Chapter 9
Sex and Gender Differences in the Susceptibility to Environmental Exposures

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Abstract In the past 50 years, the number of publications on air pollution and lung disease has increased considerably, although the number of studies considering sex (a biologic factor), or gender (a social construct), has remained low and stagnant. Accumulating data from studies assessing the effects of the environment on lung health have shown direct associations of air pollution exposures with lung inflammation. Sex-specific disaggregation of data has indicated that substantial – but frequently overlooked – differences exist between men and women, highlighting the importance of sex- and gender-stratified analyses to guide the deployment of safe and effective therapeutics options for males and females. In this chapter, we present an overview of the scientific evidence on differential effects of environmental exposures in men and women. We summarize clinical studies and research using animal models aiming to elucidate sex-specific mechanisms of inflammation and toxicity from a wide range of air pollutants. Understanding these mechanisms can lead to the development of more personalized prevention efforts and better-informed environmental policies accounting for sex, gender, and hormonal status.

Keywords Air pollution · Ozone · Particulate matter · Sulfur dioxide · Nitrogen dioxide · Carbon monoxide · Sex · Hormones

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9.1 Introduction

Environmental exposures have become a significant health risk in the past few decades. Epidemiological studies have shown that the onset and clinical course of several diseases including cardiovascular and lung conditions are strongly influenced by poor air quality. According to the World Health Organization, exposure to pollutants has accounted for almost a quarter of total global deaths, with over eight million yearly deaths worldwide due to household or ambient air pollution exposure. Inhalation of air pollutants including particulate matter of diameter equal to or less than 10 μm (PM), sulfur dioxide (SO₂), ground-level ozone (O₃), nitrogen dioxide (NO₂), biomass fuels, and carbon monoxide (CO) has been strongly associated with increased mortality from cardiopulmonary disease and multiple negative lung health effects (Jerrett et al. 2009; Chen et al. 2017; Rice et al. 2013; Guarnieri and Balmes 2014; Nascimento et al. 2006; Arbex et al. 2012) (Table 9.1). These pollutants are present in the environment as a mixture of gases and particles that are products of combustion of fossil fuels, diesel traffic, wood smoke, industrial processes, and some sources of domestic energy.

Despite growing epidemiological evidence indicating that males and females exhibit different health responses to air pollution exposures, many studies in the field still do not consider sex as a biological variable. For many decades, there were limited information on the interactions between air pollution exposures and

| Air pollutant       | Main health effects                                      | References                                                                 |
|---------------------|----------------------------------------------------------|---------------------------------------------------------------------------|
| Ozone               | Decreased lung function                                  | Abramson et al. (2020); Wang et al. (2019b); Kehrl et al. (1999); Li et al. (2019b); Malley et al. (2017) |
|                     | Increased airway reactivity                              |                                                                           |
|                     | Increased lung inflammation                              |                                                                           |
|                     | Increased hospital visits for lung disease               |                                                                           |
|                     | Increased mortality for lung and cardiovascular disease  |                                                                           |
| Particulate matter  | Decreased lung function                                  | Hwang et al. (2015); Pope (2014); Shamsipour et al. (2019); Chen et al. (2017) |
|                     | Increased respiratory symptoms                           |                                                                           |
|                     | Increased mortality for lung and cardiovascular disease  |                                                                           |
| Nitrogen dioxide    | Increased airway reactivity                              | Kelly and Fussell (2011); McCreanor et al. (2007); Tager et al. (2005)    |
|                     | Reduced lung function                                   |                                                                           |
|                     | Bronchitis (children)                                    |                                                                           |
| Carbon monoxide     | Poisoning (headache, altered mentation, coma, cardiac dysfunction) | Rose et al. (2017)                                                      |
| Sulfur dioxide      | Increased respiratory mortality                          | Reilly et al. (2019); Johannson et al. (2014); Nishimura et al. (2013); Katanoda et al. (2011) |
|                     | Increased hospital visits for lung disease               |                                                                           |
|                     | Aggravation of lung disease                             |                                                                           |
|                     | Increased lung inflammation                             |                                                                           |
biological sex differences and much less about gender effects. Regarding associations of lung disease and air pollution exposures, the proportion of total studies including sex or gender as variables has remained low for the past 50 years. More recently, researchers have been encouraged to include sex as a biological variable in all experimental designs, data collection, and analyses and to better understand biological sex-specific effects in physiological and behavioral outcomes (Clayton 2016). This required the development of new models and multidisciplinary approaches to environmental health research (Keitt et al. 2004). To date, a limited number of studies have addressed sex differences in health outcomes in response to air pollution exposure. Combined, these have identified a majority of effects in women, as indicated in Table 9.2.

The gender variable has traditionally been more commonly included in occupational health epidemiology than in environmental health research due to job stratification (Artazcoz et al. 2007). Societal changes occurring in recent decades have led to more women entering certain occupations, using tobacco products, and spending less time exposed to indoor pollutants and more time exposed to outdoor pollution (Artazcoz et al. 2007; Clougherty 2011). This has resulted in changes in patterns of disease prevalence and susceptibility and the consequent need to reevaluate research models to consider the sex and gender variables, but also the intersection of both. The integration of these new data will likely lead to the development of better-

### Table 9.2 Sex differences in health outcomes

| Air pollutant           | Health outcome                     | Sex differences | References                                                                 |
|-------------------------|------------------------------------|-----------------|---------------------------------------------------------------------------|
| Ozone                   | Mortality                          | Higher in women | (Medina-Ramón and Schwartz 2008; Stafoggia et al. 2010; Bell et al. 2014; Ren et al. 2010; Liang et al. 2019) |
|                         | Hospitalization                    |                 |                                                                           |
|                         | Exacerbation of lung disease       |                 |                                                                           |
| Particulate matter      | Hospitalization                    | Higher in women | (Liang et al. 2019; Bell et al. 2015)                                      |
|                         | Exacerbation of lung disease       |                 |                                                                           |
| House biomass fuel use  | COPD                               | Higher in women | (Capistrano et al. 2017; Barnes 2016; Rivera et al. 2008; Kurmi et al. 2012; Bruce et al. 2015; Qureshi 1994; Schei et al. 2004; Majdic 2020; Adhikari and Yin 2020) |
|                         | Lung Cancer                        | Higher in women |                                                                           |
|                         | Asthma                             | Higher in women |                                                                           |
|                         | Virus-induced respiratory inflammation | Higher in men   |                                                                           |
| Carbon monoxide         | Elimination time                   | Longer in men   | (Zavorsky et al. 2014)                                                    |
| Nitrogen dioxide        | Chronic bronchitis                 | Higher in women | (Sunyer et al. 2006; Luginaah et al. 2005; Oiamo and Luginaah 2013)        |
|                         | Mortality                          |                 |                                                                           |
| Sulfur dioxide          | Mortality                          | Higher in women | (Oiamo and Luginaah 2013)                                                 |
|                         | Hospitalization                    |                 |                                                                           |
informed and more effective air quality standards and policies that take into consideration sex and gender. Below, we present an overview of basic, clinical, and translational studies assessing sex and gender differences in the response to environmental exposures. Below, we have summarized epidemiological and clinical data by air pollutants, as well as results from animal and in vitro studies investigating sex-specific mechanisms.

9.2 Sex Differences in the Response to Ozone Exposure

Ground-level (tropospheric) ozone is one of the dominant air pollutants worldwide (WHO 2016). Different from the ozone layer present in the upper atmospheric layer, ground-level ozone is a reactive oxidant gas formed by the phytochemical reactions of carbon monoxide, nitric dioxide, and volatile organic compounds, found at higher concentrations in major cities (Makri and Stilianakis 2008). Exposure to ambient ozone has been associated with decreased lung function, increased airway reactivity, increased lung inflammation, higher hospital visits related to lung disease, and exacerbation of preexisting respiratory disease in men and women (Arjomandi et al. 2018; Bromberg 2016). Chronic ozone exposure has also been correlated with shortened life expectancy and higher risk of death from both cardiovascular and pulmonary disease (Malley et al. 2017). In the past decade, emerging epidemiological and clinical data have indicated that sex, gender, and inter-individual differences influence susceptibility to ozone exposure effects (Silveyra and Floros 2012; Stafoggia et al. 2010; Abramson et al. 2020; Bell et al. 2014). For example, acute exposure to ambient ozone at levels close to the national ambient air quality standard has been correlated with decreased lung function, impaired lung immunity, and increased oxidative stress in healthy individuals (Tager et al. 2005; Holland et al. 2015), with different responses in men vs. women (Bell et al. 2014; Medina-Ramón and Schwartz 2008). The results from these investigations have influenced the development of policies and regulations aimed to improve air quality standards and allowed the development of guidelines to help prevent disease exacerbations in vulnerable populations.

