

SEX, HORMONES, AND LUNG HEALTH

Sex, hormones, and lung health

AUTHORS

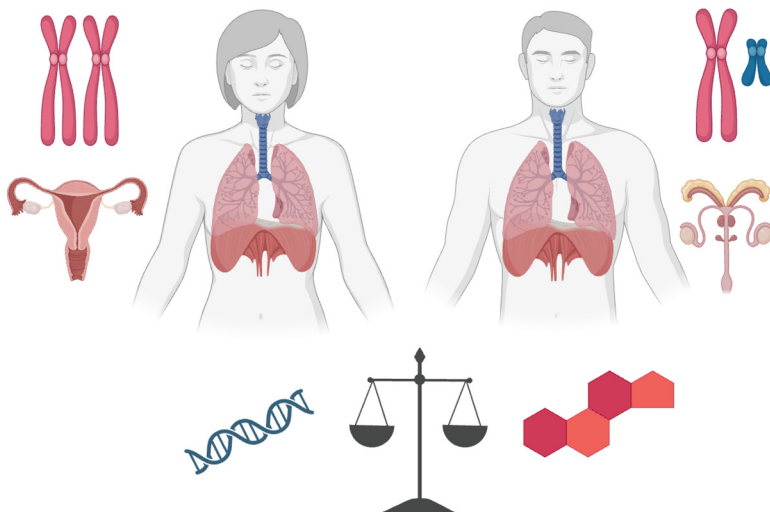
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KEY WORDS

lung disease; lung inflammation; sex
chromosomes; sex hormones; sex steroids



Lung inflammation
Immune response
Response to environmental exposures
Lung disease susceptibility
Response to treatment

CLINICAL HIGHLIGHTS

- The health of men and women is profoundly influenced by biological sex, which can also intersect with gender (a social construct).
- Sex differences are evident in multiple lung diseases across the lifespan, with some conditions switching patterns during puberty or menopause and/or almost exclusively affecting female patients.
- While some lung conditions are more common in women, cause different symptoms, and are more likely to be fatal in women than in men, sex-specific treatments and prevention strategies are not yet available.
- Integrating sex analyses in research studies is fundamental, going beyond simply including women in clinical trials and female subjects in experimental designs.
- The role of sex hormones in women's health during key life stages (e.g., menstrual cycles, pregnancy, menopause) remains unclear. Still, it is crucial in conditions affected by female steroids, such as asthma and responses to environmental challenges.
- In situations unique to women, as well as during life events affecting both sexes, such as puberty and aging, the distinct impacts of female and male sex hormones contribute to their complex and multidimensional connections to lung function.
- Both endogenous and exogenous hormones can influence lung disease mechanisms, responses to environmental challenges, and lung disease therapeutics. Understanding these mechanisms is key to improving disease prevention and outcomes.

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SEX, HORMONES, AND LUNG HEALTH

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Abstract

Sex plays an essential role as a biological variable in lung health, leading to observed differences in lung disease susceptibility. Some respiratory conditions are more common in women than men, especially after puberty, indicating the influence of ovarian hormones on disease mechanisms. Other conditions display sex disparities that begin in utero and progress throughout the life span. Preclinical and clinical studies have indicated that both sex chromosomes and hormones can influence lung disease outcomes, immune responses, susceptibility to viral and bacterial infection, and responses to environmental challenges. This review summarizes the latest research on how sex affects lung physiology and health, drawing on a wide range of studies in respiratory physiology and anatomy, genetics, molecular and cellular biology, environmental health, and immunity. We emphasize how biological sex, gonadal hormones, and occupational and environmental exposures can impact disease mechanisms and outcomes. As clinical outcomes among women have not improved at the same rate as men over the past few decades, it is crucial to understand the role played by the sex variable in designing strategies to prevent and mitigate disease. The collective research indicates that sex-induced differences in the respiratory system are essential determinants of physiological responses and clinical outcomes.

lung disease; lung inflammation; sex chromosomes; sex hormones; sex steroids

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1. INTRODUCTION

The respiratory system exhibits intrinsic anatomical and physiological sex differences that affect lung disease development, manifestation, and severity across the life span (1–9). Appreciating these sex differences is crucial to understanding the mechanisms of disease development and response to treatment and developing personalized therapies (10–16). Starting from the embryonic stages and continuing over the life course, the sex variable significantly influences the development of the respiratory system and its response to endogenous and exogenous factors. Overall, ample epidemiological, clinical, and experimental data emphasize the need to study sex differences in the lung and the regulatory roles of sex hormones. Understanding these concepts is essential not only to appreciate intrinsic sex differences in normal pulmonary physiology across age groups but also to

gain insights into disease development and the development of sex-based therapies.

2. SEX AND GENDER VARIABLES AND THEIR INFLUENCE ON LUNG HEALTH

While the terms “sex” and “gender” are often used interchangeably, they refer to distinct concepts (FIGURE 1). Sex pertains to the biological differences between males and females, including sex organs, hormones, anatomical and physiological variances, and sex chromosomes. Biological sex can influence physiological aspects underlying respiratory disease and response to environmental challenges. On the other hand, gender is a broader concept encompassing social roles, behaviors, expectations, and identities within historical or cultural contexts (17–20). As such, gender can influence environmental responses and disease processes due to occupational or social roles, as well as exposure to exogenous hormone treatments (21–23). Moreover, sex and gender can intersect to influence lung disease outcomes (24, 25).

In medicine, understanding how gender is influenced by culture, work environments, and psychosocial exposures is crucial for providing comprehensive healthcare. While it has been shown that sex can affect certain diseases differently due to biological, genetic, and hormonal

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variations, gender can influence healthcare-seeking patterns and response to treatment (26–28). Similarly, changes in gender roles and expectations can alter disease prevalence patterns over time. For instance, as more women have entered the workforce and used tobacco products, patterns of associated lung disease

prevalence have shifted, which may necessitate reevaluating environmental and occupational policies and air quality standards (21, 29).

3. SEX DIFFERENCES IN LUNG DISEASE PREVALENCE AND OUTCOMES

Over the past several decades, multiple studies have indicated that the prevalence, progression, and outcomes of diseases in women and men are influenced by both biological sex and gender (4). Disease epidemiology and clinical manifestations also vary between sexes across the lifespan (FIGURE 2). These differences are observed as early as infancy, when respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) rates are higher for male than female newborns (10, 30, 31), and continue throughout childhood when asthma and chronic cough are more common in boys than girls (5). Certain respiratory infections like respiratory syncytial virus (RSV) are also more predominant in boys than girls (32, 33). Interestingly, after puberty, women have higher rates of asthma prevalence, severity, exacerbations, hospitalizations, and mortality compared to men (28, 34–36). Adult women are also more disproportionately affected by conditions such as pulmonary hypertension (PH) (37, 38), chronic obstructive pulmonary disease (COPD) (9, 39, 40), bronchiectasis (41–43), and lung cancer. Men present with

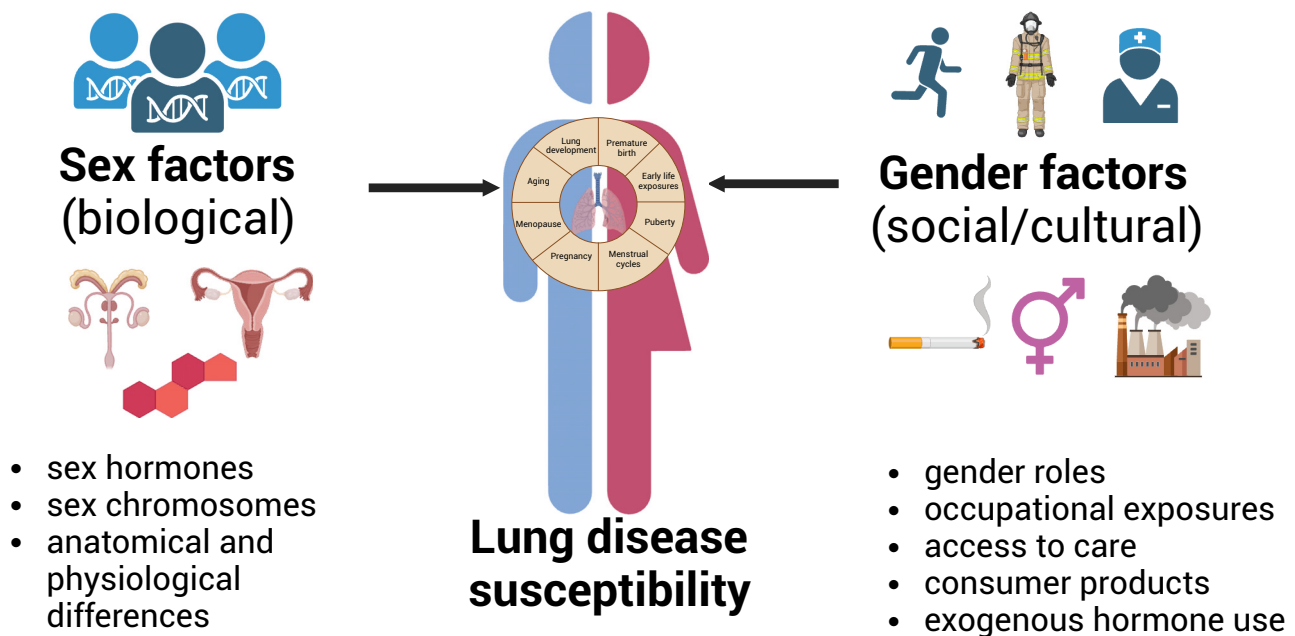


FIGURE 1. The sex and gender variables and their influence on lung disease susceptibility. The sex variable (*left*) is biological and includes chromosomal and hormonal factors that can influence the susceptibility to lung diseases through physiological responses. The gender variable (*right*) is a social construct that can influence environmental exposures through established roles and normative habits, affecting lung disease risk. Both sex and gender can intersect to influence lung disease presentation, responses to environmental challenges, and disease treatment. Figure created with a licensed version of BioRender.com.

