Sex and Gender Differences in Lung Disease

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Abstract

Sex differences in the anatomy and physiology of the respiratory system have been widely reported. These intrinsic sex differences have also been shown to modulate the pathophysiology, incidence, morbidity, and mortality of several lung diseases across the life span. In this chapter, we describe the epidemiology of sex differences in respiratory diseases including neonatal lung disease (respiratory distress syndrome, bronchopulmonary dysplasia) and pediatric and adult disease (including asthma, cystic fibrosis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, lung cancer, lymphangioleiomyomatosis, obstructive sleep apnea, pulmonary arterial hypertension, and respiratory viral infections such as respiratory syncytial virus, influenza, and SARS-CoV-2). We also discuss the current state of research on the mechanisms underlying the observed sex differences in lung disease susceptibility and severity and the importance of considering both sex and gender variables in research studies' design and analysis.

Keywords

Sex · Gender · Lung disease · Hormones · Chronic disease

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14.1 Introduction

Sex-related differences exist in many lung diseases throughout the life span [36, 277]. In neonates, the male disadvantage is a well-established clinical fact, especially in the preterm population [16] to the point that guidelines to predict outcomes from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and Neonatal Research Network (NRN) for extremely preterm birth outcomes include sex as a critical biological variable [225]. In children and adults, some lung conditions are more commonly found in women and men, respectively, and can present with different degrees of severity and symptoms.

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Overall, the literature shows that most lung diseases are more commonly found or present with higher degree of severity, exacerbation rate, hospitalizations, and mortality in women than in men [89]. These include asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and some types of lung cancer such as adenocarcinoma [211, 228, 316]. Furthermore, some rare and less-understood lung conditions such as lymphangioleiomyomatosis (LAM) are almost exclusively found in women [309].

Although the terms sex and gender are commonly used interchangeably, they represent different concepts. According to the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), "sex" refers to the biological differences between females and males, including chromosomal, anatomical, hormonal, and other physiological and functional differences. "Gender," on the other hand, refers to the characteristics that a society or culture delineates as masculine or feminine, including social, environmental, cultural, and behavioral factors and choices that influence an individual's self-identity. As opposed to sex, gender is a social construct and not defined biologically. Importantly, an individual's gender does not necessarily need to be consistent with their biological sex given at birth nor be fixed or binary. However, because the health of men and women is influenced by both sex and gender, including these variables in research studies is crucial. In basic science, this means including both male and female cells and/or experimental animal models in study designs, as well as examining the influence of sex hormones down to the molecular level. For clinical, behavioral, and outcomes research, this means considering gender-specific social influences and their impact on health and disease. Only when we incorporate sex and gender factors in research studies, we will be able to understand the mechanisms underlying the numerous sex disparities observed in lung disease prevalence and severity and provide more efficient and personalized sex- and gender-specific medicine.

14.2 Sex and Gender Differences in Respiratory Disease

It is not possible to talk about sex differences in respiratory disease without discussing first sex differences in lung biology. From the 16th week of gestation to adult life, significant differences exist in the male and female lung. In addition, changes in sex hormone levels throughout development, puberty, and physiological events such as pregnancy and menopause also influence lung function and health. Early in life, while female sex hormones are beneficial, promoting lung development and maturation, androgens appear to exert the opposite effect [245]. After puberty, the opposite occurs in diseases such as severe asthma, where improvement is observed with increasing androgen levels, and fluctuations in female hormones throughout the menstrual cycle promote asthma exacerbations. Overall, the available body of research shows that the effect of sex hormones on lung health appears to depend on the timing of exposure and thus differentially affects disease prevalence and severity in males and females throughout the life span. Table 14.1 summarizes the information available on some of the most common lung diseases affecting men and women disproportionately. In the sections below, we describe the epidemiological information available as well as the status of the research aiming to understand the mechanisms behind the observed sex differences for each disease.

14.3 Neonatal Lung Disease

Infants born prematurely are at higher risk for cardiopulmonary and neurological comorbidities such as retinopathy, pulmonary hypoplasia, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and chronic neurocognitive developmental disorders [190]. Many of these comorbidities exhibit significant sex disparities that could be a consequence of differences in lung development and/or caused by a complex interaction between immunological, hormonal, and genetic factors earlier in life [189]. Overall,

Table 14.1 Sex differences in neonatal, pediatric, and adult lung disease prevalence

Disease	Population	Sex differences	References
Asthma	Children	Boys > girls	[3, 36, 185]
	Adults	Women > men	
Bronchopulmonary dysplasia (BPD)	Neonates	Boys > girls	[17, 85, 276]
Chronic bronchitis	Adults	Women > men	[11]
Chronic cough	Children	Boys > girls	[27]
Chronic obstructive pulmonary disease (COPD)	Adults	Women > men	[2, 111]
Cystic fibrosis	Children	Girls > boys[a]	[92, 289]
	Adults	Women > men	
Coronavirus disease 19 (COVID-19)	Adults	Men > women	[234]
Emphysema	Adults	Men > women	[160]
Idiopathic pulmonary fibrosis	Adults	Men > women	[213, 314]
Lung cancer	Adults	Women > men	[209, 252]
	Adults	Women > men	[309]
Pulmonary arterial hypertension	Adults	Women > men	[170]
Obstructive sleep apnea	Adults	Men > women	[144, 184]
Respiratory distress syndrome (RDS)	Neonates	Boys > girls	[17, 85, 276]
Respiratory syncytial virus infection (RSV)	Neonates/children	Boys > girls	[182]

[a]Infection rates and outcomes worse in girls than boys, but no sex differences in incidence

male infants are presumed to have an intrinsic disadvantage and to be more sensitive to adverse environmental exposures during development and after birth [181]. This sex-related disparity is particularly manifested during the neonatal period and is more pronounced in prematurely born infants.

14.3.1 Sex Differences in Lung Development

The development of the male and female lung is a highly regulated process controlled by genetic, epigenetic, hormonal, and environmental factors. This process is divided into five stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar (Table 14.2). Each stage is characterized by specific cellular and structural events that are controlled by the expression of multiple developmental genes [296, 297]. Sex differences in structural, mechanical, and functional aspects of lung development, as well as in its control by sex hormones, have been widely documented [36, 37, 163]. These differences are thought to be associated with the sexual dimorphism observed not only in neonatal lung disease but also later in life [245]. Respiratory diseases such as RDS and BPD contribute to a large proportion of the morbidity and mortality of prematurely born infants [276]. Importantly, even late preterm infants, born at gestational ages of 34–36 weeks, have been found to be greater risk for adverse respiratory morbidity and mortality than infants born at term [87].

