Chapter 10
Respiratory Sex Differences in Response to Smoke Exposure

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Abstract Smoke exposure is ubiquitous throughout the world and prevalent in a variety of types including tobacco smoke, wildfire smoke, and biomass and wood smoke. These exposures have all been shown to induce deleterious effects in the respiratory tract and induce lung disease. Additionally, there is considerable epidemiological evidence of smoke exposure-induced sex-biased disease; however, there have been few investigations into mechanisms behind this sex-biased disease manifestation. This chapter will describe what is known about sex differences in smoke exposure, exposure-induced disease, and mechanisms of effects. Additionally, it will enumerate areas of critical need for future investigation to fully understand sex-specific respiratory effects of smoke exposure.

Keywords Lung · Respiratory · Inhalation · Sex differences · Sex-biased · Tobacco smoke · Cigarette smoke · Wildfire smoke · Wood smoke · Biomass smoke · Toxicology

10.1 Introduction

Adverse respiratory responses to air pollution are a growing global health problem. One of the largest contributors to environmental air pollution is smoke exposure. Smoke originates from a variety of sources but most commonly comes from tobacco products, such as cigarettes, wildfires, and fires or stoves used for home heating and cooking. With such a variety of sources, smoke exposure is ubiquitous around the world, though types of smoke, duration, and dose vary. There is considerable evidence of the deleterious effects of smoke on respiratory health, including the
development and exacerbation of lung disease, yet our understanding of subgroup susceptibility and vulnerability is limited. There is a particular gap in the understanding of sex differences in responses to exposure, which includes exposure-related disease development, progression, and mortality, and the mechanisms behind those responses.

Interestingly, the majority of the diseases related to smoke exposure are sex-biased, where one sex is more predominantly affected, including COPD, asthma, lung cancer, and susceptibility to viral infection. For example, in a study of hospital mortality, women with chronic lung disease who were exposed to either tobacco smoke or cooking stove smoke were at higher risk of mortality compared to other groups (Giri et al. 2019). However, we know very little about the mechanisms behind these sex differences in disease incidence and manifestation. Many hypothesize that these mechanisms may be due to anatomical, physiological, and exposure-related differences between males and females, but research on this topic is in its early stages, and there are still many areas in the field with key knowledge gaps. In this chapter, we will address known anatomical sex differences which may influence exposure, sex differences in exposure to environmental smoke including cigarette smoke and biomass smoke, and sex-biased respiratory disease outcomes related to smoke exposure.

10.2 Anatomy

Males and females are known to have differing lung anatomy. Some of the differences include smaller general size, absolute lung volume, and smaller conducting airways, which were recently discovered using advances in computed tomography (Ekstrom et al. 2018; Dominelli et al. 2018). Anatomical differences likely partially mediate the observed sex-specific disease development, due to their effect on relative dose via surface area; however, they do not fully explain differences in response to respiratory toxicant exposure like smoke. Emerging evidence also suggests differing physiology, but the mechanisms behind the development of mechanistic differences are not well understood. Sex-biased disease development after exposure is more likely mediated by mechanisms that are currently only hypothesized (hormonal differences, developmental differences mediated by genetics, etc.) or in early stages of examination in this growing field. To examine these potential contributors, sex differences in exposure will be described in the following section, followed by sex-specific mechanistic contributors to disease.
10.3 Exposure

10.3.1 Tobacco Product Smoke

Smoking cigarettes and other tobacco products (hookah, cigars, etc.) is widely understood to be toxic to the human body and a significant contributor to lung disease and overall mortality. Tobacco smoke is known to be composed of several thousand chemicals, many of which have been identified as carcinogenic; however, the complex mixture depends on the type of tobacco product used as composition varies (Table 10.1). While education on the effects of tobacco smoke exposure has induced a decline in use in high-income, more-developed countries, it is still a prevalent source of smoke exposure in many parts of the world. Interestingly as patterns of use change over time, sex and gender differences in use trends have emerged and changed (Pampel 2006). In more developed countries, cigarette smoking use in men and women has become more uniform, while in developing countries, there are still significant divides in use patterns, with men smoking cigarettes much more prevalently than women. Examples include China, where women smoke at a prevalence of 1.8% and men at 47.6%, South Africa (women 6.5%, men 31.4%), and Argentina (women 18.4%, men 29.5%) as of 2015 according to the World Health Organization (WHO) (World Health Organization 2018). Low- and middle-income countries include 80% of tobacco users worldwide. Interestingly, use trends have been complicated by the introduction of e-cigarettes and heat-not-burn tobacco products to the global market, where they have reversed the downward trend of tobacco product use in developed countries, like the United States, especially in younger portions of the population (Barrington-Trimis et al. 2016). As of 2017, the Global Youth Tobacco Survey indicates that the prevalence of e-cigarette use is higher in males than females (Rodriguez-Bolanos et al. 2019). While e-cigarettes are known to emit an aerosol, rather than combusted smoke, they will be included in this chapter due to their inclusion as heated inhaled tobacco product.

10.3.2 Wildfire, Wood, and Biomass Smoke

Exposure to air pollutants causes over seven million premature deaths worldwide, and environmental smoke, particularly wildfire smoke, is a major contributor (Lelieveld et al. 2020). Wildfires have become a dominant source for ambient particulate matter (PM), and the increased number and severity in recent years have been associated with climate change and increasing land area being burned each decade (five million acres in 2008 and ~nine million acres in 2018). It has been estimated that over 50% of all summer fine PM concentrations over the daily average National Ambient Air Quality Standard (NAAQS, 35 ug/m³) occur when wildfire smoke plumes are present; thus the closer the vicinity to the wildfire and wildfire
Table 10.1  Major chemical constituents in tobacco smoke exposure. Tobacco smoke is composed of thousands of chemicals. This table lists some of the most commonly measured components of tobacco smoke in exposure studies, as well as other measured compounds and classes of compounds. Sex differences in respiratory effects due to tobacco smoke exposure are listed when they have been studied. Chemical compounds or classes which overlap with biomass smoke (Table 10.2) are bolded.

| Sex differences                                      | References                                                                 |
|-------------------------------------------------------|---------------------------------------------------------------------------|
| Most commonly measured components                     |                                                                           |
| Tobacco-specific nitrosamines                         | Centers for Disease Control and Prevention (2002)                          |
| Nicotine                                              | Rahmanian et al. (2011)                                                   |
| Other measured compounds                              |                                                                           |
| Acetaldehyde                                          |                                                                           |
| Acetone                                               | Nomiyama and Nomiyama (1974)                                              |
| Acrolein                                              | Dwivedi et al. (2015)                                                     |
| Ammonia                                               |                                                                           |
| Carboxylic acids                                      |                                                                           |
| Formaldehyde                                          | Increased risk of genotoxicity and breathlessness in females             |
| Hydrocarbons                                          |                                                                           |
| Hydrogen cyanide                                      |                                                                           |
| Methane                                               |                                                                           |
| Methanol                                              |                                                                           |
| Phenols                                               |                                                                           |
| Polycyclic aromatic hydrocarbons                      | Higher susceptibility to lung cancer in females                           |
| Terpenoids                                            |                                                                           |
| Acidic additives, like levulinic acid                 |                                                                           |
| Carbonyl compounds                                    |                                                                           |
| Catechols                                             |                                                                           |
| Carbon dioxide                                        | Females at increased risk of carbon dioxide-induced hypoxemia            |
| Flavoring compounds                                   |                                                                           |
| Humectants                                            |                                                                           |

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smoke, the larger the exposure (Reid and Maestas 2019). Furthermore, fine PM levels in the areas surrounding wildfires have been observed at approximately 400ug/m³ for daily concentrations, which is substantially higher than the NAAQS and thus presents a respiratory health risk. Wildfire smoke contains a mixture of chemical constituents, and its composition is dependent upon their fuel source (tree type, leaf litter, inclusion of large structures and vehicles, etc.) as well as other environmental factors like fire intensity, rate of burn, weather, wind patterns, etc. (Table 10.2). As an example, tree/wood type contribution to smoke mixtures has been carefully examined, and these studies have also determined that fuel source can also contribute to varying smoke toxicity (Kim et al. 2019, 2018; Mutlu et al. 2016; Reinhardt and Ottmar 2004). In this study, it was found that fuel sources heavy in eucalyptus likely have the highest toxicity when controlling for combustion temperature and dose.

Another source of smoke exposure includes wood and biomass burning for heating and cooking. Throughout the world, over 2 billion people rely on the burning of biomass, including wood, as their main source of domestic energy (Smith et al. 2000). The use of biomass contributes to high concentrations of particulate matter in the air, in the mg/m3 range which is well above the WHO and NAAQS recommended daily averages, and is a major contributing source of air pollution (Molnár et al. 2005). Additionally, wood burning for heating or cooking has been estimated to contribute to up 30% of ambient fine particles (PM_{2.5}) in some areas of the US during the winter, so exposure is not limited to developing countries (Croft et al. 2017). Similar to the complex composition of wildfire smoke, smoke generated during the home heating and cooking process can vary by the fuel source: wood type, wood condition (wet, dry, chemically treated, etc.), biomass type and condition (animal dung, plant matter, charcoal, etc.), as well as the style of fire or cook stove used. Smoke for heating and cooking has been estimated to consist of over 200 different compounds, making it a complex mixture (Table 10.2). The duration and level of smoke exposure can also vary, depending on whether the fire is indoors or outdoors, home and stove ventilation, and weather patterns.

Interestingly, these differing sources of environmental smoke exposure, wildfires and wood/biomass smoke for cooking and heating, also result in different vulnerable

Table 10.1 (continued)

| Sex differences | References |
|-----------------|------------|
| Hydrogen sulfide | Increased risk of lung cancers and mortality in females, based on one small population study in New Zealand | Chou et al. (2003) |
| Nitric acid | No difference detected | Soskolne et al. (2011); Raizenne et al. (1996) |
| Nitrosamines | -- | |
| Paraffin waxes | -- | |

Reviewed in Centers for Disease et al. (2010); “--:” potential for sex differences not yet investigated, not reported, not enough evidence for definitive conclusion, or large class of compounds that all have not been investigated.
Table 10.2  Major chemical constituents in biomass smoke exposure. Biomass smoke is composed of hundreds of chemicals. This table lists some of the most commonly measured components of biomass smoke in exposure studies, as well as other measured compounds and classes of compounds. Sex differences in respiratory effects due to biomass smoke exposure are listed when they have been studied. Chemical compounds or classes which overlap with tobacco smoke (Table 10.1) are bolded

| Sex differences                                                                 | References                                      |
|-------------------------------------------------------------------------------|------------------------------------------------|
| Carbon dioxide                                                               | Females at increased risk of carbon dioxide-induced hypoxemia | LoMauro and Aliverti (2018) |
| Carbon monoxide                                                              | Shorter half-time of carbon monoxide elimination in females | Zavorsky et al. (2014) |
| Particulate matter ($\text{PM}_{2.5}$ and $\text{PM}_{10}$)                   | Higher rates of hospitalization and exacerbation of lung disease in females | Liang et al. (2019); Bell et al. (2015) |
| Other measured compounds                                                      |                                                 |
| Acetaldehyde                                                                  | --                                              |
| Acetone                                                                        | Higher respiratory uptake, retention, and excretion in men | Nomiyama and Nomiyama (1974) |
| Propanal                                                                      | No difference detected                          | Dwivedi et al. (2015) |
| Ammonia                                                                       | --                                              |
| Carboxylic acids                                                              | --                                              |
| Formaldehyde                                                                  | Increased risk of genotoxicity and breathlessness in females | Agency for Toxic Substances and Disease Registry (ATSDR) (2010); Zhao et al. (2008) |
| Hydrocarbons                                                                  | --                                              |
| Hydrogen cyanide                                                              | --                                              |
| Methane                                                                       | --                                              |
| Methanol                                                                      | No difference detected                          | Ernstgard et al. (2005) |
| Phenols                                                                       | --                                              |
| Polycyclic aromatic hydrocarbons                                              | Higher susceptibility to lung cancer in females | Uppstad et al. (2011) |
| Terpenoids                                                                     | --                                              |
| Carbonyl sulfide                                                              | --                                              | US EPA (2015) |
| Acetonitrile                                                                  | --                                              | Agency for Toxic Substances and Disease Registry (ATSDR) (2007) |
| Benzene                                                                       | --                                              | Wong et al. (2016) |
| Levoglucosan                                                                  | --                                              | Wong et al. (2016) |
| Nitric oxide                                                                  | No difference detected                          | Wong et al. (2016) |
| Nitrous oxide                                                                 | No difference detected                          | Wong et al. (2016) |
| Phenolic compounds (e.g., isoflavonoids)                                      | --                                              |                        |

