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Personalized treatment of asthma: the importance of sex and gender differences

Christine R. Jenkins, MB.BS, MD, FRACP¹, Louis-Philippe Boulet, MD, FRCPC,², Kim L. Lavoie, PhD, FCPA, FABMR³, Chantal Raheison-Semjen, MD, PhD^{4,5}, Dave Singh, MD⁶

¹The George Institute for Global Health, Sydney, Australia; ² Quebec Heart and Lung Institute, Laval University, Québec City, Canada; ³Department of Psychology, University of Quebec at Montreal (UQAM) and Montreal Behavioural Medicine Centre, CIUSSS-NIM, Hopital du Sacre-Coeur de Montreal, Montreal, Canada; UK; ⁴Centre Hospitalier Universitaire (CHU) de Guadeloupe, Guadeloupe, France; ⁵INSERM U1219, EpiCene Team, University of Bordeaux, Bordeaux, France; ⁶University of Manchester, Manchester University NHS Foundation Trust, Manchester, UK.

Corresponding author:

Christine R. Jenkins

The George Institute for Global Health, Level 5, 1 King Street, Newtown, Sydney, NSW 2042, Australia

Email: christine.jenkins@sydney.edu.au

Telephone: +61 2 9767 6712

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Abbreviations: **BMI**, body mass index; **CI**, confidence interval; **ECHRS**, European Community Respiratory Health Survey; **ED**, emergency department; **FEV₁**, forced expiratory volume in one second; **GINA**, Global Initiative for Asthma; **HCP**, healthcare professionals; **HRT**, hormone replacement therapy; **ICS**, inhaled corticosteroids; **IgE**, immunoglobulin E; **IL**, interleukin; **ILC2**, group 2 innate lymphoid cells; **LABA**, long-acting bronchodilator; **OCS**, oral corticosteroids; **SABA**, short acting beta-2 agonist

ABSTRACT

An individual's sex (nominally 'male' or 'female', based on biological attributes) and gender (a complex term, referring to socially constructed roles, behaviors, and expressions of identity) influences the clinical course of asthma in several ways. The physiological development of the lungs and effects of sex hormones may explain why more boys have asthma than girls, and post-puberty, more women have asthma than men. Female sex hormones have an impact throughout the lifespan and are associated with poor asthma control. Gender may influence exposure to asthma triggers, and sex and gender can influence the prevalence of comorbidities and interactions with healthcare professionals (HCPs). Despite widely reported sex and gender-based differences in asthma and asthma management, these issues are frequently not considered by HCPs. There is also inconsistency around use of 'sex' and 'gender' in scientific discourse, and research is needed to better define sex and gender-based differences and how they might interact to influence asthma outcomes. This review outlines the impact an individual's sex and gender can have on the pathogenesis, clinical course, diagnosis, treatment, and management of asthma.

INTRODUCTION

Asthma affects ~300 million people globally,¹ with more than one in three patients with asthma being uncontrolled, despite the availability of effective treatments.² Physiological and behavioral differences between women and men can impact asthma severity, control, and management.³ In scientific discourse, there is frequent inconsistency around use of 'sex' and 'gender'. Sex is usually defined as 'male' or 'female', based on anatomical and physiological attributes that are genetically determined. The concept of gender is more complex and refers to socially constructed roles, behaviors, and expressions of identity in girls, women, boys, men, and gender diverse people.⁴⁻⁶ There is no universally recognized definition of gender. Due to a lack of knowledge/misunderstanding/unawareness, or because 'sex' and 'gender'-related effects can be difficult to differentiate, the terms are not always clearly defined and may erroneously be used interchangeably.^{5, 6} This often prevents accurate data interpretation and hinders research.⁵

It is important that healthcare professionals (HCP) are aware of the distinct impacts that sex and gender can have on asthma care.⁶ For example, patients of different sexes/genders may report their symptoms differently^{7, 8} and experience different exposures that affect their asthma;⁹ women's reproductive cycles can also affect asthma in unpredictable ways.¹⁰ If these aspects go unnoticed by HCPs they may contribute to clinical mismanagement and poor asthma control. The interest in precision medicine makes this a timely opportunity to raise awareness of sex and gender differences as a key first step in the provision of optimized, personalized asthma treatment.^{6, 11} This narrative review summarizes current evidence for sex and gender-related differences that influence asthma pathogenesis, clinical course, severity, symptoms, and management. As publications are limited on gender-diverse people with asthma and many studies have been carried out only defining males and females by sex, we have used the terminology of 'women' and 'men' throughout this review, unless the research referenced specifically relates to 'females' and 'males'. A structured

literature search was conducted to ensure comprehensive appraisal of this topic (see Supplementary Appendix for more information).

