

Improving Screening and Diagnosis of Exercise-Induced Bronchoconstriction: A Call to Action

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This article summarizes the findings of an expert panel of nationally recognized allergists and pulmonologists who met to discuss how to improve detection and diagnosis of exercise-induced bronchoconstriction (EIB), a transient airway narrowing that occurs during and most often after exercise in people with and without underlying asthma. EIB is both commonly underdiagnosed and overdiagnosed. EIB underdiagnosis may result in habitual avoidance of sports and physical activity, chronic deconditioning, weight gain, poor asthma control, low self-esteem, and reduced quality of life. Routine use of a reliable and valid self-administered EIB screening questionnaire by professionals best positioned to screen large numbers of people could substantially improve the

detection of EIB. The authors conducted a systematic review of the literature that evaluated the accuracy of EIB screening questionnaires that might be adopted for widespread EIB screening in the general population. Results of this review indicated that no existing EIB screening questionnaire had adequate sensitivity and specificity for this purpose. The authors present a call to action to develop a new EIB screening questionnaire, and discuss the rigorous qualitative and quantitative research necessary to develop and validate such an instrument, including key methodological pitfalls that must be avoided. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:275-80)

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Exercise-induced bronchoconstriction (EIB) is a common clinical problem in persons with asthma and also occurs in some people who lack other features of asthma. Despite evidence-based clinical practice guidelines for the diagnosis and management of EIB,^{1,2} physicians frequently underdiagnose and overdiagnose EIB, which suggests that many physicians are not adhering to these recommendations. Physicians' poor performance in diagnosing EIB may be due to a number of issues, including a lack of awareness of the prevalence and burden of this condition, the absence of an effective screening questionnaire to help detect EIB, and inadequate knowledge about how to further evaluate and treat patients with suspected EIB.

In November 2012, an expert panel composed of 6 nationally recognized allergists and pulmonologists met to discuss unmet needs regarding the detection of EIB in the general population. (Teva Pharmaceuticals sponsored the meeting but had no role in the development of this article.) This article summarizes the panel's findings, and constitutes a call to action to improve widespread screening for EIB and appropriate follow-up for individuals with positive screening results.

PREVALENCE AND BURDEN OF EIB

EIB is an acute bronchoconstriction triggered by exercise, which may occur in the presence of established asthma or in the absence of other features of chronic asthma.^{1,2} Common symptoms of EIB include shortness of breath, wheezing, cough, and chest tightness during or immediately after exercise.^{1,2} More subtle symptoms that may be suggestive of EIB include fatigue, feeling out of shape, feeling unable to keep up with peers, symptoms that occur repeatedly in specific environments (such as pools, ice rinks, or freshly mowed fields), performances that fall

Abbreviations used

AHR- Airway hyperresponsiveness
 ATS- American Thoracic Society
 EIB- Exercise-induced bronchoconstriction
 EVH- Eucapnic voluntary hyperventilation
 FEF_{25-75%}- Forced expiratory flow between 25% and 75% of vital capacity
 FEV₁- Forced expiratory volume in 1 second
 FRAST- Free-running athletic screening test
 NPV- Negative predictive value
 PEFR- Peak expiratory flow rate
 PPV- Positive predictive value
 PRO- Patient reported outcome
 SABA- Short-acting β_2 agonist

consistently below expectations given an athlete's conditioning level, and abdominal discomfort.^{3,4} Exercise is one of the most common triggers of bronchoconstriction in people with asthma and may be the first indication of asthma or an indicator of poorly controlled asthma.⁵ Approximately 40% to 60% of individuals with asthma have EIB.⁶⁻¹¹ Estimates of the prevalence of EIB in the general healthy population (individuals without underlying asthma) range from approximately 5% to 20%.¹ Elite athletes, particularly those who participate in endurance winter sports, are at greater risk for experiencing EIB without a history of asthma than the general population.^{1,12}

EIB reduces participation in sports and physical activities, contributes to poor physical conditioning and obesity, and negatively impacts physical and emotional functioning. Children and adolescents with EIB have significantly lower overall quality of life scores than those without EIB,^{13,14} irrespective of previous asthma diagnosis.¹⁴ The EIB Landmark Survey found that asthma limited participation in sports, recreational, and outdoor activities in 25% to 30% of children and 50% of adults.^{5,15} Almost one-third of children (32%) and one-half of adults (46%) with asthma reported that they avoid activities because of their exercise-related symptoms.^{5,15} Avoidance of exercise and physical activity due to a fear of experiencing EIB symptoms may be the best explanation for the finding of poorer cardiovascular fitness in people with asthma compared with their peers.¹⁶ Low levels of physical activity may contribute to the link between asthma and obesity¹⁷⁻¹⁹ and can adversely affect self-esteem and mental health in both healthy children and those with asthma.^{19,20} In contrast, results of studies showed that exercise may increase fitness and exercise capacity in people with EIB, reduce severity of EIB, improve asthma control, and enhance quality of life.²¹⁻²³

THE CHALLENGES OF DIAGNOSING EIB

Underdiagnosis

Research findings indicate that EIB is frequently underdiagnosed, possibly due to insufficient awareness of EIB and its burden and the lack of a questionnaire to screen effectively for this condition. Many individuals who report symptoms suggestive of EIB or who objectively test positive for EIB have never been formally diagnosed with EIB. In a general population survey, 26% of respondents reported experiencing respiratory symptoms with exercise, but only 5% had been diagnosed with EIB by a physician.⁵ Among 39% of collegiate athletes who objectively tested positive for EIB, only 14% had received a physician diagnosis of asthma or EIB.²⁴ Almost 80% of elite

athletes who had a positive result to bronchoprovocation testing had not been diagnosed with EIB.²⁵ Together, these findings suggest that EIB is underdetected in a variety of populations.