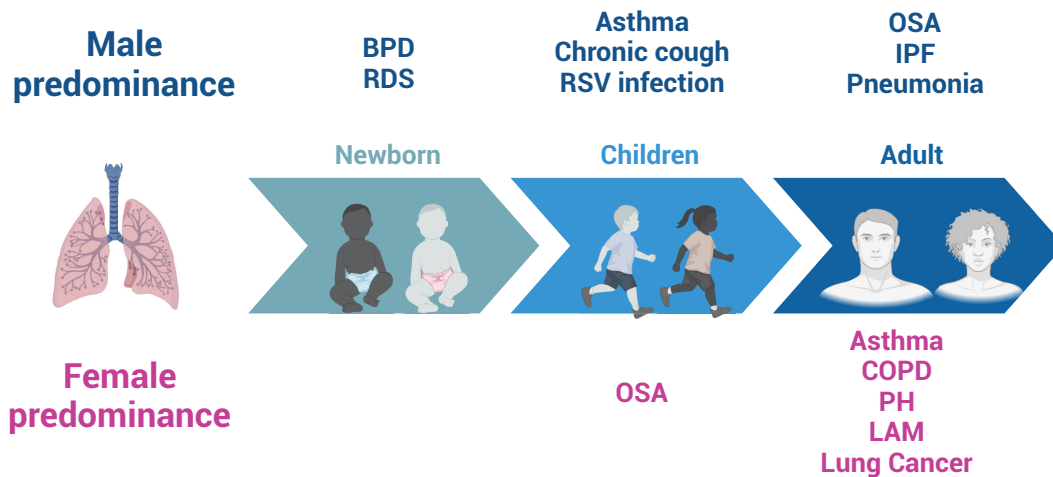


FIGURE 2. Sex differences in lung disease incidence across the life span. While some diseases display marked sex differences across all ages, others (asthma and obstructive sleep apnea) show inverse patterns before and after puberty. Hormonal, genetic, and environmental factors have been implicated in the sex disparities observed for respiratory conditions. BPD, bronchopulmonary dysplasia; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; OSA, obstructive sleep apnea; PH, pulmonary hypertension; RDS, respiratory distress syndrome; RSV, respiratory syncytial virus. Figure created with a licensed version of BioRender.com.

higher rates of idiopathic pulmonary fibrosis (IPF) (44, 45) and obstructive sleep apnea (OSA) (46). Sleep disorders are also more common in women, particularly during pregnancy, and conditions like lymphangioleiomyomatosis (LAM) are almost exclusive to women (47–50). On the other hand, lung infections resulting in pneumonia and COVID-19 display higher severity in men in the acute phase, while their chronic counterparts and long-term consequences (e.g., long-COVID) affect more women (51, 52). Thus, considering sex and gender in research helps us comprehend disease mechanisms and identify ways to enhance personalized medicine and lung health outcomes. To understand the mechanisms underlying sex differences in lung disease, a variety of animal models have been developed to recapitulate specific disease phenotypes. Most of these studies have been conducted in mice, taking advantage of genetically modified models. The sections below summarize known sex-specific features of lung conditions disproportionately affecting males and females throughout life, as well as the mechanisms identified using animal models.

3.1. Respiratory Distress Syndrome

Previously known as hyaline membrane disease, RDS is a condition that primarily affects prematurely born infants due to their underdeveloped lungs and insufficient surfactant expression. This results in widespread lung collapse and reduced lung function, leading to complications such as pneumothorax. Before the use of antenatal corticosteroids and postnatal surfactant replacement therapy, this condition significantly increased neonatal mortality, with a higher risk observed in male neonates (30, 53). A meta-

analysis of data from over 500,000 preterm newborns reported that RDS was almost twice as prevalent in newborn males as in females (54). This increased risk persists even after controlling for factors such as gestational age (GA), birth weight, and other clinical parameters (55).

It is known that RDS partially results from surfactant deficiency and dysfunction in the immature lung. Produced by alveolar type 2 (AT2) cells, pulmonary surfactant forms a lipid layer over the inner surface of the alveoli, reducing surface tension and preventing alveolar collapse at the end of expiration (56). As a result, the more developed the fetal lung, the lower the risk of developing RDS after birth. Female fetal lungs tend to be more advanced structurally than male lungs at earlier GA, a process mediated by sex hormones (11, 57, 58). Pulmonary surfactant is produced earlier in females than in males during gestation, stimulated by female sex hormones and inhibited by male sex hormones (31, 59, 60) (FIGURE 3).

Both maternal and fetal sex steroids play essential roles in lung development and, thus, RDS susceptibility (FIGURE 4). Production of testosterone and anti-Müllerian hormone (AMH) by fetal testes contributes to delayed surfactant production in the male lung. The fetal androgens inhibit AT2 development and surfactant production in male embryos (61, 62). In addition, androgen receptors (ARs) are highly concentrated on epithelial cells that control bronchial development (56). These cells also contain high levels of 5- α reductase, suggesting that dihydrotestosterone and other androgens influence early bronchiole formation (63). Additionally, androgens inhibit surfactant production by suppressing epidermal growth factor (EGF) and transforming growth factor- β 1 (TGF β 1) in AT2 cells (64). Research in rabbits

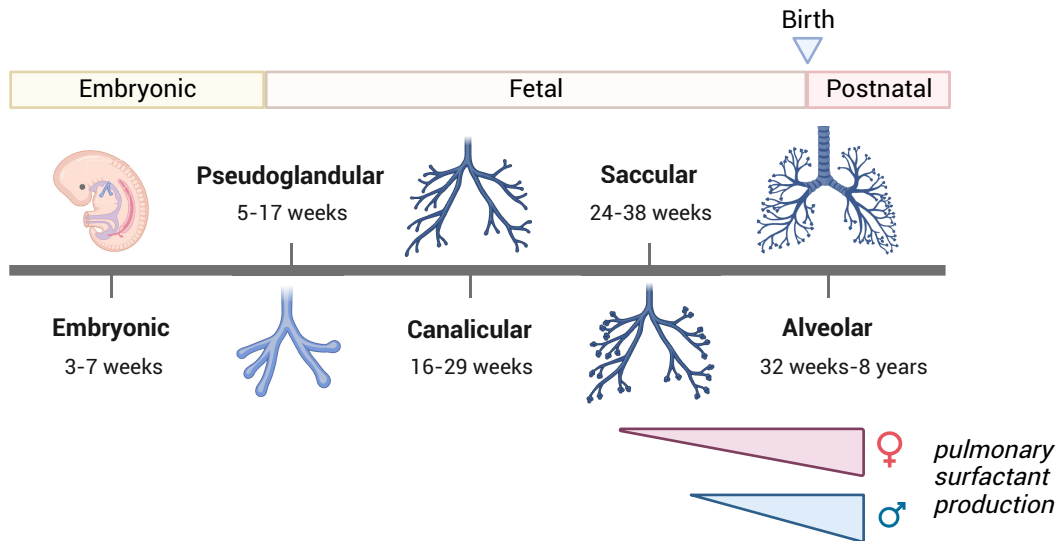


FIGURE 3. Sex differences in lung development. The development of the human lung is divided into 5 main phases: the embryonic phase (3–7 weeks of gestation), the pseudo-glandular phase (5–17 weeks of gestation), the canalicular phase (16–29 weeks of gestation), the saccular phase (24–38 weeks of gestation), and the alveolar phase (32 weeks of gestation through adolescence). The expression and secretion of pulmonary surfactant begin about 2 weeks earlier in female lungs than in male lungs (26–28 weeks of gestation). Figure created with a licensed version of BioRender.com.

has demonstrated that female fetuses exposed to androgens show delayed lung development, while blocking androgens in male fetuses eliminates the typical sex-based differences in surfactant production (65). Conversely, placental estradiol induces female fetuses to produce surfactant much earlier and display enhanced alveolar maturation due to higher expression, signaling, and activity of estrogen receptors (66, 67). Estrogen also influences lung development through platelet-derived growth factor (PDGF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling to affect alveolar structure, lung elasticity, and surfactant production (66–68). Studies have shown that removing estrogen receptor- β in female

mice results in increased alveolar size and decreased alveolar surface area, creating characteristics that resemble male lungs (60). These structural differences significantly impact RDS risk in premature infants by affecting both surfactant levels and the lung's ability to facilitate gas exchange.

Pregnant women at risk of preterm birth are administered antenatal steroids to accelerate lung maturity in the preterm fetus, reducing the likelihood of RDS and the need for respiratory support after birth. This treatment also has varying effects based on fetal sex. Following antenatal betamethasone therapy, female neonates derive more benefit compared to similarly treated males. However, some studies have shown that

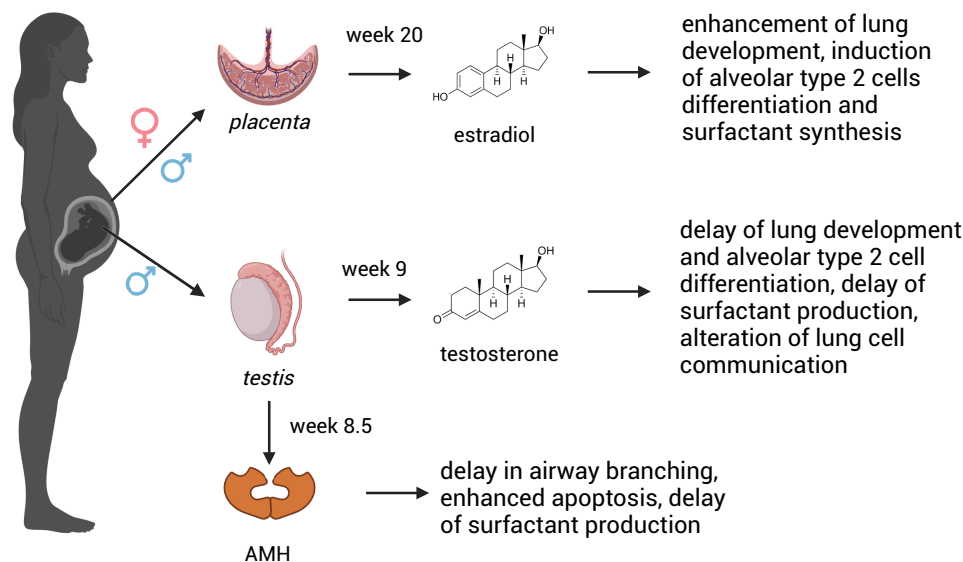


FIGURE 4. Hormonal secretion and regulatory effects during lung development. Male fetuses produce anti-Müllerian hormone (AMH) and testosterone at 8.5 and 9 weeks of gestation, respectively, which delay lung development. In week 20, the placenta produces estradiol, which affects the expression of surfactant in both male and female fetuses. Figure created with a licensed version of BioRender.com.

antenatal steroids may not provide a protective effect in preterm male neonates weighing less than 1,000 g at birth (69). Another study reported that betamethasone treatment prevents RDS with higher potency in preterm females (53). Furthermore, preterm females exhibit better preservation of microvascular blood flow following glucocorticoid exposure (70, 71), although a subsequent systematic review and meta-analysis found no sex-specific differences (10). The administration of antenatal corticosteroids not only enhances the infant's response to subsequent surfactant treatment but also makes this effect more prominent in female infants than male infants of the same age (72). Treatment with surfactant results in better responses in females than males, with males requiring higher doses to acquire similar outcomes and reduce mortality (73). Together, these differences in disease presentation and response to treatment have been postulated to influence the development of other complications of prematurity, including pulmonary, neurological, ocular, and gastrointestinal (74, 75). The relationship between sex hormones and fetal lung development helps explain why male infants face higher rates of RDS than females, even when antenatal corticosteroids are administered. While corticosteroids enhance the airway sodium-potassium pump activity to clear fetal lung fluid, male neonates have fewer alveolar sodium transport channels compared to females (76). This reduced sodium transport capacity can lead to fluid retention in the lungs, compromising gas exchange and increasing RDS risk (77).

