Clinical Commentary Review

Personalized Treatment of Asthma: The Importance of Sex and Gender Differences

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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) influence the clinical course of asthma in several ways. The physiologic development of the lungs and effects of sex hormones may explain why more boys than girls have asthma, and after puberty, more women than men have asthma. Female sex hormones have an impact throughout the life span 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 health care professionals. Despite widely reported sex- and gender-based differences in asthma and asthma management, these issues frequently are not considered by health care professionals. There is also inconsistency regarding the use of "sex" and "gender" in scientific discourse; research is needed to define sex- and gender-based differences better 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. **(J Allergy Clin Immunol Pract 2022;■:■-■)**

Key words: *Asthma; Sex; Gender; Comorbidities; Gender differences; Sex differences*

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This study was funded by Novartis Pharma AG, Basel, Switzerland. Medical writing support for the development of the manuscript, under the direction of the authors, was provided by Ellen Maxwell, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by Novartis.

Conflicts of interest: C.R. Jenkins reports personal fees from AstraZeneca, Boehringer Ingelheim, and Sanofi-Genzyme; writing support and personal fees from Novartis; and grant and personal fees from GlaxoSmithKline, outside the submitted work. L.-P. Boulet reports research grants, consulting fees, and honoraria from AstraZeneca, GlaxoSmithKline, Merck, Novartis, and Sanofi-Regeneron; research grants from Amgen; and honoraria from Covis, outside the submitted work. K.L. Lavoie reports consulting fees and honoraria from AstraZeneca, Novartis, GlaxoSmithKline, AbbVie, and Boehringer Ingelheim; consulting fees from Bausch and Sojecci, Inc; and honoraria from Astellas, Janssen, xFacto, and Respiplus, outside the submitted work. C. Raherison-Semjen reports grants and personal fees from Novartis, Chiesi, and AstraZeneca; and personal fees from GlaxoSmithKline, outside the submitted work. D. Singh reports personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Epiendo, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Kinaset, Menarini, Novartis, Pulmatrix, Sanofi, Synairgen, Teva, Theravance, and Verona, outside the submitted work.

Received for publication November 15, 2021; revised January 18, 2022; accepted for publication February 3, 2022.

Available online ■■

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2213-2198

https://doi.org/10.1016/j.jaip.2022.02.002

INTRODUCTION

Asthma affects approximately 300 million people globally.[1] More than one in three patients with asthma are uncontrolled despite the availability of effective treatments.[2] Physiologic and behavioral differences between women and men can affect asthma severity, control, and management.[3] In scientific discourse, there is frequent inconsistency regarding the use of "sex" and "gender." "Sex" is usually defined as male or female, based on anatomic and physiologic 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. Because of a lack of knowledge, misunderstanding, and 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 for health care professionals (HCPs) to be aware of the distinct impacts that sex and gender can have on asthma care.[6] For example, patients of different sexes and genders may report symptoms differently[7,8] and experience different exposures that affect 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. Interest in precision medicine makes this a timely opportunity to raise awareness about sex and gender differences as a key first step in providing 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,

Abbreviations used
BMI- Body mass index
HCP- Health care professional
HRT- Hormone replacement therapy
ICS- Inhaled corticosteroids
OCS- Oral corticosteroids

symptoms, and management. Because publications on gender-diverse people with asthma are limited and many studies have been carried out defining males and females only 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 Appendix E1 in this article's Online Repository at www.jaci-inpractice.org).

EFFECTS OF SEX AND GENDER ON ASTHMA DEVELOPMENT AND RISK

Sex hormones

Before puberty, asthma is more prevalent and severe in males than females, and this is reversed after puberty when asthma is more common in females.[12] This indicates that fluctuations in sex hormones have 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, whereas 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% to 45% of women.[10,15] These women tend to have more severe asthma, a higher body mass index (BMI), longer duration of asthma, and a greater likelihood of aspirin sensitivity than do women who do not report premenstrual asthma.[10] Hormonal contraceptives (mini pill, combined oral contraceptives, emergency pills, hormonal intrauterine device, injections, or implants) may help reduce asthma exacerbations in these women[16,17] and reduce the risk for 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 for new-onset asthma.[19] Hormone replacement therapy (HRT) has also been associated with an increased risk for developing asthma, although the risk may differ according to the type of HRT. A case-control study based on Danish registers (N = 379,649) found that estrogen as monotherapy and combined with progesterone increased the risk for new asthma, whereas monotherapy with progesterone decreased the risk.[20] Other studies found a reduced risk for the development of asthma in menopausal women receiving only estrogen HRT 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 with 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 it was also high in male-to-female transgender individuals.[22] This study does not give a causative effect of gender-affirming surgery; further studies in these patients with asthma are needed.

