Chapter

Asthma-COPD Overlap: Focus on Sex Differences

Yosima Gonzalez and Patricia Silveyra

Abstract

Asthma-COPD Overlap (ACO), also known as asthma-COPD overlap syndrome (ACOS), is a condition where patients exhibit features of both asthma and chronic obstructive pulmonary disease (COPD). Recently, it has been shown that biological sex plays a significant role in ACO. Women with ACO typically experience more severe symptoms, higher rates of exacerbations, and worse quality of life compared to men. Differences in airway anatomy may partly explain this disparity, as women tend to have proportionally smaller airways than men. Additionally, women are often more sensitive to environmental triggers and display stronger inflammatory responses. Hormonal factors such as estrogen levels can also influence airway inflammation and reactivity, contributing to ACO phenotypes. Despite women being more severely affected by ACO, they are often diagnosed later than men, which can lead to delayed treatment and poorer outcomes. In this chapter, we describe the ACO pathophysiology and risk factors, and we discuss the current state of the field in elucidating mechanisms underlying sex differences.

Keywords: asthma, COPD, sex differences, ACOS, lung inflammation, lung disease, women's health

1. Introduction

Asthma-COPD Overlap (ACO), formerly referred to as asthma-COPD overlap syndrome (ACOS), is a clinical phenotype characterized by features of both asthma and chronic obstructive pulmonary disease (COPD) [1]. The term was introduced to acknowledge a subset of patients who defy classical distinctions between these conditions, necessitating a unique clinical approach [2, 3]. Asthma is a chronic respiratory disease characterized by variable airflow obstruction, airway hyperresponsiveness, and inflammation, often with an eosinophilic or allergic background. COPD, in contrast, is defined by persistent, largely irreversible airflow limitation associated with a chronic inflammatory response to inhaled irritants, typically tobacco smoke, air pollution, or biomass fuel exposure. Thus, chronic airway inflammation is a significant factor in ACO and contributes to airway remodeling, airflow obstruction, and multiple disease symptoms, including wheezing and dyspnea, which tend to worsen during acute exacerbations [4].

The public health implications of ACO are substantial, representing a significant population health burden that affects millions of patients with disproportionate impact on socioeconomically disadvantaged populations [5]. The condition serves as a major driver of healthcare costs and resource utilization, highlighting the critical need for targeted screening programs, specialized treatment protocols, and interventions that address the socioeconomic barriers to care that characterize this population [6].

2. Clinical presentation, pathophysiology, and risk factors

Patients with ACO typically present with persistent airflow limitation that shows significant bronchodilator reversibility, along with a history of childhood asthma, allergies, or atopy [7]. These patients typically present at age 40 or older with persistent post-bronchodilator airflow limitation (FEV1/FVC <0.70), characteristic of COPD, combined with significant bronchodilator reversibility (improvement of>15% and > 400 mL in FEV1), typical of asthma [8]. Additional diagnostic criteria include a history of asthma before age 40 or elevated blood eosinophils, at least 10 pack-years of smoking [2, 9], and variable symptoms that often worsen at night or early morning [10].

Since asthma and COPD present with similar symptoms and ACO encompasses multiple phenotypic variations, establishing clear diagnostic criteria has remained challenging [11]. ACO does not result from a single, distinct etiology but rather reflects a convergent pathophysiological process in which risk factors for both asthma and COPD interact along a continuum of airflow obstruction [12]. Thus, the development of ACO typically involves the simultaneous presence of risk factors from both constituent diseases, with cigarette smoking and environmental exposures serving as primary drivers [13].

Tobacco use has emerged as the predominant risk factor for ACO, with epidemiological evidence demonstrating its profound impact on obstructive airway disease development [14]. A large retrospective cohort study revealed that continuous cigarette smoking increased COPD risk nearly five-fold compared to non-smokers (36% versus 8% incidence), establishing smoking as a critical pathway toward ACO development in susceptible individuals [15]. Moreover, among current cigarette smokers, adults with ACO have a notably higher rate of heat tobacco products (HTP) use, with an adjusted odds ratio (OR) of 5.81 compared to smokers without ACO [16]. HTPs are electronic devices designed to heat tobacco leaves, creating aerosols that contain nicotine, carcinogens, additives, and flavored compounds [17].