Overdiagnosis

Overdiagnosis of EIB also may occur when physicians base their diagnosis on history and presentation alone, and do not confirm with an objective diagnostic test.^{1,2} Among 142 children who presented with dyspnea that had been previously attributed to asthma, the symptom was reproduced in 117 during exercise testing, but only 11 (8%) met criteria for EIB.²⁶ Most children who did not meet criteria for EIB demonstrated normal physiologic limitation, with poor conditioning identified as the cause of dyspnea in 35% of this group. A survey of athletic trainers affiliated with National Collegiate Athletic Association programs revealed that two-thirds diagnosed EIB on a history of symptoms alone and that only 17% used objective testing.²⁷ In another study, only half of professional soccer players who had a physician diagnosis of EIB had objective evidence of EIB.²⁸ Among 148 athletes referred to an asthma clinic for evaluation, 24% had previously been diagnosed with EIB, but only 8% had prior objective testing for EIB.²⁹ When this sample was objectively tested for EIB, only 50% of the patients previously diagnosed with EIB had their diagnosis confirmed. Among 52 children referred to a respiratory specialist clinic for poorly controlled EIB, only 15% met diagnostic criteria for EIB upon objective testing.³⁰ In contrast, the remaining children were diagnosed with vocal cord dysfunction (27%), poor physical fitness (23%), habit cough (14%), and no abnormality (21%).

Prescribing a trial of short-acting β_2 agonists (SABA) for patients who report symptoms of EIB without objectively establishing the diagnosis appears to be a common practice. In a survey of US family practitioners and pulmonologists, approximately 80% of family practitioners and 50% of pulmonologists reported that they would prescribe SABAs without ordering any diagnostic testing for a patient who presents with exercise-related respiratory symptoms without a history of asthma.³¹ Although it may be convenient to prescribe SABAs based on symptoms alone, this practice may result in suboptimal care for some patients. Patients who do not actually have EIB and who fail to respond to treatment with SABA or other asthma medication may be subjected to the burden of inappropriate therapy, persistent impairment, and a delay in appropriate diagnosis and treatment.¹²

Diagnostic testing

The most recent American Thoracic Society (ATS) EIB clinical practice guidelines recommend laboratory exercise testing, a standardized exercise challenge performed on treadmill (preferably) or bicycle ergometer, to diagnosis EIB (see Figure 1 for the complete algorithm for evaluating patients with suspected EIB).² In a laboratory exercise challenge, exercise intensity is ramped up over 2 to 4 minutes until the target heart rate (80%-90% of the predicted maximum) is reached; the test ends when the patient has exercised at the target ventilation or heart rate for 4 to 6 minutes (for a total exercise time of approximately 10 minutes).² During challenge, relative humidity is controlled so that the subject inspires dry air.³² Lung function tests are performed before exercise and serially after exercise for up to 30 minutes to determine if EIB is present and to quantify the severity of the disorder.²

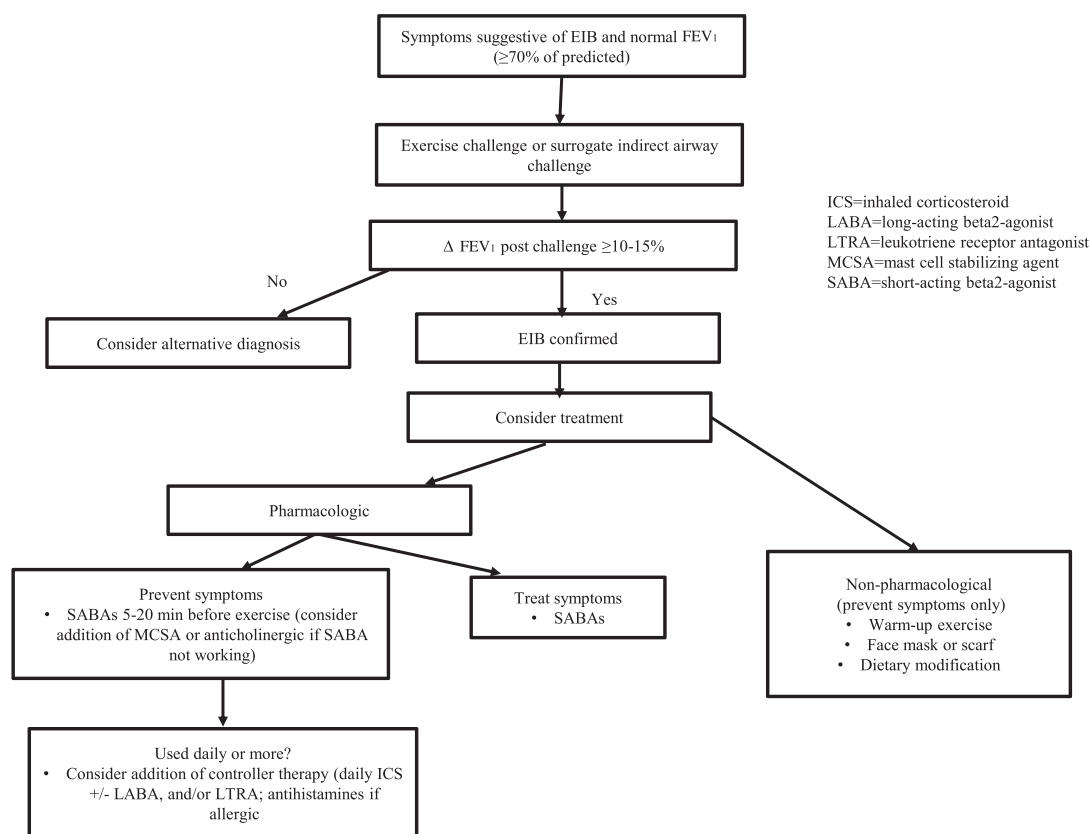


FIGURE 1. Algorithm for evaluating and managing patients with suspected EIB. Reprinted with permission of the American Thoracic Society from Parsons et al.² Copyright © 2013 American Thoracic Society.

