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Sex and Gender in Asthma

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Abstract

Asthma is a heterogenous disease, and asthma prevalence and severity are different in males vs. females through various ages. As children, boys have an increased prevalence of asthma. As adults, women have an increased prevalence and severity of asthma. Sex hormones, genetic and epigenetic variations, social and environmental factors, and response to asthma therapeutics are important factors in the sex differences observed in asthma incidence, prevalence, and severity. For women, fluctuations in sex hormone levels during puberty, the menstrual cycle, and pregnancy are associated with asthma pathogenesis. Further, sex differences in gene expression and epigenetic modifications and responses to environmental factors, including SARS-CoV-2 infections, are associated with differences in asthma incidence, prevalence, and symptoms. We review the role of sex hormones, genetics, epigenetics, and their interactions with the environment in the clinical manifestations and therapeutic response of asthma.

SUMMARY OF REVIEW:

Dysanaptic lung growth through life, hormonal and genetic differences affect phenotypic manifestations of asthma and response to therapy between males and females. These sex and gender differences in asthma are discussed in this review.

Keywords

Asthma; Sex; Gender; Phenotype; Sex hormones; Environmental factors; Lifespan

Overview of sex and gender in asthma

Asthma prevalence ranges from as low as 1% in some countries to as high as 18% in others, with a total of more than 339 million asthmatics worldwide. There is a clear sex disparity in asthma. While there is a higher preponderance of asthma in boys under age 13 (65%

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prevalence), rates are higher (65% prevalence) in adult women compared to men (Figure 1) (1, 2). This shift in asthma prevalence in males and females over time suggests a role by sex hormones and a complex interplay of socioeconomic factors, differential access to resources (nutrition, air quality, etc.), comorbidities, and healthcare in developing vs. developed countries (Figure 2). Underpinning all these factors are genetic variations, including gene expression and epigenetic modifications, between male and female asthmatics (3–5). Throughout their lifetime, females have a higher likelihood of developing asthma and developing a more severe form of asthma than their male counterparts (6). In developed countries, higher healthcare utilization correlates directly with higher prevalence in the varying age categories (higher in boys 2–13 and women 23–64 years of age) (2).

Asthma is a heterogenous disease with different phenotypes and responses to current therapeutics. Multi-variate cluster analyses on adults with asthma or controls determined that different phenotypes of asthma require different utilization of primary or secondary healthcare. Sex differences are seen in these various clusters, with female predominance in less atopic, less corticosteroid responsive patients, and in obese patients with steroid refractory asthma (7, 8). Prior studies also showed, using cluster analysis based on utilization of primary and secondary healthcare for asthma, that a female predominance is seen in clusters that have increased asthma symptoms and utilization of care for eosinophilic driven asthma (9). Yet, these cluster analysis studies also showed that men have increased prevalence in severe asthma that is associated with nasal polyps or that are associated with environmental exposures including cigarette smoke or diesel exhaust (8). Combined, these clustering studies demonstrate the complexity of asthma and the many different phenotypes.

Immune mechanisms associated with different asthma phenotypes are shown in Figure 3. Type 2 (T2) asthma is often characterized by allergies and/or inflammation consisting of production of IL-4, IL-5, IL-13, and IL-9 from type 2 innate lymphoid cells (ILC2s), and/or CD4+ T helper type 2 cells (Th2). The increased production of type 2 cytokines leads to increased IgE, mast cell activation, mucus, and fractional exhaled nitric oxide (FeNO) production, eosinophil infiltration and activation, and airway hyperresponsiveness (AHR). Non-T2 inflammation is present in some endotypes of asthma with increased neutrophil infiltration, mucus production, and AHR that is mediated by increased IFN-γ or IL-17A production from T cells or IL-6, TNF, and IL-1β. Children with asthma primarily manifest the T2 eosinophilic or allergic asthma phenotypes, but children with asthma also have increased association with genes important in the IFN-γ signalling pathways (15). T2, non-T2, or mixed endotypes of asthma are seen amongst adults. As summarized in the chart at the bottom of Figure 3 and in prior publications, oestrogen signalling through oestrogen receptor (ER)-α increased AHR, IL-33 production, type 2 cytokine production, and eosinophil infiltration into the airway while oestrogen signalling through ER-β decreased AHR and eosinophil infiltration (16–18). Testosterone and other androgens signalling through the androgen receptor (AR) decreased ILC2 proliferation, eosinophil infiltration, IL-33 and TSLP production, and type 2 cytokine production (16, 17, 19–21).

Environmental factors and exposures interact with airway architecture, immunology, and hormones, and thus contribute to sex and gender differences worldwide. The economy, geography, pre-morbid vaccinations, maternal parity, breast feeding, environmental smoke

and pollution, urbanization, and other factors contribute to the balance between T2-mediated and non-T2 mediated inflammation and are understudied but likely differentially expressed in male and female asthmatics (22–29, 30). Further, fixed airway obstruction is also observed in more severe phenotypes of asthma in adults and is more prevalent in males compared to females (10–14, 31). Persistent, irreversible or fixed airflow obstruction (FAO) may ensue in ~50% of asthmatics (10, 11), proposed to be from impaired airway smooth muscle (12) and abnormal response to steroids and/or beta-2-agonist therapy. FAO may be associated with male gender in both younger and older asthmatics (10, 11, 13). The younger FAO asthmatic group represented more atopy and steroid resistance than their elder male counterparts. Two FAO endotypes (eosinophilic and neutrophilic) were identified, suggesting a complex relationship of FAO to asthma severity and medication response, beyond gender (14). This review specifically discusses the role of sex hormones and genetics, and their interaction with the environment in the clinical manifestation and therapeutic response in asthma.