From a clinical management perspective, ACO presents unique challenges that traditional single-disease approaches often fail to address adequately [18–20]. The complexity of the condition requires the use of combination therapies that target symptoms of both asthma and COPD simultaneously [21], and early identification is crucial to prevent irreversible lung damage [11, 22]. The pathophysiology of ACO involves a complex, dual inflammatory process that combines Type 2 (eosinophilic) inflammation, typical of asthma, with Type 1 (neutrophilic) inflammation characteristic of COPD [13, 23, 24]. This results in a mixed inflammatory profile that contributes to more severe disease than either asthma or COPD alone [25]. Thus, patients with ACO experience more severe symptoms, faster lung function decline, and higher exacerbation rates compared to those with asthma or COPD individually

and thus display increased healthcare utilization [26–28]. Effective treatment often requires personalized, combination approaches targeting both asthma and COPD pathways [29, 30].

Another key feature bridging asthma and COPD is airway hyperresponsiveness (AHR) to allergens and environmental triggers. Longitudinal data from 9651 subjects followed for 11 years revealed that heightened AHR independently predicts COPD onset, underscoring this shared pathophysiological pathway in ACO [15]. Furthermore, atopy and early allergic sensitization play essential roles in connecting asthma to subsequent COPD development. An observational study of 1025 men with a mean age of 61 demonstrated that atopic individuals were at significantly higher risk for COPD, suggesting that early allergic inflammation predisposes patients to the mixed inflammatory patterns seen in ACO [4]. Collectively, these findings illustrate how the convergence of smoking-related airway injury, allergic sensitization, and AHR creates a complex pathophysiological environment that leads to ACO development.

3. Epidemiology

The absence of standardized diagnostic criteria for ACO represents a challenge to determining its actual epidemiological burden [31]. Current prevalence estimates suggest that ACO affects approximately 2–3% of the general adult population [5, 8, 32]. When examining ACO within the context of its component diseases, the condition demonstrates considerable prevalence variability, occurring in 2–12% of patients with COPD and 5–17% of those with asthma, depending on the diagnostic criteria and population studied [32, 33]. In some population-based cohorts, approximately 26% of asthma patients and up to 30% of COPD patients meet the criteria for ACO.

In general, ACO is more prevalent among older adults, especially those who have experienced childhood-onset asthma and a significant history of smoking [7]. More recently, multiple studies have reported a higher prevalence of ACO in women, who may also present with more pronounced symptoms and greater health-related quality-of-life impairments [34–37]. However, compared to asthma or COPD alone, ACO is associated with more frequent exacerbations, increased hospitalizations, more extended hospital stays, greater medication use, and higher healthcare resource utilization [11].

Geographic variations in prevalence have also been reported, with estimates ranging from 3.7% in the United States to 0.61% in China, likely reflecting differences in genetic susceptibility, environmental exposures, and diagnostic practices across populations [26, 38, 39]. ACO patients also demonstrate a distinct demographic profile with a mean age of 64.0 years, positioning them younger than typical COPD patients (67.1 years) but older than typical asthma patients (59 years). This age distribution suggests either the occurrence of early-onset COPD with asthmatic features, or progressive asthma that develops fixed obstruction over time [18, 21, 40]. A study in Japan indicated that the incidence could range from 4.2% to 49.7%, depending on the population and criteria used [41]. The same study reported that ACO patients are typically younger than non-ACO COPD patients, have a higher rate of physician-diagnosed asthma, and use more medications, especially inhaled corticosteroids [41].

ACO also presents a substantially greater clinical burden than other obstructive airway diseases [42]. Comorbidity rates are exceptionally high, with an overwhelming 90.2% of ACO patients reporting at least one additional condition. These rates are

significantly higher than those of COPD alone (84%) and far exceeding asthma or control populations [5]. Main comorbidities include cardiovascular disease, diabetes, hypertension, depression, anxiety, and metabolic disorders [43, 44]. The high comorbidity burden likely reflects the systemic inflammatory nature of the condition and shared risk factors between respiratory and other chronic diseases. These patients also report higher rates of disability (70.8% compared to 58.6% of those with COPD alone) and work absences, as well as reduced rates of physical activity and lower quality of life scores [5, 45, 46].

