Online publication ahead of print, AJMHS Vol 64, 2024

Impact of Physical Activity on Exercise Induced Asthma with a Focus on Possible Allergies in Young Athletes: An Overview

Ornela Marko[1*], Klotilda Vrenjo[2], Surven Metolli[1]

[1] Sports University of Tirana, Department of Movement and Health, Tirana, Albania
[2] Sports University of Tirana, Department of Sports Medicine, Tirana, Albania

Abstract

This study explores the impact of physical activity on exercise-induced asthma (EIA) with a particular focus on potential allergens affecting young athletes. Physical activity is widely recognized for its health benefits; however, it can also exacerbate respiratory conditions, especially during endurance sports, as suggested in recent studies. Exercise-induced asthma, characterized by bronchial obstruction post-physical activity, affects the lungs by declining their function. In many cases, this type of asthma is associated with individuals who already suffer from the disease. Various theories explain the causes of EIA, including mediator release from mast cells, osmotic theory, inflammatory responses, and neurogenic origins. It has been shown that endurance athletes are at an increased risk of developing asthma, emphasizing the need for effective diagnosis and management strategies. Exercise-induced asthma, representing an important problem for both recreational and competitive athletes, poses significant challenges for athletes, affecting their performance, health, and quality of life. However, there are studies supporting that when organized exercise, mainly on a recreational level, takes place, athletes and other individuals may experience many

Address for correspondence: Ornela Marko*, Sports University of Tirana, Department of Movement and Health, Tirana, Albania. E-mail: omarko@ust.edu.al

health advantages.

Sensitization to environmental allergens further complicates the condition, making it crucial to understand and monitor these risk factors. This study aims to compile and present the main causes of EIA in young athletes to aid researchers in developing rapid diagnostic and treatment strategies. The findings underscore the importance of balancing physical activity's health benefits with the risks it poses to individuals with underlying respiratory conditions.

Keywords: Asthma, Athletes, Exercise-induced asthma, Allergies, Respiratory health

INTRODUCTION

Exercise-induced asthma (EIA) is considered an important medical condition affecting the lower respiratory tract, mainly characterized by obstruction of the bronchi after physical activity. Thus, it is deduced that physical activity is one of the many stimuli that can cause episodes of airway blockage in young individuals. This is particularly important for individuals who participate in competitive sports. The fact that athletes participating in endurance and winter sports such as swimming or running have a higher probability of being affected by asthma development is well known (1,2,3,4). Previous studies have shown that there are two distinct clinical entities of asthma among elite athletes (5). Different theories attempt to explain the threshold of physical exertion that triggers asthma from effort. The osmotic theory (6), the change of airway epithelium (7), and the cold temperatures that pass through the airways, which cause heat loss, are some of the traditional mechanisms postulated.

Based on these theories, it appears that mast cell activation and mast cell inflammation are the primary causes of exercise-induced asthma flare-ups (8,9). Exercise-induced bronchoconstriction (EIB), caused by physical activity and appearing in athletes during their daily exercising activities without other symptoms of clinical asthma, has recently been subject of discussion. The comparison between these two asthma entities, clinical asthma and exertional asthma, is made to determine the similarity or differences in their pathophysiology and clinical manifestations. The explanatory model for EIB among athletes still leaves several questions unanswered (10,11).

Speculations have been made regarding the influence of rigorous training activity on the autonomic system and its functions. Indeed, enhanced parasympathetic activity of the pupillary light reflex was observed in endurance athletes whose autonomic nervous system activity was measured by pupillometry. Increased parasympathetic tone may stimulate broncho-motor tone, increasing the risk of bronchospasm. However, to the best of the authors' knowledge, there is only limited research on how dysautonomia affects asthma and bronchial hyper responsiveness (BHR) (12,13).

Theoretically, it should be possible to observe the therapeutic effects of anticholinergic drugs in these athletes as a proof-of-concept for this notion. Asthmatic top athletes would need to exhibit a higher exhaled breath temperature during exercise to support the cooling hypothesis as the mechanism causing EIA, which would also be anticipated in the presence of airway inflammation. Young competitive swimmers are more likely to develop asthma, suggesting that airway inflammation and hyper responsiveness develop over their training career. Although the latter appears to be a temporary event, the question of whether airway inflammation persists is still up for debate.