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populations and affected individuals. With wildfire smoke, first responders are particularly vulnerable to extreme exposures of acute duration, which have resulted in general reports of respiratory symptoms, reductions in lung function, and inflammation, but few connections to disease are likely due to a lack of longitudinal or long-term exposure studies in this subpopulation (Swiston et al. 2008; Adetona et al. 2016). With the use of wood and biomass for cooking and heating, those vulnerable to smoke exposure are primarily individuals who spend the majority of their time in the home (women and young children), which results in a much more chronic and prolonged duration (3–7 hours per day), with identified associations with disease including COPD and asthma (Capistrano et al. 2017). In epidemiological studies, these two groups have been separately analyzed, which is logical as smoke and particulate profiles do differ between the groups. However, another unintended analytical separation also took place as first responders are predominantly male, while those most affected by indoor wood and biomass smoke exposure are primarily female. While progress in both exposure models has been made to understand the effects of wildfire, wood smoke, and biomass exposure, there is a large gap in the comparison and understanding of sex-specific effects that needs to be addressed (Wu et al. 2018). The studies that have examined effects by sex, typically large population studies, are inconsistent, with findings of effects primarily in women, primarily in men, and no difference between groups (reviewed in Reid and Maestas (2019)); however, the analytical approaches and endpoints for these studies also differ substantially, which may explain some of the variability in findings. Consensus on the analytical approach to determine differences by sex in large population studies, wildfire and air pollution modeling, as well as endpoints of interest would be helpful in assessing sex differences in effects of exposure in large population studies in the future. However, there is a growing literature of smaller studies, controlled exposure studies, animal models, and in vitro models that suggest that there are indeed sex-specific effects of smoke exposure.

Table 10.2 (continued)

| Phenylpropenes | Sex differences | References |
|----------------|-----------------|------------|
| Sulfur dioxide | Female increased rates of mortality and hospitalization | Oiamo and Luginaah (2013) |
| Toluene        | --              | U.S. EPA (2005) |
| Xylenes        | Excretion via exhaled air higher in women, while higher volume distribution and urinary excretion in men. Larger FVC decrement after exposure in women as compared to men | Ernstgard et al. (2002, 2003) |

Reviewed in Kim et al. (2018), Vicente et al. (2013), and Ottmar et al. (2008); “--”: potential for sex differences not yet investigated, not reported, not enough evidence for definitive conclusion, or large class of compounds that all have not been investigated.
With both tobacco smoke exposure and wildfire, wood, and biomass smoke exposure, respiratory diseases are commonly linked with smoke exposure, including chronic obstructive pulmonary disease (COPD), asthma, lung cancer, and increased risk of viral infection. Furthermore, these diseases and susceptibilities are also sex-biased, and there is emerging evidence of sex and exposure interactions and sex-specific exposure-induced susceptibilities. The remainder of the chapter will focus on the above-listed diseases and the susceptibility to viral infection, which are commonly identified to be affected by environmental smoke exposure. An overview of the disease or susceptibility, disease links to smoke exposure, known disease-specific sex differences, and emerging evidence of sex-specific effects of exposure or an interaction between sex and exposure will be described and are additionally summarized in Table 10.3.

10.4 Exposure-Related Sex-Biased Respiratory Diseases

10.4.1 COPD

Chronic obstructive pulmonary disease (COPD) is a progressive disease of the respiratory tract which includes chronic bronchitis and emphysema. It is most commonly associated with symptoms like mucus-producing cough, wheeze, shortness of breath, and chest tightness. Decreased airflow is induced in several ways, including loss of airway elasticity and destruction of air sac walls, features of emphysema, and/or airway inflammation, thickening of the airways, and airway obstruction due to increased mucus production, features of chronic bronchitis. COPD is most commonly diagnosed in middle-aged or older individuals but can develop slowly and worsen over time. COPD is the fourth leading cause of mortality in the United States, with 16 million people currently diagnosed, yet it is often thought of as a preventable disease due to its initial association with cigarette smoking. More recently COPD has been associated with other irritant exposures including wildfire smoke, wood smoke, and biomass smoke. Additionally, exacerbations of pre-existing COPD are also associated with smoke exposure (Reid and Maestas 2019). Unfortunately, there is no cure for COPD, and current treatments are primarily designed to reduce symptoms and slow disease progression.

COPD was initially characterized as a disease of cigarette smoking older men (Barnes 2016). While incidence is higher in men in some countries, especially where smoking rates are more dichotomous and male heavy, more recently it has been shown that women are likely more susceptible to the disease than men, with more severe and earlier onset disease, despite smoking less (Barnes 2016; Wang et al. 2018). It has also been shown that exposure to indoor air pollution from biomass or wood smoke may also contribute to increased rates of COPD, particularly in females who are more frequently exposed to these types of smoke (Capistrano et al. 2017). Additionally, mortality rates due to COPD in the United States have increased in women, surpassing men in the United States (Barnes 2016). However, there is some
| Exposure                                                                 | Females | Males |
|------------------------------------------------------------------------|---------|-------|
| Use rates (cigarettes, e-cigarettes)                                   | ↓       | ↑     |
| Duration of exposure (chronic, biomass for heating/cooking)            | ↑       | ↓     |
| Intensity of exposure (acute, wildfire first responders)               | ↓       | ↑     |
| **COPD**                                                               |         |       |
| Disease severity                                                       | ↑       | ↓     |
| Early onset                                                            | ↑       | ↓     |
| Emphysema                                                              | ↓       | ↑     |
| Small airway disease                                                   | ↑       | ↓     |
| Exacerbations                                                          | ↑       | ↓     |
| FEV1%predicted                                                         | ↑       | ↓     |
| RV/%TLC                                                               | ↑       | ↓     |
| Prognosis                                                             | ↓       | ↑     |
| Fibrosis                                                               | ↑       | ↓     |
| **Lung cancer**                                                        |         |       |
| Incidence                                                              | ↑       | ↓     |
| Earlier age of onset                                                   | ↑       | ↓     |
| Relative risk                                                          | ↑       | ↓     |
| Odds ratio                                                             | ↑       | ↓     |
| Asthma                                                                 |         |       |
| Long-standing cough                                                    | ↑       | ↓     |
| Sputum production                                                      | ↑       | ↓     |
| Uncontrolled asthma                                                    | ↑       | ↓     |
| Healthcare visits due to asthma                                        | ↑       | ↓     |
| **EVALI**                                                              |         |       |
| Incidence                                                              | ↓       | ↑     |
| Morbidity                                                              | ↓       | ↑     |
| Viral infections                                                       |         |       |
| Morbidity and mortality                                                | ↓       | ↑     |
| Disease severity                                                       | ↓       | ↑     |
| Early viral replication                                                | ↑       | ↓     |
| Total viral replication                                                | ↓       | ↑     |
| Inflammation                                                           | ↑       | ↓     |
| Autophagy                                                              | ↑       | ↓     |
| Type 1 interferon signaling                                            | ↓       | ↑     |
| **Other respiratory effects**                                          |         |       |
| Idiopathic pulmonary fibrosis (FVC% and TLC%)                          | ↑       | ↓     |
| Reporting of chest symptoms                                           | ↑       | ↓     |
| Rheumatoid arthritis-associated interstitial lung disease             | ↓       | ↑     |

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evidence that COPD may be overdiagnosed in women (due to incorrect disease diagnosis), particularly in those with an absence of smoking history (Golpe et al. 2017).

In addition to differences in susceptibility, COPD etiology also differs by sex with common parallel associations with smoking cigarettes or smoke exposure; women experience less emphysema and more small airway disease, increased prevalence of symptoms and triggering stimuli, higher risk of airflow obstruction, impaired quality of life, and increased comorbidities as compared to men (Barnes 2016; Amaral et al. 2017; Cote and Chapman 2009; Rodriguez-Gonzalez Moro et al. 2009). Females with COPD have also been shown to have a worse prognosis, with lung function reduction including changes in forced expiratory volume in 1 s (FEV1%predicted) and residual volume/total lung capacity (RV/%TLC), particularly after menopause, as well as higher risk of expiratory central airway collapse (Grabicki et al. 2019; Yang et al. 2018; Bhatt et al. 2016). Furthermore, it has been shown that females show higher rates of exacerbator and asthma-COPD overlap syndrome (ACOS) phenotypes, while males show higher rates of exacerbator with chronic bronchitis in some cohorts (Trigueros et al. 2019). Interestingly for the ACOS sex differences, the ACOS phenotype has been shown to be more common in biomass exposure groups, a smoke exposure which is globally more common in females than in males. Additionally, studies have found COPD to differ based upon which smoke an individual is exposed to; unique to women exposed to biomass smoke exposure, they found increased pigment deposition and fibrosis, thickened pulmonary arterial intima, but reduced emphysema (Rivera et al. 2008).

These differences are hypothesized to be due to the smaller airway size and thus larger dose of smoke exposure in females, as well as sex differences in metabolizing enzymes like cytochrome P450. Additional hypotheses include hormonal differences between males and females. Interestingly, despite differences in pathophysiology of the disease, recommendations for and response to treatment of COPD do not seem to differ between men and women. However, women are known to be underdiagnosed, especially early in the disease as compared to men, yet they have also been found to have more actively managed COPD than men, with increased use of triple therapy, maintenance treatment, smoking cessation support, and pneumococcal vaccination (Aberg et al. 2019). While the more active management of COPD

Table 10.3 (continued)

| Effects observed in studies with only one sex | Females | Males |
|---------------------------------------------|---------|-------|
| Wildfire, wood smoke, biomass               | COPD, asthma, reductions in lung function | Inflammation, general respiratory symptoms |

Table 10.3

| Condition                        | Females | Males |
|----------------------------------|---------|-------|
| Sustained maximal inspiratory pressure | ↑       | ↓     |
| Chronic airway obstruction       | ↑       | ↓     |
| Acquired pneumoconiosis (“particulate lung disease”) | ↑       | ↓     |
in women is encouraging, further awareness of sex differences and increasing burden of COPD in women is still needed to improve outcomes and care.

10.4.1.1 Mechanisms

Using a rodent model, the role of cigarette smoking and estrogen to mediate COPD etiology was explored (Tam et al. 2016). It was found that while traditional sex differences in COPD pathophysiology were observed, with increased emphysema in males and small airway disease in females, ovariectomy and tamoxifen (ESR1 antagonist) resulted in more male-like patterns in females. These findings strongly implicate a role of sex hormones, particularly estrogen in sex-biased COPD. Furthermore, in the same study, ESR1 activation was associated with the activation of TGF-B and Nrf2, as well as increased oxidative stress and decreased antioxidants and antioxidant regulators.

