Minireview

Asthma, atopy, and exercise: Sex differences in exercise-induced bronchoconstriction

Daniel Enrique Rodriguez Bauza[1] and **Patricia Silveyra**[2,3]

[1]Clinical Simulation Center, The Pennsylvania State University College of Medicine, Hershey, PA 17 033, USA; [2]Biobehavioral Laboratory, The University of North Carolina at Chapel Hill, School of Nursing, Chapel Hill, NC 27599, USA; [3]Department of Environmental and Occupational Health, Indiana University School of Public Health, Bloomington, IN 47405, USA
Corresponding author: Patricia Silveyra. Email: psilveyr@iu.edu

Impact statement

Exercise-induced bronchoconstriction (EIB) occurs in individuals with and without asthma and is commonly associated with both a physical and an emotional burden in athletes. It is estimated that EIB affects 90% of patients with asthma, a disease known to differentially affect adult men and women. Despite the well-described sexual dimorphism in pediatric atopic asthma and adult non-atopic asthma, very little is known about sex differences in EIB, and in the relationship among sex, atopy, and EIB. This study summarizes research conducted on these topics, and in studies aimed to identify sex and atopic status as factors associated with EIB prevalence. Understanding the mechanisms underlying EIB in men and women may help in the development of better-personalized training and management plans for male and female athletes with underlying asthma and/or atopy.

Abstract

Asthma is a chronic inflammatory lung disease affecting approximately 7.7% of the US population. Sex differences in the prevalence, incidence, and severity of asthma have been widely described throughout the lifespan, showing higher rates in boys than girls before puberty, but a reversed pattern in adults. Asthma is often associated with atopy, i.e. the tendency to develop allergic diseases, and can be worsened by environmental stimuli and/or exercise. While not exclusive to patients with asthma, exercise-induced bronchoconstriction (EIB) is a common complication of athletes and individuals who exercise regularly. Currently, there is limited research on sex differences in EIB and its relationship with atopy and asthma in men and women. In this minireview, we summarize the available literature on this topic. Overall, the collective knowledge supports the notion that physiological changes triggered during exercise affect males and females differently, suggesting an interaction among sex, exercise, sex hormones, and atopic status in the course of EIB pathophysiology. Understanding these differences is important to provide personalized management plans to men and women who exercise regularly and suffer from underlying asthma and/or atopy.

Keywords: Inflammation, atopy, exercise-induced asthma, exercise-induced bronchoconstriction, sex differences, hormones

Experimental Biology and Medicine **2021; 246: 1400–1409. DOI: 10.1177/15353702211003858**

Introduction

According to data from national and state surveillance systems of the Centers for Disease Control and Prevention, the national prevalence of asthma is about 7.7% in the US general population, with higher estimates for female adults (9.1%) than male adults (6.2%).[1] Sex differences in asthma prevalence, but also incidence, severity, and response to treatment, have been widely described, and shown to display a reversed pattern in pre- and post-pubertal patients.[2,3] Prior to puberty, asthma is more frequently found in boys than girls, but in adults of reproductive age, asthma is more commonly found in women than men.[4–7] These sex differences have been attributed to anatomical, physiological, and hormonal factors, as well as occupational and environmental exposures.[8–10]

A condition often associated with asthma is atopy.[11] Defined as the tendency to develop an enhanced immune response to allergens, atopy is found in 80% of US childhood asthma cases and over 50% of adult asthma cases.[12] Interestingly, this percentage that is greater among male than female patients with asthma and athletes, and is also higher in athletes and individuals who exercise regularly than in sedentary people.[13–15] In addition, athletes with atopy often experience exercise-induced bronchoconstriction (EIB). EIB, also known as exercise-induced bronchospasm, is defined as the transient narrowing of the lower airways that occurs during or after exercise in the presence

ISSN 1535-3702

or absence of clinically recognized asthma. While an episodic bronchospasm following exercise is sometimes defined as "exercise-induced asthma", this wording is potentially misleading since exercise is not an independent risk factor for asthma, but rather a trigger of bronchoconstriction in patients with underlying asthma.[16–18] Although EIB has been estimated to occur in up to 90% of patients with underlying asthma, it also occurs in individuals with no prior history of asthma and no symptoms outside exercise.[19] EIB is also a relatively common condition that is frequently unrecognized, especially in schoolchildren and competitive athletes, because its symptoms are easily confused with "lack of fitness" or "being out of shape". Current guidelines recommend that health care providers consider the patient's history regarding respiratory symptoms associated with exercise and asthma when evaluating patients with bronchospasm.[16]

Despite the well-established sex differences in asthma prevalence mentioned above, very few studies have addressed sex differences in EIB in athletes and individuals who exercise regularly. The limited evidence available to date suggests that a relationship exists between sex and atopic status in the course of EIB in these populations, and that sex hormones may influence severe symptoms of EIB in female athletes.[20,21] In the sections below, we summarize the current knowledge on the topic, focusing on sex differences in EIB epidemiology, diagnosis, pathophysiology, and physiological and environmental influences.

EIB epidemiology

Because most studies on this topic have focused on asthma in general, and not specifically on EIB, the epidemiology of EIB has not been very well described. As a result, the reported prevalence for EIB varies across studies, and is estimated to range between 5% and 20% in the general population (Figure 1).[19,22–26] Among elite or Olympic-level athletes, however, the reported prevalence is much higher, ranging from 30% to 70% (Figure 1).[19,27] Importantly, because only a few studies have differentiated individuals with and without asthma, the true prevalence of EIB within the non-asthmatic general population is currently unknown.[28] Regarding sex differences in EIB epidemiology, only a fraction of published studies has included male and female participants, and an even smaller fraction has assessed differences between males and females (athletes or not). We have recently systematically reviewed these studies and found that the average prevalence of EIB in athletes is around 23% (Figure 1).[15] We also found that the prevalence of atopy was reportedly higher in male vs. female athletes, and in athletes with EIB vs. those without EIB. Collectively, the reviewed studies indicate that the prevalence of atopic EIB is higher in male athletes and regular exercisers than in females on these groups.[15] Identifying such differences has clear implications for understanding sex and gender specific adaptations to exercise for athletic performance and overall health.[29]

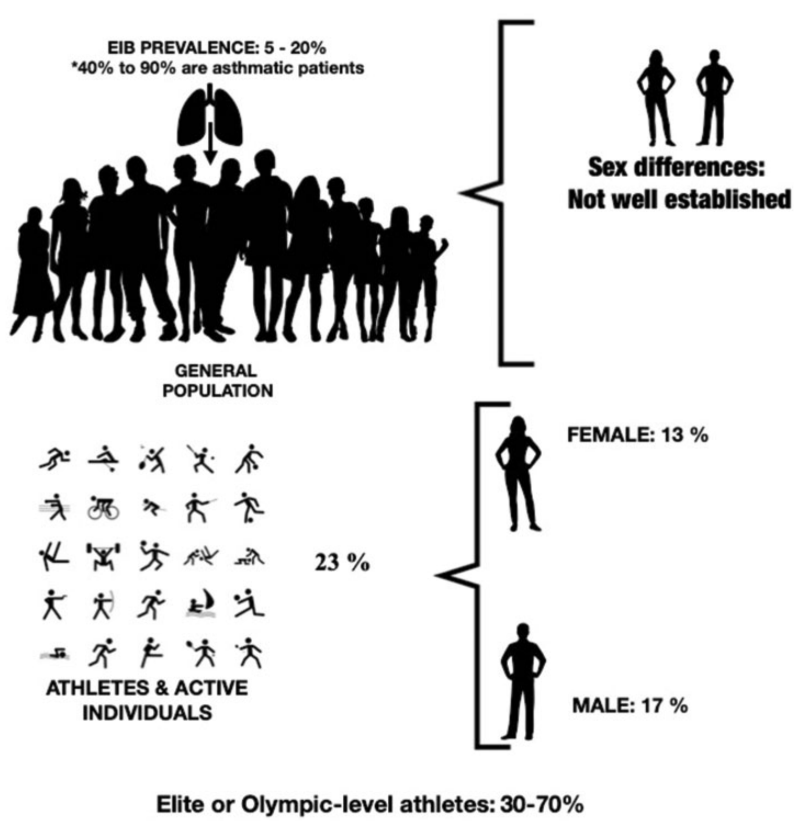

Figure 1. EIB prevalence in general and athletic/active individual populations and known sex differences.[19–27]