9.2.1 Epidemiological Studies

The American Lung Association has stated that anyone who spends time outdoors in areas where ozone levels are high is at risk of adverse effects (ALA 2020). They have identified five groups as especially vulnerable to ozone: (1) children and teenagers, (2) elder individuals (age 65 and older), (3) individuals who work or exercise outdoors, (4) people with existing inflammatory lung disease, and (5) individuals with existing cardiovascular disease. The effects observed in these individuals range from reduced lung function to airway obstruction, to reduced life expectancy (Huang et al. 2018b; Romieu et al. 2012). In addition, accumulating
evidence suggests that other groups are also at high risk, including women and obese individuals, cancer patients, and patients with allergies (Stafoggia et al. 2010).

A growing number of studies have shown that patients suffering from respiratory disease are at higher risk of experiencing the negative effects of ozone exposure (Wang et al. 2019b; Kurt et al. 2016; Ciencewicki et al. 2008). Specifically, patients suffering from diseases that disproportionately affect more women than men, such as asthma and chronic obstructive pulmonary disease (COPD), also show higher sensitivity to ozone exposure (Guarnieri and Balmes 2014; Collaborators 2020). Smokers and patients with asthma, emphysema, and COPD display greater bronchoconstriction, decreased lung function, and higher mortality rates following both acute and chronic ozone exposure (Kreit et al. 1989; Butter 2006; Liu et al. 2019). Pregnant women have also been reported to be more susceptible to ozone exposure, which can result in premature delivery and complications of pregnancy such as low birth weight, preterm birth, and stillbirth (Bekkar et al. 2020; Zang et al. 2019; Díaz et al. 2016). These effects appear to be time-dependent and more severe in women in the third trimester of pregnancy (Rammah et al. 2019; Grippo et al. 2018; Mendola et al. 2017).

Sex-specific disaggregation of data in the Global Burden of Disease study shows that there are substantial differences between men and women in their response to air pollution exposure, although these differences are frequently overlooked (The Lancet 2018). The available literature on epidemiological and clinical studies assessing ozone effects suggest that both sex and age simultaneously contribute to the response in healthy individuals and patients with lung disease (Vinikoor-Imler et al. 2014; Bell et al. 2014; Galizia and Kinney 1999; Tager et al. 2005; Arjomandi et al. 2018; Khatri et al. 2009). Studies in children and teenagers have reported that children growing up in areas with higher ozone pollution face an increased risk of having underdeveloped lungs and that children of both sexes who spend more time outdoors in areas with higher levels of ozone show significant reductions in lung function. These detrimental effects are also more predominant in girls than boys with asthma (Peters et al. 1999a, b). The risk of emergency room visits after exposure to ozone in patients with asthma, COPD, and respiratory infections is also higher in younger populations (Strosnider et al. 2019). However, older adults are also impacted by ozone exposure (Abramson et al. 2020; Strosnider et al. 2018; Arjomandi et al. 2018; Stafoggia et al. 2010), particularly if they suffer from idiopathic pulmonary fibrosis (IPF) (Sesé et al. 2018; Johansson et al. 2014, 2018), which is more prevalent and severe in males, but reduces quality of life measures to a greater extent in females (Zaman et al. 2020; Han et al. 2010). Older adults also with acute respiratory distress syndrome (ARDS), which is more likely to be developed by females than men following critical injury (Heffernan et al. 2011), are also more likely to be affected by ozone exposure. Chronic exposure to ozone has been reported to increase the risk of ARDS in adults aged 65 and older (Rhee et al. 2019), even at levels below the current national ambient air quality standard of 70 ppb (Reilly et al. 2019). While these studies have adjusted results by sex, race, and age, they did not specifically evaluate sex differences in measured outcomes. More recently, it has been found that severe cases of coronavirus disease (COVID-19) are typically marked by ARDS.
with respiratory failure requiring oxygen support and mechanical ventilation (Zhou et al. 2020). The available epidemiological and clinical data indicate that males display an increased susceptibility and death risk for COVID-19 (Klein et al. 2020). While sex differences in pro-inflammatory gene expression combined with potential steroid hormones modulation of the immune response to respiratory viral pathogens could contribute to an enhanced risk of death in males, the mechanisms underlying these observed differences remain unexplored (Scully et al. 2020).

9.2.2 Clinical Studies

Limited clinical studies assessing the effects of acute and chronic ozone exposures in men and women have yielded inconclusive or conflicting results. Studies employing controlled human exposures to ozone in adult men and women consistently show decrements in lung function, increased lung neutrophilia, and increased airway levels of pro-inflammatory cytokines and metabolites (Mumby et al. 2019; Devlin et al. 1991; Cheng et al. 2018; Seltzer et al. 1986), although only a few studies assessed differences between sexes. These studies have consistently reported significant reductions in forced expiratory volumes and forced vital capacity with repeated ozone exposures. One study using 0.4 ppm exposures found that this decline was 2.5 times higher in younger women (aged 18–35 years old) vs. younger men and older women (36–60 years old) (Hazucha et al. 2003). Prolonged chronic exposure studies using lower doses and longer time periods (0.08 ppm for 6.6 hours) revealed significant increases in pro-inflammatory factors in the airway, although the majority of these studies were only conducted in male individuals (Devlin et al. 1991).

Two studies using the same low-level ozone exposure protocol in 7 females and 8 males, and 36 females and 24 males, respectively, all aged 19–35 years, revealed increases in airway inflammation, inflammatory cell numbers, and expression of pro-inflammatory markers in sputum, as well as significant declines in lung function (Alexis et al. 2010; Kim et al. 2011). While the first study did not assess or mentioned sex differences (Alexis et al. 2010), the second study identified differences in the male and female decline in forced expiratory volume (−0.86% in males vs. -2.43% in females) and forced vital capacity (−1.26% in males vs. -3.22% in females) following ozone exposure (Kim et al. 2011). The decline in forced expiratory volume and forced vital capacity was found to be statistically significant in females exposed to ozone and not in males, but the authors did not find significant sex differences when comparing results from males vs. females. In contrast, the increase in inflammatory cells was significantly higher in the male group vs. the female group, with a threefold increase in males and no change in females, indicating that the response to ozone differs between the sexes depending on the endpoints assessed (Kim et al. 2011).

Another study conducted on nine female and six male healthy volunteers exposed to 0.4 ppm of ozone or lipopolysaccharide revealed similar increases in neutrophilia and inflammation triggered by both agents, although no sex differences were
analyzed or reported either (Hernandez et al. 2010a). The same group also evaluated this ozone exposure protocol in 27 female and 23 male subjects divided into 3 groups (control, atopic, and atopic asthmatic) and found a decline in lung function in all groups exposed to ozone, with significant differences in inflammatory cells and pro-inflammatory cytokines (IL-1β, IL-6, IL-8) in the atopic asthmatic groups vs. atopic and healthy controls. This study also omitted analysis of sex differences in the results or discussion (Hernandez et al. 2010b). An older study in three women and seven men exposed to 0.4 or 0.6 ppm of ozone found significant increases in bronchoalveolar lavage neutrophilia and increases in airway responsiveness to inhaled methacholine at 3 hours after exposure but did not analyze sex differences. The authors also reported significant increases in the concentrations of cyclooxygenase and lipoxygenase metabolites of arachidonic acid, such as prostaglandins E2, F2 alpha, and thromboxane B2 when analyzing combined results, but did not stratify results by sex (Stavert et al. 1986).

Another controlled exposure study on 19 subjects with and without asthma of average age 32 years, including 12 females (5 healthy/7 asthmatic) and 7 males (3 healthy/4 asthmatic), evaluated transcriptomic profiles in bronchoalveolar lavage fluid at 20 hours after exposure to different doses of ozone (0, 100, or 200 ppb for 4 hours). Using a gene chip microarray, the authors identified dose-dependent differential expression of pro-inflammatory genes and genes related to chemokine and cytokine secretion, activity, receptor binding, metalloproteinase and endopeptidase activity, as well as cell growth, adhesion, and migration in the asthma group exposed to ozone. While results found significantly higher levels of these markers in the asthma group (1.7–3.8-fold greater than healthy controls), stratification of data and unsupervised clustering analysis did not reveal a sex effect. The authors also validated their main findings using 16HBE14o- cells, a bronchial epithelial cell line derived from a male individual (Leroy et al. 2015).