For several decades, excessive oxidative stress combined with weak antioxidant defenses has been postulated as an underlying mechanism of diseases of prematurity (78, 79). This theory has gained significant support, with oxidative stress now recognized as a central factor in premature infant complications. Importantly, research has revealed that male and female preterm infants differ in their ability to defend against oxidative stress, with females showing higher antioxidant enzyme activity than males (80). In this context, the glutathione system plays a particularly crucial role. Multiple studies have identified significant sex differences in glutathione levels; the enzymatic activity of glutathione peroxidase, reductase, and S-transferase; and cysteine metabolism in the placenta, umbilical cord, and immune cells (81–83). Based on these findings, it has been suggested that new treatments to protect against oxidative stress in premature infants should both address the glutathione system and account for the infant's sex.

While research in the past few decades has revealed associations of genetic, hormonal, and cellular factors (FIGURE 5), the key biological mechanism driving the observed sex differences in RDS appears to be the effect of sex hormones on fetal lung development. Estrogen promotes, and androgen delays, lung maturation and

surfactant production, giving female fetuses an advantage during premature birth.

3.2. *Bronchopulmonary Dysplasia*

Also found in prematurely born infants, BPD is a condition characterized by an arrest in alveolarization and abnormal development of the pulmonary blood vessels, currently diagnosed based on the need for oxygen or respiratory support at 36 weeks of postmenstrual age (84, 85). The risk of developing BPD is higher in extremely premature boys, with male sex considered an independent predictor for BPD and its severity (86–88). Children with BPD may also experience long-term complications such as the need for tracheostomy and mechanical ventilation, pulmonary hypertension of the newborn, and poor neurodevelopmental outcomes (85, 89–93). Long-term lung function in premature boys with BPD is also worse than in girls, leading to the earlier onset of chronic adult diseases (94–99).

Studies have suggested that the lungs of preterm females may adapt to the postnatal environment more successfully than those of males, since the developing female fetal lung may be more advanced in lung maturation. In this regard, a prospective cohort study identified male sex and intrauterine growth restriction as essential risk factors for persistent respiratory morbidity in extremely premature newborns (100, 101). Studies have also shown that males experience impaired lung repair and recovery mechanisms despite exposure to similar perinatal insults and treatments as females (102, 103). Still, more research is needed before a sex-specific therapy can be claimed, as several other factors have been shown to influence therapeutic responses (104–107).

Clinical studies have attempted to identify the mechanisms underlying sex disparities in BPD (108, 109). Differences in lung development and response to hyperoxia have been postulated as the main contributors, with genes involved in angiogenesis, inflammation, and epithelial and mesenchymal transition (EMT) displaying sex-specific expression (FIGURE 6). A recent cohort study showed that while in female neonates BPD was associated with inflammatory responses mediated by CCL2 and galectin-1, in males it was linked to decreased expression of mesenchymal cell (MSC) genes that are crucial for distal lung development (110). These included platelet-derived growth factor receptor- α (PDGFR α), fibroblast growth factor 7 (FGF7), WNT2, SPRY1, matrix metalloproteinase 3 (MMP3), and forkhead box F2 (FOXF2) (110).

Mouse models of neonatal lung disease, typically involving prenatal exposure to hyperoxia, have also revealed sex differences. Neonatal male mice show greater arrest in alveolarization and vascularization, as

Respiratory distress syndrome



- less common in females
- influenced by surfactant protein genetics
- earlier surfactant production (24–25w GA)
- earlier differentiation of AT2 cells
- higher AT2 Na⁺/K⁺ pump activity
- higher expression of estrogen receptors
- estrogen induction of lung cell proliferation
- estrogen increases PDGF and GM-CSF expression and signalling to enhance AT2 function
- higher antioxidant enzyme activity and glutathione levels
- better response to exogenous surfactant treatment

- 2X more prevalent in males
- influenced by prematurity and surfactant protein genetics
- delayed surfactant production (26–27w GA)
- slower differentiation of AT2 cells
- lower AT2 Na⁺/K⁺ pump activity
- higher expression of androgen receptors and 5- α reductase
- androgens inhibit AT2 development and proliferation
- androgens suppress TGF β and EGF expression, limiting surfactant production
- lower antioxidant levels and enzyme activity
- require higher doses of exogenous surfactant

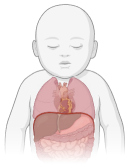
FIGURE 5. Sex-specific factors and mechanisms associated with respiratory distress syndrome in male and female neonates. Sex disparities in respiratory distress syndrome incidence and presentation result from a combination of developmental, hormonal, genetic, and physiological factors. AT2, alveolar epithelial type 2 cells; EGF, epidermal growth factor; GA, gestational age; GM-CSF, granulocyte-macrophage colony-stimulating factor; PDGF, platelet-derived growth factor; TGF β , transforming growth factor β 1. Figure created with a licensed version of BioRender.com.

well as greater alveolar simplification than female mice (108, 111–113). Mice also displayed sex-specific lung transcriptomic profiles, with upregulated EMT transition genes in females, but downregulation in males, and increased expression of lung repair and angiogenesis genes [including Vegf, Vegf receptor 2 (VegfR2), and prolyl hydroxylase domain 2 (Phd2)] in females (114). Grimm et al. (115) also demonstrated that genes in the female sex chromosomes could be protective against neonatal lung injury. A study investigating gene expression in alveolar macrophages (AMs) from neonatal mice exposed to hyperoxia also revealed high expression of sex-chromosome-specific transcripts in male mice that were associated with inflammation, as well as pathways related to glucose and carbohydrate metabolism (113). On the other hand, female AMs showed higher expression of the female-specific transcript *Xist*, which attenuated the acute inflammatory response to hyperoxia, and elevated interferon signaling and pathways related to DNA damage (113).

Besides changes in inflammatory, MSC, developmental, and metabolic gene expression, researchers have established associations of intracellular and secreted microRNAs (miRNAs) with BPD (116–120). MiRNAs play

important roles in posttranscriptional gene expression regulation and could mediate sex-specific phenotypes (121, 122). MiRNAs modulate oxidative stress, proliferation, apoptosis, senescence, inflammatory responses, and angiogenesis, which play pivotal roles in the development of BPD. Recently, Zhang et al. (123) reported that while male and female mice exposed to hyperoxia expressed similar levels of lung miR-30a at postnatal day 7 (PND 7; acute phase), in the recovery phase (PND 21), females expressed significantly higher levels of miR-30a in lung tissue than males. Moreover, female neonatal human pulmonary microvascular endothelial cells had greater expression of miR-30a in response to hyperoxia exposure, as well as increased sprouting. The authors suggested that miR-30a mediates sex-specific angiogenesis and BPD outcomes via regulation of the delta-like ligand 4 (Dl4) gene, with increased miR-30a inhibiting Dl4 expression and stimulating angiogenesis in females, and the opposite effect in males (123). In a follow-up study using miR-30 knockout mice, the same group demonstrated that the sex-specific phenotypic effect of hyperoxia exposure was abrogated and that miR-30 mediated sex-specific transcriptomic responses in the bronchial epithelium (124).

Bronchopulmonary Dysplasia



Risk factors

- male sex
- mechanical ventilation
- prematurity
- intrauterine growth restriction



Sex specific mechanisms



- delayed lung development
- hyperoxia-induced arrest in alveolarization and vascularization
- decreased expression of MSC genes (PDGFR α , FGF7, WNT2, SPRY1, MMP3, FOXF2)
- sex chromosomes affect alveolar macrophage inflammation and metabolic pathways
- reduced miR-30a and increased Dll4 inhibits angiogenesis and repair

- inflammatory response mediated by CCL2 and galectin 1
- X chromosome complement protective of hyperoxia-induced injury
- alveolar macrophages expression of sex chromosome genes that attenuate inflammation
- increased interferon and angiogenesis signaling genes (Vegf, VegfR2, Phd2)
- higher miR-30a induces angiogenesis via Dll4

FIGURE 6. Male- and female-specific mechanisms of bronchopulmonary dysplasia in the infant lung. Risk factors associated with bronchopulmonary dysplasia (BPD) and a summary of main genetic, cellular, and molecular mechanisms associated with BPD in clinical and preclinical models of BPD including the sex variable. Dll4, delta-like canonical notch ligand 4; FGF7, fibroblast growth factor 7; FOXF2, forkhead box F2; MMP3, matrix metalloproteinase 3; MSC, mesenchymal cells; PDGFR α , platelet-derived growth factor receptor- α ; Phd2, prolyl hydroxylase domain 2; VegfR2, vascular endothelial factor receptor 2.

Sex differences have also been reported for surfactant protein gene expression and associated gene variants, suggesting an interaction of genetic and hormonal factors in the development of BPD (125–127). For example, gene variants of the surfactant protein A genes (SFTPA1 and SFTPA2) differ in their expression in males and females and their ability to regulate lung function mechanics and survival in response to infection challenge (128, 129). Data from experimental models indicate that surfactant protein genetics interact with sex to influence immune function and response to exogenous surfactant treatment (130, 131). A recent study in an animal model of perinatal hyperoxia using surfactant protein A (SP-A) knockout mice revealed that female SP-A-deficient mice responded more negatively to oxidative stress challenge than males, although sex-specific mechanisms were not investigated (132). On the other hand, the increase in surfactant protein D (SP-D) levels after birth has been postulated to

inversely associate with BPD (133). Interestingly, there is a drop in SP-D serum levels in neonate males, as opposed to an increase in females, from PND 3 to 7, although the association with BPD outcomes remains unclear (134). Overall, the impact of sex on genetic susceptibility to BPD remains an area needing further exploration, as existing studies have not consistently investigated or reported sex-based differences.