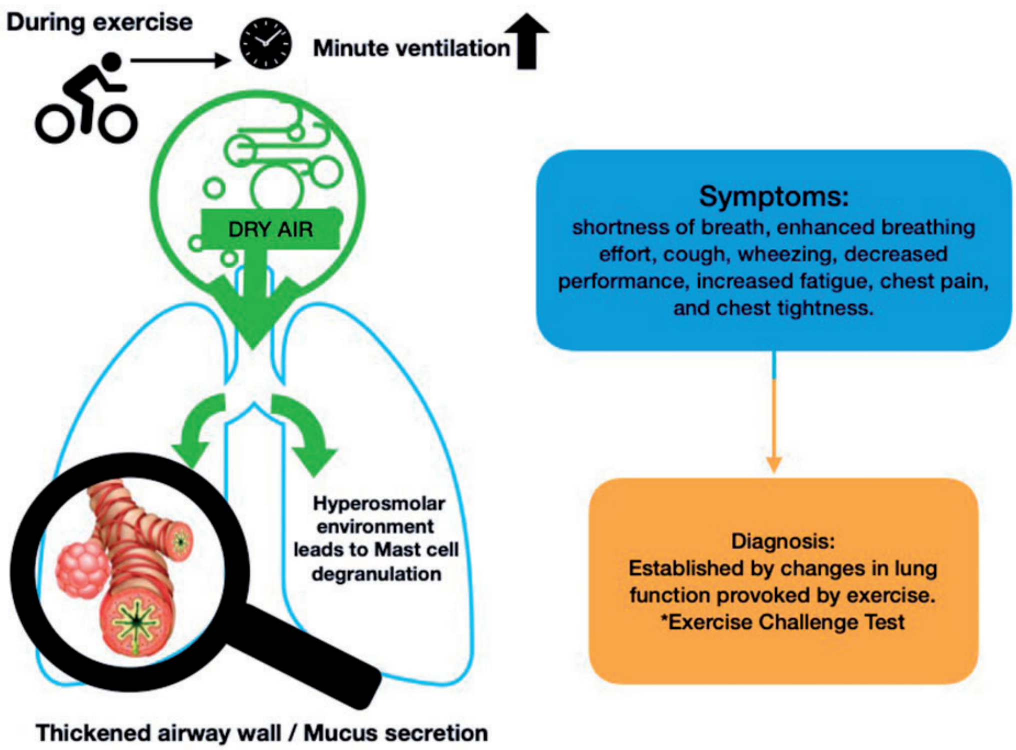

Figure 2. Pathogenesis of EIB (left), clinical presentation and objective diagnostic test (right).[25,28–34,45] (A color version of this figure is available in the online journal.)

EIB diagnosis

The clinical presentation of EIB includes cough, wheezing, shortness of breath, and/or chest tightness (Figure 2), generally occurring within 5 to 30 min after intense physical activity. Patients with symptoms of suspected EIB are evaluated with a detailed history and physical examination (including examination of the ears, nose, and throat, and cardiac and chest assessments), and/or spirometry in conditions that mimic prolonged exercise (eucapnic voluntary hyperventilation), in which lung function measurements are performed before and after a short-acting beta agonist is given (Figure 2). In many patients, bronchial hyperresponsiveness is also evaluated in the laboratory with an exercise challenge or a surrogate bronchoprovocation challenge (e.g. with cold air hyperventilation, methacholine, adenosine monophosphate, or mannitol) to exclude asthma.[30–34] The objective documentation of EIB via questionnaires permits the identification of individuals who may be at risk during a recreational sporting activity, or when exercising as an occupational duty. In general, it is recommended that the diagnosis of EIB is confirmed by demonstration of airways reversibility or challenge in association with a history consistent with EIB, because the use of self-reported measures or symptoms to diagnose EIB is not predictive of whether athletes have objectively documented EIB.[27,35] In our prior review of the literature,[15] we found that in studies including both males and females, 43% used exercise challenge alone as a diagnostic measure, whereas 14.2% used it in combination with a bronchial provocation test such as mannitol or methacholine, and 9% used self-reporting data via questionnaires. While we do not know whether a sex bias exists in the ability of these tests to accurately diagnose EIB, sex differences in self-reported measures of airway hyperresponsiveness and other symptoms during exercise have been documented. In a study including 798 athletes (698 taking a survey), females were 1.6 times more likely to report respiratory symptoms during exercise than males, despite no differences in physician-diagnosed asthma between the genders.[36]

EIB pathophysiology

To date, the pathogenesis of EIB has not been fully elucidated, although it is likely the result of physiological changes occurring in the lung during exercise.[37,38] Minute ventilation, the volume of air inhaled or exhaled from a person's lungs per minute, rises with exercise (Figure 2).[39] A major trigger for bronchoconstriction is water loss during periods of high ventilation. Thus, the water content of the inspired air during exercise is also a major determinant of EIB.[35] Strenuous exercise creates a hyperosmolar environment by introducing dry air into the airway, and the resulting compensatory water loss triggers a transient osmotic change on the airway surface.[40] This hyperosmolar environment leads to mast cell degranulation with release of mediators, predominately leukotrienes, but also including histamine, tryptase, and prostaglandins.[41] This is supported by evidence showing that mannitol challenge can trigger mast cell activation and release of mediators of bronchoconstriction in patients with and without asthma, indicating that increased osmolarity of the airway fluid lining is a general stimulus for activation of mast cells.[42] In addition, eosinophils are also activated, producing further mediators including leukotrienes.[43] In turn, this can lead to bronchoconstriction and inflammation of the airway, as well as stimulation of sensory nerves with neurokinin release, stimulating the release of the gel-forming mucin MUC5AC.[35,44] These findings are sustained by experimental evidence showing that it is not the type of exercise, but the ventilation demand and humidity of the inspired air, that are the main determinants of the occurrence and degree of bronchoconstriction.[45,46] Thus, the major trigger for bronchoconstriction in a vulnerable subject is either water loss during periods of high ventilation, or the addition of an osmotically active agent. Importantly, alterations in airway temperature developed during exercise, or other thermal factors, are thought to have only a minor effect on the amount of bronchoconstriction that occurs.[47]

