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Exercise-induced bronchoconstriction in children: Delphi study and consensus document about definition and epidemiology, diagnostic work-up, treatment, and follow-up

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Abstract

Background Exercise-induced bronchoconstriction (EIB) is common in children with asthma but can be present also in children without asthma, especially athletes. Differential diagnosis includes several conditions such as exercise-induced laryngeal obstruction (EILO), cardiac disease, or physical deconditioning. Detailed medical history, clinical examination and specific tests are mandatory to exclude alternative diagnoses. Given the high prevalence of EIB in children and its potential impact on health, sport performance, and daily levels of physical activity, health care professionals should be aware of this condition and able to provide a specific work-up for its identification. The aims of the present study were: (a) to assess the agreement among hospital pediatricians and primary care pediatricians of Emilia-Romagna Region (Italy) about the management of EIB in children and (b) formulate statements in a consensus document to help clinicians in daily clinical practice.

Methods According to Delphi method, a panel of specialists scored 40 statements that were then revised and discussed during online meetings to reach full consensus. Statements were then formulated.

Results To obtain full consensus, the questionnaire was administered in two rounds after full discussion of the uncertain topics on the basis of the latest evidence on EIB published over the last 10 years. Despite an overall agreement on EIB management, some gaps emerged in the sections dedicated to diagnosis and treatment. Nine summary statements on definition, pathogenesis, diagnostic work-up, treatment, and follow-up were eventually formulated.

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Conclusions This study describes the knowledge of EIB in a group of pediatricians and highlights gaps and uncertainties in diagnosis and treatment. The creation of statements shared by the specialists of the same area may improve the management of EIB in children. However, more research and evidence are needed to better clarify the best treatment and to standardize the best diagnostic protocol limiting useless examinations but at the same time assuring the best management.

Keywords EIB, Asthma, Exercise induced asthma, Exercise induced bronchoconstriction, Children, EILO, Vocal cord dysfunction, Athletes, Deconditioning, Consensus

Introduction

Exercise-induced respiratory symptoms were first described in 1962 [1].

The term "exercise-induced bronchoconstriction" (EIB) was coined in the 70's and indicated the narrowing of the airways after or during physical activity that could occur both in asthmatic or non-asthmatic patients [2–5].

The American Thoracic Society (ATS) Clinical Practice Guideline proposed to differentiate the use of the term EIB between EIB occurring in asthmatic patients (EIBa—EIB with asthma) and EIB in patients without typical signs or symptoms of asthma (EIBwa—EIB without asthma) highlighting that some people with EIB may not have a diagnosis of asthma [5]. An underlying undiagnosed asthma, individual susceptibility, presence of atopy, duration and intensity of physical exercise [6, 7] and environmental conditions, such as cold air, high atmospheric pressure, relative humidity and pollutants [8, 9] are the factors that can influence onset and severity of EIB. The prevalence of EIB in children can be high especially in subjects with asthma and in athletes [10–14]. Accurate medical history about reported symptoms including onset, characteristics and duration, full physical examination and specific tests can suggest and demonstrate EIB [15, 16].

A prompt diagnosis followed by targeted treatment can prevent children from not doing regular physical activity, improve exercise tolerance and guarantee high performance in those involved in competitive sports.

The aim of the present study was to assess the agreement between specialists of Emilia-Romagna Region (Italy) about the management of EIB in children and formulate statements in a consensus document to help clinicians in daily clinical practice. Clear definition of EIB and indications on diagnosis, treatment and follow-up should help to identify children with EIB, consider referral to tertiary care and promote physical activity also in children with asthma.

Methods

This consensus document has been achieved with Delphi method. A Delphi procedure aims for refinement of collective opinions by participating experts of the panel in order to reach a final consensus on a particular topic. Participants are involved in a series of discussion sessions to assess their opinion on different and controversial topics, based on the published literature. This method is based on the scoring of a series of statements that are revised, scored and discussed by experts in increasing detail in multiple rounds to minimize any disagreement in the answers and until consensus is reached. Their feedback is anonymous [17, 18].

Panel selection

The scientific committee of this study included a multidisciplinary panel of hospital pediatricians experts in pediatric pulmonology or allergology and primary care pediatricians representative of Emilia-Romagna Region. This group is named Emilia-Romagna Asthma (ERA) Study Group and has been described in details in previous publications [19–21]. All panelists were recruited via phone and email contact.

Questionnaire

The project coordinators and the scientific committee developed a questionnaire with 40 statements focusing on 4 main topics selected on the basis of available literature and clinical experience: (1) definition, epidemiology and clinical features; (2) pathogenesis; (3) diagnostic work-up; (4) treatment and follow-up. The complete questionnaire is available in the Supplementary Materials.

The statements were formulated after a careful review of the current scientific literature. Seven reviewers (RG, AG, AR, GZ, MM, NM, SP) independently searched for experimental studies, reviews, systematic reviews, metanalysis and guidelines using the MEDLINE database via the PubMed interface from 1 January 2014 to 30 April 2024 using the following query string: ("pediat*" OR "paediatr*" OR "child" OR "youth") AND ("exercise induced bronchoconstriction" OR "exercise-induced bronchoconstriction" OR "EIB" OR "exercise induced asthma" OR "exercise-induced asthma" OR "bronchoconstriction" OR "exertional asthma"). Only English-language articles were selected. The search was also implemented with older papers when necessary.

In our study Delphi procedure was performed over two rounds with the application Google Forms. In each round, panel members were e-mailed a unique link to the questionnaire. Questionnaires were completed online in a dedicated web platform and voted by the panel of experts using a five-point Likert scale (1 = strongly disagree, 2 = somewhat disagree, 3 = neutral, 4 = somewhat agree, 5 = strongly agree). Statements for which at least 75% of the responses were 1 and 2 (expression of disagreement) or 4 and 5 (expression of agreement) were considered as having reached the consensus. On the other side, statements answered with less than 75% of agreement or disagreement among the experts indicated uncertainty among responders. The results of the questionnaires for each round were analyzed by an independent statistician and reported to participants in plenary discussion during a virtual meeting. During the meeting each statement was supported by related references and those revealing different opinions among the participants (< 75% in agreement or disagreement), were debated and clarified.

A second round of the online questionnaire was then provided to reach the consensus in all the statements; this was followed by a further virtual meeting where the difference between the results of the first and second round was discussed and the panel of experts formulated the final summary statements. Figure 1 shows the diagram of the study design.