EFFECTS OF SEX AND GENDER ON ASTHMA DEVELOPMENT AND RISK

Sex hormones

Prior to puberty, asthma is more prevalent and severe in males than females, and this is reversed following puberty when asthma is more common in females.¹² This indicates that fluctuations in sex hormones play an important role in the pathogenesis of asthma. As summarized in **Figure 1**,¹²⁻¹⁵ estrogen and progesterone directly modulate immune pathways involved in asthma pathogenesis, while testosterone could be protective against inflammatory processes that cause asthma, although the mechanisms involved are not fully understood.

Some women with asthma experience worse symptoms in specific phases of the menstrual cycle, and during pregnancy.^{10, 15} Cyclical deterioration of asthma during the luteal phase, when estrogen and progesterone levels rise (premenstrual asthma) affects 11–45% of women.^{10, 15} These women tend to have more severe asthma, higher body mass index (BMI), longer duration of asthma, and a greater likelihood of aspirin sensitivity than women who do not report premenstrual asthma.¹⁰ It is interesting to note that hormonal contraceptives (mini pill, combined oral contraceptives, emergency pills, Mirena coil, injections or implants) may help reduce asthma exacerbations in these women^{16, 17} and reduce risk of new-onset asthma in women of reproductive age.¹⁷ Although the mechanism of action is unknown, it is possible that hormonal contraceptives suppress levels of estrogen and progesterone that fluctuate during the menstrual cycle.

In terms of the menopause, studies have demonstrated that it is associated with more severe asthma,¹⁸ and an increased risk of new-onset asthma.¹⁹ Hormone replacement therapy (HRT) has also been associated with an increased risk of developing asthma, although the risk may differ according to type of HRT: a case-control study based on Danish

registers (N=379,649) found that estrogen as monotherapy and in combination with progesterone increased the risk of new asthma, whereas monotherapy with progesterone decreased the risk.²⁰ Other studies have found a reduced risk of development of asthma in menopausal women on estrogen-only, and combined estrogen and progesterone HRT.²¹

It is possible that gender-affirming surgery may have an impact on asthma, but studies are limited. In a large cross-sectional study (N=50,009,780), transgender individuals (n=7,210) and those who had undergone gender-affirming surgery (n=490) had a higher prevalence of asthma compared to non-transgender individuals of the same birth sex.²² Asthma risk was highest in individuals who had undergone male-to-female gender-affirming surgery, but was also high in male-to-female transgender individuals.²² This study does not give a causative effect of gender-affirming surgery and further studies in these patients with asthma are needed.

Anatomical differences

Sex differences in lung architecture and respiratory function have been implicated in the sex-disparity in asthma.^{3, 23} An explanation for the greater predominance of boys with asthma in the pre-pubertal years could result from dysanaptic lung growth.²⁴ In girls, bronchial airways and lung parenchyma grow proportionally, but in boys, bronchial airway growth lags behind parenchymal growth, resulting in disproportionately fewer alveoli for the number of airways.²⁵ On maturation, males develop larger diameter airways, lung volumes, maximum expiratory flow and diffusion surface than females.²³ Some propose that size, rather than any other aspects of sex-related biology/physiology, is the reason for these differences.²³

Sex-specific phenotypes

Cluster analysis studies have identified neutrophilic asthma with obesity as a distinct phenotype in women.²⁶⁻²⁸ People with obesity are more likely to have asthma, and this risk is higher in women.²⁹ Obese-asthma is associated with higher morbidity and a poorer response to inhaled corticosteroids (ICS; likely due to neutrophilia) compared with non-obese

asthma.^{28, 30} As the origins of obesity are multifactorial, the mechanisms behind the interaction between obesity and asthma in women is still a subject of debate. However, sex hormones may mediate the neutrophilic obese-asthma phenotype in women: studies have shown that testosterone and oral contraceptive use are negative predictors of sputum neutrophils.^{31, 32} This protective effect of oral contraceptives gives credence to the possibility of synthetic or exogenous sex hormones for therapeutic applications for asthma.³³ Clinicians should be aware that neutrophilic asthma with obesity differs from conventional asthma, and therefore women with obese asthma should have their airway inflammation type determined before treatment. Corticosteroids may be inappropriate, as would biologics targeting Type 2 asthma.²⁸ Inappropriate treatment may further contribute to the vicious cycle of obesity and asthma symptoms.

Gender-specific lifestyle and behaviors

Different behaviors influenced by/associated with gender (eg, occupation, smoking habits, diet, lifestyle) can increase asthma risk, and affect asthma control and outcomes.

