Sex Differences in Obstructive Lung Disease

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INTRODUCTION

Sex differences in lung diseases represent a critical yet historically overlooked dimension in pulmonary research and clinical care. From infancy to older adulthood, males and females experience distinct patterns of disease incidence, severity, progression, and therapeutic response. These disparities are shaped by both biological sex (driven by genetic, hormonal, and developmental factors) and gender-related influences, such as health behaviours, occupational exposures, and access to healthcare. Despite mounting evidence that sex significantly impacts nearly every facet of respiratory health,[1,2] most diagnostic criteria and treatment guidelines continue to follow a 'one-size-fits-all' approach. This perspective highlights recent advances in our understanding of sex-based mechanisms in respiratory conditions, identifies persistent knowledge gaps, and proposes strategies for incorporating sex and hormonal variables into research, treatment, and prevention efforts.

FROM DEVELOPMENTAL DIVERGENCE TO LIFELONG DISPARITY

The roots of sex differences in lung diseases can be traced back to the fetal stage of life.[3] Anatomical and functional disparities between male and female lungs are evident as early as the initial stages of organogenesis. Female fetuses generally produce pulmonary surfactant earlier than their male counterparts, a process promoted by the positive regulatory effects of oestrogens on alveolar Type II cells. Conversely, androgens inhibit surfactant synthesis, contributing to the delayed pulmonary maturation observed in male fetuses. Clinically, this translates into a markedly higher risk of respiratory distress syndrome among preterm male infants, who are nearly twice as likely to develop the condition compared to females of the same gestational age. Additionally, *in utero* exposures such as maternal asthma, smoking, air pollution, obesity, and hyperglycaemia can impair fetal lung development and increase the risk of respiratory disease in offspring.[4-6]

After birth, male infants remain at elevated risk for bronchopulmonary dysplasia, a chronic lung disease commonly linked to premature birth and mechanical ventilation. This susceptibility is partly due to sex-based differences in lung injury repair mechanisms and immune regulation. In contrast, girls tend to exhibit more efficient lung development during infancy and early childhood, with superior baseline airway function and greater resistance to environmental injury. However, this early female advantage fades at puberty, when rising levels of gonadal sex hormones lead to a shift in disease patterns. Notably, asthma becomes more prevalent and severe in adolescent and adult females than in males, with greater airway hyperresponsiveness and symptom burden.[7]

An additional structural factor likely contributing to these differences is dysanapsis, defined as the disproportionate relationship between airway calibre and lung parenchyma volume.[8] In general, boys tend to have larger lung volumes relative to airway size even in childhood, whereas girls generally exhibit proportionally larger airways for a given lung volume.[1] During adolescence, rapid lung growth in boys further accentuates this mismatch, while girls maintain a more balanced airway-lung relationship. This developmental divergence contributes to sex-specific patterns of airflow limitation and helps contextualise shifts in respiratory disease prevalence across the lifespan.[9]

With ageing, lung function declines in both sexes, but sex-specific trajectories become increasingly pronounced, particularly during midlife transitions. Menopause is a critical inflection point for many women, marked by accelerated declines in pulmonary function and increased risk of new-onset asthma and COPD progression.[10] These changes are modulated by hormonal shifts, notably declining oestrogen levels, as well as by exogenous influences such as air pollution and the use of hormone replacement therapy (HRT). The net impact of these factors varies depending on exposure history, comorbidities, and timing of hormonal interventions.

Overall, while sex hormones play an important role in shaping respiratory health throughout life, other modifying factors such as smoking, obesity, and environmental exposures also substantially influence susceptibility, severity, and treatment responses in lung disease.[11,12]

HORMONAL INFLUENCES ON LUNG DISEASE

As outlined above, sex hormones do not exert uniform or static effects on respiratory health. Rather, their roles shift across the life course, influenced by developmental stage, reproductive status, and environmental exposures. Oestrogen, progesterone, and androgens have been shown to modulate lung physiology through multiple mechanisms, including airway smooth muscle tone, mucociliary clearance, immune cell activity, and gene expression.