While the field of environmental health has recently recognized a role for sex hormones in lung inflammatory mechanisms and lung disease, only a few studies conducted over 20 years ago have assessed the influence of the menstrual cycle in the response to controlled ozone exposures (Fuentes and Silveyra 2018; Naeem and Silveyra 2019). These studies were conducted in young adults, athletes and non-athletes, and exposures to ozone were evaluated under a mild exercise protocol. Combined, these studies have provided limited and conflicting information pointing to a potential role of progesterone in modulating ozone responses, but to our knowledge, they have not been replicated since. In 1993, Fox et al. (1993) hypothesized that females in the follicular menstrual phase were more susceptible to ozone exposure effects than those in the luteal phase. To test the hypothesis, they recruited nine female subjects, who were randomized in four groups exposed to either 0.3 ppm of ozone or filtered air for 1 hour, in the luteal or follicular menstrual phase of their cycle (n = 3 ozone/follicular, n = 4 ozone/luteal vs. n = 1 filtered air/follicular, n = 2 filtered air/luteal). They assessed changes in pulmonary function by spirometry and used blood hormone levels to monitor the menstrual cycle phase. Despite the low number of subjects, their results revealed an interactive effect of ozone exposure and menstrual phase for forced expiratory volumes, with larger decrements...
in women exposed in the follicular phase (i.e., low progesterone phase) vs. the mid-luteal phase (i.e., high progesterone phase) (Fox et al. 1993).

Two years later, a different group assessed small airway function changes in response to 0.35 ppm ozone exposure for 2 hours by conducting a preliminary study in 9 women and a larger study in 24 subjects (12 males and 12 females). In the main study, seven females were in the luteal phase and five in the follicular phase. Instead of monitoring regular hormone levels, this study instructed participants to self-monitor daily changes in body temperature and menses to estimate their menstrual cycle phase and only measured blood hormone levels on the day of exposure. In addition, this study conducted repeated exposures in the same subjects (first in the follicular and next in the luteal phase), separated by 2–14 weeks, and compared spirometry results in the two menstrual phases. While their results reproduced the decline in lung function with ozone exposure, the preliminary study reported a non-significant difference between the follicular and luteal phases. Moreover, the exercise protocol was not matched for males vs. females nor for the subjects exposed in two phases, being 35% reduced for the subjects exposed in the luteal phase. When comparing males and females, they also found lower forced expiratory volumes and forced vital capacity in females vs. males, although the interaction of exposure and gender was not significant (Weinmann et al. 1995).

Finally, a study conducted in 1995 recruited 372 individuals (Seal et al. 1996) to test the effects of a broader range of ozone concentrations (0, 0.12, 0.18, 0.24, 0.3, or 0.4 ppm). A mixed population of males and females aged 18–35 was exposed to these concentrations for 2 hours, and pulmonary function testing was conducted before and after exposure. This study found a relationship between age and socio-economic status with lung function decrements in response to ozone (higher decrements with lower age), but also reported no impact of the menstrual cycle in the response to ozone from the 150 women participants. To monitor the menstrual cycle phase, women were asked the date of their last menstrual cycle and regularity of periods in a questionnaire conducted on the day of exposure, and this information was used to categorize results. When discussing their data, the investigators recognize that they did not attempt to expose women in a specific cycle phase, nor hormone levels were measured as part of the study, and that the numbers of women exposed to ozone in different phases may not be balanced (Seal et al. 1996).

Overall, the literature on the effects of the menstrual cycle and hormone levels on ozone exposure-related outcomes is limited and conflictive and has not been resumed since the late 1990s. Moreover, controlled exposure studies have predominantly been conducted in Caucasian populations despite multiple reports showing that racial disparities exist in air pollution exposure responses and incidence of lung disease (Miranda et al. 2011; Nishimura et al. 2013; Ash and Boyce 2018; Celedón et al. 2014; Collins et al. 2017; Forno and Celedon 2009). More clinical research incorporating sex and gender variables and assessing the influence of hormones to these responses in racially diverse cohorts is needed in this area. These new studies should follow the new recommendations to incorporate the “Four Cs” of studying sex to strengthen science (Consider, Collect, Characterize, and Communicate), utilizing validated research designs and statistical methods (Diester et al. 2019).
9.2.3 Animal Models

For the past several decades, numerous animal models ranging from mice to nonhuman primates have been used to study responses to inhaled ozone. These models have provided information on inflammatory mechanisms, physiological factors, and potential genes involved in ozone exposure susceptibility that were found to be age-, strain-, and species-dependent (Snow et al. 2016; Kleeberger et al. 2000; Chalfant and Bernd 2014; Herring et al. 2015; Avdalovic et al. 2012; Miller et al. 2009; Schelegle et al. 2003). Moreover, studies comparing responses related to acute lung injury, gene expression profiles, cellular responses, cytokine and chemokine activation, and other pathways have identified correlations between the responses observed in animal models vs. human studies (Sweeney et al. 2017). However, most of these comparisons have not been stratified by sex or gender, and only a few recent studies have considered the intersection of sex and other factors such as mouse strain, age, hormones, and microbiome in the response to ozone (Vancza et al. 2009; Cho et al. 2018c, b, 2019; Mishra et al. 2016; Kasahara et al. 2019). We have summarized the main effects observed in commonly used exposure models in males and females in Table 9.3.

The timing and concentration of ozone also affect the response phenotype in a strain-dependent manner. For example, exposure to ozone for 9 days at 0.8 ppm and 4 hours/day induced an asthma-like phenotype with airway eosinophilia, mucus cell metaplasia, and activation of type 2 innate lymphoid (ILC2) cells in C57BL/6 mice. In contrast, an acute exposure to 3 ppm for 2 hours induced airway neutrophilia, eosinophilia, and IL-5 expression, but this effect was observed in BALB/c mice and not C57BL/6 mice (Kumagai et al. 2017; Yang et al. 2016). The ILC2s of exposed BALB/c mice also expressed greater mRNA levels of Il5 and I13 than C57BL/6 mice, indicating that the role of ILC2 cells in ozone-induced inflammation is also strain-dependent.

These strain differences in airway responses to repeated ozone exposures indicate that genotype is an important factor, suggesting that an individual’s genetic background may determine the clinical manifestation of ozone-induced lung disease or exacerbation of lung disease. The collaborative cross strain, derived from an eight-way cross using several founder strains (Churchill et al. 2004), has been used to investigate genes associated with ozone susceptibility, although no sex differences have been reported to date (Tovar et al. 2020).

Ozone exposure also affects and contributes to the development of chronic pulmonary diseases such as pneumonia (Silveyra et al. 2017). In this regard, animal models of exposure followed by infection have been widely used and provided insight into the physiological processes involved. One study showed that mice infected with Klebsiella pneumoniae following exposure to ozone at 2 ppm for 3 hours had decreased ability to clear bacteria from the lungs. Ozone-exposed females were more affected and showed higher mortality after infection than males (Mikerov et al. 2008, 2011). Contrastingly, in the absence of ozone pre-exposure, males displayed higher mortality from infection compared to females. These
Table 9.3  Sex differences in animal models of ozone exposure

| Animal model                                                                 | Effect/outcome                                      | Sex differences     | References                                                                 |
|------------------------------------------------------------------------------|-----------------------------------------------------|---------------------|---------------------------------------------------------------------------|
| Ozone exposure (2 ppm, 3 h) followed by *Klebsiella pneumoniae* infection    | Bacterial clearance from lungs                      | Higher in males     | Mikerov et al. (2011); Mikerov et al. (2008); Durrani et al. (2012)      |
|                                                                               | Mortality from infection                             | Higher in females   |                                                                           |
| Ozone exposure (2 ppm, 3 h)                                                  | Pro-inflammatory mRNA gene expression in lung tissue | Higher in females   | Cabello et al. (2015)                                                     |
|                                                                               | Basal and ozone-induced miRNA expression in lung tissue | Differential pathways in males/females | Fuentes and Silveyra (2019); Fuentes et al. (2018) |
|                                                                               | Pro-inflammatory protein expression in BALF          | Higher in females   | Mishra et al. (2016); Kasahara et al. (2019); Cho et al. (2018b)          |
|                                                                               | BALF total cells                                     | Higher in females   | Cabello et al. (2015)                                                     |
|                                                                               | BALF total protein                                   | No difference       | Birukova et al. (2019)                                                    |
|                                                                               | BALF cellularity                                     | No difference       | Birukova et al. (2019)                                                    |
|                                                                               | BALF total protein                                   | Higher in females   | Birukova et al. (2019); Kasahara et al. (2019)                           |
|                                                                               | BALF albumin.                                        | Higher in females   | Birukova et al. (2019); Cabello et al. (2015)                            |
|                                                                               | Airway hyperresponsiveness                            | Higher in males     | Cho et al. (2018b); Birukova et al. (2019); Card et al. (2006)           |
|                                                                               | BALF neutrophilia                                    | Higher in females (proestrus stage) | Fuentes et al. (2019)                                                     |
|                                                                               | BALF macrophages                                     | Higher in males     | Kasahara et al. (2019); Tashiro et al. (2020)                            |
|                                                                               |                                                      | No difference       | Cho et al. (2018b)                                                        |
|                                                                               |                                                      | Higher in females   | Birukova et al. (2019); Tashiro et al. (2020)                            |

