Diagnostic approach to lower airway dysfunction in athletes: a systematic review and meta-analysis by a subgroup of the IOC consensus on "acute respiratory illness in the athlete"

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ABSTRACT

Objectives: To compare the performance of various diagnostic bronchoprovocation tests (BPT) in the assessment of lower airway dysfunction (LAD) in athletes and inform best clinical practice. **Design:** Systematic review with sensitivity and specificity meta-analyses. **Data sources:** PubMed, EBSCOhost and Web of Science (1 January 1990-31 December 2021). **Eligibility criteria:** Original full-text studies, including athletes/physically active individuals (15-65 years) who underwent assessment for LAD by symptom-based questionnaires / history and/or direct and/or indirect BPTs. **Results:** In 26 studies containing data for quantitative meta-analyses on BPT diagnostic performance (n = 2624 participants; 33% female); 22% had physician diagnosed asthma (PDA) and 51% reported LAD symptoms. In athletes with symptoms of LAD, eucapnic voluntary hyperpnoea (EVH) and exercise challenge tests (ECTs) confirmed the diagnosis with a 46% sensitivity and 74% specificity, and 51% sensitivity and 84% specificity, respectively, while methacholine BPTs were 55% sensitive and 56% specific. If EVH was the reference standard, the presence of LAD symptoms was 78% sensitive and 45% specific for a positive EVH, while ECTs were 42% sensitive and 82% specific. If ECTs were the reference standard, the presence of LAD symptoms was 80% sensitive and 56% specific for a positive ECT, while EVH demonstrated 65% sensitivity and 65% specificity for a positive ECT. **Conclusion:** In the assessment of LAD in athletes, EVH and field-based ECTs offer similar and moderate diagnostic test performance. In contrast, methacholine BPTs have lower overall test performance.

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Key words: Asthma, athlete, exercise-induced bronchoconstriction, diagnosis, respiratory symptoms, bronchoprovocation tests.

SUMMARY BOX

What is already known?

- Lower airway dysfunction (LAD) (including exercise-induced asthma and/or exercise-induced bronchoconstriction and/or airway hyperresponsiveness), is highly prevalent affecting approximately one in five athletes.
- Studies have consistently demonstrated a poor relationship between the presence of respiratory symptoms and objective evidence of LAD in athletes.
- Bronchial provocation testing is recommended to confirm a diagnosis of LAD, but there is no clear or established "gold standard" test in this context.

What are the new findings?

- There exists a lack of consistency in studies describing the use of bronchial provocation tests in the diagnosis of LAD in athletes, with heterogenous application of protocols and cut-off values.
- In athletes reporting symptoms of LAD, both the eucapnic voluntary hyperpnoea (EVH) and field-based sport specific exercise challenge test had a moderate specificity for the detection of LAD.
- Field-based sport specific exercise challenge tests, particularly if performed in a dry environment and at a high intensity / workload, demonstrated greater test performance in comparison to EVH in this context.

INTRODUCTION

Lower airway dysfunction (LAD) is a term used to describe asthma-related issues in athletes, including exercise-induced asthma (EIA), exercise-induced bronchoconstriction (EIB) and/or airway hyperresponsiveness (AHR). These entities collectively represent the most common reason for an athlete to seek medical review (1).

In the diagnostic assessment of LAD, several challenges arise. The typical symptoms of LAD (i.e. wheeze, cough, chest tightness / dyspnoea and excessive mucus) are non-specific and present in several of the differential diagnoses, including but not limited to exercise-induced laryngeal obstruction (EILO) and breathing pattern disorder (2). This limits the diagnostic precision of a symptom-only / clinician-based approach to the assessment of LAD (2), and prompts the need for objective testing (3). In this context, a broad range of diagnostic tests are frequently utilised, however, there remains equipoise on the optimal approach. It also remains unclear how test modalities compare with each other and their utility for 'ruling in' or 'ruling out' a diagnosis of LAD, in an athletic population.