The difference between the pre-exercise FEV₁ value and the lowest FEV₁ value (of the best values at each of the time points) recorded within 30 minutes after exercise is expressed as a percentage of the pre-exercise value. A postexercise decrease in FEV₁ of 10% represents 2 SDs lower than the mean in healthy subjects and is often used as the cutoff for defining a positive exercise challenge.^{1,2} However, because the maximum percentage decrease in FEV₁ after exercise challenge is normally distributed, there is no obvious cutoff that is diagnostic of EIB. In past clinical studies, investigators have used thresholds that ranged from 6.5% to 20% to diagnose EIB.³³ Confidence in the diagnosis is increased when the decrease in FEV₁ after exercise is well above 10%. In some pharmaceutical studies, a decrease of as much as 20% to 25% may be required to confirm that EIB is present. Increasing the threshold for a positive exercise challenge may increase the specificity of the test but reduce sensitivity, whereas lowering the threshold may improve sensitivity but increase the false-positive rate. A lower threshold (6.5%) may be appropriate for diagnosing EIB in elite athletes who have a lower mean maximum decrease in FEV₁ than the general population.³³ To develop an evidence-based rationale for defining a positive exercise challenge, studies may be needed to examine the normal distribution curves for exercise challenges in the general population, people diagnosed with EIB, and elite athletes.

The reproducibility of the laboratory exercise challenge response in the general population is unknown, but some variation in response has been seen in people with signs and

symptoms suggestive of asthma. In a study of 373 subjects (ages 6-50 years) who were evaluated for asthma and who completed 2 consecutive standardized laboratory exercise challenge protocols, the majority (76%) had the same outcome on both challenges, but 24% had a positive result on only 1 test.³⁴ Of the 117 subjects who had a positive response to first exercise challenge, 38.5% (n = 45) had a negative response to second challenge. Of the 256 subjects who had a negative response to the first challenge, 17.2% (n = 44) had a positive response to second challenge. Reproducibility was very high in subjects with more severe EIB (average decrease in FEV₁ ≥ 15%) and lowest among those with mild or no EIB (average decrease in FEV₁ < 10%). Analysis of the results of this study suggests that more than 1 challenge conducted days (eg, 5-7 days) apart may be required to establish a definitive diagnosis of EIB. Although repeated exercise challenges may be impractical to evaluate all patients seen in clinical practice, repeated testing would be ideal to determine a definitive diagnosis of EIB in research to validate an EIB screening questionnaire in the general population. Exercise challenge reproducibility data derived from this research, in conjunction with the study described above, would help inform recommendations for both research and clinical practice.

ATS guidelines acknowledge that a number of surrogates for laboratory exercise testing have been developed that may be easier to implement and have some utility for diagnosing EIB, even though they cannot diagnose EIB with 100% sensitivity and specificity.² The advantages and disadvantages of these tests

TABLE I. Advantages and disadvantages of indirect EIB diagnostic tests

	Advantages	Disadvantages
Laboratory exercise challenge	Is the most well-studied diagnostic test; allows for the standardization of the cardiovascular workload and environmental conditions of temperature and humidity	Is not sports specific; is not performed in the environment in which the exercise usually occurs; requires specialized equipment; is time consuming, expensive, and may not be readily available; results may not be highly reproducible; has no dose-response curve; can result in severe decreases in FEV ₁
Field exercise challenge	Can be sports specific; is usually performed in the environment in which exercise typically occurs	Does not allow for standardization of the cardiovascular workload or environmental conditions of temperature and humidity; is time consuming; has no dose-response curve; can result in severe decreases in FEV ₁
Eucapnic voluntary hyperventilation	Is easy to administer; is easily standardized; can be performed quickly; is reproducible; has good sensitivity	Is laboratory dependent; available only in specialized centers; its accuracy compared with laboratory exercise testing has not been well established; has no dose-response curve; can result in severe decreases in FEV ₁ ; may be overly sensitive
Dry mannitol powder	Is easy to administer; can be performed quickly; does not require specialized equipment; can be performed in the office; is safe, reproducible and approved by the US Food and Drug Administration	Its accuracy compared with laboratory exercise testing has not been well established

are summarized in Table I. Eucapnic voluntary hyperventilation appears to be more sensitive than laboratory exercise testing for detecting EIB in some individuals (eg, those with active asthma and athletes) because it can reliably achieve and sustain a higher minute ventilation than that which can be obtained with exercise.³⁵ Therefore, eucapnic voluntary hyperventilation may be considered as a reasonable alternative to laboratory exercise testing as a diagnostic test for EIB.^{36,37}

Physicians' preferred diagnostic tests for EIB are often inconsistent with guideline recommendations. In a survey of US family practitioners and pulmonologists, methacholine challenge (a direct challenge that has poor sensitivity for identifying EIB¹¹ and is not recommended as an alternative to laboratory exercise testing²) was the preferred method of diagnostic testing among both groups; in contrast, exercise testing was the preferred diagnostic method for only 18% and 32% of family practitioners and pulmonologists, respectively.³¹ In a survey of primary care physicians in the United Kingdom, only 12% selected exercise testing with spirometry (FEV₁) as their initial management strategy for an elite athlete who presents with exercise-related respiratory symptoms and mild intermittent asthma.³⁸ In both studies, investigators surmised that limited access to recommended bronchoprovocation testing may influence physicians' selection of EIB diagnostic tests.^{31,38}

Unmet need for an EIB screening questionnaire

We conducted a systematic literature review to synthesize findings from published research studies on the accuracy of existing EIB screening questionnaires to determine if there was a reliable and valid screening questionnaire that might be adopted for widespread EIB screening in the general population. The detailed methods and results of this literature review are presented in Appendix E1 and Table E1 (in this article's Online Repository at www.jaci-inpractice.org). Results of this literature review indicate that there are insufficient data to advocate the

adoption of any existing EIB screening questionnaire for widespread screening in the general population.