During the fetal period, male lung maturation is usually delayed in comparison to female maturation. Pulmonary surfactant production initiates later in the male vs. the female lung [36, 235]. Consequently, male neonates are at increased risk of developing respiratory distress syndrome (RDS) and a higher risk of morbidity and mortality due to RDS compared with female neonates of similar gestational age [107, 269]. Furthermore, sex differences in overall neonatal survival and pulmonary outcomes have been described with a significantly higher incidence in males versus females [96]. One example is the high incidence observed in males for the development of bronchopulmonary dysplasia (BPD), a pulmonary pathology of the neonate for which RDS is not always an anterior event [207]. Differences in gene expression, particularly at the late developmen-

Table 14.2 Stages of human lung development

Developmental stage (gestational age)	Main events	Sex differences	References
Embryonic (3–6 weeks)	Lung buds emerge (foregut), and trachea and bronchial buds form	None reported	–
Pseudoglandular (6–16 weeks)	Bronchial development, airway branching	Fetal growth and breathing movements are detected earlier in the female fetus. AMH delays branching by promoting apoptosis in males	[41, 98]
Canalicular (16–26 weeks)	Subdivision of distal airways into canaliculi, vascularization Differentiation of type I and II cells, surfactant production	Surfactant secretion and phospholipid maturation are inhibited in males (androgens) and promoted in females (estrogens)	[207, 235, 274]
Saccular (26–36 weeks)	Cell differentiation, type II cell maturation, surfactant secretion Formation of sacs and primary septa	Surfactant production and phospholipid profile remain more advanced in females	[71]
Alveolar (36 weeks–adolescence)	Alveolar multiplication, enlargement, and maturation Lung growth continues and lung function increases with age and peaks in adolescence	Faster alveolarization in females. Higher flow rate per lung volume, but smaller lung size in girls. Better response to surfactant therapy in female newborns with RDS. FEV1 peaks earlier in females than males	[23, 30, 231, 271]

AMH Anti-Müllerian hormone, *FEV1* Forced expiratory volume in 1 minute

tal stages, have been shown to play significant roles in this sex disparity in lung health outcomes [6, 23, 85].

14.3.2 Respiratory Distress Syndrome

Respiratory distress syndrome is a condition of the premature born characterized by a deficiency in pulmonary surfactant [9]. Infants presenting with RDS show widespread alveolar atelectasis and a reduction in lung compliance, with secondary complications such as pneumothorax. Prior to the introduction of antenatal corticosteroids and postnatal surfactant replacement therapy, RDS was a major contributor to neonatal mortality, particularly in male newborns [194].

The main factors involved in the pathophysiology of RDS are surfactant deficiency and dysfunction in the immature lung, which occur at higher rates in males than females of the same gestational age [181]. Thus, the less developed or mature the lung, the higher the chance of disease manifestation after birth. As mentioned earlier, pulmonary surfactant is produced earlier in females than males during gestation, and its production is stimulated by female sex hormones, and inhibited by male sex hormones [263, 278]. A meta-analysis of data from over 500,000 preterm newborn infants found that RDS was between 1.56 and 1.84 times higher to occur in newborn males than females [145]. This report indicated that males were also at higher risk for other diseases of the newborn, such as BPD, as well as lower respiratory tract infections, bronchiolitis, and pneumonia.

Preventative and treatment options for RDS include postnatal surfactant administration and antenatal corticosteroid therapy [276]. For a long time, corticosteroids (e.g., betamethasone) have been reported to have sex-specific effects on placental oxidative balance and microvascular blood flow [254, 255], as well as to improve the subsequent response of infants to surfactant administration [120], with more beneficial effects in females than males [194]. However, a more recent systematic review and meta-analysis on the topic did not find sex-specific differences, although the type of antenatal glucocorticoid

used (betamethasone vs. dexamethasone) displayed a sex-specific effect [221].

14.3.3 Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia is a lung disease of the prematurely newborn, characterized by an arrest in alveolarization and aberrant pulmonary vascular development [17, 113]. The disease diagnosis is performed by assessing the need for mechanical ventilation and oxygen respiratory support at 36 weeks' postmenstrual age [16] and displays a higher incidence in extremely low birth weight neonates [38].

The widespread use of antenatal corticosteroids, neonatal exogenous surfactant, and protective ventilation strategies has led to increased survival of more extremely preterm infants, with a consequent increase in BPD incidence in the past few decades [112, 113]. While mortality from the disease has declined significantly in the past several decades, children diagnosed with BPD still display long-term complications in lung health ranging from the need for tracheostomy and mechanical ventilation to pediatric pulmonary arterial hypertension and poor neurodevelopmental outcomes [55, 219]. Recent studies have also reported that adults who were born preterm display a higher incidence of airflow obstruction, gas trapping, and reduced gas exchange than those born term [310] and that worsening of lung function persists throughout childhood, particularly in males [93].

Multiple clinical studies have reported sex differences in BPD, including a higher incidence in males vs. females that persists after adjusting for other confounders. Moreover, males display higher death and oxygen dependency rates, as well as pulmonary hemorrhage and use of postnatal steroids [28, 112, 113]. Male sex is considered not only an independent major risk predictor of BPD but also to worsening of lung function during the neonatal and early childhood periods [268]. However, despite the well-established sexual dimorphism in the incidence of BPD, the mechanisms associated with these disparities are not completely understood. Recent studies in animal models have suggested a role for microRNAs (miRNAs) in mediating sex biases in BPD [138, 210, 317]. Others have related the sexual dimorphism of PBD to sex-specific differential activation of hypoxia-inducible factors and genes related to angiogenesis, supporting the pulmonary angiogenesis dysregulation in the pathobiology of BPD [49, 138].

14.4 Pediatric and Adult Lung Disease

Sex differences in lung and airway development persist throughout infancy and early childhood [270, 293]. While females display larger airways than males, the number of alveoli per unit area and the alveolar size do not differ between sexes. The age- and height-adjusted lung volume, however, is higher in boys than girls, which may result in a larger alveolar surface area and a higher diffusion capacity of carbon monoxide (DLCO) in males [20, 233, 270]. With age, differences in lung volumes, as well as in lung size and shape, become more evident [270, 275]. Together with differences in the distending forces of the lungs, these result in differences in the recoil pressure between males and females [51]. This sexual dimorphism in human lung morphometrics and function, together with physiological differences observed by pulmonary function testing, spirometry, and other techniques, has been used to partially explain the observed sex disparity in multiple pulmonary conditions.

Overall, while the majority of lung diseases presented below affect more adult women than men, several conditions are observed at higher rates in men than women and/or show opposite trends in childhood vs. adult life. A multitude of intrinsic factors, such as sex hormones, genetic and epigenetic factors, and comorbidities, along with other extrinsic factor,s have been suggested to contribute to these trends. In the next sections, we summarize the recent epidemiological data, as well as research aiming to understand the mechanisms behind sex disparities in lung disease throughout the life span.

14.4.1 Asthma

Asthma is a heterogeneous disease characterized by chronic airway inflammation. Some of its symptoms are wheezing, shortness of breath, chest tightness, cough, and airflow limitation [83]. Asthma is one of the most prevalent inflammatory diseases of the lung, affecting a significant portion of the world's population. The World Health Organization reported that more than 339 million people suffer from asthma, resulting in more than 400,000 deaths per year [42].