Intuitively, the best way to diagnose an exercise-related pulmonary issue would be to assess lung function and specifically the physiology of airflow limitation, before and following a relevant period of exercise, i.e. by performing an exercise challenge test (ECT). This approach, however, is challenging because of the need to employ certain standardised work protocols (i.e. there is a requirement for a short, very high intensity exercise bout with no preceding warm-up) and to control environmental conditions; all factors that influence the specificity and sensitivity of a subsequent result (4, 5). Thus, the athlete must be able to exercise at high intensity (>80% of maximum heart rate) and cannot be injured or recovering from injury, and ECTs may be challenging to schedule, given they will impact on an athlete's training and competition schedule. Several guidelines have recommended the use of 'surrogate' tests for EIB, most often with bronchoprovocation testing (BPT), using inhaled challenge methodologies (4). Indirect BPT, with the eucapnic voluntary hyperpnoea (EVH) or inhaled tests (e.g. inhaled mannitol or nebulized adenosine 5′-monophosphate [AMP]) are often cited as representing the 'gold standard' for diagnosing EIB, given they act to mimic the desiccating process that promotes EIB in susceptible athletes (3). In contrast, other forms of BPT, such as direct BPTs, act by inhalation of e.g. either methacholine or histamine, to directly stimulate sensitized bronchial smooth muscle and thereby provoke bronchoconstriction independent of inflammation (6, 7). In the assessment of asthma in the general population, it has been proposed that indirect BPT are helpful in 'ruling in' a diagnosis of asthma when positive, whereas, direct BPT have their highest utility when negative, i.e. in terms of 'ruling out' a diagnosis (8).

In the assessment of LAD in athletes, the sports and exercise medicine clinician is typically faced with a decision on the choice of diagnostic test for LAD in two common clinical scenarios: 1) to confirm a diagnosis of LAD in an athlete presenting with non-specific symptoms of LAD (i.e. wheeze, cough, chest tightness / dyspnoea and excessive mucus), and 2) to potentially screen for LAD in athletes, during a periodic health assessment / pre-season or pre-competition assessments (9). The aim of any approach to diagnostic testing should be to inform the selection of a subsequent treatment plan, that is enacted to optimise an athlete's health and ability to undertake exercise without symptoms (10).

With these considerations in mind, the aim of this work was to systematically review the available evidence comparing diagnostic test modalities in the context of 1) confirming a symptom-based diagnosis of LAD, and 2) screening for LAD in athletes, regardless of symptoms. The study utilises a sensitivity and specificity meta-analysis, to inform clinicians regarding the rule in and rule out value of different diagnostic approaches for the diagnosis of LAD. In the absence of a reference diagnostic test or 'gold standard', we report and compare the performance of a symptom-based diagnosis against different diagnostic tests modalities.

METHODOLOGY

Protocol and registration

This systematic review and meta-analysis was performed in accordance with the 2020 Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). The PRISMA checklist is presented in Supplementary File 1. The review was registered prospectively with the PROSPERO database (registration number: CRD42020170915).

Study selection and eligibility criteria

PubMed, EBSCOhost and Web of Science (core collection) databases were used to search for published articles between 1990 and December 2021 using a combination of the terms (e.g., asthma OR EIB AND athletes AND screening OR diagnosis) and relevant exclusions. For the full search string for each database see online supplementary file 2. The results of these searches were combined, and duplicate articles removed. Any additional relevant articles identified by the authors or sourced from the reference list of identified studies were included. All article screening and selection was undertaken using the online tool CADIMA (12).

Inclusion and exclusion criteria

Studies were required to meet the following criteria for inclusion: (1) study participants were athletes / physically active individuals (adult [aged 15-65 years]**,** athletes or physically active individuals at either amateur or professional level) (2) participants had undergone assessment for LAD symptoms by patient recall or questionnaires and/or objective testing (i.e., direct or indirect BPT's) for LAD; (3) original full-text studies (i.e., not research correspondence or case studies) of observational, prospective, retrospective, cross-sectional, longitudinal or intervention design, written in English. Animal or non-human studies were excluded. Articles were also excluded if the study was conducted with a heterogeneous sample (i.e. mixed sample of athletic and non-athletic populations) without reporting group findings separately, or if it was a review article, expert opinion or consensus position statement. The articles were screened independently by three reviewers in pairs (either TRN/LP or TRN/BC) first by title/abstract and then full text, and any conflicts were resolved through discussion to reach consensus.