Triggers/exposures

Women and men tend to be exposed to different triggers due to gender roles and occupations.⁹ Traditionally “male” occupations (carpentry, metalworking, auto-spray painting, baking) can result in exposure to asthma triggers such as wood dust, cooling lubricants, or flour.⁹ Traditionally “female” occupations (cleaning, hairdressing, salons) may result in exposure to chemicals that are implicated in airway inflammation, allergic sensitization, and lung function decline.³⁴⁻³⁶ Women may also have more exposure to cleaning chemicals at home: a 2019 US survey reported women spend an average of 1.34–1.87 hours/day on housework versus 0.40–0.84 hours for men.³⁷

Smoking

Tobacco smoke can be a powerful trigger of asthma symptoms.³⁸ The prevalence of smoking varies by country, culture and socioeconomic status.^{39, 40} Interestingly, although

women have more severe asthma than men, proportionally more men than women smoke worldwide.^{39, 41, 42} For example, in China, 52% of men versus 3% of women smoke.^{42, 43} This indicates that smoking may not be a major factor explaining the gender-disparity in asthma; however, it is still important for HCPs to consider gender aspects of smoking, including passive smoking, vaping and marijuana use. Smoking is more common in women with asthma than without, including during pregnancy.^{44, 45} Tobacco smoke and vaping during pregnancy could increase risk of the child developing asthma^{46, 47} and developing more severe asthma into early adulthood,⁴⁸ and newborn admission to hospital.⁴⁹

Physical activity and diet

Adults with asthma tend to have lower levels of physical activity than those without asthma,⁵⁰ which is associated with poor asthma outcomes.⁵¹ Engaging in regular physical activity improves asthma control and quality of life,⁵² and is linked to a lower risk of early-onset asthma.⁵³ Women are less likely to partake in physical activity than men.⁵⁴ Physical inactivity and poor diet is linked to high BMI, and obesity is associated with increased asthma risk and severity.³⁰ Furthermore, the association between obesity and asthma is stronger in women than men.^{55, 56} Although risk factors for obesity are multifactorial, physical inactivity and poor diet remain the primary behavioral factors leading to obesity, and interventions that address these behaviors have been shown to improve asthma outcomes.⁵⁷

EFFECTS OF SEX AND GENDER ON ASTHMA SEVERITY AND SYMPTOMS

Asthma severity

While some studies suggest no significant difference in the distribution of asthma severity between women and men,⁵⁸⁻⁶¹ others report a higher proportion of women with severe asthma than men.^{62, 63} Women with asthma tend to have a greater morbidity and mortality than men with asthma.³ Women have an increased risk of hospitalization due to asthma compared to men,⁶³ and higher mortality rates.¹ Asthma is also often reported to have a greater impact on the health status and daily activities of women than men.^{7, 64}

The reproductive cycle may also affect asthma severity in women. Some women report symptom worsening prior to menstruation,^{65, 66} which may relate to sex hormone levels.⁶⁷ Pregnancy may also affect asthma control and severity in ways that are difficult to predict. In some women pregnancy has no impact on their asthma, and some may even experience asthma improvement; however, some women experience asthma worsening.^{10, 68} Exacerbations and poor asthma control are also common in pregnancy,^{10, 68, 69} and may be due to hormonal changes, or potentially to cessation/reduction of asthma medication due to unfounded safety concerns.¹⁰ Smoking during pregnancy may also contribute to poor control.⁴⁴

Impact of sex or gender-related comorbidities on symptoms

The presence of a chronic comorbidity with asthma is more common in women than in men.⁷⁰ Compared with men, women with asthma are more likely to have comorbid osteoporosis,⁷⁰ obesity,⁷¹ anxiety,⁷¹ and depression.⁷¹ Asthma is also linked to an increased risk of postpartum depression.⁷² There is so far no conclusive evidence that men with asthma are more likely to present with a particular comorbidity more often than women. In a large retrospective cohort study from the Netherlands of 32,787 patients with asthma, men were more likely to have coronary heart disease than women.⁷⁰ However, two meta analyses suggest a significantly increased risk of comorbid cardiovascular disease in women but not men with asthma.^{73, 74} There is also evidence that obesity may have a larger impact on asthma-related quality of life in men with asthma compared to women with asthma.⁷⁵

These comorbidities can be linked with sex-specific hormones. Osteoporosis is common in women after the menopause due to declining estrogen levels, and an increased risk of adverse events related to bone density is associated with long-term use of high-dose ICS or oral corticosteroids (OCS).⁷⁶ In women, obesity increases levels of circulating estrogen and leptin (a proinflammatory hormone), with negative effects on lung function, response to medication, and asthma control.^{77, 78} Anxiety and depression are more common in women than men in the general population, and estrogen and progesterone may play a

significant part in driving these conditions.⁷⁹ However, it should be noted that obesity, anxiety and depression may also be gender-related; women may experience different exposures to psychosocial stressors than men, and respond differently. The same could be said for individuals across gender and sexual minorities, who report significantly higher rates of depression and anxiety compared with cisgender/heterosexual individuals.⁸⁰ An indication of this may be seen in results showing that transgender status is associated with higher risk of lifetime asthma.²²

Compared with men, women with asthma are also more likely to have dyslipidaemia, type 2 diabetes mellitus, and hypertension, although the reasons for this are unknown.⁸¹