While asthma imposes a substantial public health burden in terms of impaired quality of life and mortality in men and women, clear sex differences exist in its risk, prevalence, and severity across life span [66, 89, 180, 237]. Depending on the sex and age of the patient, striking differences are observed in asthma incidence, prevalence, and severity [162]. An interesting fact is that asthma in children is more prevalent in boys than girls, and studies in adult populations frequently report more negative lung health outcomes for women than men, suggesting an involvement of sex hormones in mediating these effects [129, 228].

Epidemiological studies of childhood asthma have shown that prepubertal boys have more asthma than girls, especially at younger ages [75, 143]. Chronic cough in early childhood, whether from asthma or other causes, is also more common in boys than girls [27]. According to the Centers for Disease Control and Prevention, in the United States, it is estimated that 8.3% of boys and 6.7% of girls under 18 years old currently suffer from asthma. Interestingly, these patterns are reversed after puberty, where asthma prevalence rates for women are almost twice as those for men (5.5% vs. 9.8% for women and men over 18 years of age, respectively) [42]. These statistics have led investigators to hypothesize that hormonal changes starting in puberty contribute to asthma development. This notion is further supported by studies showing that girls who undergo menarche at an earlier age have a higher risk of developing asthma after puberty than girls in which menarche occurs later [226].

Studies showing variations in asthma symptoms and hospitalization rates throughout the menstrual cycle and a decline in asthma incidence in women after menopause also support this hypothesis [33, 204]. Also, women are more susceptible to asthma induced by air pollution and show worse adverse pulmonary health outcomes than men [141, 147]. In this regard, clinical studies and experimental evidence from mouse models have reported that female hormones such as estrogen can trigger lung inflammatory and allergic reactions, while male hormones such as androgens play the opposite role [76, 186, 307]. Interestingly, the severity of asthma in men increases later in life when androgen levels decrease [35]. Overall, more research is needed to elucidate the mechanisms underlying the observed sex differences in disease susceptibility and progression.

Sex differences in asthma have been linked to immunological factors, lung physiology and growth, and behavioral factors [74–130], as well as exposure to air pollutants [88, 86]. Human studies and in vivo models of asthma have shown that female hormones can trigger lung inflammatory and allergic reactions, and male hormones usually play the opposite role [77]. Interestingly, researchers have discovered that sex hormones can alter macrophage polarization and other immune-related cells such as the group 2 innate lymphocytes (ILC2s) and airway smooth muscle cells [22]. ILC2s that lack a killer cell lectin-like receptor G1 accumulate in the lungs of females after they have reached reproductive age but not in males [115]. Others have found that estrogen and testosterone increase and decrease Th2-mediated airway inflammation, respectively [78]. The authors of this study also concluded that females have augmented IL-17A-mediated airway inflammation compared to males [78].

Genetic associations with asthma have also been reported and found to be sex specific [105]. Two single nucleotide polymorphisms (SNPs) in the thymic stromal lymphopoietin (TSLP) gene (rs1837253 and rs2289276) have been associated with asthma in a sex-specific manner. Specifically, rs1837253 is associated with a lower risk for asthma in men, and rs2289276 is associated with

a higher risk of asthma in women. While the underlying mechanisms for these sex-specific associations have not been elucidated, these genetic variants have been associated with changes in immunoglobulin E (IgE) levels, which in children are correlated with higher airway resistance and exacerbations triggered by dust, pollen, and pets [94].

14.4.2 Exercise-Induced Bronchoconstriction

Exercise-induced bronchospasm/bronchoconstriction (EIB) is a phenomenon of acute airway narrowing that occurs during or after exercise or physical exertion. As such, EIB can occur in the presence or absence of asthma. Traditionally, the terms exercise-induced asthma (EIA) and (EIB) have been used interchangeably. However, the current consensus is that EIB represents a more accurate reflection of the underlying pathophysiology of the condition, since exercise is not an independent risk factor for asthma but rather a trigger of bronchoconstriction in patients with underlying asthma [175, 196, 258].

As mentioned above, asthma prevalence is higher in boys than in girls; however, after puberty the prevalence is around 20% higher in women than men, indicating a potential contribution of hormones after puberty [195]. Moreover, sex and gender differences in response to exercise have clear implications for understanding gender-specific adaptations to exercise for athletic performance and overall health [188].

The estimated prevalence of EIB varies from approximately 5% to 20% in the general population to an estimated 30% to 70% in elite winter athletes and athletes who participate in summer endurance sports, and at least 90% in individuals with persistent asthma [298]. This condition has been reported in a range of sporting activities but is most common in participants of cold weather sports (e.g., Nordic skiing) and indoor sports (e.g., ice-skating and swimming) [224]. Shinohara et al. investigated whether sex differences influence the prevalence and severity of EIB in prepubertal children aged 5–6 years. They found that the prevalence of EIB was higher in girls than in boys. In addition, the time to maximal bronchoconstriction was slower in girls than in boys, and the pattern of recovery after exercise was also faster in females than males [243]. Therefore, it is recommended that when evaluating the prevalence and severity of EIB in prepubertal children, the influence of sex is considered.

The pathogenesis of EIA is not fully elucidated. Minute ventilation, the volume of air inhaled or exhaled from a person's lungs per minute, rises with exercise. It is believed that EIB probably results from changes in airway physiology triggered by the large volume of relatively cool, dry air inhaled during vigorous activity [8, 167]. One of the major triggers for bronchoconstriction is water loss during periods of high ventilation. Strenuous exercise creates a hyperosmolar environment by introducing dry air into the airway with compensatory water loss, leading to transient osmotic changes in the airway surface. This hyperosmolar environment leads to mast cell degranulation and eosinophil activation with consequent release of inflammatory mediators, including leukotrienes. This process triggers bronchoconstriction and inflammation of the airway, as well as stimulation of sensory nerves and release of neurokinin and mucins [299]. All this is supported by several research findings concluding that it is not the type of exercise but the ventilation demand and humidity of the inspired air that are the main determinants of the occurrence and degree of bronchoconstriction [58, 119]. Therefore, the diagnosis of asthma in athletes should be confirmed by lung function test, usually with bronchial provocation testing [166] in association with a history consistent with EIB, because self-reported symptoms are not adequate. Varsity athletes show a high incidence of EIB when objectively diagnosed by a variety of pulmonary function criteria. The use of symptoms to diagnose EIB is not predictive of whether athletes have objectively documented EIB [197].

Management of EIB should be based on the understanding that EIB susceptibility varies widely among asthmatic patients, and it could

also be present in individuals without underlying asthma. A study by Parsons et al. found that 36 out of 42 EIB-positive athletes (86%) had no prior history of EIB or asthma [197]. In patients with asthma, EIB can also be an indicator of poorly controlled disease, and underlying asthma should be treated prior to controlling EIB [299]. As mentioned above, asthma can deteriorate during the peri-menstrual period, a phenomenon known as peri-menstrual asthma (PMA) which is usually much more severe and troublesome than the reported periovulatory worsening of asthma [246]. In this context, Stanford et al. demonstrated for the first time that the menstrual cycle phase is an important determinant of the severity of EIB in female asthmatic athletes [253]. This study reported deterioration in the severity of EIB during the mid-luteal phase accompanied by worsening asthma symptoms and increased bronchodilator use [253]. Aiming that exercise is not avoided by patients with EIB, general measures and pharmacologic interventions can be assessed subjectively in terms of symptom control and exercise tolerance, considering the fact that sex hormones play an important role in lung inflammation. Thus, medical evaluation and medication adjustment would likely be based on the understanding of sex differences.