To better understand the role of the adaptive immune system in mediation of respiratory inflammation in COPD, a study of smokers, nonsmokers, and COPD patients was conducted (Forsslund et al. 2017). BAL and blood samples were analyzed for T-cell-related mediators and surface markers. They found elevated CCR5 on CD8+ T cells in BAL and CXCR3+ CD8+ T cells in blood in female smokers with COPD compared to those without, while CCR5 expression was lower in BAL T cells in male smokers with COPD compared to those without COPD. This study also linked Th1 mediator responses with BAL macrophage numbers and goblet cell density and Th2 mediator levels with emphysema in female smokers with COPD. The authors suggest that these sex-dependent T-cell responses which are smoke-dependent may provide insights into sex-specific mechanisms of disease manifestation in females.

Multiple studies have also identified sex differences in the proteome of COPD patients, particularly proteins related to immune cell function and oxidative stress. One study used two-dimensional difference gel electrophoresis for relative quantification of proteins and found a downregulation in lysosomal pathways and upregulation of oxidative stress pathways, particularly in females with COPD (Kohler et al. 2013). The authors hypothesize that this may link dysregulation of macroautophagy to female-dominated COPD phenotypes. This was further supported by a subsequent study where, using ex vivo proteomic profiling of lung immune cells, it was found that there was very low overlap in the proteomic differences between the sexes (Yang et al. 2018). It was also found that bronchoalveolar lavage cells showed increased alterations in proteins associated with both the dysregulation of the FcγR-mediated phagocytosis-lysosomal axis and increased oxidative stress, particularly in females with smoking-induced COPD. Furthermore, differences in actin cytoskeleton regulation, which is critical for phagocytosis, were also observed. These differences were correlated with increased levels of airway obstruction, disease severity, and emphysema. Together these data suggest that sex differences in affected phagocytosis-related pathways, which may permit increased bacterial colonization and risk of exacerbation, as well
as increased risk of oxidant formation which contributes to disease pathology, may mediate some sex biases in COPD manifestation. Furthermore, studies from the same group have also identified sex differences in the lipidome and the metabolome of individuals with COPD, with increases in linoleic acid-derived lipid mediators in female COPD patients compared to males (Balgoma et al. 2016) and enhanced metabolic dysregulation in females with COPD (Naz et al. 2017).

10.4.2 Lung Cancer

Cancer is a spectrum of disease resulting from the accumulation of genetic aberrations, including mutations (Xiao et al. 2016). Key “driver” mutations are thought to underlie the onset of the disease. Interestingly, smoke exposure, both cigarette and biomass, is known to induce genetic mutations and other aberrations like DNA adduction and epigenetic modifications and has been found to contribute to increased susceptibility to lung cancer, as well as other types of cancer (Blackford et al. 2009; Centers for Disease Control and Prevention 2010; de Oliveira Alves et al. 2017; Delgado et al. 2005). Cigarette smoke is a known carcinogen, and biomass smoke has been classified a probable carcinogen by the International Agency for Research on Cancer (IARC) (Sigsgaard et al. 2015).

Lung cancer is the most frequently diagnosed cancer and is the leading source of cancer-related mortality worldwide, particularly among men. For women, lung cancer is the third most frequently diagnosed cancer and second most frequent cause of cancer-related mortality. Incidence of lung cancer is also highly correlated with smoke exposure, particularly cigarette smoke and biomass smoke, which is hypothesized to contribute to the sex difference in incidence and mortality, where men are more likely to be diagnosed and die of cancer due to a higher prevalence of cigarette smoking, along with other factors (Sheng et al. 2018). A variety of epidemiological studies also suggest sex differences in susceptibility to smoke-induced lung cancer. For cigarette smoke, increased relative risk and odds ratios of lung cancer in cigarette smoking women were observed, along with incidence and earlier ages of diagnosis, despite lower smoking rates (reviewed in Haugen (2002)). However, there are a few studies which contradict these findings (reviewed in Haugen (2002)). In contrast, men were found to be more likely to develop of both lung cancer and COPD with cigarette smoking (Miao et al. 2018). In addition, there have also been sex differences observed in disease progression. For example, one study found that self-reported cough assessment using a visual analog scale in individuals with lung cancer was worse in females (Harle et al. 2019). The majority of the individuals in this study were also ever-smokers (current and former smokers).

For wildfire, wood smoke, and biomass, multiple studies investigating a variety of fuel types have also found associations, mostly with increased risk in women rather than men. For example, in a meta-analysis of solid fuel use, e.g., coal, Chinese females were at higher risk of developing lung cancer, likely due to higher use of coal in the household (Kurmi et al. 2012). Another meta-analysis found increased
risk of cancer development with household biomass use for cooking in both men and women but found higher risk estimates for women (Bruce et al. 2015).

10.4.2.1 Mechanisms

Many of the mechanistic studies investigating the causes of cancer focus on genetic aberrations, from mutations to epigenetic modifications; however, only a few studies have specifically investigated sex differences in mechanisms of cancer development and progression. Here we describe the few studies that have included sex as a factor in their analysis.

First a study of lung adenocarcinoma in a Chinese cohort found that male tumors harbor a greater burden of genetic alterations, including missense, frameshift, and synonymous gene mutations (Xiao et al. 2016). This greater burden of genetic alteration was also associated with worse overall survival. The authors suggest that mutation burden may explain some of the sex differences in cancer-related clinical outcomes, particularly in lung adenocarcinoma, but it is possible that this may also apply to other types of cancers. It is interesting to note that multivariate analysis found no difference between smokers and nonsmokers; however univariate analysis found an association between sex and smoking status, with males and smokers more likely to have higher mutation burden.

In a study of lung cancer patients, PAH-DNA adduct levels were used to measure the potential for development of lung cancer (Haugen 2002). Women were shown to have higher adduct levels, indicating a potential mechanism of increased susceptibility, despite lower cigarette smoking dose. This study also identified an essential PAH metabolizing enzyme as a critical factor, CYP1A1, which was increased in women. However, the mechanism behind increased CYP1A1 levels in women has not been identified. Again, hormonal regulation was hypothesized as a potential regulator due to previous studies indicating cross talk between estrogen receptor and the aryl hydrocarbon receptor signaling pathways, which are hypothesized to affect PAH metabolizing enzymes. Furthermore, the GSTM1 gene is suggested to be important in PAH detoxification and plays a critical role in phase II metabolism.

Other mechanisms that are hypothesized to play a role in cancer development, like variability in DNA repair and induction of cell proliferation by bombesin-like peptides, have very little information on potential for sex differences. The one study that has DNA repair potential has shown that women have lower DNA repair capacity than men, as measured using a host cell reactivation assay. Another study identified that the bombesin-like peptide, gastrin-releasing peptide, located on the X chromosome and expressed in airway cells, is expressed at a higher percentage in female smokers at lower smoking rates than males. Another mechanism that is proposed to contribute to cancer development is exposure to nicotine, which can promote cellular proliferation and tumor growth, migration, and invasion (Warren and Singh 2013). Interestingly, female sex and oral contraceptive use have been shown to alter nicotine metabolism, promoting increases in toxic nicotine metabolites; thus sex-specific xenometabolism likely contributes to increased susceptibility
to tobacco smoke-related disease (Yang et al. 2019). Finally, early in vitro work has also shown that female airway cell cultures exposed to cigarette smoke produce increased amounts of oxidants, identifying a potential driver of airway damage and lung disease onset, like cancer (Yang et al. 2019).

### 10.4.3 Asthma

Asthma is a heterogeneous lung disease affecting the lungs, with symptoms that vary in intensity over time. Hallmarks of asthma include chronic airway inflammation and variable expiratory airflow limitation. Interestingly, asthma is also a complex sex-biased disease, affecting primarily males before puberty and after menopause/andropause, while females are most affected during their reproductive years (Naeem and Silveyra 2019). These flips in susceptibility are thought to be primarily due to changes in the circulating hormonal milieu with life stage transitions, though careful characterization of the effects of hormones on asthmatic airway and immune cells has not been conducted at any life stage. Furthermore, asthma incidence and severity is also affected by environmental exposures, including cigarette smoke and biomass smoke (reviewed in Shah and Newcomb (2018)) (Holm et al. 2018; Stowell et al. 2019).

Asthma exacerbations have been positively associated with wildfire exposure in multiple studies, particularly when considering hospitalizations, emergency department visits, and outpatient visits specific to asthma exacerbations (reviewed in Reid and Maestas (2019)). Furthermore, wood smoke and biomass exposure have been associated with asthma-related symptoms like wheeze in children in epidemiological studies (Sigsgaard et al. 2015).

Other studies have also found a higher risk of asthma development in children after in utero exposure to tobacco smoke, though some studies also contradict this in utero finding (Neophytou et al. 2018; Strzelak et al. 2018; Buelo et al. 2018; Shah and Newcomb 2018; Duijts et al. 2012). Several studies have investigated potential mechanisms of asthma development related to cigarette smoke exposure and have found that increased risk of asthma development can be observed at even low doses of exposure. In these studies, exposure induced an oxidative stress imbalance and led to mucosal inflammation via increased production of inflammatory cytokines (Neophytou et al. 2018). Cellular effects have also been investigated, linking tobacco smoke exposure in particular to more permeable mucous membranes, the overproduction of airway mucus, reduced mucociliary clearance, proinflammatory signaling, and impaired recruitment of immune cells (Strzelak et al. 2018). In contrast, fewer studies have analyzed results by sex, but the few that have have demonstrated sex-specific effects of smoking cigarettes and biomass smoke exposure on asthma outcomes.

In a Swedish population study of individuals in their late 20s with asthma, it was found that long-standing cough and sputum production were more common in women (Selberg et al. 2019). Additionally, in the same cohort, a higher proportion
of women were current smokers, and current smokers more frequently had uncontrolled asthma, which is a finding that has previously been shown in Nordic countries. Women were also more likely to report healthcare visits due to asthma in the last 12 months, which is similarly associated with those with uncontrolled asthma. Interestingly in a study of children with asthma, boys have been identified as more predominantly affected by PM, which may include biomass smoke, as demonstrated by declines in FEV1 (Delfino et al. 2004). However, other studies have identified null findings or mixed effects in children (Liu et al. 2009).

Furthermore, studies that have investigated specific effects in women have identified positive associations of biomass exposure with asthma, including symptoms of wheeze and diagnosis of asthma (Qureshi 1994; Schei et al. 2004). Interestingly, some of these studies were completed in areas where women smoking is not culturally accepted; therefore effects are likely unique to biomass burning, rather than a mixture of cigarette smoking and exposure to biomass (Schei et al. 2004). Therefore, there are likely independent risk factors for biomass exposure and cigarette smoking, particularly in women.

In a few epidemiologic and cohort studies, the effects of hormones on asthma have been assessed (reviewed in Naeem and Silveyra (2019)). Prepuberty, boys experience a higher risk factor for asthma onset, symptoms, and exacerbations (reviewed in Shah and Newcomb (2018)). In a cohort of children of pre- and postpubertal age, lung function and symptom control were found to be beneficially affected by the presence of androgens, while estradiol was found to be weakly associated with decrements in those same measures, emphasizing the role of the onset of pubertal hormone levels in mediating the flip in asthma risk between boys and girls. Furthermore, with puberty, fluctuations in hormones during the menstrual cycle are associated with alterations of asthma symptoms in girls. Similarly, hormone fluctuations in women have also been associated with changes in asthma symptoms throughout the lifespan during traditional hormonal transitions, like pregnancy and menopause.