Data analysis

Aggregate results were reported as frequencies and means. The data analysis was performed with the STATA® Statistical Software (Release 11 College Station, TX, College Station, TX, USA). The mean value with 95% confidence interval was then calculated. Microsoft Excel® was used for graphic data processing.

Results and discussion

In the first round, a panel of 25 participants joined the survey and completed the entire questionnaire. Response rate was 92% (23/25) in round 2.

The consensus following the discussion of the results of the questionnaire produced 9 summary statements divided as follows:

- Definition, clinical features and epidemiology: 3 statements;
- Pathogenesis: 1 statement;
- Diagnostic work-up: 1 statement;
- Differential diagnosis: 1 statement;
- Treatment and follow-up: 4 statements.

All statements are shown in Table 1.

Definition

Two of the 3 statements (questions 1,3) on definition ("EIB may be the only symptom of asthma" and "EIB is not common in people with asthma") showed consensus during the first survey while uncertainty was initially observed about the presence of EIB in atopic subject without a diagnosis of asthma (question 2 "EIB may be present in people with atopic diseases without asthma"). After the first round, following the discussion of the results and the review of the literature, the panelists reached the consensus also on this topic.

Initially, the term 'Exercise-Induced Asthma' (EIA) [22] was coined to indicate the narrowing of the airways occurring during or after physical exercise in asthmatic patients [2, 23, 24]. However, in 1970 the term EIB was introduced to indicate the acute and transitory narrowing of the airways during or after physical activity that could occur also in non-asthmatic patients [25].

The American Thoracic Society (ATS) Clinical Practice Guideline proposed to differentiate the use of the term EIB between EIB occurring in asthmatic patients (EIBa—EIB with asthma) and EIB in patients without typical signs or symptoms of asthma (EIBwa—EIB without asthma) [5]. When presenting in patients without asthma, EIB exhibits distinctive clinical and pathological characteristics [26] and may not be associated with bronchocostriction when the patient is not practicing physical activity [27]. However EIBwa can be a predictor of future asthma and an early sign of bronchial hyperresponsiveness [2, 4, 10]. Allergic rhinitis, a personal history of allergies, and atopic dermatitis contribute higher risk of EIB even in absence of asthma [13, 28].

Statement 1 (questions 1–3): *EIB is characterized by acute and transitory narrowing of the airways during or after physical activity. EIB can manifest as unique symptom of asthma but can be also present in people without asthma, more frequently if atopic.*

Clinical features

All statements about clinical features of EIB (questions 5 "EIB may occur during or after exercise", question 6 "EIB typical symptoms include cough, wheezing, dyspnea, and chest tightness", question 26 "Stridor is a characteristic symptom of EIB") showed consensus of the participants during the first survey.