Patient symptom perception and reporting

Evidence suggests that women tend to perceive their asthma symptoms as more bothersome than men, even if the severity of their asthma and lung function (as measured by forced expiratory volume [FEV₁]) is similar.^{7, 8} At the same FEV₁, women experience more discomfort,^{82, 83} an increased cough reflex,⁷ and greater perception of dyspnea^{84, 85} than men. The reasons for these gender discrepancies are poorly understood. It is possible this is related to sex-based physiological differences; however, a study found that 'female gender' and poor quality of life, but not airway obstruction severity, were predictors of increased perception of dyspnea, indicating a role for non-physiological factors.⁸⁴

Obesity may increase asthma symptom perception, possibly due to the misattribution of obesity-related breathing difficulties to asthma.⁸⁶ As women with asthma are more likely to have obesity than men with asthma,⁵⁶ this may contribute to differences in symptom perception. Patients with comorbid anxiety, which is more prevalent among women^{70, 71} (which could be due to reporting bias rather than a lack of anxiety and depression among men⁸⁷), tend to be high symptom perceivers and reporters,⁸⁸⁻⁹¹ and may experience breathlessness/hyperventilation as a result of a panic disorder that is misattributed to

asthma.⁹¹ Another reason for gender-disparity in symptom reporting is that men may not feel as comfortable reporting symptoms due to gender role expectations.⁹²

Differences in perception of symptoms may be problematic when patient-reported severity of symptoms is used to make treatment decisions,^{60, 93} particularly when a questionnaire relies on subjective measures of severity.

EFFECTS OF SEX AND GENDER ON ASTHMA TREATMENT/MANAGEMENT

Gender bias in HCP behavior

Implicit gender bias among HCPs is widespread and may unknowingly sway diagnosis and management decisions.⁹⁴⁻⁹⁶ In patients with chronic pain, men can be viewed as 'brave' while women are viewed as 'complaining' and 'emotional'.⁹⁶ Additionally, women frequently report not being believed by HCPs when they report their symptoms.⁹⁶ This implicit bias may prevent women from receiving adequate asthma care. In a Canadian study of health service use among older adults with asthma (≥ 66 years old, mostly urban with a mixed socioeconomic status), women had a higher rate of physician office and asthma-specific emergency department (ED) visits; however, they were less likely than men to receive spirometry and specialist care (**Figure 2**).⁹⁷ The authors hypothesized this may be due to either provider or patient behavior. Similarly, studies have shown that women are more likely to engage with their HCP when needed, have an asthma management plan, and regularly use a peak flow meter.⁶¹ Despite this, women with asthma report a lower quality of life than men, even at the same FEV₁.^{7, 8} This seems counterintuitive, and the apparent sensitivity to symptoms could be perceived by HCPs as excessive; therefore, HCPs may regard the symptoms of women with asthma to be exaggerated.⁹⁸ In some studies, men are reported to have better asthma control and health-related quality of life than women,^{64, 99, 100} which could also account for differences in care-seeking behavior, as well as receiving better or more aggressive care.

Studies also highlight that the gender of the HCP may affect how seriously symptom reporting is taken and how the patient is diagnosed and managed.^{102, 103} Women are more likely to experience clinical inertia (ie, *“provider failure to initiate or intensify treatment despite a clear indication and recognition to do so”*),^{104, 105} and less likely to receive preventative interventions than men, particularly when treated by male doctors.^{106, 107} There is evidence that having a woman HCP may be beneficial for men or women, particularly for shared decision making, preventative interventions and lifestyle modification.¹⁰⁶

Gender-based preconceptions about workplace environments that do not reflect the data on trigger exposure may adversely influence patient management. For example, despite evidence that work-related asthma is as common in women as with men,^{9, 108} women are historically viewed as working in areas perceived as “safe” and associated with less occupational exposure to triggers than men.¹⁰¹ However, it should be noted that traditional roles are changing, and this will likely reflect occupational and domestic exposures and the risk of asthma in women and men.

Gender differences in asthma treatment

Gender differences in prescribed asthma treatments are documented in several studies; however, results are conflicting and there is an urgent need for more information on sex and gender-based differences in response to interventions. Most large, randomized pharmacotherapy trials adjust for sex and/or gender and do not report sex and gender-based results, despite these studies providing a unique opportunity to do so.