14.4.3 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) affects an estimated 174 million people worldwide (104.7 million males and 69.7 million females) [53]. For many years, it was considered a disease of older men [211]. However, over the past 20 years, its prevalence and rates of hospitalization have increased among women, closing this prevalence gap [11, 56]. This phenomenon is due in part to increased rates of tobacco use – the single largest risk factor for the development of COPD – among women, together with recent evidence demonstrating that first- and secondhand tobacco smoke has more severe effects in women than men [26, 89]. Moreover, there is an increased recognition that the clinical presentation of COPD is different in women than men, which has led to better and more accurate diagnosis in women in the past few decades [111, 137]. It has been shown that women with COPD have different disease burden, symptoms, and clinical trajectory than men [89, 199] and that women tend to develop COPD earlier in life and have more frequent respiratory exacerbations than men [199].

While asthma remains the most prevalent respiratory disease in the world, COPD is the fourth leading cause of death in the United States and the eighth leading cause of disability worldwide [248]. Recently, the World Health Organization has projected that COPD will be the third leading cause of death worldwide by 2030. Moreover, although the overall prevalence of COPD is increasing in both men and women [249], recent data from US Center for Disease Control's National Center for Health Statistics has shown that COPD prevalence in the United States not only is higher in women but also increasing at a higher rate among women than men [2]. Epidemiological data show that since the year 2000, the number of women in the United States dying from COPD has surpassed the number of men [10, 157]. Some studies have suggested that both asthma and the so-called asthma-COPD overlap syndrome (ACOS), which are more common among adult women than men, can predispose women to develop COPD [61, 272].

It is possible that the increased prevalence of COPD in women is not only due to increased tobacco use but also related to longer life expectancy for women in general, as well as changes in women's occupational exposures over the past few decades [10]. Historically, professions that predispose to lung disease were predominantly held by men. However, due to the reassignment of sex roles and more single-parent households in recent decades, a higher number of women are found in these jobs [11]. This may play a role in the increasing prevalence of the disease among women. It is estimated that 15% of COPD is work-related. In addition, it has long been theorized that indoor air pollution resulting from smoke from biomass fuel combustion for cooking and other purposes also contributes to the development of COPD in never smokers, with

women being disproportionately exposed [284] and affected [202]. It is estimated that 50% of deaths from COPD are associated with indoor air pollution in developing countries, and about 75% of these are in women [227].

In recent years, there have been several clinical and experimental studies aiming to understand the contribution of sex to the biologic pathogenesis of COPD [18]. Levels of pro-inflammatory cytokines, including C-reactive protein, interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), matrix metalloproteinase 9 (MMP-9), pulmonary and activation-regulated chemokine (PARC), and vascular endothelial growth factor (VEGF), have been theorized to contribute to the development of COPD. VEGF helps regulate growth of new vessels and vascular leak and was found to be elevated in patients with COPD compared to healthy controls. In patients with COPD, statistically significant higher levels of VEGF and IL-6 have been found in men vs. women [10]. Additionally, studies in mouse models of chronic cigarette smoke have indicated that sex hormones may be contributing to the greater COPD susceptibility in females. Exposure to cigarette smoke in female mice results in higher peripheral airway obstruction and airway remodeling and less emphysema than male mice, an effect that is mediated by estrogens [267]. It was also found that in female mice, cigarette smoke was associated with activation of transforming growth factor-β (TGF-β), decreased expression of antioxidant genes and the transcription factor Nrf2 (nuclear factor erythroid-derived 2-like 2), as well as increased oxidative stress [267]. Overall, more research is needed to better understand the mechanisms behind sex differences in COPD susceptibility, as well as in the response of men and women to COPD available therapies.

14.4.4 Cystic Fibrosis

Cystic fibrosis (CF), an autosomal recessive multiorgan disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, also displays sex differences. Epidemiological studies have reported a sex-based disparity in CF outcomes, where females experience higher rates of pulmonary exacerbations and a shortened life expectancy than males [289]. While the etiology of this disparity is not fully elucidated, it appears to be multifactorial. Studies have associated the sexual dimorphism in CF outcomes to bias in diagnosis [136], anatomical differences between males and females [60], socioenvironmental factors [218], medication adherence [239], physical activity level [229], and actions of male and female sex hormones [1, 264]. A combination of poor perception of disease prognosis, withdrawal, anxiety, decreased adherence to therapies, and decrease in physical activity after puberty has been associated with increased morbidity and mortality in CF females [236]. Moreover, despite reported earlier referral to lung transplantation in females than males, survival time after transplantation does not show sex differences. Not only females with CF experience higher rates of infection and exacerbations than males, they also require more intensified treatment regarding antibiotics, macrolides, steroids, and days of hospitalization than their male counterparts [171, 193]. However, despite earlier referral to lung transplantation in females than males, survival time after transplantation does not show sex differences.

As with other lung diseases described earlier, the sexual dimorphism in CF outcomes is also age dependent. In females, the predisposition to worse outcomes in CF has been found at a young age, where girls are more susceptible to bacterial infection than boys [50]. Females not only show higher lung bacterial colonization with *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and *methicillin-resistant Staphylococcus aureus* than males [54, 103, 161, 217] but also earlier colonization in life, which is a predictor of negative outcomes and decline in survival for females [59]. Females have also been found to acquire *methicillin-sensitive Staphylococcus aureus*, *methicillin-resistant Staphylococcus aureus*, *Haemophilus influenzae*, *Achromobacter xylosoxidans*, *Aspergillus species*, and nontuber-

culous mycobacteria at earlier ages than males and often even prior to puberty [92].

During puberty and reproductive years, the predisposition to infection is enhanced in females, as well as an increased risk for pulmonary exacerbations and extrapulmonary complications [161]. Females also show a steeper decline in lung function, one of the key predictors of long-term health in CF patients, than males [50]. Because of the reduced life expectancy of patients with CF, little is known about the influence of menopause in the course of the disease [187]. A study in long-term survivors (older than 40 years old) showed that females with CF are also less likely to live to the age of 40 than males [187].