Anatomic 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 prepubertal years could be 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] Upon maturation, males develop larger diameter airways, lung volumes, maximum expiratory flow, and diffusion surface than do females.[23] Some propose that size, rather than any other aspect of sex-related biology or 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 owing to neutrophilia) compared with nonobese asthma.[28,30] Because the origins of obesity are multifactorial, the mechanisms behind the interaction between obesity and asthma in women are 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 the 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 or associated with gender (eg, occupation, smoking habits, diet, lifestyle) can increase asthma risk and affect asthma control and outcomes.

Triggers and exposures. Women and men tend to be exposed to different triggers owing to gender roles and occupations.[9] Traditionally male occupations (carpentry, metalworking, auto-spray painting, and baking) can result in exposure to asthma triggers such as wood dust, cooling lubricants, or flour.[9] Traditionally female occupations (cleaning, hairdressing, and 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 that women

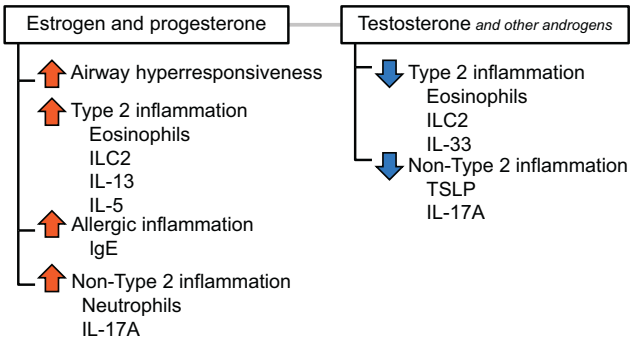

FIGURE 1. Some potential asthma-modifying effects of sex hormones.[12-14] *IgE,* immunoglobin E; *IL,* interleukin; *ILC2*, group 2 innate lymphoid cells; *TSLP,* thymic stromal lymphopoietin.

spend an average of 1.34 to 1.87 h/d on housework versus 0.40 to 0.84 h/d 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 do 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 in those without it, including during pregnancy.[44,45] Tobacco smoke and vaping during pregnancy could increase the risk for the child developing asthma[46,47] and developing more severe asthma into early adulthood,[48] and newborn admission to the hospital.[49]

Physical activity and diet. Adults with asthma tend to have lower levels of physical activity compared with 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 for early-onset asthma.[53] Women are less likely to partake in physical activity compared with men.[54] Physical inactivity and poor diet are 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 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

Whereas 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 compared with men.[62,63] Women with asthma tend to have a greater morbidity and mortality than do men with asthma.[3] Women have an increased risk for hospitalization caused by asthma compared with 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 compared with men.[7,64]

The reproductive cycle may also affect asthma severity in women. Some women report symptom worsening before 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 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 or reduction of asthma medication owing 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 for postpartum depression.[72] To date, there is no conclusive evidence that men with asthma are more likely to present with a particular comorbidity more often than are 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 were women.[70] However, two meta-analyses suggest a significantly increased risk for 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 with women with asthma.[75]

These comorbidities can be linked to sex-specific hormones. Osteoporosis is common in women after the menopause owing to declining estrogen levels, and an increased risk for 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 have a significant part in driving these conditions.[79] However, obesity, anxiety, and depression may also be related to gender; women may experience different exposures to psychosocial stressors compared with men, and respond differently. The same could be said for individuals across gender and marginalized sexual groups, who report significantly higher rates of depression and anxiety compared with cisgender or heterosexual individuals.[80] An indication of this may be seen in results showing that transgender status is associated with higher risk for lifetime asthma.[22]