Environmental factors and EIB

The environment, including exposure to temperature, humidity, aeroallergens, irritants, and pollution, can also influence EIB pathophysiology.[48] Depending on the sport practiced by the individual, the hyperosmolarity of their upper and lower airways can be caused by hyperpnea (i.e. runners) leading to bronchoconstriction, nasal congestion, rhinorrhea and impaired mucociliary function, as well as exposure to irritants, indoor and outdoor allergens, and environmental air pollutants.[49] Similarly, swimmers can experience nasal congestion, rhinorrhea, and bronchospasm secondary to inhaled chloramines derived from hypochlorite in pool water disinfectants. Divers may also develop congestion and rhinosinusitis secondary to barotrauma. On the other hand, boxers can develop increased nasal resistance, impaired secretion clearance, anosmia, and hyposmia as a result of repetitive nasal trauma. Finally, skiers and figure skaters may develop bronchospasm and rhinitis secondary to irritant effects of cold dry air or ultrafine particulates and NO_2 created by ice grooming equipment.[48] While no sex differences in the effects of these environmental exposures and effects have been studied, there are reported gender differences in sports preferences that may be linked to cultural norms.[50–52] Overall, more studies are needed to determine the contributions of the environment to the effects of exercise in the male and female lung.

Sex differences in EIB

Sex differences in response to exercise have clear implications for understanding specific adaptations to exercise for athletic performance and overall health. Unfortunately, there is still no clear consensus about whether EIB is more predominant and/or severe in males or females, because the majority of studies conducted to date have either not enrolled athletes of both sexes or failed to assess or report sex differences. We have summarized the outcomes of 23 studies reporting prevalence of EIB in different types of athletes when enrolling males and females and diagnosing EIB with the methods described in Figure 2 (Table 1). While only 1 study reported no significant differences between males and females,[53] 5 studies reported a male predominance,[54–58] 4 studies showed a female predominance,[36,59–61] and 13 studies did not assess or not reported sex differences.[62–74] As mentioned earlier, we

Table 1. Sex differences in EIB prevalence in studies involving male and female athletes.

Study population	Number of subjects enrolled	Diagnostic method(s)	Male/Female predominance	References
Elite athletes	329	Questionnaire	No difference	Lund *et al.*[53]
Elite cross-country skiers	18	EC	Male	Rundell *et al.* [54]
Boxers and swimmers	82	EVH	Male	Levai *et al.*[55]
High school student athletes	256	EC	Male	Hallstrand *et al*.[56]
High-competitive athletes	324	BT (dry powder mannitol or methacholine)	Male	Couto *et al.*[57]
Summer sports (high school and college athletes)	208	EC	Male	Becerril *et al.*[58]
Swimmers, winter athletes, endurance sports athletes	130	Questionnaire, EVH & BT	Female	Couillard *et al.*[59]
Athletes	798	BT and questionnaire	Female	Langdeau *et al.*[36]
Elite skiers and orienteers	402	Questionnaire	Female	Norqvist *et al.*[60]
Varsity sports collegiate athletes	144	EVH	Female	Parsons *et al.*[61]
Recreational athletes	180	EVH	Unknown/Not reported	Allen *et al.*[62]
Italian Olympic Delegation	659	EC & BT	Unknown/Not reported	Bonini *et al.*[63]
Swimmers and winter sport athletes	90	EVH & BT	Unknown/Not reported	Bougault *et al.*[64]
College athletes	80	EC	Unknown/Not reported	Burnett *et al.*[65]
College athletes	196	Questionnaire	Unknown/Not reported	Burnett *et al.*[66]
Ski-mountaineering athletes	31	EC	Unknown/Not reported	Durand *et al.*[67]
Paralympic athletes	44	EVH & BT	Unknown/Not reported	Osthoff *et al.*[68]
Cross-country skiers	36	EC	Unknown/Not reported	Pohjantähti *et al.*[69]
Elite athletes	107	EC	Unknown/Not reported	Sallaoui *et al.*[70]
Athletes	326	EC	Unknown/Not reported	Sallaoui *et al.*[71]
Elite athletes	107	EC	Unknown/Not reported	Sallaoui *et al.*[72]
Competitive swimmers and indoor athletes	54	EVH	Unknown/Not reported	Seys *et al.*[73]
Elite cross-country skiers	46	EVH and BT	Unknown/Not reported	Stenfors[74]

EC: exercise challenge; EVH: eucapnic voluntary hyperventilation; BT: bronchoprovocation test.

previously conducted a meta-analysis on this topic and found that atopic EIB is significantly more prevalent in male athletes than female athletes.[15] Thus, studies assessing sex differences in EIB should also consider additional intrinsic factors, such as atopy, allergic rhinitis, asthma, and lung anatomy, that can also influence EIB and athletic performance.[48,75,76]

Male and female intrinsic factors and EIB

There are well-characterized sex differences in the structure and function of the respiratory system that can impact responses during exercise.[77] Such differences can impact airway flow, lung volume and pressure, and the consequent higher work of breathing observed in women across a range of ventilations.[78] Women also have smaller airway diameter and lung volume, which results in lower peak expiratory flow and vital capacity.[79] This can predispose women, and particularly athletes, to develop expiratory flow limitation during exercise.[80,81]

Another factor to consider is that exercise can lower circulating hormone levels, specifically estrogen, in women of reproductive age.[82] While not studied in detail, this reduction in estrogen could potentially be associated with EIB in females, as it could mimic the physiological estrogen decline occurring around menses. In this regard, an estimated 33–52% of women with asthma have previously reported a premenstrual worsening of asthma symptoms, and an additional 22% have reported asthma that is worse during menses.[83] This phenomenon is known as perimenstrual or catamenial asthma, and it is characterized by an increased airway inflammation in the premenstrual period in some women with asthma.[83–88] Similarly, asthma symptoms can also present more frequently in the periovulatory phase in some women.[89,90] In female athletes with asthma, it has been found that the menstrual cycle phase can also determine the severity of EIB.[91–93] Specifically, females in the mid-luteal phase present with increased EIB severity and worsening of asthma symptoms and increased bronchodilator use than females in the follicular and menstrual phases.[91] This is consistent with reports indicating that lung function is generally worse during the late follicular phase, when estrogen levels are highest,[94] and stabilization of asthma symptoms in women using oral contraceptives that alleviate estrogen spikes.[95] Moreover, because mast cells, but not lymphocytes, macrophages, or other immune cells, express estrogen and progesterone receptors in human upper airways and nasal polyps, it has been hypothesized this region may be a major route for the involvement of sex hormones in airway inflammation.[96]

Although the mechanisms underlying the effects of the menstrual cycle on EIB and asthma have not been yet fully elucidated, several animal models of allergen sensitization and asthma have previously suggested a role of ovarian hormones in mediating lung inflammatory processes.[90,91,94,95,97–102] In an ovalbumin (OVA)-sensitized and OVA-challenged (OVA/OVA) mouse asthma model, eosinophils, lymphocytes, T-helper type 2 cytokines, and growth factors in bronchoalveolar lavage fluid (BALF) are higher in female than in male mice.[103] Accordingly, removal of ovaries prior to OVA sensitization significantly inhibits lung eosinophilia and BALF IL-5 levels. Moreover, removal of ovaries 8 days after the sensitization period induces a significant increase in BALF IL-5 levels.[104] When compared with females, males show less severe bronchial-bronchiolar inflammation and lower IL-4 levels in splenic cells, an effect that is reversed when males are castrated.[105] Overall, data from animal studies indicate that sex hormones can contribute to disease pathogenesis or serve as protective factors, depending on the disease involved.[10]

Regarding EIB, there are a variety of animal models that have helped elucidate the mechanisms by which hyperventilation results in airway obstruction and EIB.[106] These studies have helped elucidate contributions of airflow-induced bronchoconstriction, its stimulation by airway drying and inhibition by cooling stimuli, the resulting damage to the bronchial mucosa by hyperpnea with dry air, the role of the airway smooth muscle and airway epithelium, the biochemical mediators participating (including cysteinyl-leukotrienes and pro-inflammatory cytokines), as well as the airway and vascular responses to dehydration during EIB.[106–108] However, to our discernment, no studies have specifically addressed sex differences in EIB in animal models, nor assessed the roles of sex hormones EIB mechanisms.

