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Novel Insights on Sex-Related Differences in Asthma

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Abstract

Purpose of Review Asthma, a common respiratory disease that affects about 10% of the US population, represents a significant public health issue. In the last decade, cumulative evidence has demonstrated sex disparities in asthma, including significant differences in epidemiology, clinical presentation, response to therapies, and health outcomes. Understanding sex-related differences in asthma enables clinicians to provide personalized asthma care and improve asthma outcome.

Recent Findings Recent studies on sex-related differences in asthma inform us on mechanism underlying asthma pathogenesis across all age groups. Sex hormones directly modulate immune pathways crucial in asthma pathogenesis and affect individual's response to environmental triggers and medications, such as leukokotriene inhibitors. Not surprisingly, the use of external sex hormone supplementations appears to modulate asthma risk. Identification of sex-specific asthma risk loci through genome-wide association studies also provides supporting evidence on sex-related differences in asthma. There is an interaction between sex and obesity, an interaction that could place females at higher risk for systemic inflammation and, consequently, asthma.

Summary In this article, we review epidemiological and clinical studies on sex-related differences in asthma, with a special focus on the role of sex hormones, including hormonal therapies and the asthma-obesity interaction.

Keywords Asthma · Sex-related difference · Menopause · Oral contraception pills · Menopausal hormone replacement therapy · Obesity

Introduction

Asthma affects males and females differently. Initially, asthma is more prevalent and severe in pubescent males. However, a gender switch occurs after puberty, when asthma becomes more prevalent and severe among females [1, 2]. Later in life, the risk of asthma severity increases with age in males age 45 and older, but not in females [3]. While this observation has also been found in other studies, the protective effect of menopause has not been consistently shown across all studies [4–7]. In addition, asthma is affected by cyclic hormone fluctuation in females, such as during the menstrual cycle, by exogenous sex hormone supplementation (i.e., birth control and hormone replacement therapy), and by pregnancy. These cumulative epidemiological data support the important role sex hormones play in asthma.

There are multiple mechanisms through which sex differences in asthma may occur. Genetic studies have demonstrated that gene polymorphisms underlie sex differences in asthma, including sex-specific asthma risk loci [8], gene polymorphisms of thymic stromal lymphopoietin (TSLP) [9], and estrogen receptor alpha (*ESR1*) [10, 11]. Androgens directly modulate immune responses through the down-regulation of type 2 (T2) inflammation [12, 13•]. The opposite effect is thought to be exerted by estrogen [14]. In recent years, the obesity-asthma interaction gained significant research interest. Women appear to be overall more susceptible to the detrimental effect of obesity on asthma severity, and some women may develop late-onset asthma due to obesity [15, 16•].

Recognition of sex-related disease heterogeneity calls for individually tailored therapies for asthma. Study of the interactions between sex hormones, obesity, related metabolic dysfunction, and immunity could also lead to discovery of novel therapeutic targets. In this article, we review epidemiological and clinical studies on sex differences in asthma, with a special focus on the role of sex hormones and the asthma-obesity interaction.

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Physiology

Male and female respiratory systems differ distinctly. Male sex hormones have been associated with "dysynaptic growth" where younger males have relatively narrower large airways in relation to their lung size as compared to females of the same age. In adulthood, females have smaller lungs and airways compared with males of the same height [17]. As a result, adult females are more prone to experiencing expiratory flow limitations during situations with high ventilation requirements such as exercise, which contributes to increased work of breathing and subjective symptoms including dyspnea and fatigue [18].

Sex Differences in Asthma Across the Life Span

Childhood

Prior to the onset of puberty, males are more susceptible to asthma and severe asthma. A study using the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) database to longitudinally assess 3308 children before age 8 showed higher cumulative incidence of wheezing and asthma among males as compared to females [19]. Likewise, in a cross-sectional study of children younger than 12 years of age, males had higher asthma prevalence as compared to females (11.9% vs. 7.5%) and were also more likely to be hospitalized for asthma exacerbation [18].

Adolescence/Puberty

Asthma is more prevalent among young males; however, after puberty, a "sex switch" occurs where asthma becomes more prevalent among adolescent and adult females [18]. This higher prevalence in women is driven by increasing asthma incidence in females, rather than resolution of asthma in males following puberty [20]. Asthma-related health care utilization and asthma medication use also showed similar "sex switch" [21]. In one study, females 15 years and older were three times more likely to be hospitalized for asthma-related events [22].