Compared with men, women with asthma are also more likely to have dyslipidemia, 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 asthma symptoms as more bothersome than do men, even if the severity of asthma and lung function (as measured by FEV_1) is similar.[7,8]

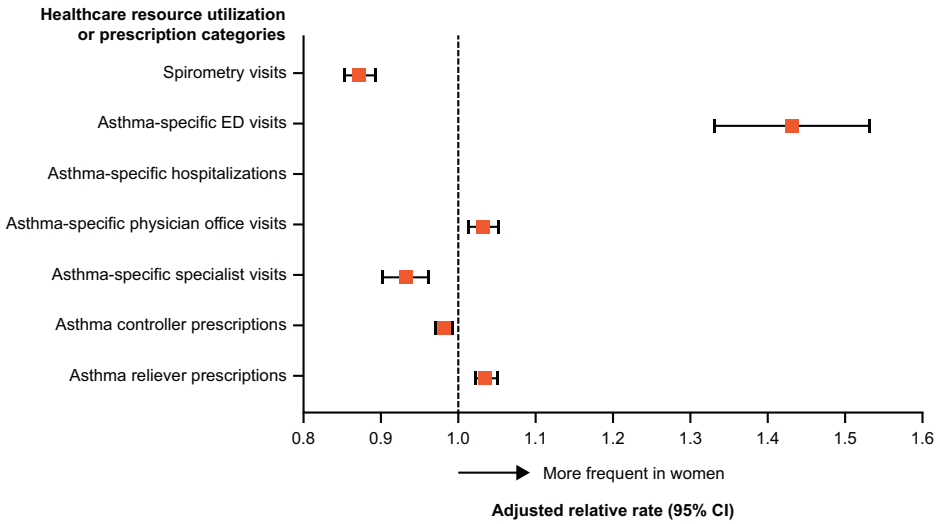

FIGURE 2. Forest plot for adjusted relative rates of asthma-specific health services use and prescriptions for women versus men (N = 209,054). *CI*, confidence interval; *ED*, emergency department. Reproduced with permission of ©ERS 2021. To T et al. ERJ Open Res 2019;5:00242-2019.[97]

At the same FEV_1, women experience more discomfort,[82,83] an increased cough reflex,[7] and greater perception of dyspnea[84,85] than do men. The reasons for these gender discrepancies are poorly understood. This may be related to sex-based physiologic 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 nonphysiologic factors.[84]

Obesity may increase asthma symptom perception, possibly because of the misattribution of obesity-related breathing difficulties to asthma.[86] Women with asthma are more likely to have obesity than are men with asthma,[56] which 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 men[87]), tend to be high symptom perceivers and reporters[88-91] and may experience breathlessness or hyperventilation as the 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 because of gender role expectations.[92]

Differences in the perception of symptoms may be problematic when the 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 AND 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 whereas women are viewed as complaining and emotional.[96] In addition, women frequently report not being believed by HCPs when they report 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 (aged 66 years and older, mostly urban with a mixed socioeconomic status), women had a higher rate of physician office and asthma-specific emergency department 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 showed 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 do men, even at the same FEV_1.[7,8] This seems counterintuitive, and the apparent sensitivity to symptoms could be perceived by HCPs as excessive; therefore, HCPs may regard 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 compared with women,[64,99-101] 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 received the diagnosis and is 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 compared with 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 data on trigger exposure may adversely influence patient management. For example, despite evidence that work-related asthma is as common in women as in men,[9,108] women are historically viewed as working in areas perceived as safe and are associated with less occupational exposure to triggers than are men.[101] However, traditional roles are changing, and this will likely reflect occupational and domestic exposures and the risk for 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, gender, or both and do not report sex- and gender-based results, even though these studies provide a unique opportunity to do so.