Influence of atopy in asthma and EIB

As mentioned earlier, atopy is a personal and/or familial genetic predisposition, to become sensitized and produce IgE antibodies in response to ordinary allergen exposures, usually in childhood or adolescence.[109] Atopy is diagnosed by an IgE sensitization test, where IgE antibodies are determined in serum or by a skin prick test. Subjects with atopy can develop typical symptoms of asthma, eczema, or rhinoconjunctivitis, as well as EIB.[48,110] Epidemiological data show that in the United States, 56.3% of asthma cases can be attributable to atopy, and this percentage is greater among men than women.[12] In athletes, we previously found that atopy is also significantly more prevalent in males than females (19% vs. 14%, respectively, $P < 0.01$), as well as in athletes with EIB versus without EIB (53% vs. 41%, respectively, $P < 0.01$), when sex is not considered.[15] Regarding differences in male and female athletes, we found that the relationship between sex and atopy in EIB athletes was also statistically significant. In a combined sample of 374 healthy and atopic athletes and regular exercisers, atopic athletes were 2.36 times more likely to be male than female ($P < 0.0001$), whereas non-atopic athletes showed a 1:1 male to female ratio. We concluded that sex specific mechanisms, potentially mediated by sex hormones, contribute to the inflammatory and physiological changes triggered by exercise in athletes.[15]

Sex steroid hormones and EIB

Multiple studies, including work from us, have provided evidence indicating that estrogen (and progesterone) signaling affects virtually every cell of the immune system, and plays an important role in lung inflammation, airway mechanics, and asthma.[111–115] The influences of estrogen on immune cells favor allergic responses, promoting Th2 polarization, encouraging class switching of B cells to IgE production, and prompting mast cell and basophil degranulation.[116–123] Estrogens also play an important role in immune modulation, and contribute to the significantly higher incidence of autoimmune and inflammatory disease in women than men, as well as variations in chronic inflammatory disease symptoms during the menstrual cycle, pregnancy, and menopause.[124,125] Interestingly, progesterone favors the switch from Th0 to a Th2 cytokine profile in lymphocytes.[98] In the context of exercise, both female hormones also have potential effects on exercise capacity and performance by affecting substrate metabolism, cardiorespiratory function, thermoregulation, and the central and peripheral components of the respiratory control system.[20,21] However, because exercise can alter hormonal and ovulation profiles in women, the relationship between female sex hormones and EIB remains inconclusive. While it is estimated that approximately half of exercising women experience subtle menstrual disturbances, such as luteal phase deficiency and anovulation, and that one-third of exercising women may be amenorrheic,[126] many of these women go undiagnosed due to the asymptomatic nature of these disturbances.[127] The hormonal patterns observed in these amenorrheic athletes also display a decrease in GnRH pulses from the hypothalamus, which results in decreased pulsatile secretion of luteinizing hormone and follicle-stimulating hormone, resulting in lack of ovarian stimulation.[128] The available evidence also indicates that women who exercise frequently also have longer follicular phase which is characterized by low levels of estrogen. Thus, while the exact mechanisms linking hormones and EIB development in different groups of patients remain elusive, it is clear that the menstrual cycle phase is an important determinant of the severity of EIB in female athletes with mild atopic asthma.[91]

Regarding male hormones, the low predominance of men with asthma after puberty have led researchers to suggest anti-inflammatory roles for androgens, including testosterone.[129,130] Given its widespread expression in many cells and tissues, the androgen receptor has been implicated in a diverse range of biological actions, including inhibitory effects in T lymphocytes and other inflammatory cells.[131–133] Collectively, the available literature suggests that androgens exert anti-inflammatory actions in the lung, although the severity of asthma in men increases later in life when androgens levels decrease.[134–136] Overall, more research is needed to elucidate the roles of male sex hormones in lung inflammation, asthma, atopy, and potentially EIB.

Conclusions

The collective clinical, epidemiological, and experimental evidence indicates that asthma, atopy, and EIB are conditions that differentially affect men and women across the lifespan, and often present simultaneously in athletes and non-athletes. Although studies involving both sexes are limited, the current available knowledge suggests that a combination of anatomical, physiological, environmental, and hormonal factors can contribute to EIB and exercise-induced asthma in men and women (Figure 3). While atopic status has been linked to EIB in athletes of both

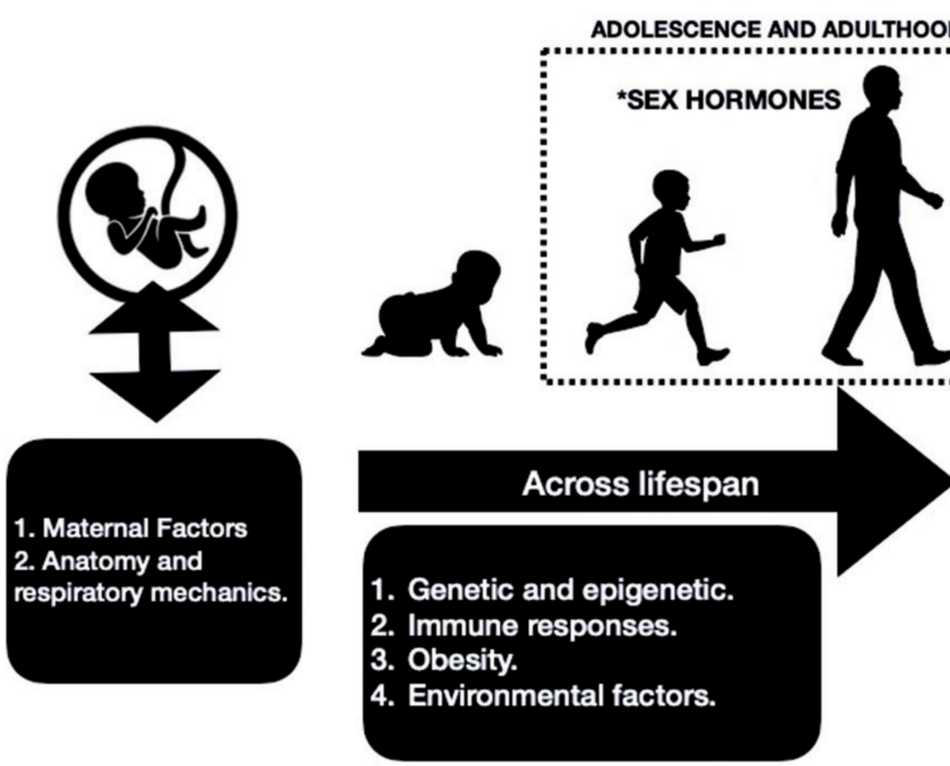

Figure 3. Factors affecting sex differences in asthma/EIB across the lifespan.[2–10]

sexes, a significantly higher rate of atopic EIB has been found in male athletes than females. In females, hormonal fluctuations and environmental exposures appear to influence EIB symptoms, although the mechanisms underlying these events remain unknown. Thus, it is imperative that more research incorporating sex as a biological variable is conducted to better understand sex-specific mechanisms of EIB in the context of asthma and atopy. Understanding these mechanisms will aid in the suture development of sex-specific therapeutics for athletes and individuals who exercise regularly.