Data extraction

The data extracted from the included studies are presented in Table 1 and divided into four groups: (1) participants (number, age, sex), (2) type of sport and athletic standard, (3) prior physician diagnosed asthma (PDA) and (4) presence of symptoms of LAD (indicating uncontrolled or undiagnosed LAD). Diagnostic methodologies and protocols are presented in Table 2. All data were extracted by TRN and BC and any conflicts resolved through discussion.

Quality assessment and risk of bias

A modified Downs and Black checklist (13) was used to determine the quality of the article including a 13-point scale (see online supplementary file 3 for modified version). Two reviewers (TRN, BC) scored the articles independently and reached consensus on the final score after discussion. The Downs and Black checklist was modified to remove domains pertaining to randomised controlled trials, and included components of reporting (up to 7 points), external (up to 2 points) and internal validity (bias and selection bias) (up to 4 points) and yielded a final score for each article. The quality assessment score was determined against the following criteria: 11-13: Excellent; 9-10: Good; 7-8: Fair; ≤6: Poor. The level of evidence was also determined using the 2009 Oxford Centre for Evidence Based Medicine Levels of Evidence (OCEBM) (14).

Outcome measures

The primary outcome was the sensitivity/specificity of the diagnostic tool to detect LAD. Diagnostic tools included symptoms of LAD and a least one form of BPT. The three ‘reference standards’ for the

Table 1. Summary of study characteristics (n = 31).

First author (ref)	Study	Number, sport and sex of participants	Age of participants (years)	Diagnosed Asthmatic Athletes (N)	Symptomatic (asthma-type) Athletes (N)
Bohm et al. 2017 (15)	Impact of a Short-Term Water Abstinence on Airway Hyperresponsiveness in Elite Swimmers	25 healthy swimmers; 25 controls. Sex: 30M/20F	18±3 swimmers 20±2 controls	0	-
Bolger et al. 2011 (16)	Hyperpnea-Induced Bronchoconstriction and Urinary CC16 Levels in Athletes	28 summer athletes; 22 untrained Sex: 50F	31.1 ± 1.7 athletes 23.3 ± 1.4 untrained	15	-
Bougault et al. 2012 (17)	Airway remodeling and inflammation in competitive swimmers training in indoor chlorinated swimming pools	23 swimmers; 10 controls Sex: 14M/19F	21 ± 2	10	-
Bougault et al. 2010 (18)	Bronchial challenges and respiratory symptoms in elite swimmers and winter sport athletes: Airway hyperresponsiveness in asthma: its measurement and clinical significance	45 swimmers; 45 amateur winter sport; 30 controls Sex: 53M/67F	20 ± 4	Swimmers: 11 Winter: 13	-
Carey et al. 2010 (19)	The acute effect of cold air exercise in determination of exercise-induced bronchospasm in apparently healthy athletes	12 distance runners Sex: 8M/4F	30.2 ± 5.1	0	-
Clearie et al. 2010 (20)	Disconnect between standardized field-based testing and mannitol challenge in Scottish elite swimmers	61 swimmers Sex: Unknown	15.2 ± 0.25	10	26
Dickinson et al. 2011 (21)	Diagnosis of exercise-induced bronchoconstriction: eucapnic voluntary hyperpnoea challenges identify previously undiagnosed elite athletes with exercise-induced bronchoconstriction	228 elite athletes (various sports) Sex: Unknown	24.0 ± 4.1	30	112
Dickinson et al. 2006 (22)	Screening elite winter athletes for exercise induced asthma: a comparison of three challenge methods	10 short-track speed skating; 4 biathlons Sex: Unknown	22.6 ± 5.7	2	-
Durand et al. 2005 (23)	Undiagnosed Exercise-Induced Bronchoconstriction in Ski-Mountaineers	31 elite ski-mountaineers Sex: 28M/3F	28 ± 1.5	6	23
Helenius et al. 1998 (24)	Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers	29 swimmers; 19 controls Sex: 26M/22F	21.7 (range 15-28)	6	8
Helenius et al. 1998 (25)	Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen	58 runners Sex: 43M/15F	24 ± 5.6	8	18
Holzer et al. 2003 (26)	Mannitol as a challenge test to identify exercise-induced bronchoconstriction in elite athletes	50 elite athletes Sex: 15M/35F	21 (range 16-42)	27	-
Holzer et al. 2002 (27)	Exercise in elite summer athletes: Challenges for diagnosis	50 summer athletes Sex: 15M/35F	21 (range 16-42)	27	42
Kennedy et al. 2019 (28)	Cold air exercise screening for exercise induced bronchoconstriction in cold weather athletes	16 cold weather athletes Sex: 9M/7F	26.9 ± 4.8	-	-

