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Review

Sex Differences in Exercise Induced Bronchoconstriction in Athletes: A Systematic Review and Meta-Analysis

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Abstract: Exercise induced bronchoconstriction (EIB) is a common complication of athletes and individuals who exercise regularly. It is estimated that about 90% of patients with underlying asthma experience EIB. Sex differences in the prevalence of asthma have been widely reported, with higher rates in boys vs. girls before puberty, and higher rates in women than men after puberty. Because atopy has been reported to occur at higher rates in athletes than in non-athletes, in this study we investigated sex differences in EIB and atopy in athletes. A systematic literature review identified 60 studies evaluating EIB and/or atopy in post-pubertal adult athletes (n=7501). Collectively, these studies reported: 1) a 23% prevalence of EIB in athletes; 2) a higher prevalence of atopy in male athletes vs. females; 3) a higher prevalence of atopy in athletes with EIB; and 4) a significantly higher rate of atopic EIB in male vs. female athletes. Our analysis indicates that the physiological changes that occur during exercise may differentially affect male and female athletes, and suggest an interaction between male sex, exercise, and atopic status in the course of EIB. Understanding these sex differences is important to provide personalized management plans to athletes with underlying asthma and/or atopy.

Keywords: inflammation; atopy; exercise induced asthma; exercise induced bronchoconstriction; sex differences

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1. Introduction

Asthma is one of the most common chronic non-communicable diseases of the airways, affecting about 339 million people worldwide [1]. The global prevalence of self-reported and physician-diagnosed asthma in adults is 4.3% (95% CI 4.2–4.4), with wide variation among countries [2]. Asthma is generally characterized by airway smooth muscle constriction (bronchospasm), excessive inflammation of the airway, and increased mucus production, although it presents in a variety of phenotypes and endotypes, ranging to mild and intermittent to severe and uncontrolled [3]. The diagnosis of asthma is determined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation [4, 5].

Asthma is a heterogeneous disease, usually characterized by chronic inflammation. The clinical course asthma is influenced by several factors, including genetics [6], environmental and occupational exposures [7], sex and gender [8], and hormones [9]. Atopy, defined as the tendency to develop a heightened immune response to allergens, is also frequently associated with asthma [10]. Worldwide, 80% of childhood asthma and over 50% of adult asthma has been reported to be allergic [11]. In the United States, 56.3% of asthma cases have been attributed to atopy, a percentage that is greater among male than female patients [12].

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Exercise and physical exertion are some of the most common triggers of bronchospasm in patients with chronic asthma [13, 14]. Bronchial hyperreactivity, a basic feature of bronchial asthma, occurs more often in athletes than non-athletes, especially in swimmers and winter sports athletes [15, 16]. Exercise-induced respiratory symptoms usually involve acute narrowing of the airways that occurs during or after exercise, and include exercise-induced bronchoconstriction (EIB) [17]. EIB is the acute (transient and reversible) airway narrowing that occurs during or after exercise, and can be observed in both patients who have or do not have chronic asthma [14].

While EIB is defined as the acute onset of bronchoconstriction occurring during or immediately after exercise, the term is often used to describe episodic bronchoconstriction that occurs following exercise. However, this wording could be misleading, since exercise is not an independent risk factor for asthma, but rather a trigger of bronchoconstriction in patients with underlying asthma [18]. Although EIB has been estimated to occur in up to 90% of patients with underlying asthma, it also occurs in subjects with no prior history of asthma and no symptoms outside exercise [19]. Similarly, there is a subset of patients who have only exercise-induced asthma, but not chronic daily asthma [18]. Overall, while the epidemiology of asthma has been widely reported and studied worldwide, the epidemiology of exercise-induced asthma and EIB has not been well described.

Sex and gender differences in the incidence, prevalence, and severity of lung diseases have been noted for years [20]. The recent implementation of regulations and policies encouraging the incorporation of sex as a biological variable in research studies has permitted the identification and characterization of sex-specific mechanisms of lung diseases, including asthma, across the lifespan. Among children, the prevalence of asthma is higher in boys than in girls [21]. However, after puberty, the prevalence is about 20% higher in women than men, indicating a potential contribution of sex hormones [22]. While sex and gender differences in the response to exercise have not been established, they have clear implications for understanding gender specific adaptations to exercise for athletic performance and overall health [23].

Although asthma has been widely reported to be more prevalent and severe in adult women than adult men [21, 22], very few studies to date have addressed sex differences in EIB and/or the overall effects of exercise in male and female patients with asthma. Minute ventilation, defined as the volume of air inhaled or exhaled from a person's lungs per minute, rises with exercise [14]. Thus, EIB likely results from changes in airway physiology triggered by the large volume of relatively cool, dry air inhaled during vigorous activity [24, 25]. This is supported by several research findings concluding that the main determinant of the occurrence and degree of bronchoconstriction is not the type of exercise, but rather the ventilation demand and humidity of the inspired air during exercise [26, 27]. Here, we have conceptualized EIB as the acute onset of bronchoconstriction occurring during, or immediately after exercise, independently of a subject’s underlying asthma. This concept is an accurate reflection of the disease’s underlying pathophysiology. The purpose of this review was to examine the available literature on sex and gender differences in EIB in athletes and recreationally active individuals, outlining epidemiological data and results from clinical studies. We identified studies conducted in adult athletes and determined the prevalence of EIB, as well as the relationship between asthma, EIB, and atopy in male and female athletes.