There are many potential explanations for the poor accuracy of EIB screening questionnaires evaluated to date. Symptoms suggestive of EIB, including shortness of breath, mucous production, chest tightness, cough, or wheezing during or immediately after sustained exercise, are not specific to EIB and may be due to other conditions (eg, vocal cord dysfunction).² People with EIB may fail to disclose symptoms when asked due to a lack of awareness of EIB, misattribution of EIB symptoms to other causes, or a desire to avoid stigma. The use of different diagnostic tests for EIB and a lack of consensus regarding the definition of a positive test result may contribute to the heterogeneity of findings on the accuracy of EIB screening questionnaires. Finally, failing to adhere to guidelines regarding the protocol for conducting laboratory exercise challenges may contribute to the wide variability of reported sensitivities and specificities of screening questionnaires and alternative diagnostic tests.³⁹

A valid exercise challenge test requires that the proper "dose" is delivered by adhering to specific standards for exercise intensity and duration, and for inspired air humidity and room temperature, and that the response is accurately measured by using serial spirometry.³² A lack of adherence to ATS exercise protocol guidelines could alter the severity of the exercise challenge, which results in the underdiagnosis or overdiagnosis of EIB.³⁹ In a review of 9 studies that used the laboratory exercise test as the reference standard for evaluating the accuracy of alternative diagnostic tests for EIB, only 1 study met all 12 criteria that defined a quality exercise challenge per ATS guidelines.³⁹

Although these barriers are important to acknowledge and address, they do not preclude the possibility of creating a reliable and valid EIB screening questionnaire for use in the general population. It should be noted that none of the EIB screening questionnaires evaluated to date have been formulated by using state-of-the-art methods for developing diagnostic screening

questionnaires, including obtaining respondent input in generating questionnaire items and pretesting questionnaires in targeted study populations using cognitive interviewing, as recommended by US Food and Drug Administration guidance on the development of patient-reported outcome (PRO) measures.⁴⁰ We present detailed recommendations for the production of a new EIB screening questionnaire in [Appendix E1](#). These recommendations include conducting initial qualitative research to develop and pretest questionnaire items, and establishing the validity of the questionnaire through studies designed to avoid common methodologic pitfalls, such as spectrum and verification bias, that have limited the interpretation and generalizability of EIB diagnostic test accuracy research.

A reliable and valid self-administered EIB questionnaire could help detect possible EIB in undiagnosed individuals. Routinely questioning people about their physical activity and exercise-related respiratory symptoms may identify people with possible EIB who are unlikely to volunteer spontaneously such information because of embarrassment about a lack of physical activity, misattribution of exercise-related respiratory symptoms to causes other than EIB (eg, deconditioning, situational fatigue, or lack of effort),²⁶ and lack of awareness of EIB in people who have stopped exercising due to these symptoms. In addition, a self-administered questionnaire could help overcome health care professionals' reluctance to regularly inquire about patients' exercise habits during clinical visits due to a lack of knowledge, time, motivation, or other factors.

CONCLUSION

EIB is a common condition that, when undiagnosed and untreated, may lead many individuals to forego regular exercise, which carries significant negative consequences. Detection of EIB early in life through screening may allow for early treatment, resulting in increased physical activity levels throughout life, improved cardiovascular conditioning, reduced rates of obesity, and better physical and emotional quality of life. Renewed efforts are needed to develop an EIB screening questionnaire by using a systematic and rigorous approach to ensure that the screening questionnaire has widespread clinical applicability. Once developed and validated, the EIB screening questionnaire should be widely disseminated to the professionals who are best positioned to screen large numbers of children, adolescents, and adults for EIB, including primary care physicians, pediatricians, school nurses, physical education instructors, and athletic coaches and trainers. To ensure adoption of the questionnaire, the dissemination plan should include education to increase awareness of the burden of EIB, the need to routinely screen for EIB, and how to appropriately manage individuals who have positive screening results.

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APPENDIX E1. Accuracy of existing EIB screening questionnaires: systematic literature review

An earlier systematic literature review on this topic was restricted to studies specifically designed to diagnose EIB and that defined the reference standard for EIB as a decrease in FEV₁ of 10% or more after a laboratory exercise challenge.^{E1} Only 2 studies in this review met inclusion criteria for evaluating the diagnostic accuracy of self-reported EIB symptoms.^{E1} Our review used broader inclusion criteria to capture all studies that reported data on the accuracy of self-reported EIB screening questionnaires by using any objective airway challenge as a reference standard.

The PubMed database was searched to identify relevant English language studies published from 1950 through 2012. The following search strategy was used: (“questionnaire” or “screen”) and “asthma, exercise-induced [MeSH]” or “asthma, exercise-induced/epidemiology [MeSH]” or “asthma, exercise-induced/diagnosis [MeSH].” Included studies reported (or presented data that allowed for the calculation of) the accuracy, including sensitivity, specificity, PPV, and/or NPV, of the EIB screening questionnaire compared with a reference standard (exercise or surrogate airway challenge). Additional potentially relevant studies were identified by examining the reference lists of retrieved studies and soliciting recommendations from experts in the field.

SEARCH RESULTS

Of the 526 references identified through the PubMed database search, 20 studies met inclusion criteria. An additional 6 relevant studies were identified through manual searches of reference lists. Table E1 summarizes the following aspects of the 26 studies identified through the literature search: sample size and characteristics, the number of questionnaire items, definition of a positive screener response (eg, at least 1 “yes” response to a questionnaire item), definition of the positive reference standard, and accuracy.

STUDY SAMPLES

To date, most studies (17/26) that evaluated the accuracy of EIB screening questionnaires were conducted in recreational (9 studies)^{E2-E10} or elite (8 studies)^{E11-E18} athletes. Of the 4 studies conducted in the general population (by using subjects recruited from schools), 1 involved children,^{E19} 2 adolescents,^{E20,E21} and 1 young adult.^{E22} The subjects of 5 studies were recruited from at-risk^{E23-E25} or clinical^{E26,E27} populations.