In a population-based study, men were more likely than women to be prescribed combination therapy (ICS/long-acting β-agonist), and there was no difference in short-acting β_2-agonist use between genders.[109] In a Canadian study in adults with asthma aged 66 years and older, women were less likely than men to be prescribed controllers (Figure 2).[97] Contrarily, a real-world study in Italy reported no gender differences in the frequency of ICS or long-acting β-agonist 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 compared with men.[110] It is possible that this is the result of the greater perception and reporting of asthma symptoms by women compared with men, as noted earlier. This is important, because evidence links even short courses of OCS with serious adverse effects.[111] To date, there are no studies on gender differences in prescribing biologics. The reason why men are treated differently from women is not understood. However, it is possible that HCP gender bias may have a role[96]: men seem to be prescribed more aggressive treatments even when women report worse symptoms.[109] It is possible that FeNO could be used to guide treatment decisions versus symptom-based treatment; however, evidence for the benefits of this is 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 compared with women,[114] but there is no clear consensus regarding a link between gender and adherence.[115-117] However, there is evidence that men are more likely than women to overuse short-acting β_2-agonists.[118,119]

Impact of sex- or gender-related comorbidities on asthma management

The presence of comorbidities can lead to misattribution of asthma symptoms, overtreatment or undertreatment of asthma, and increased risk for poor asthma outcomes.[120,121] Asthma patients with comorbid depression are less adherent to asthma treatment than are patients without depression.[122] Patients with asthma are more likely to have depression compared with the general population,[123] and women are more likely than men to have psychological comorbidities (although this could be a reporting phenomenon[87]).[70,71] Importantly, asthma symptoms can mimic those of psychological illnesses (eg, anxiety and panic disorders, dysfunctional breathing).[124] So, women may be more likely to receive an asthma misdiagnosis, which highlights the need for an accurate patient history and spirometry testing.

As mentioned earlier, women are more likely than men to be prescribed OCS for 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 show that the risk for certain comorbidities also increases with asthma severity.[72,76] In patients with asthma, an increased risk for 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 after menopause may mask an increase in osteoporosis owing to treatment with OCS. Osteoporosis is typically seen as a disease affecting older women, and osteoporosis testing is usually offered to postmenopausal 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 mothers and children for asthma control to be 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 asthma medication or stop taking it, or stop breastfeeding, because of concerns about the possible effects of medications on the child.[127,128] In some cases, this may be advised by a doctor, because some HCPs have reservations regarding the 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; the major reason is safety.[135,136] Because pregnant women are particularly susceptible to respiratory infections,[137] which can exacerbate asthma symptoms,[138] it is important for vaccination to be encouraged.

The risks for poor outcomes for mothers and children, including childhood asthma and wheezing illnesses in early childhood[139] 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 birth weight,[140,141] which in turn is associated with an increased risk for 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 are 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 that these differences are attributable to a combination of physiology (sex) and cultural expectations and 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 regarding the potential influence of sex and gender (eg, medication adherence, asthma severity). Although large randomized trials have 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 a methodology to test sex and gender differences would allow physicians to account for this better in their treatment choices. Gender differences may be influenced or confounded by socioeconomic, cultural, and other factors; these should be documented and