Since many factors and theories are involved in the induction of asthma in athletes, we hypothesize that listing all these factors would be

of great interest to researchers developing new strategies to rapidly diagnose and treat asthma in athletes. Thus, the aim of this study is to present the main known causes that may lead to exercise-induced asthma in young athletes and individuals.

1. Exercise, physical activity, and asthma

Since physical activities and sports are considered crucial elements of a healthy lifestyle, all individuals are encouraged to engage in such activities (14,15,16). It has been scientifically proven that regular physical activity can help prevent several medical conditions such as cardiovascular diseases, diabetes mellitus, obesity, and hypertension (17,18,19,20,21,22). According to international recommendations, children and teens should engage in enjoyable, moderate-intensity physical activity every day for at least 60 minutes (23). Moreover, young individuals who are physically active have shown better levels of cardiorespiratory endurance compared to those who are not (24). In terms of asthma, research has demonstrated that physical activity enhances cardiopulmonary fitness and may even improve the quality of life for asthmatics, both in children and their caregivers (25,26,27). It has been theorized that moderate-intensity physical activity may lead to lower IgE levels overall and in response to specific allergens. Furthermore, it has been demonstrated that lung capacity and airway control in children and adolescents improve with vigorous swimming training (28,29). It has also been noted that swimming training in hot, muggy weather is less asthmogenic. Thus, swimming has emerged as a very popular sport among children with and without asthma and should be suggested as an adjunctive therapy to medication in asthmatic patients (30).

However, in many cases, physical activity is considered a significant promoter of bronchoconstriction, which can exacerbate symptoms in asthmatic individuals. Since some symptoms may cause distress in asthmatic patients, they tend to avoid physical activities, which can negatively affect their social and physical well-being. When young asthmatic patients participate in professional or non-professional sports activities, symptoms can worsen, leading to flare-ups and poorer performance (31)

2. Athletes with asthma

While regular high-intensity exercise conducted by professional athletes has been linked to the development of asthma and bronchial hyper responsiveness (BHR), organized exercise at a recreational level has been found to be advantageous (32). The growing prevalence of asthma and BHR among elite athletes in endurance sports has received particular attention in recent years. Young competitive swimmers showed an increase in nonspecific bronchial reactivity following intense endurance training as early as 1989. Additional investigations verified that intense endurance training raised BHR and airway inflammation. Such findings were corroborated in the Olympic setting by the documented frequency of exercise-induced asthma (EIA), which was 11% among American

summer Olympic athletes in 1984. This prevalence climbed to over 20% among American athletes competing in the summer Olympic Games in 1996. Therefore, it is well recognized that elite athletes have a higher risk for developing asthma, especially those who participate in winter sports and endurance sports like swimming or running. Both recreational and competitive athletes struggle with asthma, which affects them more frequently than the general population. The most prevalent chronic illness among Olympic athletes is EIA, which has significant effects on their health, competitive performance, and overall quality of life. There is ample evidence that exercise-induced bronchoconstriction (EIB) affects athletes of all levels quite frequently. According to the population investigated and the methodologies used, a number of studies conducted on Olympic or elite-level athletes have confirmed a prevalence of EIB ranging between 30% and 70% (33,34).

3. Exercise-induced asthma: variability and definition

It has been documented since biblical times that exercise can cause asthma symptoms in susceptible individuals. Exercise can be the main cause of acute asthma attacks in professional athletes who have been clinically diagnosed with the condition, and up to 90% of all asthma sufferers are thought to be hypersensitive to exercise (35). However, the term "exercise-induced asthma" (EIA) didn't become well-known until the 1960s and 1970s when a few studies focused on the pattern of airway response to exercise and the impact of medications on EIA, particularly in youngsters. Defining and identifying asthma brought on by participating in sports has not always been straight forward, and the idea that exercise may only cause bronchial obstruction in asthmatic people has been called into question (36).

