ventilated homes using unvented gas stoves. In addition to NO_2, other studies have demonstrated that the frequency of stove use is also associated with significant increases in household $PM_{2.5}$ concentrations[12].

Cleaning represents a common household activity that can lead to the mobilization of particles and allergens. One study demonstrated indoor sweeping, which resuspends settled dust, was associated with increased household $PM_{2.5}$ and PM_{10}[12]. In addition, cleaning products and pesticides have direct toxic health effects that are discussed in more detail in a separate chapter of this issue.

Housing Characteristics: Ventilation, Humidity, Dampness, and Allergens from Pests

Ventilation.—One global factor that impacts household pollution concentrations is ventilation, as diminished indoor-outdoor air exchange rates can result in the accumulation of indoor pollutants. As insulation has improved, household air exchange rates have diminished[22]. The relationship between sources of pollution, air exchange rates, and health outcomes is an important consideration in understanding the respiratory health effects of indoor air pollution. In LMICs, poor ventilation, particularly around biomass-stoves, results in increased levels of indoor air pollution[23,24]. Ventilation in LMIC settings, primarily in tropical and subtropical regions of the world, often includes direct openings to the outdoors, and is typically greater compared to high income areas[25]. Households which utilize enclosed metal heating or cooking stoves with chimneys have significantly lower indoor pollutant concentrations than those that use open fires[26,27]. A number of studies have additionally demonstrated associations between ventilation and respiratory outcomes. Qian et al. demonstrated higher household ventilation was associated with lower reporting of persistent cough, phlegm, bronchitis, and wheeze among school children in four Chinese cities[24]. Household ventilation, as well as more efficient ventilated stoves has been outlined by the WHO as an important health intervention in LMICs.

Humidity and dampness are also important factors that influence indoor air quality. A number of daily activities including showering, cooking, and humidifier use, can affect indoor moisture and humidity. Many homes additionally experience leaks and some degree of water damage over their lifetime. Molds, bacteria, insects, and mites thrive in humid and damp environments[28]. These pathogens in particular have been linked to a number of respiratory disorders including asthma, chronic rhino sinusitis, and hypersensitivity pneumonitis, along with increased respiratory symptoms (cough, wheeze, and exacerbations of underlying respiratory disease)[29].

Allergens from Household Pests: Exposure to household allergens from animals and pests represent significant but modifiable contributors to respiratory disease, particularly asthma and allergic rhinitis. In urban environments allergens from house dust mites, cockroaches, and mouse infestations are important to consider. House dust mites represent a significant source of allergens, with 13 different species found in household dust[4]. Allergens arise from mite bodies and feces. Dust mites are most commonly found on furniture, carpet, and bedding. House dust mite growth further increases in high humidity and temperature environments[30]. Similar to dust mites, allergens from cockroaches are increased in high temperature environments[4]. Mouse allergen can be found in small particle sizes between 0.5 and 10 μm and can remain airborne once resuspended from settled dust[31]. Mouse allergen has been detected in high concentration in settled dust from homes of children with asthma living in urban areas, as well as in air samples, where as many as a quarter of children had

airborne mouse concentrations similar to those in mouse facilities[32]. Pest allergen, including cockroach and mouse represent important drivers of childhood asthma in urban environments.[33,34] Other sources to consider, not included in this review, include allergens from pets and domestic animals that can also contribute to morbidity.

Other important housing factors to consider include residential crowding, along with proximity to roadways and high traffic corridors, which can lead to increases in indoor particulate matter and NO_2 due to penetration from the outdoor environment.

Consequence of Indoor Air Pollution

The respiratory consequences of household air pollution are wide ranging, affecting lung development in childhood, incidence of lower respiratory tract infection, and both disease development and morbidity for COPD and asthma. The known impacts of household air pollution are described for each of these processes in both low-middle income countries and high-income countries.

Mechanisms

There have been a number of mechanisms proposed by which indoor air pollution results in pulmonary disease and alters host immune responses, leading to chronic respiratory conditions. Exposure to household air pollution results in pro-inflammatory states with associated increases in neutrophilic inflammation, proteolytic activity of matrix metalloproteinases, oxidative stress and apoptosis[35–37] (Table 1). Loss of lung function from prolonged exposure to air pollution has been proposed as a leading cause of COPD globally[38]. Additionally, recurrent respiratory infections have been associated with increased levels of household air pollution, likely due to underlying immune dysregulation. Household air pollution has been demonstrated to impair macrophage phagocytosis and surface adherence, reduce bacterial and mucociliary clearance, and disrupt the alveolar-capillary barrier in the lungs[39–41]. A number of effects also relate to alterations in the airway microbiome as well as immune dysregulation and host response to commensals[6]. In particular Streptococcus Pneumoniae carriage, the most common cause of bacterial pneumonia, is thought to be increased in individuals with high HAP exposure. One study demonstrated that particulate matter exposure from woodsmoke decreased macrophage phagocytosis of S. Pneumonia and increased the duration and density of pneumococcal carriage[42]. Additionally immune responses to respiratory viruses may be impaired, with prior literature demonstrating that increased PM_{10} exposure can blunt alveolar macrophage responses to Respiratory syncytial virus (RSV)[43]. As a result, recent literature has focused on the impacts of HAP on both viral and bacterial ALRI. Air pollution additionally may result in genetic and epigenetic changes which alter inflammatory and oxidative stress responses even after the exposure is removed[44].