The frequent exacerbations and more severe symptom burden translate directly into increased healthcare costs and morbidity, making ACO a major driver of respiratory-related healthcare expenditure [47]. It is estimated that ACO patients experience hospitalization or emergency department visits at a rate nearly double that of those with COPD alone, despite their younger average age, underscoring the severity and complexity of this condition and the urgent need for early identification and targeted management strategies [48].

Finally, notable socioeconomic disparities also characterize the ACO population [6, 49]. These include elevated body mass index (BMI), reduced household income, and diminished educational achievement [50]. These disparities perpetuate a cycle of suboptimal care through diagnostic delays, inadequate specialist access, medication non-adherence, and persistent exposure to disease-exacerbating environmental factors.

4. Sex differences

It has long been recognized that sex-based differences significantly influence the clinical presentation, management, and outcomes of both asthma and COPD [51, 52]. Women with asthma face higher hospitalization and readmission rates than men, despite receiving comparable in-hospital care, and often demonstrating superior baseline lung function and primary care management [53]. For COPD, women tend to be younger at diagnosis, have smoked less, and exhibit better lung function than men, yet they experience more frequent exacerbations, greater dyspnea, and higher morbidity [51, 54, 55]. Imaging studies show that females with COPD have smaller airways and a lower burden of emphysema than males, which, combined with biological and hormonal differences, may contribute to their heightened susceptibility and symptom severity [56, 57]. These anatomical variations, combined with biological and hormonal factors, may explain the increased vulnerability and symptom severity observed in women vs. men with ACO.

Based on the available research, several essential sex differences in ACO exist that parallel and extend beyond the known sex differences in asthma and COPD individually [58, 59]. A study conducted in aboriginal populations showed that ACO represented 1.65 and 3.53% in males and females, respectively, showing that women are more than twice as likely to develop ACO compared to men in this group [60]. Several studies have also suggested that women are at increased risk of ACO compared with men, which aligns with the broader pattern seen in adult asthma, where asthma is more prevalent and more severe in women than men [34, 35, 52, 61, 62].

Tobacco use has also shown a differential impact on the development of lung diseases, including ACO, in men and women [63]. The combination of asthma and tobacco exposure leads to a more rapid decline in lung function, greater symptom

burden, increased exacerbations, and a higher prevalence of comorbidities compared to either disease alone [18, 64]. Epidemiological studies have also shown that women with asthma are at high risk of progressing to COPD or ACO as they age, with tobacco use significantly accelerating this transition [18, 35, 65]. A study of more than 10,000 adults in South Carolina found that the prevalence of ACO in women who smoked for >10 years was more than double that of men with a comparable smoking history [34]. In contrast, women and men had a similar prevalence of ACO if they were never smokers. Similarly, in a large cohort of women with asthma, those with a history of cigarette smoking were much more likely to develop ACO, and the risk increased with greater cumulative tobacco exposure and age. Specifically, smoking more than 20 pack-years and being over the age of 60 were the strongest predictors of ACO [64]. This risk is compounded by the observation that women are more susceptible to the harmful pulmonary effects of tobacco than men, likely due to biological differences in airway size, hormonal influences, and metabolic processing of tobacco toxins [66]. Beyond smoking, other individual factors such as lower education, obesity, unemployment, and rural residence have also been shown to contribute to the increased risk of both COPD and ACO in women [2, 67, 68].

Women with ACO not only face a higher risk of disease development but also experience a more rapid decline in lung function, increased symptom burden, and a greater frequency of exacerbations compared to men [15, 69]. They are also particularly vulnerable to environmental exposures such as air pollutants and allergens [70]. Chronic and acute exposures to particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), ozone (O_3), and other traffic-related pollutants have been linked to accelerated lung function decline, increased symptoms, and heightened exacerbation risk in ACO. Biomass fuel combustion (such as wood, charcoal, and dung) used for cooking or heating is also a significant risk factor for ACO in women in low- and middle-income countries [71]. Exposure to these indoor pollutants has been associated with increased rates of chronic bronchitis, asthma exacerbations, and fixed airflow obstruction [72]. Similarly, repeated exposure to indoor and outdoor allergens, such as dust mites, mold, and pollen, can also contribute to differential ACO development and progression in women and men [73]. Collectively, these exposures may act synergistically with sex-specific genetic and immunological predispositions to accelerate disease progression [13, 74].