3.3. Asthma

Asthma is a prevalent chronic disease characterized by airway inflammation, clinically manifested by dyspnea, wheezing, cough, and chest tightness (15, 135, 136). As a heterogeneous disease, asthma is characterized by various phenotypes, inflammatory patterns, and differing responses to available treatments across the life span. For example, type 2 high (T2-high) asthma is marked by a strong Th2-driven inflammatory response, involving cytokines such as IL-4, IL-5, and IL-13, as well as eosinophilia and elevated IgE levels. T2-high asthma is more responsive to corticosteroids and is estimated to affect 50–70% of asthma patients (137, 138). In contrast, T2-low asthma exhibits less T2 inflammation, normal eosinophil counts, and low or absent IgE (139). T2-low asthma is less atopic and less responsive to corticosteroids (140). In adults, T2-low asthma shows a female predominance, particularly in obese patients (139, 141–145). On the other hand, males tend to present asthma phenotypes associated with cigarette smoking and environmental factors, as well as exercise-induced bronchoconstriction (146, 147). Extensive reviews of the literature including cross-sectional, longitudinal, observational, and randomized control trials have supported the notion that more severe asthma phenotypes are more prevalent in adult females, resulting in higher healthcare costs (12, 16). However, there are conflicting data in the literature, with some studies indicating a more predominant Th2 phenotype in females (145, 148–150) and others indicating the opposite (151, 152).

There are significant differences in asthma incidence, prevalence, and severity, including response to exercise, depending on the sex of the patient (4, 136, 146). Before puberty, asthma is more prevalent and severe in young boys compared to girls. This leads to higher rates of asthma-related emergency department visits and hospitalizations among prepubescent boys than girls of the same age (153–155). However, after puberty, the prevalence, severity, and mortality of asthma are higher in women compared to men (16) (FIGURE 7). It has been suggested that the bimodal distribution of asthma and sex differences may be due to changes in circulating sex hormone levels at puberty (i.e., adrenarche in boys and menarche in girls) as well as declining levels with

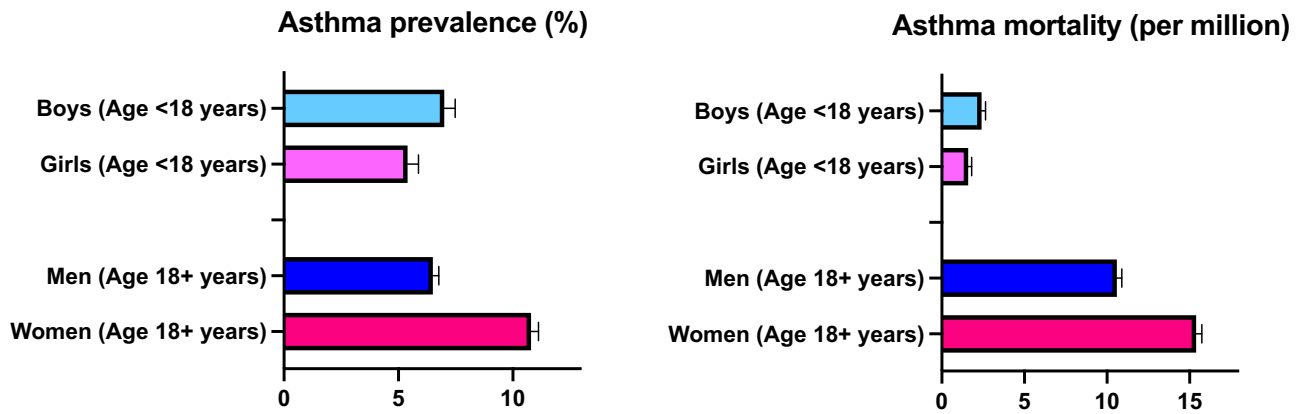


FIGURE 7. Sex differences in asthma prevalence and mortality in children and adults by sex. Data (mean and standard error) are from the 2022 database of the Centers for Disease Control and Prevention.

aging in men and with menopause in women (16, 156). Reports indicate that androgens may ameliorate, and estrogens may amplify, allergic airway inflammation, potentially accounting for some of the differences in asthma phenotypes and severity among men and women (150, 157–166).

The sex disparity in asthma during childhood has been noted in multiple cohort studies (5, 145). While the underlying mechanisms are still unclear, this disparity is attributed to genetic factors, anatomical differences, environmental exposures, and the microbiome (167–170). Regarding genetic factors, a study by Loisel et al. (170) identified notable genetic differences in asthma risk based on sex. Two single-nucleotide polymorphisms (SNPs) in the interferon gamma gene, rs2069727 and rs2430561, showed significant interactions with sex in determining asthma risk, despite having no direct main effects on asthma. Interestingly, boys who were heterozygous for these SNP variants had the highest asthma risk, while girls who were heterozygous had the lowest risk (170). Similarly, a study involving the EVE Asthma Genetics Consortium identified six sex-specific asthma risk alleles by conducting separate genome-wide association studies (GWAS) for males and females (171). Of these, 2 SNPs were male specific (rs2549003, rs17642749), while four SNPs were female specific (rs1012307, rs4673659, rs2675724, and rs9895098). While the female SNPs were mostly in intronic regions and the 3'-untranslated region (3'-UTR), the male SNPs were in genomic regions. Notably, all SNPs were ancestry specific, with the most significant sex-specific associations found in male European Americans at the interferon regulatory factor 1 (IRF1) locus on 5q31.1 (rs2549003) and a Latino female-specific association in the 3'-UTR of the RAP1GAP2 gene, which encodes a GTPase-activating protein regulating dense granule secretion in platelets (171). More recently, Espuela-Ortiz et al. (172) reported 4 independent loci that interacted with sex in a GWAS analysis. The 17q12-21 locus was

significantly associated with asthma risk in females but not in males, while other genetic variants were linked to asthma only in males (172). Enrichment and pathway analyses revealed an overrepresentation of processes related to the immune system and highlighted differences between sexes.

Multiple genomic studies have attempted to identify genetic and epigenetic associations with asthma, reporting over 3,000 genetic variants in more than 140 loci (173). However, only a fraction of these studies disaggregated data between males and females. A recent analysis by Zein et al. (174) of over 500,000 non-Hispanic white participants of the United Kingdom (UK) biobank revealed sex-specific gene associations with asthma, with 8 genes displaying sex differences (HLA-DQA1, HLA-DQB1, IL1RL1, FLG-AS1, BTNL2, IL18R1, HLA-DPA1, and IRF4). These genes were mostly associated with Th1 and Th2 activation and antigen presentation pathways, as well as glucocorticoid receptor signaling, and IL-4 signaling (174).

Other studies focusing on gene expression levels in various cells and tissues revealed sex-specific pathways in asthma. This is relevant since a recent analysis of the genotype-tissue expression (GTEx) database indicated that over 6,500 protein-coding genes showed significant sex-specific expression patterns across multiple tissues (175). The most comprehensive report to date was conducted by Gautam et al. (176), who analyzed more than 2.8 million transcripts covering 20,000 genes leveraged from five different tissues and cell types (epithelial, blood, induced sputum, T cells, and lymphoblastoids) in 711 males and 689 females. Using tissue-specific meta-analysis, the authors identified 439 male- and 297 female-specific differentially expressed genes (DEGs) in all cell types, with 32 genes in common. By linking DEGs to GWAS data, they identified four male-specific genes (FBXL7, ITPR3, and RAD51B from epithelial tissue and ALOX15 from blood) and one female-specific gene (HLA-

DQA1 from epithelial tissue) that were dysregulated during asthma (176). In epithelial cells, the main male-specific pathway associated with DEGs was hypoxia-inducible factor-1 (HIF-1) signaling, whereas in females it was IL-17 signaling. The cytokine-cytokine receptor pathway was shared between sexes in epithelial cells, but no shared pathways were identified in other tissues. Interestingly, no sex-specific pathways were identified in sputum (176).

Environmental factors like exposure to allergens, air pollution, and secondhand smoke can exacerbate asthma symptoms differently in boys and girls (177). Boys tend to be more affected by these factors early in life; however, as girls reach puberty, their increased vulnerability may be linked to hormonal changes. Studies addressing associations of parental asthma, prenatal environmental tobacco smoke, and prematurity (particularly very preterm birth) have determined that all are well-established risk factors for childhood asthma (178). However, the influence of sex on these factors has not been fully studied. It is known that children born prematurely or with lung injuries at birth are at a higher risk of developing asthma. This factor is particularly relevant for boys, who have relatively smaller airway diameters compared to lung volumes than girls and who are more prone to develop neonatal lung disease with premature birth (179, 180). Preterm infants are also more likely to develop severe viral infections and have altered microbiomes, leading to higher asthma rates (181).

It has also been reported that asthma severity, airway inflammation, and lung function can vary significantly over the menstrual cycle in adult women (FIGURE 8). Premenstrual variation of asthma symptoms has been reported in 20–40% of females with asthma, manifesting as lower forced expiratory volume in 1 s (FEV₁) and more respiratory symptoms before menses (182–184). This translates clinically into increased airway hyperresponsiveness and a higher rate of urgent healthcare utilization

(185–188). In some women, the PC20 (i.e., the provocative concentration of bronchoconstrictor causing a 20% fall in FEV₁) has been shown to decline during the luteal phase (182, 184). In others, significant airway inflammation manifested by higher fractional exhaled nitric oxide (FeNO) and sputum eosinophils has been reported in the luteal phase and midcycle (184, 189, 190). These changes in lung function over the menstrual cycle have been attributed to the effect of sex hormones on the cyclical regulation of β 2-adrenoceptors and angiogenesis in the lungs, as well as on immune cell function and inflammation (189, 191). However, to date, evidence-based therapy for premenstrual asthma is still lacking.