Lung Development in Children

Lung development begins in *utero* and by the fourth week of development nascent bronchi form. By gestation, only a small fraction of primary alveoli has developed, a process, which increases linearly up to the age of 18, with 85–90% of alveoli formed within the first six

months of life. Fetal and adolescent lung development is a critical period, which predicts future lung function. Low lung function in infancy and childhood is associated with respiratory health sequela including, wheeze, airway hyper reactivity, asthma and COPD in adulthood[45,46]. Though a comprehensive review of second-hand smoke (SHS) exposure is beyond the scope of this paper, there is a large body of evidence concerning SHS as a contributor to indoor air pollution and lung development. SHS has been identified as a risk factor for low lung function in several studies[47,48]. A study of 2,500 children followed over six decades demonstrated that parental smoking during childhood is a determinant of low lung function trajectories, low lung function in adulthood and eventual development of COPD[47,49]

Studies related to ambient air pollution have demonstrated associations between prenatal exposures, lower lung function at birth and the likelihood of respiratory disease in adolescence and adulthood. However, few studies related to in-utero exposures have evaluated HAP or assessed personal exposure monitoring[50,51]. In a LMIC setting, Lee and colleagues examined the association between maternal carbon monoxide exposure (CO) from cookstove sources (traditional three stone fires with wood as the dominant fuel) and infant lung function at 30 days, and found a dose response relationship between elevated maternal CO exposure and reduced peak tidal expiratory flow to expiratory time and higher minute ventilation [52]. Furthermore, the authors found this increase in minute ventilation was associated with increased risk for physician-assessed pneumonia and severe pneumonia in the first year of life[52]. Further works needs to be done to confirm the contribution of early exposure to household pollutants, outside of secondhand smoke, to early lung development.

Respiratory Tract Infections

A number of studies have demonstrated a strong association between household air pollution and the risk of childhood acute lower respiratory tract infection (ALRI) globally. It has been hypothesized that the contribution of HAP to lung development, along with the development of COPD and chronic bronchitis, is related to repeated infections over time.

LMICs.—In LMIC settings, HAP results in an estimated half a million deaths among children under 5 annually, specifically from pneumonia. Dherani and colleagues demonstrated exposure to HAP from solid fuel use during childhood increased the risk of ALRIs by 78% (pooled odds ratio = 1.78 (95% CI 1.45 to 2.18) in a meta-analysis of 24 studies[53]. As a result of the high prevalence and associated mortality, pediatric pneumonia has been a primary clinical outcome for interventions aiming to mitigate pollutions exposure with mixed results. (*see* Cookstove Interventions). While a number of studies have examined the association between HAP and pediatric pneumonia, the relationship with ALRI in adults is less clear. A recent systematic review limited to adults found mixed results, though some evidence of an increased risk of adult ALRI from exposure to HAP.[54]

High-Income Countries.—Within high-income countries more research exists on the association between outdoor pollution and healthcare encounters for ALRI among children and infants. A study by Horne and Colleague explored the relationship between rises in outdoor air pollution in Utah between 1999 and 2016 and odds of healthcare utilization

related to lower respiratory tract infections[55]. The study demonstrated that a $10_{ug/m}{}^{3}$ increase in ambient $PM_{2.5}$ was associated with increased healthcare utilization for ALRIs (OR 1.15; 95% CI 1.12–1.19). The majority of individuals included in this study were again young children (0–2 years), though effects were still observed to the age of 18. These results have been replicated in other areas of the United States, including among adults in New York State, where increases in outdoor $PM_{2.5}$ were associated with higher rates of Influenza and culture-negative pneumonia[56]. In contrast to the literature on ambient pollution, studies surrounding the association between household pollution and ALRI in high-income countries are much less robust, limited primarily to survey data with inconsistent findings[54]. The association between HAP and ALRI in high income countries still requires further investigation.

Asthma

Prior meta-analyses conducted across continents have demonstrated that early secondhand smoke exposure is associated with the childhood asthma development and subsequent increased risk for adult asthma[57]. As a result, many have hypothesized that particulate from other sources of HAP and airway irritants may lead to asthma development and increased morbidity for children living with asthma.

LMICS.

Studies in LMICs to date have been inconsistent regarding HAP from solid fuel smoke and asthma among children and adults. Po and colleagues did not find a statistically significant association (children: OR = 0.50, 95% CI 0.12–1.98; adults: OR = 1.34, 95% CI 0.93–1.93) among 25 studies[58,59]. Chronic exposure to HAP is associated with increased levels of airway hyperresponsivness[60]. Additionally, HAP exposure can result in airway remodeling and inflammation with similar patterns of small airway disease seen in asthma. HAP from biomass contains known endotoxins and organic compounds, which increase the risk for asthma[61]. Air pollution from solid fuel combustion and existing allergens can become amalgamated resulting in increased serum IgE, eosinophils and neutrophils[62]. Nonetheless, the lack of consistent findings related to the association between HAP and asthma in LMICs require additional investigation.