*BALF* bronchoalveolar lavage fluid
mechanisms were shown to be mediated by pulmonary surfactant proteins (Mikerov et al. 2012) and gonadal hormones (Durrani et al. 2012).

Although ozone exposure has been shown to be especially harmful to patients with asthma and COPD (Baldacci et al. 2015; Huang et al. 2018a; Kehrl et al. 1999), both displaying a sexual dimorphism in risk, prevalence, and severity (Raghavan and Jain 2016; Akinbami et al. 2012; Celli et al. 2011; Ferrari et al. 2010; de Torres et al. 2009; Hyndman et al. 1994; Johnston and Sears 2006; Control 2018; Aryal et al. 2013), experimental models of ozone exposure and lung disease have commonly been restricted to one sex or not considered sex as a biological variable. Such studies either failed to report sex in their models or extrapolated information from one sex to another, increasing the risk of erroneous conclusions. As indicated in Table 9.3, there has been a great deal of variability in the observed effects of ozone exposure in mouse models, even when using the same strains. These differences have been attributed to sampling techniques (Tighe et al. 2018), hormonal and female cycle effects (Fuentes and Silveyra 2019; Fuentes et al. 2018, 2019), and the role of diet and microbiome (Kasahara et al. 2019; Cho et al. 2018b; Tashiro et al. 2019, 2020).

9.3 Sex Differences in the Response to Air Particulate Matter Exposure

Particulate matter (PM) is a complex mixture of volatile organic and inorganic compounds, including solid particles and liquid droplets, with different physico-chemical properties and toxicity (Bell and Committee 2012; Cassee et al. 2013). The toxicity of PM is characterized by its size, surface chemistry, solubility, and ability to form reactive oxygen species. PM is typically characterized by size, PM$_{2.5}$, being particles with aerodynamic diameters that are 2.5 $\mu$m or smaller, and PM$_{10}$, being particles with aerodynamic diameters of 10 $\mu$m or smaller. Particulate matter is one of the main contributors of indoor and outdoor pollution, and exposure to PM has been associated with a range of cardiovascular and respiratory diseases (Dai et al. 2014; Kurt et al. 2016).

9.3.1 Epidemiological Studies

Several studies within the European Study of Cohorts for Air Pollution Effects (ESCAPE) have found that long-term exposure to PM is associated with decreased lung function in children and adults (Cesaroni et al. 2014; Stafoggia et al. 2010) and increased prevalence and exacerbation of chronic obstructive pulmonary disease (COPD) (Ni et al. 2015; Gehring et al. 2013). Particulate matter has also been associated with higher incidence of asthma and lung cancer in adults (Guarnieri and Balmes 2014; Li and Gao 2014; Pope et al. 2002). Despite growing evidence
indicating that PM exposure increases risks of respiratory diseases, the mechanisms underlying PM-induced inflammation and worsening of disease are still unknown. Moreover, potential modifiers, including biological sex, gender, education, and socioeconomic status, remain inconclusive or unaddressed (Samoli et al. 2013; Liu et al. 2017; Du et al. 2016; Li et al. 2019a; Bourdrel et al. 2017).

There are limited clinical and epidemiological studies assessing differences in the effects of acute and chronic PM exposures in males and females, and these have yielded inconclusive or conflicting results (Table 9.4). In a large cohort study, the authors evaluated non-accidental deaths in 27 US cities (Franklin et al. 2007) and observed an increase in respiratory-related deaths with a 10μg/m³ increase in PM$_{2.5}$ concentrations. This effect was significantly more pronounced in subjects ≥75 years of age. While gender was not identified as a statistically significant modifier, the authors found a higher risk of respiratory mortality in males. In support of these findings, another study looking at the association between air pollution and respiratory hospitalization in Windsor, Ontario, Canada (Luginaah et al. 2005), found that the effects of PM$_{10}$ on respiratory admissions were mostly elevated, but not significant, in all subject groups except for males 0–14 years of age, who had significantly higher numbers of respiratory hospitalizations.

In contrast, one study in Italy assessed the association of PM$_{10}$ exposure with mortality in subjects ≥35 years of age (Faustini et al. 2011) and found that females were more than twice as susceptible to PM$_{10}$-associated respiratory mortality than males, even after adjusting for age. In a very similar study in Spain, authors assessed the association between acute exposures to PM, measured as black smoke (atmospheric particulate black carbon) with a mix of PM$_{2.5}$ and PM$_{10}$, with respiratory mortality among subjects ≥35 years of age who had visited emergency rooms due to COPD exacerbation. The authors found that differences in gender were only observed in elderly patients, where females were at a greater risk of dying due to PM exposure than males (Sunyer et al. 2000).

In a study on healthy beach lifeguards (median age 19) exposed to PM (Thaller et al. 2008), investigators found that the forced vital capacity (FVC) and forced expiratory volume in one second (FEV$_1$) were decreased in female subjects with a 10μg/m³ increase in PM$_{2.5}$ and with peak PM$_{2.5}$ levels. However, males were not significantly affected by PM$_{2.5}$ exposure. While peak levels did not exceed the Environmental Protection Agency (EPA) National Ambient Air Quality Standards (NAAQS) 24-hour levels (65μg/m³ at the time this study was conducted, 35μg/m³ at the time this book was published), the investigators reported significant drops in lung volumes despite the fact that 8-hour average of PM$_{2.5}$ never exceeded 40μg/m³. The authors argued that a potential mediator of the observed sex differences could be particle deposition patterns. In this regard, one clinical study conducted over 20 years ago assessed how regional deposition patterns of inhaled particles affect healthy adult males (n = 11; 25 ± 4 years of age) and females (n = 11; 25 ± 3 years of age) using a serial bolus aerosol delivery technique for fine particles (particle diameter $D_p = 1 \, \mu m$), and coarse aerosols ($D_p = 3$ and $5 \, \mu m$), to a specific volumetric depth ($V_p$) (Kim and Hu 1998). In all subjects, the deposition distribution pattern was reported to be very uneven with respect to $V_p$. However, the unevenness
was more noticeable in females. Notably, total lung deposition was similar between males and females for fine particles, but was consistently greater in females than males for coarse particles (Kim and Hu 1998).

To assess whether long-term reductions in air pollution in Southern California were associated with respiratory health improvements, a cohort of 11-year-olds (healthy and asthmatic children) was followed over 4 years, and FVC and FEV₁
were measured annually (Gauderman et al. 2015). The authors found improvements in both FVC and FEV\(_1\) that were associated with declining PM\(_{2.5}\) and PM\(_{10}\), even after adjusting for confounders. There were significant improvements in lung function in both boys and girls with and without asthma, but the effect on both FEV\(_1\) and FVC was significantly larger in boys than in girls. In another study conducted in Oslo, Norway, hourly outdoor traffic-related pollutant concentrations were measured, including PM\(_{10}\) and PM\(_{2.5}\), to determine their effects on lung function in 9–10-year-old children (Oftedal et al. 2008). Long-term exposures to traffic-related pollutants were associated with reduced peak expiratory flow and forced expiratory flow, especially in girls. FVC and FEV\(_1\) were not affected in either gender.