2. Materials and Methods

2.1. Literature search

2.1.1. Databases and key terms searched

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The literature search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [28]. Studies were identified by searching PubMed/MEDLINE Complete, PubMed Central, and Google Scholar, up to July 2020. Search terms, phrases, and Medical Subject Headings (MeSH) were selected based on the purpose of the review and inclusion criteria. We used the search parameters: [('exercise' OR 'athlete') AND ('gender' OR 'sex') AND ('asthma' OR 'bronchoconstriction') AND ('atopy').

2.1.2. Inclusion criteria

The literature search was limited to human studies that were research-data based and published in only English language. Studies were selected if research study subjects were 12 years old and older, and athletes or recreational athletes training for ≥ 2 days/week or 4 h/week in aerobic activities. Selected subject's training conditions were water sports (e.g. swimming, water polo), winter sports (e.g. cross-country skiing, biathlon, skeleton, alpine skiing and ski cross), and other sports (including but not limited to running, speed skating, curling, handball, judo, triathlon, football, cycling, beach volley, rowing, athletics, sailing, badminton, canoeing, curling, equestrian, taekwondo, auto-racing, billiards, paragliding, rugby, tennis, roller hockey, kickboxing, fencing, basketball or golf).

2.1.3. Search process and study selection

The literature search was conducted using both author's university library websites by entering search terms in the databases. Records were de-duplicated using the built-in mechanisms of the university library services, and further completed manually. Articles were then assessed by their titles and abstracts for inclusion. Final selections were determined after full reading of articles. Each article was appraised based on the following five criteria: 1) relevance of the sampling strategy to address the research question, 2) representation of the sample on the target population, 3) appropriateness of the measurements, 4) risk of nonresponse bias, and 5) suitability of statistical analysis to answer the research question.

2.2. Data extraction and analysis

The following information was extracted from the studies: the first author of the study, the year of publication, the country of the study conducted, the purpose of the study, data on sample size, details of the intervention, study quality, and measured outcomes. Main outcomes included EIB prevalence through questionnaire and/or pulmonary function testing (PFT). In addition, atopic status, and self-reporting exercise-induced asthma-like symptoms in female (F) and male (M) athletes were extracted in all studies were these variables were reported. Atopy was defined as skin test reactivity (skin prick test result) and EIB was defined as a decrease of at least 15% in forced expiratory volume in one second (FEV1) or medical diagnosis of EIB.

3. Results

A flow chart of the literature search is shown in Figure 1. The search string returned 1456 potentially relevant article citations. After systematically reviewing all the abstracts, 776 irrelevant studies and 508 duplicate papers were removed. Two independent investigators screened the remaining 172 full-text studies for eligibility, and found that 35% of articles (60 studies including 7501 subjects; age range 12-67 years) met the inclusion criteria. These were categorized according to whether they reported sex differences in measured outcomes, and/or included male and female participants in the research design (Figure 2).

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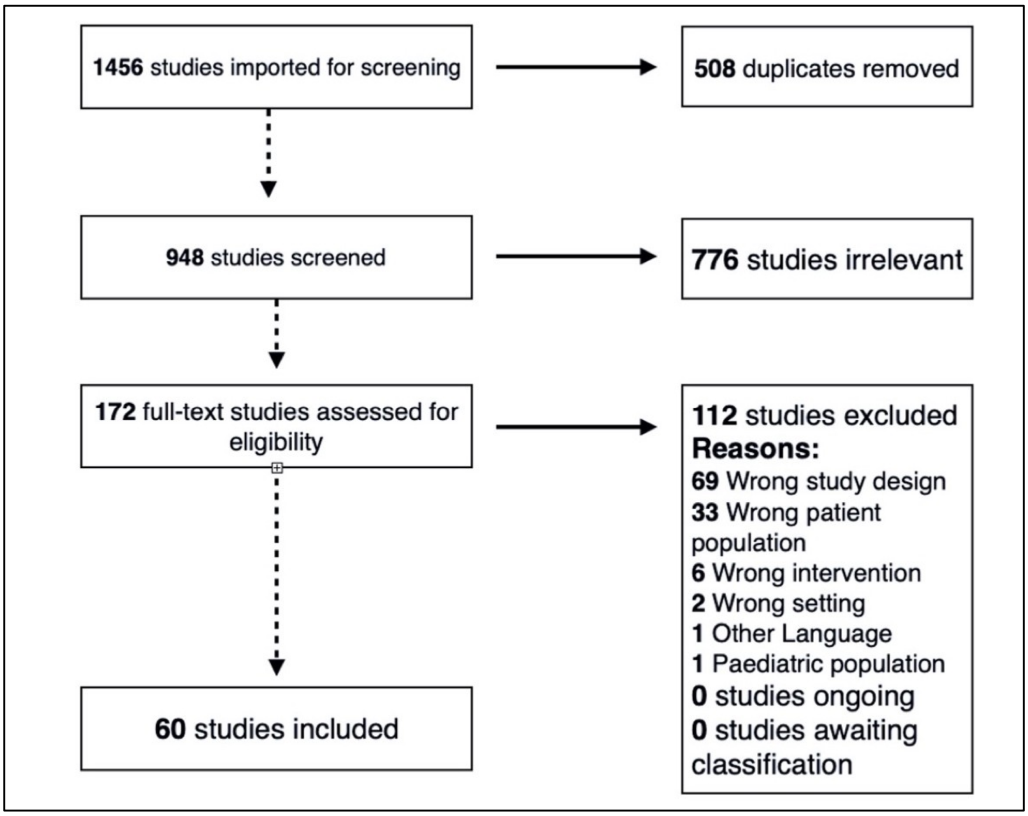