In a population-based study, men were more likely to be prescribed combination therapy (ICS/long-acting beta-agonist [LABA]) than women, and there was no difference in short-acting beta-2 agonist (SABA) use between the genders.¹⁰⁹ In a Canadian study in adults with asthma ≥ 66 years old, women were less likely to be prescribed controllers than men (**Figure 2**).⁹⁷ Contrarily, a real-world study in Italy reported no gender differences in the frequency of ICS or LABA given to patients with asthma, when corrected for age and BMI.⁵⁹

In terms of OCS-use, women are more frequently prescribed OCS for asthma than men.¹¹⁰ It is possible this results from the greater perception and reporting of asthma symptoms by women than men, as noted above. This is important as evidence links even short courses of OCS with serious adverse effects.¹¹¹ As yet, there are no studies on gender differences in prescribing biologics. The reasons for men being treated differently to women are not understood. However, it is possible that HCP gender bias may play a role:⁹⁶ men seem to be prescribed more aggressive treatments even when women report worse symptoms.¹⁰⁹ It is possible that fractional exhaled nitric oxide (FeNO) could be used in guiding treatment decisions versus symptom-based treatment; however, evidence for the benefits of this are inconclusive.^{112, 113} More research (using objective measures to eliminate HCP bias) is required to understand these gender discrepancies in asthma treatment so that interventions can be implemented.

Men are often believed to be less adherent to asthma treatment than women,¹¹⁴ but there is no clear consensus on a link between gender and adherence.¹¹⁵⁻¹¹⁷ However, there is evidence that men are more likely to overuse SABAs than women.^{118, 119}

Impact of sex or gender-related comorbidities on asthma management

The presence of comorbidities can lead to misattribution of asthma symptoms, over-/undertreatment of asthma and increased risk of poor asthma outcomes.^{120, 121} Asthma patients with comorbid depression are less adherent to asthma treatment than patients without depression.¹²² It is noteworthy that patients with asthma are more likely to have depression than the general population,¹²³ and women are more likely to have psychological comorbidities than men (although this could be a reporting phenomenon⁸⁷).^{70, 71} Importantly, asthma symptoms can mimic those of psychological illnesses (eg, anxiety and panic disorders, dysfunctional breathing).¹²⁴ And so women may be more likely to receive an asthma misdiagnosis, highlighting the need for an accurate patient history and spirometry testing.

As mentioned above, women are more likely than men to be prescribed OCS for their asthma. The prevalence and types of comorbidities associated with OCS use that present in women and men with asthma differ.⁷⁶ Increasing asthma severity usually leads to greater OCS use,^{76, 125} and data shows the risk of certain comorbidities also increases with asthma severity.^{76 72} In patients with asthma, an increased risk of adverse events related to bone density is associated with long-term use of high-dose ICS or OCS.⁷⁶ Although the increase in risk seems to be greater for men,⁷⁶ a generally increased risk and expectation of osteoporosis in women following menopause may mask any increase in osteoporosis due to treatment with OCS. Osteoporosis is typically seen as a disease affecting older women, and osteoporosis testing is usually offered to post-menopausal women as a matter of course.^{76,}
¹²⁶ Lack of routine bone mineral density testing in men could lead to underdiagnosis of osteoporosis in men with asthma, and underestimation of a possible link between corticosteroids and osteoporosis in these individuals.⁷⁶

Pregnancy may also have an impact on how women are treated for asthma. It is vital for mother and child that asthma control is optimized during pregnancy; however, this is complicated because pregnancy can affect asthma control and severity in ways that are difficult to predict. During pregnancy, women may reduce/stop taking asthma medication, or stop breastfeeding, due to concerns about possible effects of medications on their child.^{127,}
¹²⁸ In some cases, this may be on the advice of a doctor, as some HCPs have reservations regarding use of corticosteroids in pregnancy.¹²⁹⁻¹³¹ Although there is some evidence for harm to the fetus from high-dose ICS in the first trimester,¹³² the safety of ICS-use during pregnancy has been established in systematic reviews,^{133, 134} and ICS-use is recommended in the Global Initiative for Asthma strategy.¹⁰ There is also a low uptake of influenza and COVID-19 vaccination by pregnant women, with the major reason being safety.^{135, 136} As pregnant women are particularly susceptible to respiratory infections,¹³⁷ and these can exacerbate asthma symptoms,¹³⁸ it is important that vaccination is encouraged.

The risks of poor outcomes for the mother and child, including childhood asthma and wheezing illnesses in early childhood¹³⁹ resulting from reduced asthma control, are greater than the potential for adverse events associated with medication use.¹⁰ Poor asthma control during pregnancy is also associated with low birthweight,^{140, 141} which in turn is associated with an increased risk of childhood asthma.⁴⁶ Optimal assessment of asthma in pregnancy can reduce the likelihood of poor pregnancy outcomes.¹⁴² Use of FeNO to assess pregnant women appears to be a better determinant of treatment needs than clinical symptoms alone.¹⁴³

SUMMARY AND CONCLUSIONS

There are marked differences in the prevalence, severity, and presentation of asthma in women and men of different age groups. Evidence suggests these differences are attributable to a combination of physiology (sex) and cultural expectations/behaviors (gender) (**Figure 3**).