### 10.4.3.1 Mechanisms

Sex hormones have been linked to a substantial number of effects which are commonly found in asthma, such as airway immune cells and smooth muscle proliferation (estrogen affected), TH2-mediated airway inflammation (increased with estrogen and decreased with testosterone), regulation of lymphoid cell functional capacity (androgen mediated), and dendritic and alveolar macrophage number and function (increased in females and decreased in males), using translational models (reviewed in Naeem and Silveyra (2019)). An additional study also implicated progesterone as potential hormone with connections to allergic airway inflammation (Lux et al. 2009). In this study, exogenous progesterone increased allergic respiratory pathway inflammation and increased airway hyperresponsiveness as well as the presence of eosinophils in the airway. In an additional study, tobacco smoke was shown to interact with progesterone in a mouse model, implicating a potential
interaction between smoke exposure and progesterone action to induce increased allergic airway inflammation-related disease.

Reinforcing the critical role of sex hormones in mediating sex biases in asthma in children, a study of 187 children which carefully controlled for Tanner stage, hormone levels, lung function, and asthma symptoms, found that higher dehydroepiandrosterone sulfate (DHEA-S) levels in male children was positively associated with FEV1% and FVC%. However, estradiol was negatively associated with the same measures in females (DeBoer et al. 2018). In an adult clinical study, increases in testosterone were associated with increased FEV1 and FVC in males. In another adult study, type 2 innate lymphoid cells (ILC2s) were increased in females with asthma as compared to males. Supporting this finding, testosterone in mice was shown to lower the number of ILC2s (Shah and Newcomb 2018).

Those studies that have focused on the potential for smoke exposure to induce sex differences in asthma have mostly used translational models, with in utero exposure to tobacco smoke as a proxy for inducing later-life chronic lung disease like asthma. One study identified insulin-like growth factor (IGF1) as a target within the developing lung altered by in utero cigarette smoke in both a human cohort study and using a murine model (Dehmel et al. 2018). In particular, IGF1 was increased in exposed female offspring and prenatally exposed children. Alteration of IGF1, which is important for lung development, is suggested to be a potential mechanism by which cigarette smoke impairs later-life lung function and susceptibility to disease development like asthma. Another study supports the potential involvement of the IGF family in altered lung development, showing sex-specific methylation and mRNA levels within the Igf lung axis in mice (Meyer et al. 2017). Specifically, Igf1r, the Igf1 receptor gene, was hypomethylated in female offspring who were exposed in utero to cigarette smoke. This methylation reduction was also associated with reduced body weight in female offspring. These authors additionally note that prenatal smoke exposure is also associated with COPD; therefore these changes could additionally affect the development of later-life disease in addition to asthma.

Further studies implicate homeostatic mesenchymal peroxisome proliferator-activated receptor γ (PPARγ) as a contributor to the development of asthma after in utero exposure to tobacco products, specifically including nicotine (Liu et al. 2013). The parent study indicates that PPARγ is downregulated after in utero nicotine exposure. A second study from the same group showed that perinatal nicotine exposure induced increases in airway resistance and decreased airway compliance in offspring of both sexes, but these changes were more prominent in male offspring. Further, only males exposed to nicotine perinatally had altered acetylcholine-induced tracheal constriction. Treatment with a PPARγ agonist concomitantly with nicotine exposure normalized these effects (Liu et al. 2013). Together these effects implicate a potential role of PPARγ in chronic lung effects, including asthma, induced by in utero nicotine exposure.

In a larger study of the link between environmental exposures, sex, and asthma, quantitative trait loci (QTL) mapping was completed in a Hutterite population, which has relatively homogenous ancestry, little independent chromosome segregation, and a communal lifestyle which reduces variability in environmental exposures.
This study found eight asthma-associated quantitative traits, of which 50% were sex-specific, including those associated with IgE, lymphocytes, FEV1/FVC, and FVC. The authors suggest that these findings demonstrate that sex interacts with genotype as well as environmental factors to determine risk of lung disease, including asthma.

While these mechanistic studies begin to address the potential for sex and environmental exposure to influence asthma outcomes, more work especially is needed on mechanistic frameworks, direct testing of sex-specific asthma outcomes and exposure in clinical and translational models, and associations in larger cohort studies.

### 10.4.4 E-Cigarette- and Vaping-Associated Lung Injury (EVALI)

EVALI is a recent disease that has only manifested with the introduction of e-cigarettes to the global market. E-cigarettes are devices that heat solutions of humectants, flavorings, and nicotine to produce an aerosol, which is inhaled. Interestingly, cases of EVALI have been fairly limited in countries outside of the United States, though cases have been identified in countries including but not limited to the United Kingdom, Canada, Guam, and Japan. The disease is manifested with severe lung injury and associated with a variety of symptoms including fever and chills, cough, gastrointestinal issues, and chest pain. The disease is diagnosed via process of elimination and the use of e-cigarette products. The cause of the disease is linked to e-cigarettes, primarily those containing vitamin E acetate (common in tetrahydrocannabinol- (THC) containing products), though other components of e-cigarettes are also being investigated as contributors to the sudden onslaught of EVALI cases. Interestingly, in multiple case studies and series, it has been demonstrated that the majority of EVALI cases occur in males (approximately 70% of cases) and that death rates are higher in males (59%) (Perrine et al. 2019; Moritz et al. 2019). The cause of this sex difference in disease occurrence has not yet been defined biologically, though many point to higher use rates of e-cigarettes in males and increased risk-taking behavior in teen and young adult males, thus potentially more likely to use black market products, products of unknown origin, or additives, as a potential explanation for the substantial sex difference in number of cases.

#### 10.4.4.1 Mechanisms

Mechanisms of this disease are still unknown and only have been roughly associated with the inclusion of vitamin E acetate in e-cigarette products, especially those containing THC based on the type of product in use when individuals with EVALI were clinically diagnosed (Blount et al. 2020).
10.4.5 Viral Infection

Viral infections contribute to four million deaths per year worldwide (Ferkol and Schraufnagel 2014). The respiratory tract is an ideal target of infection for viruses including coronaviruses, rhinoviruses, and influenza viruses, where they are inhaled or directly come into contact with mucosal surfaces in the airway (reviewed in Subbarao and Mahanty (2020)). These viruses target the epithelial cells as a point of infection and enter after interaction with surface receptors and enzymes. They then utilize the infected cell’s machinery to replicate and are then shed by coughing or sneezing. Host cells produce proinflammatory cytokines and type 1 interferons in response to being infected, which recruits a larger immune response to the infected area and begins processes to control or eliminate the infection like apoptosis. However, viruses readily adapt and evolve specialized functions which can impair typical antiviral host defense responses like the production of type 1 interferons. Followed by the initial innate immune response, the adaptive immune system works to directly kill virus infected cells, control inflammation, repair tissue, as well as induce immune memory. Many of the components of viral infection from entry into the host cell to the cleanup of viral infection-induced damage are thought to be impacted by environmental toxicant exposures. Globally, 42% of lower and 24% of upper respiratory infections have been attributed to environmental exposures (Prüss-Üstün et al. 2016).

Smoke exposure, particularly cigarette smoke (both active and passive), has been shown to enhance viral-induced inflammation and impair immune host defense, specifically through type 1 interferon pathways, though complete mechanisms and determining whether greater risk of infection is causally linked to susceptibility, delayed pathogen clearance, or exaggerated inflammatory responses are still under investigation (Bauer et al. 2013). Additionally, cigarette smoke has also been shown to increase risk of some bacterial infections, like pneumonia and tuberculosis (Greenhalgh et al. 2020). Specific mechanistic investigations in rodent, in vitro, and limited clinical studies have found that cigarette smoke induces increased permeability of epithelial cells, impaired ciliary function, increased viral titers, suppression of type I and type II interferon responses, decrease in immune defense proteins in the airway (IL-6 and intelectin 1), and exacerbated inflammatory responses (hypothesized to be mediated by altered IL-1α signaling and/or danger-associated molecular patterns (DAMPs)) (reviewed in Bauer et al. (2013) and Greenhalgh et al. (2020)). Studies have also shown impairment of immune cell function due to cigarette smoke exposure including neutrophils, macrophages, natural killer cells, and lymphocytes, as well as decrements in antibody responses (Greenhalgh et al. 2020).

A substantial literature indicates that there are also sex differences in response to viral infection including morbidity, mortality, and viral load (Klein and Flanagan 2016; Morgan and Klein 2019; vom Steeg and Klein 2016; Ghosh and Klein 2017). Viruses that have been shown to affect males and females differently include HIV, coronavirus, and influenza (Greenhalgh et al. 2020). Additionally, emerging
evidence, described below, suggests that these sex differences can also be modified by smoke exposure (both tobacco smoke and environmental smoke); however there are limited epidemiological studies associating these interactions directly.

10.4.5.1 Mechanisms

A meta-analysis of public gene expression data sets of human airway epithelium in smokers and nonsmokers found substantial differential gene expression due to smoking status (5000+ genes), sex (100 genes), and their interaction (2600+ genes), which were independent of differences in age or pack-year history in the discovery and replication data sets (Yang et al. 2019). The chromosomes linked to gene expression differences were not limited to sex chromosomes. In fact, the majority of genes were differentially expressed on autosomes. Using a network analysis to better understand potential functional differences related to changes in gene expression, it was found that the networks were enriched for genes related to autophagy, response to virus, and type 1 interferon signaling. Autophagy was upregulated in female smokers, while viral response and type 1 interferon signaling were downregulated in female smokers as compared to males, suggesting that cigarette smoking can indeed interact with sex to influence critical antiviral pathways like type 1 interferon. Interestingly, in an enrichment analysis for transcription factor binding sites, it was found that estrogen-related receptor alpha, ESRRA, was enriched in the autophagy module. The authors indicate that this enrichment may suggest that biological differences in responses to smoking are not limited to differences in circulating hormones but may also have a genetic component. These data affirm previous findings that cigarette smoke has a large effect on respiratory gene expression. These data also demonstrate that smoking-induced respiratory effects are modified by the sex of the individual. This study was a substantial first step in understanding sex-specific effects on the respiratory transcriptome, which has not been previously investigated in other large transcriptome analyses exploring sex differences in human organs, as well as supporting interactions of sex and smoke exposure to influence viral infection. This meta-analysis is also supported by an in vitro study where estrogenic compounds on female-derived nasal cells reduced influenza virus replication but did not do the same in males (Peretz et al. 2016). Similarly, estradiol was also found to be protective against influenza A pathogenesis by suppressing inflammatory responses in females (Robinson et al. 2011).

Another example from 2019 to 2020 includes viral infection with pandemic strain of severe acute respiratory syndrome coronavirus 2 (SARs-CoV-2) and development of coronavirus disease 2019 (COVID-19). This disease has been shown to primarily increase morbidity and mortality in males, and epidemiological data from several of the pandemic epicenters demonstrate that disease susceptibility is increased with smoke exposure, such as the use of tobacco products, particularly cigarettes, and air pollution which includes PM derived from wood and biomass sources (Majdic 2020; Adhikari and Yin 2020). However, the potential for cigarette smoke and air pollution to increase disease susceptibility is still debated, and variable associations have been
found, depending on the cohort (Majdic 2020; Leung and Sin 2020; Adhikari and Yin 2020). While there is not yet significant information on the mechanisms of these susceptibilities, it has been shown that cigarette smoking can increase expression of the cell surface enzyme responsible for viral entry in the airways, the angiotensin-converting enzyme 2 (ACE2) (Leung et al. 2020). Furthermore, it has been shown that expression is higher in older individuals, which may explain the lower morbidity and mortality rates shown in children and suspected lower levels of infection (Patel and Verma 2020). While sex differences in ACE2 expression in lung tissue have not yet been evaluated, there are several studies that suggest a role in the sex specificity of COVID-19 morbidity and mortality. First, estrogen has been observed to play protective roles in SARS by activating immune responses and suppressing viral replication (Gagliardi et al. 2020). The role of ACE2 in mediating these sex differences can be further suggested by its location on the X chromosome. However, murine studies have contrastingly shown that sex chromosome dose does not affect ACE2 activity, though this conclusion should be interpreted carefully as these studies were conducted in the kidneys, an organ where ACE2 has been more readily studied, but may not accurately reflect ACE2 activity regulation in other organs, like the lung (Gagliardi et al. 2020; Liu et al. 2010). The same murine study found that ACE2 activity was dependent upon circulating estrogen levels, but not testosterone (Liu et al. 2010).