Leahy et al 2020 (44)	Diagnosis of exercise-induced bronchoconstriction in swimmers: Context matters	15 amateur college swimmers Sex: 5M/10F	21 ± 2	3	-
Levai et al 2016 (45)	Environmental influence on the prevalence and pattern of airway dysfunction in elite athletes	82 elite athletes (swimmers (44), boxers (38)) Sex: 58M/24F	Swimmers: 22.1 ± 3.1 Boxers: 21.1 ± 2.1	Swimmers: 19 Boxers: 3	Swimmers: 29 Boxers: -
Kukafka et al. 1998 (29)	Exercise-induced bronchospasm in high school athletes via a free running test: incidence and epidemiology	238 amateur high school varsity football players Sex: 238M	16.5 ± 2	32	80
Martin et al. 2012 (30)	Airway Dysfunction and Inflammation in Pool- and Non-Pool-Based Elite Athletes	118 pool and non-pool athletes Sex: 53M/65F	20 (range 16-32)	-	118
Parsons et al. 2012 (31)	Screening for Exercise-Induced Bronchoconstriction in College Athletes	144 recreational athletes (6 different varsity athletic teams) Sex: 80M/64F	20 (range 18–23)	35	64
Parsons et al. 2007 (32)	Prevalence of Exercise-Induced Bronchospasm in a Cohort of Varsity College Athletes	107 recreational athletes (Varsity College Athletes from 22 sports) Sex: 74M/33F	20 (range 17-23)	11	43
Rundell et al. 2004 (33)	Field exercise vs eucapnic voluntary hyperventilation to identify airway hyperresponsiveness in elite cold weather athletes	38 elite and amateur athletes (various sports) Sex: 13M/25F	18 ± 5.4	8	-
Rundell et al. 2001 (34)	Self-reported symptoms and exercise-induced asthma in the elite athlete	158 eite athletes (various sports) Sex: 83M/75F	22 ± 4.4	-	81
Rundell et al 2000 (42)	Exercise-induced asthma screening of elite athletes: field versus laboratory exercise challenge	23 elite athletes (biathlon (6), cross-country skiing (6), nordic combined (3), short-track speed skating (5), and kayaking (3)) Sex: 14M:9W	20 ± 4.5	7	-
Stensrud et al. 2020 (36)	Lung function and oxygen saturation after participation in Norseman Xtreme Triathlon	63 elite extreme triathletes Sex: 50M/13F	40.3 ± 9	10	-
Stensrud et al. 2007 (35)	Bronchial hyperresponsiveness in skiers: field test versus methacholine provocation?	24 cross-country skiers Sex: 16M/8F	25.7 ± 4.8	9	-
Sue-Chu et al. 2010 (37)	Airway hyperresponsiveness to methacholine, adenosine 5-monophosphate, mannitol, eucapnic voluntary hyperpnoea and field exercise challenge in elite cross-country skiers	58 cross-country and biathlon ski athletes Sex: 36M/22F	18.1 ± 1.7	10	26
Sue-Chu et al. 1999 (43)	Non-invasive evaluation of lower airway inflammation in hyperresponsive elite cross-country skiers and asthmatics	18 cross-country skiers; 14 asthmatics 15 controls Sex: 91M/111F	20.6 (range 13-61)	18	18
Sue-Chu et al 1996 (38)	Prevalence of asthma in young cross-country skiers in central Scandinavia: differences between Norway and Sweden	171 cross country elite athletes Sex: M126:W45	Norway (N=118): 17 (0) Sweden (N=53): 18 (4)	23	
Turmel et al 2012 (39)	Cardiorespiratory screening in elite endurance sports athletes: the Quebec study	133 elite athletes (cross-country (34), biathletes (10), triathletes (19), long track speed skater (20), swimmer (50)) Sex: M71:W62	20 ± 4	32	