While the mechanisms underlying these sex-disparities have not been fully elucidated, a role of sex hormones in mediating inflammatory processes [101], and types of pathogens colonizing the lung has been suggested [280]. A study by Chotirmall et al. showed that the female hormones 17β-estradiol and estriol can induce conversion of *Pseudomonas aeruginosa* from a non-mucoid to mucoid phenotype in females with CF. The same study suggested that high levels of 17β-estradiol in females result in higher capture of more mucoid strains of *Pseudomonas aeruginosa* and subsequent pulmonary exacerbations [48]. In addition, not only postpubertal increases in pulmonary exacerbations are reported in females [261], but also women display cyclical symptoms in relation to their menstrual cycle, with higher lung function measures during the luteal phase than other cycle phases [114]. Studies in bronchial epithelial cells also showed that 17β-estradiol reduces expression of proinflammatory cytokines via upregulation of the secretory leucoprotease inhibitor (SLPI), which could contribute to the higher infection rate observed in females vs. males [48]. In mouse models of CF, 17β-estradiol stimulates expression of toll-like receptor 2, IL-23, and IL-17A and results in higher lung inflammatory infiltrates and mucin [295]. Abid et al. showed that female mice inoculated with *Pseudomonas aeruginosa* died earlier and showed slower bacterial clearance than male mice [1]. This effect was reversed by treatment with the estrogen receptor (ER) antagonist ICI 182,780 and ovariectomy and recapitulated in ovariectomized females treated with exogenous 17β-estradiol [1].

Very few studies have evaluated the role of progesterone and testosterone in mediating sex differences in CF infection rates and outcomes. One study in human tracheal epithelial cells showed that exposure to progesterone results in decreased cilia beat frequency, an effect that was attenuated with the addition of 17β-estradiol [109]. While women with CF are able to carry on pregnancies, the role of progesterone in lung function and CF outcomes has not been studied in detail [191]. With regard to androgens, a few reports have indicated that adolescent and adult males with CF have lower salivary and serum levels of testosterone than healthy controls [29, 139], as well as higher rates of male infertility [312]. In rodent studies, testosterone was found to enhance expression and functional activity of epithelial sodium channels [174]. Overall, the direct impact of sex hormones on disease progression in patients with CF remains unknown.

14.4.5 Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs [212]. With a median survival of 3–5 years following diagnosis, IPF is characterized by a progressive worsening of dyspnea and decline in lung function and quality of life in most patients [68]. Sex discrepancies in this disorder have been suggested for some time. The incidence and prevalence of disease have been reported in multiple studies to be higher in males than in females, with ratios ranging from ~1.6:1 to 2:1. Prior reports have also suggested that female sex is associated with better survival [90].

Although our current understanding of the pathogenesis of IPF is incomplete, recent advances have delineated specific clinical and pathologic features. Epithelial cell dysfunction and aberrant epithelial-mesenchymal signaling lead to the activation of fibroblasts and extracel-

lular matrix deposition and remodeling. This chronic activation appears to lead to profibrotic, pathologic changes in IPF fibroblasts. The myofibroblast is the classic pathologic fibroblast phenotype described in IPF lungs. Several mediators, including TGF-β, can elicit the differentiation of fibroblasts to myofibroblasts. Compared with resident lung fibroblasts, myofibroblasts secrete excessive amounts of matrix, including type I collagen. This excess matrix deposition may lead to pathologic lung fibrosis and remodeling [303]. Although these mechanisms have provided significant advances in our understanding of the disease, there is limited information on the molecular basis underlying the observed sex disparities in IPF. A study by Smith et al. suggested that estrogen may modulate the expression of genes involved in chromatin remodeling pathways, as well as the expression of genes in extracellular matrix turnover [247]. However, results from animal studies have provided mixed results. Genome-wide association studies have pointed to genetic influences mediating sex differences, including SNP polymorphisms in mucin 5B, near A-kinase anchoring protein 13, and desmoplakin genes [7].

Sex differences in IPF have been studied in the clinic. Han et al. studied whether the rate of increase in desaturation during serial 6-min walk testing, as well as survival, displayed sex differences. They noted several important observations: (1) males with IPF demonstrate more rapid deterioration in exertional desaturation over time when compared with females; (2) survival was worse in males than females; and (3) better survival for females persisted after additional adjustment for relative change in exertional desaturation and forced vital capacity (FVC) [90].

Among the clinical conditions that have been associated with a worse IPF prognosis is the presence of comorbidities and complications such as emphysema, pulmonary hypertension, cardiovascular diseases, and bronchogenic carcinoma [68]. As mentioned in other sections, some of these conditions also present a sexual dimorphism, which could potentially influence the progression and outcomes of IPF. Finally, prompt treatment of IPF is critical to preserving the patients' lung function, reducing the risk of acute exacerbations, and improving outcomes [149]. Currently, two drugs are approved for the treatment of IPF in the United States and Europe: nintedanib and pirfenidone. In vitro studies have shown that by inhibiting signaling mediated via tyrosine kinases, nintedanib inhibits fundamental processes of fibrosis, such as the recruitment, proliferation, and differentiation of fibroblasts and fibrocytes and the deposition of extracellular matrix. Data from animal models of fibrosis suggest that nintedanib may also act to normalize the distorted microvascular architecture in the lungs. The mechanism of action of pirfenidone is less well defined, as its target remains unknown, but nonclinical studies suggest that it inhibits profibrotic behaviors in fibroblasts and fibrocytes. Both drugs have been shown to slow the disease progression but not significantly impact mortality [149]. However, studies have not addressed sex differences in the effectiveness of these and other therapies for IPF. Current efforts are directed at identifying key biomarkers that may direct more customized patient-centered healthcare to improve outcomes for these patients in the future, and it is essential that they address sex-specific mechanisms [19].

14.4.6 Lung Cancer

Lung cancer is a major public health problem worldwide and is the world's leading cause of cancer death [21]. Approximately 95% of all lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) [242, 260]. This distinction is essential for staging, treatment, and prognosis. Lung cancer is relatively rare before the fifth decade of life, and risk increases with age thereafter. Over the past decade, the cancer incidence rate (2005–2014) has been found stable in women and declined by approximately 2% annually in men, while the overall cancer death rate (2006–2015) declined by about 1.5% annually in both men and women [165]. Lung adenocarcinoma is also more common among women than men [315].

Environmental risk factors for lung cancer include smoking cigarettes and other tobacco products, as well as exposure to secondhand tobacco smoke, occupational lung carcinogens, radiation, and indoor and outdoor air pollution [4, 132, 201]. However, lung cancer incidence patterns reflect trends in sex behaviors associated with cigarette smoking [220]. Generally speaking, any form of smoking exposure increases the lung cancer risk [4, 311]. A recent US report indicated that lung cancer incidence and death rates among women have increased in 18 states. Interestingly, the states with higher prevalence of smoking among adult women had the highest rates of lung cancer. This report showed that only one state had decreasing lung cancer incidence and death rates in women [110]. Currently, lung cancer incidence rates are declining about twice as fast in men as in women, reflecting historical differences in tobacco uptake and cessation, as well as upturns in female smoking prevalence in some birth cohorts [64]. In addition, the implementation of widespread lung cancer screening holds promise for the future.