The pronounced sex differences observed in ACO likely arise from hormonal mechanisms similar to those driving sex disparities in asthma and COPD individually [52, 75–77]. Female sex hormones, including estrogen and progesterone, exert a significant influence across the lifespan, contributing to poorer asthma control and greater AHR in adult women [77]. These hormonal influences on airway inflammation, bronchial reactivity, and immune modulation are expected to similarly impact the asthmatic component of ACO, potentially contributing to the higher symptom burden and exacerbation rates observed in women.

Research on sex differences in respiratory disease treatment has revealed important patterns that likely apply to ACO management [37, 78]. In asthma, the majority of available literature reports that men respond better than women to both asthma and COPD therapeutics. This suggests that women with ACO having features of both conditions may face particular challenges in achieving optimal treatment responses. This, combined with the sex disparities in ACO prevalence and outcomes, underscores the need for the development of personalized medicine approaches that consider both biological sex differences and gender-related factors in diagnosis, treatment, and management of this complex respiratory condition [37].

5. Disease mechanisms and sex-specific features

Asthma and COPD differ fundamentally in their inflammatory and structural pathologies. Asthma is primarily driven by T-helper 2 (Th2) immune responses, leading to eosinophilic inflammation, elevated levels of pro-inflammatory cytokines (such as interleukins (IL)-4, IL-5, and IL-13), and AHR [13, 52, 75]. In contrast, COPD is primarily characterized by Th1- and Th17-mediated inflammation, marked by neutrophilic infiltration, increased IL-8 and TNFα, oxidative stress, and a protease–antiprotease imbalance, which contributes to tissue destruction and airway remodeling [13, 54]. Consequently, patients with ACO frequently exhibit a mixed inflammatory profile, displaying both eosinophilic and neutrophilic inflammation in bronchoalveolar lavage fluid, sputum, and airway tissues [24, 25]. This hybrid inflammatory pattern likely underlies the severe symptoms and increased exacerbation rates observed in ACO compared with asthma or COPD alone [26, 69].

Biological sex has a significant influence on these inflammatory pathways in both asthma and COPD [54, 60, 79, 80]. Gonadal hormones such as estrogen and progesterone modulate immune responses in women, amplifying Th2 pathways and contributing to heightened eosinophilic inflammation observed in asthma and ACO [13, 52, 75]. Conversely, androgens tend to suppress Th2 inflammation, which may partly explain why prepubertal boys have higher asthma prevalence, while postpubertal women experience greater disease burden [61, 81]. These hormonal effects likely interact with genetic and environmental factors to influence the severity, progression, and unique mixed inflammatory profile of ACO, contributing to the increased symptom burden, more frequent exacerbations, and greater healthcare needs observed in women compared to men.

Preclinical and clinical studies conducted over the past decades have indicated that both genetic and epigenetic factors contribute to the pathogenesis of ACO and related sex differences. Shared susceptibility loci, such as polymorphisms in the ADAM33, ORMDL3, and IL17F genes, have been linked to both asthma and COPD, suggesting a genetic predisposition to overlapping phenotypes [74, 82, 83]. Recent transcriptomic and epigenomic analyses of airway samples have revealed distinct gene expression patterns in ACO patients that overlap with those of asthma and COPD, while also displaying unique molecular profiles [74, 82]. These findings highlight potential targets for precision therapies. For example, differential expression of genes regulating eosinophil function (e.g., IL5RA) and neutrophil chemotaxis (e.g., CXCL8) may influence individual responses to inhaled corticosteroids or biologics targeting Type 2 inflammation [24, 25].