OBJECTIVE DIAGNOSTIC TESTS

Twenty-one studies used an exercise challenge as the objective diagnostic test for EIB. Of these, 12 studies used a field exercise challenge,^{E5-E7,E9,E12,E14,E15,E18-E21,E25} 8 used a laboratory exercise challenge^{E2-E4,E22-E24,E26,E27} and 1 required both a positive field and laboratory exercise challenge to diagnose EIB.^{E11} Of the remaining 5 studies, 3 used EVH^{E8,E10,E13} and 2 defined EIB as a positive response to any one of multiple challenges (eg, EVH, dry powder mannitol, methacholine).^{E16,E17} A positive challenge was most commonly defined as a decrease in FEV₁ of $\geq 10\%$.^{E2,E6,E10,E12,E13,E15,E23,E24} Other studies used an FEV₁ threshold of 13%^{E27} or 15%^{E4,E18,E25,E26} to define a positive challenge. Six studies defined positive challenge as a decrease in

peak expiratory flow rate (PEFR) of $\geq 15\%$.^{E5,E7,E14,E19,E20} In 7 studies, a positive challenge was defined by using multiple measures of pulmonary function.^{E8,E9,E11,E16,E17,E21,E22}

EIB SCREENING QUESTIONNAIRES

A variety of EIB screening questionnaires were evaluated, with only a few studies that evaluated the same questionnaire. Articles provided very little information regarding the development, design, and psychometric properties of the screening questionnaires. Three studies that involved elite^{E18} or recreational^{E5,E8} athletes examined the accuracy of an EIB screening questionnaire developed by the US Olympic Committee Sports Medicine Division. The 16 EIB screening items asked about allergic and respiratory disease, and were part of a 60-item general medical history questionnaire designed for Olympic athletes.^{E28,E29}

Two studies (1 of high school students^{E20} and 1 of adolescent recreational athletes^{E6}) evaluated versions of an EIB screening questionnaire developed by the Sports Committee of the American Academy of Allergy, Asthma, and Immunology.^{E29} This questionnaire included items that assessed postexercise respiratory symptoms; general asthma and/or allergy symptoms; a personal and family history of hay fever, asthma, and EIB; and whether respiratory symptoms interfered with school or work.^{E29} Six studies evaluated short (3-4 items) questionnaires that assessed only exercise-related respiratory symptoms (coughing, wheezing, excessive mucus formation, and chest tightness and/or trouble breathing during or after exercise).^{E9,E11,E12,E15,E22,E26}

In 6 studies, the EIB screening questionnaires were derived from widely used respiratory health questionnaires, including the European Community Respiratory Health Survey,^{E13,E16,E17} the Childhood Asthma Control Test,^{E27} the International Union Against Tuberculosis and Lung Disease respiratory questionnaire,^{E25} and the International Study of Asthma and Allergies in Childhood questionnaire.^{E19}

ACCURACY OF EIB SCREENING QUESTIONNAIRES

Results of studies found widely variable sensitivities and specificities and low PPVs associated with EIB screening questionnaires. No EIB screening questionnaire was both highly sensitive and highly specific. An 8-item EIB screening questionnaire (modified version of the American Academy of Allergy, Asthma, and Immunology questionnaire) was highly sensitive (94%) but was not very specific (64%) for identifying EIB in the general population (high school students).^{E20} Questionnaires that were highly specific ($>90\%$) had poor sensitivity ($<60\%$).^{E7,E9,E18,E19,E24}

There was considerable inconsistency in the performance characteristics of EIB screening questionnaires, even when similar questions were used. For example, 2 studies evaluated the accuracy of similar questionnaires in recreational adolescent athletes using the same reference standard.^{E2,E4} Both studies found the questionnaire to have moderate specificity, but 1 study reported a sensitivity of 73%^{E2} and the other a sensitivity of 36%.^{E4} Two studies evaluated a similar EIB screening questionnaire in elite athletes.^{E13,E16} The questionnaire had a sensitivity and specificity of 100% and 32%,^{E13} respectively, in 1 study and of 67% and 58%, respectively,^{E16} in the other study.

Six studies reported the accuracy of individual screening questions.^{E3,E13,E14,E17,E23,E25} In a small case-control study in

young recreational athletes, the question “do you experience cough after exercise” had a sensitivity of 89% and a specificity of 86% for identifying EIB confirmed with a laboratory exercise challenge.^{E3} In 4 studies (2 in elite athletes and 2 in survey respondents who previously self-reported wheeze),^{E13,E17,E23,E25} the question “have you had wheezing or whistling in your chest at any time in the past 12 months” was associated with a sensitivity of 50% to 90% and specificity of 60% to 72% for identifying EIB.

A multisite study was conducted by the Sports Medicine Committee of the American Academy of Allergy, Asthma, and Immunology to determine which of 24 EIB screening questionnaire items were most helpful in identifying individuals with EIB.^{E29} A total of 329 subjects (age range, 4-43 years) completed the questionnaire and exercise challenge. Three of the 24 questions independently predicted a positive exercise challenge: (1) have you ever missed school or work due to chest tightness or cough or wheezing or prolonged shortness of breath; (2) have you ever been told you have exercise-induced asthma; and (3) do you get itchy eyes? This article did not provide sufficient data to calculate the test characteristics of these questions.

RECOMMENDATIONS FOR THE DEVELOPMENT OF AN EIB SCREENING QUESTIONNAIRE

An EIB screening questionnaire is a specific type of PRO measure used as a screening or diagnostic instrument to identify which subjects have or will develop a condition.^{E30} Our recommendations for developing and validating an EIB screening questionnaire were based on relevant material in the US Food and Drug Administration guidance^{E30} as well as various published methodical standards for developing and validating diagnostic tests.^{E31-E33}

ITEM GENERATION

The first step in developing an EIB screening questionnaire is the generation of a comprehensive pool of items. Items can be generated from a number of sources, including experts in the field, existing EIB screening questionnaires, existing asthma and allergic rhinitis questionnaires, and proposed respondents. Both “bottom-up” (inductive) and “top-down” (deductive) approaches should be used to generate a comprehensive pool of items with good content validity for EIB screening. Qualitative research (eg, focus groups, one-on-one interviews) of people diagnosed with EIB should be conducted to inform the development of items that assess the experience of EIB symptoms from the patient’s perspective. Qualitative data collection continues until “saturation” is achieved, which is the point at which no new insights are obtained or new themes or concepts identified.^{E34} Questionnaire items should be worded by using simple and unequivocal terms that have the same meaning for all members of the target population. Researchers should avoid asking about multiple symptoms in the same question and complex questions, which reduce the reproducibility of responses. Each question should clearly define the reference period, which is the time frame over which respondents are asked to report symptoms (eg, within the past week, month, year, or ever). Researchers recommend that the term “activity” should be used instead of “exercise” in querying people about EIB symptoms.