Figure 1. PRISMA flow diagram of literature search and selection process

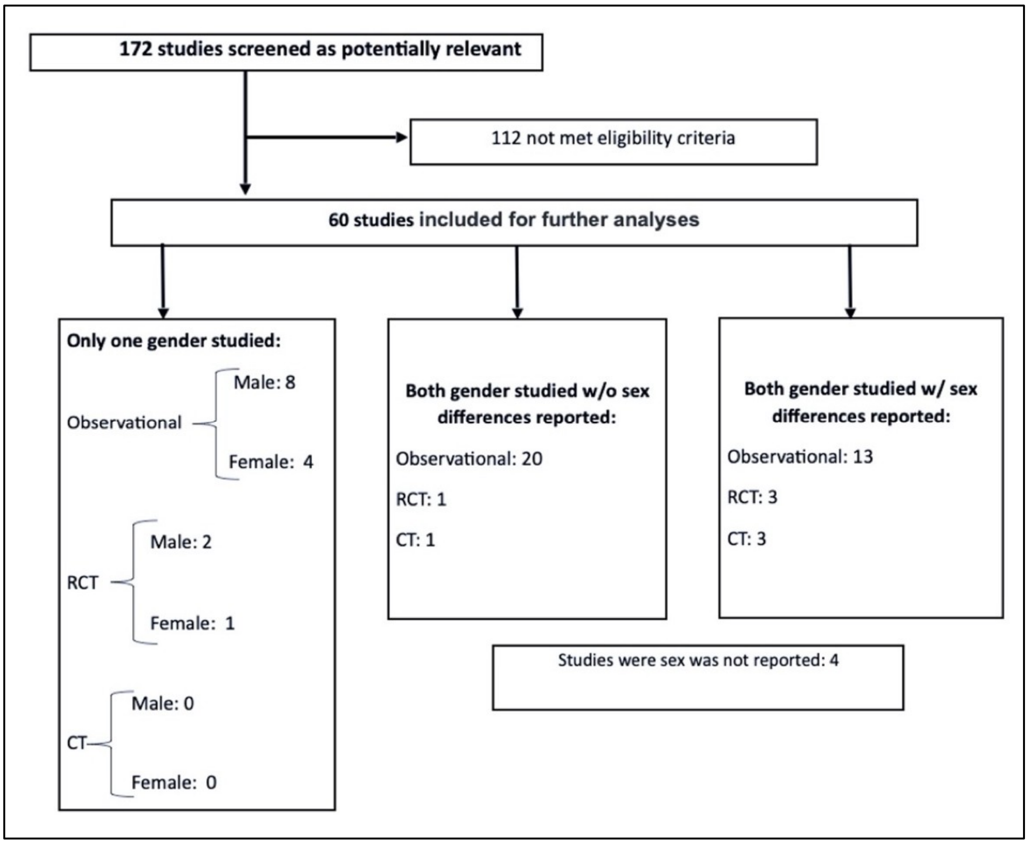

Figure 2. Screening process and classification of articles by sex/gender reporting

3.1. Prevalence of EIB in athletes

EIB is defined as a transient airway obstruction that follows or precedes a period of exercise. This concept is an accurate reflection of the underlying pathophysiology. To quantify the general prevalence of asthma and EIB in athletes, we first categorized the studies by method used for EIB diagnosis. These included exercise challenge [29, 30], eucapnic voluntary hyperpnea (EVH) with dry air [31], and EVH in combination with bronchoprovocation test with mannitol or methacholine. We found that the majority of studies (43%), collectively enrolling 1829 subjects, used exercise challenge (Figure 3), while 20% of the reviewed studies (n=829 subjects) used EVH with dry air alone, or in combination with a bronchoprovocation test. In addition, 9% percent of studies used a bronchoprovocation challenge (n=474 subjects), and 9% (n=921 subjects) used self-reporting data (questionnaires) only. The remaining 20% of studies used a combination of these methods (n=1050 subjects), and are further categorized in Figure 3. Overall, we found that the prevalence of EIB was reported in a total of 35 of the 60 reviewed studies, using a combination of the methods listed above. The studies, main findings, and ratio of male and female enrolled subjects are summarized in Table 1 [32-66]. Collectively, these studies enrolled 5103 athletes and reported a diagnosis of EIB in 1153 subjects. This corresponds to a general EIB prevalence of 23% (1153/5103).