Emerging evidence indicates that pregnant women are more susceptible to ambient air particles, resulting in adverse birth outcomes including low birth weight, impaired neonatal head circumference, and preterm birth, but significant heterogeneity is consistently observed (Fu et al. 2019; Guo et al. 2019; Sun et al. 2015). Many studies do not account for exposure time, pollutant type, socioeconomic status, and disease history. An average increase in PM\(_{2.5}\) exposure by 30\(\mu\)g/m\(^3\) for 48 hours during the second trimester resulted in significant deficits, but only in male newborns. Specifically, male newborns of mothers exposed to higher concentrations of PM showed significantly lower birth weight, shorter length at birth, and smaller head circumference in comparison to mothers with the lowest exposures to PM (Jedrychowski et al. 2009). These effects were not observed in female newborns. In a large birth cohort study (Cossi et al. 2015), the authors assessed the effects of PM exposure on four preterm birth ranges including 20–27 weeks, 28–31 weeks, 32–33 weeks, and 34–36 weeks and found that exposure to ambient PM\(_{2.5}\) and PM\(_{10}\) increased the risk of birth at 20–27 weeks of gestation, but this risk did not differ by sex. The authors also found that males had a significantly higher risk of being born at 32–33 weeks when exposed to elevated PM\(_{10}\) over the course of the entire pregnancy; however, this was not observed for females.

In addition to effects on newborns, some evidence suggests that prenatal PM exposure also has long-term impacts on the lung function of infants and children. One study found that increased PM\(_{2.5}\) exposure levels at 16–25 weeks’ gestation were significantly associated with early physician-diagnosed asthma development in children by age 6 years in males, but not females (Hsu et al. 2015). Another study found that prenatal PM\(_{2.5}\) exposure in late pregnancy was associated with reduced early childhood lung function and hypermethylation of glutathione S-transferase pi 1 (GSTP1) in DNA isolated from nasal epithelial cells. High GSTP1 methylation was associated with reduced FEV\(_1\) in males, but not females (Lee et al. 2018). In contrast, another study found that both prenatal and postnatal exposures to PM\(_{2.5}\) were associated with later development of asthma, but did not observe substantial sex differences (Jung et al. 2019). To assess sex-specific effects of gestational exposure to PM\(_{2.5}\) in cord blood transcriptomic signatures, the authors recruited a small (n = 142) cohort of mother-newborn pairs and estimated annual PM\(_{2.5}\) averages before delivery (long-term) and during the last month of pregnancy (short-term) (Winckelmans et al. 2017). For short-term exposure, significantly affected gene expression pathways were identified for both females and males that
were related to olfactory signaling, ribosomes, and DNA damage. In males, sex-specific gene expression pathways associated with short-term exposures included synaptic transmission and mitochondrial energy production. In females, immune response pathways were modulated. For long-term exposures, apoptotic execution and RhoA gene expression pathways were upregulated in males, while defensin expression and olfactory signaling were downregulated, and ribosome-related pathways were upregulated in females. Overall, this study revealed that PM exposure, both long-term and short-term, has differential effects on cord blood transcriptomics in males and females, but these findings likely need to be replicated in larger cohorts to confirm the observed responses.

### 9.3.2 Animal Models

While epidemiological research highlights that PM exposure can induce a variety of diseases, in vitro and in vivo experiments are necessary to shed light on the mechanisms involved in the process, such as oxidative stress, cytokine secretion, and inflammatory responses (Cho et al. 2018a). Experimental animal models have been used to study the underlying mechanisms of respiratory diseases caused by exposure to PM, but only a few have assessed sex differences (Table 9.5). Some common exposure approaches include intranasal instillation, intratracheal

| Table 9.5 Animal models of PM exposure |
|---------------------------------------|
| **Exposures** | **Effect/outcome** | **Sex differences** | **References** |
| Pre- and postnatal PM$_{2.5}$ (600 μg/m$^3$, 1 h), BALB/c mice | DNA damage and impaired lung function | Increased (male and female mice used but sex differences not evaluated) | (de Barros Mendes Lopes et al. 2018) |
| PM$_{2.5}$ (<10 μg/m$^3$), Sprague-Dawley rats | BALF neutrophilia, eosinophils, pro-inflammatory protein expression | Increased (only tested in male rats) | (Wang et al. 2020) |
| PM$_{2.5}$ (600 μg/m$^3$, 1 h), BALB/c mice | Tracheal hyperreactivity to methacholine | Higher in both sexes, no sex difference | (Yoshizaki et al. 2017) |
| | COX-2, TGF-α, SP, IL-8Rα protein expression in BALF | Higher in males | |
| | IL-17 and isoprostane protein expression in airway epithelium | Higher in aggregate, interaction with sex | |
| | BALF macrophages, and total cells | Higher in males | |
| | Lung parenchyma cadherin expression | Higher in proestrus females | |

*BALF* bronchoalveolar lavage fluid
instillation, nose-only inhalation, whole-body inhalation, and intravenous injection (Shang and Sun 2018).

Some advantages of using animal models in clinical studies are that PM type, exposure times, and exposure concentrations can be controlled. One study exposed male and female BALB/c mice and their offspring to concentrated urban PM2.5 in a whole-body inhalation chamber prior to stereological and transcriptomic analyses. The authors found that prenatal and early-life postnatal exposure led to DNA damage and impairment of lung function, but the study failed to account for sex differences (de Barros Mendes Lopes et al. 2018). Another study found that rats with human-like COPD features exposed to PM2.5 through whole-body inhalation resulted in emphysema, inflammation, and deterioration in lung function as reflected by increased neutrophils and eosinophils in BALF and cytokine secretion including IL-1β and IL-4 (Wang et al. 2020), but sex differences were not accounted for, as only male rats were used.

Most animal studies also disregard the estrous cycle. One study exposed BALB/c male ($n = 34$) and female ($n = 111$) mice in three phases of the estrous cycle to ambient air (AA, PM2.5 concentration equivalent to 25μg/m$^3$) or concentrated ambient particles (CAPs, 600μg/m$^3$ PM2.5) (Yoshizaki et al. 2017). Tracheal hyperactivity to methacholine was increased in both CAPs-exposed females and males compared with those exposed to AA. Male-exposed mice were hyporesponsive, with increased levels of cyclooxygenase-2 (COX-2), transforming growth factor-alpha (TGF-α), substance P (SP), and IL-8 receptor alpha (IL-8Rα) compared to all females independent of exposure. IL-17 and matrix metalloproteinase-9 (MMP-9) were increased in CAPs-exposed females, which the authors thought may lead to a chronic inflammatory response. The results indicate that lung inflammation differed between sex and phase of the estrous cycle, highlighting the importance of including sex hormones in studies of lung inflammatory mechanisms and lung disease related to air pollution exposure.

9.3.3 Cell Culture Models

Cell culture models are a useful and efficient tool to assess specific PM and their potential health effects. Several studies have identified increased inflammatory responses and oxidative stress, decreased cell viability, and increased apoptosis in response to PM exposure; however, sex differences have not been studied (Table 9.6).

In one study, ex vivo-derived normal human bronchial epithelial cells from brush biopsies of three healthy volunteers were exposed to concentrated coarse ambient PM using direct air and indirect liquid interface exposure methods (Volckens et al. 2009). The authors found significant increases in mRNA expression of interleukin 8 (IL8), homeobox A1 (HOX1), and cyclooxygenase-2 (COX2) in cells exposed with both methods. However, the sex or gender of the subjects was not reported. Another study exposed a human lung epithelial cell line (A549, male human-derived) and a monocyte-macrophage cell line (Raw264.7, male BALB/c
mouse-derived) to PM$_{2.5}$, which led to greater oxidative stress in lung epithelial cells than in monocyte-macrophage cells (Li et al. 2020). One study using BEAS-2B cells (human male-derived) treated with PM$_{2.5}$ extracts at different concentrations for 6 and 24 h found that at a concentration of 100 μg/ml, PM$_{2.5}$ upregulated IL6 and IL8 gene expression at 24 h through the activation of the IKK/NF-κB pathway (Wang et al. 2019a). Another study also using human BEAS-2B cells observed decreased cell viability and increased apoptosis, as well as oxidative stress and expression of pro-inflammatory cytokines including IL1B and IL8, after exposure to PM with high benzo (a)pyrene (BaP) content for 3 days (Raudoniute et al. 2018). Due to the nature of the cell lines used and experimental designs, none of these cell culture experiments accounted for sex differences.