Zang et al. found that the odds of developing major lung cancer types are consistently higher for women than for men at every level of exposure to cigarette smoke [315]. This sex difference, however, cannot be explained by differences in baseline exposure, smoking history, or body size, but it is likely due to the higher susceptibility to tobacco carcinogens in women [198, 26]. In this regard, higher levels of polycyclic aromatic hydrocarbon-derived DNA adducts have been reported in female smokers vs. male smokers [177]. A potential mechanism associated with these outcomes is related to the fact that estrogen synergizes with some tobacco compounds through the induction of CYP1B1, an enzyme responsible for estrogenic metabolism, which leads to enhanced reactive oxygen species formation and carcinogenesis [102]. Moreover, Kure et al. found a higher frequency of G:C-->T:A mutations and a higher average hydrophobic DNA adduct level in female patients than males, even though the level of exposure to carcinogens from cigarette smoke was lower among females than males [131]. These findings lend support to epidemiological evidence that women are at greater risk than men of contracting tobacco-induced lung cancer.

As mentioned earlier, there is considerable evidence indicating that sex hormones can influence respiratory function throughout life [24, 277]. As with other lung diseases, sex hormones have also been implicated in lung cancer [176]. For example, estrogen, known to be a risk factor for the development of adenocarcinoma of the breast, ovary, and endometrium, has been postulated to contribute to lung cancer development and progression [244, 315]. Furthermore, estrogen has also been implicated in lung cancer therapy [13]. Women with advanced NSCLC survive longer than men after adjustment for other prognostic factors in the modern chemotherapy era, suggesting that estrogen levels may interact with the efficacy of current chemotherapy prescriptions or other as yet undefined factors. This finding, if validated, could be potentially exploited in designing new therapies [230, 294].

Regarding estrogen receptors (ERs), Kadota et al. reported that stage I lung adenocarcinoma cells express higher levels of ERα in females than males (19% vs. 14%) and that ERα expression correlates with smaller tumor size. The authors concluded that nuclear ERα expression is an independent predictor of recurrence in pT1a stage lung adenocarcinoma (i.e., tumor size of 2 cm or less) and correlates with poor prognostic immune microenvironments [118]. In addition, non-small cell lung cancer lines (both squamous cell and adenocarcinoma) have been found to express estrogen receptors [192].

Hormone replacement therapy (HRT) is a common treatment used in postmenopausal women. To date, there are several controversies in the relationship between the HRT and lung cancer. The Women's Health Initiative trial concluded that treatment with estrogen plus progestin in postmenopausal women did not increase the incidence of lung cancer. However, HRT was found to increase the number of deaths from lung cancer, in particular deaths from non-small cell

lung cancer [47]. These findings should be incorporated into risk-benefit discussions with women considering combined hormone therapy, especially those with a high risk of lung cancer.

In summary, there is accumulating evidence to support the notion that the risk of development of lung cancer is different among women than among men. As expressed earlier, women may be more susceptible to the effects of carcinogens in tobacco and tobacco smoke as a result of hormonal, genetic, and metabolic differences between the sexes. Thus, the significance of sex as a separate contributing factor shall be considered in prognosis and therapeutic management.

14.4.7 Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare progressive lung disease that occurs almost exclusively in women [309]. The incidence of LAM is estimated to range between 1 and 8 per million women, and the disease mostly affects women of childbearing age [91]. The average age of symptom onset among LAM patients in the United States and Europe ranges between 34 and 37 years of age [52]. LAM is characterized by infiltration of specific dysregulated smooth muscle-like cells (LAM cells) in various organs and tissues, including lymph nodes, kidneys, and the lungs. As a result, LAM patients experience a progressive decline in lung function due to parenchymal destruction and development of cysts in lung tissue.

The mechanisms underlying LAM development, and the marked sex disparity in its incidence, have not been fully elucidated [89]. However, the neoplastic phenotype of LAM cells is known to occur as a consequence of constitutive activation of the mechanistic target of rapamycin (mTOR) due to loss of heterozygosity in the tuberous sclerosis genes (TSC1 or TSC2) [97]. Advances in the understanding of TSC biology have provided critical clues to LAM pathogenesis and treatment and led to the use of the mTOR inhibitor sirolimus (i.e., rapamycin) as an effective suppressive therapy. Alternatively, lung transplantation is also an established option for women with severe pulmonary impairment due to LAM.

The striking sex disparity observed in LAM has led multiple investigators to consider a role of sex hormones, and specifically estrogen, in the development, progression, and severity of LAM disease [63]. LAM clinical presentation occurs after puberty, accelerated progression is frequently observed during pregnancy, and menopause is associated with attenuated progression [154]. Animal models and in vitro studies have also shown that estrogen increases cell proliferation and migration [313]. Moreover, LAM cells are known to express both estrogen and progesterone receptors. However, definitive evidence is lacking regarding manipulating sex hormones as a potential therapeutic approach, and additional efforts are needed to develop strategies for disease prevention and treatment.

14.4.8 Obstructive Sleep Apnea

The prevalence of OSA is similar between the sexes before puberty but becomes more common in boys than girls after puberty [216]. This sexual dimorphism persists throughout adulthood, where both the rate and severity of OSA are higher in men compared to women. These differences have been attributed to anatomical differences in the upper airway and increased accumulation in the neck of fluid displaced from the legs during recumbency while sleeping [122, 155]. Other risk factors include craniofacial abnormalities, genetic conditions, and neuromuscular disorders. Studies in hypogonadal men and obese adolescents with low testosterone levels have suggested a role of male sex hormones in the observed sex differences in OSA [164, 172]. In females, progesterone has been found to increase the tone of upper airway muscles and stimulate ventilation via chemoreceptor responses to hypoxia and hypercapnia [203, 238]. These sex hormone-mediated mechanisms have been proposed to contribute to the lower risk and severity of OSA observed in girls and women after puberty.

14.4.9 Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a progressive and devastating disease of the pulmonary vasculature characterized by extreme elevation of pulmonary arterial pressure and subsequent right ventricular failure [72]. PAH is also characterized by progressive obstruction of the pulmonary arterial circulation due to formation of vaso-occlusive lesions arising from vigorous proliferation and migration of endothelial cells [214]. As a result of the increased pulmonary vascular resistance, higher right ventricular (RV) afterload causes adaptive RV hypertrophy that often progresses to maladaptive RV hypertrophy and fibrosis, leading to eventual premature death from RV failure. Despite improvements in the diagnosis and management of PAH, the disease continues to have a poor prognosis. A recent analysis showed that the 5-year survival for PAH is approximately 60% [169].

Accumulating evidence shows that more females than men are diagnosed with PAH; however, epidemiological data show that survival among females is better than among males, especially in older patients [12, 104, 108, 135, 159]. Interestingly, the survival benefit for females appears to decline with age [240] and correlate with declines in estradiol levels [285]. This discrepancy in incidence and disease outcomes in men and women is commonly referred to as the PAH "estrogen paradox" and has prompted research into the sex-based differences and hormonal regulation mechanisms in PAH. While the mechanisms behind the sex disparity are far from being understood, they likely involve contributions of genetics, as well as sex hormones and their metabolites.

