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AIR TRAPPING – EXERCISE-INDUCED ASTHMA (EIA): PATHOMECHANISM, DIAGNOSIS AND NOVEL PREVENTION STRATEGIES

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A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Exercise-induced asthma (EIA), also known as exercise-induced bronchoconstriction (EIB), is characterized by transient airway narrowing triggered by physical exertion, leading to symptoms such as cough, wheezing, shortness of breath, and chest tightness. The pathophysiology of EIA involves osmotic and thermal mechanisms, resulting in the release of inflammatory mediators that induce bronchospasm.

Aim of the study: This systematic review aims to elucidate the pathomechanisms, diagnostic approaches, and treatment modalities for EIA.

Material and methods: The review follows PRISMA guidelines and includes 31 studies from PubMed and ClinicalTrials.gov, focusing on adults reporting EIA symptoms. Diagnostic methods primarily include spirometry pre- and post-exercise, with a ≥10% decrease in FEV1 indicating EIA. Provocation tests, such as eucapnic voluntary hyperventilation (EVH), and novel methods like diaphragm electromyography (EMGdi), are also explored.

Results: Management strategies encompass pharmacological treatments, including short-acting beta-2 agonists (SABAs), inhaled corticosteroids (ICS), and leukotriene receptor antagonists (LTRAs), alongside non-pharmacological approaches like warm-up exercises and breathing retraining, which have been reviewed as parts of phase 3 and phase 4 clinical trials. The consistent use of standardised exercise challenge tests and FEV1 measurements, along with robust study designs, strengthens the evidence for prevention method efficacy.

Conclusions: The review highlights the need for standardized diagnostic criteria and personalised treatment plans to improve patient outcomes and quality of life.

KEYWORDS: exercise-induced asthma, bronchoconstriction, spirometry, beta-2 agonists, inhaled corticosteroids

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Background

Exercise-Induced Asthma (EIA)

Exercise-induced asthma, also known as exercise-induced bronchoconstriction (EIB), is a condition in which the airways narrow during or after intense physical exertion. It is characterized by asthma symptoms such as cough, wheezing, shortness of breath, and chest tightness, which are triggered by physical activity [1].

Exercise-induced asthma can affect both individuals with diagnosed chronic asthma [2] and those for whom it is the only form of asthmatic symptoms [3]. Athletes with asthma often experience exercise-induced bronchoconstriction [2].

The exact mechanisms of exercise-induced asthma are not fully understood, but it is believed that changes in temperature and humidity in the airways during intense breathing play a key role [4]. Airflow obstruction typically occurs shortly after the cessation of exercise, primarily due to osmotic and thermal mechanisms [2]. However, it can sometimes develop during exercise, limiting physical performance [1]. The peak of exercise-induced asthma usually occurs 5–15 minutes after exercise, and then symptoms spontaneously resolve within about an hour [1].

The intensity and duration of physical exertion are important risk factors [1]. Additionally, cold and dry air, as mentioned earlier [4], and air pollution can exacerbate symptoms.

The diagnosis of exercise-induced asthma mainly involves spirometry, which is the most commonly used method for assessing lung ventilation [5]. A decrease in FEV1 (forced expiratory volume in one second) by at least 10% after an exercise challenge test (ECT) is traditionally considered a diagnostic criterion for EIB in adults [1].

However, this criterion is characterized by low specificity and weak scientific evidence [6]. Other diagnostic methods include the exercise challenge test (ECT).

Causal treatment of chronic asthma (if present) with inhaled corticosteroids is important in controlling airway inflammation [2]. Preventive use of short-acting (less frequently long-acting) selective beta-2-adrenergic receptor agonists or leukotriene receptor antagonists before physical exertion is effective in preventing bronchoconstriction and related symptoms [2].

The symptomatology of exercise-induced asthma (EIA) may closely resemble that of exercise-induced laryngeal obstruction (EILO), and these two conditions can concurrently manifest, thereby complicating the interpretation of clinical symptoms [14]. In the diagnostic evaluation of EILO, continuous laryngoscopy during exercise (CLE) is employed, enabling direct visualization of the larynx. Untreated EILO in an athlete using asthma medications may lead to unnecessary or ineffective interventions, as asthma therapies are inefficacious for EILO [15].

In summary, exercise-induced asthma is a transient narrowing of the airways triggered by physical exertion, manifesting with typical asthma symptoms. Diagnosis is based on medical history, physical examination, and objective tests evaluating lung function before and after exercise. Proper diagnosis and treatment are crucial for enabling individuals with exercise-induced asthma to participate in physical activity safely and effectively.

Aim of the study

This review aims to thoroughly examine the pathomechanisms and the latest advancements in the understanding of exercise-induced asthma (EIA). The main objective is to evaluate prevailing diagnostic techniques and treatment modalities in managing EIA, as well as to promote awareness of the condition and its implications for overall health and physical activity.