Due to this, a Joint Task Force was established in 2008, which defined exercise-induced asthma (EIA) as asthma symptoms and indications that appear after vigorous physical activity. Exercise-induced bronchoconstriction (EIB) was defined as the decline in lung function that appears after a standardized workout. This topic has generated debate. According to the American Academy of Allergy, Asthma & Immunology Work Group Report, EIA is the condition in which exercise causes asthma symptoms in people who already have the disease, whereas EIB refers to airway obstruction that happens in connection with exercise regardless of whether a person has chronic asthma. These contrasting views highlight the challenges in not just diagnosing asthma but also in comprehending the various pathways that can be connected to asthma heterogeneity. Without other signs of clinical asthma, EIB in athletes has peculiar clinical and pathological characteristics (37).

In recent years, defining asthma phenotypes has been a top priority since it would help with etiology and pathophysiology research, targeted treatment and preventive measures, and better long-term outcome prediction. There is currently

no evidence to support clusters of grouping characteristics for asthmatic athletes, even though it is widely acknowledged that it is highly unlikely that the asthmatic condition that manifests during their athletic career is identical to what is typically considered asthma in clinical practice. Many athletes diagnosed with EIA do not report any family history of asthma, suggesting that environmental conditions may play a crucial role. However, this statement cannot be definitive since even these professional athletes do not experience any symptoms of asthma while at rest. This may imply that none of their family members experienced asthma symptoms. Additional research is mandatory to determine whether and how the asthma phenotype of professional athletes differs from that of classical asthma (37,38).

The pattern of "classical asthma" is characterized by early onset of asthma in childhood, BHR diagnosed by methacholine challenge, atopy, and signs. Cluster analysis has been used most recently to define various illness characteristics. However, these techniques have not yet been used on the population of athletes. Additionally, no attempt has been made to determine whether the various phenotypes are connected to participation in various sports. A deep understanding of such distinct phenotypes would provide further knowledge and understanding of the underlying mechanisms of asthma in elite athletes as well as improve diagnosis and treatment (37,38).

4. Asthma in athletes: underlying causes

Mediator release from mast cells was believed to be the main contributor to cause EIB. The time needed for mast cell recharging during the refractory period after a positive exercise challenge, as well as the preventative impact provided by mast cell stabilizing drugs like sodium cromoglycate, supported this notion. Although the release of mediators does play a role in the development of EIB, the pathophysiologic alterations brought on by vigorous exercise are unquestionably more complex. Even though the pathophysiology of EIA is not fully understood, it is currently commonly believed that it is multifactorial, presumably brought on by exercise-induced increased breathing, and these alterations in airway physiology are the likely culprits (38).

In order to supply the higher oxygen demands of the working muscles during exercise, the ventilatory rate must be increased. This increased ventilatory rate tests the airways' ability to prepare the inhaled air to the proper moisture and heat levels before it reaches the alveoli. Inhaling larger quantities of relatively cold and dry air due to vigorous exercise causes the respiratory mucosa to lose heat (39).

The osmotic theory, often known as the airway-drying hypothesis, is one of the traditional proposed explanations. Presumably, the primary cause of water loss, mucosal cooling, and dehydration appears to be exercise-induced increased ventilation (40). At a heart rate of 140

bpm, water is exhaled at a rate roughly four times higher than at rest, or 60–70 mL/h. Water loss is 7 mL/h when the humidity and temperature of the inspired air are 35°C and 75%, respectively. However, when these conditions are adjusted to -10°C and 25%, lung water excretion jumps to 20 mL/h. The increased ventilation causes the airway surface liquid to become hyperosmolar as water evaporates, providing an osmotic stimulus for water to move from nearby cells. This causes cell shrinkage and the release of inflammatory mediators, leading to airway smooth muscle contraction and obstruction (41).

Increased ventilation during exercise cools the surface epithelium of the airways, in addition to inflammatory mediators released by the osmotic change. Airway cooling activates cholinergic receptors, increasing the smooth muscle tone and secretions of the airways. According to the cooling hypothesis, breathing in cold air causes pulmonary vasoconstriction and heat loss from the respiratory mucosa. The process of re-warming would result in secondary hyperemia, enhancing capillary permeability and contributing to fluid leakage from the capillaries into the submucosa. Mast cells would be triggered to release inflammatory mediators, causing airway inflammation and bronchoconstriction, resulting in airway edema in predisposed individuals (8).