High Income Settings.

Within high-income countries, studies of solid fuels and asthma development are limited to rural settings, where heating with wood and coal is relatively more common. One survey of adults in Southeastern Kentucky, conducted as part of the Burden of Lung Disease (BOLD) study, described an association between cooking with wood or coal and pediatric asthma (OR 2.3, 95% CI: 1.1–5.0). The study demonstrated no effect of heating with solid fuels on asthma development (OR 0.8, 95% CI: 0.4–1.8)[63]. Research from Ward and Noonan investigated the association between woodstove use for heating and asthma symptoms among children in Libby Montana, where woodstoves were the primary source of home heating in 33% of households. Their findings suggested that woodstove use was associated with greater odds of wheezing (OR 1.74, 95% CI 0.55–5.56) though findings were not statistically significant[64].

There is more consistent evidence to suggest household pollution may increase respiratory morbidity among children with asthma in both urban and rural environments. Among populations with asthma, elevated levels of $PM_{2.5}$ and PM_{10} are associated with higher rates of asthma attacks, medication use, and emergency department visits[18,65,66]. One study of household pollution in an urban inner-city environment, where the use of solid fuels is less common, demonstrated that increases in indoor $PM_{2.5}$ were associated with greater asthma morbidity for children with both atopic and non-atopic forms of asthma[67]. In this study of 133 children ages 2–6, with repeated measured of household pollutants ($PM_{2.5}$, PM_{coarse}), higher PM_{coarse} and $PM_{2.5}$ concentrations were associated with greater risk for wheezing, rescue inhaler use, and nocturnal symptoms.[66]

In addition to PM, higher levels of elevated household NO_2 may lead to greater asthma morbidity. Higher NO_2 exposure has been tied to lower peak flow measurements in a nationwide analysis of urban asthmatic children in the National Cooperative Inner-City Asthma Study (NCICAS)[68]. A longitudinal study of asthmatic children in Baltimore demonstrated that each 20-ppb increase in NO_2 exposure over a 72-hour period was associated with an increase in the number of days with limited speech (incidence rate ratio [IRR] = 1.15; [95% CI, 1.05–1.25]), cough (IRR = 1.10; 95% CI, 1.02–1.18), and nocturnal symptoms (IRR = 1.09; 95% CI, 1.02–1.16), after adjustment for potential confounders[13]. Paulin and colleagues demonstrated that daily changes in household NO_2 exposure were associated with gas stove/oven use and led to worsened asthma symptoms and nighttime inhaler use among children with asthma[21]. Studies of school classrooms have also demonstrated that indoor NO_2 is associated with increased airflow obstruction among children with asthma[69].

There are still certain populations who are known to be more susceptible to the health effects of household pollution. Being overweight or obese may be risk factors that increases susceptibility to indoor $PM_{2.5}$ and NO_2 among children with asthma[70]. Studies have indicated that being overweight has been associated with a oxidative stress and inflammation, which may affect the ability to defend against oxidative and pro-inflammatory exposures, such as that from particulate and gaseous pollutants[71,72]. To investigate the hypothesis that obesity increases susceptibility to air pollution health effects, Lu and colleagues examined the effects of household $PM_{2.5}$ and NO_2 exposure [70]. They observed that compared to normal weight children with asthma, overweight children experienced greater symptoms (cough, wheeze, and chest tightness) and rescue medication use, when faced with similar increases in household $PM_{2.5}$ and NO_2. Wu and colleagues similarly observed that overweight and obesity increased susceptibility to household secondhand smoke exposure among children with asthma[73]. These findings suggest that diet and weight loss, in addition to pollution reduction, may be important targets in efforts to reduce the respiratory health effects of indoor air pollution among children with asthma. Investigations of differential responses to air pollution by weight may provide insights as to pathways by which air pollutants elicit respiratory health effects. The majority of the studies of household pollution and asthma morbidity are conducted among children, and further research is needed to demonstrate whether these results can be extrapolated to adults.

Multiple studies have proposed a synergistic relationship between allergen and pollutant exposure but have focused on outdoor air pollution exposures. A prospective cohort study of children followed from infancy to 4 years demonstrated that exposure to traffic-related diesel exhaust was associated with increased risk of aeroallergen sensitization[74]. Controlled exposure studies in atopic volunteers have demonstrated that diesel exhaust increases markers of allergic and non-allergic inflammation and that allergen and diesel exhaust have exposure specific responses[75,76]. Previous studies have demonstrated that increased ambient $PM_{2.5}$, NO_2, and ozone exposure are associated with a significant increases in risk for asthma and allergic rhinitis among children with allergic sensitization[77,78]. Several studies of children living in urban settings have demonstrated that pest allergen, including mouse and cockroach, are associated with increased asthma morbidity[34,79,80]. Children are often co-exposed to high levels of indoor $PM_{2.5}$, NO_2, and dust allergens[81]. The combined effects of indoor air pollution and allergen exposure are not well understood and can provide insight as to priority targets for multi-faceted intervention studies.