AUTHORS' CONTRIBUTIONS

DRB and PS conceptualized the review. DRB reviewed the literature, extracted, and analyzed the data. DRB and PS wrote and revised the manuscript.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by NIH grant HL141618 (PS).

ORCID iDs

Daniel Enrique Rodriguez-Bauza https://orcid.org/0000-0002-5928-6598
Patricia Silveyra https://orcid.org/0000-0001-7083-8915

REFERENCES

1. Centers for Disease Control and Prevention. Most recent asthma data, 2020. Available from: www.cdc.gov/asthma/most_recent_data.htm [accesed March 19, 2021]
2. Keselman A, Heller N. Estrogen signaling modulates allergic inflammation and contributes to sex differences in asthma. *Front Immunol* 2015;**6**:568
3. Shah R, Newcomb DC. Sex bias in asthma prevalence and pathogenesis. *Front Immunol* 2018;**9**:2997
4. Zein JG, Erzurum SC. Asthma is different in women. *Curr Allergy Asthma Rep* 2015;**15**:28
5. Melgert BN, Ray A, Hylkema MN, Timens W, Postma DS. Are there reasons why adult asthma is more common in females? *Curr Allergy Asthma Rep* 2007;**7**:143–50
6. Redline S, Gold D. Challenges in interpreting gender differences in asthma. *Am J Respir Crit Care Med* 1994;**150**:1219–21
7. Schatz M, Camargo CA. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol* 2003;**91**:553–8
8. Naeem A, Silveyra P. Sex differences in paediatric and adult asthma. *Eur Med J* 2019;**4**:27–35
9. Fuentes N, Silveyra P. Endocrine regulation of lung disease and inflammation. *Exp Biol Med* (Maywood) 2018;**243**:1313–22. DOI: 10.1177/1535370218816653
10. Carey MA, Card JW, Voltz JW, Arbes SJ Jr, Germolec DR, Korach KS, Zeldin DC. It's all about sex: gender, lung development and lung disease. *Trends Endocrinol Metab* 2007;**18**:308–13
11. Di Cicco M, D'Elios S, Peroni DG, Comberiati P. The role of atopy in asthma development and persistence. *Curr Opin Allergy Clin Immunol* 2020;**20**:131–7
12. Arbes SJ, Gergen PJ, Vaughn B, Zeldin DC. Asthma cases attributable to atopy: results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2007;**120**:1139–45
13. Didier A, Mazieres J, Kouevijin G, Tetu L, Rivière D. [Sport and atopy]. *Rev Mal Respir* 2003;**20**:727–34
14. Helenius IJ, Tikkanen HO, Sarna S, Haahtela T. Asthma and increased bronchial responsiveness in elite athletes: atopy and sport event as risk factors. *J Allergy Clin Immunol* 1998;**101**:646–52
15. Rodriguez BD. Silveyra P. Sex differences in exercise induced bronchoconstriction in athletes: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2020;**17**:7270. doi: 10.3390/ijerph17197270
16. Storms WW. Asthma associated with exercise. *Immunol Allergy Clin North Am* 2005;**25**:31–43
17. Molis MA, Molis WE. Exercise-induced bronchospasm. *Sports Health* 2010;**2**:311–7
18. Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, Storms WW, Weiler JM, Cheek FM, Wilson KC, Anderson SD. Bronchoconstriction ATSSoE-i. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013;**187**:1016–27
19. Weiler JM, Bonini S, Coifman R, Craig T, Delgado L, Capão-Filipe M, Passali D, Randolph C, Storms W, Ad Hoc Committee of Sports Medicine Committee of American Academy of Allergy AtI. American Academy of Allergy, Asthma & Immunology Work Group report: exercise-induced asthma. *J Allergy Clin Immunol* 2007;**119**:1349–58
20. Joseph V, Behan M, Kinkead R. Sex, hormones, and stress: how they impact development and function of the carotid bodies and related reflexes. *Respir Physiol Neurobiol* 2013;**185**:75–86
21. Constantini NW, Dubnov G, Lebrun CM. The menstrual cycle and sport performance. *Clin Sports Med* 2005;**24**:e51–82, xiii–xiv
22. Kukafka DS, Lang DM, Porter S, Rogers J, Ciccolella D, Polansky M, D'Alonzo GE Jr. Exercise-induced bronchospasm in high school athletes via a free running test: incidence and epidemiology. *Chest* 1998;**114**:1613–22
23. Ng'ang'a LW, Odhiambo JA, Mungai MW, Gicheha CM, Nderitu P, Maingi B, Macklem PT, Becklake MR. Prevalence of exercise induced bronchospasm in Kenyan school children: an urban-rural comparison. *Thorax* 1998;**53**:919–26
24. Sonna LA, Angel KC, Sharp MA, Knapik JJ, Patton JF, Lilly CM. The prevalence of exercise-induced bronchospasm among US Army recruits and its effects on physical performance. *Chest* 2001;**119**:1676–84. doi: 10.1378/chest.119.6.1676
25. Caillaud D, Horo K, Baiz N, Banerjee S, Charpin D, Lavaud F, de Blay F, Raherison C, Annesi-Maesano I. Exercise-induced bronchospasm related to different phenotypes of rhinitis without asthma in primary schoolchildren: the French Six Cities Study. *Clin Exp Allergy* 2014;**44**:858–66
26. Kuti BP, Kuti DK, Omole KO, Mohammed LO, Ologun BG, Oso BI. Prevalence and factors associated with exercise-induced bronchospasm among rural school children in Ilesa, Nigeria. *Niger Postgrad Med J* 2017;**24**:107–13
27. Parsons JP, Kaeding C, Phillips G, Jarjoura D, Wadley G, Mastronarde JG. Prevalence of exercise-induced bronchospasm in a cohort of varsity college athletes. *Med Sci Sports Exerc* 2007;**39**:1487–92
28. Weiler JM, Anderson SD, Randolph C, Bonini S, Craig TJ, Pearlman DS, Rundell KW, Silvers WS, Storms WW, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, Lang DM, Nicklas RA, Oppenheimer J, Portnoy JM, Schuller DE, Spector SL, Tilles SA, Wallace D, Henderson W, Schwartz L, Kaufman D, Nsouli T, Shieken L, Rosario N; American Academy of Allergy AtaI, American College of Allergy AtaI, Joint Council of Allergy AtaI. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. *Ann Allergy Asthma Immunol* 2010;**105**: S1–47