A few studies have suggested a genetic component in PAH. Mutations in the gene encoding for the bone morphogenetic protein (BMP) receptor type 2 (BMPR2) have been shown to increase PAH penetrance and severity in mouse models [69]. Moreover, mutations in the *BMPR2* gene are the most common genetic cause of familial PAH [65, 148]. By using the "four core genotypes" mouse model [57], it was found that the Y chromosome, and specifically upregulation of Y chromosomal genes in the lung, was protective against pulmonary vascular remodeling [281] irrespective of gonadal sex. More recent studies have investigated whether genes encoding for enzymes that mediate estrogen metabolism, such as CYP1B1, are associated with PAH in males and females. West et al. found that CYP1B1 expression was markedly downregulated in female but not male patients with PAH due to BMPR2 mutations [301].

Regarding sex hormones, there are multiple studies demonstrating that estrogens exert complex and context-dependent effects on the pulmonary vasculature [62, 133, 168, 208, 308]. Microarray analyses in animal models identified diverse set of pathways regulated by estradiol, including steroid metabolism, immune response, cytoskeletal function, extracellular matrix composition, bone morphogenetic protein (BMP), Notch, Wnt, and calcium signaling [73]. Studies in vascular cells have shown that estradiol affects proliferation [151, 152, 302]. In a rescue approach experimental animal model, it was shown that estradiol treatment reversed pulmonary vascular remodeling, fibrosis, and inflammatory signaling [282]. Overall, while some studies in animals have demonstrated that both exogenous and endogenous estradiol can be protective against PAH, others have suggested a more causative role [123, 134, 151]. Collectively, these studies demonstrate that both endogenous and exogenous estradiol can act as potent regulators of pulmonary vascular homeostasis and greatly impact the progression or resolution of vascular injury. However, these models do not display sex differences nor point to a female predisposition, indicating that more research is needed to fully understand the roles played by hormones in PAH in men and women. Accumulating evidence indicates that estrogen metabolites can also modulate PAH pathogenesis [273]. Thus, it is important to consider the role of metabolites when investigating the effects of estrogen in PAH. Interestingly, low levels of dehydroepiandrosterone (DHEA), a precursor for estrogens that can bind estrogen

receptors, are associated with PA development in men [286]. A recent study in postmenopausal women also showed that women with PAH had lower levels of DHEA and higher levels of estradiol than those without cardiopulmonary disease [14]. In patients with PAH, low DHEA and high estradiol were also associated with worse prognosis and increased risk for death [14], as well as fluctuations in pulmonary function throughout the menstrual cycle [15]. Whether DHEA is a marker or mediator of PAH remains under investigation. Overall, more research is needed to understand the mechanisms mediating sex differences in PAH, in order to develop sex-specific therapies to prevent and treat this devastating disease.

14.4.10 Respiratory Infection

Respiratory infection remains a leading cause of morbidity and mortality across all age groups. While, overall, males are disadvantaged in the occurrence and severity of lower respiratory tract infections, females appear to be more susceptible to upper respiratory infections [67]. Multiple studies have suggested that a complex interplay of genetics, sex hormones, host immunity, anatomical and physiological differences, as well as sociocultural and behavioral is likely to underlie the observed sex differences in infection rates and severity [25, 45, 106, 117]. In the following sections, we describe the epidemiology and current knowledge on respiratory diseases that present with a sexual dimorphism.

14.4.10.1 Respiratory Syncytial Virus

During infancy and early childhood, infection with respiratory syncytial virus (RSV) occurs more frequently in boys than girls, especially those born prematurely [150]. Resulting from RSV infection, bronchiolitis is also more frequent and severe in male infants and young children and is often associated with higher risk of wheezing and childhood asthma, as well as higher risk of hospitalization [95, 183].

Sex differences in RSV infection and bronchiolitis have been attributed to anatomical and immunological factors, including smaller airway diameter in males than females [40], and sex differences in the Th2/Th17 response to viral infection [128, 124]. Animal mouse models of RSV infection show that infected female mice display better viral control than males, via mechanisms involving interferon-β expression. In addition, male mice show persistent immune alterations in Th2/Th17 cells, dendritic cells, and ILC2 responses that result in delayed control of viremia [156]. Similar studies have indicated that sex hormones and their receptors can also mediate these mechanisms, although their contributions to infant and pediatric infectious disease remain unclear [116].

14.4.10.2 Influenza

Influenza is an acute respiratory infectious disease caused by several types of influenza viruses. According to the World Health Organization, there are 3 to 5 million cases annually of severe illness and about 290,000 to 650,000 respiratory deaths [305]. The severity and mortality of influenza disease are worse for young children, the elderly, individuals with chronic and immunocompromised medical conditions, and pregnant women [179].

Researchers have reported sex differences in influenza severity, mortality, vaccine tolerance, responses, and outcomes [127]. Interestingly, males are more susceptible to infection than females, and females have greater immune responses but experience more adverse reactions to influenza vaccines than males [128, 290]. In addition, females of reproductive age have the worst outcome during pandemic influenza [304]. However, the causes and mechanisms for these discrepancies in susceptibility are not well-known. Research groups have reported that immunity to viruses can vary with changes in hormone concentrations caused by fluctuations over the menstrual cycle, contraception use, pregnancy, and menopause [32].

Most experiments using murine models have shown that young adult females develop greater

respiratory inflammatory responses and have a more severe outcome from influenza infection than males, despite the sexes having similar virus titers [99, 222, 223]. For instance, proinflammatory cytokines (e.g., TNFα, IFNγ, IL6, and IL12) and chemokines (e.g., CCL2, CCL5, and CCL12) are higher in the lungs of influenza-infected females when compared to males [99]. It was also discovered that increased levels of testosterone and amphiregulin, which is an epidermal growth factor that mediates lung tissue repair, improve repair and recovery of lung damage in males [288]. Moreover, infection of female mice of reproductive age with influenza decreases ovarian function and levels of sex hormones suggesting that inhibition of sex hormones may contribute to severe outcomes in female mice [223, 287]. Independent research groups discovered that female mice with influenza that were treated with estrogen showed a decrease in the inflammatory response (e.g., CCL2, IFNγ, TNFα) and an increase in antibody response to influenza vaccine [43, 291]. Importantly, the expression of toll-like receptor-7 is higher in B cells from vaccinated females than males, and its deletion decreased sex differences in vaccine-induced antibody responses and protection [70]. Future research should focus on the molecular mechanisms that regulate how hormones and genes affect immunity to influenza and vaccines in males vs. females.

14.4.10.3 Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) is a public health crisis caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of this writing, there have been over 112 million confirmed COVID-19 cases and 2.5 million deaths worldwide. Importantly, demographic and clinical data gathered by multiple health agencies around the globe have demonstrated profound sex differences in COVID-19 outcomes [206]. While the rate of SARS-CoV-2 infection is similar between males and females, male patients infected with the SARS-CoV-2 virus have a significantly higher risk of developing severe COVID-19, being admitted to an intensive care unit (ICU), and dying when compared to female-infected patients [126].