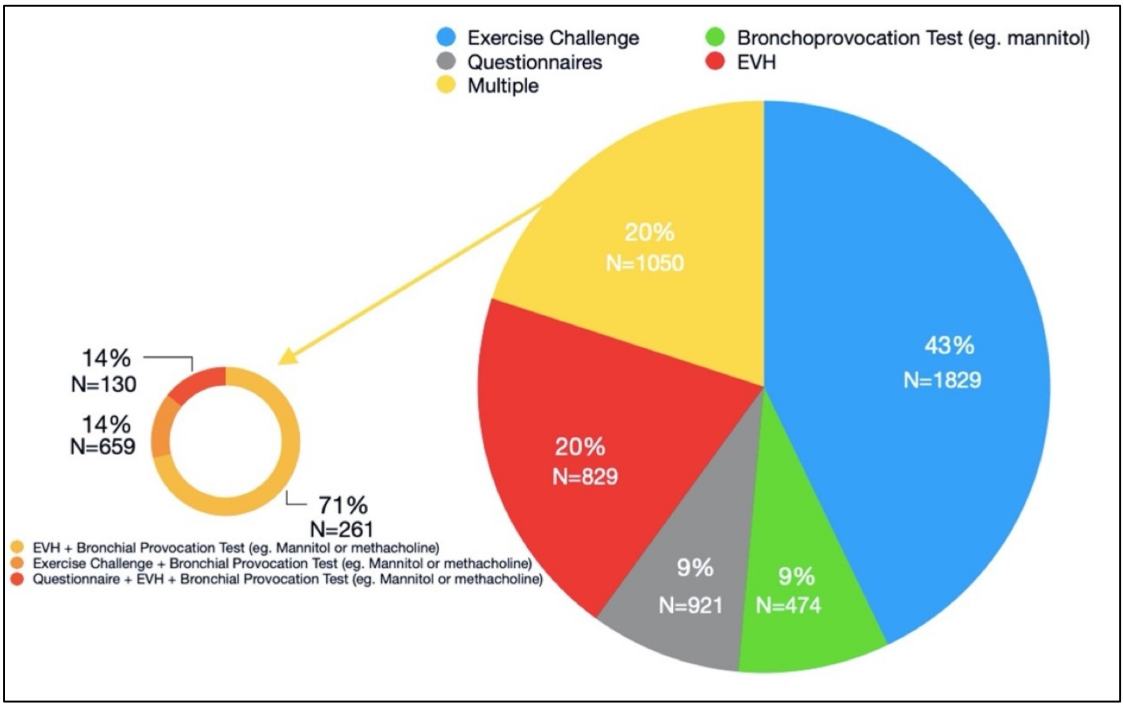

Figure 3. Diagnostic tests used to determine exercise induced bronchoconstriction in selected articles. EVH: eucapnic voluntary hyperpnea

Table 1. Prevalence of EIB among male and female athletes

AUTHOR, YEAR	METHOD FOR EIB DIAGNOSIS	STUDY POPULATION (n=subjects), SEX RATIO	EIB PREVALENCE
Ahad, Sandila, & Siddiqui, 2004	Exercise challenge	Pakistani hockey players (n=27) Male only	19%

Ahad, Sandila, Siddiqui, & Ahmed, 2003	Exercise challenge	Pakistani athletes (n=179) Male only	7%
Allen et al., 2019	EVH[1]	Recreational athletes (n=180) (120:60) M:F	37%
Ansley, Kippelen, Dickinson, & Hull, 2012	EVH & Bronchoprovocation Test (dry powder mannitol)	UK soccer players (n=65) Male only	51%
Becerril-Ángeles et al., 2017	Exercise challenge	Mexican high school and college athletes of summer sports (n=208) (115:93) M:F	7.2%
Bonini et al., 2015	Exercise challenge & Bronchoprovocation Test (dry powder mannitol or methacholine)	Italian Olympic Delegation at Summer (Sydney 2000, Beijing 2008 and London 2012) and Winter (Vancouver 2010) Olympics (n=659) (441:218) M:F	14.7%
Bougault, Turmel, & Boulet, 2010	EVH & Bronchoprovocation Test (dry powder methacholine)	Swimmers and winter sport athletes (n=45 in each group) (39:51) M:F	75% in swimmers 40% in winter sport athletes
Burnett, Burns, Merritt, Wick, & Sharpe, 2016	Exercise challenge	80 college athletes (56:24) M:F	42.5%
Burnett, Vardiman, Deckert, Ward, & Sharpe, 2016	Questionnaire	196 college athletes (56:140) M:F	28.6%
Couillard et al., 2014	Questionnaire, EVH & Bronchoprovocation Test (dry powder methacholine)	130 athlete swimmers (n=51 swimmers, n=10 synchronized swimmers), winter athletes (n=30 cross-country skiers, n=11 speed skaters training outdoors, n=9 biathletes), other endurance sports athletes (n=10 triathletes, n=7 cyclists, n=2 canoe-kayakers) (65:65) M:F	51%
Couto et al., 2015	Bronchoprovocation Test (dry powder mannitol or methacholine)	Portuguese and Norwegian athletes training at high-competitive levels (national,	46.2%