During pregnancy, the respiratory system undergoes significant changes, including lung and chest wall mechanics, ventilatory patterns, and gas exchange (54, 192). While peak flow rates remain relatively stable in nonasthmatic pregnant women, lung volumes are impacted by diaphragmatic elevation and thorax configuration changes. In addition, about a third of women with asthma experience a decrease in asthma symptoms when getting pregnant (193). Interestingly, another third of pregnant women display similar symptoms, and the remaining third have increased symptoms. Studies have also found that women with more severe asthma are more likely to experience an increase in symptoms during pregnancy compared to those with milder forms of asthma (194). However, this increase is not sustained 3 months after childbirth, indicating that changes in sex hormones during pregnancy can impact asthma symptoms and lung function (40, 193, 195). The specific mechanisms behind these changes have yet to be fully understood, but both mechanical effects of the fetus on the airways and hormonal influences have been suggested. Maternal asthma can lead to significant health issues for the newborn, including higher rates of prematurity and intrauterine

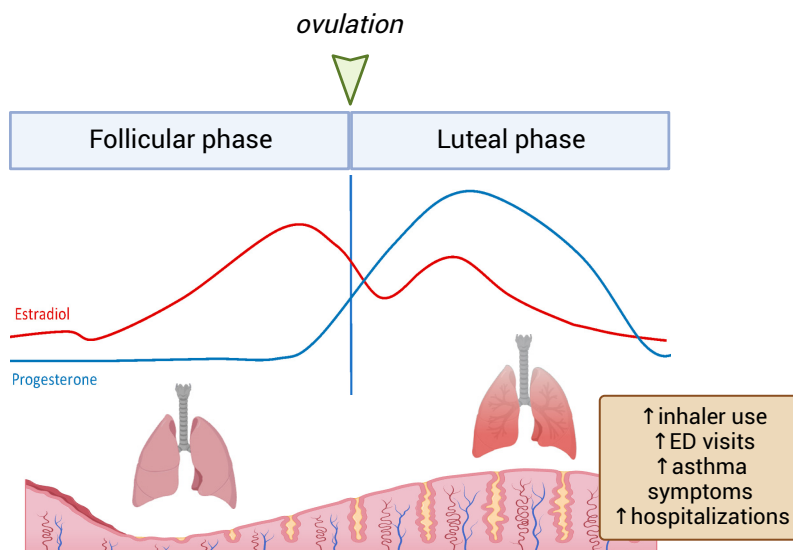


FIGURE 8. Menstrual cycle and asthma. Fluctuations in circulating ovarian hormones (estrogen and progesterone) during phases of the menstrual cycle are associated with increased asthma symptoms in women. ED, emergency department. Figure created with a licensed version of BioRender.com.

growth retardation (196). Interestingly, sex differences in fetal vulnerability have been observed, with female newborns of mothers with asthma showing lower birth weights compared to males (145).

A correlation between obesity and the likelihood of asthma has also been noted with sex differences. However, data from studies addressing these associations are conflicting. For example, two extensive cross-sectional studies from China and the Netherlands, as well as two longitudinal cohorts from the United Kingdom and Taiwan, revealed that childhood asthma is linked to obesity in young girls but not in young boys (197–199). The UK study monitored children longitudinally until the age of 8 and discovered that the risk of asthma was higher in girls with a higher body mass index (BMI) but not in boys (200). The Taiwan study followed participants prospectively for 12 months and found that asthma incidence was higher among obese adolescent girls but not boys (201). This is consistent with findings from Castro-Rodríguez et al. (202), who reported that girls, but not boys, who became overweight or obese between ages 6 and 11 were more likely to develop new asthma at age 11. One cross-sectional study of children aged 5–18 found that asthma was associated with higher BMI and higher serum leptin levels, which were higher in girls than in boys. The authors hypothesized that leptin, which is crucial in regulating body weight, stimulates Th1 immune pathways and proinflammatory cytokine secretion in a sex-specific manner (203). On the other hand, a meta-analysis of six prospective studies revealed that overweight and obese children were at a higher risk for asthma, and that this effect was larger for boys than girls (204). Similarly, a study in children with poorly controlled asthma revealed that obesity was associated with reduced lung function in males but improved lung function in females (205).

Interestingly, the negative impact of obesity on asthma becomes less significant with age. In fact, lung function is mainly reduced between the ages of 6 and 11 in both boys and girls. However, between the ages of 12 and 44, females (but not males) show more significant lung function impairment related to obesity (206–209). Although most reports, but not all, suggest a sex difference in the obese-asthma phenotype, it remains unclear whether these differences are specifically related to sex hormones (210, 211). In this regard, two major research initiatives, the European Network For Understanding Mechanisms of Severe Asthma (ENFUMOSA) and the Severe Asthma Research Program (SARP), revealed that adult women were over four times more likely than men to have severe asthma compared to nonsevere asthma (142, 212, 213) and that women with severe asthma had significantly higher BMI. Meanwhile, BMI did not differ between men with severe versus nonsevere asthma. Overall, while most studies suggest an interaction between gender and

obesity in asthma, with obesity-related asthma typically emerging later in life, presenting with more severe symptoms, and occurring predominantly in women (214), the underlying mechanisms remain unclear.

More recently, the airway and gut microbiomes have been implicated in sex-specific asthma phenotype pathogenesis. Interestingly, both microbiomes differ between men and women, and a role of the lung-gut axis has been proposed as a mediator of lung disease pathogenesis (215–219). A study analyzing induced sputum samples found that *Streptococcus salivarius* was significantly more abundant in women than in men with asthma, and that lower levels of this bacterium were associated with a higher likelihood of asthma. Additionally, increased levels of *Lactobacillus* species were observed in patients with asthma compared to healthy controls, and *Haemophilus* species were associated with asthma in men and not in women (220).

Animal models of asthma, including those employing ovalbumin (OVA) or house dust mite (HDM) challenges, have consistently shown variability in innate and adaptive immune responses in males and females (221). Compared to male mice, females tend to exhibit increased serum IgE and greater production of Th2 cytokines (e.g., IL-4, IL-5, IL-13) (221, 222). In HDM-challenged models, female BALB/c mice also show a Th17-biased response, whereas male mice demonstrate higher Th2 responses (222). This highlights the complexity of immune responses based on sex and strain. While these animal models have replicated lung inflammatory patterns observed in humans, inconsistent data have been reported for lung function parameters (reviewed in Refs. 223 and 156). These parameters not only show high variability across models but also dual roles of sex hormones in attenuating or exacerbating airway hyperresponsiveness (224).

Gonadectomy studies in mice have also provided valuable insights into the role of sex hormones in lung inflammation and asthma. Collectively, these studies have replicated hormone-related phenotypes observed in humans. For example, gonadectomized male mice exhibited airway eosinophilia and heightened Th2 inflammation when challenged with HDM (225) and increased group 2 innate lymphoid cells (ILC2) cells when challenged with *Alternaria alternata* extract (226). This suggests that testosterone may play a protective role by attenuating Th2 responses and eosinophilic inflammation. In this regard, the androgen receptor (AR) has been identified as a key mediator through which testosterone exerts its effects in the lung (159, 227–230). On the other hand, studies on gonadectomized females showed decreased levels of IL-5, IL-13, and total serum IgE, as well as a reduction in eosinophils and airway hyperresponsiveness in response to allergen challenge (231–233), indicating that ovarian hormones are crucial in allergic airway inflammation.

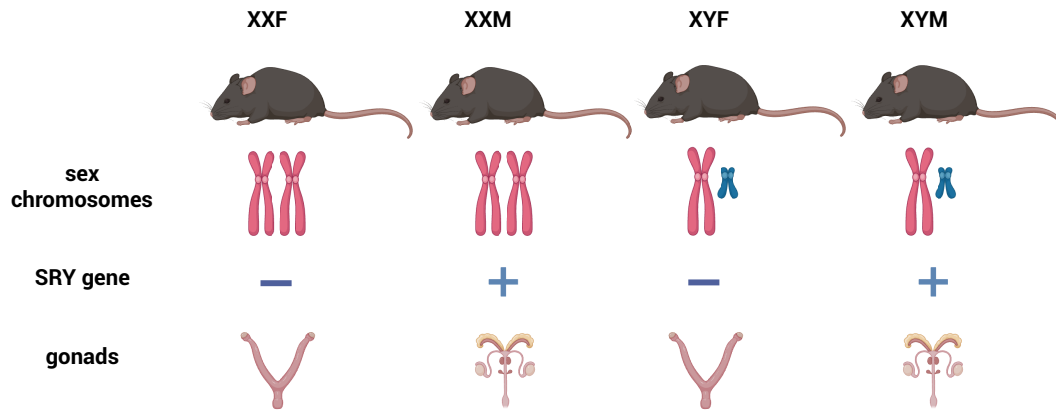


FIGURE 9. The 4 core genotypes (FCG) mouse model. The FCG model is created by deleting the testis-determining gene (SRY) from the Y chromosome and inserting it onto an autosome (nonsex chromosome). As a result, the type of gonad (testes or ovaries) is no longer strictly determined by the sex chromosomes. This genetic manipulation produces 4 possible combinations: XX mice with ovaries (XXF), XX mice with testes (XXM), XY mice with ovaries (XYF), and XY mice with testes (XYM). This model enables researchers to determine whether observed sex differences in traits are due to sex chromosome complement, gonadal hormones, or their interaction. Figure created with a licensed version of BioRender.com.

A useful tool to discern the contributions of sex hormones and sex chromosomes is the four core genotypes (FCG) mouse model, a genetically engineered system designed to separate the effects of sex chromosomes (XX versus XY) from the effects of gonadal sex (testes versus ovaries) on physiology and disease (**FIGURE 9**) (234). In this model, the Sry gene of the Y chromosome, which triggers testis development, has been moved to an autosome (chromosome 3), generating four possible combinations: XX mice with ovaries (XXF), XX mice with testes (XXM), XY mice with ovaries (XYF), and XY mice with testes (XYM). By comparing mice with the same type of gonad but different sex chromosomes (e.g., XXM vs. XYM), it is possible to identify effects due to sex chromosome complement. In contrast, by comparing mice with the same sex chromosomes but different gonads (e.g., XXF vs. XXM), the effects due to gonadal hormones can be identified. Recent studies using the FCG model in the context of HDM challenge and asthma have identified the predominant effect of female gonadal hormones on lung inflammation, with notable differences across genotypes and unique pathways affected by sex hormones and sex chromosomes (235–237).

Overall, from childhood to adulthood, biological sex is a key factor in asthma phenotypes. Multiple mechanisms involving gene expression regulation and actions of gonadal hormones have been postulated, particularly in inflammatory and immune pathways (**FIGURE 10**). Understanding the interplay between sex hormones and asthma can lead to future personalized therapeutic strategies that consider these hormonal influences.

3.4. Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease has traditionally been thought of as a disease affecting older men (238).

However, over the past two decades, it has become increasingly clear that a significant number of women are also affected by the disease (239–243). The prevalence of COPD and hospitalizations related to it has risen among women, partly due to increased rates of tobacco use across the globe (244–248). Some data even suggest that women may be more susceptible to the harmful effects of smoking (249–251), although recent data suggest that nonsmoking women are also more likely to develop COPD (252, 253). It is also recognized that the clinical presentation and progression of the disease differ between sexes (239). Evidence suggests that women develop the disease earlier in life, have fewer pack-years of smoking at the time of diagnosis, and experience more frequent respiratory exacerbations (254, 255). There is also emerging evidence of sex-related differences in the underlying pathophysiology of the disease, including variations in cytokines, proteomics, and metabolomics, which could contribute to differences in how the disease presents clinically. Clinical data also revealed that women were significantly more affected by COPD despite minimal tobacco smoke exposure (256–259). This sex bias has resulted in a decrease in the mortality rate of men with COPD in the United States, while there has been no change among females (260, 261).