COPD

LMICs.—There have been a number of studies that have examined the association between biomass and COPD in LMICs, with heterogeneity in exposure history and outcomes[60,82]. A meta-analysis of 23 papers by Kurmi and colleagues found an increased odds of COPD (OR = 2.80, 95% CI 1.85 – 4.0) and chronic bronchitis (OR =2.32, 95% CI 1.92 – 2.80)[38]. Similarly, Hu and colleagues demonstrated a similar association (OR = 2.44, 95% CI, 1.9– 3.33) between HAP and COPD, relative to those not exposed to biomass smoke. While the vast majority of studies related to COPD pertain to tobacco exposure in high-income settings, less is known about how HAP can lead to COPD development in LMICs. Although evidence of direct causal relationship between HAP and COPD is not definitive, it is likely that HAP exposure over the course of the lifespan has direct and indirect effects (recurrent ALRI, low socioeconomic status) on lung function that predispose to COPD[83].

Individuals with biomass-related COPD demonstrate a distinct pattern of lung injury with increased anthracosis, small airway thickening and peripheral fibrosis on lung biopsy compared to individuals with tobacco smoke mediated COPD[6]. Women with biomass-related COPD have lower rates of emphysema and higher rates of air trapping and bronchiectasis compared to those with tobacco-related disease[84]. In addition, individuals with biomass-related COPD have distinct patterns of airway disease, which may be related to the size of particles deposited in the airways during biomass exposure[85]. This phenotype is marked by increased cough, phlegm on respiratory symptom questionnaire, as well as higher rates of bronchodilator reversibility and hyper-responsiveness, signifying an elevated degree of airway inflammation[60]. Biomass-related COPD results in a different inflammatory profile, with higher circulating levels of CD4 inflammatory mediators (TH2, IL-4 and IL-10) than tobacco related disease[86]. Furthermore, those with biomass-related COPD have higher levels of malonylaldehyde and superoxide dismutase, measures of oxidative stress that correlate inversely to FEV_1[87].

High-Income Countries.—Given lower utilization of solid fuels in high-income countries the relationship between household use of solid fuels and COPD development in

high-income studies has not been as intensively investigated. However, a few studies have demonstrated a potential link between the utilization of solid fuels for heating and COPD development in the United States. A 2010 study by Sood and colleagues demonstrated that self-reported wood smoke exposure was associated with greater odds of airflow obstruction and chronic bronchitis (OR 1.96, 95% CI 1.52–2.54) and 1.64 (95% 1.36–2.06), respectively[88]. This study was limited to a cohort of primarily smokers in New Mexico. A subsequent, nationally representative study, which utilized the National Health Interview Survey for data on COPD prevalence and the US Census for information on community use of solid fuels (coal and wood) for heating, demonstrated that higher use of coal for heating, at the community level, was associated with greater odds of self-reported COPD (OR 1.09; P<0.001), among never-smokers[89]. A similar study which utilized data from the National Health and Nutrition Examination Survey demonstrated that increased use of wood for heating, at the community level, was associated with greater odd of COPD, defined by spirometry (OR 1.12; P<0.001), among never smokers. Both of these studies demonstrated that living in a rural region of the United States was associated with greater odds of COPD, even after taking account traditional risk factors such as smoking, community level poverty and individual socioeconomic status. Rural regions notably reported a higher percentage of homes using solid fuels (wood and coal) for heating, which may be an explanation for this disparity. All three of these studies were limited by a lack of information on individual level exposures, as they relied on the census level data, and did not contain direct measurement of pollutants. As a result, there remains a significant gap in our knowledge of the contribution of these household pollutants to COPD development in high income settings.

Among individuals living with COPD indoor air pollution has been associated with increased respiratory morbidity, even in communities that do not use solid fuels for heating or cooking. Hansel and colleagues demonstrated in an urban cohort of 84 former smokers with COPD that increases in $PM_{2.5}$ and NO_2 are associated with worsened COPD morbidity[90]. An increase of $10_{ug/m}^3$ $PM_{2.5}$ in the main living area was independently associated with increases in nocturnal symptoms, wheeze, worse respiratory status based on St. George Respiratory Questionnaire scores, and greater odds of severe exacerbation (OR 1.50; 95% CI 1.04 to 2.18). A 20_{ppb} increase in NO_2 in the main living area was associated with increased modified medical research council (mMRC) dyspnea scores while a similar increase in bedroom NO_2 was associated with increased odds of severe exacerbations (OR 2.71; 95% CI 1.05 to 6.93). One notable thing about this study is that these effects were seen despite relatively low household pollutant concentrations (median [IQR] $PM_{2.5}$ 8.3 [4.9 to 14.4] ug/m3 and NO_2 6.8 [4.2 to 14.5] ppb), which are typical of high-income countries. These studies did not show an effect of $PM_{2.5}$ or NO_2 on FEV_1, though the follow-up period was limited to 6 months. In addition to $PM_{2.5}$ and NO_2, studies have highlighted the impact of household allergen sensitization on COPD morbidity. Data from an urban COPD cohort demonstrated that sensitization to allergens from mouse, cockroach, cat, dog, and dust mites increased respiratory morbidity[91]. In this study, the authors measured detectable IgE levels for the aforementioned allergens, as well as markers of allergen exposure and sensitization, among 77 participants with COPD. After adjusting for confounders, an increasing number of sensitizations was associated higher risk for cough, wheeze, and nocturnal dyspnea, though the effects were primarily observed among those with 3 or more sensitizations. Those with

only 1–2 sensitization still had greater odds of reporting an ED visit (OR 10.0; 95% CI 1.6–60.7). This study was limited by a small sample size, with broad effect estimates, but still provides evidence to suggest that household allergen exposure and sensitization can lead to increased morbidity for those with COPD.