ITEM SCALING

The simplest scale possible offers respondents 2 choices (eg, yes or no).^{E31} This type of scale is generally not useful for a PRO measure designed to evaluate the effect of an intervention because it is not sensitive to change but may be appropriate for a predictive PRO measure.^{E31} Ultimately, the best scaling for items on a predictive PRO measure will depend on how the number of response categories for each item affects the correlation of the item with the criterion measure.^{E31}

QUESTIONNAIRE PRETESTING

The selection of items to include on the first version of the questionnaire may be based on item importance as rated by patients and providers. Researchers should sequence the items in the most logical order. Versions of the questionnaire should be systematically and iteratively pretested in respondents broadly representative of the target population to determine if

- Concepts, words, and questions are understood by respondents as intended
- The sentence structure is not too complex
- Respondents understand the response options
- The questions have a logical flow
- Item order does not bias responses

An important component of pretesting is cognitive interviewing, a methodology to determine how respondents understand, cognitively process, and respond to questionnaire items.^{E35} A cognitive interviewing protocol involves one-on-one interviews during which respondents are asked to “think aloud” and articulate their thought processes as they complete the questionnaire.^{E35} In addition, the interviewer verbally probes for respondents’ understanding of each question by asking them to paraphrase the question, define meanings of words, explain how they remembered or recalled events and/or symptoms, and articulate how they arrived at their response.^{E35} Interviewers also may code respondents’ behavior as they are completing the questionnaire to help determine areas of potential difficulty (eg, questions that are skipped or answered incorrectly).^{E35} Data collected may include an audiotape or videotape of the interview and the interviewer’s notes recorded during and after each interview.^{E35} The draft questionnaire should be revised based on review of data collected during the interviews and be subjected to subsequent rounds of pretesting as required.^{E35} Small samples (eg, 5-15 individuals) of subjects with particular characteristics of interest (eg, diagnosis of EIB) usually are sufficient for each round of testing.^{E35}

ITEM REDUCTION

The selection of items to include in the final EIB screening questionnaire should depend on the extent to which individual items discriminate between people with and those without EIB.^{E31} This can be determined by conducting a case-control study to identify the parsimonious subset of items that best discriminates between people with a definitive diagnosis of EIB (cases) and those for whom a diagnosis of EIB has been excluded (controls). A suggestive diagnosis of EIB should include a clinical history of exercise-related respiratory symptoms and a positive response to an objective diagnostic test. To exclude a diagnosis of EIB, individuals should have a clinical history free from exercise-related respiratory symptoms and a negative response to an

objective diagnostic test. Various multivariate statistical methods can be used to determine the relative importance of each item in discriminating between cases and controls.

For the purpose of developing and validating an EIB screening questionnaire, the reference standard should be defined to ensure a high level of confidence in the EIB diagnosis. Consistent with ATS guidelines,^{E36} we recommend using the laboratory exercise challenge, which is the most extensively studied diagnostic test, as the reference standard for diagnosing EIB. Based on currently available information, we recommend studies that evaluate a new EIB screening questionnaire use a postchallenge decrease in FEV₁ of at least 10% to define positive exercise challenge. Given that the reproducibility of the exercise challenge has not been established, repeated challenges conducted days apart should be used to determine a definitive diagnosis of EIB.

ESTABLISHING TEST-RETEST RELIABILITY

Reliability can refer to either internal consistency of a scale or measure or stability of responses over time (test-retest reliability). Internal consistency is not the most important feature of a predictive index because items that are highly intercorrelated may not necessarily improve the predictive power of the index and may result in a longer questionnaire with redundant items.^{E31} Researchers should seek to retain the items that best discriminate between individuals with and without EIB, and which do not significantly lower the internal consistency of the overall questionnaire. A predictive index, such as an EIB screening questionnaire, must have good stability over time, which means that the same or similar scores are obtained with repeated administration with the same group of respondents.^{E31} To establish the test-retest reliability of the EIB screening questionnaire, the time period between questionnaire administrations should be long enough that the respondents' memories of completing the questionnaire the first time do not influence their scores at the second administration and short enough to ensure that the characteristics being measured (EIB symptoms) do not change.

ESTABLISHING CRITERION VALIDITY

The criterion validity of the EIB screening questionnaire should be established by examining the relationship between questionnaire responses and the diagnostic reference standard, with both measures administered at the same time (concurrently). Based on available data regarding the reproducibility of exercise testing,^{E37} we recommend that 2 different exercise challenges be conducted to establish a definitive diagnosis of EIB in validation research. Beyond establishing the criterion validity of the EIB screening questionnaire, it is necessary to determine the accuracy of the questionnaire to help clinicians interpret responses. Indices of accuracy for a diagnostic test include sensitivity, specificity, PPV, and NPV. A receiver operating characteristics curve, which plots sensitivity against the false-positive rate for all possible cutoff points of the questionnaire score, can help identify which cutoff score maximizes sensitivity and specificity. For any diagnostic screening test, there typically is a trade-off between sensitivity and specificity, such that cutoff scores with higher sensitivity tend to have lower specificity and vice versa.^{E38} The most important characteristic of an EIB screening questionnaire is high sensitivity, which ensures that most individuals with EIB are identified and receive appropriate treatment. However, a highly sensitive diagnostic test with low

specificity will result in a large number of false positives (patients who are disease free but who have a positive screening result) who would be referred for expensive and unnecessary objective diagnostic testing. Thus, the aim is to establish a screening questionnaire with a cutoff score that is both highly sensitive and at least moderately specific for diagnosing EIB.