COPD presents a critical public health challenge, as recent research suggests that women have heightened biological susceptibility to nicotine addiction and environmental risk factors compared to men (260, 262). The impact of COPD on women also varies significantly between developed and developing nations. In developing countries, women face a dual burden: not only tobacco use but also extensive exposure to indoor air pollution from cooking with biomass fuels (263, 264). Among female smokers, mortality risk escalates with

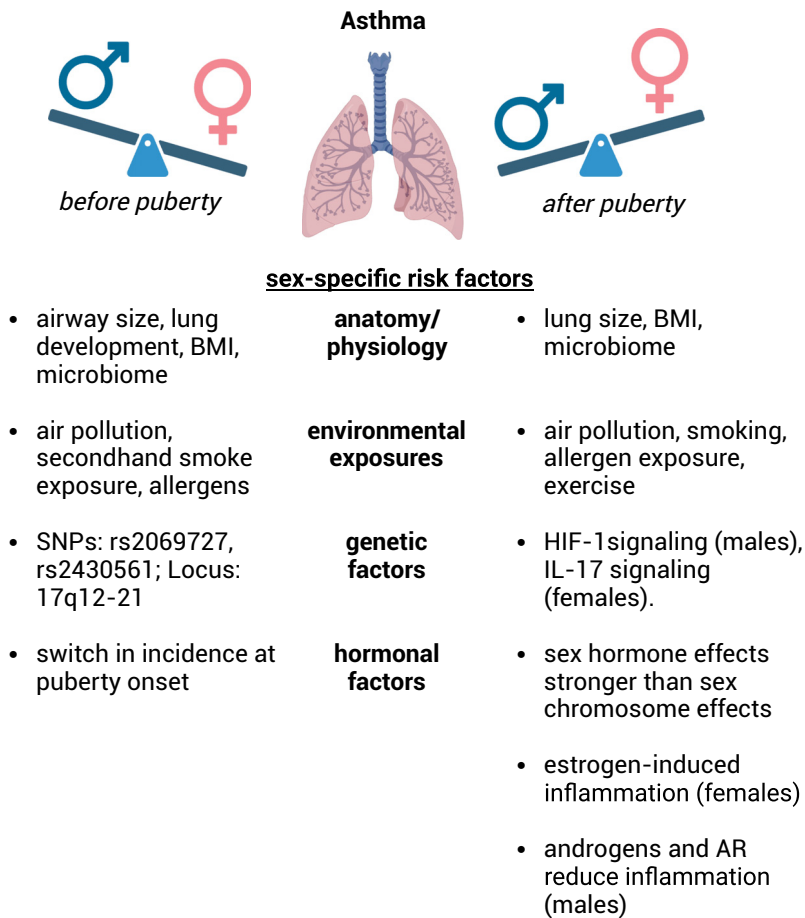


FIGURE 10. Sex-specific factors and mechanisms of childhood and adult asthma. Genetic, immune, hormonal, environmental, and physiological factors affect asthma susceptibility across the life span. The main mechanisms differentially affected by sex hormones involve lung immune responses to allergen challenges and regulation of signaling pathways. AR, androgen receptor; BMI, body mass index; HIF-1, hypoxia-inducible factor-1; SNPs, single-nucleotide polymorphisms.

both cigarette consumption and earlier onset of smoking (265, 266).

Anatomical differences between males and females contribute to the disparities observed in COPD. Females typically have smaller airways and lung volumes, which can lead to greater respiratory constraints during exertion (254). This difference necessitates a higher ventilatory effort for females compared to males, contributing to increased dyspnea. The inflammatory response to cigarette smoke also appears to differ between sexes, potentially due to hormonal influences (267). Females exhibit heightened inflammatory responses characterized by increased levels of cytokines such as IL-5 and IL-13, which are associated with allergic inflammation and could contribute to the severity of symptoms (268). Estrogen is believed to influence lung function and the progression of COPD, and interact with oxidative stress pathways, such as those involving NADPH oxidase 4 (NOX4) (9, 269). Conversely, testosterone may offer protective benefits against COPD. A recent study assessing lung tissue gene expression and DNA methylation from the Lung Tissue Research Consortium identified sex differences in COPD-related gene regulatory networks, along with sex-specific expression of extracellular matrix genes (including ITGA7, ITGA9, ITGA11, ITGB3, ITGB5,

and SV2B) that were associated with emphysema severity, cigarette smoke, aging, and lung function (270). Another study using the Canadian Longitudinal Study on Aging (CLSA) baseline comprehensive and genomic data found 28 distinct signals for a genome-wide SNP-by-sex interaction COPD outcomes, including 8 SNPs in males located in or near the MAGI1, COX18, OSTC, ELOVL5, C7orf72 FGF14, and NKAIN4 genes, and 4 SNPs in females located in or near genes CAMTA1, SATB2, PDE10A, and LINC00908 (271). The authors concluded that elucidation of functional sex-specific roles of these signatures may help improve disease endotyping in male and female patients and develop more personalized therapeutics.

Mouse models of COPD typically involve chronic cigarette smoke exposure (243). Although most animal models of COPD cannot be directly extrapolated to human phenotypes, they have revealed significant sex differences in disease progression and manifestation (254, 267). In these models, female mice tend to develop more small airway disease, airway inflammation, airflow obstruction, and airway remodeling, while male mice are more prone to emphysema (272). These differences are linked to both structural and

molecular mechanisms, including variations in airway size, extracellular matrix gene regulation, and inflammatory cell profiles between sexes. Importantly, gonadectomized females display male-like phenotypes, suggesting a role of female sex hormones in sex-specific COPD mechanisms. Continued refinement of these models will enhance their relevance and applicability to human health issues related to COPD and address sex-specific mechanisms.

3.5. Lung Cancer

Lung cancer is the second most diagnosed cancer in men and women worldwide (273). It is also the leading cause of cancer mortality for both men and women. While tobacco use has been closely associated with lung cancer in both males and females, nonsmoking women are more likely to develop lung cancer than nonsmoking men (9, 274). There is also a higher occurrence of squamous cell carcinoma in males and a higher occurrence of adenocarcinoma in females (275). Moreover, there has been a rise in the number of deaths related to lung cancer in women but not in men (276). Even with lower tobacco use rates, women smokers are also more likely to develop lung cancer than men.

Female sex hormones are believed to play a role in this phenomenon, leading to molecular aberrations resulting from the carcinogenic effects of tobacco, as well as modulating the metabolism of tobacco-containing toxins (277–281). For example, estrogen synergizes with some tobacco compounds through the induction of CYP1B1, leading to enhanced reactive oxygen species formation and carcinogenesis (282, 283). There have been numerous reports on the association between sex hormones and lung cancer (277, 284, 285). These studies have shown that estrogen can be produced by lung cancer cells and induce cell proliferation (286). In line with the idea that estrogens promote lung cancer, a noticeable increase in lung cancers was observed in males who were administered estrogens to treat heart disease, prompting the early termination of the clinical trial (287). Estrogens can also influence the effects of other carcinogenic factors, such as smoking-related genetic mutations (288). The role of estrogens in promoting cancer is further supported by the frequent expression of estrogen receptors in lung cancers and by their ability to stimulate lung cancer growth directly or indirectly via aromatase in cell culture studies (289). These findings suggest that estrogen contributes to lung cancer growth both in clinical settings and experimental models. Estrogen has also been shown to promote cell proliferation and tumor growth. Thus, anti-estrogen

treatment strategies have been implemented to decrease tumor size, growth, and cell proliferation, leading to improved patient outcomes (290, 291). For example, a study using antiestrogen for breast cancer patients revealed a reduced risk of subsequent lung cancer in older patients, suggesting that antiestrogen therapy can modify lung cancer carcinogenesis in older women (292). There have also been reports on progesterone inhibiting lung cancer growth in vivo and higher levels of testosterone being associated with higher lung cancer risk (293–295). Moreover, progesterone has also been shown to play a potential role in the development of lung cancer, as its receptors are commonly expressed in nontumor tissues compared with malignant lung tissue (296–298). Finally, testosterone has been reported to potentiate cancer-promoting effects of estrogen while suppressing overall immune responses (299–301). While a role of androgen receptors has been postulated (302), more research studies and clinical trials are needed to determine therapeutic options considering gonadal hormones in lung cancer (303, 304).

Genetic differences have also been identified between lung cancers in men and women, with women more frequently having lung cancer with driver mutations in the EGFR, ALK, or KRAS genes (305–307). A few studies have indicated that female patients with lung cancer are more likely to harbor EGFR mutations compared to their male counterparts (308–310). Women with ALK-positive lung cancers also tend to be younger than their male counterparts and are often nonsmokers (311, 312). This demographic is particularly prevalent in Asian populations, where studies have shown that ALK rearrangements account for a significant portion of mutations in lung adenocarcinoma (309, 313). Female smokers also tend to have higher levels of aromatic/hydrophobic DNA adducts and greater expression of CYP1A1 in lung tissue compared to males (314), leading to increased metabolism of polycyclic aromatic hydrocarbons (PAHs) from cigarette smoke into carcinogenic intermediates. Despite lower exposure to tobacco carcinogens, female smokers show higher levels of PAH-DNA adducts, potentially due to estrogen's role in cell proliferation (315). Moreover, females generally metabolize nicotine faster, partly because of enhanced CYP2A6 activity linked to higher estrogen levels (316, 317). Research has also shown that the X-linked gastrin-releasing peptide receptor (GRPR), which promotes cell proliferation, is more highly expressed in female nonsmokers than in males. Additionally, female smokers exhibit higher GRPR expression at lower levels of tobacco exposure, suggesting that two copies of the GRPR gene might increase susceptibility to lung cancer in women (318, 319). The methylation profiles of genes

in lung adenocarcinoma exhibit a female bias, involving categories linked to interferon- α response, TGF β , and TNF α signaling, as well as apoptosis (320).

The landscape of lung cancer is changing, with increasing incidence rates among younger women and notable differences in histology and outcomes compared to men. Continued research into the biological underpinnings of these sex differences is essential for developing personalized approaches to prevention, diagnosis, and treatment. Understanding the interaction of hormones and expression of sex-specific genes with environmental factors can lead to better-targeted interventions that consider the unique characteristics of male and female patients.