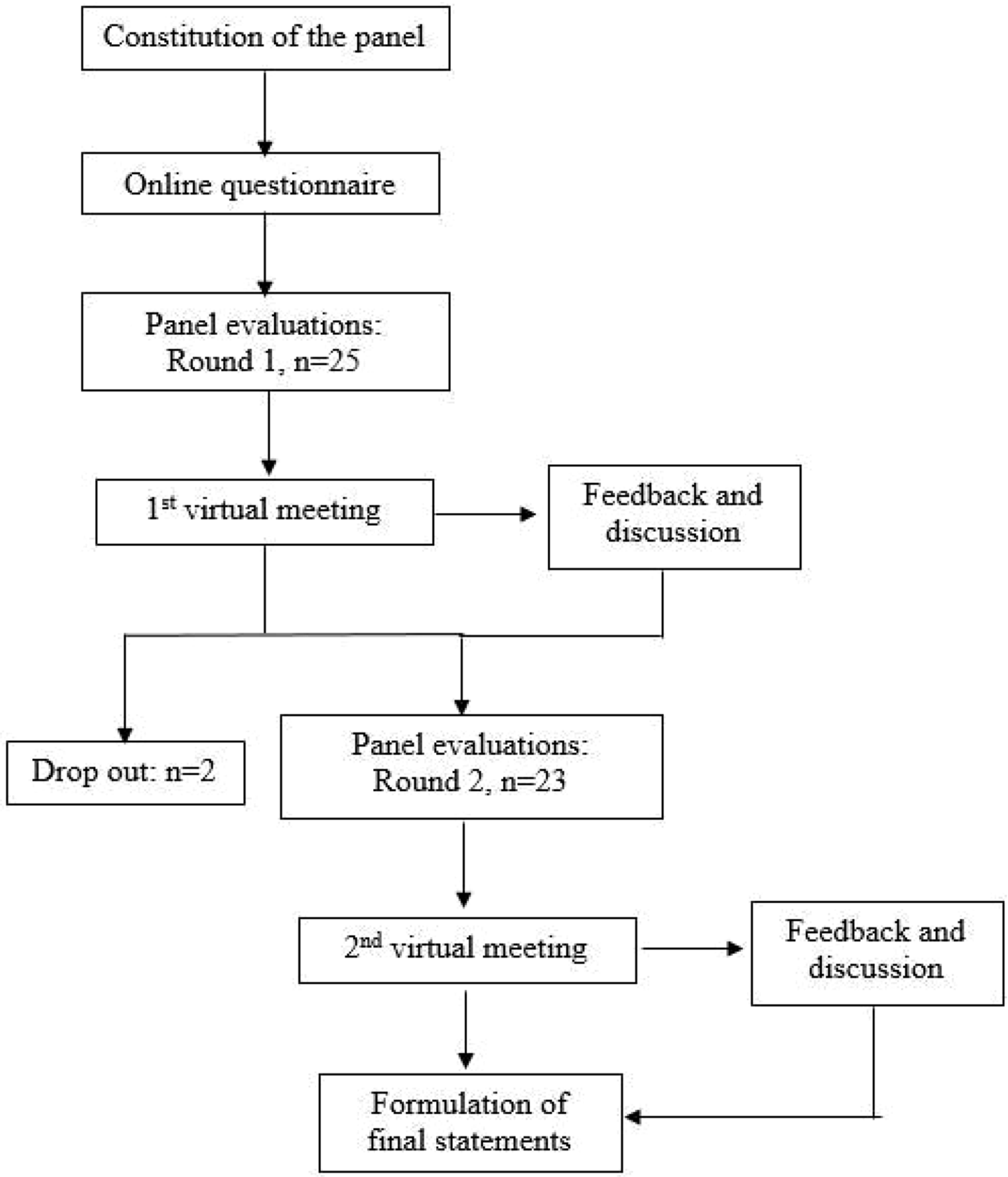

Fig. 1 Study design

Common symptoms of EIB include cough, dyspnea, wheezing, chest tightness, increased respiratory effort, diminished performance, and increased fatigue or sense of reduced fitness in physically fit patients [11, 29]. In children stomachache or sore throat may also be indicators of EIB [29–32]. EIB usually manifests after exercise and typically starts within 15 min, after 5 to 8 min of high-intensity aerobic training and with a peak after 10 min. Symptoms spontaneously resolve within approximately 60 min [11, 32–34]. In asthmatic children, the time to reach maximal bronchoconstriction after exercise is shorter compared to non-asthmatic children [29, 31].

Statement 2 (questions 5, 6, 26): *Typical symptoms of EIB include coughing, shortness of breath, wheezing, fatigue, and chest tightness. They usually manifest after 5–10 min of high intensity aerobic training and resolve within 15–60 min.*

Epidemiology

All statements about epidemiology of EIB showed consensus of the participants during the first survey (Question 4 "EIB is a contraindication to competitive sport activity", question 5 "EIB may occur during or after

Table 1 Final summary statements

Definition, clinical features and epidemiology
● Statement 1: EIB is characterized by acute and transitory narrowing of the airways during or after physical activity. EIB can manifest as unique symptom of asthma but can be also present in people without asthma, more frequently if atopic
● Statement 2: Typical symptoms of EIB include coughing, shortness of breath, wheezing, fatigue, and chest tightness. They usually manifest after 5–10 min of high intensity aerobic training and resolve within 15–60 min
● Statement 3: The prevalence of EIB is higher in asthmatic patients than in general population, ranging from 40 to 90%, especially in children and in severe and poorly controlled asthma. In non-asthmatic patients, EIB is more frequent in athletes (especially those who practice endurance sports, exposed to cold air, allergens or pollutants), atopic, and obese subjects
Pathogenesis
● Statement 4: The underlying mechanisms responsible for EIB are complex and not fully understood. "Osmotic" and "thermal" theories have been proposed. Environmental factors, such as low temperature, low humidity, exposure to allergens and pollution, and individual factors like atopy and airway inflammation play a role in triggering EIB
Diagnostic work-up
● Statement 5: Exercise challenge test on the treadmill is used to diagnose EIB in adults and in older children. Free running test should be used in younger and/or not collaborative children. After at least 6 min of maximal exercise the subject stops and performs spirometry after 5, 10, 15 and 30 min. A reduction in FEV_1 of at least 10% within 30 min after the exercise test is diagnostic for EIB
Differential diagnosis
● Statement 6: EILO can mimic EIB but EILO typically manifests with inspiratory stridor during the activity, does not respond to salbutamol, and it is more common in female athletes. Deconditioning and several medical conditions like cardiac or neuromuscular diseases should be taken into consideration as differential diagnosis depending on medical history, symptoms, and examinations
Treatment and follow-up
● Statement 7: SABA 15–20 min before physical exercise is the first therapeutic choice in patients with EIB. In children with EIB symptoms despite SABA or requiring frequent and/or daily administration of SABA, daily asthma treatment with ICS, LTRA or ICS/LABA should be considered to control bronchial inflammation. In children aged ≥ 12 years on maintenance and reliever treatment with ICS/formoterol, an extra dose can be administered as needed before activity to prevent EIB
● Statement 8: Some behaviors are strongly recommended to prevent EIB: warm-up and cool-down exercises before and after exercise, avoid physical activity when the temperature is cold or in excessively polluted environments (consider the use of a mask), avoid active and passive smoking, practice physical exercise routinely, avoid exposure to allergens, correct weight excess
● Statement 9: Children with EIB can practice physical activity and competitive sports if symptoms and asthma are under control with adequate treatment. Sports where the inhalation of salbutamol would be difficult, like diving, are generally discouraged. Regular assessments are suggested to review treatment and guarantee the recommended levels of physical activity

exercise", question 7 "EIB may be a cause for which the child avoids physical activity", question 8 "EIB is more frequent in patient with poorly controlled asthma", question 9 "EIB does not occur if physical activity takes place indoors").

EIB prevalence varies among populations depending on age, type and level of activity, coexistence of asthma or atopy. Exercise intolerance caused by EIB can be a limitation for children who practice physical activity contributing to sedentary habits and low performance if engaged in competitive sports.

The prevalence of EIB in the general population ranges between 5 and 20% [28, 34], with children and adolescents being more susceptible to EIB with prevalence up to 45% [35]. This reported variability is influenced by demographic and geographical factors and also by methods used for detecting the condition [28].

In children and adolescents with asthma, the prevalence of EIB is higher and estimated to range between 20 and 90% [10–14]. EIB is more frequent in severe or poorly controlled asthma patients compared to those with well-controlled or mild asthma [10, 11, 36].

Atopy plays a major role in EIB: not only asthma but also atopic dermatitis, sensitization to house dust mites [37] or cats [38], and elevated IgE levels are associated with greater risk of EIB [37, 38].

Furthermore, polysensitization rather than monosensitization, significantly increased the risk of EIB in children aged 5 to 10 years [28].

The prevalence of EIB in athletes is higher than in general population but varies depending on the studied population, with a higher occurrence observed in those engaged in endurance activities such as long-distance running, cycling, triathlon, and pentathlon [11]. According to a recent systematic review, the prevalence rate of EIB among general athletes is 23% [39], higher than in general population, while for Olympic athletes is 8% [40].