5. The inflammatory theory

Few studies have been performed to show the inflammatory basis of exercise-induced bronchoconstriction (EIB), but in general, injury to the airway epithelium, overexpression of cysteinyl leukotrienes, relative under protection of prostaglandin E2, and greater airway eosinophilia are the main distinctive features indicating an inflammatory basis of asthma (42,43). Hallstrand and colleagues confirmed a connection between columnar epithelial cells in induced sputum and the severity of EIB, as well as a link between the number of these cells and the concentration of histamine and cysteinyl leukotrienes in the airways, demonstrating the importance of mediator release (44). Other authors state that athletes have higher quantities of chemical mediators such as histamine, cysteinyl leukotrienes, and chemokines, as well as cellular inflammatory markers in their airways (45). Eosinophilia and/or an increase in epithelial cells are two examples of these cellular indicators. Damage-associated molecular patterns (DAMPs) have recently been found to be more prevalent in the sputum of athletes, and they may function as precursors to pro-inflammatory cytokines (46).

Interestingly, lung function, BHR, or illness exacerbations are not always associated with the inflammatory markers found in athletes' airways. Studies on the impact of asthma medications, such as the anti-inflammatory medicine inhaled corticosteroids in professional ice hockey players and cross-country skiers, have shown no benefit or just a partial effect on asthma-like symptoms, BHR, or airway resistance or inflammation within cells. Whether they had asthma or not, adolescent cross-country skiers showed

symptoms of inflammation over one competitive winter season, according to Sue-Chu and colleagues (47). Considering all the above, it has recently been suggested that the elevated levels of inflammatory cells in the airways found in athletes may be the result of a secondary physical injury brought on by intense hyperpnoea that heals with rest, rather than a primary component suggesting adverse consequences on respiratory health (48).

Exhaled breath temperature (EBT) has been studied recently with the presumption that airway inflammation will affect the temperature of the air leaving the alveoli and will correlate with the severity of airway inflammation. In fact, research has demonstrated a correlation between EBT and bronchial blood flow, percentage of exhaled nitric oxide (FeNO), and the quantity of eosinophils in sputum in both asthmatic adults and children (49,50).

6. The theory of neurogenic origin

The presumption that atropine, which blocks post-ganglionic vagal pathways, may decrease the excessive bronchoconstriction to non-immunological stimuli showed the participation of a parasympathetic neural reflex in the constrictor response of asthma. Since the discovery of the non-adrenergic, non-cholinergic (NANC) system and neuropeptides, the idea that asthma is purely an immunological disease has given way to the idea that there is a complicated interaction between immunological and neurogenic systems, or even a state of imbalance. In reality, the parasympathetic nervous system is crucial for controlling bronchial secretory activity and airway tone (51,52,53). While β2-adrenergic sympathetic and/or non-cholinergic parasympathetic nerves bronchodilate, cholinergic-parasympathetic nerves induce bronchoconstriction. In humans, parasympathetic (cholinergic) innervation predominates at the bronchial level, whereas sympathetic innervation is far less common. However, regarding EIB, cooling of the airways caused by hyperpnea of cold air induces reflex parasympathetic nerve stimulation, leading to bronchoconstriction through stimulation of the vagal nerve. Further studies are mandatory to observe mechanisms of bronchial tone modulation and their potential role in the development of BHR (54).

The autonomic dysregulation brought on by high-intensity and extended physical training may be an individual and exercise-specific etiologic factor for EIB. Cross-sectional research indicates that, compared to untrained subjects, endurance-trained individuals exhibit increased parasympathetic activity. According to De la Cruz and colleagues, intense endurance training is thought to affect autonomic control, boosting vagal activity predominance as a protective mechanism against the sympathetic stimulation brought on by frequent, severe training (55). The parasympathetic system modulates airway tone, so it makes sense to assume that hyperactivity of that system would produce an increase in basal broncho-motor tone and contribute to a greater likelihood of developing BHR. The vagal

hegemony also causes the well-known resting bradycardia of athletes (56).

After intense exercise, elevated levels of substance P, one of the main triggers of neurogenic inflammation, have been observed in the blood. Additionally, long-term, vigorous activity is linked to higher serum levels of nerve growth factor in athletes (57,58).