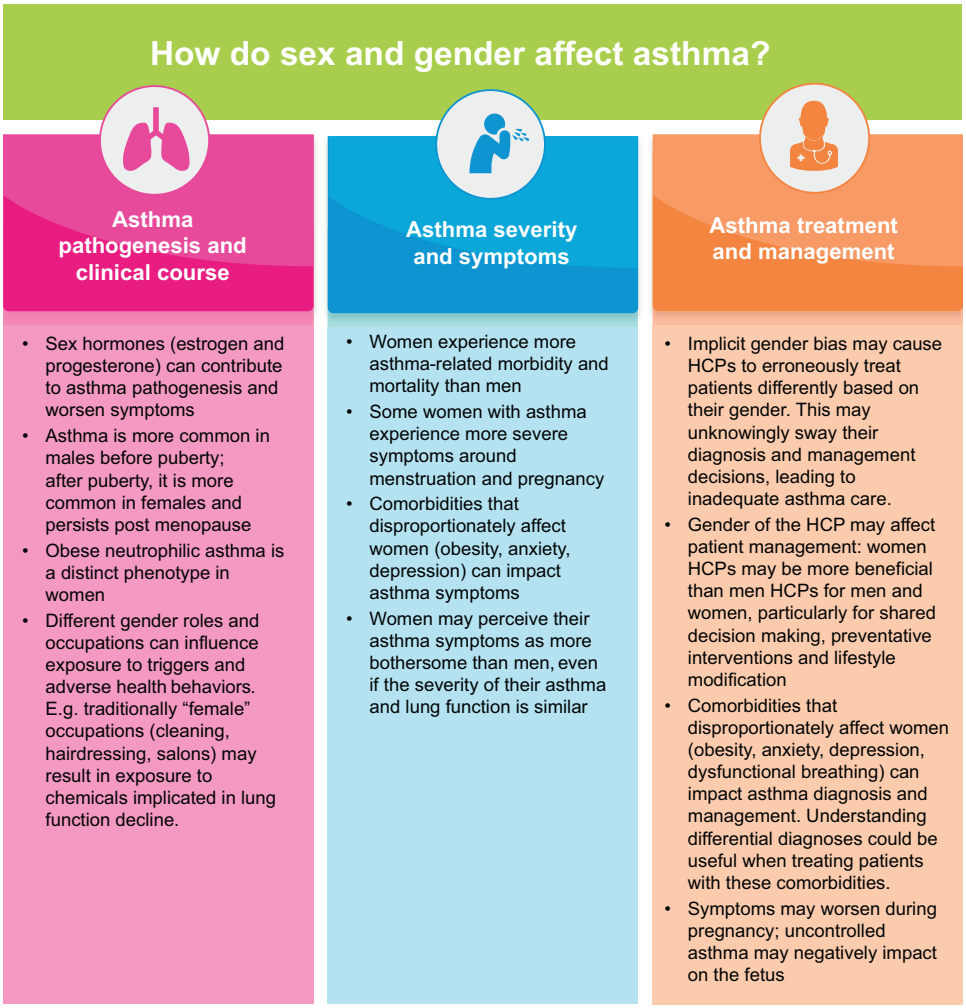

FIGURE 3. How do sex and gender affect asthma pathogenesis, clinical course, severity, symptoms, treatment, and management?[3,9,12,27,68,71,77,86,91,97,104,107,125,140,141,144] *HCP,* health care professional.

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, in which 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 physiologic 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 and expectations). Disparities in asthma caused by gender include trigger exposure, the propensity to seek treatment, symptom perception, and symptom recognition and assessment by HCPs.

Health care providers 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. Improving access to innovative treatments for all patients will help people with asthma receive optimal treatment according to their needs.

Finally, future education directed to HCPs and patients should provide a better understanding of sex- and gender-based differences in asthma outcomes, should be based on evidence rather than preconceptions or biases (eg, HCP training to recognize their own implicit bias), and should empower patients to become 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 and clinical outcomes, and address some of the wider unmet needs in asthma.

Acknowledgements

This publication was written in accordance with Good Publications Practice guidelines (http://www.ismpp.org/gpp3).

D. Singh is supported by the National Institute for Health Research Manchester Biomedical Research Centre, UK.

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ONLINE REPOSITORY

APPENDIX E1

Search strategy and reference selection

References were identified through literature searches via PubMed and Google, using the terms listed in Table E1. Results were subsequently filtered for papers published in the past 10 years and ranked by the additional terms listed in Table E2. Ranked results were screened for relevance to 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.

TABLE E1. 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 past 10 y
AND	
Search terms related to asthma	Search ("Asthma"[Majr] OR "Asthma"[TI] OR "Asthmas"[TI]) Filters: published in past 10 y

TABLE E2. Additional search terms used to rank search results according to relevance to various topics and categories

Topic or category	Term
Asthma type	
Allergic asthma	Allergic asthma, Allergen asthma, Allergic, Allergen, Allergies
Eosinophilic asthma	Eosinophilic asthma, Eosinophilic asthmas
T_H2 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-Esophageal Reflux, Gastro Esophageal Reflux, Gastroesophageal 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 and epidemiology	
Prevalence	Prevalence, Prevalences, Prevalent
Epidemiology	Epidemiology, Epidemiologies, Incidence
Risk, history, and 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
Quality of life and 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