Sex differences in childhood asthma

Childhood differences in asthma manifestation between boys and girls is traced back to foetal and post-natal lung development (22, 32, 33). Dysanaptic lung development, a mismatch between the size of the airway tree and lungs, in relation to airway flow rates was first described by Mead in 1980 and noticed most prominently in boys compared to girls (34). Dysanapsis was also described in adult women compared to men, and dysanapsis was found to be exacerbated by obesity in women and children (35). Obese women and children manifested lower flow rates for a given vital capacity, a correlate of lung size (34). Dysanaptic lung growth does not correlate with methacholine induced airway hyperresponsiveness but could correlate with allergen sensitization (36). In boys (n=149) and girls (n=66) less than 13 from South Korea, increased airway hyperresponsiveness was independently associated with mold sensitization or increased blood eosinophil counts in only the boys (37). In addition to boys having higher IgE levels than their counterparts (38), pre-puberty versus late-puberty boys demonstrate increased dehydroepiandrosterone sulfate (DHEA-S) with positive correlation with forced expiratory volume for 1 second (FEV_1%), that is different from the negative correlation observed in girls (39). These differences were apparent despite correction for body mass index (BMI) and steroid use. Differences in detected higher atopy, higher IgE levels and DHEA-S mediated improvement in FEV_1% are interlinked with the dysanaptic hypothesis proposed decades ago occurring in boys compared with girls and reverse during the late or post-pubertal years.

Sex hormones in asthma

Sex hormones are key mediators of the transition of differences in asthma prevalence across sexes from childhood into adulthood. As shown in Figure 1, these changes occur during adolescence and result in higher prevalence of asthma in adult women compared with adult men.

Menstruation and asthma

Oestrogen and progesterone fluctuate during the menstrual cycle, peaking in the late follicular and midluteal phases. Decreased FEV_1 and forced vital capacity (FVC), increased airway hyperresponsiveness, and increased asthma-related healthcare utilization have been noted during the luteal phase (40–42). Early studies showed that 20–40% of women with asthma had increased symptoms during the pre- and peri-menstrual period with associated decreases in peak expiratory flow rates (43–48). In the Severe Asthma Research Program (SARP) cohort, women with pre- and peri-menstrual asthma (PMA) had increased hospitalization, healthcare utilization, and use of oral corticosteroids compared to women who did not have PMA (41, 44). During the premenstrual phase, studies have shown that patients had increased sputum eosinophils and FeNO compared to after menses (49, 50) as well as higher aspirin sensitivity (51). Expanding upon this, Eid et al. recently showed that 24% of women with aspirin-exacerbated respiratory disease (AERD) had PMA (52). Patients with AERD-associated PMA had increased emergency department visits and hospitalisations but no differences in asthma medications, baseline percent predicted FEV_1, or Global Initiative for Asthma (GINA) scores (52). These studies suggest hormone-dependent cyclic variations in asthma control and healthcare utilization. However, other studies in women with or without self-reported PMA found no association with asthma and the menstrual cycle in terms of spirometry or airway reactivity (45, 47), emergency department visits or asthma-related events (53), timing of asthma exacerbations (53), or FeNO and ventilation parameters (54). While PMA clearly occurs in many women with asthma, additional research is needed to gain a better mechanistic understanding of this process and how it affects different women.

Pregnancy and Asthma

Changes in asthma control may occur during pregnancy in 5–8% of pregnant women in developed countries such as the United States but in up to 13% worldwide (55–57). Understanding these shifts in asthma control is essential for preventing adverse pregnancy outcomes, including preeclampsia, low birth weight, small sizes for gestational age, and increased risk of newborn mortality (58–60), particularly in developing nations. In the 1980s, Schatz et al. reported that one-third of women with asthma had worsened symptoms, one-third had no change, and one-third had improvement of their asthma symptoms based on daily diaries and monthly spirometry (61). In those who had worsened symptoms, patients returned to their pre-pregnancy lung function baseline by three months post-partum. However, these studies were conducted prior to defining various phenotypes and endotypes of asthma. Follow-up studies showed that women with more severe asthma were linked to worsening symptoms and increased exacerbations during pregnancy (62). Continuation of asthma medication use during pregnancy showed no significant changes in asthma symptom score by interview-based data (63), further supporting the National Heart, Lung, and Blood Institute and GINA guideline recommendations to maintain asthma medication use during pregnancy. The Vitamin D Antenatal Asthma Reduction Trial (VDAART) had suggested a role of decreased Vitamin D during early pregnancy as a contributor for poor asthma control based on lower Vitamin D levels in less well controlled asthmatics (64, 65), but do not demonstrate an underlying mechanism to this association. Although we now know that

prenatal Vitamin D supplementation alone does not affect childhood asthma incidence (66), further study regarding association of Vitamin D and asthma in pregnancy is needed.