		international or Olympic teams) (n=324) (107:43) M:F	
Dickinson, McConnell, & Whyte, 2011	EVH	Elite British athletes (n=228) Sex not reported	34%
Durand et al., 2005	Exercise challenge	ski-mountaineering athletes (n=31) (28:3) M:F	48.3 %
Hallstrand et al., 2002	Exercise challenge	adolescents participating in organized sports from 3 suburban high schools (n=256) (136:120) M:F	9.4%
Hunt et al., 2017	Exercise challenge	N=92 players from three senior inter-county hurling teams Male only	9.8%
Kippelen, Caillaud, Coste, Godard, & Préfaut, 2004	Exercise challenge	N=97 athletes Male only	5.3%
Kukafka et al., 1998	Exercise challenge	high school football players (n=238) Male only	9%
Langdeau et al., 2009	Bronchoprovocation Test (dry powder methacholine)	N=100 athletes (65:35) M:F	AHR higher in females (60%) vs. males (21.5%), p<0.0001
Leuppi, Kuhn, Comminot, & Reinhart, 1998	Bronchoprovocation Test (dry powder methacholine)	Elite ice hockey players (n=26) and floorball players (n=24) Male only	34.6% (ice hockey); 20.8% (floorball players)
Levai et al., 2016	EVH	38 boxers (33:5) M:F 44 swimmers (25:19) M:F	68% (elite swimmers); 8% (boxers)
Lund, Pedersen, Larsson, & Backer, 2009	Questionnaire	329 elite athletes (198:131) M:F	55%

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Molphy et al., 2014	EVH	recreationally active individuals (n=136)	13.2%
Norqvist, Eriksson, Söderström, Lindberg, & Stenfors, 2015	Questionnaire	N=402 Swedish elite skiers, orienteers, and former Olympic athletes (cross-country and biathlon) (218:184) M:F	11%
Osthoff et al., 2013	EVH & Bronchoprovocation Test (dry powder mannitol)	N=44 athletes aiming to participate at the 2008 Beijing Paralympic Games (30:14) M:F	20%
Parsons et al., 2012	EVH	N=144 athletes from 6 different varsity sports at a large National Collegiate Athletic Association Division I collegiate athletic program (79:65) M:F	3%
Pedersen, Winther, Backer, Anderson, & Larsen, 2008	EVH & Bronchoprovocation Test (dry powder methacholine)	16 elite swimmers Female only	50%
Pohjantähti et al., 2005	Exercise challenge	N=20 healthy elite cross-country skiers (14:6) M:F N=18 non-asthmatic controls (7:11) M:F	45%
Rundell, Spiering, Evans, & Baumann, 2004	Exercise challenge	United States national ice hockey team players (n=43) Female only	21%
Rundell et al., 2003	Exercise challenge	N=18 elite athletes, cross-country skiers (13:5) M:F	50%
Sallaoui et al., 2007	Exercise challenge	N=107 elite athletes (63:44) M:F	13%
Sallaoui et al., 2009	Exercise challenge	N=326 athletes (188: 138) M:F	9.8%
Sallaoui et al., 2011	Exercise challenge	N=107 elite athletes (63:44) M:F	13%
Seys et al., 2015	EVH	Swimmers (n=26), indoor athletes	23% of swimmers,

		(basketball/volleyball, n=13), and controls (not exercising more than 4h/week, n=15). Swimmers (16:10) M:F Indoor athletes (8:5) M:F Controls (7:8) M:F	0% of indoor athletes, 1% of controls
Stenfors, 2010	EVH and Bronchoprovocation Test (dry powder mannitol or methacholine)	N=46 Swedish elite cross-country skiers (24: 22) M:F	17%
Teixeira et al., 2012	EVH	20 Brazilian long-distance runners. Male only	25%

EVH: Eucapnic voluntary hyperpnoea, M: male, F: female.

3.2. Sex differences in EIB prevalence

Of the 60 studies focusing on EIB, 41 studies incorporated both male and female subjects, and only 19 reported sex/gender differences in measured outcomes (Figure 4). However, only 15 studies that included both males and females reported EIB prevalence [41, 42, 49, 51, 53, 56, 59, 67-73]. These studies collectively enrolled 2077 athletes, and were 65% observational studies, 21% randomized control trials, and 14% clinical trials (Figure 4). The combined male to female ratio (M:F) in these studies was 1137:940, and the prevalence of EIB in this population was 30.3%. Sex differences in EIB prevalence were outlined as 17% in males and 13% females. To examine the relationship between EIB and subjects' sex, we performed a chi-square test of independence (Table 2), and found no significant differences in the relationship of these variables [$\chi 2$ (1, N= 2077) = 0.7654, p= .3811656].

Table 2. Prevalence of EIA/EIB in studies incorporating male and female athletes.