Although the exact mechanism is not well known, dramatic change of male and female sex hormones during puberty is thought to underlie the asthma "sex switch" phenomenon. Multiple studies have shown an association between early menarche (< 12 years old) and the risk of asthma and severe asthma [23, 24•]. DeBoer et al. analyzed 187 children 6–18 years of age enrolled in a cross-sectional study of the NHLBI-sponsored Severe Asthma Research Program (SARP) which showed that increasing dehydroepiandrosterone-sulfate (DHEA-S) levels in males were associated with better lung function and better asthma symptom control, while increasing levels of estradiol in females were associated with worse lung function and asthma symptoms [25•]. Furthermore, irregular menstrual cycles were also associated with increased risk of having asthma in the past year (OR: 1.59; 95% CI, 1.23–2.05) [24•]. This further suggests a link between sex hormone changes and asthma.

Conflicting results remain on the role of late-onset menarche in asthma risk. A meta-analysis of five studies previously indicated that late menarche (> 13 years) was associated with higher lifetime risk of asthma (OR 1.11; 95% CI, 1.07–1.15) [24•]. The results are in contrast to a more recent study involving 243,316 adult females from the UK, which suggests a continuous protective effect with a drop of 6% per year of the risk of asthma with increasing age of menarche ($p = 1.6 \times 10^{-4}$) [26]. Interestingly, while females are overall at higher risk of developing asthma during puberty, a subset of both females and males can still "outgrow" severe asthma during adolescence. The resolution of severe asthma during adolescence is characterized by peripheral eosinophilia, suggesting complex interplay between balances of different sex hormones and immunity [27].

Menstrual Cycle

Studies have shown that spirometry measurements are influenced by the hormone shifts that occur within each menstrual cycle. During the luteal phase of the menstrual cycle, the forced expiratory volume in the first second (FEV1) and the forced vital capacity (FVC) were lower, and airway hyperreactivity was higher as compared to baseline [28, 29]. These changes are associated with more respiratory symptoms during the premenstrual and menstrual period in about 20–25% of women with asthma, a condition known as premenstrual asthma (PMA) [29–31]. Women with PMA tend to be older, have higher body mass index (BMI), and are more likely to exhibit dysmenorrhea, premenstrual syndrome, shorter menstrual cycles, and longer menstrual bleeding. PMA was also associated with greater likelihood of aspirin sensitivity, a longer asthma duration, more severe asthma, and higher healthcare utilization [31–33].

Pregnancy

Pregnancy is characterized by dramatic changes in physiology and sex hormone levels. As expected, pregnancy and asthma significantly affect each other, with profound implications on both maternal and fetal outcomes. However, the effect of pregnancy on asthma severity is variable, and about 30% of women report of worsening asthma severity and loss of disease control during pregnancy, particularly during the second and third trimester [18, 34]. Poorly controlled maternal asthma is strongly associated with multiple adverse maternal and fetal outcomes such as preeclampsia, placental abruption, placenta previa, obstetric hemorrhage, increased rates of cesarean

section, low birth weight, small for gestational age, and increased risk of newborn mortality [35, 36]. In addition to its negative effect on newborn and pregnancy outcomes, asthma has been associated with altered fertility in females, expressed as a longer time to pregnancy and reduced incidence of pregnancy [37].

The interaction between asthma and pregnancy also appears to be influenced by the sex of the fetus. For example, pregnancy with a female fetus was associated with greater maternal peak expiratory flow variability compared with those carrying a male fetus [38]. Similarly, reduced fetal birth weight was more pronounced in female newborns as compared to male newborns when maternal asthma was a factor [39]. Possible reasons include differential gene expression in the female versus male placenta involving inflammation and immune pathways [40], and the relative glucocorticoid resistance in male placenta due to presence of different glucocorticoid receptor isoforms [41].