Emerging research has also indicated that sex-specific molecular mechanisms contribute to differences in disease severity and treatment response in ACO. Transcriptomic studies have identified sex-biased gene expression in immune pathways, including those involved in interferon signaling and antigen presentation, suggesting that hormonal regulation of these pathways may exacerbate airway inflammation in women [74, 84]. Additionally, sex-specific epigenetic modifications, such as DNA methylation of genes involved in airway remodeling or oxidative stress responses, may further contribute to differential disease progression [74, 85]. Understanding these complex, intertwined mechanisms is essential for advancing personalized medicine for ACO that integrates sex-specific molecular insights into clinical practice.

6. Conclusion

ACO represents a clinically distinct and epidemiologically significant condition that bridges traditional asthma and COPD categories. The epidemiological evidence demonstrates that this dual diagnosis population, while younger than typical COPD patients, carries a disproportionate burden of comorbidities, disability, and healthcare utilization. Clinical recognition and proper management of ACO are essential given the associated healthcare costs, morbidity, and the vulnerable socioeconomic profile of affected patients. The concept remains clinically useful despite evolving terminology, emphasizing the need for individualized care approaches that address both asthmatic and COPD features simultaneously. The substantial population burden and clinical complexity of ACO underscore the importance of continued research, targeted interventions, and specialized care protocols for this challenging patient population.

Conflict of interest

The authors declare that they have no conflicts of interest.

Author details

Yosima Gonzalez and Patricia Silveyra*
Indiana University School of Public Health-Bloomington, Bloomington, IN, USA

*Address all correspondence to: psilveyr@iu.edu

References

[1] Leung C, Sin DD. Asthma-COPD overlap: What are the important questions? Chest. 2022;**161**(2):330-344

[2] Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: What are its features and how important is it? Thorax. 2009;**64**(8):728-735

[3] Sin DD et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. The European Respiratory Journal. 2016;**48**(3):664-673

[4] Tu X et al. Asthma-COPD overlap: Current understanding and the utility of experimental models. European Respiratory Review. 2021;**30**(159):190185-190198

[5] Kumbhare S et al. Characteristics and prevalence of asthma/chronic obstructive pulmonary disease overlap in the United States. Annals of the American Thoracic Society. 2016;**13**(6):803-810

[6] Venkata AN. Asthma-COPD overlap: Review of diagnosis and management. Current Opinion in Pulmonary Medicine. 2020;**26**(2):155-161

[7] Fouka E et al. Asthma-COPD overlap syndrome: Recent insights and unanswered questions. Journal of Personalized Medicine. 2022;**12**(5):708-722

[8] Leung JM, Sin DD. Asthma-COPD overlap syndrome: Pathogenesis, clinical features, and therapeutic targets. BMJ. 2017;**358**:j3772

[9] Alsayed AR, Abu-Samak MS, Alkhatib M. Asthma-COPD overlap in clinical practice (ACO_CP 2023): Toward precision medicine. Journal of Personalized Medicine. 2023;**13**(4):677-691

[10] Ding B, Enstone A. Asthma and chronic obstructive pulmonary disease overlap syndrome (ACOS): Structured literature review and physician insights. Expert Review of Respiratory Medicine. 2016;**10**(3):363-371

[11] Hines KL, Peebles RS Jr. Management of the Asthma-COPD overlap syndrome (ACOS): A review of the evidence. Current Allergy and Asthma Reports. 2017;**17**(3):15

[12] Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulmonary Medicine. 2011;**11**:36

[13] Hikichi M, Hashimoto S, Gon Y. Asthma and COPD overlap pathophysiology of ACO. Allergology International. 2018;**67**(2):179-186

[14] Løkke A et al. Developing COPD: A 25 year follow up study of the general population. Thorax. 2006;**61**(11):935-939

[15] de Marco R et al. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): Prevalence and risk factors in young, middle-aged and elderly people from the general population. PLoS One. 2013;**8**(5):e62985

[16] Noguchi S et al. Association of cigarette smoking with increased use of heated tobacco products in middle-aged and older adults with self-reported chronic obstructive pulmonary disease, asthma, and asthma-COPD overlap in Japan, 2022: The JASTIS study. BMC Pulmonary Medicine. 2023;**23**(1):365