EIB can be particularly present in endurance athletes because of the high intensity and frequency of training. In these subject EIB is primarily associated with the significant increased minute ventilation through mouth breathing (bypassing nasal filtration) and with the exposure to external factors such as cold temperature (like for athletes involved in winter sports), pollutants, chlorine (like for swimmers) or allergens (like athletes of indoor sports sensitized to house dust mite) [41, 42]. Regarding winter sports, the prevalence of asthma and EIB in cross-country skiers increases with age and higher prevalence has been identified in athletes with longer history of competitions [43–45]. The increased risk of EIB in subjects practicing winter sports could be attributed to the greater inhalation of cold air during training and competitions that favors bronchoconstriction according to the "osmolar theory" (see Pathogenesis section) [46, 47] as demonstrated by a reported prevalence of EIB in summer sports of 23%, and in winter sports of 55% [48]. On the other hand, in physical activities performed on ice surfaces like hockey or figure skating, the increased release of pollen from fossil-fueled ice resurfacing machines and the presence of ultrafine particles from polishing machines [47] on ice rinks used by the players can increase the risk of EIB [49, 50]. Swimming, traditionally considered a safe sport for asthmatic patients, may also be associated with EIB. This risk for EIB has been explained by the "pool chlorine hypothesis" [51] that associates the exposure to chlorine and organic chlorine products used for pool disinfection, such as trichloramine [52, 53], with development of EIB in certain subjects. On the contrary, other data suggested that pool swimmers may have some protection against bronchoconstriction [54]. Hence, the hypothesis regarding chlorinated pools remains debated and long-term studies are required to definitively determine whether chlorinated swimming pools plays any role in the development of EIB.

Obesity can negatively impact the respiratory system [55] but the threshold where obesity starts to harm lung function and physical performance is not clearly defined, as it may differ significantly among individuals [56, 57]. In children the relationship between asthma, physical fitness, and overweight is complex and not completely understood [57–59].

Ozgen et al. [60] found that obese children exhibited lower functional exercise and lung capacities compared to non-obese children. Body mass index (BMI)-z-score was strongly associated with EIB in asthmatic boys, even in children with normal weight and the severity of EIB was significantly higher in overweight or obese children [61]. Furthermore, Forno et al. [62] showed how obesity and overweight were harmful to lung function with lower lung volumes, especially in patients without asthma. Several potential mechanisms have been proposed to explain this association [132]: truncal adiposity can exert pressure on the diaphragm and chest wall (with a reduction in lung volumes and functional residual capacity); metabolic dysregulation (including insulin resistance, dyslipidemia, and altered adipokine secretion) can have systemic effects on inflammatory pathways and immune responses, which may influence airway inflammation by the secretion of various proinflammatory cytokines and adipokines (leptin above all) [134]; and airway dysanapsis may contribute to airflow limitation, increased airway resistance, and potentially exacerbate asthma symptoms [130].

Malmberg et al. [63] assessed the association between BMI and EIB in a large sample of children with respiratory symptoms and they found that higher BMI was associated with lower exercise performance and increased perception of respiratory symptoms, such as coughing and dyspnea, but not with EIB or exercise-induced wheeze. The absence of a direct association between BMI and EIB or exercise-induced wheeze suggests that other factors, such as airway inflammation or hyperresponsiveness may play a role. On the other hand, Souza de Almeida et al. [64] demonstrated that obese asthmatic children were at increased risk of experiencing bronchoconstriction, particularly those with moderate or severe asthma, with a more delayed recovery than their non-obese peers.

Furthermore, obese children may exhibit obesity-related issues and conditions such as gastroesophageal reflux disease (GERD) and chest tightness that might lead to dyspnea, which could be misinterpreted as asthma [58]. Further studies in children with EIB and overweight or obesity are essential for developing evidence-based strategies for preventing and managing both conditions effectively.

Statement 3 (questions 4, 5, 7–9): *The prevalence of EIB is higher in asthmatic patients than in general population, ranging from 40 to 90%, especially in children and in severe and poorly controlled asthma. In non-asthmatic patients, EIB is more frequent in athletes (especially those who practice endurance sports, exposed to cold air, allergens or pollutants), atopic, and obese subjects.*

Pathogenesis

The survey revealed uncertainty about the underlying cause of EIB and especially about the "thermal theory" (question 10 "EIB is caused by the cooling of airways due to increased ventilation") and about the role of cold as a triggering factor for EIB (question 12 "Cold temperature is one of the factors that contributes to the onset of EIB"). Both topics were clarified during the discussion after the first round and consensus was reached in the second round. The remaining statements showed consensus already during the first survey (question 11 "EIB is caused by dehydration of the airways following increased ventilation", question 13 "Air pollution is one of the factors that contribute to the onset of EIB", question 14 "Exposure to allergens is one of the factors that contributes to the occurrence of EIB").

The mechanisms involved in EIB are complex and not yet fully understood. Two main theories have been proposed: the "osmotic theory" and the "thermal or vascular theory". Both theories might work together and are based on bronchoconstriction and airway edema occurring during exercise [6]. According to the "osmotic theory", bronchoconstriction is induced by hyperosmolarity of airway cells, caused by water loss through evaporation when airways need to warm and humidify the cold and dry air inspired into the airways during the hyperventilation of exercise. The hyperosmolarity resulting from drying and cooling of the airways causes hyperflux and degranulation of eosinophils and mast cells with release of inflammatory mediators (histamine, interleukins, tryptase, leukotrienes and prostaglandins) responsible for smooth muscle contraction and mucus production in the bronchial tree [9, 51, 65]. Several studies have demonstrated the predominant role of cysteinyl leukotrienes (CysLTs) as bronchoconstriction mediators in bronchoalveolar lavage (BAL) of asthmatic patients [66, 67].

On the other hand, the "thermal or vascular theory" consists in bronchial vasoconstriction and subsequent rapid rewarming with vasodilation following the contact with cold air. As a result, vascular congestion and increased microvascular permeability results in bronchial edema and bronchoconstriction [9, 51, 65].

Environmental conditions such as low air temperature and low air humidity have been shown to damage the airway epithelial barrier promoting bronchial inflammation and hyperresponsiveness. There is strong evidence that athletes exposed to these conditions have increased levels of epithelial damage and airway inflammation [38, 50, 68]. In sports with elevated risk factors, such as swimmers exposed to chlorine and athletes exposed to cold air, the prevalence is up to 75% [48, 51, 69]. The climatic condition is crucial for EIB. Several studies, conducted in pediatric populations, demonstrated that EIB is more severe in cold and dry environments than in humid and warm regions with greater reduction of forced expiratory volume in the first second (FEV_1), peak expiratory flow (PEF) and maximum expiratory flow rate at 50% of vital capacity (MEF_{50}) [68, 70].