Menopause

Data on the effect of menopause on asthma show conflicting results. The early prospective study by Troisi et al. using Nurses' Health Study cohort showed that menopausal females who never used menopausal replacement therapy (MRT) had significantly lower age-adjusted risk of new onset asthma (RR = 0.65; 95% CI 0.46 to 0.92) [4]. However, later studies indicated higher risk of asthma with increased respiratory symptoms during menopausal transition [5, 6]. New onset asthma occurring during or after menopause was more likely to be severe and less responsive to anti-inflammatory therapy [42]. Triebner et al. longitudinally followed 2322 adult females enrolled in the Respiratory Health in Northern Europe cohort and demonstrated higher risk of new-onset asthma in either premenopausal, early, or late post-menopausal individuals not treated with MRT (ORs 2.40, 2.11, and 3.44, respectively). Of note, it was unclear if COPD and other chronic pulmonary conditions were excluded or accounted for in this study [43]. A recent report from the French E3N cohort which prospectively followed 67,872 adult females without asthma at baseline for 843,243 person-years showed higher asthma incidence among overweight/obese females (BMI > 25), but not lean females, during the peri- and post-menopausal period as compared to the pre-menopausal period (HR = 1.91, 95% CI 1.00–3.66; and HR = 2.08, 95% CI 1.07–4.06, respectively). This association between menopause and asthma risk was no longer present during subgroup analysis after excluding 24% females who previously used MRT. These cumulative findings suggest an interaction between obesity, MRT use, and menopause and the risk of asthma incidence. Interestingly, surgical menopause was also associated with increased risk of asthma onset (HR = 1.33, 95% CI 1.01–1.75) [7]. Reports studying the association between menopause and asthma prevalence and incidence, pooled in two large meta-analyses, have also been inconsistent. While a prior meta-analysis by Zemp et al. found no significant association between menopause and asthma prevalence or incidence except for in females who used MRT [44], a more recent meta-analysis showed that menopause onset was associated with increased risk of current asthma (OR, 1.25; 95% CI, 1.04–1.51) and current wheeze (OR, 1.16; 95% CI, 1.05–1.30) [24•].

Aging

As compared to younger individuals, asthma in older adults is prone to exacerbations and is less responsive to inhaled corticosteroids [45]. Noticeably, elderly males were reported to be at higher risk of having severe asthma and asthma-related morbidities compared to elderly females. For example, the probability of having severe asthma increases in males over age 45, but not in females of the same age [3]. Similarly, analysis of a sample of 94,611 asthma hospitalizations extracted from National Inpatient Samples (NIS) 2011–2012 database showed that the risk of asthma-related respiratory failure continued to rise in elderly males 60 years and older, but not in age-matched females. Similar findings of increased risk of asthma-related hospitalization among elderly males were also observed in a group of patients with asthma enrolled in SARP [46]. Greater elastic recoil of the lungs among elderly females was thought to underlie severe asthma and higher healthcare utilization among elderly males as compared to elderly females [18]. In a study involving 14,076 elderly patients (age 65 years and older) with asthma, females were more prone to depression and obesity and had more financial barriers, while males were more affected by medical comorbidities, including diabetes mellitus and coronary artery diseases [47].

The Role of Intrinsic and Extrinsic Sex Hormones in Asthma

Sex hormones modulate immune processes involved in asthma. Following ovalbumin challenge, female mice developed more pronounced TH-2 inflammation and airway remodeling compared with male mice [14]. Animal studies suggested that estrogen signaling through ER-α, enhances allergic airway inflammation via M2 macrophage polarization in the lung and bone marrow [48, 49•]. Testosterone, on the other hand, modulated TH-2 inflammation by inhibiting group 2 innate lymphoid cells (ILC2s) in animal model [12, 13•]. This could explain higher numbers of circulating ILC2 in human females as compared to males with asthma [13•]. Collectively, female sex hormones up-regulate whereas testosterone down-regulates important molecules of the TH-2 inflammatory

pathway. Selected interaction between sex hormones and immune pathway is summarized in the Table 1.

The effect of sex hormones expands beyond immune cells. DHEAS, the major adrenal androgen, mediatedairway smooth muscle relaxation and bronchodilatation in a guinea pig model [56]. In human subjects, inhaled DHEAS for 6 weeks improves asthma control in a group of patients with moderate-to-severe asthma [57].

Genomic data also supports sex-related differences in asthma. Genome-wide association revealed 2 male-specific and 4 female-specific asthma risk loci. One of the loci involves the gene encoding interferon regulatory factor-1 (*IRF1*) and likely associates with male-specific asthma susceptibility [8]. Tthymic stromal lymphopoietin (*TSLP*) polymorphisms associate with asthma risk differently between males and females. For example, a single nucleotide polymorphisms (SNP denoted as an rs number) rs1837253 is protective in males only, while SNP rs2289276 is associated with higher asthma risk in females [9]. Sex-specific asthma risk was also related to estrogen receptor-alpha gene (*ESR1*) variants. In a family-based association study of two hundred families (1249 individuals), five SNPs in *ESR1*were independently associated with bronchial hyperresponsiveness and faster decline in lung function in female subjects, but not in males [10]. Likewise, analysis of data from three large cohorts (Vanderbilt BioVU MEGA Project, the UK Biobank, and Vanderbilt's BioVU databank) linked an *ESR1* SNP (rs1999805 in particular) and an aromatase gene (*CYP19A1*) polymorphism to asthma [11].