Material and methods

Search strategy

This review follows the PRISMA guidelines for systematic reviews [21]. It is based on scientific articles found through a search in PubMed databases using the following MeSH terms: ((Exercise-induced asthma) AND (Exercise-induced)) AND (asthma). The aim was to collect the most recent available studies; therefore, the following filters were applied: "in the last 5 years" and "free full text availability." A total of 163 publications in English were selected. Additionally, a search using the term "Exercise-Induced Asthma" was performed on ClinicalTrials.gov, filtered for phase 3 and 4 studies only, with 25 clinical trials selected for screening. The searches were performed in March 2025.

Eligibility criteria

We selected the following inclusion criteria for the retrieved studies:

- **Population**: adults over the age of 18 reporting symptoms of exercise-induced asthma.
- **Prognostic factor**: studies describing risk factors for exercise-induced asthma.
- **Outcome**: articles identifying risk factors and possible prophylactic and treatment measures for exercise-induced asthma.

- **Language**: publications written in English.
- **Text availability**: free full text available.

The exclusion criteria were studies on the pediatric population, systematic or literature reviews, expert opinions, letters to the editor, conference reports, and publications without free full text available.

Data collection

An independent literature review was conducted by each author. Initially, the abstracts of the identified articles were screened to determine their relevance to the topic of exercise-induced asthma (EIA). Articles that fulfilled the inclusion criteria were subjected to full-text analysis. These articles were systematically evaluated based on various parameters such as the demographic groups addressed, diagnostic approaches described, and therapeutic outcomes reported. To ensure reliability and precision, the collected data were cross-verified by the authors. The finalized dataset was meticulously organized and synthesized to present a comprehensive analysis of the current understanding of EIA, emphasizing existing challenges and recent progress in the field. Overall, a total of 31 studies from PubMed and ClinicalTrials.gov were chosen for conducting the systematic review on exercise-induced asthma.

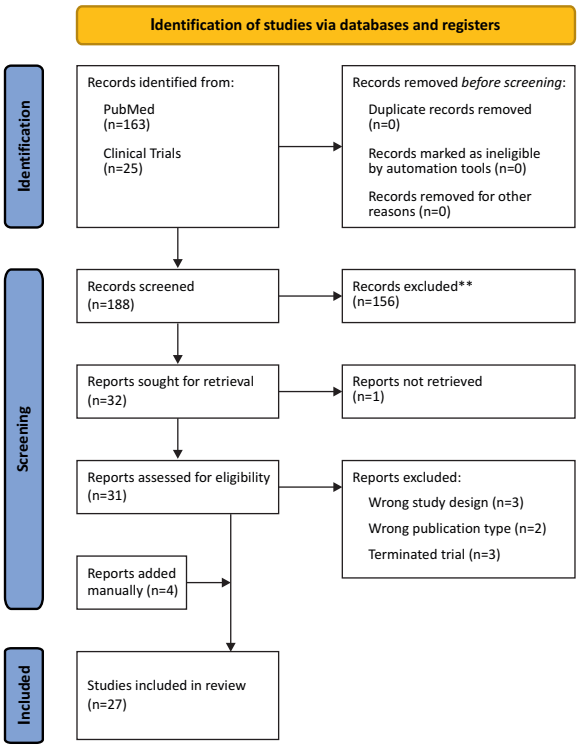

Figure 1. PRISMA flowchart for conducting the literature search

Reports and publications from seven clinical trials were manually examined, and relevant information was recorded in a spreadsheet. Figure 2 represents the recorded parameters from clinical trial protocols.

Section	Checklist Item	Compliance
Title	Identify the report as a systematic review	Done (updated in title)
Abstract	Structured summary following PRISMA guidelines	Present
Introduction	Rationale and objectives stated	Present
Methods – Protocol and Registration	Registration information (PROSPERO/OSF)	Not registered (added to limitations)
Methods – Eligibility Criteria	Explicit inclusion and exclusion criteria	Present
Methods – Information Sources	Databases and registers described	Present
Methods – Search Strategy	Full search strategy provided	Present
Methods – Selection Process	Study screening and selection process explained	PRISMA flowchart included
Methods – Data Collection	Process of data extraction described	Present
Methods – Risk of Bias	Assessment of study quality	Not performed (added to limitations)
Methods – Synthesis of Results	Meta-analysis justification or description	Not performed (justified in limitations)
Results	Study characteristics and outcomes presented	Present
Discussion	Summary of evidence, limitations, and implications	Present
Funding	Sources of support disclosed	Present in references/conflicts of interest
Conclusions	Directly answering the research question	Revised and focused