Certain factors can also increase susceptibility to the impact of household pollutants for those living with COPD. Similar to what has been observed among children with asthma, obesity may increase susceptibility to the effects of HAP among adults with COPD. One study of 84 participants with moderate to severe COPD demonstrated that obese individuals had exaggerated increases in nocturnal symptoms, dyspnea and rescue medication use compared to non-obese in response to $PM_{2.5}$ and PM_{coarse} [92]. Other studies have demonstrated that extremes of temperature – both hot and cold –may also influence the effects of indoor pollution on COPD morbidity[93,94]. One study in particular demonstrated that high heat increased the effect of $PM_{2.5}$ and NO_2 exposures on rescue inhaler use, cough, and sputum production[95]. We do note the majority of the data presented here regarding the effects of household pollution on COPD morbidity in high income countries are from urban environments. To date there are few studies, with direct measurements of household pollutants, in rural regions of the United States that have studied the effects of household pollution on COPD morbidity. While the literature is suggestive of this, we do not know if there is a difference in the impact of household air pollution between urban and rural environments in the United States remains an important area for future study. The present studies have also not shown that increases in household $PM_{2.5}$ or NO_2 exposure are associated with more accelerated lung function decline for those with COPD. This may ultimately be related to relatively short-term follow-up (<1-year followup) in the studies performed to date.

Strategies for Reducing Household Air Pollution

A number of strategies have been attempted to reduce pollutant exposure in diverse settings. Interventions have been attempted to reduce a wide range of indoor pollutants including, particulate matter, gases, allergens, and mold (Table 2). Certain strategies outlined focus on source reduction (i.e LPG stove interventions and smoking bans) while others focus on secondary reduction (air cleaner interventions).

Cookstove Interventions

Over the past decade, a number of studies have attempted to lower the levels of HAP through cleaner burning biomass stoves. RESPIRE was one of the first randomized controlled trials to demonstrate a reduction in deleterious health outcomes, in their case severe pediatric pneumonia[96]. Romieu and colleagues demonstrated reduced respiratory symptoms (odds ratio 0.29, 95% CI 0.11– 0.77; for wheeze) and declines in lung function (31 mL *vs.* 62 mL over 1 year, p=0.01) over a 12 month period among those randomized to cook stove intervention, though few other studies have replicated these results despite evidence of increased cookstove uptake (Table 3)[97].

Design of stove interventions to reduce the burden of disease has additionally been challenged by a limited understanding of exposure-response relationships[101]. Many studies

were limited by small samples size, limited length of follow up, variability in intervention and level of adoption, as well as protocol deviations[102]. Importantly, most studies have failed to capture meaningful exposure reduction to gain a complete understanding of exposure-response across a range of relevant and targeted exposures. Few HAP studies have included low exposure groups (i.e., clean fuel users) to demonstrate the maximum benefit that can be expected. Because of financial and technical constraints associated with performing large-scale HAP measurements in LMIC settings, many studies have relied on imprecise, proxy exposure measures. Measurement of fine particulate matter ($PM_{2.5}$), the best exposure indicator of health risk, has been particularly challenging due to the limitations of affordable, feasible, and reliable instrumentation[103,104].

The evidence from clinical trials to date do not support the efficacy of cleaner-burning cook stoves to improve pulmonary health or reduce mortality in LMICs[102]. Liquified petroleum gas (LPG) stoves may sufficiently reduce HAP levels to deliver meaningful health gains. Ongoing trials utilizing LPG stoves with inclusion of participants across the lifespan (fetal, childhood and elderly participants), sufficient follow up and exposure monitoring may add additional value in understanding the pulmonary benefits of reduction in HAP. A multicenter RCT, funded by the NIH, with sites in Rwanda, Peru, Guatemala and India aims to address additional gaps in evidence[105].

Air Cleaner Interventions

Portable air cleaner devices may be effective for reducing household air pollution in high income countries. Air cleaner interventions have been studied in both urban and rural regions of the United States including both HEPA cleaners and HEPA and activated carbon filters to address household gases (i.e. NO_2) Table 4.

While air purifiers have been shown to improve indoor air quality and reduce household $PM_{2.5}$ concentrations, the long-term health benefits of these devices are still being uncovered. A study of healthy adults in woodsmoke-impacted community, demonstrated improved endothelial function (based on the reactive hyperemia index) and decreased concentrations of inflammatory biomarkers (serum CRP) after a weeklong HEPA filter intervention[106]. As noted previously, studies of air purifier interventions have shown promise for improving childhood asthma outcomes. Two trials in urban settings have shown improvements in symptom free days and healthcare utilization with air cleaner interventions[107,108]. In contrast for adults with COPD the effects of an air cleaner intervention remain unknown, given a lack of high-quality intervention trials. The effects of an area cleaner intervention for adults with COPD remains an area in need of ongoing research and studies are underway[109].