Environmental exposures affect male and female asthma patients differently as well, a phenomenon that was linked to sex hormones. Pollution-related asthma symptoms were more pronounced in atopic girls and non-atopic boys [58]. Likewise, the effect of tobacco was more pronounced in adult females as opposed to adult males [59, 60]. A recent animal study showed that female mice had higher inflammatory gene expression following ozone exposure during follicular phase as compared to the luteal phase. This gene expression pattern was associated with higher BAL neutrophilia and higher airway resistance post ozone exposure [61].

In addition to sex differences in response to environmental exposure, sex-specific responses to asthma medications have also been reported. The 5-lipoxygenase (5-LO)/5-LO-activating protein (FLAP) complex, an enzyme responsible for leukotriene (LT) production, is inhibited by androgens. Consequently, lower LT production is anticipated to occur in males, which makes them less responsive to exogenous LT biosynthesis inhibitors as compared to females [62••]. Retrospective studies from two Italian and Danish cohorts showed that adult males were more likely to discontinue montelukast therapy, and, subsequently, require other asthma therapy including systemic steroid bursts, suggesting potential differential therapeutic responses between adult males and females to medications that affect the LT pathway [63].

Use of Oral Contraceptive Pills (OCPs)

Many controversies surround the effect of hormonal contraception and asthma. While OCP were reported to improve premenstrual asthma and lower airway hyper-reactiveness by dampening cyclic hormonal change in small case series [64], they were also associated with higher risk of current asthma in other studies. Similar controversy was reported when studying OCPs' effect on asthma control and severity. In one cross-sectional study of 905 adult females, OCP use was associated with current wheezing in non-asthmatic patients (OR 1.75; 95% CI, 1.15–2.65) but reduced wheezing symptoms in asthmatic patients (OR, 0.18; 95% CI, 0.06–0.56) [23]. Similarly, another cross-sectional study involving 5791 adult females aged 25–44 from 5 European countries (961 patients, 17% of study population) showed that OCPs were associated with increased risk for asthma (OR 1.42; 95% CI, 1.09–1.86) in normal weight (BMI 20–25 kg/m^2, OR: 1.45; 95% CI, 1.02–2.05) and overweight females (BMI > 25 kg/m^2; OR: 1.91; 95% CI 1.20–3.02), but not in lean female patients (BMI < 20 kg/m^2: 0.41; 0.12–1.40) [65]. In contrast, a population-based analysis, using data from serial Scottish Health surveys, showed that the use of OCP was associated with lower likelihood of current physician-diagnosed asthma (OR 0.68; 95% CI 0.47–0.98). This association seemed to be seen mostly in lean adult females [66]. Collectively, these data suggest an interaction between hormonal contraception and obesity in asthma in female patients.

Table 1 Sex hormones and their interactions with immune pathways

Sex hormones [references]	Interaction	T1 pathway	T2 pathway	Other pathway
Estrogen [50, 51]	Upregulate	IL-6, TNF-α, INF-γ		TLR8
	Downregulate			IL-10, TGF-β1
Progesterone [52–54]	Upregulate	IL-6, TNF-α	IL-4, IL-5, IL-9, IL-13	IL-10
	Downregulate	INF-γ		TGF-β1
Testosterone [12, 13•, 55]	Upregulate	INF-γ		
	Downregulate		IL-4, IL-5, IL-13	IL-33, TSLP

Conversely, pooled analysis of data from two cross-sectional and three prospective cohort studies that evaluated the effect of previous OCP use on current asthma and wheezing showed mixed results [24•]. Importantly, one key factor to consider is the differences in "standard dose" and components of OCPs over time. While current OCPs usually contain ethinyl estradiol at doses of 20–35 mcg, earlier OCP contained estradiol doses up to 150 mcg [67].