Figure 2. PRISMA 2020 Checklist

Table 1. Analysed parameters from clinical trial protocols

Category	Parameter	Details
Study Info	Study ID	Unique identifier
	Author, Year	First author, publication year
	Journal	Name of journal
	Country	Location of study
	Study Type	RCT, cohort, etc.
Population	Sample Size	Number of participants
	Age (Mean ± SD)	Age distribution
	Gender (% M/F)	Male/Female ratio
	Asthma Diagnosis Criteria	Criteria used
	Asthma Severity	Mild, moderate, severe
	Inclusion/Exclusion Criteria	Key criteria
Intervention & Control	Exercise Type	Treadmill, cycling, etc.
	Intensity & Duration	HR, VO_2 max, time
	Environmental Conditions	Temperature, humidity, etc.
	Intervention Details	Medication, warm-up, etc.
	Control Group Description	Placebo, no exercise, etc.
Outcomes	Primary Outcome(s)	FEV1 drop %, bronchoconstriction
	Secondary Outcome(s)	Symptom score, biomarkers
	Time Points	Pre-, post-, follow-up
	Measurement Tools	Spirometry, eNO, etc.

Table 1 contd.

Category	Parameter	Details
Results	FEV1 Change (%)	% Drop in lung function
	Other Lung Function Data	PEF, FVC, FEV1/FVC
	Symptom Score Changes	Reported symptoms
	Biochemical Markers	eNO, histamine, etc.
	Adverse Events	Side effects, complications
Quality & Bias	Randomization Method	Yes/No, details
	Blinding	Single, double, none
	Dropout Rate (%)	% Lost to follow-up
	Funding Source	Industry, government, etc.
	Conflict of Interest Stated	Yes/No

Results

Pathophysiology of Exercise-Induced Bronchoconstriction (EIB)

The precise pathophysiological mechanisms underlying exercise-induced bronchoconstriction (EIB) remain incompletely elucidated; however, it is widely recognized that exercise-mediated alterations in the respiratory tract culminating in bronchospasm play a pivotal role [1].

The primary mechanisms implicated in post-exercise airway narrowing are osmotic and thermal in nature [1]. During periods of heightened ventilatory demand associated with physical exertion, there is a consequential loss of heat and moisture from the epithelial surfaces of the airways [1].

The osmotic mechanism is characterized by the cooling and desiccation of the airway mucosa, resulting in an elevation of the osmolarity of the epithelial lining fluid [1]. This, in turn, triggers the release of inflammatory mediators from mucosal cells, including mast cells and eosinophils [1]. These mediators, such as histamine and leukotrienes, induce smooth muscle contraction in the bronchi, mucosal oedema, and augmented mucus secretion, ultimately leading to luminal narrowing and airflow limitation [1].

The thermal mechanism involves the direct cooling of the airways. This process can also contribute to the activation of sensory nerves and the elicitation of reflex bronchoconstriction in individuals with bronchial hyperreactivity [1].

Furthermore, research indicates that a subset of asthmatic individuals with EIB may experience dynamic hyperinflation (DH) during exercise, characterized by a progressive increase in end-expiratory lung volume [2]. Asthmatic subjects with EIB and DH have demonstrated an earlier decline in forced expiratory volume in one second (FEV1) following exercise, as well as significantly lower mean forced expiratory flow between 25% and 75% of forced vital capacity (FEF25–75%) at rest, and greater bronchial hyperreactivity compared to asthmatic subjects with EIB without DH [2].

It is noteworthy that exercise can also induce bronchodilation in some individuals with asthma, which may mask or delay the onset of post-exercise bronchoconstriction [3]. In summary, the pathophysiology of EIB is complex and encompasses osmotic and thermal alterations in the airways, precipitated by heightened ventilation during exercise, leading to the release of inflammatory mediators and bronchospasm. Dynamic hyperinflation may also occur in certain patients, further influencing their response to exercise [1].

Diagnosis of exercise-induced asthma

In a scientific approach to diagnosing exercise-induced bronchoconstriction (EIB), it is essential to employ objective methods for assessing respiratory function, as subjective patient reports of exercise-related symptoms exhibit low specificity and may not correlate with actual airflow limitation [17]. Consequently, scientific literature emphasizes laboratory- or field-based provocation tests to document exercise-induced bronchial hyperreactivity.

Spirometry pre- and post-exercise

Spirometry before and after physical exertion remains the cornerstone of EIB diagnosis [11]. The testing protocol includes spirometry measurements (primarily forced expiratory volume in one second – FEV1) at rest, prior to controlled exercise [14]. The exercise test should be sufficiently intense and prolonged to elicit EIB symptoms, such as running, stationary cycling, or other activities reaching approximately 80–90% of maximum heart rate. After exercise, spirometry measurements are repeated at regular intervals, typically at 3, 5, 10, and 15 minutes, and sometimes up to 20–30 minutes to capture the nadir of FEV1 [14], [16]. A decrease in FEV1 of at least 10% from baseline (pre-exercise) is considered diagnostically significant for EIB [14], [16].