Integrated Approaches for Pollutant and Allergen Reduction

Integrated approaches have additionally been attempted that combine education on allergen reduction and remediation, pest management, and air cleaners to reduce household particulates. These studies have primarily focused on children with asthma, and their effects on other populations are not yet known. One multi-center randomized trial of 937 inner-city children with asthma demonstrated improvements with a 12 month environment intervention

centered around the bedroom that included HEPA air cleaners, allergen remediation and allergen prevention education for caretakers[110]. Children who underwent this intervention saw an improvement in the symptom free days during the intervention year (3.39 vs 4.20 days, P<0.001) and the year after (2.62 vs 3.21 days, P<0.001). This was accompanied by a significant reduction in dust mite and cockroach allergens. A smaller study that employed air cleaner use and cockroach extermination among 100 asthmatic children, demonstrated a 51% reduction in cockroach allergen along with a 36% reduction in $PM_{2.5}$ at one-year followup[111]. In this study participants who received the intervention reported fewer daytime symptoms (OR 0.55, 95% CI 0.31–0.97). Studies that have focused solely on pest allergen reduction have had mixed results[29,79,112,113]. A more recent randomized trial did not demonstrate a benefit of an integrated pest management intervention over providing pest management education alone to families of children with asthma[29]. However, a post-hoc analysis demonstrated that mouse allergen reduction was associated with greater increases in lung function over a year, suggesting that allergen exposure reduction may improve lung growth[114]. In this study pest management education alone (providing written material and demonstration about and pest management and housekeeping practices) resulted in a 65% reduction in household mouse antigen, suggesting that detailed education may provide benefit in reducing environmental exposures.

Community Level Interventions

Community level strategies, bolstered by policy, have been utilized to reduce sources of pollution in high income countries. Successful campaigns have been implemented to reduce pollution from solid fuels and address the use of wood stoves, in rural communities. One community-wide wood stove exchange program in Libby Montana led to a 27.6% (95% CI 3.0% to 44.5%) decrease in ambient $PM_{2.5}$ levels, with an associated decrease in odds of both wheeze and respiratory infections among school children in this community[115]. A similar study in Tasmania, Australia observed a significant reduction in outdoor PM_{10} (from $43.6_{ug/m}^3$ to $27.0_{ug/m}^3$), after community wide efforts to replace wood burning stoves with cleaner electric appliances. Community level woodstove exchange programs have also been effective in reducing ambient concentration of phenolics and PAHs[116]. Despite observed improvements in ambient pollutant levels and potential health benefits, there has not been a consistent long-term decrease in household $PM_{2.5}$ from these efforts alone[117]. Given that significant legislative and regulatory action is often required to implement similar community level interventions, further research is needed in order to confirm their long-term benefits.

Smoke-free legislation provides examples of successful interventions with the potential to impact health at a population level. For example, meta analyses of studies investigating the effect of smoke-free legislation in North America and Europe have demonstrated reductions in emergency department visits for asthma and hospitalizations for asthma and respiratory tract infections[118,119]. Recent legislation on smoking bans in public housing more specifically addresses residential smoke exposure. Effective February 2017, the U.S. Department of Housing and Urban Development published a rule requiring each public housing agency to implement a smoke-free policy within 18 months[120]. Implementation of this rule poses challenges and studies investigating health effects are not yet available.

Schools represent another venue for community-level interventions. Despite the strong evidence base for health effects of air pollution, including indoor air pollution, on children's respiratory health, there has been relatively little investigation of interventions in schools. Children spend a substantial proportion of their time in schools and thus, school environments represent an opportunity to improve health at a population level by reducing harmful exposures. The School Inner-City Asthma Study demonstrated that mouse allergen exposure in schools was associated with increased asthma symptoms and decreased lung function[80]. Studies of school-based environmental interventions are logistically challenging but studies, some of which are currently underway, are needed in order to provide evidence of the magnitude of potential health benefits for children[121,122].

Future Areas for Study

Today there is robust data to suggest that indoor air pollution is associated with a multitude of respiratory effects across the lifespan, including impaired lung development in childhood, greater risk for acute lower respiratory tract infections, risk for developing chronic lung disease and increased morbidity related to asthma and COPD. While longitudinal cohort studies of participants followed for decades has informed our understanding of the effects of outdoor air pollution and the benefits of pollution reduction, analogous studies of the long-term health effects of indoor air pollution are lacking[123]. While there is a relatively limited number of studies investigating interventions to reduce household pollutants, existing evidence has been inconsistent in demonstrating benefit. Challenges of studying the health effects of indoor air pollution include the need for individual exposure assessment, and interventions that require long-term implementation at the household level. Opportunities to longitudinally study the health effects of legislation aimed at improving indoor air quality and interventions at community levels with the potential to improve health of local populations provide a means of efficiently understanding the health benefits of improved indoor air quality. As individuals spend the majority of their time indoors and most of their time in the home environment, this continues to be an important target for improving respiratory health. Ongoing investigations are needed in order to more clearly identify targetable mechanisms by which indoor pollutants may influence respiratory morbidity, interventions with long term benefit, and susceptible populations who are most likely to benefit from these interventions.