7. Athletes' asthma risk factors

The patient's pre-exercise health or sport-specific factors may influence how exercise-induced asthma is affected. For instance, an amplification of these mechanisms should be anticipated when there is pre-existing airway inflammation or bronchial hyper responsiveness (BHR), such as in a patient with allergic asthma. Athletes who regularly engage in severe exercise may be more susceptible to upper respiratory tract infections during high exercise times and for a few weeks after competition events. The type of exercise (for example, indoor or outdoor) and the conditions unique to the sport (for example, winter and aquatic sports) affect the quality of inspired air. Additionally, it has long been known that atopy has a favorable correlation with asthma and a higher BHR in athletes (59). It is well established that extrinsic and intrinsic elements can both have an impact on an athlete's quality of life and athletic performance. The proportional roles of these factors in understanding the severe bronchospasm observed in different populations of athletes are still unknown, though (60)

Swimming and cold-weather training have both been linked to an increased risk of developing asthma. Athletes who are exposed to environments with high concentrations of particulate matter and/or gaseous irritants, such as indoor swimming pools, are more likely to develop asthma and exercise-induced bronchoconstriction (EIB). Athletes who engage in high ventilation sports like cross-country skiing, long-distance running, and swimming are more likely to develop EIB than those who engage in low ventilation sports because the deposition of pollutants during high-ventilation exercise is greater than at rest, allowing more irritants to reach the distal airways. According to studies, swimming has the highest frequency of asthma and EIB compared to other aquatic disciplines, and aquatic endurance sports have a greater prevalence of asthma and EIB than aquatic non-endurance sports (61).

It has been previously observed that exposure to cold air causes parasympathetic activation of airways, which contributes to EIB, and that hyperpnea with cold, dry air represents a considerable environmental stress to airways. Adolescent cross-country skiers have been seen to have evidence of inflammation (lymphoid follicles and tenascin deposition) in their bronchial biopsies over the course of one competitive winter season (62).

8. The significance of effective management

More focus is needed for professional athletes regarding the fast diagnosis and management of exercise-induced asthma, since their general health and competitive abilities can both be

affected by the condition. Many times, asthma is misdiagnosed and frequently left untreated (63). However, medical physicians and researchers have to face the fact that making a proper diagnosis may be challenging due to moderate and mild symptoms, which may not be severe enough to significantly affect breathing and athletic performance. Thus, symptoms are often considered poor indicators of asthma in athletes. Conversely, some athletes might not be very motivated to report respiratory issues to avoid the stigma associated with having asthma and doping suspicions from their peers. Recent revelations indicate that Olympic competitors' compliance with therapy was quite low. Lack of knowledge about the symptoms of exercise-induced breathing problems, the prevalence of exercise-induced bronchoconstriction (EIB) and bronchial hyper responsiveness (BHR) among athletes, and the side effects of asthma medications may make it difficult for athletes, especially young ones, to recognize these symptoms. There is evidence that in many cases, the prevalence of physician-diagnosed asthma is low (64), while there are others stating the contrary in highly developed countries (4), especially when self-reporting is used as a routine method to diagnose these medical conditions.

Considering all of the above-mentioned facts, screening of all athletes may be of great interest to avoid late diagnosis and management of asthma in professional athletes. Indeed, many organizations support testing athletes for asthma, while many athlete organizations have created EIB screening programs for their internationally competitive athletes.

CONCLUSIONS

Several factors can exacerbate Exercise-Induced Asthma (EIA) in both young athletes and other individuals. Current theories and research predominantly focus on mediators released from mast cells, the osmotic and inflammatory theories, neurogenic origins, and other asthma risk factors. EIA can manifest through various clinical symptoms that, in many cases, are not distinct enough to facilitate a diagnosis, as they resemble symptoms of common asthma and other respiratory medical conditions. However, greater attention from medical physicians is essential to ensure early and accurate diagnosis. Implementing self-reporting measures should be prioritized and tailored for use in both low-income countries and higher-developed ones, aiming for earlier detection of these medical conditions.

Acknowledgements: None declared.

Conflict of Interest Statement: The author declares that have no conflict of interest.

REFERENCES

1. Korini G, Kocova O, Abani L, Vikani E, Vini T. Polymorphisms of cytochrome P464 genes in three ethnic groups from Albania. Albanian J Med Health Sci 2012;29:252-60.

2. Elers J, Pedersen L, Backer V. Asthma in elite athletes. Expert Review of Respiratory Medicine 2011;5(3):343-51.

3. Pedersen L, Elers J, Backer V. Asthma in elite athletes: pathogenesis, diagnosis, differential diagnoses, and treatment. The Physician and Sports medicine 2011;39(3):163-71.