In reproductive-aged women, asthma symptoms frequently fluctuate with the menstrual cycle.[13] Up to 40% of women with asthma report symptom worsening in the days preceding menstruation, a condition termed premenstrual asthma. This exacerbation typically occurs during the luteal phase, when oestrogen and progesterone levels drop, potentially leading to heightened airway inflammation and reduced bronchodilation. Similar patterns have been observed in female athletes, where hormonal fluctuations are postulated to influence the severity of exercise-induced bronchoconstriction.[14]

The use of oral contraceptives (OC) can ameliorate or worsen these symptoms, as research studies have reported conflicting results.[15,16] For example, one study found that among women without asthma, OC use was associated with an increased odds of current wheeze, whereas in women with asthma history, OC use was inversely associated with wheeze.[15] More recent work reported a dual potential for oestrogen and progesterone to either exacerbate or ameliorate airway inflammation, depending on context and dose.[16] Among women with asthma, the use of OC has also been linked to the risk of severe exacerbations, although findings were not uniform across populations and can be modified by exogenous factors such as obesity.[17,18]

Pregnancy also introduces profound hormonal changes, with substantial elevations in oestrogen and progesterone that can affect immune function and lung disease presentation.[19] Interestingly, about one-third of patients who are pregnant report symptom improvement, one-third report worsening, and the remainder experience no change.[20] Oestrogen is known to enhance vascular permeability and promote airway relaxation, while progesterone increases respiratory drive. Despite these physiological benefits, uncontrolled asthma during pregnancy is associated with serious complications, including preeclampsia, low birth weight, and preterm birth, necessitating close monitoring and multidisciplinary care.

In the postmenopausal period, the decline in endogenous oestrogen is associated with a range of adverse respiratory outcomes. These include accelerated lung function decline, late-onset asthma, and greater susceptibility to COPD progression. However, some women with asthma experience a decline in symptoms and even remission after the menopausal transition.[21] While HRT has been explored as a potential modifier of these outcomes, studies report inconsistent findings, depending on dose, composition, and delivery method.[21] Given this uncertainty, the author refrains from making definitive clinical recommendations regarding the use of HRT solely for lung protection. Further research is needed to clarify the risks and benefits of HRT in the management of respiratory diseases.

Together, these hormonal dynamics across menarche, pregnancy, menopause, and ageing highlight the need for individualised treatment strategies that consider reproductive history, hormone levels, and timing of exposures.

GENOMICS AND SEX-SPECIFIC IMMUNE PATHWAYS

The immune system is deeply influenced by biological sex, contributing to well-documented differences in susceptibility, severity, and treatment response across respiratory diseases.[22] Females generally mount more robust humoral and cell-mediated immune responses than males, which can result in enhanced pathogen clearance but also a heightened risk of autoimmune and allergic conditions, including asthma. Oestrogen contributes to this immune amplification by modulating T cell differentiation, cytokine expression, and B cell survival. In contrast, testosterone tends to exert immunosuppressive effects, dampening inflammatory responses and providing a degree of protection against hyperactive immune-mediated disease.

Advances in transcriptomics have further elucidated the molecular basis of these sex-based immune differences.[23] Large-scale studies have identified thousands of genes with sex-biased expression across human tissues, including the lung. In asthma, sex-specific transcriptomic signatures reveal that males and females activate distinct inflammatory pathways in response to allergen exposure.[23] For instance, IL-17 signalling, a pathway associated with neutrophilic inflammation and particularly relevant in obesity-related asthma, is more prominent in females than males.[24] In contrast, hypoxia-inducible factor-1 and interferon pathways tend to be more active in males, consistent with studies highlighting sex-dependent regulation of these axes.[7,25] Beyond T helper 17 biology, females also mount more robust Th2 responses and harbour higher numbers of group 2 innate lymphoid cells, which are implicated in eosinophilic, non-allergic, late-onset asthma phenotypes.[25] Together, these observations underscore that asthma is not a uniform disease but rather a spectrum of phenotypes influenced by sex-specific immune pathways. Translationally, recognition of these pathways holds promise for precision medicine, as targeted biologic therapies may yield different efficacy depending on the patient's sex-specific immune profile.

Genome-wide association studies (GWAS) also support the role of sex in shaping genetic risk for asthma and other lung conditions.[23] Several asthma-associated loci demonstrate sex-specific effects, some of which vary by ancestry, further complicating the genetic landscape. These findings emphasise the importance of incorporating sex-stratified analyses into all-omics studies, not only to ensure biological relevance but also to uncover precision medicine insights that might otherwise be masked in aggregated data.

THE ENVIRONMENTAL INTERFACE: WHERE GENDER AND SEX INTERSECT

While biological sex shapes the intrinsic immune and physiological landscape of lung disease, gender plays an equally critical role by influencing exposures, behaviours, and healthcare access. Gender refers to the sociocultural norms, roles, and expectations associated with being male, female, or non-binary, and these constructs significantly impact health outcomes. The intersection of sex and gender is particularly salient in respiratory health, where environmental exposures and social determinants compound biological vulnerabilities.

In low- and middle-income countries, for example, women are disproportionately exposed to biomass smoke due to traditional cooking practices, resulting in elevated rates of COPD.[26] In more industrialised settings, occupational roles shaped by gender can lead to differential exposure to industrial dust, cleaning chemicals, or second-hand smoke.[27] Gendered patterns of tobacco use, stress exposure, and physical activity also contribute to disparities in lung health and disease progression.