In a study by Pigakis et al. on professional cyclists, in addition to FEV1, 1-FEV3/FVC, representing the fraction of forced vital capacity (FVC) not exhaled within the first 3 seconds of forced expiration, was analysed. This value was higher in athletes with EIB and those with isolated exercise-induced small airway dysfunction (SAD). The authors suggest that 1-FEV3/FVC may be a promising marker of air trapping and hyperinflation. However, the primary diagnostic criterion for EIB remains the percentage decrease in FEV1 [11].

Provocation tests

Provocation tests are crucial for EIB diagnosis, as they mimic conditions that trigger bronchoconstriction [19]. They are divided into:

- **Direct tests** (e.g., methacholine or histamine), acting directly on airway smooth muscles; more sensitive in detecting general bronchial hyperreactivity characteristic of asthma and EIB.
- **Indirect tests** (e.g., exercise, eucapnic voluntary hyperventilation (EVH), hypertonic saline, AMP, and mannitol), which induce inflammatory mediator release from airway cells; these better reflect EIB mechanisms.

Among provocation tests, exercise testing is a primary method for provoking EIB. A 10% or greater decrease in FEV1 post-exercise is a diagnostic criterion. In elite athletes, some experts suggest a more stringent FEV1 decrease threshold (>6.5%) considering their physiology. Exercise testing requires controlled conditions (20–25°C, <50% humidity) and sport-specific protocols, though reproducibility can be challenging [19].

Eucapnic Voluntary Hyperventilation (EVH)

Eucapnic voluntary hyperventilation (EVH) is an alternative bronchial provocation method with high specificity [17]. The EVH protocol involves intense breathing of a controlled CO2 gas mixture for 4–6 minutes, leading to significant minute ventilation [17]. As with exercise testing, FEV1 is measured pre- and post-hyperventilation, with a ≥10% FEV1 decrease indicating EIB [17].

Differential diagnosis

Differentiating EIB from other conditions, especially exercise-induced laryngeal obstruction (EILO), is crucial [12]. Rogde et al. highlight that EILO involves adduction of glottic/supraglottic tissues during exercise, causing transient airflow limitation [10]. EILO and EIB symptoms can be indistinguishable, and both conditions may coexist [12]. EILO diagnosis relies on direct visualization of laryngeal function during exercise via continuous exercise laryngoscopy (CLE) [12].

Fractional Exhaled Nitric Oxide (FeNO)

Fractional exhaled nitric oxide (FeNO) measurement can complement EIB diagnosis [19]. Elevated FeNO (≥40 ppb) in athletes may strengthen suspicion of EIB, but due to limitations in sensitivity and predictive value, it should not replace indirect provocation tests [19].

Novel diagnostic methods

Novel EIB diagnostic methods include diaphragm electromyography (EMGdi) with surface electrodes. Wang et al. found a significantly higher relative change in the EMGdi/tidal volume ratio (ΔEMGdi/VT%) in EIB participants (124%) compared to controls (21%) [16]. The area under the ROC curve (AUC) for ΔEMGdi/VT% in EIB detection was 0.92, with 92% sensitivity and 88% specificity, suggesting EMGdi/VT may assess post-exercise airway resistance changes and differentiate EIB [16]. Increased EMGdi reflects increased respiratory muscle effort in response to airway resistance [16].

Accurate EIB diagnosis requires objective confirmation of bronchial hyperreactivity via provocation tests such as exercise spirometry or EVH. Differential diagnosis, especially for EILO, and consideration of novel methods like EMGdi analysis, are essential for precise EIB diagnosis [11]. Reliance on subjective symptoms alone is insufficient in both scientific and clinical contexts [17].

Management and treatment of exercise-induced asthma

Managing exercise-induced bronchoconstriction (EIB), also known as exercise-induced asthma (EIA), is a challenge that requires a holistic therapeutic approach encompassing both pharmacological and non-pharmacological strategies [18]. Particularly for physically active individuals and athletes, effective management of this condition is crucial for achieving full potential and maintaining well-being [18].

Pharmacological treatment of EIB

In the arsenal of EIB pharmacotherapy, medications aimed at both prevention and immediate relief of symptoms such as shortness of breath and bronchospasm, which may occur during or after exercise, take precedence [19]. Short-acting beta-2 receptor agonists (SABAs), such as the commonly known salbutamol and terbutaline, are the first line of defence against an expected EIB attack [7], [20]. Taken 15–20 minutes before planned activity, they effectively relax the bronchi, facilitating airflow [18], [19].