Menopause and asthma

During menopause, there is a large fluctuation in sex hormones and an increased number of co-morbidities that have resulted in various findings from investigators on the effects of menopause on asthma prevalence and control. The Respiratory Health in Northern Europe (RHINE) study reported a new phenotype of asthma in a subset of women who have onset of disease after menopause (67, 68), and in the French E3N cohort, surgical menopause was associated with increased risk of asthma onset. The European Community Respiratory Healthy Survey I (ECRHS I) included 884 menopausal women (aged 46–54 years old, 540 using hormone replacement therapy [HRT]) and found no association in self-reported asthma and HRT use in pre-menopausal or post-menopausal women (69). Yet in the ECRHS II trial, women going through menopause (amenorrhoeic for at least 6 months) had decreased lung function and had increased asthma symptoms compared to pre-menopausal patients (70).

Additional studies using the US Nurse's Health Study (NHS) cohort showed decreased asthma incidence in pre-menopausal women compared to post-menopausal women (71). Consistent with the US NHS, severe asthma was more likely to occur in men than women in SARP study participants aged 45 or older, opposite of what is observed in their younger adult counterparts (72). In 2020, Scioscia et al. demonstrated in a cohort of 33 women diagnosed with post-menopausal asthma and 30 healthy menopausal controls that with increasing asthma severity, women had significantly increased circulating 17β-estradiol levels (73). The relationship of menopause remains unclear, given that some women develop menopause-associated onset of asthma, increased number of comorbidities, and the use of HRT during menopause.

The effect of HRT therapy during menopause on asthma risk and control has been studied in various cohorts. In the RHINE study, there was a significantly stronger association of asthma in lean (BMI<25) women taking HRT that was not seen in women on HRT with BMI >25 (69). Additionally, the US NHS showed increased risk of asthma incidence in ever use of HRT in a dose-dependent manner (71, 74). Studies using the Explorys clinical registry with 1,793,810 women aged 50 or above or a Danish nested case-control study (229, 871 cases and 2,250,610 controls) showed that HRT was associated with increased asthma incidence and asthma prevalence (75, 76). On the other hand, women from the Optimum Patient Care Database in the United Kingdom showed that any use of HRT was associated with reduced risk of asthma onset and longer duration of use was associated with a dose-response reduction of risk of asthma incidence (77). It is unclear why HRT has varied responses on asthma risk and control, but other factors are certainly at play and additional studies are needed.

Hormonal contraceptive use and asthma

Menstrual cycle fluctuations in asthma symptoms occur in many women with asthma, and mechanistic studies showed that oestrogen and progesterone increased pathways important

in asthma pathogenesis (17). Therefore, use of hormonal contraceptives are likely to impact asthma incidence, prevalence, and control. Data from 3257 premenopausal Scottish women showed that hormonal contraceptives reduced asthma incidence, decreased asthma-related healthcare utilization, driven by a significant decrease in lean women (78), as well as decreased wheezing in asthma patients (79). Recently, these results were verified in the Optimum Patient Care Research Database (a cohort of 564,896 premenopausal women), showing that risk of asthma incidence is reduced by hormonal contraceptive use and time of use (80, 81). Combined, these studies showed hormonal contraceptives decreases asthma incidence and asthma symptoms, but additional research is also needed to determine the type of hormonal contraceptive that is most effective at reducing asthma incidence and symptoms.

Androgens and asthma

Androgens, such as testosterone or dehydroepiandrosterone (DHEA), reduce asthma incidence and may reduce asthma symptoms. Increased levels of DHEA in boys were associated with decreased risk of asthma risk in adolescents in the SARP paediatric cohort (39). Additionally, decreasing testosterone levels in men older than 45 years was associated with increased asthma prevalence (82). Participants with asthma aged 6–80 years old from the National Health and Nutrition Examination Survey (n=7584), it was found that in both men and women greater than 12 years old, increased serum testosterone was associated with decreased asthma prevalence in a dose-dependent manner and was associated with increased FEV_1 (83). In another large cross-sectional study of 256,219 adults aged 40–69 years old in the United Kingdom, increased free testosterone levels were significantly associated with decreased symptoms of asthma, decreased hospitalizations due to asthma in women, and decreased FEV_1 and FVC in men (4).

The use of exogenous androgens reduced asthma burden. In a Phase II clinical trial, 70mg nebulized DHEA-S reduced Asthma Control Questionnaire (ACQ) scores of women with moderate-to-severe asthma compared to those who received placebo (84). Further, orally administered DHEA increased FEV_1 compared to placebo in premenopausal mild-moderate asthmatic women with low baseline DHEA-S levels (DHEAS <200 μg/dL). No significant changes in FEV_1 were observed between DHEA or placebo groups in women who had baseline DHEA-S ≥ 200 μg/dL (85).