These data support the aforementioned "theories" on the pathogenesis of EIB. In addition, the presence of air pollutants can significantly increase the risk of EIB. A study conducted among young competitive athletes, aged 12 to 18 years, showed the increased bronchial hyperresponsiveness in those exposed to air pollution, especially particulate matter 10 μm (PM_{10}). Air pollution exposure was responsible for greater epithelial damage and airway inflammation [50]. Another pollutant, which contributes to the onset of EIB is nitrogen dioxide (NO_2), as shown by Sanchez KM et al. who demonstrated in their cross-sectional pilot study that the personal daily exposure to NO_2 correlated with decrease in lung function after physical exercise [52].

Allergic rhinitis, a personal history of allergies, and atopic dermatitis contribute to higher risk of EIB [13]. Indeed, according to epidemiological evidence, as many as 40% of patients with allergic rhinitis (AR) suffer from EIB, especially those with persistent untreated signs and symptoms [13]. Other studies have shown that atopy, elevated IgE levels, and sensitization to house dust mites are associated with EIB [37, 38]. Another risk factor that may expose the subject to the onset of EIB are frequent respiratory tract infections, since the increasing level of damage-associated molecular patterns (DAMPs) released by the damaged airway epithelium have been shown to facilitate the release of proinflammatory cytokines like TNF, IL-1b or IL-6 [13, 71] that may lead to bronchial hyperresponsiveness and onset of EIB symptoms.

Statement 4 (questions 10–14): *The underlying mechanisms responsible for EIB are complex and not fully understood. "Osmotic" and "thermal" theories have been proposed. Environmental factors, such as low temperature, low humidity, exposure to allergens and pollution, and individual factors like atopy and airway inflammation play a role in triggering EIB.*

Diagnostic work-up

Some concerns have emerged in the discussion of this section. Uncertainty emerged about: spirometry as gold standard test to diagnose EIB (question 15 "Spirometry is the gold standard test to diagnose EIB"), heart rate percentage to be achieved during the exercise test (question 17 "During an exercise challenge test the child must reach at least 50% of its maximum heart rate"), timing of spirometry after the test (question 19 "The first spirometry is performed after 3 min of running" and question 20 "The first spirometry is performed 5 min after the end of the exercise challenge test"), value of FEV_1 needed to diagnose EIB severity (question 24 "The severity of EIB can be classified based on the reduction of FEV_1") and the possibility that a normal spirometry could exclude EIB (question 25 "The exercise challenge test may be negative even if the subject suffers from EIB"). The remaining statements obtained sufficient agreement during the first survey (question 16 "Exercise challenge test is the gold standard test to diagnose EIB", question 18 "During an exercise challenge test the child must reach at least 80% of its maximum heart rate", question 21 "Forced Expiratory Volume in the first second (FEV_1) is assessed in the exercise challenge test", question 22 "The exercise challenge test is considered positive if FEV1 is reduced by 5%", question 23 "The exercise challenge test is considered positive if FEV1 is reduced by 10%".

In children, EIB diagnosis is based on measurement of lung function changes caused by physical exercise or surrogate challenges [5]; medical history and physical examination cannot demonstrate EIB or predict EIB severity [4, 72]. However, a basal spirometry can confirm a suspicion of asthma in case of bronchial obstruction and positive response to bronchodilator [73]. Exercise challenge test, a non-invasive test conducted in real-life setting, usually takes place in a controlled environment such as pulmonary function testing laboratory or clinic, and assess bronchial response to exercise through spirometry [74]. The standardized treadmill running (TR) test is the most widely adopted exercise challenge test [5] and can be performed by collaborative children. The performance on treadmill is usually more accurate if children are used to run during their regular physical activity [74]. When the child does not cooperate or when treadmill test is not available, cycle ergometer exercise, free running or 3-min step test can provide alternative method to assess response to physical activity [75, 76]. In all cases, the child has to reach a rapid rise in work rate to stimulate bronchoconstriction and to avoid the bronchoprotective effect of prolonged warm-up or low-level exercise [77–79]. The test on the treadmill is usually performed in a controlled environment, in an air-conditioned room with a temperature between 20 and 25 °C and low humidity, ideally 50% or less [80]. The target heart rate (95% of maximal heart rate calculated as 208—0.7 * age) or minute ventilation should be achieved within 2–3 min by progressively but rapidly increasing speed and incline, and then maintained for at least 6 min [80–84]. When possible, measuring ventilation through a mouthpiece or a mask provides a more accurate assessment of bronchial reactivity [80]. FEV_1 is then measured at specific intervals after exercise, typically at 5, 10, 15, and 30 min [5, 85]. Further time points above 30 min (occasionally 45 to 60 min after exercise) can be added depending on clinical history.

The pre-exercise FEV_1 value must be compared with the lowest FEV_1 value recorded at the different time points and this reduction must be expressed as a percentage [5]. EIB can be diagnosed if the decrease of FEV_1 at any time point is $\geq 10\%$ [3–5, 81, 84]. This value must increase to 15% for the exercise challenges using cycle ergometry or for the free running test [4]. EIB severity is categorized according to FEV_1 reduction as mild ($\geq 10\%$ but $< 25\%$), moderate (≥ 25 but $< 50\%$), and severe ($\geq 50\%$) [4, 5]. For severe EIB, a further classification takes into consideration steroid treatment and describes as severe a decrease in FEV_1 after exercise $\geq 50\%$ in steroid-naïve patients and $\geq 30\%$ in steroid-treated patients [85]. Onset of symptoms of EIB with interruption of the test is diagnostic for EIB. False negatives may occur mainly due to suboptimal test conditions and cannot exclude EIB [77–79, 86].

Absolute contraindications to exercise test include fever, heart diseases (such as pericarditis, myocarditis or uncontrolled heart failure), dyspnea at rest, $SpO_2 < 85\%$ in air, predicted $FEV_1 < 50\%$, uncontrolled hypertension or diabetes, acute kidney disease or acute hepatitis, recent pneumothorax/pneumomediastinum and recent thoracic surgery.

Short-acting beta$_2$-agonists (SABA), long-acting beta$_2$ agonists (LABA), theophylline, ipratropium or leukotriene receptor antagonists (LTRA), antihistaminic and systemic steroids should be avoided before the test (SABA: 8 h; LABA: 24 h; anticholinergic drugs: 12 h; antileukotrienes: 24 h; cetirizine: 3 days).