However, it is important to remember that although they provide rapid relief, they should not be the sole pillar of EIB therapy, and their excessive use

can lead to a weakening of their effect [7]. Studies have shown that albuterol significantly reduced the maximum decrease in FEV1 after exercise compared to placebo [20].

In the context of long-term control and in individuals with frequent symptoms, inhaled corticosteroids (ICS) play an indispensable role [20]. These cornerstones of asthma therapy also have a beneficial effect in EIB by reducing airway hyperreactivity and making the bronchi less susceptible to the provoking effect of exercise [19]. Regular use of ICS, especially when the need for SABAs arises more than twice a week, is an important step towards stabilizing health [20].

An interesting solution, especially for patients with coexisting asthma, is combination preparations that unite ICS with long-acting beta-2 receptor agonists (LABAs) [7]. Moreover, modern research opens new perspectives, indicating the effectiveness of on-demand use of a combination of ICS (budesonide) and formoterol (LABA), which was more effective than on-demand use of SABAs in reducing EIB in patients with mild asthma and EIB [20].

A new approach is a combination preparation of albuterol (SABA) and budesonide (ICS), which, when administered as a single dose about 30 minutes before physical exertion, proved to be significantly more effective than placebo in preventing EIB in adolescents and adults with asthma and EIB, regardless of ICS use in maintenance therapy [20]. In the TYREE study, albuterol/budesonide significantly reduced the maximum decrease in FEV1 after exercise compared to placebo (5.45% vs. 18.97%) [20].

In the spectrum of supportive drugs, leukotriene receptor antagonists (LTRAs), such as montelukast, are also effective in contributing to EIB prevention [7], [18]. Short-acting anticholinergic drugs, such as ipratropium, can cause bronchodilation, but their use before exercise to prevent EIB remains controversial [19].

Non-pharmacological strategies

Alongside pharmacotherapy, non-pharmacological strategies are invaluable in managing EIB. When used in combination with medications, they help minimize the risk of symptoms [18]. A key element is awareness of triggering factors and actively avoiding them. Allergens, cold or dry air, and pollution – identifying individual „triggers" and limiting exposure to them – is the foundation of prophylaxis. Athletes training in cold conditions should be particularly aware of the risk of post-exercise cough. Using a mask that exchanges heat and moisture can prevent cold air-induced asthma [18], [19].

Proper and thorough warm-up before intense physical exertion is another important element that can significantly reduce the likelihood of EIB [19]. Breathing retraining techniques, which re-educate the breathing pattern, can support symptom control in athletes with asthma. These programs, conducted under the supervision of a physiotherapist, can include various methods, such as controlling the volume and frequency of breaths [18]. Although mentioned less frequently in the context of EIB, inspiratory muscle training (IMT) can potentially have a beneficial effect on overall respiratory function, particularly in individuals with other respiratory problems such as exercise-induced laryngeal obstruction (EILO). Respiratory muscle rehabilitation, including IMT, is considered in the treatment of EILO [18].

In summary, effective treatment of exercise-induced asthma is an individually tailored plan that combines pharmacotherapy with conscious use of non-pharmacological strategies. Regular assessment and adjustment of this plan to changing needs and conditions are key to an active and full life without limitations from EIB.

Phase 3 and 4 Clinical trials on exercise-induced bronchoconstriction

Seven completed phase 3 and phase 4 clinical trials investigating treatments for exercise-induced bronchoconstriction (EIB) in asthma patients were analysed. The studies included in this review exhibit a range of characteristics concerning their design, participant populations, interventions, control groups, and the duration of their investigations. Figure 3 represents a summary of the clinical trials.

A predominant study design employed across several trials was the randomised, double-blind, crossover model, often incorporating a double-dummy technique to maintain blinding when comparing different routes of administration (e.g., oral vs. inhaled) [24–28]. This design allows for within-subject comparisons of different treatments, potentially reducing inter-individual variability. Double-dummy techniques were employed where required to mask differences in drug appearance or dosing. Two of the reviewed trials focused on the paediatric population [22, 27], four on young adults [23, 25, 26, 28], and one on middle-aged adults [24]. Gender distributions across studies were reasonably balanced or slightly skewed, ensuring that the findings remain generalisable across sexes.