[17] Nakama C, Tabuchi T. Use of heated tobacco products by people with chronic diseases: The 2019 JASTIS study. PLoS One. 2021;**16**(11):e0260154

[18] Freiler JF. The asthma-COPD overlap syndrome. Federal Practitioner. 2015;**32**(Suppl. 10):19s-23s

[19] Chang J, Mosenifar Z. Differentiating COPD from asthma in clinical practice. Journal of Intensive Care Medicine. 2007;**22**(5):300-309

[20] Cosentino J et al. Analysis of asthma-chronic obstructive pulmonary disease overlap syndrome defined on the basis of bronchodilator response and degree of emphysema. Annals of the American Thoracic Society. 2016;**13**(9):1483-1489

[21] Bakakos A et al. Asthma with fixed airflow obstruction: From fixed to personalized approach. Journal of Personalized Medicine. 2022;**12**(3):333-347

[22] Albertson TE et al. The pharmacological management of asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS). Expert Opinion on Pharmacotherapy. 2020;**21**(2):213-231

[23] Hardin M et al. The clinical features of the overlap between COPD and asthma. Respiratory Research. 2011;**12**(1):127

[24] Sunata K et al. Inflammatory profile of eosinophils in asthma-COPD overlap and eosinophilic COPD: A multi-omics study. Frontiers in Immunology. 2024;**15**:1445769

[25] Fangal VD et al. Distinct physiological, transcriptomic, and imaging characteristics of asthma-COPD overlap compared to asthma and COPD in smokers. eBioMedicine. 2024;**110**:105453

[26] Vaz Fragoso CA et al. Asthma-COPD overlap syndrome in the US: A prospective population-based analysis of patient-reported outcomes and health care utilization. International Journal of Chronic Obstructive Pulmonary Disease. 2017;**12**:517-527

[27] Chung JW et al. Characteristics and self-rated health of overlap syndrome. International Journal of Chronic Obstructive Pulmonary Disease. 2014;**9**:795-804

[28] Bonten TN et al. Defining asthma–COPD overlap syndrome: A population-based study. European Respiratory Journal. 2017;**49**(5):1602008

[29] Maselli DJ et al. Clinical approach to the therapy of asthma-COPD overlap. Chest. 2019;**155**(1):168-177

[30] Yanagisawa S, Ichinose M. Definition and diagnosis of asthma–COPD overlap (ACO). Allergology International. 2018;**67**(2):172-178

[31] Hosseini M et al. Global prevalence of asthma-COPD overlap (ACO) in the general population: A systematic review and meta-analysis. Respiratory Research. 2019;**20**(1):229

[32] Uchida A, Sakaue K, Inoue H. Epidemiology of asthma-chronic obstructive pulmonary disease overlap (ACO). Allergology International. 2018;**67**(2):165-171

[33] Alshabanat A et al. Asthma and COPD overlap syndrome (ACOS): A systematic review and meta analysis. PLoS One. 2015;**10**(9):e0136065

[34] Wheaton AG et al. Gender and asthma-chronic obstructive pulmonary disease overlap syndrome. The Journal of Asthma. 2016;**53**(7):720-731

[35] To, T et al. Asthma and chronic obstructive pulmonary disease overlap in women. Incidence and risk factors. Annals of the American Thoracic Society. 2018;**15**(11):1304-1310

[36] Sodhi A et al. Sex and gender in lung disease and sleep disorders: A state-of-the-art review. Chest. 2022;**162**(3):647-658

[37] Rogliani P et al. Sex differences in adult asthma and COPD therapy: A systematic review. Respiratory Research. 2022;**23**(1):222

[38] Ding B et al. Asthma-chronic obstructive pulmonary disease overlap syndrome in the urban Chinese population: Prevalence and disease burden using the 2010, 2012, and 2013 China National Health and wellness surveys. International Journal of Chronic Obstructive Pulmonary Disease. 2016;**11**:1139-1150

[39] Song JH et al. Differences in prevalence of asthma-COPD overlap according to different criteria. Medicine (Baltimore). 2018;**97**(36):e12049