Statement 5 (questions 15–25): *Exercise challenge test on the treadmill is used to diagnose EIB in adults and in older children. Free running test should be used in younger and/or not collaborative children. After at least 6 min of maximal exercise the subject stops and performs spirometry after 5, 10, 15 and 30 min. A reduction in* FEV_1 *of at least 10% within 30 min after the exercise test is diagnostic for EIB.*

Differential diagnosis

In the first round, exercise-induced laryngeal obstruction (EILO) and deconditioning were not considered as limitations for physical activity (question 27 "EILO does not limit physical activity" and question 29 "Deconditioning enters into differential diagnosis with EIB"). These two statements were discussed and clarified in the first virtual meeting and reached the consensus in the second-round questionnaire.

The need for cardiological evaluation (question 28 "A cardiological examination should always be carried out in case of EIB") remained a matter of debate also in the second round since the statement did not reach full consensus and was further discussed in the second virtual meeting.

The remaining statements obtained sufficient agreement during the first survey.

The differential diagnosis of reduced exercise tolerance includes many potential causes. When spirometry is not suggestive for peripheral bronchial obstruction, typical sign of asthma, or when anomalies in lung function test do not improve after short-acting beta$_2$-agonists administration, more considerations must be done.

EILO is a laryngeal disorder characterized by inappropriate closure or narrowing of the vocal folds and/or supraglottic structures during physical exercise [87–92]. The reported prevalence is between 5 and 10% [88, 90, 93, 94] with higher rates in adolescents and young adults [95], particularly girls [88, 94]. The narrowing of the vocal folds occurs during high-intensity exercise and ventilation, typically during inspiration. Symptoms include breathing difficulty, coughing, chest pain and throat tightness during physical activity [95], with the hallmark feature of stridor, a wheeze or whistle sound during inspiration. Symptoms usually resolve within a few minutes of stopping the exercise and when ventilation is normalized

[90, 96]. In contrast, asthma and EIB typically present with expiratory breathing difficulties and wheezing, especially after exercise [44, 90]. EILO and EIB can coexist, explaining persistent breathing problems during exercise despite effective asthma therapy in some subjects [88, 94]. The test to diagnose EILO is continuous laryngoscopy during exercise (CLE) [95, 97–99]. This involves visualizing the laryngeal structures with a flexible laryngoscope while the patient exercises on a treadmill or stationary bicycle. The ear-nose-throat (ENT) specialist observes real-time changes in the larynx during peak exertion, with the laryngoscope secured in place through the nose. Simultaneously, cardiopulmonary data are collected [90, 97, 98, 100]. Spirometry can be useful but not conclusive, as patients with EILO often have normal flow volume loops with no signs of obstruction [101].

Dyspnea, cough, wheezing, and chest pain are not exclusive to EIB [18]. Physical deconditioning is a common cause of dyspnea and exercise intolerance in children and adolescents, even in those who are physically trained, as it depends on overall health, particularly cardiovascular and pulmonary conditions [102, 103]. Deconditioning leads to reduced physical activity, worsening performance, and metabolic changes that promote inflammation and decrease muscle mass [104–106]. Cardiopulmonary exercise testing (CPET) helps distinguishing between functional physical limitation and deconditioning. Deconditioned subjects show reduced anaerobic threshold (< 50%) or maximal oxygen consumption (VO_2) max (< 80%) at symptom onset and an excessive heart rate increase for a given workload, while those with physiological limitations have a normal or elevated VO_2 max. If medical history is strongly suggestive for EIB and CPET is normal, the test can be repeated to confirm or discard the diagnosis to confirm that during the test maximal values have been achieved and that submaximal values have not mistakenly accepted [107].

Also having high BMI is associated with lower exercise performance and increased respiratory symptoms [57–59, 63]. Increased BMI is associated with low FEV_1/Forced vital capacity (FVC) ratio, suggesting bronchial obstruction [59, 108, 109]. Some studies showed that BMI correlates with EIB in asthmatic boys and that its severity is greater in overweight or obese children [60], while other studies did not confirm this association [63]. Additionally, obese children may exhibit gastroesophageal reflux (GERD) and chest constriction, causing dyspnea misinterpreted as asthma [58].

When spirometry and reversibility tests are inconclusive, the exercise challenge test can differentiate pulmonary dyspnea from other causes and confirm EIB [82, 83]. Spirometry can sometimes help to differentiate other causes of reduced exercise tolerance. When the expiratory flow–volume curve is flattened in the initial stage of expiration, central airways obstruction like a vascular ring can be suspected. In these cases, a full cardiac examination including echocardiography and sometimes a chest X-ray must be performed. On the contrary, when the inspiratory curve is flattened, laryngeal obstruction can be considered [110]. Cardiac conditions that mimic EIB include cardiomyopathies, arrhythmias, pericarditis/myocarditis, shunting, vascular malformations, pulmonary hypertension, and valvular abnormalities. According to the Italian regulations, electrocardiogram (ECG) must be performed in all children aged 6 years to obtain a certificate and start non-competitive sports; further examinations can be considered depending on clinical history. When medical history reveals dyspnea associated with chest pain and palpitations during physical activity a heart examination is needed. A cardiac work-up is also essential especially with a positive family history for sudden death in young age or cardiac anomalies. Hypertrophic cardiomyopathy causes dyspnea due to left ventricular obstruction during exercise. Diagnosis is supported by echocardiography and high-intensity activities should be avoided due to arrhythmia risks. Paroxysmal tachycardias, especially supraventricular, may occur during fitness testing without underlying heart disease, causing palpitations and exercise-induced dyspnea.

In rare cases, dyspnea and breathlessness can indicate metabolic (e.g., glycogen storage, mitochondrial disorders) and neuromuscular diseases (e.g., myasthenia gravis, demyelinating diseases), with symptoms like easy fatigue and early muscle cramps during physical effort [74]. Myasthenic syndromes, characterized by increased fatigue and evening symptom peaks, require specialist investigation. The prevalence of EIB or asthma in these conditions is unknown. Lung function should be monitored, and CPET can be performed when possible [111]. Salbutamol may improve dyspnea and muscle strength in myasthenic syndromes [112].

Other conditions that can manifest with dyspnea during exercise are dysfunctional breathing disorders including hyperventilation syndrome, exercise-associated gastroesophageal reflux, anemia, severe pectus excavatum, anxiety, hyperventilation syndrome, tracheobronchomalacia, infectious diseases, foreign body inhalation, tumors, and interstitial diseases.