	EIB	Healthy	Marginal Row Total
Male	350 (339.03) [0.36][1]	779 (789.97) [0.15]	1129
Female	268 (278.97) [0.43]	661 (650.03) [0.19]	929
Marginal Column Total	618	1440	2058 (Grand Total)

[1] Numbers indicate: observed cell total (expected cell total) [cell chi-square statistic]

3.3. Sex differences in atopic status

Atopy, defined as the genetic predisposition for the development of an immunoglobulin E (IgE)-mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma [74]. In the US population, self-reported allergy symptoms are most consistently associated with increased levels of plant-, pet-, and mold-specific IgE [75]. Repeated and strong exposure to pollen and other allergens causes bronchial and upper respiratory symptoms in athletes, although very few studies have investigated occurrence of atopic status in athletes [76]. We identified 6 studies reporting sex differences in EIB that also reported atopy status (determined by skin prick) (Figure 4) [49, 63, 67, 69, 70, 72]. Combined, these included 980 participants (485 males, 495 females), including EIB-diagnosed athletes and healthy controls. Positive atopic status was reported in 323 subjects (33% prevalence) with an M:F ratio of 184:139 (Table 3). A chi-square test of independence determined that the prevalence of atopy was significantly higher in male athletes than in female athletes, $\chi 2$ (1, N= 980) =10.7727, p=.00103 (Table 4).

Table 3. Sex differences in atopic status.

	Male	Female	Row Total
Positive atopic status	184 (19%)	139 (14%)	323 (33%)
Negative atopic status	301 (30%)	356 (36%)	657 (67%)
Column Total	485	495	980 (Grand Total)

Table 4. Chi-square statistic of athletes' atopic status

	Male	Female	Row Totals
Positive atopic status	184 (159.85) [3.65][1]	139 (163.15) [3.57]	323
Negative Atopic status	301 (325.15) [1.79]	356 (331.85) [1.76]	657
Column Totals	485	495	980 (Grand Total)

[1] Numbers indicate: observed cell total (expected cell total) [cell chi-square statistic]

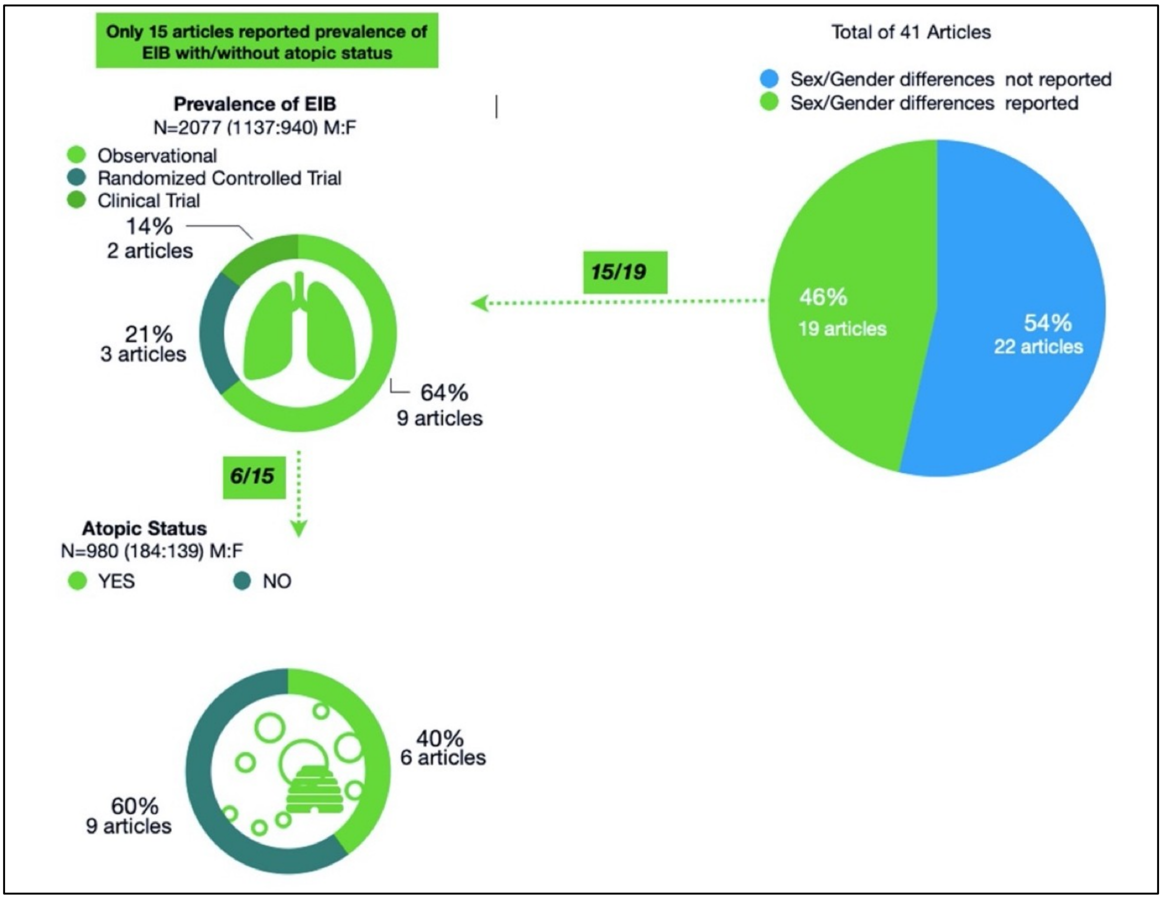

Figure 4. Articles reporting sex and gender differences and atopic status in EIB.