[40] Cukic V et al. Asthma and chronic obstructive pulmonary disease (COPD) - Differences and similarities. Materia Socio Medica. 2012;**24**(2):100-105

[41] Hashimoto S et al. Asthma and chronic obstructive pulmonary disease overlap according to the Japanese respiratory society diagnostic criteria: The prospective, observational ACO Japan cohort study. Advances in Therapy. 2021;**38**(2):1168-1184

[42] Pleasants RA et al. Chronic obstructive pulmonary disease and asthma-patient characteristics and health impairment. COPD. 2014;**11**(3):256-266

[43] Akmatov MK et al. Comorbidity profile of patients with concurrent diagnoses of asthma and COPD in Germany. Scientific Reports. 2020;**10**(1):17945

[44] Nielsen M, Bårnes CB, Ulrik CS. Clinical characteristics of the asthma-COPD overlap syndrome--a systematic review. International Journal of Chronic Obstructive Pulmonary Disease. 2015;**10**:1443-1454

[45] Miravitlles M et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. Respiratory Medicine. 2013;**107**(7):1053-1060

[46] Dierick BJH et al. Work absence in patients with asthma and/or COPD: A population-based study. NPJ Primary Care Respiratory Medicine. 2021;**31**(1):9

[47] Blanchette CM et al. Economic burden in direct costs of concomitant chronic obstructive pulmonary disease and asthma in a Medicare advantage population. Journal of Managed Care Pharmacy. 2008;**14**(2):176-185

[48] Mekov E et al. Update on asthma-COPD overlap (ACO): A narrative review. International Journal of Chronic Obstructive Pulmonary Disease. 2021;**16**:1783-1799

[49] Kim MH et al. Heterogeneity of asthma and COPD overlap. International Journal of Chronic Obstructive Pulmonary Disease. 2018;**13**:1251-1260

[50] Zhu M, Chen A. Epidemiological characteristics of asthma-COPD overlap, its association with all-cause mortality, and the mediating role of depressive symptoms: Evidence from NHANES 2005-2018. BMC Public Health. 2024;**24**(1):1423

[51] Whittaker H et al. Sex differences in asthma and COPD hospital admission, readmission and mortality.

BMJ Open Respiratory Research. 2025;**12**(1):e002808-e002815

[52] Silveyra P, Fuentes N, Rodriguez Bauza DE. Sex and gender differences in lung disease. Advances in Experimental Medicine and Biology. 2021;**1304**:227-258

[53] Zein JG et al. Impact of age and sex on outcomes and hospital cost of acute asthma in the United States, 2011-2012. PLoS One. 2016;**11**(6):e0157301

[54] Czarnota P et al. Sex differences in chronic obstructive pulmonary disease: Implications for pathogenesis, diagnosis, and treatment. International Journal of Molecular Sciences. 2025;**26**(6):2747-2760

[55] Siegfried JM. Sex and gender differences in lung cancer and chronic obstructive lung disease. Endocrinology. 2022;**163**(2):1-8

[56] Milne KM et al. Sex-differences in COPD: From biological mechanisms to therapeutic considerations. Frontiers in Medicine (Lausanne). 2024;**11**:1289259

[57] Hong Y et al. Sex differences of COPD phenotypes in nonsmoking patients. International Journal of Chronic Obstructive Pulmonary Disease. 2016;**11**:1657-1662

[58] Diaz-Guzman E, Khosravi M, Mannino DM. Asthma, chronic obstructive pulmonary disease, and mortality in the U.S. population. COPD. 2011;**8**(6):400-407

[59] Baarnes CB et al. Incidence and long-term outcome of severe asthma-COPD overlap compared to asthma and COPD alone: A 35-year prospective study of 57,053 middle-aged adults. International Journal of Chronic Obstructive Pulmonary Disease. 2017;**12**:571-579

[60] Koleade A et al. Female-specific risk factors associated with risk of ACO (asthma COPD overlap) in aboriginal people. The Journal of Asthma. 2020;**57**(9):925-932

[61] Zein JG, Erzurum SC. Asthma is different in women. Current Allergy and Asthma Reports. 2015;**15**(6):28