Summary

Indoor air pollution, from sources that include indoor tobacco smoke, the burning of solids fuels, and noxious gases from cooking and heating, is associated with greater risk for chronic lung disease development and respiratory morbidity worldwide. While the impact is most pronounced in Low- and Middle Incomes countries, significant health effects are still observed at lower pollutant concentrations typical of high-income settings. It is important to raise awareness of common sources of pollution among clinicians, policy makers, and patients with chronic respiratory disease alike, in order to improve health education and promote efforts that can reduce pollutant exposure across households and address environmental health disparities. While the long-term benefits of efforts to reduce indoor air pollution are yet to be defined, multiple intervention strategies at the household and

community levels (including indoor smoking bans and air cleaner interventions) have been effective in reducing pollutant exposure. Future research may help to define optimal strategies for reducing indoor air pollution at the individual, household, community and population level to improve long-term lung health and reduce health disparities.

Acknowledgments

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Key Points:

- Over 4 million people die prematurely annually due to household air pollution.

- A large number of factors contribute to household air pollution including household characteristics (ventilation, dampness, humidity), behaviors (cooking practices and use of solid fuels), as well as allergens related to pests.

- Indoor air pollution is associated with impaired lung development, increased risk for respiratory tract infection, and increased prevalence of and morbidity attributable to asthma and chronic obstructive pulmonary disease.

- Research is ongoing into effective strategies to reduce pollutant exposure and improve lung health.
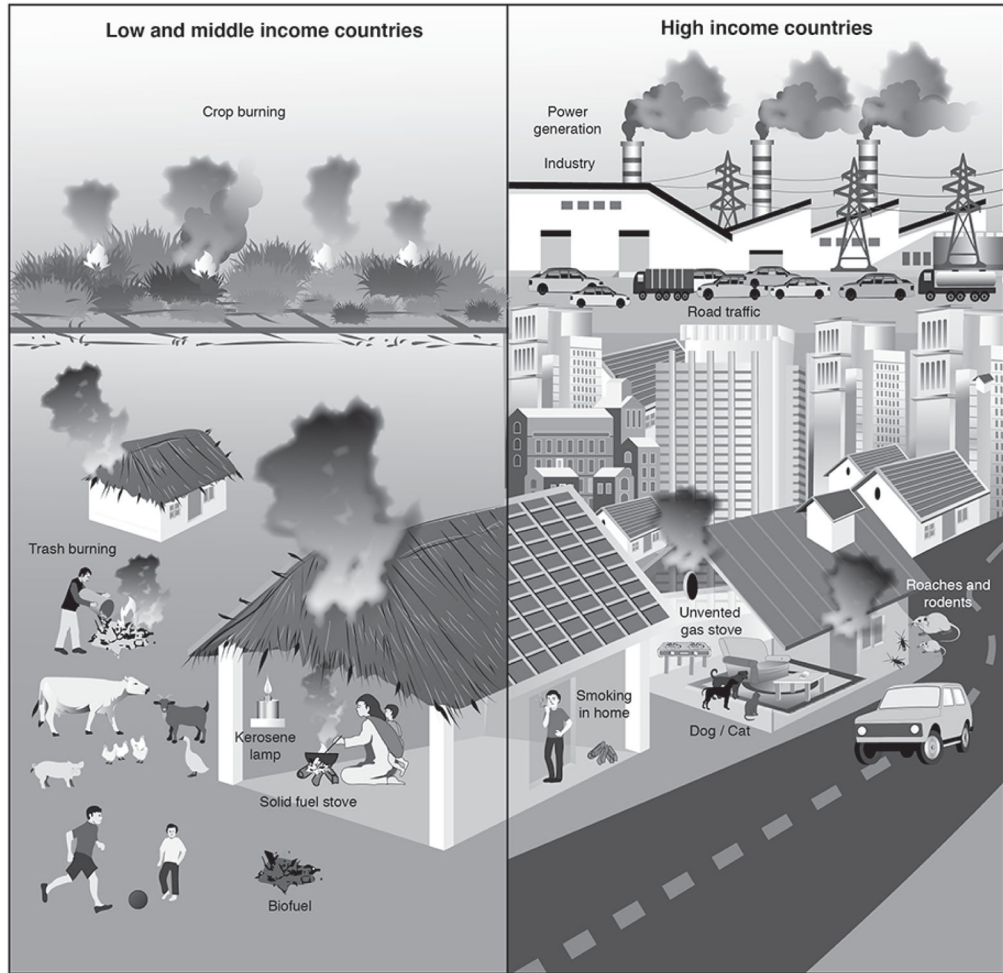
Fig 1.
Indoor air pollution: the respiratory effects in low-middle income and high-income countries.

Table 1.

Mechanism by Which Household Pollution Can Impact Respiratory Health

• Neutrophilic Inflammation
• Reduced Bacterial Clearance and Alterations in Microbiome
• Increased Matrix Metalloproteinase Activity and Gene Expression
• Greater Oxidative Stress
• Increased Apoptosis
• Pulmonary Surfactant Deactivation
• Reduced Mucociliary Clearance
• Epigenetic Changes - DNA Damage and Methylation
• Disruption of Lung Endothelial Cell Barrier

Table 2.