29. Northoff H, Symons S, Zieker D, Schaible EV, Schäfer K, Thoma S, Löffler M, Abbasi A, Simon P, Niess AM, Fehrenbach E. Gender- and menstrual phase dependent regulation of inflammatory gene expression in response to aerobic exercise. *Exerc Immunol Rev* 2008;**14**:86–103
30. Holzer K, Anderson SD, Douglass J. Exercise in elite summer athletes: challenges for diagnosis. *J Allergy Clin Immunol* 2002;**110**:374–80
31. Holzer K, Brukner P. Screening of athletes for exercise-induced bronchoconstriction. *Clin J Sport Med* 2004;**14**:134–8
32. Anderson SD, Argyros GJ, Magnussen H, Holzer K. Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. *Br J Sports Med* 2001;**35**:344–7
33. Brannan JD, Porsbjerg C. Testing for exercise-induced bronchoconstriction. *Immunol Allergy Clin North Am* 2018;**38**:215–29
34. Brannan JD, Anderson SD, Perry CP, Freed-Martens R, Lassig AR, Charlton B. The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline. *Respir Res* 2005;**6**:144
35. Weiler JM, Brannan JD, Randolph CC, Hallstrand TS, Parsons J, Silvers W, Storms W, Zeiger J, Bernstein DI, Blessing-Moore J, Greenhawt M, Khan D, Lang D, Nicklas RA, Oppenheimer J, Portnoy JM, Schuller DE, Tilles SA, Wallace D. Exercise-induced bronchoconstriction update-2016. *J Allergy Clin Immunol* 2016;**138**:1292–5.
36. Langdeau JB, Day A, Turcotte H, Boulet LP. Gender differences in the prevalence of airway hyperresponsiveness and asthma in athletes. *Respir Med* 2009;**103**:401–6
37. McFadden ER, Ingram RH. Exercise-induced asthma: observations on the initiating stimulus. *N Engl J Med* 1979;**301**:763–9
38. Anderson SD, Schoeffel RE, Black JL, Daviskas E. Airway cooling as the stimulus to exercise-induced asthma – a re-evaluation. *Eur J Respir Dis* 1985;**67**:20–30
39. Krafczyk MA, Asplund CA. Exercise-induced bronchoconstriction: diagnosis and management. *Am Fam Physician* 2011;**84**:427–34
40. McFadden ER. Hypothesis: exercise-induced asthma as a vascular phenomenon. *Lancet* 1990;**335**:880–3
41. Hallstrand TS, Altemeier WA, Aitken ML, Henderson WR. Role of cells and mediators in exercise-induced bronchoconstriction. *Immunol Allergy Clin North Am* 2013;**33**:313–28, vii
42. Brannan JD, Gulliksson M, Anderson SD, Chew N, Kumlin M. Evidence of mast cell activation and leukotriene release after mannitol inhalation. *Eur Respir J* 2003;**22**:491–6
43. Kippelen P, Anderson SD, Hallstrand TS. Mechanisms and biomarkers of exercise-induced bronchoconstriction. *Immunol Allergy Clin North Am* 2018;**38**:165–82
44. Hallstrand TS, Debley JS, Farin FM, Henderson WR. Role of MUC5AC in the pathogenesis of exercise-induced bronchoconstriction. *J Allergy Clin Immunol* 2007;**119**:1092–8
45. Deal EC, McFadden ER, Ingram RH, Strauss RH, Jaeger JJ. Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol Respir Environ Exerc Physiol* 1979;**46**:467–75
46. Kallings LV, Emtner M, Bäcklund L. Exercise-induced bronchoconstriction in adults with asthma–comparison between running and cycling and between cycling at different air conditions. *Ups J Med Sci* 1999;**104**:191–8
47. Evans TM, Rundell KW, Beck KC, Levine AM, Baumann JM. Cold air inhalation does not affect the severity of EIB after exercise or eucapnic voluntary hyperventilation. *Med Sci Sports Exerc* 2005;**37**:544–9
48. Sacha JJ, Quinn JM. The environment, the airway, and the athlete. *Ann Allergy Asthma Immunol* 2011;**106**:81–7; quiz 88
49. Schwartz LB, Delgado L, Craig T, Bonini S, Carlsen KH, Casale TB, Del Giacco S, Drobnic F, van Wijk RG, Ferrer M, Haahtela T, Henderson WR, Israel E, Lötvall J, Moreira A, Papadopoulos NG, Randolph CC, Romano A, Weiler JM. Exercise-induced hypersensitivity syndromes in recreational and competitive athletes: a PRACTALL consensus report (what the general practitioner should know about sports and allergy). *Allergy* 2008;**63**:953–61
50. Peral-Suárez Á, Cuadrado-Soto E, Perea JM, Navia B, López-Sobaler AM, Ortega RM. Physical activity practice and sports preferences in a group of Spanish schoolchildren depending on sex and parental care: a gender perspective. *BMC Pediatr* 2020;**20**:337
51. Tsai LT, Lo FE, Yang CC, Keller JJ, Lyu SY. Gender differences in recreational sports participation among Taiwanese adults. *Int J Environ Res Public Health* 2015;**12**:829–40
52. Butt J, Weinberg RS, Breckon JD, Claytor RP. Adolescent physical activity participation and motivational determinants across gender, age, and race. *J Phys Act Health* 2011;**8**:1074–83
53. Lund T, Pedersen L, Larsson B, Backer V. Prevalence of asthma-like symptoms, asthma and its treatment in elite athletes. *Scand J Med Sci Sports* 2009;**19**:174–8
54. Rundell KW, Spiering BA, Judelson DA, Wilson MH. Bronchoconstriction during cross-country skiing: is there really a refractory period? *Med Sci Sports Exerc* 2003;**35**:18–26
55. Levai IK, Hull JH, Loosemore M, Greenwell J, Whyte G, Dickinson JW. Environmental influence on the prevalence and pattern of airway dysfunction in elite athletes. *Respirology* 2016;**21**:1391–6
56. Hallstrand TS, Curtis JR, Koepsell TD, Martin DP, Schoene RB, Sullivan SD, Yorioka GN, Aitken ML. Effectiveness of screening examinations to detect unrecognized exercise-induced bronchoconstriction. *J Pediatr* 2002;**141**:343–8
57. Couto M, Stang J, Horta L, Stensrud T, Severo M, Mowinckel P, Silva D, Delgado L, Moreira A, Carlsen KH. Two distinct phenotypes of asthma in elite athletes identified by latent class analysis. *J Asthma* 2015;**52**:897–904
58. Becerril-Ángeles M, Vargas MH, Hernández-Pérez L, Rivera-Istepan NJ, Pérez-Hidalgo RI, Ortega-González AG, Rubio-Domínguez S, Rodríguez-Gutiérrez MC, Gaxiola-Cortés R, Dosal-Ulloa R, Gochicoa-Rangel LG. Prevalence and characteristics of exercise-induced bronchoconstriction in high school and college athletes at 2,240 m altitude. *Rev Invest Clin* 2017;**69**:20–7
59. Couillard S, Bougault V, Turmel J, Boulet LP. Perception of bronchoconstriction following methacholine and eucapnic voluntary hyperpnea challenges in elite athletes. *Chest* 2014;**145**:794–802
60. Norqvist J, Eriksson L, Söderström L, Lindberg A, Stenfors N. Self-reported physician-diagnosed asthma among Swedish adolescent, adult and former elite endurance athletes. *J Asthma* 2015;**52**:1046–53
61. Parsons JP, Cosmar D, Phillips G, Kaeding C, Best TM, Mastronarde JG. Screening for exercise-induced bronchoconstriction in college athletes. *J Asthma* 2012;**49**:153–7
62. Allen H, Hull JH, Backhouse SH, De Carné T, Dimitriou L, Price OJ. The Allergy Questionnaire for Athletes provides value in ruling-out exercise-induced bronchoconstriction. *Allergy* 2019;**74**:1794–6
63. Bonini M, Gramiccioni C, Fioretti D, Ruckert B, Rinaldi M, Akdis C, Todaro A, Palange P, Carlsen KH, Pelliccia A, Rasi G, Bonini S. Asthma, allergy and the Olympics: a 12-year survey in elite athletes. *Curr Opin Allergy Clin Immunol* 2015;**15**:184–92
64. Bougault V, Turmel J, Boulet LP. Bronchial challenges and respiratory symptoms in elite swimmers and winter sport athletes: airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010;**138**:31s–7s
65. Burnett DM, Burns S, Merritt S, Wick J, Sharpe M. Prevalence of exercise-induced bronchoconstriction measured by standardized testing in healthy college athletes. *Respir Care* 2016;61:571–6. doi: 10.4187/respcare.04493. Epub 2016 Feb 9
66. Burnett DM, Vardiman JP, Deckert JA, Ward JL, Sharpe MR. Perception of exercise-induced bronchoconstriction in college athletes. *Respir Care* 2016;**61**:897–901
67. Durand F, Kippelen P, Ceugniet F, Gomez VR, Desnot P, Poulain M, Préfaut C. Undiagnosed exercise-induced bronchoconstriction in ski-mountaineers. *Int J Sports Med* 2005;**26**:233–7
68. Osthoff M, Michel F, Strupler M, Miedinger D, Taegtmeyer AB, Leuppi JD, Perret C. Bronchial hyperresponsiveness testing in athletes of the Swiss Paralympic team. *BMC Sports Sci Med Rehabil* 2013;**5**:7
69. Pohjantähti H, Laitinen J, Parkkari J. Exercise-induced bronchospasm among healthy elite cross country skiers and non-athletic students. *Scand J Med Sci Sports* 2005;**15**:324–8