The reviewed trials focused on protective measures against EIB in asthma patients, using treadmill exercise to provoke bronchoconstriction. Exercise durations typically ranged from 6 to 10 minutes, with target intensity set to achieve a heart rate of 80% to 95%

Table 2. Clinical trials' characteristics

Study ID	NCT00092131	NCT00245570	NCT00090142	NCT02730351	NCT04234464	NCT00118716	NCT00127166
Author	Pearlman, D.S. [28]	Philip, G. [25]	Philip, G. [26]	Martin, N. [23]	LaForce, C. [24]	Pearlman, D.S. [22]	Fogel, R.B. [27]
Year	2006	2007	2007	2019	2021	2009	2009
Journal	Annals of Allergy, Asthma and Immunology	CHEST	Journal of Asthma	Journal of Asthma	Annals of Allergy, Asthma and Immunology	Pediatric Pulmonology	Annals of Allergy, Asthma and Immunology
Study design	Double-blind randomised crossover interventional study	Double-blind, double-dummy, three-way crossover interventional study	Double-blind randomised crossover interventional study	Double-blind, double-dummy, randomised, crossover interventional study	Double-blind, double-dummy, randomised, crossover interventional study	Double-blind randomised crossover interventional study	Double-blind, double-dummy, randomised, crossover interventional study
Sample size	51	47	62	74	60	248	144
Age (mean SD)	24.5±5.9	26±7.92	24.4±6.9	27.8±10.35	40.5±11.76	11.1±3.45	10±2.0
Gender (% M/F)	47.1/52.9	48.9/51.1	53.2/46.8	41.9/58.1	36.7/63.3	60.1/39.9	57.8/42.2
Exercise	6-minute treadmill run until HR increased to 80-90% of age-predicted maximum	6-minute treadmill run until HR increased to 80-90% of age-predicted maximum	6-minute treadmill run until HR increased to 80-90% of age-predicted maximum	10-minute stepped treadmill challenge, with ≥6 min at 80–95% of maximum predicted heart rate	Treadmill running 6 to 8 minutes at approximately 80 to 95% of maximal heart rate (220 bpm minus age in years)	Treadmill running 6 to 8 minutes at above 80% of maximal heart rate for age	Treadmill running for at least 6 minutes at increased heart rate to 50 – 70% of predicted in 2 minutes and 80 – 90% after
Spirometry time points	2, 12, and 24 hours after dosing	2, 8.5, and 24 hours postdose	2, 12, and 24 hours after dosing	Day 1 (23-h post first dose), Day 14 (12 and 23-h post evening dose) of each 2-week treatment period	5 minutes pre-dose, 30 minutes post-dose (5 minutes pre-exercise), 5, 10-, 15-, 30-, and 60-minutes post-exercise	prior to exercise, 5, 10, 15, 30 and 60 minutes after completion of exercise	At baseline (pre-randomization) and after each 4-week treatment period, exercise challenges were performed 8–10 hours after the morning dose and 20–24 hours after the evening dose.
Intervention	Montelukast 10 mg tablet before exercise Placebo	Montelukast Salmeterol Placebo	Montelukast 10 mg tablet before exercise Placebo	Fluticasone furoate/ Vilanterol 100 mcg/25 mcg via ELLIPTA inhaler Placebo via DISKUS/ACCUHALER	Budesonide/albuterol sulphate metered-dose inhaler 160/180 µg Placebo inhalation aerosol single dose	Fluticasone propionate/ salmeterol Fluticasone propionate	Montelukast 5 mg chewable tablet once daily Salmeterol 50 mcg dry powder per actuation inhaled twice daily Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily Matching placebo to montelukast oral tablet administered once daily. Matching placebo to salmeterol dry powder for inhalation administered twice daily

of the participant's age-predicted maximum [22–26, 28]. The study by Fogel et al. specified a lower initial intensity (50–70% of predicted in the first 2 minutes, then 80–90%) [23]. Treadmill speed and incline were adjusted to help participants reach and maintain their target heart rate [26]. In most cases, the inspired air conditions were strictly controlled, with patients inhaling room-temperature dry air, achieved using compressed air tanks or face masks [22–27].

Exercise challenges were performed at specific time points relative to the administration of the study drug to assess onset and duration of action, including 2, 8.5, 12, and 24 hours post-dose [25, 26, 28]. To minimize variability, studies implemented pre-exercise restrictions, such as avoiding strenuous physical activity for 24–72 hours, abstaining from caffeine for 4–6 hours [23], and withholding short-acting beta-agonists (SABAs) like albuterol for at least 6–8 hours before testing [23, 25, 27]. One study also required participants to refrain from exercising in cold air for 24 hours [23]. In the study comparing fluticasone furoate/vilanterol (FF/VI) and fluticasone propionate (FP), patients withheld their daily study drug on clinic visit days [23].

Forced expiratory volume in 1 second (FEV1) was the primary outcome measure for bronchoconstriction, assessed by spirometry at several critical time points. Baseline measurements were taken before the exercise challenge to establish a pre-exercise FEV1, with multiple readings recorded and the highest acceptable and repeatable value used [24]. In some studies, baseline measurements were taken both before dosing and immediately before exercise. Post-exercise FEV1 was measured at various intervals after the exercise challenge to assess recovery.