There is also evidence of sex and smoke exposure interaction to induce compromised responses to infection when considering wood, wildfire, and biomass smoke, although the understanding of mechanisms is less well studied than with cigarette smoke exposure. Epidemiologic studies suggest that wildfire, wood smoke, and biomass smoke exposures are associated with an increased risk of respiratory infection and reduced lung function (Fullerton et al. 2011; Garcia-Sancho et al. 2009; Mishra 2003; Oloyede et al. 2013; Opotowsky et al. 2008; Perez-Padilla et al. 2001). Controlled exposure studies of acute effects of wood smoke have also shown evidence of the role of smoke exposure and respiratory dysfunction, increased BAL glutathione, respiratory symptoms, and systemic and respiratory inflammation in clinical studies (Rebuli et al. 2018). Mechanistically, these effects are linked by a recent controlled exposure study, which contributed the first evidence of the interaction of wood smoke and sex in response to a model of influenza infection (Rebuli et al. 2018). This study found that in addition to baseline differences in respiratory gene expression between the sexes, males and females responded differently to wood smoke exposure in the context of a viral infection. It showed increased inflammatory gene expression and protein production in males, while there was more mild suppression of host defense responses in females after exposure, which agrees with the above described meta-analysis of gene expression in respiratory tissue. This study was a particularly important advance in understanding the biological underpinnings of epidemiologically associated sex differences with wood smoke exposure as previous controlled studies had only found few or limited effects. It is suggested that the previous lack of findings in controlled exposure studies was due to analysis of data in aggregate and that effects in opposite directions in males and females may have contributed to an
observational effect neutralization. Early exposure to wildfire smoke has been shown to result in sex-specific alteration of immune response to infection by attenuating systemic TLR responses (Black et al. 2017). Indoor biomass smoke exposure has been associated with increased risk for infection and morbidity, especially in children (Smith et al. 2000; Ezzati and Kammen 2001).

10.4.6 Other Respiratory Effects

Other substantial respiratory outcomes are also associated with smoke exposure, though evidence is more limited. For example, percent of predicted forced vital capacity (FVC%) and percent of predicted total lung capacity (TLC%) were lower in males compared to females in a study of idiopathic pulmonary fibrosis (IPF) in Sweden (Kalafatis et al. 2019). When smoking history was considered, male ex-smokers showed lower FVC%, TLC%, and percent of predicted diffusing capacity for carbon monoxide (DLCO%), compared to female ex-smokers. However, in IPF, asthma was increased in never-smoker females as compared to males. Females were also more likely to report chest symptoms. This study suggests that cigarette smoking and sex are both factors in disease outcomes. Furthermore, an association with male sex and cigarette smoking has been identified as contributors to increased risk of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) and decrements in sustained maximal inspiratory pressure in another study (Formiga et al. 2018; Salaff et al. 2019). Additionally, chronic airway obstruction (CAO), a characteristic of both COPD and chronic asthma, was assessed in three Nordic countries, and it was found that for only female participants, there was a difference in prevalence in CAO where lower prevalence seemed to be associated with lower smoking rates, while no difference was seen in males. For biomass smoke exposure, additional disease states, such as acquired pneumoconiosis or “particulate lung disease,” have been described, mostly affecting women (Torres-Duque et al. 2008).

10.5 Conclusions

There is overwhelming epidemiologic evidence of sex bias in a variety of respiratory diseases, many of which have been linked to environmental smoke exposure. Generally, this chapter indicates that females may be more susceptible to COPD and asthma after smoke exposure, while males are more susceptible to lung cancer, EVALI, and viral infection. However, mechanistic research into the origins of these sex differences in disease susceptibility is only beginning. There is early work that suggests roles for circulating estrogen and estrogen receptors in mediating some female-specific susceptibility to smoke-induced respiratory disease, which begins to address this issue. However, there is also early research suggesting baseline sex differences in gene expression, xenobiotic metabolism pathways, and ability to
mediate smoke-induced genetic mutations and epigenetic alterations which may also contribute to sex-biased smoke-induced disease development, response, progression, and mortality. This work demonstrates that hypotheses in addition to those on the role of sex hormones also need to be investigated further. Overall, this substantial evidence of sex biases in smoke-related respiratory disease indicates that more sex-specific research is needed to effectively prevent, treat, and manage smoke-induced disease, particularly in women, who have so often been neglected in the development of treatment and preventative strategies. This work also suggests the need to address sex in regulatory evaluations of exposure and safety limits to protect those most susceptible, rather than the aggregate general population.

10.6 Future Directions

While intensive study on the mechanisms behind the development of chronic lung diseases like COPD and lung cancer has taken place, there is still a paucity of information on the potential role of sex in differentiating disease onset, pathophysiology, and progression, as the majority of previous research has been completed in males or on both males and females in aggregate. Therefore, there is still a critical need for mechanistic experiments investigating sex differences. A common theme is the lack of study of the role of circulating sex hormones on the susceptibility, initiation, promotion, and progression of disease, despite it being a commonly hypothesized mechanism explaining the sex differences observed. While circulating sex hormones are an obvious hypothesized influence on these factors, others should be considered, such as sex differences in receptor expression and localization established during development and the role of X and Y chromosome genes critical to the regulation of cellular response pathways. Furthermore, there is an additional complexity to consider with environmental exposures, which are interactive effects of sex and exposure on respiratory health. While these interactions are beginning to be explored in controlled exposure studies (Rebuli et al. 2018, 2019), there are still many more inhaled toxicant exposures to be considered and validated and many more subpopulations to explore. Additionally, a substantial number of studies are either only including one sex (Du et al. 2019) or reporting inclusion of both males and females and only analyzing in aggregate or adjusting for sex as a factor (Obiebi and Oyibo 2019; Hu et al. 2018; Guevara-Rattray et al. 2017). Therefore, there is still a critical need to analyze using sex as a biological variable and disaggregating data by sex to better understand sex differences in the effects of smoke exposure on respiratory health. Finally, to facilitate data transparency, rigor, and reproducibility, previously generated data and future data need to be available to the research community; therefore, uploading to data repositories is highly suggested. Overall, the study of sex differences in the respiratory toxicology field is just beginning, with many open questions waiting to be answered which can ultimately improve public health by identifying susceptible groups and targets for smoke exposure-induced disease prevention and treatment.
References

Aberg J, Hasselgren M, Montgomery S, Lisspers K, Stallberg B, Janson C, Sundh J (2019) Sex-related differences in management of Swedish patients with a clinical diagnosis of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 14:961–969. https://doi.org/10.2147/COPD.S193311

Adetona O, Reinhardt TE, Domitrovich J, Broyles G, Adetona AM, Kleinman MT, Ottmar RD, Naeher LP (2016) Review of the health effects of wildland fire smoke on wildland firefighters and the public. Inhal Toxicol 28(3):95–139. https://doi.org/10.3109/08958378.2016.1145771

Adhikari A, Yin J (2020) Short-term effects of ambient ozone, PM2.5, and meteorological factors on COVID-19 confirmed cases and deaths in Queens, New York. Int J Environ Res Public Health 17(10):4047. https://doi.org/10.3390/ijerph17114047

Agency for Toxic Substances and Disease Registry (ATSDR) (2007) Toxicological profile for Benzene. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA

Agency for Toxic Substances and Disease Registry (ATSDR) (2010) Addendum to the toxicological profile for formaldehyde. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA

Amaral AFS, Strachan DP, Burney PGJ, Jarvis DL (2017) Female smokers are at greater risk of airflow obstruction than male smokers. UK Biobank. Am J Respir Crit Care Med 195(9):1226–1235. https://doi.org/10.1164/rccm.201608-1545OC

Balgoma D, Yang M, Sjodin M, Snowden S, Karimi R, Levanen B, Merikallio H, Kaarteenaho R, Palmberg L, Larsson K, Erle DJ, Dahlen SE, Dahlen B, Skold CM, Wheelock AM, Wheelock CE (2016) Linoleic acid-derived lipid mediators increase in a female-dominated subphenotype of COPD. Eur Respir J 47(6):1645–1656. https://doi.org/10.1183/13993003.01080-2015

Barnes PJ (2016) Sex differences in chronic obstructive Pulmonary disease mechanisms. Am J Respir Crit Care Med 193(8):813–814. https://doi.org/10.1164/rccm.201512-2379ED

Barrington-Trimis JL, Urman R, Leventhal AM, Gauderman WJ, Cruz TB, Gilreath TD, Howland S, Unger JB, Berhane K, Samet JM, McConnell R (2016) E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. Pediatrics 138(2):e20153983. https://doi.org/10.1542/peds.2015-3983

Bauer CMT, Morissette MC, Stampfl MR (2013) The influence of cigarette smoking on viral infections: translating bench science to impact COPD pathogenesis and acute exacerbations of COPD clinically. Chest 143(1):196–206. https://doi.org/10.1378/chest.12-0930

Bell ML, Son JY, Peng RD, Wang Y, Dominici F (2015) Ambient PM2.5 and risk of hospital admissions: do risks differ for Men and women? Epidemiology 26(4):575–579. https://doi.org/10.1097/EDE.0000000000000310

Bhatt SP, Terry NL, Nath H, Zach JA, Tschirren J, Bolding MS, Stinson DS, Wilson CG, Curran-Everett D, Lynch DA, Putcha N, Soler X, Wise RA, Washko GR, Hoffman EA, Foreman MG, Dransfield MT, Genetic Epidemiology of CI (2016) Association between expiratory central airway collapse and respiratory outcomes among smokers. JAMA 315(5):498–505. https://doi.org/10.1001/jama.2015.19431

Black C, Gerriets JE, Fontaine HJ, Harper RW, Kenyon NJ, Tablin F, Schelegle ES, Miller LA (2017) Early life wildfire smoke exposure is associated with immune Dysregulation and Lung function decrements in adolescence. Am J Respir Cell Mol Biol 56(5):657–666. https://doi.org/10.1165/rcmb.2016-0380OC

Blackford A, Parmigiani G, Kensler TW, Wolfgang C, Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Eshleman JR, Goggins M, Jaffe EM, Iacobuzio-Donahue CA, Maitra A, Klein A, Cameron JL, Ollin R, Schulick R, Winter J, Vogelstein B, Velculescu VE, Kinzler KW, Hruban RH (2009) Genetic mutations associated with cigarette smoking in pancreatic cancer. Cancer Res 69(8):3681–3688. https://doi.org/10.1158/0008-5472.CAN-09-0015

Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentim-Blasini L, Gardner M, Braselton M, Brosius CR, Caron KT, Chambers D, Corstvet J, Cowan E, De Jesus VR, Espinosa P, Fernandez C, Holder C, Kuklenyik Z, Kusovschi JD, Newman C, Reis GB,
Rees J, Reese C, Silva L, Seyler T, Song MA, Sosnoff C, Spitzer CR, Tevis D, Wang L, Watson C, Wewers MD, Xia B, Heitkemper DT, Ghinai I, Layden J, Briss P, King BA, Delaney LJ, Jones CM, Baldwin GT, Patel A, Meaney-Delman D, Rose D, Krishnasamy V, Barr JR, Thomas J, Pirkle JL, Lung Injury Response Laboratory Working G (2020) Vitamin E acetate in Bronchoalveolar-lavage fluid associated with EVALI. N Engl J Med 382(8):697–705. https://doi.org/10.1056/NEJMoa1916433