Statement 6 (question 27–29): *EILO can mimic EIB but EILO typically manifests with inspiratory stridor during the activity, does not respond to salbutamol, and it is more common in female athletes. Deconditioning and several medical conditions like cardiac or neuromuscular diseases should be taken into consideration* *as differential diagnosis depending on medical history, symptoms, and examinations.*

Treatment and follow-up

Pharmacological treatment

Uncertainty was initially observed in the first round about: the prescription of salbutamol in competitive athletes (question 32 "Salbutamol cannot be prescribed to the athlete involved in competitive sport because it is a prohibited drug"), the prescription of daily treatments with inhaled corticosteroids (ICS) when SABA alone are not sufficient to solve EIB (question 33 "If salbutamol before physical activity does not prevent EIB, daily therapy with inhaled steroids can be considered") and the prescription of the combination ICS/formoterol as needed before physical activity (question 37 "In subjects with EIB aged > 12 years on daily treatment with ICS/formoterol, an extra inhalation 5–20 min before physical activity is recommended").

These topics reached consensus among the participants during the second-round questionnaire. On the contrary the role of LTRA was uncertain also during the second round questionnaire and further discussed during the second virtual meeting (question 34 "If medication with salbutamol before physical activity does not prevent EIB, daily therapy with leukotriene receptor antagonist can be considered", question 35 "If medication with salbutamol before physical activity does not prevent EIB, administration of leukotriene receptor antagonist before physical activity can be considered", Question 36 "For the prevention of EIB both antileukotrienes and salmeterol are effective").

The remaining statements obtained sufficient agreement during the first survey (question 30 "Salbutamol is the first-choice medication for treating EIB", question 31 "Salbutamol can be taken within 10–15 min before starting physical activity").

SABA is considered the first-choice medication used for prevention and treatment of EIB [113, 114]. SABA [115] must be administered maximum one hour before exercise, preferably 10–15 min before [5, 116]. Medication with inhalation of salbutamol 200 mcg (2 puffs) is usually effective [115, 117] but the dose can be increased up to 400 mcg (4 puffs).

Considering the high prevalence of asthma among athletes [118, 118, 119], the World Anti-Doping Association (WADA) released guidelines about the use of medications for asthma treatment. According to current indications, athletes suffering from documented asthma (spirometry with positive bronchodilator response) can take inhaled SABA, in compliance with the permitted doses [120]. In particular salbutamol is permitted without specific authorization at the maximum dose of 1600 mcg/24 h and 800 mcg/12 h [121]. In all cases, the athlete must provide a certificate with evidence of EIB to be permitted to use medications during competition.

For children with EIB who continue to have symptoms despite using inhaled SABA before exercise, or who require inhaled SABA daily or more frequently, daily therapy should be started to improve control of bronchial inflammation. According to asthma recommendations, this treatment can include ICS, LTRA or ICS/LABA [5] and all are permitted in athletes suffering from documented asthma [120]. Excessive use of SABA (particularly in athletes who practice frequent training) can cause tachyphylaxis and loss of the bronchoprotective effect during physical exercise [122], which is probably caused by desensitization of the beta$_2$ receptors on mast cells and airway smooth muscle [123].

ICS effectiveness on EIB is dependent on duration of therapy and dosage [114]. In children with asthma, prolonged treatment with ICS, alone or in combination with LTRA or LABA, seems to reduce the onset of clinical symptoms induced by exercise challenge test [123]. However, LTRAs are less effective than beta2 agonists [124]. In 2020, the U.S. Food and Drug Administration (FDA) released a warning on LTRA (Montelukast in particular) due to its possible effects on mental health and behavior [125]. Careful assessment of the patient must be considered.

The short-term treatment (for 14 days) with ICS and LTRA in children and adolescents with EIB decreased airway hyperresponsiveness to exercise [126]. Taking a single dose of ICS before exercise seemed to be effective in preventing EIB in children with mild asthma [127] and in one of the most recent studies, a single administration of ICS (beclomethasone dipropionate 200 ug) appeared to be predictive of the effectiveness of a more prolonged treatment (beclomethasone dipropionate 100 ug twice a day for 4 weeks) [128]. A single dose of LTRA is effective in a proportion of children in preventing EIB two hours after administration and up to 24 h later [129, 130].

Regarding LABA, these are not recommended alone and as-needed, since they cause a progressive decrease in their efficacy even after 30 days of treatment, with high risk of asthma exacerbations and greater morbidity and mortality [5]. Alternatively, other preventive medications before exercise such as mast cell stabilizing agents (like sodium cromoglycate and nedocromil sodium) and inhaled anticholinergic agents (like ipratropium bromide) can be considered [5].

On the contrary, the combination ICS/LABA as-needed is an effective medication for EIB. In particular, preventive medication with budesonide/formoterol (200/6 μg) with a single inhalation 5 to 20 min before exercise, in a population with mild asthma aged ≥ 12 years, has proven to be more effective than premedication with SABA in preventing EIB.

EIB was respectively reduced by 28.5% in patients treated with budesonide/formoterol on-demand and increased by 8.9% in those treated with terbutaline on demand [131]. In addition, the inhalation of this combination as needed was not inferior to regular treatment with ICS alone but with a lower dose of taken steroid [131].

Other studies have shown that treatment with fluticasone furoate/vilanterol (92/22 μg) once a day for 30–60 days resulted in a preventive effect against EIB in adolescents with asthma [132].

Some athletes who responded poorly to ICS-only therapy improved after starting ICS/LABA therapy [133]. Formoterol and salmeterol associated with ICS are permitted in asthmatic athletes, at the maximum dose 54 mcg/24 h and 200 mcg/24 h, respectively [121].

Statement 7 (questions 30–37): *SABA 15–20 min before physical exercise is the first therapeutic choice in patients with EIB. In children with EIB symptoms despite SABA or requiring frequent and/or daily administration of SABA, daily asthma treatment with ICS, LTRA or ICS/LABA should be considered to control bronchial inflammation. In children aged ≥ 12 years on maintenance and reliever treatment with ICS/formoterol, an extra dose can be administered as needed before activity to prevent EIB.*

Non-pharmacological treatment

Uncertainty was initially observed about non-pharmacological strategies to prevent EIB, especially for the exercises to practice before intense physical activity (Question 38 "Preventive measures of EIB include warming up and cooling down before and after exercise, respectively") and about the use of a mask in cold environments (question 40 "Warming the breathing air can reduce EIB symptoms"). After review of recent literature and collective discussion, panelists agreed about all non-pharmacological recommendations to prevent EIB. Overall, all the remaining statements in this section obtained sufficient consensus during the first survey (question 39 "For those who suffer from EIB, activity should start with a very intense exercise).