Moreover, gender affects health-seeking behaviours and access to care. While men may be more likely to underreport symptoms or delay seeking medical attention, women may encounter diagnostic bias, particularly in diseases like COPD, where they are historically underdiagnosed or misdiagnosed. Additionally, women have higher rates of anxiety and depression, conditions that are known to worsen asthma control and COPD outcomes.[28] These psychosocial factors often intersect with biological susceptibility, creating a layered vulnerability that is uniquely gendered.

THERAPEUTIC IMPLICATIONS: THE NEXT FRONTIER IN PERSONALISED RESPIRATORY CARE

Sex differences in lung disease mechanisms strongly suggest that one-size-fits-all treatment paradigms may be suboptimal. In asthma, for example, adult women are more likely to present with corticosteroid-resistant, non-eosinophilic phenotypes.[29] Emerging data from clinical trials indicate that androgen supplementation may improve asthma control in women with low levels of dehydroepiandrosterone sulfate, pointing to a potential role for sex hormone modulation in refractory disease.[30] These examples underscore the need for sex-informed phenotyping when selecting or tailoring asthma therapies. Similarly, in COPD, sex-specific cytokine profiles and patterns of airway inflammation may underlie differential responses to bronchodilators, inhaled corticosteroids, and anti-inflammatory agents.[31,32] Yet, few studies stratify treatment responses by sex, limiting the generalisability of findings and potentially overlooking critical therapeutic insights. This highlights opportunities for sex-stratified treatment algorithms that optimise efficacy for both women and men.

Lung cancer also illustrates the clinical relevance of sex differences.[33] Women are more likely than men to harbour *EGFR* mutations, which respond well to targeted tyrosine kinase inhibitors. Additionally, sex-based differences in carcinogen metabolism, tumour microenvironment, and oestrogen receptor expression in lung tumours suggest a potential role for anti-oestrogen therapies in selected cases. Taken together, these findings show

how sex-informed therapy selection can enhance precision oncology approaches. However, most clinical trials fail to analyse or report outcomes by sex, representing a missed opportunity for precision medicine. Future treatment strategies must account for sex-specific pharmacokinetics, receptor expression profiles, and the influence of endogenous and exogenous hormones to optimise efficacy and safety.

CHALLENGES AND OPPORTUNITIES

Despite growing recognition of the importance of sex and gender in respiratory research, several challenges continue to hinder meaningful progress. Many studies are underpowered to detect sex differences due to limited sample sizes and the absence of sex-stratified analyses. Even when both sexes are included, researchers often fail to analyse or report sex-disaggregated results, reducing the interpretability and clinical applicability of findings. Moreover, hormonal data, such as menstrual phase, menopausal status, or the use of hormonal therapies, are frequently excluded from study designs, despite their relevance to disease mechanisms and treatment responses.

There is also a notable lack of mechanistic research using models that reflect hormonal variability across the lifespan, particularly in ageing populations. The continued reliance on male-dominated datasets, especially in preclinical research, perpetuates a biased view of disease processes and limits the discovery of sex-specific targets. These gaps are compounded by limited funding dedicated to sex- and gender-informed research and a lack of formal training in how to incorporate these variables into study design, analysis, and interpretation.

Nonetheless, the field is advancing. Federal funding policies, along with updated journal editorial standards, are promoting more equitable research practices.

Moving forward, sustained progress will require dedicated funding mechanisms to support sex- and gender-aware studies, expanded education and mentorship in sex-based research methodologies, and the routine inclusion of sex and hormonal variables across all stages of the research process. Interdisciplinary collaboration, bringing together experts in pulmonology, immunology, endocrinology, genomics, and social sciences, will be essential to build a more comprehensive and inclusive understanding of lung health.

CONCLUSION

Sex and gender influence nearly every aspect of lung health, from prenatal development to late adulthood. Yet, these factors remain underrepresented in both research and clinical practice.

Decades of male-dominated studies and sex-agnostic trial designs have led to treatment guidelines and disease models that fail to reflect the full spectrum of respiratory pathophysiology. Integrating sex and hormonal biology into the study of pulmonary conditions will not only improve diagnostic accuracy but also enhance the precision and equity of respiratory care.

As we enter an era of personalised medicine, it is essential to advance beyond sex-neutral paradigms. This requires the systematic inclusion of sex- and gender-based variables in study design, hormonal profiling in clinical cohorts, and intentional recruitment of underrepresented populations, including transgender individuals. By embracing sex-informed research and inclusive methodologies, we can build a more equitable framework for understanding, preventing, and treating lung disease.

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