Bruce N, Dherani M, Liu R, Hosgood HD 3rd, Sapkota A, Smith KR, Straif K, Lan Q, Pope D (2015) Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study. Thorax 70(5):435–441. https://doi.org/10.1136/thoraxjnl-2014-206625

Buelo A, McLean S, Julious S, Flores-Kim J, Bush A, Henderson J, Paton JY, Sheikh A, Shields M, Pinnock H, Group ARC (2018) At-risk children with asthma (ARC): a systematic review. Thorax 73(9):813–824. https://doi.org/10.1136/thoraxjnl-2017-210939

Capistrano SJ, van Reyk D, Chen H, Oliver BG (2017) Evidence of biomass smoke exposure as a causative factor for the development of COPD. Toxics 5(4):36. https://doi.org/10.3390/toxics5040036

Centers for Disease Control and Prevention, National Center for Chronic Disease P, Health P, Office on S, Health (2010) Publications and reports of the surgeon general. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the surgeon general. Centers for Disease Control and Prevention (US), Atlanta (GA)

Centers for Disease Control and Prevention (2002) Women and smoking: a report of the surgeon general. executive summary. MMWR Morb Mortal Wkly Rep 51(Rr-12):1–13

Centers for Disease Control and Prevention (2010) How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the surgeon general. Centers for Disease Control and Prevention, Atlanta (GA)

Chou CHSJ, World Health O, International Programme on Chemical S (2003) Hydrogen sulfide: human health aspects. World Health Organization, Geneva

Cote CG, Chapman KR (2009) Diagnosis and treatment considerations for women with COPD. Int J Clin Pract 63(3):486–493. https://doi.org/10.1111/j.1742-1241.2008.01987.x

Croft DP, Cameron SJ, Morrell CN, Lowenstein CJ, Ling F, Zareba W, Hopke PK, Utell MJ, Thurston SW, Thevenet-Morrison K, Evans KA, Chalupa D, Rich DQ (2017) Associations between ambient wood smoke and other particulate pollutants and biomarkers of systemic inflammation, coagulation and thrombosis in cardiac patients. Environ Res 154:352–361. https://doi.org/10.1016/j.envres.2017.01.027

de Oliveira Alves N, Vessoni AT, Quinet A, Fortunato RS, Kajitani GS, Peixoto MS, Hacon SS, Artaxo P, Saldiva P, Menck CFM, Batistuzzo de Medeiros SR (2017) Biomass burning in the Amazon region causes DNA damage and cell death in human lung cells. Scirep 7(1):10937. https://doi.org/10.3390/scientific7010024

DeBoer MD, Phillips BR, Mauger DT, Zein J, Erzurum SC, Fitzpatrick AM, Gaston BM, Myers R, Ross KR, Chmiel J, Lee MJ, Fahy JV, Peters M, Ly NP, Wenzel SE, Fajt ML, Holguin F, Moore WC, Peters SP, Meyers D, Bleeker ER, Castro M, Coverstone AM, Bacharier LB, Jarjour NN, Sorkness RL, Ramratnam S, Irani AM, Israel E, Levy B, Phipatanakul W, Gaffin JM, Gerald Teague W (2018) Effects of endogenous sex hormones on lung function and symptom control in adolescents with asthma. BMC Pulm Med 18(1):58. https://doi.org/10.1186/s12890-018-0612-x

Dehmel S, Nathan P, Bartel S, El-Merhie N, Scherb H, Milger K, John-Schuster G, Yildirim AO, Hylkema M, Irmler M, Beckers J, Schaub B, Eickelberg O, Krauss-Etschmann S (2018) Intratracheal smoke exposure deregulates lung function, pulmonary transcriptomes, and in particular insulin-like growth factor (IGF)-1 in a sex-specific manner. Scirep 8(1):7547. https://doi.org/10.3390/scientific80102576

Delfino RJ, Quintana PJ, Flore J, Gastanaga VM, Samimi BS, Kleinman MT, Liu LJ, Bufalino C, Wu CF, McLaren CE (2004) Association of FEV1 in asthmatic children with personal and
microenvironmental exposure to airborne particulate matter. Environ Health Perspect 112 (8):932–941. https://doi.org/10.1289/ehp.6815

Delgado J, Martinez LM, Sanchez TT, Ramirez A, Iturria C, Gonzalez-Avila G (2005) Lung cancer pathogenesis associated with wood smoke exposure. Chest 128(1):124–131. https://doi.org/10.1378/chest.128.1.124

Dominelli PB, Ripoll JG, Cross TJ, Baker SE, Wiggins CC, Welch BT, Joyner MJ (2018) Sex differences in large conducting airway anatomy. J Appl Physiol (1985) 125(3):960–965. https://doi.org/10.1152/japplphysiol.00440.2018

Du X, Yuan L, Wu M, Men M, He R, Wang L, Wu S, Xiang Y, Qu X, Liu H, Qin X, Hu C, Qin L, Liu C (2019) Variable DNA methylation of aging-related genes is associated with male COPD. Respir Res 20(1):243. https://doi.org/10.1186/s12931-019-1215-7

Duijs L, Jaddoe VVW, van der Valk RJP, Henderson JA, Hofman A, Raat H, Steegers EAP, Moll HA, de Jongste JC (2012) Fetal exposure to maternal and paternal smoking and the risks of wheezing in preschool children: the generation R Study. Chest 141(4):876–885. https://doi.org/10.1378/chest.11-0112

Dwivedi AM, Johanson G, Lorentzen JC, Pulmberg L, Sjögren B, Ernstgård L (2015) Acute effects of acrolein in human volunteers during controlled exposure. Inhal Toxicol 27(14):810–821. https://doi.org/10.3109/08958378.2015.1115567

Ekstrom M, Sundh J, Schioler L, Lindberg E, Rosengren A, Bergstrom G, Angeras O, Hedner J, Brandberg J, Bake B, Toren K (2018) Absolute lung size and the sex difference in breathlessness in the general population. PLoS One 13(1):e0190876. https://doi.org/10.1371/journal.pone.0190876

Ernstgard L, Gullstrand E, Lof A, Johanson G (2002) Are women more sensitive than men to 2-propanol and m-xylene vapours? Occup Environ Med 59(11):759–767. https://doi.org/10.1136/oem.59.11.759

Ernstgård L, Sjögren B, Warholm M, Johanson G (2003) Sex differences in the toxicokinetics of inhaled solvent vapors in humans 1. M-xylene. Toxicol Appl Pharmacol 193(2):147–157. https://doi.org/10.1016/j.taap.2003.08.004

Ernstgard L, Shibata E, Johanson G (2005) Uptake and disposition of inhaled methanol vapor in humans. Toxicol Sci 88(1):30–38. https://doi.org/10.1093/toxsci/kf281

Ezzati M, Kammen D (2001) Indoor air pollution from biomass combustion and acute respiratory infections in Kenya: an exposure-response study. Lancet 358(9282):619–624

Ferkol T, Schraufnagel D (2014) The global burden of respiratory disease. Ann Am Thorac Soc 11(3):404–406. https://doi.org/10.1513/AnnalsATS.201311-405PS

Formiga MF, Campos MA, Cahalin LP (2018) Inspiratory muscle performance of former smokers and nonsmokers using the test of incremental respiratory endurance. Respir Care 63(1):86–91. https://doi.org/10.4187/respcare.05716

Forsslund H, Yang M, Mikko M, Karimi R, Nyren S, Engvall B, Grunewald J, Merikallio H, Kaarteenaho R, Wahlstrom J, Wheelock AM, Skold CM (2017) Gender differences in the T-cell profiles of the airways in COPD patients associated with clinical phenotypes. Int J Chron Obstruct Pulmon Dis 12:35–48. https://doi.org/10.2147/COPD.S113625

Fullerton DG, Suseno A, Semple S, Kalambo F, Malamba R, White S, Jack S, Calverley PM, Gordon SB (2011) Wood smoke exposure, poverty and impaired lung function in Malawian adults. Int J Tuberc Lung Dis 15(3):391–398

Gagliardi MC, Tieri P, Ortona E, Ruggieri A (2020) ACE2 expression and sex disparity in COVID-19. Cell Death Dis 6:37. https://doi.org/10.1038/s41420-020-0276-1

Garcia-Sanchez MC, Garcia-Garcia L, Baez-Saldana R, Ponce-De-Leon A, Sifuentes-Osorio J, Bobadilla-Del-valle M, Ferreyra-Reyes L, Cano-Arellano B, Canizales-Quintero S, Palacios-Merino Ldel C, Juarez-Sandino L, Ferreira-Guerrero E, Cruz-Hervert LP, Small PM, Perez-Padilla JR (2009) Indoor pollution as an occupational risk factor for tuberculosis among women: a population-based, gender oriented, case-control study in southern Mexico. Rev Investig Clin 61(5):392–398
Ghosh S, Klein RS (2017) Sex drives dimorphic immune responses to viral infections. J Immunol 198(5):1782–1790. https://doi.org/10.4049/jimmunol.1601166

Giri S, Rogne T, Uleberg O, Skovlund E, Shrestha SK, Koju R, Damas JK, Solligard E, Risnes KR (2019) Presenting complaints and mortality in a cohort of 22 000 adult emergency patients at a local hospital in Nepal. J Glob Health 9(2):020403. https://doi.org/10.7189/jogh.09.020403

Golpe R, Diaz-Fernandez M, Mengual-Macenlle N, Sanjuan-Lopez P, Martin-Robles I, Cano-Jimenez E (2017) Over-diagnosis of chronic obstructive pulmonary disease in primary care prevalence and determining factors. SEMERGEN 43(8):557–564. https://doi.org/10.1016/j.semerg.2016.11.006

Grabicki M, Kuznar-Kaminska B, Rubinsztajn R, Brajer-Luftmann B, Kosacka M, Nowicka A, Piorunek T, Kostrzewska M, Chazan R, Batura-Gabryel H (2019) COPD course and comorbidities: are there gender differences? Exp Med Biol 1113:43–51. https://doi.org/10.1007/5584_2018_160

Greenhalgh E, Scollon M, Winstanley M (2020) Tobacco in Australia: facts and issues. Available from www.TobaccoInAustralia.org.au

Guevara-Rattray EM, Garden FL, James AL, Wood-Baker R, Abramson MJ, Johns DP, Sonia Buist A, Burney PGJ, Haydn Walters E, Toelle BG, Marks GB (2017) Atopy in people aged 40 and over: relation to airflow limitation. Clin Exp Allergy 47(12):1625–1630. https://doi.org/10.1111/cea.13038

Harle ASM, Blackhall FH, Molassiotis A, Yorke J, Dockry R, Holt KJ, Yuill D, Baker K, Smith JA (2019) Cough in patients with lung cancer: a longitudinal observational study of characterization and clinical associations. Chest 155(1):103–113. https://doi.org/10.1016/j.chest.2018.10.003

Haugen A (2002) Women who smoke: are women more susceptible to tobacco-induced lung cancer? Carcinogenesis 23(2):227–229. https://doi.org/10.1093/carcin/23.2.227

Holm SM, Balmes J, Gillette D, Hartin K, Seto E, Lindeman D, Polanco D, Fong E (2018) Cooking behaviors are related to household particulate matter exposure in children with asthma in the urban East Bay Area of northern California. PLoS One 13(6):e0197199. https://doi.org/10.1371/journal.pone.0197199

Hu YH, Liang ZY, Xu LM, Xu WH, Liao H, Li R, Wang K, Xu Y, Ou CQ, Chen X (2018) Comparison of the clinical characteristics and comprehensive assessments of the 2011 and 2017 GOLD classifications for patients with COPD in China. Int J Chron Obstruct Pulmon Dis 13:3011–3019. https://doi.org/10.2147/COPD.S174668