Use of Menopausal Hormone Replacement Therapy (MRT)

There are more consistent data to suggest that MRT increases the risk of asthma. The Nurses' Health Study showed increased risk of asthma incidence in ever use, past use, or current use of MRT (OR equal to 1.49, 1.52, and 1.50, respectively). Among current users of conjugated estrogens in this study, there was a positive dose-response demonstrated between daily conjugated estrogen dose and asthma risk (p for trend = 0.007) [4]. These results were replicated in other studies as well. Pooled results showed, as compared to adult females who never used MRT, those who ever MRT use (hazard ratio [HR], 1.37; 95% CI, 1.22–1.54), past use (HR, 1.41; 95% CI, 1.22–1.63), currently used (HR, 1.48; 95% CI, 1.22–1.78), and currently used an estrogen-only MRT (HR, 1.85; 95% CI, 1.50–2.28) had an increased risk of new-onset asthma [24•]. These findings were also replicated in a large database cohort in the USA (1,793,810 adult females aged 50 or above, among whom 356,410 ever used MRT, and 90,960 ever used anti-estrogen therapies) and found, in addition to the detrimental effect of MRT and estrogen-based MRT, that anti-estrogens (AE) were associated with lower lifetime asthma prevalence. However, this beneficial effect of AE was reversed by MRT [68].

Sex-Specific Obesity Risk on Asthma

In the USA, over 60% of patients with asthma are over-weight or obese [69]. Obesity was also associated with severe difficult-to-control asthma [16]. However, the effect of obesity is, at times, sex-specific suggesting an interaction between sex and obesity that differentially affects asthma outcomes.

Childhood Obesity and Asthma

The obesity-asthma association is already present in the pediatric population. For example, obese children had lower prevalence of bronchial hyper-reactivity (BHR) compared with non-obese children [70]. Multiple studies indicated that girls are more affected by obesity than boys. Longitudinal observational studies showed a positive association between BMI and asthma-like symptoms such as wheezing in young females but not in males [71, 72]. Similarly, obesity was associated with higher risk of asthma among adolescent females but not males [73]. An international cross-sectional study involving over 30,000 Chinese children aged 2–14 showed a significant association between obesity and asthma diagnosis (OR 1.28, 95% CI 1.02–1.60) or presence of wheezing (OR 1.46, 95% CI 1.20–1.79) in only females, but not males, [74] associations also described in population-based studies from the Netherlands [75] and Sweden [76]. In the latter Swedish study (BAMSE birth cohort) where 2818 children were followed longitudinally from birth until adolescence, high BMI was consistently associated with persistent asthma throughout childhood among females but not males [76]. These results were replicated in another cohort from Canada that includes 571,790 males and 549,230 females. Once again, females, but not males, with increasing BMI trajectory throughout childhood were more likely to report persistent asthma (OR = 4.9, 95%CI 1.04–16.15) as compared to children with stable BMI trajectory [77].

Overall, female sex likely modulates the obesity-asthma interaction even before completion of puberty. The exact mechanism for such sex-related differences remains unclear, but are likely multi-factorial. Differences in lung development, symptom perception, and even difference in immune response to environmental triggers may play a role in this asthma interaction [78].

Adult Obesity and Asthma

The sex-specific effect of obesity is also seen among adults with asthma. Obese adult females tend to have higher prevalence, incidence, and severity of asthma. Longitudinal studies indicated that higher baseline BMI (> 30) was associated with increased risk of asthma incidence and prevalence in adult females (OR 1.9, 95% CI 1.1–3.4), but not adult males [79, 80]. In the SARP cohort, BMI differences were seen between adult females with severe versus non-severe asthma, but not between adult males of different asthma severity [81]. Similarly, the effect of obesity on asthma exacerbation and quality of life (AQLQ) was also sex-specific. In a retrospective study from Japan, obesity was associated with asthma exacerbations among adult females but not adult males (OR 2.29, 95% CI 1.24–4.22) [82]. Likewise, BMI, waist circumference, and abdominal subcutaneous fat area were all associated with lower AQLQ in adult females but not in adult males [83]. Although the exact mechanism that underlies sex-specific association between obesity and asthma remains unclear, a recent study on human airway smooth muscle (HASM) cells obtained from patients of reproductive age (20–40 years old) showed that HASM from obese female patients had greater response to contractile agonists and greater cell shortening than HASM from obese male subjects [84].

Multiple factors likely contribute to this sexually different interplay between asthma and obesity. First, males with the same BMI have lower percentage of body fat than females. Furthermore, males have higher percentage of visceral (abdominal) fat, while females have more subcutaneous fat, mostly in gluteal-femoral region [85]. The effect of fat distribution on lung function was reported in 16,186 older Chinese patients. In this study, only central adiposity defined by waist circumference (WC: ≥ 90 cm in males, ≥ 80 cm in females) but not general obesity defined by BMI ≥ 28 was associated with lower pulmonary function and higher risk of restrictive respiratory defect [86]. Similar results were reported in a Canadian cohort [87]. These results suggest differential effects of visceral versus subcutaneous adipose tissue and, thus, could contribute to differences in asthma risk or severity between obese males and females.