Some behaviors can prevent the onset of EIB. For example, it is recommended to practice warm-up exercises before carrying out physical activity and cool-down exercises at the end [5, 9]. Warming up 10–15 min before exercise is particularly effective to induce a refractory period for EIB of approximately two hours [5]. Also breathing through the nose during exercise can contribute to humidification and warming of the inspired air reducing the risk of EIB [34].

Interestingly, in asthmatic patients practicing regular continuous aerobic exercise, FEV_1, PEF, FVC, and forced expiratory flow $(FEF)_{25-75}$ improve as well as patients' symptoms and quality of life [9]. From an environmental point of view, it is preferable to avoid physical activity in cold climates, in polluted environments or if the exposure to allergens is high. When not possible, the routine use of a device (for example a mouth mask) that warms and humidifies the inspired air during exercise is recommended [5]. In addition, despite the lack of clear evidence, a healthy lifestyle helps to reduce the onset of EIB: exposure to smoking (both active and passive) must be avoided and a healthy diet (for example, preferring a diet rich in vitamin D and omega 3 fatty acids and low in salt) [5, 105] is suggested.

Statement 8 (questions 38–40): *Some behaviors are strongly recommended to prevent EIB: warm-up and cool-down exercises before and after exercise, avoid physical activity when the temperature is cold or in excessively polluted environments (consider the use of a mask), avoid active and passive smoking, practice physical exercise routinely, avoid exposure to allergens, correct weight excess.*

Follow-up

Adequate levels of physical activity are strongly recommended to children with EIB and the condition should not be a limitation. The physical activity pattern practiced by children with EIB should be monitored. Child and the caregivers must be adequately educated on EIB prevention and management of a possible acute episode of EIB. Clear indications on long-term management and follow-up of children with EIB are currently lacking. As suggested for asthma management, follow-up visits can be performed every 3–6 months. EIB symptoms, their occurrence, efficacy of treatment and adherence including administration technique should be assessed. Spirometry should be performed at every visit while exercise challenge test can be repeated depending on symptoms and, when needed, to assess the effectiveness of treatment [5].

Step down or discontinuation of treatment can be considered after a period of wellbeing

Statement 9: *Children with EIB can practice physical activity and competitive sports if symptoms and asthma are under control with adequate treatment. Sports where the inhalation of salbutamol would be difficult, like diving, are generally discouraged. Regular assessments are suggested to review treatment and guarantee the recommended levels of physical activity.*

Conclusions

This study assessed the knowledge on EIB in a group of specialists of our Region highlighting some gaps and stimulating discussion on critical topics. Summary statements have been formulated on the basis of scientific literature and expert opinion to standardize diagnostic and therapeutic approach in patients with suspected EIB and offer guidance to healthcare professionals of our area.

EIB is a common condition in children, especially if they have asthma. Despite the high prevalence, this survey has revealed that specialists were not familiar with some topics, particularly when related to diagnosis and treatment. Not all exercise intolerance is asthma or EIBwa, a child with symptoms triggered by physical activity can have multiple conditions. A systematic approach supported by objective tests is crucial to reach the right diagnosis.

The choice of perform a cardiac examination was a matter of debate. The panel eventually agreed that this is not a first line examination when the symptoms suggest a respiratory condition (i.e. cough or wheezing). However, uncertain diagnosis or the presence of red flags like thoracic pain, syncopal events or family history for sudden cardiac death should lead to further cardiac work-up. A recent diagnostic flowchart for EIB has been proposed by our group [134].

Alternative therapies to SABA must be considered when EIB is not controlled or when the subject needs reliever very often (i.e. multiple times a day or a week). The role of preventer therapies with ICS, LTRA or ICS/LABA was deeply discussed since in the first round several uncertainties had emerged. In these cases, referral to respiratory specialists should be considered since EIB can be the first sign of underlying asthma.

EIB can be the reason why children do not practice regular physical activity. Children with diagnosed EIB are involved in less physical activity than their healthy counterparts and the activity in these children is also reduced in terms of intensity [135]. Chronic absence during school exercise lessons or during athletic training can be a consequence of EIB symptoms. Awareness of this condition among healthcare professionals and families is the first step to improve the management of EIB in this age group and promote physical exercise.

Regular exercise improves asthma control and quality of life, contrast inflammation and airway remodeling [136]. Therefore, asthma is not a contraindication for physical activity or competitive sport, but the disease must be well controlled and the athlete guaranteed with proper training. EIB can be the tip of the iceberg in subjects with underdiagnosed asthma where bronchial inflammation needs to be treated with daily asthma medications such as ICS or a warning sign that asthma is getting worse.

Many are the therapeutic options for EIB, both behavioral and pharmacological, that can be tailored to patient's needs.

The standardization of clinical practices including a specific diagnostic work up can improve the management of EIB in children. However, "research and evidence are needed to better clarify the best treatment and to standardize the best diagnostic protocol limiting useless examinations but at the same time assuring the best management".

Abbreviations

AR	Allergic rhinitis
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BMI	Body mass index
CPET	Cardio-pulmonary exercise testing
CysLTs	Cysteinyl leukotrienes
EIA	Exercise-induced asthma
EIB	Exercise-induced bronchoconstriction
EIBa	Exercise-induced bronchoconstriction with asthma
EIBwa	Exercise-induced bronchoconstriction without asthma
EILO	Exercise-induced laryngeal obstruction
ENT	Ear-nose-throat
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
ICS	Inhaled corticosteroid
LABA	Long-acting $beta_2$ agonist
LTRA	Leukotriene receptor antagonist
MEF	Maximal expiratory flow
MVV	Maximum voluntary ventilation
NO_2	Nitrogen dioxide
PEF	Peak expiratory flow
PM_{10}	Particulate matter 10
SABA	Short-acting $beta_2$ agonist
TR	Treadmill running
WADA	World anti-doping association

Supplementary Information

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Supplementary material 1.

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