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3.5. Association of EIB and atopy in athletes

To evaluate the relationship between EIB and atopy in athletes, we analyzed studies reporting EIB and atopy, regardless of sex. We found 5 studies including 506 subjects combined, enrolling 262 athletes with EIB and 244 healthy athletes [49, 67, 69, 70, 72]. The prevalence of atopy was presented in 53% (n=139) of EIB patients and 41% (n=100) of healthy controls, respectively. A chi-square test of independence indicated that the relationship between atopy status and EIB was statistically significant in athletes, when the sex variable is not considered, $\chi2$ (1, N= 506) = 7.4, p= .006578 (Table 5).

Table 5. Atopic status in athletes with and without EIB.

	EIB	Healthy controls	Total row
Atopy	139 (123.75) [1.88][1]	100 (115.25) [2.02]	239
No atopy	123 (138.25) [1.68]	144 (128.75) [1.81]	267
Total column	262	244	506 (Grand Total)

[1] Numbers indicate: observed cell total (expected cell total) [cell chi-square statistic]

3.6. Sex differences in atopic status in athletes with EIB

To assess sex differences in atopy in athletes diagnosed with EIB, we found 4 studies (n=379 subjects combined) where both sex and EIB diagnosis was reported [42, 69, 70, 72]. We observed that positive atopic status was more than twice as high in male (36%) than female (15%) athletes with EIB. Conversely, no sex differences were observed when comparing non-atopic male and female athletes with EIB (Table 6). A chi-square test of independence revealed that the relationship between sex and atopy in EIB athletes was statistically significant, $\chi2$ (1, N=379) =16.2439, p=.000056 (Table 7).

Table 6. Sex differences in atopic status in athletes with diagnosis of EIB.

EIB athletes	Atopy	No Atopy	Total Row
Male	137 (36%)	92 (24%)	229 (60%)
Female	58 (15%)	92 (24%)	150 (40%)
Total Column	195	184	379 (Grand Total)

Table 7. Relationship between atopy and sex in athletes with EIB

	Atopy	No Atopy	Marginal Row Totals
Male	137 (117.82) [3.12][1]	92 (111.18) [3.31]	229
Female	58 (77.18) [4.77]	92 (72.82) [5.05]	150
Marginal Column Totals	195	184	379 (Grand Total)

[1] Numbers indicate: observed cell total (expected cell total) [cell chi-square statistic]

4. Discussion

Exercise-induced bronchoconstriction, the transient narrowing of the lower airway during or after exercise, occurs in the presence or absence of clinically recognized asthma. A sex disparity exists in individuals suffering from asthma throughout life, calling for the question of whether sex also influences EIB. In this review, we studied the prevalence of EIB in adult professional and recreational athletes, and its relationship with atopic status in males and females enrolled in 60 studies. Our analysis of the literature confirmed the previously described positive association of atopy and EIB in athletes [66], and showed that while the prevalence of EIB does not display an overall sex dimorphism, atopy is more prevalent in male athletes than in female athletes. Moreover, our analysis indicates that male athletes are twice as likely to present with atopic EIB than females. These results indicate that potential sex specific mechanisms exist in the inflammatory and physiological changes triggered by exercise in athletes.

One of the major triggers for bronchoconstriction in a vulnerable subject is water loss during periods of high ventilation. Strenuous exercise creates a hyperosmolar environment by introducing dry air into the airway with compensatory water loss, leading to transient osmotic changes in the airway surface. This hyperosmolar environment leads to mast cell degranulation and eosinophil activation with consequent release of inflammatory mediators, including leukotrienes. This process triggers bronchoconstriction and inflammation of the airway, as well as stimulation of sensory nerves and release of neurokinin and mucins [77]. Prior studies in animal models and human cells have reported sex differences in mast cell functionality and suggested a potential regulation by sex hormones [78-81]. Mast cells expressing estrogen, progesterone and androgen receptors have also been identified in the human upper airway and nasal polyps, indicating that this may be a major route for the involvement of sex hormones in exercise-induced airway inflammation [82, 83]. Similarly, studies have suggested a relationship between mast cell-derived mediators, sex hormones, and the development of asthma and allergic lung disease [84, 85]. The biosynthesis of leukotrienes and other pro-inflammatory eicosanoids and prostaglandins by mast cells is also sex biased, and has been shown to be mediated by androgens [86-88]. At the neural level, sex differences in neurokinins and their receptors have been reported in adults [89, 90], and sex hormones have been shown to regulate neurokinin-dependent activation of airway smooth muscle in allergic asthma [91-93]. Together, these studies illustrate the complexity of mechanisms involved in EIB in males and females and suggest a potential regulation by sex steroids at the immune and neural level.