Clarity regarding the use and definition of 'male' and 'female' would help researchers determine whether sex or gender is the appropriate term, even when the definitions evolve in the future. We have identified several areas where there is no consensus on the potential influence of sex/gender (eg, medication adherence, asthma severity). Despite large, randomized trials having a unique opportunity to report sex and gender-based results, most do not build sex and/or gender into their study design. Studies that carefully build in methodology to test sex/gender differences would allow physicians to better account for this in their treatment choices. Gender differences may be influenced or confounded by socio-economic, cultural, and other factors; these should be documented and appropriately analyzed. There is also a distinct lack of studies involving patients with asthma who are transgender or have undergone gender-affirming surgery. Although affecting a small number of people worldwide, this is a growing population, and the link between estrogen (in feminizing hormone therapy) and worsening pulmonary outcomes exacerbates the need for further studies in these individuals.

The major reason for differences according to sex are changes in sex hormones, where asthma may be affected by life transitions such as puberty in women and men, and the monthly cycle, pregnancy, and menopause in women. Sex differences may also be attributable to genetic, cellular, or physiological aspects, although research into this is ongoing. Comorbidities that occur more often in women (eg, obesity, depression, anxiety) may affect quality of life and disease management in those with asthma. These comorbidities may be sex-specific (eg, driven by sex hormones), or gender-specific (driven by cultural behaviors/expectations). Disparities in asthma caused by gender include trigger

exposure, propensity to seek treatment, symptom perception, and symptom recognition and assessment by HCPs.

HCPs should be aware of clinically relevant risk factors in women and men, and of behaviors associated with gender, so that these can be factored into personalized asthma management. Furthermore, there is a need for greater consideration of sex and gender in the design and analysis of clinical trials and improving access to innovative treatments for all patients will help people with asthma receive optimal treatment according to their needs.

Lastly, future education directed to HCPs and patients should provide a better understanding of sex and gender-based differences in asthma outcomes, be based on evidence rather than preconceptions or biases (eg, HCP training to recognize their own implicit bias), and empower patients to be more involved in treatment and management decisions. Fostering a collaborative, patient-centric approach to decision making, tailored to the individual's sex and gender could help to improve adherence to treatment, clinical outcomes, and address some of the wider unmet needs in asthma.

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FIGURE 1: Some potential asthma-modifying effects of sex hormones¹²⁻¹⁴

IgE, immunoglobulin E; IL, interleukin; ILC2, group 2 innate lymphoid cells.

FIGURE 2: Forest plot for adjusted relative rates of asthma-specific health services use and prescriptions for women versus men (n=209,054).

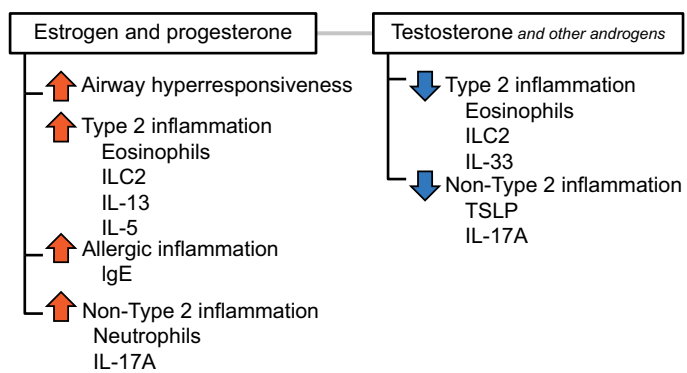
#The negative binomial regression model did not converge.

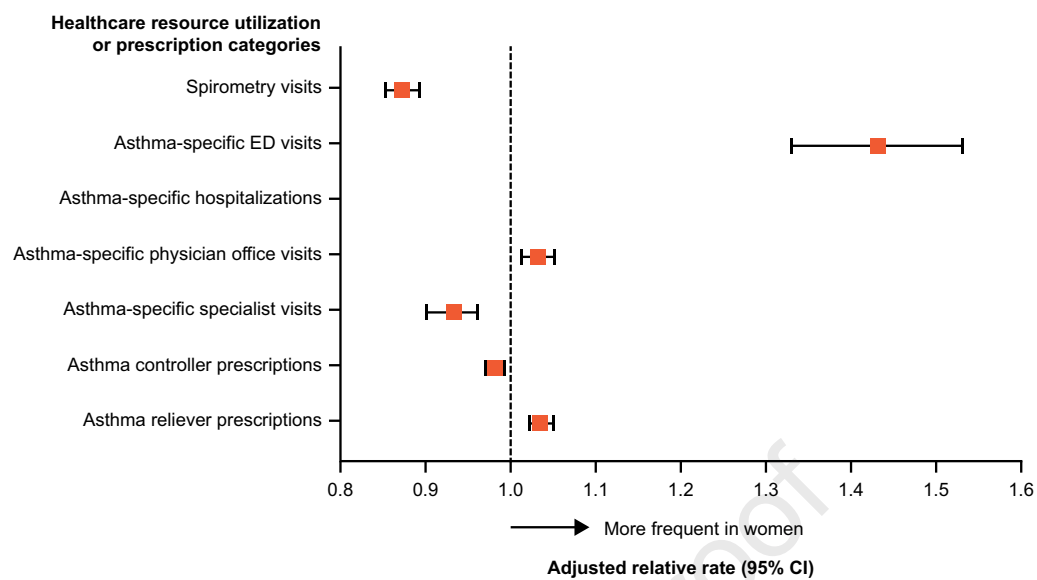
CI, confidence interval; ED, emergency department.