Sex specific genetic and epigenetic differences in asthma

Genetic variability has long been recognized as important in asthma pathogenesis, and researchers have linked over 200 genetic variations to asthma risk and severity (3, 86). Sex specific single nucleotide polymorphisms (SNPs) in genes or epigenetic variabilities in paediatric and adult asthma cohorts are described below and are summarized in Table 1. SNPs in several genes important in initiating or sustaining T2 inflammation, including *ORMDL3*, *TSLP*, *IL4RA*, and *IL1RL1*, have been implicated in asthma (3). Polymorphisms in *TSLP* were linked to sex in the Costa Rican Childhood asthma management program, California children's health study, and Genomic research on asthma in the African diaspora cohorts (87). In these cohorts, *TSLP* SNP rs1837253 decreased asthma risk in males

and *TSLP* SNP rs2289276 decreased asthma risk in females (87). Sex-specific variations in interferon (IFN) signalling, which is important for type 1 inflammation, were also associated with asthma in both paediatric and adult asthma cohorts. Using the Childhood Origins of Asthma (COAST) birth cohort at high-risk for asthma and allergic disease, *IFNG* SNPs rs2069727 heterozygosity in boys resulted in higher risk for asthma where the same SNP in girls had the lower risk (15). Further, cord blood cells treated with lipopolysaccharide from the COAST cohort had increased IFN-γ production only in girls heterozygous for rs2069727. Genome-wide genotype-by-sex interactions in asthma using the EVE Asthma Genetics Consortium also showed sex-specific associations with asthma in six genes with the strongest associations for SNPs in *IRF1* in European Americans and *RAP1GAP2* in Latino females. Interactions between these two SNPs and asthma were independently verified in GWAS and gene regulation studies (88). Vitamin D signalling is also important for many immune processes, including airway inflammation associated with asthma. Vitamin D receptor polymorphisms were associated with females in both the Childhood Asthma Management Program paediatric cohort and in the NHS longitudinal cohort of women (89). These studies show that several sex-specific variations in immune pathways are important for asthma pathogenesis in children and adults.

Genetic variations in genes associated with pulmonary function are also sex specific. A variant in the β1 subunit of the BK channel (*KCNMB1* C818T), a Ca2+ and voltage-dependent potassium channel that is a negative regulator muscarinic receptor stimulated contraction, was associated with decreased percent predicted FEV1 in African American men from the Study of Asthma, Genes, and the Environment (SAGE) and the Chicago Initiative to Raise Asthma Health Equity (CHIRAH) asthma cohorts (90). Additionally, β2-adrenergic receptor polymorphisms were associated with wheeze and asthma in males before and after the onset of puberty in the Tucson Children's Respiratory Study cohort (91).

Genetic variations in pathways or signalling of oestrogen and androgens have also been associated with asthma. Oestrogen signals through the nuclear receptors, oestrogen receptor-α (ER-α) and ER-β. In a phenome-wide association study (PheWAS), significant associations ($P < .05$) between selected SNPs and asthma ICD-9 phecodes were observed. The rs1999805 SNP in ESR1, ER-α, was significantly associated with increased asthma electronic health data from the Vanderbilt BioVU databank and UK BioBank (92). HSD3B1 is an enzyme that converts DHEA to testosterone and a missense variant in HSD3B1(1245) was associated with glucocorticoid responsiveness in asthma. Women from the SARP I, II and III cohorts homozygous for HSD3B1(1245A), the restrictive allele preventing DHEA conversion into testosterone, had lower %predicted FEV_1 on glucocorticoid therapies compared to patients not on glucocorticoids (93). Combined, these data show sex-specific linkage in pathways important in asthma pathogenesis spans from childhood into adulthood.

Additional studies also determined that DNA methylation due to environmental exposures and sex hormones (at CpG motifs before and after puberty) are linked to asthma susceptibility (94–96), leading to a potential "switch" in asthma prevalence. CpG sites cg20891917 located on interferon-related developmental regulator 1 (IFRD1) were linked to sex-specific effects in asthma transition (96). These data suggest that DNA methylation changes in puberty are important in post-pubertal asthma incidence. Additional research is

needed to determine if DNA methylation alters mechanisms like Th2 cell differentiation and cytokine production.

Effectiveness of therapies

Therapeutic interventions in asthma vary between males and females more often in adults than children. Sex differences in response to a variety of medications may be due to compliance, variability in airway size and flow, hormonal, or sex-based pharmacogenetic and pharmacokinetic differences. Many asthma treatments are targeted towards T2 inflammation (e.g. inhaled and systemic corticosteroids, biologics targeted at IL-4, IL-5, IL-13), which has been shown to be less common in women compared with men (97, 98). This could contribute to poorer control of asthma in women, regardless of treatment and compliance (99), and a more severe clinical manifestation or perception of asthma (100, 101).

Amongst inhalers, steroid based therapies may be more effective amongst men (99), presumably due to some of the above described reasons. However, studies show discordant data in children, presumed to be affected by known inhaled corticosteroid (ICS) response, T2 inflammation, and/or differences in ethnicity (102–105). Monotherapy is often initiated as first-line treatment for asthma in women; whereas combination therapy of ICS and long-acting β-agonist is used as first-line in men (100, 106). However, differences in sex-related long-acting β-agonist effectiveness in asthma were not found. Tiotropium, a long-acting muscarinic antagonist, did not distinguish its favourable effects between males and females (107). Antileukotrienes are commonly used therapies in asthma, and antileukotrienes have better efficacy in women compared to men. Androgens attenuated the 5-lipoxygenase activating protein (FLAP), a protein required for the activation of 5-lipoxygenase and the production of leukotrienes, leading to a better response to antileukotrienes in women compared to men (108). In children aged 2–9, boys treated with montelukast - an antagonist to the cysteinyl leukotriene type 1 receptor that inhibits the actions of cysteinyl leukotrienes – had decreased asthma symptoms compared to boys administered placebo control (109). This was not seen in girls aged 2–9 with no differences in asthma symptoms when administered montelukast or placebo control. These results are concordant with previously described androgen shifts with age.