4. Rasmussen SM, Hansen ESH, Backer V. Asthma in elite athletes - do they have Type 2 or non-Type 2 disease? A new insight on the endotypes among elite athletes. Frontiers in Allergy 2022;21 (3):973004.

5. Irewall T, Söderström L, Stenfors N. High incidence rate of asthma among elite endurance athletes: a prospective 4-year survey, Journal of Asthma 2021;58 (6):735-741.

6. Haahtela T, Malmberg P, Moreira A. "Mechanisms of asthma in Olympic athletes - practical implications." Allergy 2008;63(6): 685-694.

7. Kudo M, Ishigatsubo Y, Aoki I. Pathology of asthma. Frontiers in Microbiology 2013;10 (4):263,2013.

8. Anderson SD, Kippelen P. "Airway injury as a mechanism for exercise induced bronchoconstriction in elite athletes." Journal of Allergy and Clinical Immunology 2008;122 (2): 225-235.

9. Hallstrand TS, Altemeier WA, Henderson WR. Jr. Role of cells and mediators in exercise-induced bronchoconstriction. Immunology and Allergy Clinics of North America 2013;33(3):313-28.

10. Amin K. The role of mast cells in allergic inflammation. Respiratory Medicine 2012;106 (1) 9 – 14.

11. Park HK, Jung JW, Cho SH, Min KU, Kang HR. What makes a difference in exercise-induced bronchoconstriction: an 8 year retrospective analysis. PLoS One 2014;30:9(1):e87155.

12. Oliver JP, Andrew J. Simpson, Exercise and asthma – trigger or treatment?, Respiratory Medicine 2023; 213,107247.

13. de Freitas Dantas Gomes EL, Costa D. Evaluation of functional, autonomic and inflammatory outcomes in children with asthma. World J Clin Cases 2015;16;3(3):301-9.

14. Couto M, Silva D, Santos P, Queirós S, Delgado L, Moreira A. Exploratory study comparing dysautonomia between asthmatic and non-asthmatic elite swimmers, Revista Portuguesa de Pneumologia (English Edition) 2015;21,(1):22-29.

15. Malm C, Jakobsson J, Isaksson A. Physical Activity and Sports-Real Health Benefits: A Review with Insight into the Public Health of Sweden. Sports (Basel) 2019;7(5):127.

16. Eather N, Wade L, Eime R. The impact of sports participation on mental health and social outcomes in adults: a systematic review and the 'Mental Health through Sport' conceptual model. Systematic Reviews, 2023;12:(102).

17. Congsheng L, Kayani S, Khalid A. An empirical study of physical activity and sports affecting mental health of university students. Frontiers in Psychology 2022;13:917503.
18. Pojednic R, D'Arpino E, Bantham A. The Benefits of Physical Activity for People with Obesity, Independent of Weight Loss: A Systematic Review. International Journal of Environmental Research and Public Health 2022;19 (9):4981.
19. Cleven L, Krell-Roesch J, Woll A. The association between physical activity with incident obesity, coronary heart disease, diabetes and hypertension in adults: a systematic review of longitudinal studies published after 2012. BMC Public Health 2020;20,(726).
20. Wyszynska J, Ring-Dimitriou S, Mazur A. Physical Activity in the Prevention of Childhood Obesity: The Position of the European Childhood Obesity Group and the European Academy of Pediatrics. Frontiers in Pediatric 2020; 8:535705.
21. Kriska AM, Rockette-Wagner B, DPP Research Group. The Impact of Physical Activity on the Prevention of Type 2 Diabetes: Evidence and Lessons Learned From the Diabetes Prevention Program, a Long-Standing Clinical Trial Incorporating Subjective and Objective Activity Measures. Diabetes Care 2021;44 (1):43-49.
22. Wake AD. Antidiabetic Effects of Physical Activity: How It Helps to Control Type 2 Diabetes. Diabetes, Metabolic Syndrome and Obesity 2020;1913:2909-2923.
23. Arija V, Villalobos F, Pas a Pas Research Group. Effectiveness of a physical activity program on cardiovascular disease risk in adult primary health-care users: the “Pas-a-Pas” community intervention trial. BMC Public Health 2017;17 (1) 576.
24. Physical Activity Guidelines Advisory Committee "Physical Activity Guidelines Advisory Committee report, 2008. To the Secretary of Health and Human Services. Part A: executive summary." Nutrition Reviews 2009;67 (2): 114-120.
25. Refaat A, Gawish M. Effect of physical training on health-related quality of life in patients with moderate and severe asthma. Egyptian Journal of Chest Diseases and Tuberculosis 2015 64 (4); 761-766.
26. Zhu Q, Zhu J, Xu Q. A Meta Analysis of Physical Exercise on Improving Lung Function and Quality of Life Among Asthma Patients. Journal of Asthma and Allergy 2022;(15):939-955.
27. Denche-Zamorano Á, Pastor-Cisneros R, Barrios-Fernández S. Physical Activity Frequency and Health-Related Quality of Life in Spanish Children and Adolescents with Asthma: A Cross-Sectional Study. International Journal of Environmental Research and Public Health 2022; 19, 14611.
28. Bovard JM, Welch JF, Sheel AW. Does competitive swimming affect lung growth? Physiological Report 2018 6 (15):e13816.
29. Päivinen M, Keskinen K. Tikkanen H.