Kalafatis D, Gao J, Pesonen I, Carlson L, Skold CM, Ferrara G (2019) Gender differences at presentation of idiopathic pulmonary fibrosis in Sweden. BMC Pulm Med 19(1):222. https://doi.org/10.1186/s12890-019-0994-4

Kim YH, Warren SH, Krantz QT, King C, Jaskot R, Preston WT, George BJ, Hays MD, Landis MS, Higuchi M, DeMarini DM, Gilmour MI (2018) Mutagenicity and Lung toxicity of smoldering vs. flaming emissions from various biomass fuels: implications for Health effects from Wildland fires. Environ Health Perspect 126(1):017011. https://doi.org/10.1289/EHP220

Kim YH, King C, Krantz T, Hargrove MM, George IJ, McGee J, Copeland L, Hays MD, Landis MS, Higuchi M, Gavett SH, Gilmour MI (2019) The role of fuel type and combustion phase on the toxicity of biomass smoke following inhalation exposure in mice. Arch Toxicol 93 (6):1501–1513. https://doi.org/10.1007/s00204-019-02450-5

Klein SL, Flanagan KL. (2016) Sex differences in immune responses. Nat Rev Immunol 16 (10):626–638. https://doi.org/10.1038/nri.2016.90

Koehler M, Sandberg A, Kjellqvist S, Thomas A, Karimi R, Nyren S, Eklund A, Thevis M, Skold CM, Wheelock AM (2013) Gender differences in the bronchoalveolar lavage cell proteome of patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 131(3):743–751. https://doi.org/10.1016/j.jaci.2012.09.024

Kurmi OP, Arya PH, Lam KB, Sorahan T, Ayres JG (2012) Lung cancer risk and solid fuel smoke exposure: a systematic review and meta-analysis. Eur Respir J 40(5):1228–1237. https://doi.org/10.1183/09031936.00099511
Lelieveld J, Pozzer A, Pöschl U, Fnais M, Haines A, Münzel T (2020) Loss of life expectancy from air pollution compared to other risk factors: a worldwide perspective. Cardiovasc Res 116(11):1910–1917. https://doi.org/10.1093/cvr/cvaa025

Leung JM, Sin DD (2020) Smoking, ACE-2, and COVID-19: ongoing controversies. Eur Respir J 5(5):1–8. https://doi.org/10.1183/13993003.01759-2020

Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, Dorscheid DR, Sin DD (2020) ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J 55(5):2000688. https://doi.org/10.1183/13993003.00688-2020

Liang L, Cai Y, Barratt B, Lyu B, Chan Q, Hansell AL, Xie W, Zhang D, Kelly FJ, Tong Z (2019) Associations between daily air quality and hospitalisations for acute exacerbation of chronic obstructive pulmonary disease in Beijing, 2013–17: an ecological analysis. Lancet Planet Health 3(6):e270–e279. https://doi.org/10.1016/S2542-5196(19)30085-3

Liu L, Poon R, Chen L, Frescura AM, Montuschi P, Ciabattoni G, Wheeler A, Dales R (2009) Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children. Environ Health Perspect 117(4):668–674. https://doi.org/10.1289/ehp11813

Liu J, Ji H, Zheng W, Wu X, Zhu JJ, Arnold AP, Sandberg K (2010) Sex differences in renal angiotensin converting enzyme 2 (ACE2) activity are 17beta-oestradiol-dependent and sex chromosome-independent. Biol Sex Differ 1(1):6. https://doi.org/10.1186/2042-6410-1-6

Liu J, Naem E, Tian J, Lombardi V, Kwong K, Akbari O, Torday JS, Rehan VK (2013) Sex-specific perinatal nicotine-induced asthma in rat offspring. Am J Respir Cell Mol Biol 48(1):53–62. https://doi.org/10.1165/rcmb.2011-0344OC

LoMauro A, Aliverti A (2018) Sex differences in respiratory function. Breathe (Sheff) 14(2):131–140. https://doi.org/10.1183/20734735.000318

Lux R, Awa W, Walter U (2009) An interdisciplinary analysis of sex and gender in relation to the pathogenesis of bronchial asthma. Respir Med 103(5):637–649. https://doi.org/10.1016/j.rmed.2009.01.006

Majdic G (2020) Could sex/gender differences in ACE2 expression in the lungs contribute to the large gender disparity in the morbidity and mortality of patients infected with the SARS-CoV-2 virus? Front Cell Infect Microbiol 10:327. https://doi.org/10.3389/fcimb.2020.00327

Meyer KF, Krauss-Etschmann S, Kooistra W, Reinders-Luinge M, Timens W, Kobzik L, Plosch T, Hylkema MN (2017) Prenatal exposure to tobacco smoke sex dependently influences methylation and mRNA levels of the Igf axis in lungs of mouse offspring. Am J Phys Lung Cell Mol Phys 312(4):L542–L555. https://doi.org/10.1152/ajplung.00271.2016

Miao JL, Cai JJ, Qin XF, Liu RJ (2018) Analysis of the Clinicopathological characteristics and risk factors in patients with lung cancer and chronic obstructive pulmonary disease. Biomed Res Int 2018:8398156. https://doi.org/10.1155/2018/8398156

Mishra V (2003) Indoor air pollution from biomass combustion and acute respiratory illness in preschool age children in Zimbabwe. Int J Epidemiol 32(5):847–853

Molnár P, Gustafson P, Johannesson S, Boman J, Barregård L, Sällsten G (2005) Domestic wood burning and PM2.5 trace elements: personal exposures, indoor and outdoor levels. Atmos Environ 39(14):2643–2653. https://doi.org/10.1016/j.atmosenv.2005.01.016

Morgan R, Klein SL (2019) The intersection of sex and gender in the treatment of influenza. Curr Opin Virol 35:35–41. https://doi.org/10.1016/j.coviro.2019.02.009

Moritz ED, Zapata LB, Lekiachvili A, Glidden E, Annor FB, Werner AK, Ussery EN, Hughes MM, Kimball A, DeSisto CL, Kenemer B, Shamout M, Garcia MC, Reagan-Steiner S, Petersen EE, Koumans EH, Ritchey MD, King BA, Jones CM, Briss PA, Delaney L, Patel A, Polen KD, Sives K, Meaney-Delman D, Chatham-Stephens K, Lung Injury Response Epidemiology/Surveillance G, Lung Injury Response Epidemiology/Surveillance Task F (2019) Update: characteristics of patients in a National Outbreak of E-cigarette, or Vaping, product use-associated Lung injuries - United States, October 2019. MMWR Morb Mortal Wky Rep 68(43):985–989. https://doi.org/10.15585/mmwr.mm6843e1
Mutlu E, Warren SH, Ebersviller SM, Kooter IM, Schmid JE, Dye JA, Linak WP, Gilmour MI, Jetter JJ, Higuchi M, DeMarini DM (2016) Mutagenicity and pollutant emission factors of solid-fuel Cookstoves: comparison with other combustion sources. Environ Health Perspect 124(7):974–982. https://doi.org/10.1289/ehp.1509852

Naeem A, Silveyra P (2019) Sex differences in paediatric and adult asthma. Eur Med J (Chelmsf) 4(2):27–35

Naz S, Kolmert J, Yang M, Reinke SN, Kamleh MA, Snowden S, Heyder T, Levanen B, Erle DJ, Skold CM, Wheelock AM, Wheelock CE (2017) Metabolomics analysis identifies sex-associated metabolotypes of oxidative stress and the autotaxin-lysoPA axis in COPD. Eur Respir J 49(6):1602322. https://doi.org/10.1183/13993003.02322-2016

Neophytou AM, Oh SS, White MJ, Mak ACY, Hu D, Huntsman S, Eng C, Serebrisky D, Borrell LN, Farber HJ, Meade K, Davis A, Avila PC, Thyne SM, Rodriguez-Cintron W, Rodriguez-Santana JR, Kumar R, Brigino-Buenaventura E, Sen S, Lenoir MA, Williams JK, Benowitz NL, Balmes JR, Eisen EA, Burchard EG (2018) Secondhand smoke exposure and asthma outcomes among African-American and Latino children with asthma. Thorax 73(11):1041–1048. https://doi.org/10.1136/thoraxjnl-2017-211383

Nomiyama K, Nomiyama H (1974) Respiratory retention, uptake and excretion of organic solvents in man. Int Arch Arbeitsmed 32(1):75–83. https://doi.org/10.1007/BF00539097

Ober C, Pan L, Phillips N, Parry R, Kurina LM (2006) Sex-specific genetic architecture of asthma-associated quantitative trait loci in a founder population. Curr Allergy Asthma Rep 6(3):241–246. https://doi.org/10.1007/s11882-006-0041-4

Obiebi IP, Oyibo PG (2019) A cross-sectional analysis of respiratory ill-health among charcoal workers and its implications for strengthening occupational health services in southern Nigeria. BMJ Open 9(1):e022361. https://doi.org/10.1136/bmjopen-2018-022361

Oiamo TH, Luginaah IN (2013) Extricating sex and gender in air pollution research: a community-based study on cardinal symptoms of exposure. Int J Environ Res Public Health 10(9):3801–3817. https://doi.org/10.3390/ijerph10093801

Oloyede IP, Ekrikpo UE, Ekanem EE (2013) Lung function indices of children exposed to wood smoke in a fishing port in south-South Nigeria. J Trop Pediatr 59(5):399–402. https://doi.org/10.1093/tropej/fmt033

Opotowsky AR, Vedanthan R, Mamlin JJ (2008) A case report of cor pulmonale in a woman without exposure to tobacco smoke: an example of the risks of indoor wood burning. Medscape J Med 10(1):22

Ottmar RD, Miranda AI, Sandberg DV (2008) Chapter 3: Characterizing sources of emissions from Wildland fires. In: Bytnerowicz A, Arbaugh MJ, Riebau AR, Andersen C (eds) Developments in environmental science, vol 8. Elsevier, London, pp 61–78. https://doi.org/10.1016/S1474-8177(08)00003-X

Pampel FC (2006) Global patterns and determinants of sex differences in smoking. Int J Comp Sociol 47(6):466–487. https://doi.org/10.11177/0020715206070267

Patel AB, Verma A (2020) Nasal ACE2 levels and COVID-19 in children. JAMA 323(23):2386–2387. https://doi.org/10.1001/jama.2020.8946

Peretz J, Pekosz A, Lane AP, Klein SL (2016) Estrogenic compounds reduce influenza a virus replication in primary human nasal epithelial cells derived from female, but not male, donors. Am J Phys Lung Cell Mol Phys 310(5):L415–L425. https://doi.org/10.1152/ajplung.00398.2015

Perez-Padilla R, Perez-Guzman C, Baez-Saldana R, Torres-Cruz A (2001) Cooking with biomass stoves and tuberculosis: a case control study. Int J Tuberc Lung Dis 5(5):441–447

Perrine CG, Pickens CM, Boehmer TK, King BA, Jones CM, DeSisto CL, Duca LM, Lekiachiwili A, Kenemer B, Shamout M, Landen MG, Lynfield R, Ghinai I, Heinzerling A, Lewis N, Pray JW, Tanz LJ, Patel A, Briss PA, Response LI (2019) Epidemiology/surveillance G (2019) characteristics of a multistate outbreak of lung injury associated with E-cigarette use, or Vaping – United States. MMWR Morb Mortal Wkly Rep 68(39):860–864. https://doi.org/10.1585/mmwr.mmm6839e1
Prüss-Üstün A, Wolf J, Corvalán C, Organization WH, Bos R, Neira M (2016) Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks. World Health Organization, Geneva