Notably, while cell culture models, especially using immortalized cell lines, are efficient tools to begin probing mechanisms of response to environmental exposures, cell lines also have significant limitations including translatability to whole-organ responses, interaction with other cell types, as well as the majority of immortalized lines being male-derived or of unknown origin, complicating the ability to study sex differences. Contrastingly, ex vivo cell cultures can be used to study potential sex differences in culture, though efficiency is reduced compared to the use of cell lines due to the increased time needed to grow and maintain cells. Thus, the study of sex differences needs careful consideration in the design of cell culture experiments in addition to animal and human studies. Overall, further investigations need to be completed to fully understand mechanisms of response to PM, particularly using models that allow the study of sex differences.

### Table 9.6 Cell culture models of PM exposure and sex effects

| Cell model | Effect/outcome | Sex effects | References |
|------------|----------------|-------------|------------|
| PM$_{2.5}$/PM$_{10}$ exposure (200 L/min, 5 mg/mL, 1 h) | Pro-inflammatory mRNA expression in NHBE cells | Increased (sex of subjects was not reported) | (Volckens et al. 2009) |
| PM$_{2.5}$ exposure (0–200 μg/mL) | Pulmonary oxidative stress in HLE | Increased (only tested in male-derived cell line) | (Li et al. 2020) |
| PM$_{2.5}$ exposure (6–400 μg/mL) | Pro-inflammatory protein expression in BEAS-2B cells | Increased at 100 μg/ml, 24 h (only tested in male-derived cell line) | (Wang et al. 2019a) |
| | IKK/NF-κB pathway | Activated at 100 μg/ml, 6 h (only tested in male-derived cell line) | |
| PAHs PM$_1$ exposure (20 μl/ml, 72 h) | Pro-inflammatory protein and mRNA expression in BEAS-2B cells | Increased (only tested in male-derived cell line) | Raudoniute (et al. 2018) |
| | Cell viability | Decreased (only tested in male-derived cell line) | |
| | Apoptosis | Increased (only tested in male-derived cell line) | |

NHBE normal human bronchial epithelial cells, HLE human lung epithelial cells, BEAS-2B human bronchial epithelial cell line, PAHs poly-aromatic hydrocarbons, PM$_1$ particulate matter less than 1 μm in diameter
9.4 Sex Differences in the Response to Carbon Monoxide Exposure

Carbon monoxide (CO) is a gas that is colorless, tasteless, and odorless. CO is typically present during carbon compound combustion which can occur during fires, in vehicle or generator engine exhaust, and with furnace malfunction, among other sources. CO is a poisonous gas, which affects 50,000 people per year in the USA, and acts by competitively binding hemoglobin in the blood, preventing normal delivery of oxygen, and depriving critical organs of the needed oxygen to function, leading to hypoxia and neurological injury, as well as increased reactive oxygen species productions, resulting in cardiac injury. Clinical diagnosis is typically made via presenting symptoms (headache, dizziness, fatigue, loss of consciousness, altered mentation, chest pain, and nausea/vomiting) and elevated levels of bound CO and hemoglobin (COHb), though measurements of ambient CO levels can also be utilized to confirm diagnosis. Standard of care currently includes normobaric or hypobaric oxygen, which dissociates CO from the hemoglobin, though both pharmacologic and nonpharmacologic are also in development (Rose et al. 2017).

9.4.1 Human Studies

There are a limited number of human studies specifically assessing the effect of CO exposure on sex/gender. The majority of studies assess CO in a mixture of other ambient air pollution and adjust for sex, rather than analyzing by sex or stratifying by sex. There are also recent studies that include CO measurements that are still only including male participants (Obaseki et al. 2014). However, there are a few limited studies that describe heterogeneous results in terms of effects on sex/gender.

In a cohort of adults living in rural Malawi, effects of air pollutant exposures on lung function trajectories were studied. PM$_{2.5}$ and CO were measured with 48-hour personal exposure monitors. Female sex was associated with increased CO exposure, as well as decreased FEV$_1$ and FVC (Rylance et al. 2020).

In a retrospective study of sex differences in severity and prognosis after CO poisoning, it was found that in 66 heterosexual couples, females had higher outcome scores as well as cure and improvement rates compared to their male partners from the same CO poisoning environment. Interestingly, in this cohort, investigators categorized women into premenopausal or postmenopausal groups and found that the higher outcome scores and cure and improvement rates were limited to the premenopausal group and were not found in the postmenopausal group (Huijun et al. 2016). This led the authors to speculate that sex is an important prognostic indicator in CO poisoning. Interestingly, these findings have been supported by a publication by Zavorsky et al. (2014) that investigated factors accounting for previously observed sex differences in CO elimination half-time. This study found that there is a gender difference in CO clearance rates, where male clearances are longer in duration than those of females, but that the gender difference is heavily
influenced by alveolar ventilation rate differences and total hemoglobin differences between males and females. The authors concluded that a shorter half-time for CO elimination may contribute to the higher outcome scores and cure and improvement rates observed in the cohort study above. Interestingly, while younger females, premenopausal vs. postmenopausal, were shown to have higher outcome scores in recovery from CO poisoning, studies of prenatal exposures indicate that young females may be more vulnerable than young males. The GRAPHS study, focused on the role of prenatal household air pollution and infant lung function, identified associations of prenatal CO exposure with reductions in the infant’s time to peak tidal expiratory flow and expiratory time and increases in respiratory rate and minute ventilation. These data were then sex-stratified, leading to the identification of female infants as particularly vulnerable to all four measures of lung function (Lee et al. 2019).

Combined, these studies suggest that sex, age, and exposure window may affect responses to CO exposure. Some of the observed sex-specific effects may be induced by physiological and anatomical differences between males and females, such as alveolar ventilation rate and total hemoglobin. As there are a very limited number of studies examining the effect of CO sex specifically, as well as CO alone rather than in aggregate with other air pollutants, more research is needed to define sex-specific effects of CO exposure, as well as better define sex-specific effect mechanisms.

9.5 Sex Differences in the Response to Nitrogen Dioxide and Sulfur Dioxide Exposure

Oxides of nitrogen and sulfur are highly reactive compounds that may play an important role in lung disease pathology. Known as major sources of indoor and outdoor pollution, concerns regarding the toxicity of nitrogen dioxide (NO₂) and sulfur dioxide (SO₂) have been frequently expressed in clinical and toxicological studies. SO₂ and NO₂ gases are generated primarily from burning fossil fuels containing sulfur and nitrogen. The 1-hour standard concentrations of NO₂ and SO₂ established by the EPA in 2010 are 100 ppb and 75 ppb, respectively. NO₂ and SO₂ have been observed to potentiate adverse health consequences including increased all-cause mortality (Burnett et al. 2004; Stieb et al. 2002; Yorifuji et al. 2019) and exacerbation of asthma (Park et al. 2001; Andersson et al. 2006; Sunyer et al. 2002). While NO₂ exposure has been linked to aggravation of COPD (Lamichhane et al. 2018; Gao et al. 2020; Zhang et al. 2018) and cardiovascular mortality (Bourdrel et al. 2017; Faustini et al. 2014; Mills et al. 2015), this association remains unclear for SO₂ exposure. Long-term impacts of SO₂ have been associated with respiratory mortality (Atkinson et al. 2016) and increased risk of developing lung cancer (Lee et al. 2002). Despite growing concerns regarding the impacts of NO₂ and SO₂ exposure on human health, very few studies have stratified results by gender nor compared the impact of NO₂ and SO₂ exposure in males and females. It also remains unclear whether pollution-derived NO₂ and SO₂ act directly
on human health or contribute to adverse effects in combination with other ambient pollutants.