Sex and gender differences in biologic asthma therapy has not been extensively studied. Retrospective analysis of anti-IgE treatment did not demonstrate difference between sexes in therapeutic response (110, 111). Differences in response to other biologics such as anti-IL5 or anti-IL4 have not been studied.

Androgens and their precursors may be considered as targets for therapy. As described in the previous section, sulfonated DHEA (DHEA-S) levels are associated with FEV_1, and women with low DHEA-S levels have greater risk for airflow limitation and asthma severity (85, 112). DHEA-S levels, already low in women, can further be suppressed by systemic glucocorticoids (113), thereby potentially worsening asthma control (93). Further, the variant of HSD3B1(1245A) is associated with glucocorticoid resistance, particularly

in women (93). Therefore, differential responses by sex are important in asthma anti-leukotriene and glucocorticoid use.

The effects of exogenous hormone on asthma symptomology and severity would best be studied in transgender patients receiving regular hormone therapy. However, there have not been extensive studies on asthma in this population. Zein et al. reported that in 7210 patients with gender identity disorder and 490 patients who underwent gender affirming surgery, asthma risk was highest in male to female transgender individuals but was also significantly increased in female to male transgender individuals (114). Further studies in these populations would be beneficial in our understanding of the effects of sex hormones on disease.

Social and Environmental factors

Sex and gender differences in environmental exposures and healthcare utilization are important factors to consider in asthma as summarized in Table 1. Occupational exposures to vapours, dust, and fumes exacerbate asthma, and gender differences in occupational asthma vary by country and occupation. In the German Statutory Accident Insurance department 2017 report on occupational exposures that lead to allergic diseases, the most common occupational allergen exposure was to flour or flour/bakery products (baker's asthma), and this was disproportionally found in men (66%) compared to women (34%)(115). Gender differences in other occupational allergens have also been observed: there is a higher prevalence of hair product related allergy in women and wood or wood component dust in men. In the ECRHS, occupational exposures leading to new onset of asthma were similar in men and women (116). However, in the United States, women are more likely to have occupational-related asthma compared to men (115). These studies show that geographical and country differences in industry and industry standards affect gender differences in occupational asthma.

Gender differences in respiratory symptoms to various exposures have also been reported. Women are more likely to have shortness of breath and asthma when exposed to inorganic dust, while exposure to organic dust decreased lung function in men more than women (115). Women are more likely to utilize cleaning and disinfecting products in the workplace. However, no gender differences in cleaning-produced related asthma was determined in a recent systematic review (117). Ozone exposure decreases lung function, induces airway hyperresponsiveness, and increases asthma symptoms in patients with asthma (118), and has a more pronounced effect on reducing FEV_1 in women compared to men (119). While men are more likely to smoke compared to women (22.8% vs. 18.3%), women who smoke have increased asthma and asthma symptoms (120). Combined, these data show that gender should be considered in occupational exposures and the potential effect on asthma or respiratory symptoms.

COVID19, Sex/Gender, and Asthma

SARS-CoV-2, the virus that is the cause of the COVID19 pandemic, can give rise to a range of symptoms from a mild respiratory illness to severe multisystem disease and

death. Sex and gender differences of asthma associated with SARS-CoV-2 infection are still unclear. Multiple studies have reported that although women have a similar rate of SARS-CoV-2 infections, men have a higher risk of more severe disease and hospitalization (121–123). One potential explanation for this sex difference in COVID19 disease severity is variation in expression levels of ACE2, a receptor for the SARS-CoV-2 virus. An Australian group recently showed increased ACE2 gene expression level in older and male subjects and lower in asthmatics (124). The SARP III cohort in the US also showed significantly increased expression of ACE2 in the sputum of men (125). Several others have shown that ACE2 expression may be lower in children, IgE sensitized asthmatic subjects (126) and with IL-13 induction (127), without a known sex differentiation. Extrapolated from these data is the likelihood that T2 inflammation in asthma may be protective and result in less severe forms of COVID (128), Camiolo et al. postulated the possibility that non-T2 asthma, particularly those with high IFN-γ, may be associated with increased risk for COVID19 infection (129). This is particularly interesting since non-T2 asthma is more commonly seen in women. Further investigation is needed regarding association of non-T2 asthma and COVID19 infection, as many published papers suggesting that asthma is not a risk factor for COVID19 infection do not distinguish between the two endotypes of asthma and their varying prevalence in men and women.