3.6. Obstructive Sleep Apnea

Obstructive sleep apnea is a sleep disorder characterized by repeated episodes of partial or complete blockage of the upper airway during sleep. The prevalence and severity of OSA are higher in men compared to women, with male-to-female ratios ranging from 2:1 to 3.5:1 in the general population (46). This has been related to anatomical differences leading to increased airway compliance and collapsibility in men compared to women (321). Like with other conditions described earlier, the disease incidence is similar between sexes before puberty. However, after puberty, the pathogenesis of OSA diverges, and OSA becomes more common in males than females (321). The lower risk and severity in postpubertal girls have been related to the protective effect of female sex hormones on airways and ventilatory drive. This is further demonstrated by the increased rates of OSA in women postmenopause (322), as well as reduced OSA symptoms in transgender women receiving estrogen therapy (323). One additional proposed mechanism in females involves progesterone, which is known to increase the tone of the upper airway muscles and stimulate ventilation by increasing the chemoreceptor response to hypoxia and hypercapnia (324). In addition, studies in hypogonadal men and obese men with low testosterone levels revealed that androgens may be protective for OSA (325).

4. SEX DIFFERENCES IN LUNG PHYSIOLOGY

Sex differences in the lung have been reported as early as during fetal development. Female fetuses display smaller airways and fewer bronchi than male fetuses. After birth, a higher ratio of large to small airways characterizes female neonates with higher flow rates and airway conductance than males. This has been attributed

to the surfactant action of maintaining patency of the smaller airways.

These differences continue throughout adult life, resulting in larger male lungs containing smaller airways (65). Indeed, women's airway luminal areas and length are 20–30% and 10–14% smaller than men's, respectively (326). Interestingly, the differences in airway size between sexes were first noted in 1894 by Ellis (327), where it was reported that “in nearly every dimension man's larynx is larger, the entire male larynx being about one third larger than the female.”

The lungs of girls and women are generally smaller than those of boys and men of the same height. However, when measuring lung function parameters, females tend to have higher forced expiratory flow rates than males (after normalizing for differences in body size). In fact, the ratios of forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC) are higher for girls and women. This is because when the lung develops and grows, a disproportional scaling of airway dimensions relative to lung size can occur, resulting in a mismatch between the airway lumen caliber and lung volume, a concept known as dysanapsis (from Greek: dys = unequal and anaptixy = growth) (180) (FIGURE 11). While males are more likely to have isotropic lung growth, females tend to experience higher rates of dysanapsis.

Overall, three main factors contribute to the sex differences in airway structure and function: 1) dimensional factors, addressed with the concept of dysanapsis during lung growth; 2) immune factors, associated with sex differences in lung inflammation, atopy, and infection; and 3) hormonal factors, such as influences of reproductive cycles, puberty, menopause, and pregnancy.

We elaborated on these in detail in the sections below.

4.1. Dimensional Factors: Sex Differences in Lung Development

Lung development in humans is a well-established process involving several stages (328–330). The lung begins to grow from the foregut endoderm at an early stage of gestation, progresses to establish conducting airways by birth, and continues alveolar development for up to 8 years postnatally (330). There are five major stages during development: embryonic, pseudo-glandular, canalicular, saccular, and alveolar (FIGURE 3). The embryonic stage initiates at 3–7 weeks of GA and is characterized by the primary right and left lung bud formation. From 5 to 17 weeks of GA, the pseudo-glandular stage occurs, where branching morphogenesis establishes the airway tree and cellular differentiation begins. Fetal breathing begins once tracheal cartilage, smooth

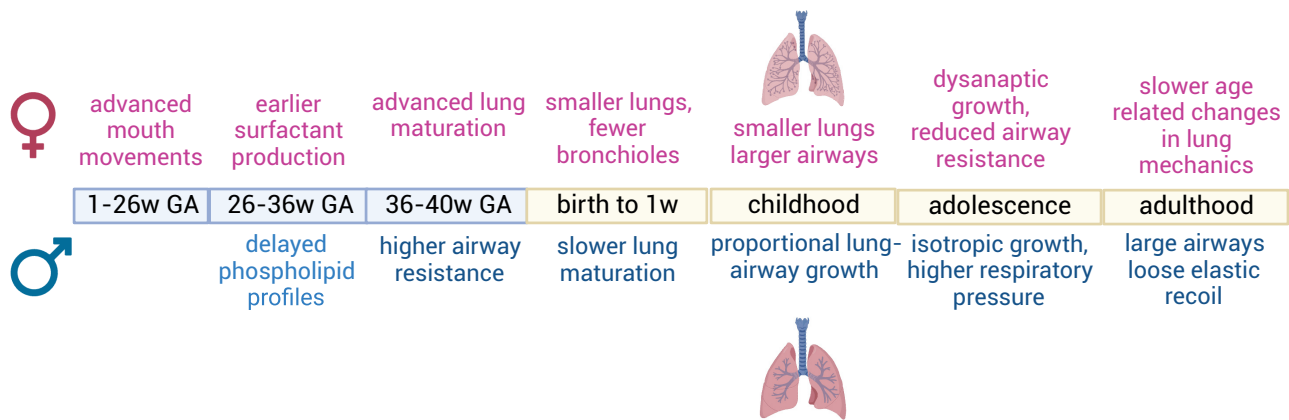


FIGURE 11. Sex differences in lung growth and dysanapsis. Male and female embryonic/fetal (blue) and postnatal (yellow) lung development presents sex-specific characteristics. A timeline of sex-specific features related to lung growth and respiratory mechanics is shown. GA, gestational age; w, week. Figure created with a licensed version of BioRender.com.

muscle, and blood vessels develop (331). In the following canalicular stage, ranging from 16 to 29 weeks of GA, epithelial branching and cell differentiation occur, giving rise to alveolar epithelial cells alongside a capillary network around distal epithelial airspaces. In the subsequent saccular stage, at 24–38 weeks of GA, branching morphogenesis ends, and saccules form at the ends of airways. Alveolar epithelial cells begin to differentiate into AT2 cells, which produce surfactant. The final stage is alveolarization, starting at 32 weeks of GA and continuing through adolescence, when alveoli are fully formed and their surrounding capillary network matures. As indicated in the prior sections, lung development is a process that is heavily influenced by sex hormones, including maternal and fetal steroids (FIGURES 3 AND 4). Recently, Savchuk et al. (58) identified testosterone presence in embryos as early as 6–7 weeks of gestation, with levels peaking between weeks 11 and 14. The delay in male versus female fetuses due to the actions of sex hormones (31) provides an advantage in premature birth for female newborns, leading to sex differences in lung disease susceptibility (31, 332).

Anatomical differences may also explain the observed sex-specific physiological responses in infancy and puberty. At birth, male babies have larger lungs than females, with more respiratory bronchioles (333). However, the female airways and their lung parenchyma grow more proportionately than those of males throughout infancy, childhood, and adolescence (65, 334). Because early postnatal lung development involves exponential increases in the number and size of alveoli, the female lung is smaller compared to the male lung, and the male's total number of alveoli and surface area is consistently higher throughout childhood. As a result of these growth patterns, airway resistance is lower in females, resulting in

higher forced expiratory flow rates, giving an advantage to prepubertal girls versus boys regarding airflow. While males have larger lungs and longer airways, they are at a disadvantage for expiration. Then, after puberty, adult men's and women's expiratory flow rates become comparable. Additionally, lung development is influenced by the timing of puberty. Later pubertal age is also associated with a lower risk for asthma-like symptoms in early adulthood (156, 335, 336).

4.2. Immune Factors: Sex Differences in Lung Immunity

Throughout the different life stages, males and females display distinct immunological responses to foreign and self-antigens, exhibiting differences in both innate and adaptive immunity (337, 338). Like lung diseases, sex differences in lung immunity can start as early as infancy or emerge after puberty and are often attributed to hormonal influences (339–342). Furthermore, environmental exposures and exercise can impact immune function in a sex-specific manner (146, 147, 343). Notably, these sex-based immunological distinctions may play a role in the varying occurrence of autoimmune diseases, cancers, susceptibility to infection, and responses to vaccines (344, 345). Overall, females tend to mount stronger lung immune responses with higher basal immunoglobulin levels, antibody responses, and B-cell counts than men (346). However, while the stronger immune responses in females may contribute to faster pathogen clearance, they can also increase susceptibility to chronic inflammatory and autoimmune lung diseases (347).

Numerous reports indicate sex differences in respiratory infections (348, 349). While the exact mechanisms are not fully understood, strong evidence suggests that males are more susceptible to respiratory infections and have a harder time recovering compared to females,

except for some upper respiratory tract infections (350). Variations in lung structure and function, as well as the influence of sex hormones, may explain these differences in susceptibility and response to respiratory infections (6, 351). For example, differences in lung development and maturity due to sex hormones may contribute to the higher frequency of lower respiratory tract infections in young males (261). Estrogens lead to more effective immune responses, while androgens reduce immune competence, making males more susceptible to infection (158, 340, 352, 353). It is also important to consider the influence of cyclical changes in female sex hormone concentrations, particularly during the menstrual cycle and pregnancy, on the immune response to respiratory infections (354–356). Reports have indicated that specific respiratory symptoms (wheezing, cough, and shortness of breath) were most frequent in women at the mid-luteal to midfollicular phases (357). Also, physiological changes during pregnancy can increase susceptibility to viral infections, with a higher risk of pulmonary infections for pregnant women (358). Genetic and chromosomal factors also contribute to observed differences in susceptibility to infection, as several immune-cell-related genes are located on the X chromosome (337, 359). In this regard, X-chromosome inactivation, an epigenetic mechanism ensuring the silencing of one X chromosome in female individuals, may also contribute to the observed sex disparities in lung infection (52, 360).

Respiratory infections are a significant cause of illness and death in people of all ages. Research has indicated that immunity to viruses may vary with changes in hormone concentrations due to fluctuations during the menstrual cycle, contraception use, pregnancy, and menopause (340). While males generally experience more severe lower respiratory tract infections, females seem to be more prone to upper respiratory infections (351). Sex differences in infection rates and outcomes have been postulated due to genetic, hormonal, anatomical, and immunological factors (361–364). In infancy, boys are more likely to be affected by respiratory syncytial virus (RSV) compared to girls (365), resulting in more frequent and severe cases of bronchiolitis and often associated with a higher risk of wheezing, childhood asthma, and hospitalization (366, 367). Regarding other common infections, such as influenza, studies have shown that there are sex differences in influenza severity, mortality, vaccine tolerance, responses, and outcomes (368). 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 (344, 369).