Leukotriene receptor antagonists (montelukast) were the most frequently studied treatment (n = 4), followed by ultra-long-acting beta-2 agonists (ultra-LABAs) in the form of fluticasone furoate with vilanterol (n = 3), and short-acting beta-2 agonists (SABAs) such as albuterol/budesonide (n = 2).

In a paediatric study comparing montelukast and salmeterol added to inhaled fluticasone, montelukast significantly reduced the mean maximum percentage decrease in FEV1 compared to salmeterol (10.6% vs. 13.8%; $P \leq 0.009$) after 4 weeks of treatment [27]. Montelukast also resulted in a smaller mean area under the curve for the first 20 minutes after exercise and a shorter median time to recovery [27]. Furthermore, the response to albuterol rescue after exercise challenge was significantly greater with montelukast ($P \leq 0.001$) [27]. The study concluded that both attenuation of EIB and response to albuterol rescue were significantly better with montelukast than with salmeterol [27].

Another study in adults demonstrated that a single dose of montelukast provided significant protection against EIB at 2, 8.5, and 24 hours post-dose compared to placebo, as measured by the maximum fall in FEV1 [25]. Despite montelukast and salmeterol having similar efficacy at 2.5 and 8 hours, only montelukast was effective at 24 hours, suggesting it might be the preferred prophylactic measure against EIB. Similarly, a study by Pearlman et al. demonstrated that a single oral dose of montelukast provided significant bronchoprotection, reducing the maximum percentage decrease in FEV1 at 2, 12, and 24 hours post-exercise compared to placebo ($P < 0.05$) [28].

In a paediatric cohort aged 6 to 14 years, montelukast treatment resulted in a statistically significant shift toward a lower category of maximum FEV1 decrease after exercise compared to salmeterol ($P \leq 0.004$). Specifically, a greater proportion of patients treated with montelukast exhibited a post-exercise maximum FEV1 decline of less than 10%, suggesting enhanced protection against EIB relative to salmeterol [28].

A single-dose crossover study in adolescents and adults with asthma evaluated the efficacy of albuterol/budesonide versus placebo in mitigating EIB. Albuterol/budesonide significantly reduced the least squares mean maximum percentage fall in FEV1 up to 60 minutes post-exercise challenge compared to placebo (5.45% vs. 18.97%; $P \leq 0.001$) [24]. Additionally, a significantly higher proportion of subjects were fully protected (maximum FEV1 fall <10%) when treated with albuterol/budesonide compared to placebo (78.3% vs. 28.3%; $P \leq 0.001$) [24]. Moreover, the median recovery time post-exercise challenge was accelerated by 25 minutes with albuterol/budesonide relative to placebo, reinforcing its rapid and effective bronchoprotective action [24].

Another study investigated whether once-daily fluticasone furoate/vilanterol (FF/VI) conferred superior long-term protection against post-exercise FEV1 decline compared to twice-daily fluticasone propionate (FP) in asthma patients receiving low- to mid-dose maintenance ICS. The primary endpoint, defined as the mean maximal percentage decrease in pre-exercise FEV1 at 12 hours post-exercise challenge on day 14, was 15.02% with FF/VI versus 16.71% with FP, a difference that did not reach statistical significance [23]. Although the study failed to demonstrate a definitive advantage of FF/VI over FP for long-term protection against EIB, numerical trends favoured FF/VI at both 12 and 23 hours post-dose [23].

The tolerability and safety profiles of the investigated treatments were generally favourable across studies, with most adverse events classified as mild to moderate. Dropout rates were low and rarely attributable to the study medications. In the paediatric study comparing montelukast and salmeterol added to inhaled fluticasone [27], both treatments demon-

strated good tolerability, with no significant differences in the occurrence of clinical adverse events. No drug-related adverse events were reported, and no patients discontinued treatment due to an adverse event [27].

The most reported adverse events included pharyngitis, asthma, and tonsillitis, occurring in both treatment groups [27]. Two serious adverse events were instances of oral study drug overdose (one in each group), which were not considered related to the medications [27]. Out of 154 patients randomised, 145 completed the study, indicating a dropout rate of approximately 5.8% [27].