Qureshi KA (1994) Domestic smoke pollution and prevalence of chronic bronchitis/asthma in a rural area of Kashmir. Indian J Chest Dis Allied Sci 36(2):61–72

Rahmanian SD, Diaz PT, Wewers ME (2011) Tobacco use and cessation among women: research and treatment-related issues. J Women’s Health (Larchmt) 20(3):349–357. https://doi.org/10.1089/jwh.2010.2173

Raizenne M, Neas LM, Damokosh AI, Dockery DW, Spengler JD, Koutrakis P, Ware JH, Speizer FE (1996) Health effects of acid aerosols on north American children: pulmonary function. Environ Health Perspect 104(5):506–514. https://doi.org/10.1289/ehp.96104506

Rebuli ME, Speen AM, Martin EM, Addo KA, Pawlak EA, Glista-Baker E, Robinette C, Zhou H, Noah TL, Jaspers I (2018) Wood smoke exposure alters human inflammatory responses to viral infection in a sex-specific manner: a randomized placebo-controlled Study. Am J Respir Crit Care Med 199(8):996–1007. https://doi.org/10.1164/rccm.201807-1287OC

Rebuli ME, Glista-Baker E, Speen AM, Hoffman JR, Duffney PF, Pawlak E, Dang H, Ghosh A, Tarran R, Noah TL, Jaspers I (2019) Nasal mucosal immune response to infection with live-attenuated influenza virus (LAIV) is altered with exposure to E-cigarettes and cigarettes. Am J Respir Crit Care Med 201:A4170

Reid CE, Maestas MM (2019) Wildfire smoke exposure under climate change: impact on respiratory health of affected communities. Curr Opin Pulm Med 25(2):179–187. https://doi.org/10.1097/MCP.0000000000000552

Reinhardt TE, Ottmar RD (2004) Baseline measurements of smoke exposure among wildland firefighters. J Occup Environ Hyg 1(9):593–606. https://doi.org/10.1080/15459620490490101

Rivera RM, Cosio MG, Ghezzo H, Salazar M, Perez-Padilla R (2008) Comparison of lung morphology in COPD secondary to cigarette and biomass smoke. Int J Tuberc Lung Dis 12(8):972–977

Robinson DP, Lorenzo ME, Jian W, Klein SL (2011) Elevated 17beta-estradiol protects females from influenza a virus pathogenesis by suppressing inflammatory responses. PLoS Pathog 7(7):e1002149. https://doi.org/10.1371/journal.ppat.1002149

Rodriguez-Bolanos R, Arillo-Santillan E, Barrientos-Gutierrez I, Zavala-Arciniega L, Ntansah CA, Thrasher JF (2019) Sex differences in becoming a current electronic cigarette user, current smoker and current dual user of both products: a longitudinal study among Mexican adolescents. Int J Environ Res Public Health 17(1):196. https://doi.org/10.3390/ijerph17010196

Rodriguez-Gonzalez Moro JM, Izquierdo JL, Anton E, de Lucas P, Martin A, Group MS (2009) Health-related quality of life in outpatient women with COPD in daily practice: the MUVICE Spanish study. Respir Med 103(9):1303–1312. https://doi.org/10.1016/j.rmed.2009.04.002

Salaffi F, Carotti M, Di Carlo M, Tardella M, Giovagnoni A (2019) High-resolution computed tomography of the lung in patients with rheumatoid arthritis: prevalence of interstitial lung disease involvement and determinants of abnormalities. Medicine (Baltimore) 98(38):e17088. https://doi.org/10.1097/MD.0000000000017088

Schei MA, Hessen JO, Smith KR, Bruce N, McCracken J, Lopez V (2004) Childhood asthma and indoor woodsmoke from cooking in Guatemala. J Expo Anal Environ Epidemiol 14(Suppl 1):S110–S117. https://doi.org/10.1038/sj.ejea.7500365

Selberg S, Hedman L, Jansson SA, Backman H, Stridsman C (2019) Asthma control and acute healthcare visits among young adults with asthma-a population-based study. J Adv Nurs 75(12):3525–3534. https://doi.org/10.1111/jan.14174

Shah R, Newcomb DC (2018) Sex Bias in asthma prevalence and pathogenesis. Front Immunol 9:2997. https://doi.org/10.3389/fimmu.2018.02997

Sheng L, Tu JW, Tian JH, Chen HJ, Pan CL, Zhou RZ (2018) A meta-analysis of the relationship between environmental tobacco smoke and lung cancer risk of nonsmoker in China. Medicine (Baltimore) 97(28):e11389. https://doi.org/10.1097/MD.0000000000011389
Sigsgaard T, Forsberg B, Annesi-Maesano I, Blomberg A, Bolling A, Boman C, Bonløkke J, Brauer M, Bruce N, Heroux ME, Hirvonen MR, Kelly F, Kunzli N, Lundback B, Moshammer H, Noonan C, Pagels J, Sallsten G, Sculier JP, Brunekreef B (2015) Health impacts of anthropogenic biomass burning in the developed world. Eur Respir J 46(6):1577–1588. https://doi.org/10.1183/13993003.01865-2014

Smith KR, Samet JM, Romieu I, Bruce N (2000) Indoor air pollution in developing countries and acute lower respiratory infections in children. Thorax 55(6):518–532

Soskolne CL, Jhangri GS, Scott HM, Brenner DR, Siemiatycki J, Lakhani R, Gérin M, Dewar R, Miller AB, Risch HA (2011) A population-based case-control study of occupational exposure to acids and the risk of lung cancer: evidence for specificity of association. Int J Occup Environ Health 17(1):1–8. https://doi.org/10.1179/107735211799031077

Stowell JD, Geng G, Saikawa E, Chang HH, Fu J, Yang CE, Zhu Q, Liu Y, Strickland MJ (2019) Associations of wildfire smoke PM2.5 exposure with cardiorespiratory events in Colorado 2011-2014. Environ Int 133(Pt A):105151. https://doi.org/10.1016/j.envint.2019.105151

Strzelak A, Ratajczak A, Adamiec A, Feleszko W (2018) Tobacco smoke induces and alters immune responses in the Lung triggering inflammation, allergy, asthma and other lung diseases: a mechanistic review. Int J Environ Res Public Health 15(5):1033. https://doi.org/10.3390/ijerph15051033

Subbarao K, Mahanty S (2020) Respiratory virus infections: understanding COVID-19. Immunity 52(6):905–909. https://doi.org/10.1016/j.immuni.2020.05.004

Swiston JR, Davidson W, Attridge S, Li GT, Brauer M, van Eeden SF (2008) Wood smoke exposure induces a pulmonary and systemic inflammatory response in firefighters. Eur Respir J 32(1):129–138. https://doi.org/10.1183/09031936.00097707

Tam A, Churg A, Wright JL, Zhou S, Kirby M, Coxson HO, Lam S, Man SF, Sin DD (2016) Sex differences in airway remodeling in a mouse model of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 193(8):825–834. https://doi.org/10.1164/rcrm.201503-0487OC

Torres-Duque C, Maldonado D, Perez-Padilla R, Ezzati M, Viegi G, Forum of International Respiratory Studies Task Force on Health Effects of Biomass E (2008) Biomass fuels and respiratory diseases: a review of the evidence. Proc Am Thorac Soc 5(5):577–590. https://doi.org/10.1513/pats.200707-100RP

Trigueros JA, Riesco JA, Alcazar-Navarrete B, Campuzano A, Perez J (2019) Clinical features of women with COPD: sex differences in a cross-sectional study in Spain (“the ESPIRAL-ES Study”). Int J Chron Obstruct Pulmon Dis 14:2469–2478. https://doi.org/10.2147/COPD.S217921

U.S. EPA (2005) Toxicological review of toluene (CAS no. 108-88-3). U.S. Environmental Protection Agency, Washington, DC

U.S. EPA (2015) Provisional peer-reviewed toxicity values for carbonyl sulfide. U.S. Environmental Protection Agency, Washington, DC

Uppstad H, Osnes GH, Cole KJ, Phillips DH, Haugen A, Mollerup S (2011) Sex differences in susceptibility to PAHs is an intrinsic property of human lung adenocarcinoma cells. Lung Cancer 71(3):264–270. https://doi.org/10.1016/j.lungcan.2010.09.006

Vicente A, Alves C, Calvo AI, Fernandes AP, Nunes T, Monteiro C, Almeida SM, Pio C (2013) Emission factors and detailed chemical composition of smoke particles from the 2010 wildfire season. Atmos Environ 71:295–303. https://doi.org/10.1016/j.atmosenv.2013.01.062

vom Steeg LG, Klein SL (2016) SeXX matters in infectious disease pathogenesis. PLoS Pathog 12(2):e1005374. https://doi.org/10.1371/journal.ppat.1005374

Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, Kang J, Ran P, Shen H, Wen F, Huang K, Yao W, Sun T, Shan G, Yang T, Lin Y, Wu S, Zhu J, Wang R, Shi Z, Zhao J, Ye X, Song Y, Wang Q, Zhou Y, Ding L, Yang T, Chen Y, Guo Y, Xiao F, Lu Y, Peng X, Zhang B, Xiao D, Chen CS, Wang Z, Zhang H, Bu X, Zhang X, An L, Zhang S, Cao Z, Zhan Q, Yang Y, Cao B, Dai H, Liang L, He J, China Pulmonary Health Study G (2018) Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national
cross-sectional study. Lancet 391(10131):1706–1717. https://doi.org/10.1016/S0140-6736(18)30841-9

Warren GW, Singh AK (2013) Nicotine and lung cancer. J Carcinog 12:1. https://doi.org/10.4103/1477-3163.106680

Wong SL, Coates AL, To T (2016) Exposure to industrial air pollutant emissions and lung function in children: Canadian health measures survey, 2007 to 2011. Health Rep 27(2):3–9

World Health Organization (2018) WHO global report on trends in prevalence of tobacco smoking 2000–2025. In: 2nd ed edn. World Health Organization, Geneva

Wu W, Jin Y, Carlsten C (2018) Inflammatory health effects of indoor and outdoor particulate matter. J Allergy Clin Immunol 141(3):833–844. https://doi.org/10.1016/j.jaci.2017.12.981

Xiao D, Pan H, Li F, Wu K, Zhang X, He J (2016) Analysis of ultra-deep targeted sequencing reveals mutation burden is associated with gender and clinical outcome in lung adenocarcinoma. Oncotarget 7(16):22857–22864. https://doi.org/10.18632/oncotarget.8213

Yang M, Kohler M, Heyder T, Forsslund H, Garberg HK, Karimi R, Grunewald J, Berven FS, Nyren S, Magnus Skold C, Wheelock AM (2018) Proteomic profiling of lung immune cells reveals dysregulation of phagocytotic pathways in female-dominated molecular COPD phenotype. Respir Res 19(1):39. https://doi.org/10.1186/s12931-017-0699-2

Yang CX, Shi H, Ding I, Milne S, Hernandez Cordero AI, Yang CWT, Kim EK, Hackett TL, Leung J, Sin DD, Obeidat M (2019) Widespread sexual dimorphism in the transcriptome of human airway epithelium in response to smoking. Sci Rep 9(1):17600. https://doi.org/10.1038/s41598-019-54051-y

Zavorsky GS, Tesler J, Rucker J, Fedorko L, Duffin J, Fisher JA (2014) Rates of carbon monoxide elimination in males and females. Phys Rep 2(12):e12237. https://doi.org/10.14814/phy2.12237

Zhao Z, Zhang Z, Wang Z, Ferm M, Liang Y, Norback D (2008) Asthmatic symptoms among pupils in relation to winter indoor and outdoor air pollution in schools in Taiyuan, China. Environ Health Perspect 116(1):90–97. https://doi.org/10.1289/ehp.10576