[62] Naeem A, Silveyra P. Sex differences in Paediatric and adult asthma. European Medical Journal (EMJ). 2019;**4**(2):27-35

[63] Menson KE, Coleman SRM. Smoking and pulmonary health in women: A narrative review and behavioral health perspective. Preventive Medicine. 2024;**185**:108029

[64] Kiljander T et al. Prevalence of asthma–COPD overlap syndrome among primary care asthmatics with a smoking history: A cross-sectional study. NPJ Primary Care Respiratory Medicine. 2015;**25**(1):15047

[65] James AL et al. Decline in lung function in the Busselton health study: The effects of asthma and cigarette smoking. American Journal of Respiratory and Critical Care Medicine. 2005;**171**(2):109-114

[66] Gan WQ et al. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: A systematic review and meta-analysis. Respiratory Research. 2006;**7**(1):52

[67] Aryal S, Diaz-Guzman E, Mannino DM. Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. International Journal of Chronic Obstructive Pulmonary Disease. 2014;**9**:1145-1154

[68] Holtjer JCS et al. Identifying risk factors for COPD and

adult-onset asthma: An umbrella review. European Respiratory Review. 2023;**32**(168):230009-2300026

[69] Menezes AMB et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. Chest. 2014;**145**(2):297-304

[70] Han CH et al. Short-term effects of exposure to particulate matter on hospital admissions for asthma and chronic obstructive pulmonary disease. Medicine (Baltimore). 2022;**101**(35):e30165

[71] Morgan BW et al. Epidemiology and risk factors of asthma-chronic obstructive pulmonary disease overlap in low- and middle-income countries. The Journal of Allergy and Clinical Immunology. 2019;**143**(4):1598-1606

[72] Torres-Duque C et al. Biomass fuels and respiratory diseases: A review of the evidence. Proceedings of the American Thoracic Society. 2008;**5**(5):577-590

[73] Wang B et al. Analysis of allergen positivity rates in relation to gender, age, and cross-reactivity patterns. Scientific Reports. 2024;**14**(1):27840

[74] DeMeo DL. Sex and gender Omic biomarkers in men and women with COPD: Considerations for precision medicine. Chest. 2021;**160**(1):104-113

[75] Shah R, Newcomb DC. Sex bias in asthma prevalence and pathogenesis. Frontiers in Immunology. 2018;**9**:2997

[76] Fuseini H, Newcomb DC. Mechanisms driving gender differences in asthma. Current Allergy and Asthma Reports. 2017;**17**(3):19

[77] Tam A et al. The role of female hormones on lung function in chronic lung diseases. BMC Womens Health. 2011;**11**:24

[78] Jenkins CR et al. Personalized treatment of asthma: The importance of sex and gender differences. The Journal of Allergy and Clinical Immunology. In Practice. 2022;**10**(4):963-971.e3

[79] Sansores RH, Ramírez-Venegas A. COPD in women: Susceptibility or vulnerability? European Respiratory Journal. Jan 2016;**47**(1):19-22

[80] Aryal S, Diaz-Guzman E, Mannino DM. COPD and gender differences: An update. Translational Research. 2013;**162**(4):208-218

[81] Yung JA, Fuseini H, Newcomb DC. Hormones, sex, and asthma. Annals of Allergy, Asthma and Immunology. 2018;**120**(5):488-494

[82] Lopes-Ramos CM et al. Sex-biased regulation of extracellular matrix genes in COPD. American Journal of Respiratory Cell and Molecular Biology. 5 Aug 2024;**72**(1):72-81

[83] Mauvais-Jarvis F et al. Sex and gender: Modifiers of health, disease, and medicine. Lancet. 2020;**396**(10250):565-582

[84] Han MK et al. Female sex and gender in lung/sleep health and disease. Increased understanding of basic biological, pathophysiological, and behavioral mechanisms leading to better health for female patients with lung disease. American Journal of Respiratory and Critical Care Medicine. 2018;**198**(7):850-858

[85] Koo HK et al. Sex-specific associations with DNA methylation in lung tissue demonstrate smoking interactions. Epigenetics. 2021;**16**(6):692-703