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FIGURE 3: Summary: How do sex and gender affect asthma pathogenesis, clinical course, severity, symptoms, treatment, and management? ^{3, 9, 12, 27, 68, 71, 77, 86, 91, 97, 104, 107, 125, 140, 141, 144}

HCP, healthcare professional





How do sex and gender affect asthma?



Asthma pathogenesis and clinical course

- Sex hormones (estrogen and progesterone) can contribute to asthma pathogenesis and worsen symptoms
- Asthma is more common in males before puberty; after puberty, it is more common in females and persists post menopause
- Obese neutrophilic asthma is a distinct phenotype in women
- Different gender roles and occupations can influence exposure to triggers and adverse health behaviors. E.g. traditionally "female" occupations (cleaning, hairdressing, salons) may result in exposure to chemicals implicated in lung function decline.



Asthma severity and symptoms

- Women experience more asthma-related morbidity and mortality than men
- Some women with asthma experience more severe symptoms around menstruation and pregnancy
- Comorbidities that disproportionately affect women (obesity, anxiety, depression) can impact asthma symptoms
- Women may perceive their asthma symptoms as more bothersome than men, even if the severity of their asthma and lung function is similar



Asthma treatment and management

- Implicit gender bias may cause HCPs to erroneously treat patients differently based on their gender. This may unknowingly sway their diagnosis and management decisions, leading to inadequate asthma care.
- Gender of the HCP may affect patient management: women HCPs may be more beneficial than men HCPs for men and women, particularly for shared decision making, preventative interventions and lifestyle modification
- Comorbidities that disproportionately affect women (obesity, anxiety, depression, dysfunctional breathing) can impact asthma diagnosis and management. Understanding differential diagnoses could be useful when treating patients with these comorbidities.
- Symptoms may worsen during pregnancy; uncontrolled asthma may negatively impact on the fetus

Supplementary Appendix

Search strategy and reference selection

References were identified through literature searches via PubMed and Google, using the terms listed in **Supplementary Table 1**. Results were subsequently filtered for papers published in the last 10 years and ranked by the additional terms listed in

Supplementary Table 2. Ranked results were screened for relevance to the topics under discussion and information gaps were supplemented by additional references selected by the authors. When conducting this search, we focused on women and girls with asthma; however, we now believe that the focus should be on all genders and so extended our scope to focus on the impact of men and women's sex and gender on the pathogenesis, clinical course, diagnosis, treatment, and management of asthma.

Supplementary Table 1. Search string used to identify literature via PubMed.

Search terms related to women	Search ("Women"[Majr] OR "Woman"[TI] OR "Women"[TI] OR "Girls"[TI] OR "Girl"[TI] OR "Women's"[TI] OR "Womens"[TI] OR "Woman's"[TI] OR "Womans"[TI] OR "Girl's"[TI] OR "Female"[Majr] OR "Female"[TI] OR "Females"[TI] OR "Sex"[Majr] OR "Gender Identity"[Majr] OR "Gender"[TI] OR "Gender Identity"[TI] OR "Gender Identities"[TI] OR "Sex"[TI] OR "Phenotypic Sex"[TI] OR "Genotypic Sex"[TI] OR "Sex Role"[TI] OR "Sex Roles"[TI] OR "Gender Role"[TI] OR "Gender Roles"[TI] OR "Woman's Role"[TI] OR "Woman's Roles"[TI] OR "Women's Role"[TI] OR "Women's Roles"[TI] OR "Sex Characteristics"[Majr] OR "Gender differences"[TI] OR "Gender difference"[TI] OR "Sex Characteristic"[TI] OR "Sex Differences"[TI] OR "Sex Difference"[TI] OR "Sex characteristics"[TI]) Filters: published in the last 10 years
AND	
Search terms related to asthma	Search ("Asthma"[Majr] OR "Asthma"[TI] OR "Asthmas"[TI]) Filters: published in the last 10 years

Supplementary Table 2. Additional search terms used to rank search results according to relevance to various topics/categories.