### 9.5.1 Epidemiological Studies

The studies that have assessed results by gender have identified effects of NO$_2$ and SO$_2$ on respiratory outcomes including asthma, all-cause and respiratory mortality, lung function, pneumonia, and lung cancer (Table 9.7). However, these studies are

| Exposure | Effect/outcome | Sex differences | References |
|----------|----------------|-----------------|------------|
| NO$_2$   | Cardiovascular mortality | Higher in females | (Sunyer et al. 2002) |
|         | Respiratory mortality | Higher in males | |
|         | Respiratory hospitalization | Higher in females 0–14 years of age | (Luginaah et al. 2005) |
|         | Respiratory symptoms | Higher in females | (Oosterlee et al. 1996) |
|         | FVC and FEV$_1$ | Higher in males | (Gauderman et al. 2015) |
|         | FEV$_1$ | Lower in females | (Mölter et al. 2013) |
|         | Asthma | Higher in males | |
|         | RPEF and FEF | Lower in females | (Oftedal et al. 2008) |
|         | Lung cancer | No sex differences | (Katanoda et al. 2011) |
|         | Umbilical cord leptin | Higher in females | (Lavigne et al. 2016) |
|         | Umbilical cord adiponectin | No sex differences | |
|         | Preterm birth | Higher in males | (Cossi et al. 2015) |
| NO$_2$ and SO$_2$ | Asthma | Higher in females | (Dong et al. 2011) |
|         | Pneumonia | No sex differences | (Katanoda et al. 2011) |
|         | Respiratory mortality | No sex differences | |
|         | Cardiorespiratory mortality | Higher in females and the elderly | (Kan et al. 2008) |
| SO$_2$  | Respiratory hospitalization | Higher in females | (Luginaah et al. 2005) |
|         | COPD diagnosis | Higher in males | (Nuvolone et al. 2011) |
|         | FEV$_1$/FEV | Lower in males | (Nuvolone et al. 2011; Rosser et al. 2020) |
|         | Dyspnea | Higher in females | (Nuvolone et al. 2011) |
|         | Asthma diagnosis | Higher in females | |
| Traffic-related pollutants | FVC and FEV$_1$ | No sex differences | (Oftedal et al. 2008) |

*FVC* forced vital capacity, *FEV$_1$* forced expiratory volume in one second, *RPEF* reduced peak expiratory flow, *FEF* forced expiratory flow
limited in number and cohort size, indicating that more research on sex-specific effects are needed to understand comprehensive effects of exposure.

Overall, epidemiological data show that exposure to air pollution including NO₂ and SO₂ is associated with increased prevalence and exacerbation of asthma, especially in children (Burbank and Peden 2018). In a large cohort study, the relationship between SO₂ and NO₂ exposure and asthmatic symptoms was assessed in children 3 to 12 years of age in China. This study revealed that children with allergic predispositions were more susceptible to negative effects of air pollutants than children without allergic predispositions (Dong et al. 2011).

The same study showed that among children without an allergic predisposition, air pollution effects on asthma were stronger in males compared to females. However, the opposite effect was observed among children with an allergic predisposition. An increased prevalence of doctor-diagnosed asthma was also significantly associated with SO₂ and NO₂ exposure only among females (Dong et al. 2011).

In addition to increasing asthma symptoms and diagnosis, NO₂ exposure has also been associated with all-cause mortality, but particularly for respiratory mortality. In particular, patients with asthma and patients with more than one emergency room admission for asthma were the most affected (Sunyer et al. 2002). In patients admitted only once, the main causes of death were primarily cardiovascular-related in females and respiratory-related in males. However, no difference was observed between males and females admitted more than once. Moreover, in subjects with more than one admission and diagnosis of both asthma and COPD, females and younger patients had a higher risk of death with NO₂ exposure than males and older patients (Sunyer et al. 2002). SO₂ and NO₂ exposure was also significantly associated with all-cause mortality, including cardiorespiratory diseases, and the effects of air pollutants were more evident in females and the elderly (Kan et al. 2008). In another study, the effects of SO₂ and NO₂ exposure on respiratory admissions were mostly elevated, but not significant, in all subject groups, except for females 0–14 years of age where there was significant effect on respiratory admissions; however, the effect of SO₂ on female respiratory admissions was consistently elevated in all age groups (groups 15–64 and ≥65 years of age) (Luginaah et al. 2005).

Exposure to NO₂ and SO₂ has also been shown to affect lung function, though results are inconsistent across studies. A longitudinal study found that long-term exposure to NO₂ in children from birth to 11 years of age was associated with significantly less growth in FEV₁ over time, both before and after bronchodilator treatment (Mölter et al. 2013). Changes in FEV₁ were also more likely to happen in females. Girls were less likely than boys to develop asthma in early life, but by 8 years of age, there were no differences in asthma between males and females (Mölter et al. 2013). Similarly, in a study following a cohort of 11-year-old healthy and asthmatic children over 4 years, declining NO₂ concentrations were associated with improvements in both FVC and FEV₁ (Gauderman et al. 2015). There were significant improvements in lung function in both males and females with and without asthma, but the effect on both FEV₁ and FVC was significantly larger in males than in females, indicating sustained changes in FEV₁ due to exposure were
more likely in females, similar to the longitudinal study above. In contrast, a study on traffic-related pollutants, including NO₂, found that long-term exposures in children, who were 9 and 10 years of age, were associated with reduced peak expiratory flow and forced expiratory flow, especially in females (Oftedal et al. 2008), but FVC and FEV₁ were not affected in either gender studied. In another traffic study, children (0–15 years of age) exposed to environmental NO₂ and living along busy traffic streets experienced a higher prevalence of most respiratory symptoms than children living on quiet streets. In this study, risks were higher for females than for males, but only mild dyspnea was reported among adults (Oosterlee et al. 1996).

In addition to effects, of NO₂, effects of SO₂ were also studied. In a traffic study of effects of SO₂, it was found that males living within 100 meters of a main road had increased risk of COPD diagnosis and reduced FEV₁/FVC, while females had increased risks of dyspnea and asthma diagnosis (Nuvolone et al. 2011), when compared to those living 250–800 meters from the main road. Supporting these lung function findings, a study of Puerto Rican children 6 to 14 years of age found that annual SO₂ exposure was significantly associated with lower FEV₁/FVC, especially in children with asthma. In the same study, annual SO₂ exposure was not significantly associated with total IgE, FEV₁, or FVC, but this study did not stratify results by gender (Rosser et al. 2020).

While there is considerable evidence that daily exposure to NO₂ and SO₂ throughout adolescence can affect lung function, there is very little to no evidence that prenatal SO₂ and NO₂ exposure has impacts on the lung function of infants and children. In one study, umbilical cord blood samples (n = 1257) were analyzed to measure levels of leptin and adiponectin, which are mediators of inflammatory profiles in the airway, in response to air pollutants, including NO₂. Greater prenatal exposure to NO₂ was associated with higher cord blood levels of adiponectin, but there was no difference between male and female infants. Leptin concentrations were significantly higher for female infants, and increased exposure to air pollution during pregnancy was associated with higher levels of umbilical cord blood leptin (Lavigne et al. 2016). In a larger study (n = 321,029), the effects of NO₂ exposure were assessed on four preterm birth ranges including 20–27 weeks, 28–31 weeks, 32–33 weeks, and 34–36 weeks, and a statistically significant higher risk for males to be born at 20–27 weeks of gestation, as compared to females, when exposed to NO₂ during the second trimester was observed (Cossi et al. 2015). The authors also found that males had a significantly higher risk of being born at 32–33 weeks when exposed during the entire pregnancy to high NO₂ but this was not observed for females.

Finally, NO₂ and SO₂ exposures have also been associated with other adverse effects in both males and females, including pneumonia and lung cancer. In a large study in Japan, development of respiratory diseases, particularly pneumonia, and mortality from respiratory diseases were significantly associated with all air pollutants, including NO₂ and SO₂ exposure in both males and females (Katanoda et al. 2011). A significantly higher risk of lung cancer mortality was observed at a level of
20 ppb or higher for NO\textsubscript{2} in both males and females. These associations were not observed for COPD.

### 9.5.2 Clinical Studies

As mentioned earlier, the literature on sex differences in NO\textsubscript{2} and SO\textsubscript{2} in clinical studies is limited. In a small clinical trial, 21 healthy adults (9 females and 12 males, 18–40 years of age) were exposed to 0.6 and 1.5 ppm NO\textsubscript{2} for 3 hours in an environmental chamber with intermittent moderate exercise. Bronchoalveolar lavage fluid (BALF) circulating total lymphocytes and T-cells were decreased, and polymorphonuclear leukocytes were increased with NO\textsubscript{2} exposure in both males and females. However, these changes were not significant. There were also no significant effects of NO\textsubscript{2} exposure on FVC, FEV\textsubscript{1}, and FEV\textsubscript{1}/FVC in males and females (Frampton et al. 2002), which contrasts with some of the epidemiological findings above. No clinical studies conducted to date have explored or reported sex differences in SO\textsubscript{2} exposures. Overall, to better understand the effects of NO\textsubscript{2} and SO\textsubscript{2} alone and in combination with other air pollutant components, more clinical controlled exposure studies are needed.