Secondly, adipose tissue represents a very active endocrine organ [88]. The molecule secretion profile of adipose tissue varies between the two sexes and modulates systemic inflammation differently. Adipokines, proteins secreted by adipose tissue, are crucial links between obesity and systemic inflammation. Leptin and adiponectin, two important adipokines, are associated with obesity [88]. Interestingly, both leptin [89, 90] and adiponectin [91] are lower in adult males compared in adult females with same BMI, partly due to differences in testosterone levels and body fat distribution [92]. In addition, a high leptin level was associated with airway hyperresponsiveness in animal models [93]. Lower adiponectin levels were associated with asthma [94], and extrinsic atopic dermatitis (but not intrinsic atopic dermatitis), which is characterized by pronounced TH-2 inflammation, similar to asthma with predominant TH-2 inflammation [95].

One of the many metabolic derangements in obesity is insulin resistance. Some recent studies suggest a link between insulin resistance and worsening respiratory health including asthma. Insulin and glucose levels are frequently used to calculate the homeostatic model assessment of insulin resistance (HOMA-IR). In a study involving 98 pubescent children, FVC was significantly lower in insulin-resistant children with high HOMA-IR ($p = 0.03$). Likewise, other spirometry measurements showed a trend to be lower with high HOMA-IR without reaching statistical significance [96].

Insulin resistance is also seen in adult females with polycystic ovarian syndrome (PCOS) in association with obesity and ovarian hyperandrogenism. We previously reported significantly higher lifetime asthma prevalence in patients with PCOS (21.6% vs. 13.7%). While hyperandrogenism can be theoretically beneficial, we speculated that the higher asthma prevalence among patients with PCOS could be either related to insulin resistance or to the un-opposed estrogen secretion present with anovulatory menstrual cycles [97]. Our results were replicated in two large groups of Danish women with PCOS (N1 = 1358, N2 = 17,123). Compared with healthy controls, adult females with PCOS had both higher asthma prevalence (OR 1.45, 95% CI 1.24–1.70) and higher average daily dose of inhaled corticosteroids (ICS). However, asthma severity gauged by ICS dose in patients with or without PCOS was not statistically different. Of note, the asthma prevalence was relatively high in this study, with 16.6% of patients in control group also diagnosed with asthma, defined as use of asthma medications and/or physician diagnosis [98].

Increasing evidences suggest that the "obese asthma" phenotype in adult female is partially driven by neutrophilic inflammation. In a study of 423 asthma patients, high BMI was associated with higher levels of blood neutrophils in females, but not in males [99]. Likewise, sex-specific difference in sputum neutrophilia was also seen in a small study that compared obese ($n = 39$) and non-obese adult females ($n = 42$), to obese ($n = 24$) and non-obese adult males ($n = 25$) with asthma. There was higher percentage of sputum neutrophils in obese versus non-obese reproductive age females, but no differences of sputum neutrophil percentage between obese versus non-obese male or older females. Interestingly, BMI and age were not significant predictors in multivariate regression models. Positive predictors of percentage sputum neutrophils included C-reactive protein (CRP) and IL-6, while use of testosterone and OCP was associated with lower percentage sputum neutrophils [100]. This study raises important questions regarding causality, the interplay between obesity, insulin resistance and cytokines, and whether the effect of obesity on asthma is mediated by insulin resistance and IL-6.

Overall, the obesity-asthma link is clearly differentially modified by sex. Some researchers propose two possible phenotypes of (1) asthma complicated by obesity, which affects both adult males and adult females and (2) asthma consequent to obesity, which appears to be more common in adult females [15, 16].

Conclusions

Asthma is a heterogeneous disease that results from an interaction between the internal (genetic or hormonal) milieu and environmental exposures. Endogenous or exogenous sex hormones are thought to interact with obesity and external exposures to directly impact airway inflammation and contraction, or indirectly modulate gene transcription. Such complex interactions underlie sex differences in asthma across the lifespan. Mechanistic studies will provide novel insight on asthma pathogenesis and potential intervention targets. Overall, sex-related differences in asthma are complex and multifactorial and remain an important factor to consider in moving towards devising personalized therapies for asthma.

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Compliance with Ethical Standards

Conflict of Interest Peng Zhang and Joe Zein declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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