As mentioned earlier, sex-specific immune responses to a diverse array of viral pathogens have been reported [31, 81, 200, 232, 290]. In addition, there are also prominent sex differences in the immune responses mounted by individuals receiving viral vaccines [127, 158]. In the case of infection with coronaviruses, there have been reports of sex differences during prior outbreaks, including the 2003 severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics, which had a higher case fatality rate and number of deaths in males than females [5, 121, 140].

While not all countries provide sex-disaggregated data, the Sex, Gender and COVID-19 Project [84] has combined efforts from agencies located in several continents to increase reporting of data by sex for confirmed cases, testing, hospitalizations, ICU admissions, confirmed cases among healthcare workers, and deaths. In almost all countries, a significant male predominance in COVID-19 morbidity and mortality has been reported, suggesting a biological mechanism involved [234]. In the United States, most of the states have made public sex-disaggregated data on COVID-19 morbidity and mortality. In an article published in June of 2020, Klein et al. reported that in states providing sex-disaggregated information, data shows that men are twice as likely to die from COVID-19 than women [126]. Moreover, sex differences in the immune response to SARS-CoV-2 have also been reported, where males with mild disease had higher plasma levels of pro-inflammatory cytokines and chemokines than females, but females had higher CD4 and CD8 T-cell activation than males [265]. A study comparing responses to convalescent plasma also showed higher microneutralization and IgG responses to SARS-CoV-2 in males than to females, which correlated with worse COVID-19 outcomes [125].

Some of these sex effects have been attributed to chromosomal differences, since the X chromo-

some has been shown to express a large number of immune-related genes, including some involved in cytokine and toll-like receptor (TLR) signaling, NF-kB signaling, and MAPK signaling [251]. In addition, the gene encoding the human angiotensin-converting enzyme 2 (ACE2), which serves as the receptor for the spike (S) protein of SARS-CoV-2 [46] is also expressed in the X chromosome and can escape X inactivation and be expressed from both the active and inactive X chromosome [39]. This has been shown to lead to sex differences in ACE2 gene expression [80, 142, 279], which has potential consequences for the vulnerability to SARS-CoV-2.

As with other inflammatory lung diseases and infectious processes, a role of sex hormones has been postulated in mediating sex differences in COVID-19 [250, 259, 266]. Estrogen can regulate the expression of SARS-CoV-2 viral entry receptors, including ACE2 and the transmembrane protease, serine 2 (TMPRSS2) [100, 153]. In this context, a recent report showed that postpubertal females have lower levels of serum ACE2 when compared to age-matched males [262]. Furthermore, the serum activity of ACE2 is higher in postmenopausal women when compared to younger women, suggesting a regulation by sex hormones like estrogen [79]. Interestingly, Stelzig et al. recently showed that estrogen can downregulate the expression of ACE2 in normal human bronchial epithelial (NHBE) cells but had no effect on TMPRSS2 [256]. This correlates with prior work conducted in the four core genotypes model indicating that sex differences in enzymatic activity of ACE2 in mice are estrogen-dependent and sex chromosome-independent [146].

Regarding male sex hormones, it is unclear whether androgen levels contribute to SARS-CoV-2 or COVID-19 outcomes [178]. A recent report showed that in males with SARS-CoV-2 pneumonia, low testosterone levels were associated with higher rates of ICU admission and death [215]. This correlates with prior studies showing that testosterone can upregulate IL-1 and downregulate IL-1β, IL-6, and TNF-α leading to a suppression of inflammation [173, 205]. Future studies investigating the effects of androgen levels on COVID-19 should consider the timing of the androgen measurement in the course of the SARS-CoV-2 infection [259]. Testosterone can also regulate the expression of TMPRSS2 [82, 257], thus contributing to viral infection and disease outcomes. Interestingly, TMPRSS2 is also highly expressed in urogenital organs, such as the prostate [44].

Finally, it has been hypothesized that gender factors, i.e., smoking habits, handwashing, caregiver gender roles, etc., can influence the outcome of SARS-CoV-2 infections [34, 79, 283, 300]. There are also significant sex and gender differences in comorbidities that have been associated with COVID-19 progression and outcomes [241]. In general, these comorbidities tend to be more prevalent in men than women [306]. Thus, several structural gender health disparities will need to be addressed in order to effectively mitigate the negative effects of the COVID-19 pandemic [250].

14.5 Conclusion

Gender and sex differences in the prevalence, severity, and susceptibility to a variety of lung diseases have been reported across the life span (Fig. 14.1). While the causes of these disparities have not been fully elucidated, a lot has been accomplished in the past few decades. These investigations have revealed associations of biological factors (sex) such as airway anatomy and physiology, chromosomal contributions, genetics and epigenetics, and sex hormones with lung disease onset and outcomes in men and women. Others have shown that sociocultural and environmental factors (gender) can also influence differential outcomes in lung disease. Understanding the contributions of sex and gender, as well as their complex interplay in the context of respiratory health, represents a fundamental step toward precision medicine and the future development of more effective options to prevent and treat lung disease.

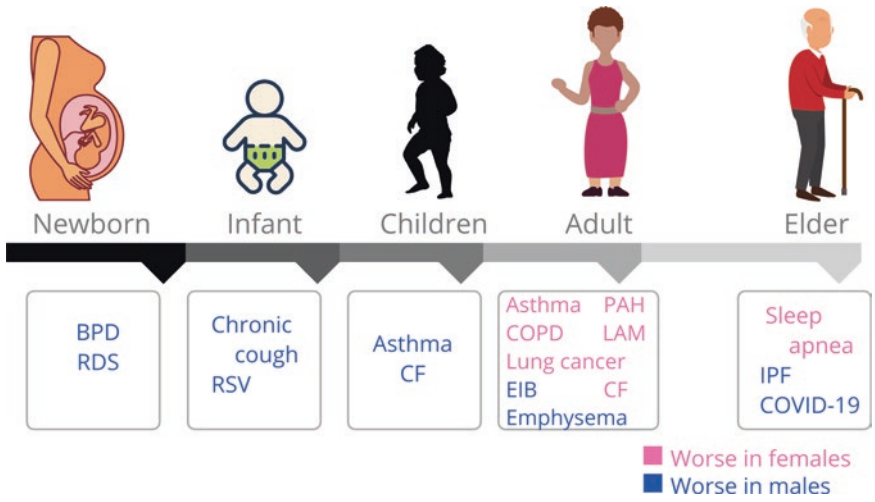

Fig. 14.1 Sex differences in lung disease progression across life span. There are sex differences in the prevalence of several lung diseases across the life span. In pink are lung diseases that are more prevalent in females than males (blue). (Abbreviations: BPD Bronchopulmonary dysplasia, RDS Respiratory distress syndrome, RSV Respiratory syncytial virus, CF Cystic fibrosis, PAH Pulmonary arterial hypertension, COPD Chronic obstructive pulmonary disease, LAM Lymphangioleiomyomatosis, EIB Exercise-induced bronchoconstriction, IPF Idiopathic pulmonary fibrosis, COVID-19 Coronavirus disease 2019)

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