Swimming-induced changes in pulmonary function: special observations for clinical testing. BMC Sports Science, Medicine and Rehabilitation 2021;13, (55).

30. Nyenhuis MSH, Kahwash B., Nanda A. Recommendations for Physical Activity in Asthma: A Work Group Report of the AAAAI Sports, Exercise, and Fitness Committee. The Journal of Allergy and Clinical Immunology: In Practice 2022;10 (2) 433-443.

31. Del Giacco SR, Firinu D, Carlsen KH. Exercise and asthma: an overview. European Clinical Respiriry Journal 2015;3(2):27984.

32. Correia Junior MAV, Costa EC, Barros LCB, Soares AA, Sarinho ESC, Rizzo JA, Sarinho SW. Physical activity level in asthmatic adolescents: cross-sectional population-based study. Revista Paulista de Pediatria 2019;37(2):188-193.

33. Pigakis KM, Stavrou VT, Gourgoulianis K. Exercise-Induced Bronchospasm in Elite Athletes. The Cureus Journal of Medical Science 2022;3;14(1):e20898.

34. Zeiger SJ, Weiler MJ. Special Considerations and Perspectives for Exercise-Induced Bronchoconstriction (EIB) in Olympic and Other Elite Athletes. The Journal of Allergy and Clinical Immunology: In Practice 2020;8;(7);2194-2201.

35. Gawlik R, Kurowski M, Bartuzi Z. Asthma and exercise-induced respiratory disorders in athletes. The position paper of the Polish Society of Allergology and Polish Society of Sports Medicine. Advances in Dermatology and Allergology 2019;36(1):1-10.

36. Koya T, Ueno H, Kikuchi T. Management of Exercise-Induced Bronchoconstriction in Athletes, The Journal of Allergy and Clinical Immunology: In Practice 2020;8 (7); 2183-2192.

37. Bonini M, Palange P. Exercise-induced bronchoconstriction: new evidence in pathogenesis, diagnosis and treatment. Asthma research and practice 2015; 1(2).

38. 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, Asthma & Immunology. American Academy of Allergy, Asthma & Immunology Work Group report: exercise-induced asthma. Journal of Allergy and Clinical Immunology 2007;119(6):1349-58.

39. Hallstrand TS. New insights into pathogenesis of exercise-induced bronchoconstriction. Current Opinion in Allergy and Clinical Immunology 2012;12(1):42-8.

40. Julien DP, Thijs MHE, Hein AMD. Exercise under heat stress: thermoregulation, hydration, performance implications, and mitigation strategies. Physiological Reviews 2021;101(4), 1873-1979.