Poorly designed validation studies can lead to biased estimates of diagnostic accuracy.^{E32,E39} Researchers who evaluate EIB screening questionnaires should be particularly vigilant against spectrum bias, verification bias, and review bias. These methodologic weaknesses, particularly spectrum bias, have occurred so often in studies that evaluated the diagnostic test characteristics of airway challenges that the ability to interpret study findings has been significantly limited.^{E1} Spectrum bias may occur if study subjects are not representative of the population for whom the screening instrument is intended.^{E40} Although a case-control study, in which the questionnaire is administered to patients already known to have EIB or who have been excluded from having EIB, is useful to determine which questionnaire items best distinguish between these groups, this design will overestimate the diagnostic accuracy of the questionnaire.^{E40} The optimal design for evaluating the accuracy of a diagnostic test is a prospective, blind comparison of the diagnostic test and reference standard in a consecutive series of patients drawn from a relevant clinical population that includes individuals with a wide range of disease states that are likely to be encountered in future use of the test.^{E40}

Even if a broad spectrum of subjects is included in the evaluation, the performance of the diagnostic test may vary by patient characteristics (eg, demographics, disease severity), such that separate indices of accuracy for pertinent subgroups are appropriate.^{E32} Therefore, it is important that the EIB screening questionnaire be validated separately in people ages 6-11 years, 12-17 years, and 18-70 years. The first priority should be to establish the validity of the screening instrument in adults, followed by adolescents, and then children. In addition, the questionnaire should be validated in subgroups with varying levels of cardiovascular fitness (nonathletes, recreational athletes, and elite athletes). Further, each separate study should be adequately powered to permit the evaluation of test performance by relevant subgroups (eg, age, frequency of exercise, asthma diagnosis). Because the optimal cutoff for defining a positive EIB screening response may vary by cardiovascular fitness level, validation studies should assess subjects' self-reported frequency of exercise to determine if different cutoffs should be used to identify positive screeners in regular exercisers versus nonexercisers.

Verification bias occurs when not all subjects who are screened undergo the criterion standard diagnostic test, and when the likelihood of criterion standard confirmation depends on the screening test.^{E32} Case-control studies are particularly vulnerable to this bias because patients with positive results (cases) are likely to have preferentially received the criterion standard diagnostic test.^{E32} In cohort studies, verification bias can be minimized if all the participants receive both the screening test and the criterion standard reference test.^{E32} In conducting validation studies of EIB screening questionnaires, all the participants who complete the screener should complete the criterion standard reference test.

Review bias may occur when knowledge of the diagnostic test results can affect interpretation of the criterion standard reference test or vice versa.^{E32,E33} The extent to which a test is open to

subjective interpretation increases the likelihood of review bias. Although exercise challenge tests and screening questionnaires are fairly objective, investigators who are administering these tests should be blinded to the results of the other tests and the subject's clinical status to avoid reviewer bias.

ESTABLISHING DISCRIMINANT VALIDITY

After determining the diagnostic accuracy of the EIB screening questionnaire in the general population, a case-control study should be conducted to confirm its discriminant validity. The study would compare EIB screening questionnaire results in patients with an established EIB diagnosis (clinical history of EIB and a positive response to the objective diagnostic test) and patients for whom a diagnosis of EIB has been excluded (no clinical history of EIB and a negative response to the objective diagnostic test).

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TABLE E1. Studies evaluating the accuracy of EIB screening questionnaires

Study	Sample	No. of screening items	Positive screener	Positive reference standard	EIB cases (%) [*]	Accuracy [†]			
						Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Recreational athletes									
Rice et al, ^{E2} 1985	41 Recreational athletes (college undergraduates)	11	≥1 Yes	Postlaboratory ECT decrease in FEV ₁ ≥10%	2.8	73 (50-89)	84 (60-96)	84 (60-96)	73 (50-89)
Frobese et al, ^{E3} 1992	40 Recreational athletes (age range, 11-15 y)	Do you experience cough after exercise?	Yes	Postlaboratory ECT decrease in FEV ₁ ≥10%	—	89 (67-99)	86 (64-97)	—	—
Rupp et al, ^{E4} 1993	166 Recreational athletes (age range, 12-18 y)	9	≥1 Yes	Postlaboratory ECT decrease in FEV ₁ ≥15%	13.2	36	85	27	88
Thole et al, ^{E5} 2001	114 Recreational athletes (age range, 17-24 y)	16	Yes to ≥1 of 6 questions	Post-FRAST decrease in PEFR ≥15%	14.0	81 (54-96)	50 (40-60)	21 (12-33)	94 (84-99)
Hallstrand et al, ^{E6} 2002	256 Recreational athletes (age range, 11-17 y)	14	≥2 Yes	Post-FRAST decrease in FEV ₁ ≥10%	9.4	71	47	12	94
Hammerman et al, ^{E7} 2002	755 Recreational athletes (age range, 13-18 y)	4	≥3 Yes	Post-FRAST decrease in PEFR ≥15%	5.7	42	95	42	97
Parsons et al, ^{E8} 2007	107 Recreational athletes (age range, 17-23 y)	16	≥1 Yes	Post-EVH decrease in FEV ₁ of >10%, FVC of >5% or PEF of >20%	39	36 (22-52)	57 (44-69)	35 (21-51)	58 (45-70)
Bavarian et al, ^{E9} 2009	371 Recreational athletes (age range, 7-16 y)	4	≥2 Yes	Post-sports-specific ECT decrease in FEV ₁ ≥15% or decrease in PEFR or FEF _{15%-75%} ≥25%	19.9	13	90	24	80
Parsons et al, ^{E10} 2012	144 Collegiate athletes (age range, 18-23 y)	16	≥1 Yes	Post-EVH decrease in FEV ₁ of ≥10%	2.7	50 (8-92)	56 (47-64)	3 (0-11)	97 (91-100)
Elite athletes									
Rundell et al, ^{E11} 2000	23 Elite athletes (mean ± SD age, 20 ± 4.5 y) identified as EIB positive in a previous study and 23 elite athletes identified as EIB negative in a previous study	4	≥1 Yes	Post—sports-specific ECT decrease in FEV ₁ ≥10%, FEF _{25%-75%} ≥15% or PEFR ≥10% followed by a positive laboratory ECT by using same criteria	50.0	91 (72-99)	52 (31-73)	66 (47-81)	86 (57-98)