Sex-specific immune responses to various viral pathogens have been documented in recent studies (360, 370–373). Previous outbreaks of coronaviruses such as

severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have shown higher fatality rates in males compared to females (374–376). However, COVID-19 revealed sex differences in hospitalizations, intensive care unit admissions, and deaths, with a significant male predominance (377, 378), partially mediated by the androgen effects on the TMPRSS2 gene (379). In addition, sex differences in the immune response to SARS-CoV-2 showed higher levels of proinflammatory cytokines and chemokines in males with mild disease, while females displayed higher activation of adaptive immunity pathways (380). These differences were attributed to a combination of hormonal and chromosomal factors playing a role in the immune response to the viral infection (381). Additionally, long-term consequences of COVID-19, such as postacute sequelae of COVID (PASC), have been reported with higher rates in female than male patients (382, 383).

4.3. Hormonal Factors: Sex Steroids and Lung Disease

Sex steroids are primarily produced by three central organ systems: the gonads, the adrenal glands, and the fetoplacental unit (65). They are also metabolized in several nonendocrine peripheral tissues and organ systems (2, 384). The local production of sex steroids within specific tissues, mainly from nongonadal sources, depends on the concentration of the enzymes in cholesterol metabolism (385, 386). The first step in the synthesis of sex steroids is the conversion of cholesterol to pregnenolone via the cholesterol side-chain cleavage enzyme. After a cascade of downstream metabolic conversions, two active sex steroids are created: testosterone and estradiol. Several other estrogenic and androgenic precursors are assembled along the pathway, some of which are metabolized into active precursors by cytochrome enzymes (162). Each of these sex steroid hormones acts mainly through specific receptors to mediate sex steroid-dependent actions (233, 387–389). Importantly, all the sex steroid receptors have been detected in lung tissue.

Due to their diverse nature, the role of sex hormone signaling in lung function and disease states is still inconclusive. Multiple studies have reported proinflammatory and anti-inflammatory effects in different cell types and life stages (150, 158, 390–393). While androgens have been shown to have primarily inhibitory effects, estrogens have been linked to the protective impacts on fetal lung maturation. This suggests a definite physiological role for sex steroids in the lungs before birth. Additionally, fetal lungs undergo specific changes during the third trimester to prepare for life outside the womb, some of which can be attributed to the

effects of sex steroids (6). These changes can also impact lung health in adults (394).

As mentioned in the sections above, studies have found that respiratory allergic diseases are more prevalent in males during childhood (150, 159, 395, 396). Evidence suggests that androgens like dehydroepiandrosterone (DHEA) and its sulfate metabolite, DHEA-S, decrease with age and are associated with airway diseases (23, 397–399). However, the impact of sex steroids on the prepubertal age group is unclear and requires further study. Further research is also needed to explain the observed sex differences in the prevalence and severity of lung diseases during adolescence (400, 401). Additionally, understanding the differences in disease mechanisms as individuals mature into puberty is essential.

5. ENDOGENOUS AND EXOGENOUS SEX HORMONES AND LUNG DISEASE

As discussed in prior sections, sex hormones, particularly estrogens and androgens, have significant and complex effects on lung physiology and various lung diseases. Both endogenous fluctuations in circulating hormone levels due to physiological events (e.g., puberty, reproductive cycles, menopause, pregnancy) or changes due to exogenous hormone administration (e.g., oral contraceptive use, hormone replacement therapy, hormonal treatment of gender dysphoria) can impact lung disease presentation and symptoms. Many studies in this field suggest that asthma severity varies during the reproductive state, menstrual cycle, and pregnancy in females (40, 402, 403). Similarly, studies in patients with cystic fibrosis (CF) suggest that symptoms vary during the menstrual cycle and are affected by sex hormone levels (191, 404–406). We expand on these topics in the sections below.

5.1. Puberty and Lung Disease

During puberty, sex steroids cause significant changes that lead to sexual maturation. Apart from the differences in physical and sexual characteristics between males and females, there is an intriguing role of sex steroids in lung health and disease. There is a higher number of lung-related hospital admissions for boys than for girls, but after puberty, a gender switch occurs. For example, in asthma cases following childhood, severity decreases postpuberty and into early adulthood only among males, while asthma incidence increases in females during late adolescence (5, 335, 403). Studies have indicated that the trend is more common in children with mild to moderate asthma, who tend to

“outgrow” their asthma during puberty and into adulthood. Moreover, early-onset menarche in some females suggests a likely differential role of sex steroids among individuals, as females with early-onset menarche have cumulatively higher levels of estrogen and progesterone (16, 336, 407).

Severe asthma is equally likely to improve with puberty in both boys and girls when androgen levels, dehydroepiandrosterone sulfate (DHEA-S), increase in both sexes (23). This suggests that the beneficial role of increasing androgen levels during adolescence exceeds the adverse respiratory effects of female hormones (159, 408). Recent research has explored the potential of DHEA as a therapeutic agent in specific patient populations. A pilot study showed that women with asthma and low DHEA-S (<200 µg/dL) experienced improved lung function with oral DHEA-S supplementation (409). Similarly, inhaled (nebulized) DHEA-S has also shown benefit in moderate-to-severe asthma, improving asthma control questionnaire scores in a randomized, placebo-controlled trial over six weeks, with a favorable safety profile and no significant hormonal side effects (410).

5.2. Menopause and Lung Disease

Sex differences also manifest in the aging lung. Physiologically, aging results in a reduction of elastic recoil of the lungs and increased alveolar air volume (411, 412). Circulating concentrations of sex steroids also decrease steeply. The abundance of connective tissue also increases, leading to impaired respiratory function, which is more pronounced in males (413). Aging also influences chronic lung diseases such as acute lung injury, acute respiratory distress syndrome (ARDS), IPF, and COPD, which become more prevalent as age advances (414, 415). Menopause is associated with lower levels of estrogen and progesterone, which coincides with new asthma onset (416, 417). The relationship between menopause and asthma is quite varied and may be influenced by other health conditions, such as obesity and the use of hormone replacement therapies. Furthermore, women going through perimenopause have been found to experience reduced lung function and increased asthma symptoms (416). These findings highlight the importance of further research into how ovarian hormones affect asthma in women at different stages of reproductive life.

5.3. Exogenous Hormones and Lung Disease

Exogenous administration of sex hormones through oral contraceptive use, hormone replacement therapy, or treatment of gender dysphoria can also affect lung health. Data from observational studies and clinical trials

revealed the effects of exogenous hormones in a variety of lung diseases, including asthma, CF, PH, and lung cancer (418–422). Regarding asthma, there have been only a few studies that have looked at how the use of hormonal contraceptives affects risk. Some studies have found no link between using any hormonal contraceptive, including combined oral contraceptives, and asthma or asthma symptoms. Other studies have shown a decreased risk, while some have observed an increased risk of asthma, wheezing, and other allergies (423–425). However, it is not clear whether different types of hormonal contraceptive formulations may have different effects on asthma, as research on the topic is limited. Among postmenopausal women, both estrogen-only and estrogen/progesterone hormone replacement preparations have been linked to an increased risk of asthma, as well as having contrasting effects (407, 426, 427). In terms of PH and CF, oral contraceptive use appears to show beneficial effects, although studies are limited and conducted with low numbers of participants (428). While several contradictory studies have discussed the effects of oral contraceptive use on lung cancer, a recent analysis on cohorts of women who either never smoked or were smokers showed that oral contraceptive use was associated with an increased risk of developing lung cancer (429, 430). Regarding the care of transgender patients receiving hormone therapy and its impact on lung disease outcomes, research is even more limited, with a few reports of increased rates of asthma and CF symptoms (22, 431).

6. CURRENT CHALLENGES AND GAPS IN KNOWLEDGE

Almost a decade after the establishment of the 2016 NIH policy encouraging researchers to consider sex as a biological variable when designing studies and assessing results, several key research gaps persist in our understanding of the role of sex and sex hormones in lung disease susceptibility and outcomes (432, 433). First, there is a need for more mechanistic studies addressing the biological underpinnings of a wide variety of lung diseases. Specifically, more studies are needed to elucidate the roles that sex hormones (e.g., estrogen, testosterone, progesterone) and sex chromosomes play in lung disease development and progression. Second, research gaps continue to exist in understanding how sex hormones influence lung health change across the lifespan, including during key transitions like puberty, pregnancy, and menopause. Third, more data are needed to understand how sex hormones affect responses to treatments for lung diseases. Studies examining potential sex differences in therapeutic efficacy and side effects are required in order to

personalize treatment for different patient populations. While sex differences in asthma pathophysiology and type 2 inflammation biomarkers exist, these have not translated into clinically significant differences in response to T2 biologics in the available studies (434, 435). However, most clinical trials have included more women than men, reflecting the higher prevalence of severe asthma in adult women, but few trials have analyzed efficacy outcomes separately by sex (436). Additionally, more studies are needed to understand how sex hormones interact with genetic, environmental, and lifestyle factors to influence lung disease risk and progression, as well as on the intersection of sex and gender in disease risk and presentation (437). This is particularly important as environmental challenges such as air pollution and comorbidities such as obesity and nutritional challenges are on the rise. Finally, there are multiple gaps in our ability to translate basic science findings on sex hormone effects into clinical applications for lung disease prevention, diagnosis, and treatment, particularly in transgender patients. Additional studies are needed to develop sex-specific or hormone-based strategies for personalized lung disease management (35). Addressing these crucial research gaps could significantly advance our management and prevention of sex-based differences in lung diseases and lead to improved, tailored, and equitable approaches for treatment.

7. CONCLUSIONS

Sex differences significantly affect lung health throughout life, beginning as early as lung development during gestation. Male and female sex hormones affect lung development and function at different stages. For instance, female sex hormones have been found to enhance alveologensis and promote lung maturation during late gestation and early neonatal periods, whereas androgens seem to have the opposite effect. However, after puberty, higher levels of androgens have been associated with improvement in conditions such as severe asthma. This demonstrates the complex and dynamic interplay of sex hormones on lung health, contributing to disease prevalence and severity variations between males and females. Despite extensive evidence from epidemiological and research studies supporting the role of sex hormones in multiple lung diseases, the potential of hormonal modifications in treating these conditions remains an area of limited exploration. This presents an exciting opportunity to advance personalized medicine beyond conventional therapeutic approaches.

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AUTHOR CONTRIBUTIONS

P.S. prepared figures; P.S., M.B., and C.D.E. drafted manuscript; P.S., M.B., and C.D.E. edited and revised manuscript; P.S., M.B., and C.D.E. approved final version of manuscript.

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