Summary

Asthma prevalence, incidence, and severity are impacted by sex and gender differences in genetics/epigenetics, sex hormones, social and environmental factors, and response to therapeutics. Further, it is difficult to fully assess gender- and sex-specific risks in asthma due to confounding comorbidities and factors. Higher asthma prevalence is associated with other diseases and disorders, including obesity, attention deficit/hyperactivity disorder, and gastroesophageal reflux disease, as well as geographic location, socioeconomic status, pollutants, smoking, occupational exposures, race and ethnicity, and many others. Although many large cohort studies, including SARP and ECHRS, attempt to control for these comorbidities by including the factors in their assessments and collecting data from a broad range of people, it would be difficult to attempt to correct for all confounding factors. Although more study of the correlation between genetic, environmental and hormonal differences between males and females is needed, a complex but relevant role of gene polymorphisms (e.g. rs1999805 in ESR1, HSD3B1(1245A)), sex hormones (e.g. oestrogen, ER-α, testosterone, AR, DHEA-S)), and environmental factors (organic dust exposure, consequential DNA methylation) result in increased T2 inflammation and possibly worse AHR seen in males (16–21, 39, 82, 85, 92–96, 112, 115). T2 asthma does appear to be more prevalent in pro-androgenic periods in both males and females (late puberty boys, luteal phase in pre-menopausal women, post-menopause), with worse asthma possibly in low androgen states (low DHEA in late pubertal boys, low testosterone in adult men and women)(4, 39, 82, 83).

Response to therapy is also dependent on the complex interactions between these biologic processes. Mechanistic data in mouse models of asthma show that oestrogen signalling increased while androgens decreased T2 or non-T2 inflammation (17), but additional clinical and epidemiological studies are needed to determine how changes in sex hormones or

use of exogenous hormonal therapies alter asthma pathogenesis and response to current therapeutics. Further, with the additional approved biological therapies available for patients with asthma, it will be important to determine the efficacy of these therapeutics based on sex and gender at various ages. These studies will increase our understanding of asthma pathogenesis and provide personalized approaches for treating asthma through various reproductive stages of life.

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ABBREVIATIONS:

AHR	airway hyperreactivity
ACQ	Asthma Control Questionnaire
AERD	Aspirin exacerbated respiratory disease
BMI	body mass index
CHIRAH	Chicago Initiative to Raise Asthma Health Equity
COAST	Childhood Origins of Asthma
DHEA	dehydroepiandrosterone
DHEA-S	dehydroepiandrosterone
ECRHS	European Community Respiratory Healthy Survey
FeNO	exhaled nitric oxide
FAO	fixed airway obstruction
FEV1	forced expiratory volume for one second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GWAS	genome wide association study
HRT	hormone replacement therapy
ICS	inhaled corticosteroid
ILC2	type 2 Innate Lymphoid Cell

IFN	interferon
NHS	Nurses' Health Study
PMA	peri-menstrual asthma
PheWAS	Phenome-wide association study
RHINE	Respiratory Health in Northern Europe
SAGE	Study of Asthma, Genes, and the Environment
SARP	Severe asthma research program
SNPs	single nucleotide polymorphisms
T2	type 2
Th2	CD4 T helper
VDAART	Vitamin D Antenatal Asthma Reduction Trial

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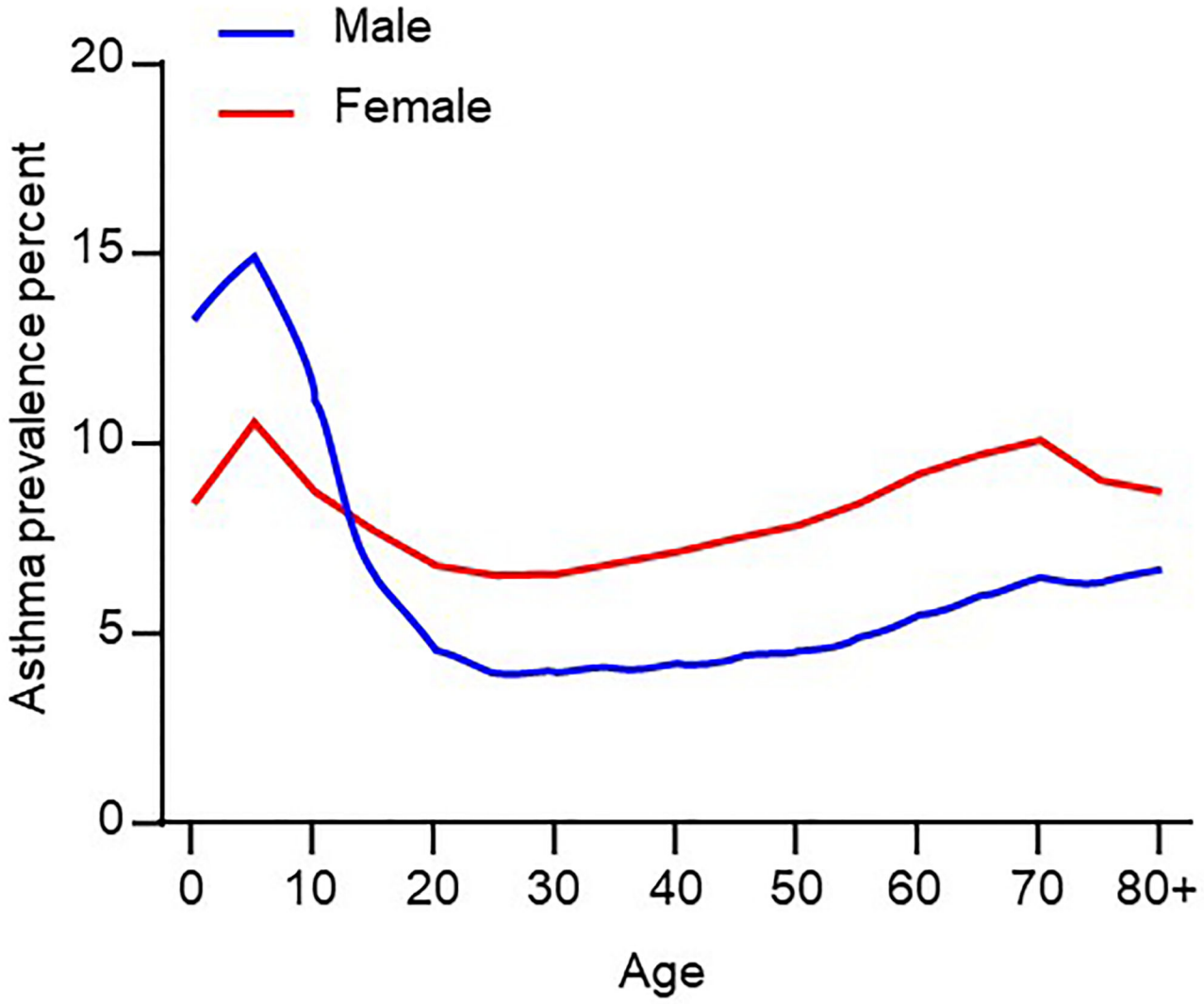