70. Sallaoui R, Chamari K, Chtara M, Alaranta A, Manai Y, Ghedira H, Amri M. Asthma in Tunisian elite athletes. *Int J Sports Med* 2007;**28**:571–5
71. Sallaoui R, Chamari K, Mossa A, Tabka Z, Chtara M, Feki Y, Amri M. Exercise-induced bronchoconstriction and atopy in Tunisian athletes. *BMC Pulm Med* 2009;**9**:8
72. Sallaoui R, Zendah I, Ghedira H, Belhaouz M, Ghrairi M, Amri M. Exercise-induced bronchoconstriction in Tunisian elite athletes is underdiagnosed. *Open Access J Sports Med* 2011;**2**:41–6
73. Seys SF, Hox V, Van Gerven L, Dilissen E, Marijsse G, Peeters E, Dekimpe E, Kasran A, Aertgeerts S, Troosters T, Vanbelle V, Peers K, Ceuppens JL, Hellings PW, Dupont LJ, Bullens DM. Damage-associated molecular pattern and innate cytokine release in the airways of competitive swimmers. *Allergy* 2015;**70**:187–94
74. Stenfors N. Self-reported symptoms and bronchial hyperresponsiveness in elite cross-country skiers. *Respir Med* 2010;**104**:1760–3
75. Krafczyk MA, Bautista FD. When an athlete can't catch his breath. *J Fam Pract* 2009;**58**:454–9
76. Rundell KW, Im J, Mayers LB, Wilber RL, Szmedra L, Schmitz HR. Self-reported symptoms and exercise-induced asthma in the elite athlete. *Med Sci Sports Exerc* 2001;**33**:208–13
77. LoMauro A, Aliverti A. Sex differences in respiratory function. *Breathe* 2018;**14**:131–40
78. Harms CA, Rosenkranz S. Sex differences in pulmonary function during exercise. *Med Sci Sports Exerc* 2008;**40**:664–8
79. McClaran SR, Harms CA, Pegelow DF, Dempsey JA. Smaller lungs in women affect exercise hyperpnea. *J Appl Physiol (1985)* 1998;**84**:1872–81
80. Guenette JA, Witt JD, McKenzie DC, Road JD, Sheel AW. Respiratory mechanics during exercise in endurance-trained men and women. *J Physiol* 2007;**581**:1309–22
81. Sheel AW, Guenette JA. Mechanics of breathing during exercise in men and women: sex versus body size differences? *Exerc Sport Sci Rev* 2008;**36**:128–34
82. Kossman DA, Williams NI, Domchek SM, Kurzer MS, Stopfer JE, Schmitz KH. Exercise lowers estrogen and progesterone levels in premenopausal women at high risk of breast cancer. *J Appl Physiol (1985)* 2011;**111**:1687–93
83. Chandler MH, Schuldheisz S, Phillips BA, Muse KN. Premenstrual asthma: the effect of estrogen on symptoms, pulmonary function, and beta 2-receptors. *Pharmacotherapy* 1997;**17**:224–34
84. Skoczyński S, Semik-Orzech A, Szanecki W, Majewski M, Koodziejczyk K, Sozańska E, Witek A, Pierzchaa W. Perimenstrual asthma as a gynecological and pulmonological clinical problem. *Adv Clin Exp Med* 2014;**23**:665–8
85. Oguzulgen IK, Turktas H, Erbas D. Airway inflammation in premenstrual asthma. *J Asthma* 2002;**39**:517–22
86. Eliasson O, Scherzer HH, DeGraff AC. Morbidity in asthma in relation to the menstrual cycle. *J Allergy Clin Immunol* 1986;**77**:87–94
87. Gibbs CJ, Coutts II, Lock R, Finnegan OC, White RJ. Premenstrual exacerbation of asthma. *Thorax* 1984;**39**:833–6
88. Wulfsohn NL, Politzer WM. Bronchial asthma during menses and pregnancy. *S Afr Med J* 1964;**38**:173
89. Brenner BE, Holmes TM, Mazal B, Camargo CA. Relation between phase of the menstrual cycle and asthma presentations in the emergency department. *Thorax* 2005;**60**:806–9
90. Skobeloff EM, Spivey WH, Silverman R, Eskin BA, Harchelroad F, Alessi TV. The effect of the menstrual cycle on asthma presentations in the emergency department. *Arch Intern Med* 1996;**156**:1837–40
91. Stanford KI, Mickleborough TD, Ray S, Lindley MR, Koceja DM, Stager JM. Influence of menstrual cycle phase on pulmonary function in asthmatic athletes. *Eur J Appl Physiol* 2006;**96**:703–10
92. Statham G. Understanding the effects of the menstrual cycle on training and performance in elite athletes: a preliminary study. *Prog Brain Res* 2020;**253**:25–58
93. Matteis M, Polverino F, Spaziano G, Roviezzo F, Santoriello C, Sullo N, Bucci MR, Rossi F, Polverino M, Owen CA, D'Agostino B. Effects of sex hormones on bronchial reactivity during the menstrual cycle. *BMC Pulm Med* 2014;**14**:108
94. Pauli BD, Reid RL, Munt PW, Wigle RD, Forkert L. Influence of the menstrual cycle on airway function in asthmatic and normal subjects. *Am Rev Respir Dis* 1989;**140**:358–62
95. Tan KS, McFarlane LC, Lipworth BJ. Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill. *Am J Respir Crit Care Med* 1997;**155**:1273–7
96. Zhao XJ, McKerr G, Dong Z, Higgins CA, Carson J, Yang ZQ, Hannigan BM. Expression of oestrogen and progesterone receptors by mast cells alone, but not lymphocytes, macrophages or other immune cells in human upper airways. *Thorax* 2001;**56**:205–11
97. Agarwal SK, Marshall GD Jr. Perimenstrual alterations in type-1/type-2 cytokine balance of normal women. *Ann Allergy Asthma Immunol* 1999;**83**:222–8
98. Balzano G, Fuschillo S, Melillo G, Bonini S. Asthma and sex hormones. *Allergy* 2001;**56**:13–20
99. Hanley SP. Asthma variation with menstruation. *Br J Dis Chest* 1981;**75**:306–8
100. Mirdal GM, Petersson B, Weeke B, Vibits A. Asthma and menstruation: the relationship between psychological and bronchial hyperreactivity. *Br J Med Psychol* 1998;**71**:47–55.
101. Oertelt-Prigione S. Immunology and the menstrual cycle. *Autoimmun Rev* 2012;**11**:A486–92
102. Tam A, Morrish D, Wadsworth S, Dorscheid D, Man SF, Sin DD. The role of female hormones on lung function in chronic lung diseases. *BMC Womens Health* 2011;**11**:24
103. Takeda M, Tanabe M, Ito W, Ueki S, Konnno Y, Chihara M, Itoga M, Kobayashi Y, Moritoki Y, Kayaba H, Chihara J. Gender difference in allergic airway remodelling and immunoglobulin production in mouse model of asthma. *Respirology* 2013;**18**:797–806
104. Riffo-Vasquez Y, Ligeiro de Oliveira AP, Page CP, Spina D, Tavares-de-Lima W. Role of sex hormones in allergic inflammation in mice. *Clin Exp Allergy* 2007;**37**:459–70
105. Hayashi T, Adachi Y, Hasegawa K, Morimoto M. Less sensitivity for late airway inflammation in males than females in BALB/c mice. *Scand J Immunol* 2003;**57**:562–7
106. Freed AN. Models and mechanisms of exercise-induced asthma. *Eur Respir J* 1995;**8**:1770–85
107. Kodesh E, Zaldivar F, Schwindt C, Tran P, Yu A, Camilon M, Nance DM, Leu SY, Cooper D, Adams GR. A rat model of exercise-induced asthma: a nonspecific response to a specific immunogen. *Am J Physiol Regul Integr Comp Physiol* 2011;**300**:R917–24
108. Ueno H, Koya T, Takeuchi H, Tsukioka K, Saito A, Kimura Y, Hayashi M, Watanabe S, Hasegawa T, Arakawa M, Kikuchi T. Cysteinyl leukotriene synthesis via phospholipase A2 group IV mediates exercise-induced bronchoconstriction and airway remodeling. *Am J Respir Cell Mol Biol*. Epub ahead of print 2020
109. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;**113**:832–6
110. Toskala E, Kennedy DW. Asthma risk factors. *Int Forum Allergy Rhinol* 2015;**5 Suppl 1**:S11–6
111. Fuentes N, Nicoleau M, Cabello N, Montes D, Zomorodi N, Chroneos ZC, Silveyra P. 17b-estradiol affects lung function and inflammation following ozone exposure in a sex-specific manner. *Am J Physiol Lung Cell Mol Physiol*. Epub ahead of print 2019
112. Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. *Adv Protein Chem Struct Biol* 2019;**116**:135–70
113. Yung JA, Fuseini H, Newcomb DC. Hormones, sex, and asthma. *Ann Allergy Asthma Immunol* 2018;**120**:488–94
114. Bonds RS, Midoro-Horiuti T. Estrogen effects in allergy and asthma. *Curr Opin Allergy Clin Immunol* 2013;**13**:92–9
115. Zierau O, Zenclussen AC, Jensen F. Role of female sex hormones, estradiol and progesterone, in mast cell behavior. *Front Immunol* 2012;**3**:169