(continued)

TABLE E1. (Continued)

Study	Sample	No. of screening items	Positive screener	Positive reference standard	EIB cases (%) [*]	Accuracy [†]			
						Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Rundell et al, ^{E12} 2001	158 Elite athletes (mean $\pm$ SD age, 22 $\pm$ 4.4 y)	4	≥ 1 Yes	Post-sports-specific ECT decrease in FEV ₁ >10%	26	41 (26-58)	46 (37-56)	20 (12-31)	70 (59-80)
Holzer et al, ^{E13} 2002	50 Elite athletes (age range, 16-42 y)	11	≥ 1 Yes	Post-EVH decrease in FEV ₁ $\geq 10\%$	50	100 (86-100)	32 (15-54)	59 (43-74)	100 (63-100)
Ahad et al, ^{E14} 2003	179 Male elite athletes (mean $\pm$ SD age, 27 $\pm$ 6 y)	15	Each item evaluated separately	Post-FRAST decrease in PEFR $\geq 15\%$	7	0-92	32-100	0-33	76-98
Rundell et al, ^{E15} 2004	43 Female elite athletes (mean $\pm$ SD age, 22.9 $\pm$ 3.6 y)	4	≥ 1 Yes	Post-sports-specific ECT decrease in FEV ₁ $\geq 10\%$	20.9	67 (30-92)	55 (39-70)	23 (9-44)	89 (70-97)
Bougault et al, ^{E16} 2010	90 Elite athletes (mean age 18-20 y)	14	≥ 1 Yes	Post-EVH decrease in FEV ₁ $\geq 10\%$ or positive methacholine challenge (PC ₂₀ ≤ 4 mg/mL)	31.1	67 (50-80)	58 (43-72)	58 (43-72)	67 (50-80)
Stenfors 2010 ^{E17}	46 Elite athletes (age range, 19-31 y)	8	Each item evaluated separately	Post-EVH decrease in FEV ₁ $\geq 10\%$ or post-mannitol challenge decrease in FEV ₁ $\geq 15\%$ or positive methacholine challenge (PD ₂₀ ≤ 1812 μ g)	17.4	12-88	50-97	14-50	82-95
Sallaoui et al, ^{E18} 2011	107 Elite athletes (age range, 17-23 y)	16	≥ 1 Yes	Post-FRAST decrease in FEV ₁ $\geq 15\%$	13	36	97	—	—
General population									
Pitsios et al, ^{E19} 2010	268 Elementary school children (age range, 8-12 y)	8	≥ 1 Yes	Post-FRAST decrease in PEFR >15%	4.1	27 (6-61)	100 (99-100)	100 (30-100)	97 (94-99)
Randolph et al, ^{E20} 1997	112 High school students (age range, 13-17 y)	8	Yes to all	Post-FRAST decrease in PEFR $\geq 15\%$	7	94 (71-99)	64 (50-77)	44 (28-62)	97 (86-100)
Marefati et al, ^{E21} 2011	144 Female students (age range, 12-14 y)	5	≥ 2 Symptoms or previous asthma diagnosis	Post-FRAST decrease in FEV ₁ , PEFR, FVC, MMEF, MEF ₇₅ , MEF ₅₀ , or MEF ₂₅ >15%	20.8	43 (24-63)	68 (59-76)	25 (13-39)	83 (74-90)
Mansournia et al, ^{E22} 2007	463 Postgraduate students (mean $\pm$ SD age, 19.3 $\pm$ 2.7 y)	4	≥ 2 Yes	Postlaboratory ECT decrease in FEV ₁ $\geq 15\%$, in PEFR ≥ 25 or in FEF _{25%-75%} $\geq 25\%$	10.8	26 (15-40)	85 (85-88)	17 (10-28)	90 (87-93)

Clinical and/or at-risk populations									
West et al, ^{E23} 1996	46 Children (age range, 12-13 y) with self-reported wheeze and 50 matched controls without self-reported wheeze	Have you had wheezing or whistling in your chest at any time in the past 12 mo?	Yes	Postlaboratory ECT decrease in FEV ₁ ≥10%	30.2	90 (73-98)	70 (58-81)	57 (41-71)	94 (83-99)
Minov, 2005 ^{E24}	63 Workers exposed to tea dust (age range, 36-55 y)	5	≥1 yes	Postlaboratory ECT decrease in FEV ₁ ≥10%	6.4	98	24	—	—
Denboba et al, ^{E25} 2008	374 Questionnaire respondents with self-reported wheeze (age range, 5-38 y)	Have you had wheezing or whistling in your chest at any time in the past 12 mo?	Yes	Post-FRAST decrease in FEV ₁ ≥15%	8.6	50 (25-75)	72 (67-76)	7 (3-14)	97 (94-99)
		Have you ever had asthma?	Yes			31 (9-61)	91 (88-94)	12 (3-28)	97 (95-99)
Hildebrand et al, ^{E26} 2011	42 Pulmonary outpatient clinic patients (mean ± SD age, 30 ± 8 y)	3	≥1 yes	Postlaboratory ECT decrease in FEV ₁ ≥15%	23.8	80	87	67	93
Chinellato et al, ^{E27} 2012	92 Children with asthma (age range, 4-11 y)	1	Score ≥1	Postlaboratory ECT decrease in FEV ₁ ≥13%	21.7	30 (12-54)	81 (70-89)	30 (12-54)	81 (70-89)

MEF, Maximal expiratory flow; MMEF, maximal mid expiratory flow; PD₂₀, provocative dose of methacholine causing a 20% fall in FEV₁; PPV, Positive predictive value; NPV, negative predictive value; ECT, exercise challenge test; FRAST, free-running athletic screening test; PEF, peak expiratory flow rate; EVH, eucapnic voluntary hyperventilation; FEF_{25-75%}, forced expiratory flow between 25% and 75% of vital capacity.

*Percentage of sample diagnosed with EIB per reference standard.

†CIs were calculated in studies that provided sufficient data. In studies that evaluated the test performance of individual questionnaire items, the range of values across all items is shown.