Figure 1: Asthma prevalence percentage throughout life in developed countries.
Graph is based on 2018 Global Health Data Exchange https://ghdx.healthdata.org

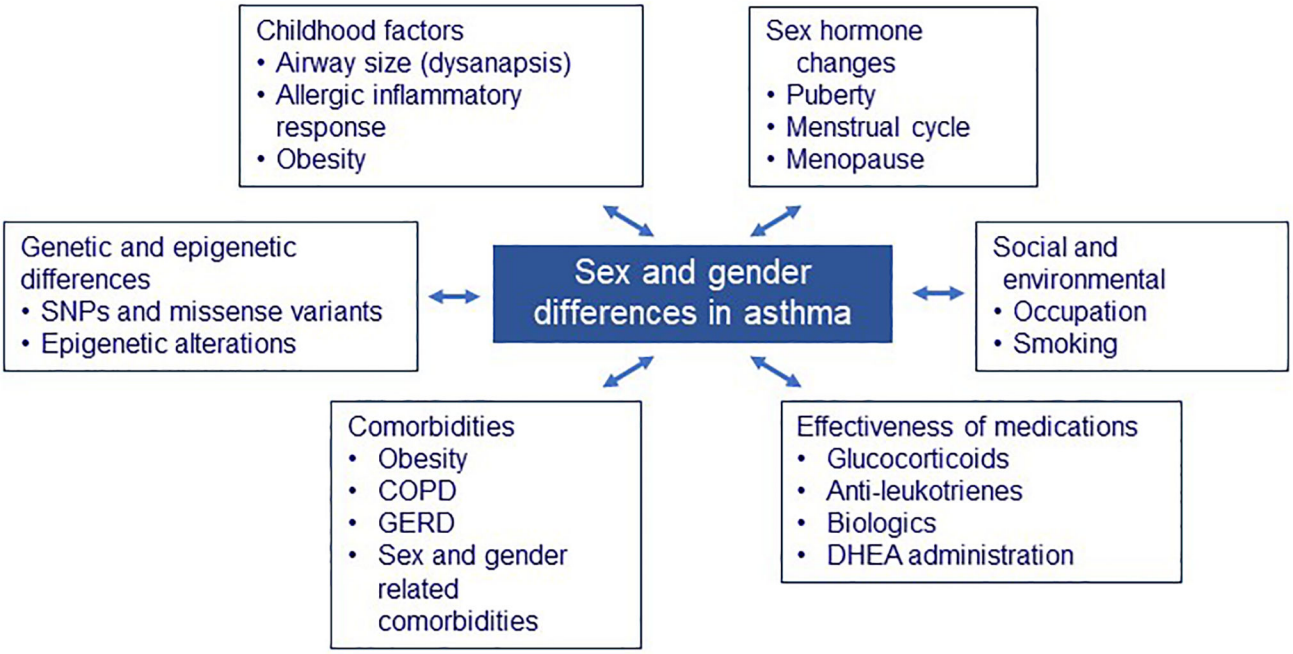
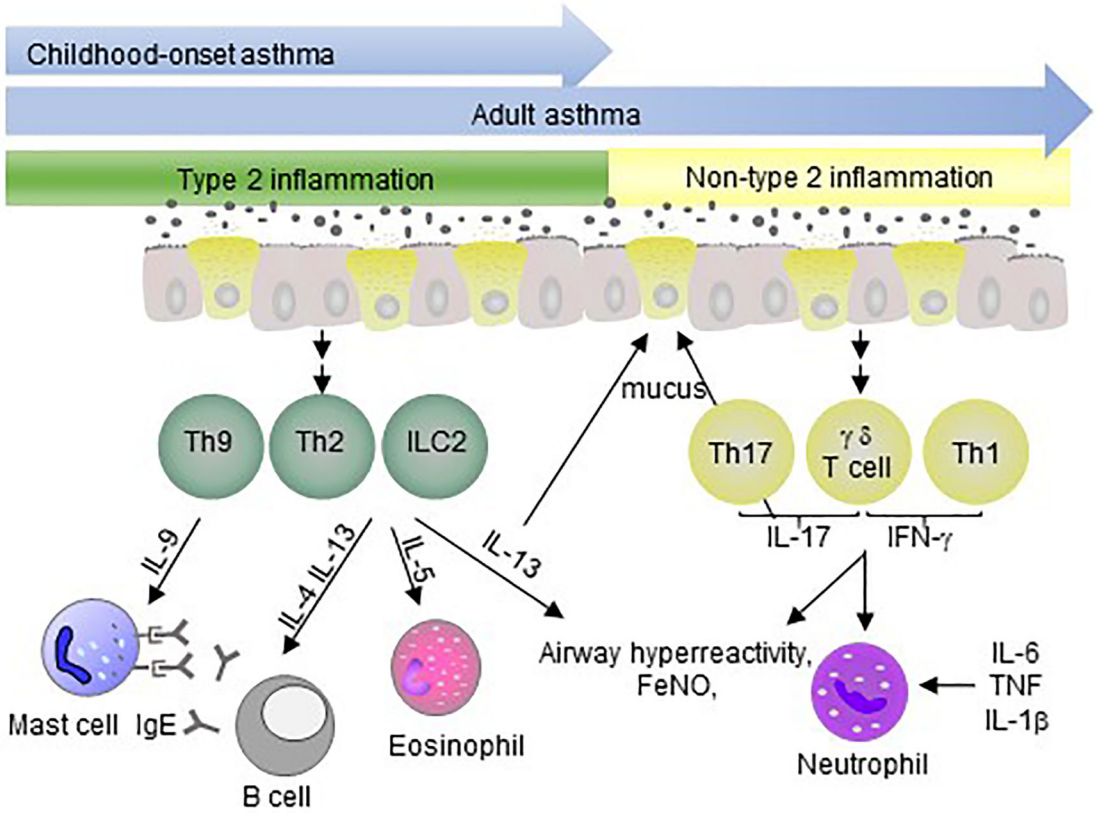