116. Brabin L. Interactions of the female hormonal environment, susceptibility to viral infections, and disease progression. *AIDS Patient Care STDS* 2002;**16**:211–21
117. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008;**63**:1418–27
118. Cunningham M, Gilkeson G. Estrogen receptors in immunity and autoimmunity. *Clin Rev Allergy Immunol* 2011;**40**:66–73
119. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. *Nat Rev Immunol* 2008;**8**:737–44
120. Kovats S, Carreras E. Regulation of dendritic cell differentiation and function by estrogen receptor ligands. *Cell Immunol* 2008;**252**:81–90
121. Kovats S. Estrogen receptors regulate innate immune cells and signaling pathways. *Cell Immunol* 2015;**294**:63–9
122. Leffler J, Stumbles PA, Strickland DH. Immunological processes driving IgE sensitisation and disease development in males and females. *Int J Mol Sci* 2018;**19**:1554. doi: 10.3390/ijms19061554
123. Marriott I, Huet-Hudson YM. Sexual dimorphism in innate immune responses to infectious organisms. *Immunol Res* 2006;**34**:177–92
124. Straub RH. The complex role of estrogens in inflammation. *Endocr Rev* 2007;**28**:521–74
125. Sternberg EM. Neuroendocrine regulation of autoimmune/inflammatory disease. *J Endocrinol* 2001;**169**:429–35
126. De Souza MJ, Toombs RJ, Scheid JL, O'Donnell E, West SL, Williams NI. High prevalence of subtle and severe menstrual disturbances in exercising women: confirmation using daily hormone measures. *Hum Reprod* 2010;**25**:491–503
127. De SM, Miller BE, Loucks AB, Luciano AA, Pescatello LS, Campbell CG, Lasley BL. High frequency of luteal phase deficiency and anovulation in recreational women runners: blunted elevation in follicle-stimulating hormone observed during luteal-follicular transition. *J Clin Endocrinol Metab* 1998;**83**:4220–32
128. Warren MP, Goodman LR. Exercise-induced endocrine pathologies. *J Endocrinol Invest* 2003;**26**:873–8
129. Zannolli R, Morgese G. Does puberty interfere with asthma? *Med Hypotheses* 1997;**48**:27–32
130. Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. *BMJ* 1992;**304**:873–5
131. Davey RA, Grossmann M. Androgen receptor structure, function and biology: from bench to bedside. *Clin Biochem Rev* 2016;**37**:3–15
132. Araneo BA, Dowell T, Diegel M, Daynes RA. Dihydrotestosterone exerts a depressive influence on the production of interleukin-4 (IL-4), IL-5, and gamma-interferon, but not IL-2 by activated murine T cells. *Blood* 1991;**78**:688–99
133. Liva SM, Voskuhl RR. Testosterone acts directly on CD4+ T lymphocytes to increase IL-10 production. *J Immunol* 2001;**167**:2060–7
134. Wulfsohn NL, Politzer WM, Henrico JS. Testosterone therapy in bronchial asthma. *S Afr Med J* 1964;**38**:170–2
135. Newcomb DC, Peebles RS Jr. Th17-mediated inflammation in asthma. *Curr Opin Immunol* 2013;**25**:755–60
136. Canguven O, Albayrak S. Do low testosterone levels contribute to the pathogenesis of asthma? *Med Hypotheses* 2011;**76**:585–8