Uçok et al. 2004 (40)	Prevalence of exercise-induced bronchospasm in long distance runners trained in cold weather	19 sedentary subjects; 20 long distance runners Sex: 39M/0F	18.7 ± 2	0	
Verges et al 2005 (41)	Bronchial hyperresponsiveness, airway inflammation, and airflow limitation in endurance athletes	39 athletes (29 Skiers, 10 Triathletes) Sex: 26M:13F	BHR pos: 23 ± 6 BHR neg: 22 ± 4	4	

sensitivity/specificity meta-analysis were: (1) symptoms of LAD, (2) an ECT and (3) EVH. Other studies, where there were a limited number of studies reporting use of a BPT (e.g. adenosine 5′-monophosphate [AMP]), or where the authors only compared multiple ECT protocols were not included in the quantitative meta-analyses as they did not have another reference to compare with.

Data synthesis and analysis

A qualitative synthesis of evidence was conducted for all studies. Data are reported as mean +/- SD or 95% confidence intervals (95% CI) unless otherwise stated. A diagnostic random effects (DerSimonian and Laird) model with a correction factor of 0.5 (only applied to cells where a 0 was present) was used for the sensitivity and specificity analysis. The 95% CIs for the sensitivity and specificity are also presented, as well as the I^2 values (a measure of the heterogeneity of the data). A separate analysis was performed for each 'reference standard' (1: symptoms of LAD, 2: an ECT, and 3: EVH). An HSROC analysis was not possible due to low numbers (the model did not converge). OpenMetaAnalyst was used for all analyses, a 0.05 level of significance was accepted, and data was plotted using PRISM for visual purposes.

RESULTS

Included studies and quality characteristics

In total, 968 studies were identified. Of these, 31 studies (15-45) were included in the qualitative synthesis of study characteristics (Table 1); five studies were excluded from the quantitative sensitivity and specificity meta-analyses on BPT performance because they did not report all data required for analyses (Figure 1). Indirect BPT data were reported in 18 studies and direct BPT results in three studies, whilst seven studies reported data on both direct and indirect BPT's. Three studies reported data on symptoms only, with no BPT data included (Table 2). Downs & Black Quality Assessment Scores ranged from 10-12 and studies were rated as excellent (n=30) or good (n=1) (Supplementary File 4).