Figure 2: Sex and gender differences in asthma are influenced by several factors that vary across the lifespan.

As shown by bi-directional arrows, these factors affect the sex and gender differences observed in asthma or be affected by sex hormones.



Summary of in vivo mouse model results

	Type 2 inflammation	IL-17A-mediated inflammation
ER-α signaling	↑ AHR ↑ IL-33 production and release to increase type 2 inflammation ↑ M2 macrophages	↑ IL-17A production ↑ neutrophil infiltration, AHR, mucus produciton
ER-β signaling	↓ AHR, eosinohil infiltration	
AR signaling	↓ ILC2 proliferation and cytokine expression ↓ eosinophils, AHR, mucus, IgE, IL-5 and IL-13 cytokine production ↓ IL-33 and TSLP production	↓ IL-17A production ↓ neutrophil infiltration, AHR, and mucus production

Figure 3: Mechanisms driving airway inflammation in asthma pathogenesis.

Type 2 (green) and non-type 2 (yellow) adaptive immune responses associated with asthma pathogenesis. This cartoon shows how increased activation and differentiation of type 2 responses leads to increased IL-4, IL-5, IL-9, IL-13 production as well as increased eosinophil infiltration, B cell production of IgE, AHR, FeNO, and mucus production. Non-type 2 inflammation is more common in adults with asthma. Non-type 2 inflammation results in increased production of IL-17A or IFN-γ from T cells or increased IL-6, TNF, and IL-1β leading to increased neutrophil infiltration, AHR FeNO, and mucus production.

Table 1.

Factors Impacting Sex and Gender Difference in Asthma

Factor	Association by sex	References
Dysanapsis during development	increased risk in males	34
SNPs in genes		
TSLP	rs1837253 decreased asthma risk in males	87
	s2289276 decreased asthma risk in females	87
IFNg	rs2069727 heterozygosity increased risk in males but decreased in females	15
IRF1	increased risk in females	88
RAP1GAP2	increased risk in females	88
Vitamin D receptors	increased risk in females	89
KCNMB1	decreased FEV1 in males	90
B2 adrenergic receptor	increased risk in males	91
ESR1	increased risk	92
HSD3B1	decreased responsiveness to therapeutics in females	93
CpG methylation	increased risk in females	96
Obesity	increased risk in females	7, 8, 35
Environmental exposures		
Cigarette smoke	increased risk in men but when comparing within smokers, increased risk in women	8, 120
Diesel	increased risk in men	8
Flour/baker products	increased risk in men	115
Hair product related allergy	increased risk in women	115
Wood or wood component dust	increased risk in men	115
Inorganic dust	increased risk of symptoms in women, decreased lung function in men	115
Cleaning products	no gender differences	117
Ozone	decreased lung function in women	115, 116
Healthcare Utilization	increased risk in women	99, 101
Perception of asthma	increased risk in women	100, 101