The single-dose study of albuterol/budesonide compared to placebo in adolescents and adults reported a low incidence of adverse events [24]. Two subjects in the placebo group experienced mild adverse events (dyspnoea and anxiety), with one case of anxiety considered drug-related [24]. Importantly, there were no adverse events that led to death or discontinuation of treatment in either group [24]. The study enrolled 60 subjects, and while the exact number completing both treatment periods of the crossover design isn't specified, the analysis is based on 29 and 31 subjects in each sequence, suggesting a high completion rate. In the study comparing fluticasone furoate/vilanterol (FF/VI) and fluticasone propionate (FP), the number of patients experiencing adverse events was also low for both treatments, and there was no significant difference between the groups [23]. 16% of patients on FF/VI and 15% on FP experienced at least one adverse event [23]. Only one non-serious adverse event (increased tendency to bruise) was considered related to FF/VI. One patient in each treatment arm withdrew from the study due to non-serious adverse events (worsening asthma and sinusitis with FF/VI, and cough with FP). One serious adverse event (gastroenteritis reported with FF/VI) was deemed unrelated to the study treatment. Out of 74 patients randomised, several did not complete all aspects of the study, including the washout period or the second treatment period, as detailed in the patient disposition figure [23]. The single-dose study of montelukast for EIB by Philip et al. showed a safety profile comparable to placebo [26]. 7 out of 61 participants experienced clinical adverse effects, but no serious adverse events nor discontinuations due to them occurred [26]. Drug-related adverse experiences were reported by single patients in each group (arthralgia/myalgia with montelukast, flushing/headache with placebo, and diarrhoea/headache/nausea with placebo), and all these patients recovered and completed the study [26]. Of 62 randomised patients, 53 completed the study, yielding a dropout rate of about 14.5%, none of which were linked to clinical adverse experiences. Another single-dose study comparing montelukast and salmeterol to placebo also reported a low incidence of adverse events [25]. Six adverse events were observed with montelukast, seven with placebo, and two with salmeterol, with none being serious [25]. Headache was the most common event, occurring more frequently with placebo. One patient was discontinued during the washout period following placebo due to worsening respiratory allergies that required an excluded medication [25]. 47 participants were enrolled, and the analysis included those with data at specific time points in at least two of the three crossover periods. In the study by Pearlman et al. The safety profile of single-dose montelukast was comparable to placebo [28]. No clinical adverse experiences were reported in 42 out of 51 randomised patients, and no serious clinical or laboratory adverse experiences occurred [28]. Two patients receiving montelukast reported mild to moderate drug-related adverse experiences (nausea and nervousness), and both completed the study [28]. Out of 51 patients randomised, 49 completed the study [28], with two discontinuations (asthma and influenza) occurring while taking montelukast. Overall, the investigated treatments – montelukast, salmeterol, albuterol/budesonide, FF/VI, and FP – were well tolerated, with most adverse effects being mild and infrequent. Serious adverse events were rare and generally unrelated to the study medications. Dropout rates varied across studies, but most discontinuations were due to non-drug-related factors, reinforcing the overall safety and tolerability of these therapies for managing EIB.

In summary, montelukast demonstrated sustained protection against EIB, often outperforming salmeterol. Albuterol/budesonide provided rapid, significant protection. The FF/VI versus FP comparison did not show statistically significant differences in long-term bronchoprotection, though numerical trends favoured FF/VI. The consistent use of standardized exercise challenge tests and FEV1 measurements, along with robust study designs, strengthens these findings.

Limitations

This review has several limitations that should be considered when interpreting the findings. Firstly, the number of completed phase 3 and 4 clinical trials investigating EIB remains limited, reducing the ability to draw firm conclusions. Secondly, there was marked heterogeneity in study populations, including differences in age groups, fitness levels, and asthma severity, which limits generalisability. Publication bias may have influenced the analysis, as studies with positive results are more likely to be published. Furthermore, the absence of long-term follow-up in many trials restricts evaluation of sustained intervention effects.

Importantly, this review was not registered in PROSPERO or OSF, reducing transparency and reproducibility. In addition, a formal risk of bias assessment and evidence quality grading (e.g., GRADE) was not performed, lowering the certainty of the conclusions.

Finally, a meta-analysis was not conducted. This decision was based on substantial clinical and methodological heterogeneity across the included studies. The reviewed trials varied in design (randomised vs. observational), patient populations (children vs. adults, different asthma severities), interventions (different drugs, doses, and administration schedules), and outcome definitions (spirometric thresholds, symptom scores, recovery times, or biomarkers). Such variability precluded generation of a valid pooled effect estimate and would risk producing misleading results.

Conclusions

This systematic review shows that exercise-induced asthma (EIA) is primarily mediated by osmotic and thermal mechanisms leading to transient airway narrowing. Diagnosis relies on spirometry and standardized exercise challenge tests, with emerging methods such as diaphragm electromyography offering potential improvements. Effective prevention and treatment combine pharmacological strategies – short-acting beta-2 agonists, inhaled corticosteroids, and leukotriene receptor antagonists – with non-pharmacological approaches such as warm-up routines and breathing retraining. However, the lack of standardized diagnostic criteria and robust long-term trials underscores the need for further research to optimize patient-specific managemen.

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