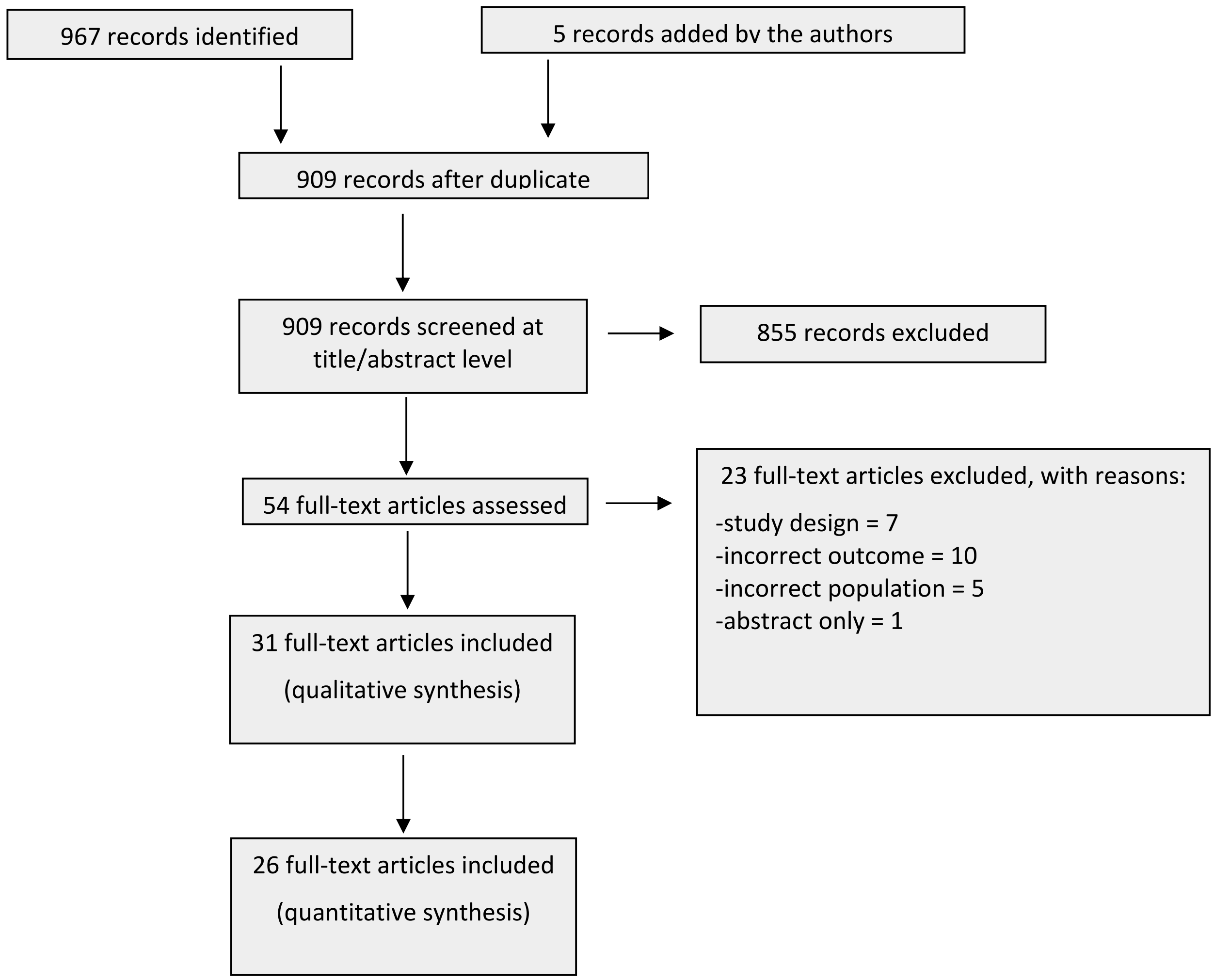

Figure 1. PRISMA flowchart representing search results.

Table 2: Summary of study methods and protocols (n = 31). Airway hyperresponsiveness to both direct and indirect bronchial provocation agents.		
First author (ref)	Test modality and protocol employed	Cut-off for positive test result
Bohm et al. 2017 (15)	Methacholine bronchial provocation test (methacholine BPT)	The PD20 (a ≥20% fall in FEV_1) was reached within a cumulative dose of 4.896 micromole (960 microgram) methacholine
Bolger et al. 2011 (16)	Eucapnic voluntary hyperpnoea (EVH): Demanded 85% of predicted maximum ventilation volume (MVV) for 8 min	Fall in FEV_1 of ≥10% from baseline in two consecutive blows
Bougault et al. 2012 (17)	Two modalities: 1: EVH: The EVH challenge demanded 85% of predicted MVV for 6 mins 2: Methacholine BPT	1: Fall in FEV_1 of ≥10% from baseline in two consecutive blows within 20 minutes post challenge 2: The methacholine BPT was defined positive by a fall in FEV_1 of ≥20% from baseline within administering a single concentration of 4 mg/mL
Bougault et al. 2010 (18)	Two modalities: 1: EVH: The EVH challenge demanded 85% of predicted MVV for 6 mins 2: Methacholine BPT	1: Fall in FEV_1 of ≥10% from baseline in two consecutive blows within 30 minutes post challenge 2: The methacholine BPT was defined positive by a fall in FEV_1 of ≥20% from baseline within administering a single concentration of 4 mg/mL
Carey et al. 2010 (19)	Exercise challenge test (ECT), comparing outdoor running in cold (January) and warm conditions (laboratory treadmill inside)	Fall in FEV_1 of ≥10% from baseline or a 15% fall in PEF
Clearie et al. 2010 (20)	Mannitol challenge	Fall in FEV_1 of ≥15% fall in FEV_1 from baseline once, or ≥10% fall in two consecutive blows before the maximum of 635 mg mannitol was administered
Dickinson et al. 2011 (21)	EVH: Demanding 85% of predicted MVV for 8 min	Fall in FEV_1 of ≥10% in one blow within 15 minutes post challenge
Dickinson et al. 2006 (22)	Three modalities: 1: EVH: Demanded 85% of predicted MVV for 6 min 2: Sport specific ECT 3: Laboratory based ECT on treadmill	1: Fall in FEV_1 of ≥10% from baseline within 20 minutes post challenge 2 and 3: The ECT was defined positive by a fall in FEV1 of ≥10% from baseline
Durand et al. 2005 (23)	Sport specific ECT, post-race ski mountaineers, high altitude	
Helenius et al. 1998 (24)	Histamine challenge Dosimetric method with controlled tidal breathing	Fall in FEV_1 of ≥10% post challenge
Helenius et al. 1998 (25)	Outdoor ECT Running for 2 km	Fall in FEV_1 of ≥10% from baseline within 20 minutes post challenge
Holzer et al. 2003 (26)	Two modalities: 1: EVH: Demanded 85% of predicted MVV for 6 min 2: Mannitol challenge	1: Fall in FEV_1 of ≥10% from baseline within 10 minutes post challenge 2: The mannitol challenge was defined positive by ≥15% fall in FEV_1 (PD_{15}) from baseline once, or ≥10% fall (PD_{10}) before the maximum of 635 mg mannitol was administered
Holzer et al. 2002 (27)	Two modalities: 1: EVH: Demanded 85% of predicted MVV for 6 min 2: Methacholine BPT	1: Fall in FEV_1 of ≥10% from baseline within 10 minutes post challenge 2: The PD20 was reached within a cumulative dose of 9.47 micromol (1856 microgram) methacholine
Kennedy et al. 2019 (28)	Two modalities:	1: Fall in FEV_1 of ≥10% from baseline within 15 minutes post challenge