41. Xiong D, Martin JG, Lauzon AM. Airway smooth muscle function in asthma. Frontiers in Physiology 2022;13:993406.

42. Montuschi P. Role of Leukotrienes and Leukotriene Modifiers in Asthma. Pharmaceuticals (Basel) 2010;3(6):1792-1811.

43. Peebles RS Jr. Prostaglandins in asthma and allergic diseases. Pharmacology & Therapeutics 2019;193:1-19.
44. Hallstrand TS, Moody MW, Henderson WJR. "Airway immunopathology of asthma with exercise-induced bronchoconstriction." Journal of Allergy and Clinical Immunology 2005;116(3): 586-593.
45. Lumme A, Haahtela T, Helenius I. "Airway inflammation, bronchial hyperresponsiveness and asthma in elite ice hockey players." European Respiratory Journal 2003;22(1): 113-117.
46. Seys SF, Hox V, Bullens DM. "Damage-associated molecular pattern and innate cytokine release in the airways of competitive swimmers." Allergy 2015;70(2): 187-194.
47. Sue-Chu M, Karjalainen EM, Bjermer L. "Lymphoid aggregates in endobronchial biopsies from young elite cross-country skiers." American Journal of Respiratory and Critical Care Medicine 1998; 158: 597-60.
48. Jatakanon A, Lim S, Barnes P J. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. Thorax 1998;53(2):91-5.
49. Bonsignore MR, Morici G, Vignola AM, Riccobono L, Bonanno A, Profita M, Abate P, Scichilone N, Amato G, Bellia V, Bonsignore G. Increased airway inflammatory cells in endurance athletes: what do they mean? Clinical and Experimental Allergy 2003;33(1):14-21.
50. Gao J, Wu F. Association between fractional exhaled nitric oxide, sputum induction and peripheral blood eosinophil in uncontrolled asthma. Allergy, Asthma and Clinical Immunology 2018;14, (21).
51. Wine JJ. Parasympathetic control of airway submucosal glands: central reflexes and the airway intrinsic nervous system. Autonomic Neuroscience 2007;30;133(1):35-54.
52. Canning BJ. Reflex regulation of airway smooth muscle tone. Journal of Applied Physiology 1985;101(3):971-85.
53. Audrit KJ, Delventhal L, Nassenstein C. The nervous system of airways and its remodeling in inflammatory lung diseases. Cell and Tissue Research 2017;(367) 571–590.
54. De la Cruz F, Geisler M, Bär KJ. Central autonomic network alterations in male endurance athletes. Scientific Reports 2022;12, 16743.
55. D'Amato M, Molino A, Calabrese G, Cecchi L, Annesi-Maesano I, D'Amato G. The impact of cold on the respiratory tract and its consequences to respiratory health. Clinical and Translational Allergy 2018;30 (8):20.
56. Coote JH, White MJ. Cross Talk proposal: bradycardia in the trained athlete is attributable to high vagal tone. Journal of Physiology 2015;15;593(8):1745-7.
57. El-Sayes J, Harasym D, Nelson AJ. Exercise-Induced Neuroplasticity: A Mechanistic Model and Prospects for Promoting Plasticity. The Neuroscientist 2019;25(1):65-85.
58. Lippi G, Mattiuzzi C, Gomar FS. Updated overview on interplay between physical exercise, neurotrophins, and cognitive function in humans.

Journal of Sport and Health Science 2020; 9(1);74-81.

59. Suh DI, Koh YY. Relationship between atopy and bronchial hyperresponsiveness. Allergy, Asthma and Immunology Research 2013;5(4):181-8.

60. Mountjoy M, Fitch K, Verhagen E. Prevalence and characteristics of asthma in the aquatic disciplines. Journal of Allergy Clinical Immunology 2015;136(3):588-94.

61. Almagro BJ, Sáenz-López P, Fierro-Suero S, Conde C. Perceived Performance, Intrinsic Motivation and Adherence in Athletes. International Journal of Environmental Research and Public Health 2020;16;17(24):9441.

62. Ciprandi G, Vizzaccaro A, Canonica GW. Underdiagnosis and Undertreatment of Asthma: A 9-Year Study of Italian Conscripts. International Archives of Allergy and Immunology 2001; 125:211-215.

63. Mäki-Heikkilä R, Karjalainen J, Parkkari J, Valtonen M, Lehtimäki L. Asthma in Competitive Cross-Country Skiers: A Systematic Review and Meta-analysis. Sports Medicine 2020;50(11):1963-1981.

64. Langdeau JB, Boulet LP. Prevalence and mechanisms of development of asthma and airway hyperresponsiveness in athletes. Sports Medicine 2001;31(8): 601-616.