### 9.5.3 Cell Culture Models

While epidemiological and clinical studies are limited, there is evidence that exposure to NO\textsubscript{2} and SO\textsubscript{2} may have detrimental effects within the airway. To assess this potential, a limited number of cell culture experiments have been conducted, which indicate potential mechanisms of action. A study using ciliated epithelial cells cultured from nasal brushings from 12 healthy adults (5 females and 7 males, mean age 32 ± 5 years of age) exposed to SO\textsubscript{2} concentrations of 2.5–12.5 ppm for 30 min reported a dose-dependent decrease in ciliary beat frequency (CBF) and pH after SO\textsubscript{2} exposure (Kienast et al. 1994). A 30-min exposure to 2.5 ppm and 12.5 ppm SO\textsubscript{2} resulted in a 42.8% and 96.5% decrease in CBF, respectively, suppressing cell activity. Interestingly, increasing the pH partially reversed the damage (Kienast et al. 1994). Another study assessed the cellular pro-inflammatory responses of commercial normal human bronchial epithelial (NHBE) cells (sex not disclosed) to NO\textsubscript{2} exposure (Ayyagari et al. 2004). In this model, cells were pre-treated with pro-inflammatory cytokines including IFN-\textgamma, TNF-\textalpha, IL-1\textbeta, and IL-8 to simulate preexisting lung diseases and exposed for 6 hours and 24 hours to 45 ppm NO\textsubscript{2} in a gas-phase exposure system. NO\textsubscript{2} exposure resulted in a significant increase in the generation of IL-8, TNF-\textalpha, IL-1, and NO/nitrite, suggesting that NO\textsubscript{2} exposure may contribute to lung inflammation and injury via increasing levels of pro-inflammatory cytokines. Overall, the number of cell culture experiments conducted on the effects of NO\textsubscript{2} and SO\textsubscript{2} is limited, but some plausible mechanisms of action, decreased pH, and increased
pro-inflammation and injury were identified. These findings should be investigated further to confirm the results described here, as well as explore other pathways and mechanisms that might be affected by exposure.

### 9.5.4 Animal Models

While there are several animal studies regarding SO$_2$ and NO$_2$ effects of health (Table 9.8), sex differences have not yet been considered. However, these studies may shed some light on potential mechanisms of action that may result in the health

| Animal model | Effect/outcome | Sex differences | References |
|--------------|----------------|----------------|------------|
| NO$_2$ (10 ppm, 4 w), Brown Norway rats | End-expiratory lung volume | No change (only tested in male rats) | (Layachi et al. 2012) |
| | Pro-inflammatory protein expression and inflammatory cell infiltration in BALF | Increased in NO$_2$ + OVA (only tested in male rats) | |
| | Airway reactivity | Decreased in NO$_2$ + OVA + CNP (only tested in male rats) | |
| NaHSO$_3$, Na$_2$SO$_3$ (125–500 mg/kg), Kunming albino mice | OTM of DNA in lung cells | Increased (only tested in male mice) | (Meng et al. 2004) |
| SO$_2$ (3.8 ppm), C57BL/6 mice | Eosinophilia, BALF pro-inflammatory mRNA expression, and Stat6 mRNA expression | Increased in SO$_2$ + OVA (only tested in male rats) | (Li et al. 2018) |
| SO$_2$ (2200 ppm, 10 min), Sprague-Dawley rats | Neutrophils, Macrophages, Airway infiltration, Bronchial damage TGFβ-1 expression | Increased (only tested in female rats) | (Wigenstam et al. 2016) |
| SO$_2$ (600 ppm, 7 d), Sprague Dawley rats | CD19 mRNA and protein expression, CD19+ in NS, CD19+/CD23+ in NS | Decreased (only tested in male rats) | (Chai et al. 2018) |
| | IgG, IgA, IgE | No changes (only tested in male rats) | |
| SO$_2$ (5–80 ppm), Sprague Dawley rats | Hypersecretion | Increased: 20 ppm, 20–25 d (only tested in male rats) | (Wagner et al. 2006) |
| | Inflammatory infiltrates in tracheal epithelial cells | Increased: ≥10 ppm, 3 d, Increased: 20 ppm 20–25 d (only tested in female rats) | |

*BALF* bronchoalveolar lavage fluid, *OVA* ovalbumin sensitization, *CNP* concentrated nanoparticles
effects observed and should further be investigated by sex. One study assessed the DNA-damaging effects of SO$_2$ derivatives in cells from various organs (brain, lung, heart, liver, stomach, spleen, thymus, bone marrow, and kidney) of male Kunming albino mice. SO$_2$ derivatives and sodium sulfite were administered by intraperitoneal injections at 125, 250, or 500 mg/kg body weight, and all doses significantly increased the olive tail movement (OTM) of DNA in cells from all organs, including the lungs in a dose-dependent manner, suggesting that SO$_2$ and its derivatives are systemic oxidative DNA-damaging agents (Meng et al. 2004).

Another study assessed the effect of exposure to NO$_2$ on a rodent asthma model and ovalbumin sensitization (OVA) in male brown Norway rats (Layachi et al. 2012). Th2 cytokines, IL-4, IL-5, and IL-13, were significantly increased in the NO$_2$ + OVA-treated rats. Additionally, control (NO$_2$ + air) and NO$_2$ + OVA treatments resulted in inflammatory infiltration, but end-expiratory lung volume (EELV) was not significantly altered in any treatment groups. Similarly, SO$_2$ exposure in an OVA model also resulted in inflammatory changes, particularly, increased counts of eosinophil-rich leukocytes and elevated expression of TNF-α and Th2 cytokines, IL-4, IL-5, and IL-13 and STAT6 (Li et al. 2018).

Interestingly, inflammation as a result of SO$_2$ exposure is not limited to models of asthma. In female Sprague-Dawley rats exposed to a single dose of 2200 ppm SO$_2$ for 10 min and then treated with a single dose of anti-inflammatory corticosteroid dexamethasone, exposure resulted in labored breathing, decreased body weight, and acute inflammation with neutrophil and macrophage airway infiltrates and bronchial damage (Wigenstam et al. 2016). Furthermore, rats displayed hyperreactive airways and increased expression of the pro-fibrotic cytokine, TGFβ-1. Additionally, male Sprague-Dawley rats exposed to 600 ppm SO$_2$ 2 h/day for seven consecutive days showed a reduction in the expression of CD19 at both the mRNA and protein levels, indicating compromise of the potential for immunoglobulin-induced activation of B cells in the airway; however, IgG, IgA, and IgE levels were not affected (Chai et al. 2018).

Finally, SO$_2$ and NO$_2$ have been shown to so significantly adversely affect the airway that exposures have been used to develop rodent disease models, such as COPD induced by NO$_2$ in pathogen-free male rats (Wagner et al. 2006). Use of SO$_2$ exposure in rodent models was found to induce a model of pneumonia (Lebowitz and Fairchild 1973); however, it did not induce emphysema (Stavert et al. 1986).

Based on these epidemiological and clinical studies, results on the toxicity of SO$_2$ and NO$_2$ remain inconclusive, especially concerning sex differences. All epidemiological studies assess ambient air pollution; therefore, attributing the observed health consequences to SO$_2$ and NO$_2$ is challenging due to the presence of confounding factors such as smoke, particulates, and other air pollutants. Stratification by education, race, socioeconomic status, and occupational exposure remains an issue that is rarely addressed in most cases. While, overall, exposure to NO$_2$ and SO$_2$ is associated with potentiating and exacerbating many respiratory diseases in human and animal studies, more clinical in vivo and in vitro experiments, particularly those focused on sex differences and specific pollutants, are necessary to develop and
implement personalized prevention methods and therapeutics for both males and females.

9.6 Conclusion

Based on epidemiological and clinical studies, it is evident that males and females respond differently to ozone and PM exposure, yet significant heterogeneity is consistently observed. It remains unclear whether modifications are attributable to biological sex differences, gender roles, or a combination of the two. Overall, very few studies have taken sex into account when modeling the effects of environmental pollutants. Most studies investigate ambient air pollution, which includes a mix of PM, ozone, nitrogen dioxide, and sulfur dioxide, but speculate and attribute air pollution exposure outcomes to specific pollutants based on their concentration relative to other pollutants and association with health outcomes. Thus, to specifically identify effects of individual pollutants and their mixtures, more clinical in vivo and in vitro controlled experiments are required. They are also additionally needed to understand the underlying mechanisms of known sex differences in pollutant effects on human health.

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