Common Strategies for Reducing Household Pollutants

Pollutant	Interventions
Particulate Matter ($PM_{2.5}$, PM_{10})	Cookstove Exchanges (In homes burning biomass fuels), Air Cleaner Interventions, Woodstove Replacement
Gases (NO_2)	Air Cleaners (HEPA with carbon filter), Gas Stove Replacement, Vented Hoods for Stoves
Allergens	Air Cleaners, Integrated Pest Management, Pest Education
Molds	Remediation of household dampness and humidity
Environmental Tobacco Smoke	Smoking Cessation, Indoor Smoking Bans

Table 3.

Cookstove Interventions to Improve Respiratory Health. *Data from* Refs[96–100]

Author/Year	Intervention	Location/ Participants	Findings
Romieu et al. 2009[97]	RCT of chimney stove vs traditional open fire *Primary Outcomes:* Respiratory symptoms and Lung Function	Rural Mexico, n=552 women	No statistically significant effect seen in intention-to-treat (ITT) analyses, although a significant effect on both cough and annual rate of decline in forced expiratory volume in 1 second (FEV_1; 31 vs. 62 ml) was observed for women who reported using the chimney stove.
Smith et al. 2011[96]	RCT of chimney stove vs traditional open fire *Primary Outcomes:* Physician diagnosed pneumonia	Rural Guatemala, n= 518 children under 19 mo age	No statistically significant effect on physician-diagnosed pneumonia was found, although physician-diagnosed severe pneumonia (defined by the presence of hypoxemia) was significantly reduced among children in the intervention group. The chimney stove intervention was reported to improve respiratory symptoms in the mothers of the study children, but not rate of decline in lung function in ITT analyses. A subsequent analysis demonstrated reduced carbon monoxide exposure was associated with a lower rate of decline in FEV_1
Tielsch et al. 2016[98]	Cluster-randomized, step-wedge, community-based trial of a cleaner-burning biomass stove vs traditional open stove *Primary outcome:* Acute lower respiratory tract infection	Rural Nepal, n= 5,254 children under the age of 3 yo	No statistically significant effect on the incidence of acute lower respiratory tract infection in the intervention compared with the control group (relative risk = 0.87 [95% confidence interval = 0.67–1.13]). Potentially beneficial effects were seen in selected secondary analyses on cough, wheeze, and burn injury.
Asante et al. 2017[99]	Three-arm household-level RCT of liquefied petroleum gas versus a cleaner-burning biomass-fueled cookstove *Primary Outcome:* Birthweight and physician-diagnosed severe pneumonia in the first year of life	Rural Ghana, n = 1,415 pregnant women	Although children born to mothers with higher HAP CO exposures during pregnancy were at increased risk for impaired lung function measured 1 month after birth, no significant difference in birth weight or physician-assessed IMCI pneumonia in either of the intervention arms in IIT analysis
Mortimer et al. 2017[100]	Community-level C-RCT of two cleaner-burning, biomass-fueled cookstoves with a solar charger vs traditional open fire *Primary Outcome*: Pneumonia	Rural Malawi, n = 10,750 children under 5 yo	No effect of the intervention on the primary outcome of WHO Integrated Management of Childhood Illness–defined pneumonia in an ITT analysis.

Table 4.

Air Cleaner Interventions to Improve Respiratory Health

Author/ Year	Intervention	Location/ Participants	Findings
Ward et al. 2017	Randomized placebo-controlled trial of woodstove change out and air filtration *Primary Outcomes:* PM2.5 and CO concentration	Missoula Montana, n=98 households	Homes randomized to the air purifier intervention had a 63% (95% CI 47–75%) reduction in household $PM_{2.5}$. The air purifier intervention arm was more efficacious and less expensive than a employing a woodstove changeout, which resulted in no significant change in household $PM_{2.5}$.
Butz et al. 2011	RCT of health coaching and high-efficiency particle air (HEPA) filter vs HEPA filter vs control *Primary Outcomes:* Change in PM, air nicotine, urine cotinine concentration and symptom-free days	Baltimore MD, n=125 children with asthma who resided with smokers	Homes randomized to receive an air cleaner observed a 50% reduction in $PM_{2.5}$, representing a change of ~$20_{ug/m}{}^3$ for children living in smoking homes. These improvements were observed with only modest adherence (59%) to the intervention itself. No reduction was observed in markers of tobacco exposure; air nicotine levels or cotinine measurements. The intervention still led to an improvement in symptom free days (1.36; P=0.03), though did not result in a significant improvement in nocturnal symptoms or a reduction in acute asthma events
Paulin et al. 2014	RCT of gas stove replacement with electric stoves vs instillation of hood over exisiting stoves vs placement of HEPA and carbon purifiers in the house *Primary Outcomes:* Indoor NO_2 concentrations	Baltimore MD, n= 100 households	Homes where the air cleaners were placed in the kitchen and bedroom of homes using gas stoves had an immediate decrease in median NO_2 concentrations in both the kitchen (27%; P<0.01) and bedroom (22%, P=0.02). However, at 3-month follow-up improvements were only observed in the kitchen (20%; P=0.05). Notably in this study adherence data was missing from the bedroom air purifier, which potentially could account for the lack of long-term benefit