Compared to the general population, elite athletes have a higher prevalence of EIB that varies with the intensity of exercise and the environment [77]. Increased bronchial responsiveness and asthma are strongly associated with atopic disposition and its severity in elite athletes [94], and atopic diseases are overall more common in athletes [95]. Our analysis of the literature revealed that 23% of the athlete population studied presented with EIB. Interestingly, the severity and prevalence of EIB was even higher (30.3%) in studies that reported sex differences. Our data also concurs with prior research reporting a greater prevalence of EIB in high-performance athletes than in the general population. These studies suggested that prolonged inhalation of cold, dry air, and airborne pollutants are some of the factors influencing the high prevalence of EIB in athletes [14]. Other studies have reported a prevalence of EIB between 30-70% among elite or Olympic-level athletes [19, 56], as opposed to 5-20% in the general population [77, 96]. While EIB is frequently documented with asthma and reflects insufficient control of underlying asthma, few epidemiological studies of EIB have categorized participants by asthma status. Thus, the true prevalence of EIB within the non-asthmatic general population has not been fully established, preventing researchers from evaluating and quantifying sex and gender differences as well. In this regard, a sex disparity in EIB and airway hyperresponsiveness (AHR) has been reported in young adults, with lower rates of mild AHR males vs. in females but higher rates of moderate AHR and atopy in males [97]. In the United States, 56.3% of asthma cases are attributable to atopy, a percentage that is greater among males than females [12, 98]. Our analysis revealed that male sex and atopic status are potential risk factors for EIB in athletes. We also identified a 2:1 ratio of atopic EIB in male vs. female athletes. However, female athletes were overall underrepresented in studies assessing EIB, as it is the case for studies in many lung diseases [99].

Estimating the prevalence of EIB has also been problematic due to the lack of a gold standard for diagnosis. Since 2016, a joint taskforce (JTF) including the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology [77], has recommended that the diagnosis of EIB should rely on performing a standardized bronchoprovocation challenge (exercise or a surrogate), because the presentation of EIB will vary with the type of challenge and the conditions under which the challenge is performed.51 In our review of the literature, we found that 43% of the selected papers used exercise challenge alone as a diagnostic tool, whereas 14.2% used it in combination with a bronchial provocation test such as mannitol or methacholine. While we do not know the exact conditions in which these tests were performed, there is a possibility that a sex bias exists in their ability to serve as EIB diagnostic tools. In this regard, 9% of the studies included used self-reporting data via questionnaires. The JTF recommends that a diagnosis of EIB is confirmed by demonstration of airways reversibility or challenge in association with a history consistent with EIB [77], because self-reported symptoms are not always accurate [71]. In our analysis, we observed that there was an overall higher rate of self-reporting EIB asthma-like symptoms in females than males, indicating that the sex differences observed in atopic EIB in athletes may be even more striking due to underreporting of symptoms by male athletes. Moreover, none of the studies accounted for the menstrual phase of female participants nor oral contraceptive use at the time they were surveyed. This represents a limitation since hormonal status has been shown to potentially alter self-reported asthma like symptoms in women [100, 101].

Recent studies have yielded significant advances in our understanding of how intrinsic and extrinsic factors can impact airway function in athletes. Extrinsic factors include environmental exposure to temperature, humidity, aeroallergens, irritants, and pollution. Intrinsic factors include atopy, allergic rhinitis, asthma, body mass index, and airway anatomy. These factors can affect both the athlete's quality of life and athletic performance, but also contribute to sex differences in exercise physiology and EIB [102]. In this regard, the menstrual cycle phase is an important determinant of EIB severity in female athletes with mild atopic asthma [103]. An estimated 33–52% of women with asthma report a premenstrual worsening of asthma symptoms, and an additional 22% report asthma that is worse during menses [101, 104]. However, the temporal correlation between asthma symptoms and steroid levels does not provide a simple answer to whether estrogen and/or progesterone improve or worsen asthma. The female sex steroid hormones could affect exercise capacity and performance through numerous psychologic mechanisms, including substrate metabolism, cardiorespiratory function, and thermoregulation [105-107]. Thus, hormone level changes may lead to either improved or decreased performance at various times throughout the menstrual cycle [108, 109]. It is also possible that the reduction in estrogen levels and other menstrual cycle disturbances that occur with exercise are associated with the lower prevalence in atopic EIB observed in female athletes [110, 111]. Overall, relationship between exercise and menstrual cycle is an important variable to consider when analyzing sex differences in EIB and atopy. More research that accounts for sex and gender variables and incorporates factors such as hormone fluctuations is needed to better understand sex-specific mechanisms of EIB and other pulmonary conditions, and potentially develop sex-specific therapeutics [112].

5. Conclusions

In conclusion, we show here that a relationship exists male sex and atopic status in the course of EIB in athletes. Understanding sex differences in EIB and atopy in athletes could lead to the development of better personalized training and disease management plans for athletes with these underlying conditions.

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