Topic/Category		Terms
Asthma type	Allergic asthma	Allergic asthma, Allergen asthma, Allergic, Allergen, Allergies
	Eosinophilic asthma	Eosinophilic asthma, Eosinophilic asthmas
	Th2 asthma	Th2, Th-2, TH 2, Th2 cytokines, Th-2 cytokines, TH 2 cytokines, Th2 asthma, Th-2 asthma, TH 2 asthma
Comorbidities		Comorbidity, Comorbidities, Rhinitis, Rhinitides, Nasal Catarrh, Nasal Catarrhs, Sinusitis, Sinusitides, Sinus Infections, Sinus Infection, Gastric Acid Reflux, Gastric Acid Reflux Disease, Gastro-Esophageal Reflux, Gastro Esophageal Reflux, Gastroesophageal Reflux, Gastro-oesophageal Reflux, Gastro oesophageal Reflux, Gastrooesophageal Reflux, GERD, Esophageal Reflux, Oesophageal Reflux, Obstructive Sleep Apnea, Obstructive Sleep Apneas, OSAHS, Sleep Apnea, Hypopnea, Sleep Apnea Hypopneas, Upper Airway Resistance Sleep Apnea Syndrome, Hormonal, Hormonal disorder, Hormonal disorders, Hormonal disease, Hormonal diseases, Osteoporosis, Osteoporoses, Bone loss, Bone losses, Osteopenia, Osteopenias, Diabetes, Diabetes Mellitus, Diabetes Insipidus, Diabetic, Type 2, Type II, Adult-Onset, Adult onset, maturity onset, maturity-onset, Noninsulin Dependent, Noninsulin-Dependent, Non insulin dependent, Non insulin-dependent, Non-insulin dependent, Non-insulin-dependent, Slow-Onset, Slow Onset, NIDDM, T2DM, T2D, T2
Prevalence / epidemiology	Prevalence	Prevalence, Prevalences, Prevalent
	Epidemiology	Epidemiology, Epidemiologies, Incidence
Risk / History / Susceptibility	Susceptibility	Diathesis, Diatheses, Susceptibilities, Susceptible
	Natural history	Natural history
	Risk Factors	Risk Factor, Risk Factors, Risk, Family history, Medical history, Family medical history, Respiratory infection, Viral respiratory infection, Viral infection, Occupational, Workplace, Dust, Dusts, Chemical fumes, Chemical, Chemicals, Chemical vapour, Chemical vapours, Chemical vapor, Chemical vapors, Mould, Molds, Smoking, Cigarette, Cigar, Tobacco, Smoker, Smokers, Air pollution, Pollution, Smog, Obesity, Obese, Overweight, Oestrogen, Estrogen, Exercise, Exercise-induced bronchoconstriction, Exercise induced bronchoconstriction, Exercise-induced bronchoconstrictions, Exercise induced bronchoconstrictions, EIB, Bronchoconstriction, Bronchoconstrictions, Bronchial Constriction, Bronchial Constrictions, Exercise, Exercise-induced, Exercise induced, Exercise-induced bronchospasm, Exercise induced bronchospasm, Exercise-induced bronchospasms, Exercise induced bronchospasms, Bronchospasm, Bronchospasms, Bronchial Spasm, Bronchial Spasms
QoL / Outcomes	Outcomes	Outcome, Outcomes, Outcome assessment, Outcome measure, Outcomes assessment, Outcomes measure, Outcome assessments, Outcome measures, Outcomes assessments, Outcomes measures
	Quality of life	Quality of life, Life Quality, Health-Related Quality Of Life, Health Related Quality Of Life, HRQOL, QOL, Q-O-L

Corticosteroids	Inhaled corticosteroids	Inhaled corticosteroid, Inhaled corticosteroids, Inhaled, ICS, Luticasone, Flonase, Flovent HFA, Budesonide, Pulmicort Flexhaler, Rhinocort, Flunisolide, Aerospan HFA, Ciclesonide, Alvesco, Omnaris, Zetonna, Beclomethasone, Qnasl, Qvar, Mometasone, Asmanex, fluticasone furoate, Arnuity Ellipta
	Oral corticosteroids	Oral corticosteroid, Oral corticosteroids, Oral, OCS, Cortisone Acetate
	Systemic corticosteroids	Systemic corticosteroids, Dexamethasone, Hydrocortisone, Cortef, Methylprednisolone, Medrol, Prednisolone, Prednisone, Orapred, Prelone, Pediapred
Phenotype		Phenotype, Phenotypes
Diagnosis		Diagnosis, Diagnoses, Diagnose, Diagnosed, Examination, Recognise, Recognize, Recognition, Spirometry, Peak flow, Pulmonary function test, Pulmonary function tests, Lung function test, Lung function tests
Management		Management, Managements, Control
Treatment		Treatment, Treatments, Therapy, Therapies, Long-term, Long term, Quick-relief, Quick relief, Rescue
Exacerbations		Exacerbation, Exacerbations, Exacerbate, Shortness of breath, Breathlessness, Breathless, Cough, Chest tightness, Tight chest, Disease progression, Asthma progression
Wheeze		Wheeze, Wheezing