	1: EVH: Demanded 85% of predicted MVV for 6 min 2: Outdoor ECT: The cold air exercise challenge was a 5 km run in -15°C	2: Fall in FEV_1 of ≥10% from baseline within 20 minutes post challenge
Kukafka et al. 1998 (29)	Outdoor ECT: Running 1 mile (6-8 minutes)	Fall in peak expiratory flow (PEF) of ≥10% from baseline within 30 minutes post challenge
Leahy et al. 2020 (44)	Two modalities: 1: EVH: Demanded 85% of predicted MVV for 6 min 2: ECT swimming: A consecutive 200- and 400-m freestyle at minimum 85% of self-reported season's best time	1: Fall in FEV_1 of ≥10% from baseline in at least two consecutive time points post challenge 2: Fall in FEV_1 of ≥10% from baseline in at least two consecutive time points post challenge
Levai et al 2016 (45)	EVH: Demanded 85% of predicted MVV for 6 min	Fall in FEV_1 of ≥10% from baseline in at least two consecutive time points post challenge
Martin et al. 2012 (30)	EVH: Demanded 85% of predicted MVV for 8 min	Fall in FEV_1 of ≥10% from baseline in at least two consecutive time points at least 5 minutes apart
Parsons et al. 2012 (31)	EVH: Demanded 85% of predicted MVV for 6 min	Fall in FEV_1 of ≥10% from baseline within 15 minutes post challenge
Parsons et al. 2007 (32)	Two modalities: 1: EVH: Demanded 85% of predicted MVV for 6 min 2: Methacholine BPT	1: Fall in FEV_1 of >10% from baseline/or fall in PEF of >20% from baseline in at least two consecutive time points at least 5 minutes apart and within 20 mins post challenge 2: The methacholine BPT was defined positive by a fall in FEV_1 of ≥20% from baseline within administering a single concentration of 4 mg/mL
Rundell et al. 2004 (33)	Two modalities: 1: EVH: Demanded 85% of predicted MVV for 6 min 2: Outdoor ECT: Unspecific, lasting for 6-8 minutes	1: Fall in FEV_1 of ≥10% from baseline within 15 minutes post challenge 2: Fall in FEV_1 of ≥10% from baseline within 15 minutes post challenge
Rundell et al. 2001 (34)	Various duration (speed skaters 1 min 30 sec, to cross-country 1 hour) outdoor ECT -20 to +4°C	Fall in FEV_1 of ≥10% from baseline, not described time-interval post challenge
Rundell et al 2000 (42)	Two ECTs: Outdoor sport specific and indoor laboratory treadmill ECT -not further described	Not described
Stensrud et al. 2020 (36)	Sport specific ECT: Post race triathlon	Fall in FEV_1 of ≥10% from baseline, not described time-interval post challenge
Stensrud et al. 2007 (35)	Two modalities: 1: ECT: Post race cross-country 2: Methacholine BPT	1: Fall in FEV_1 of ≥10% from baseline, not described time-interval post challenge 2: The PD20 (a ≥20% fall in FEV1) was reported for doses reached within a cumulative dose of 4 micromol as well as within a cumulative dose of 8 micromol
Sue-Chu et al. 2010 (37)	Compared EVH, methacholine BPT, ECT, mannitol test and adenosine 5'-monophosphate (AMP) challenge EVH: Demanded 85% of predicted MVV for 6 min	1: For mannitol challenge, a positive test was defined by a fall in FEV1 of ≥15% fall in FEV_1 from baseline before the maximum of 635 mg mannitol was administered 2: For methacholine BPT, the PD20 (a ≥20% fall in FEV_1) was reported for doses reached within a cumulative dose of 4 micromol as well as within a cumulative dose of 8 micromol
Sue-Chu et al. 1999 (43)	Compared methacholine BPT and AMP challenges	For methacholine BPT, the PD20 (a ≥20% fall in FEV_1) was reported for doses reached within a cumulative dose of 4 micromol as well as within a cumulative dose of 8 micromol
Sue-Chu et al 1996 (38)	Compared respiratory symptoms and methacholine BPT	For methacholine BPT, the PD20 (a ≥20% fall in FEV_1) was reported for doses reached within a cumulative dose of 9.1 micromol

Turmel et al 2012 (39)	NA	NA
Uçok et al. 2004 (40)	NA	NA
Verges et al 2005 (41)	NA	NA

Abbreviations:

AMP - adenosine 5'-monophosphate; ECT - exercise challenge test; EVH - eucapnic voluntary hyperpnoea; FEV_1 - forced expiratory volume in one second; methacholine BPT - methacholine bronchial provocation test; MVV - maximum ventilation volume; PEF - peak expiratory flow; PD20 – the provocation dose that results in a ≥20% fall in FEV1 compared with baseline

Participant demographics and clinical characteristics

The qualitative synthesis from the included studies, describe a total sample size of n = 3083 athletes, with an age range of 15 to 61 years (Table 1). Of the 28 studies that provided full demographic details, 36.0% of the participants were female, whilst in the 26 studies included for the quantitative meta-analyses on BPT performance (n = 2624; 33% female). Winter sport-based athletes were the most common athletic group described (10 studies, n = 477 winter athletes), followed by summer sport athletes (9 studies, n = 507 various summer sports) and swimmers (7 studies, n = 267 swimmers). In the qualitative analyses, the presence of a prior PDA was reported in 25 studies (n = 400; 22.0% of the 1811 participants), whilst a diagnosis of LAD based on the presence of specific respiratory symptoms was reported in n = 688 (51.3% of the 1342 participants), detailed in 14 studies. In the quantitative meta-analyses, n = 319 (23.6% of 1352 participants) had a prior PDA and n = 651 (59.7% of 1311 participants) had a symptom-based LAD diagnosis.

The characteristics and proportion of prior PDA and symptoms of LAD in the included papers are summarised in Table 1. The presence of respiratory symptoms was reported in 15 papers (20, 21, 23-25, 27-32, 34, 37, 43, 45). These data were obtained using existing or modified standardised questionnaires (Allergy Questionnaire for Athletes [AQUA]) (46) in four studies (23, 28, 30, 31) and non-validated investigator initiated questionnaires in eight studies (20, 21, 24, 25, 29, 34, 42, 45); three papers did not report on the use of questionnaires (27, 37, 43).

Diagnostic test protocols reported

A wide variety of test protocols and cut-off levels were reported (Table 2). All nine papers including methacholine BPT required ≥20% fall in FEV_1 post challenge and at a specific accumulated provocation dose (PD_{20}), or accumulated provocation concentration (PC_{20}), as per convention. In papers using PD_{20},, the diagnostic cut-off levels for a positive methacholine BPT ranged from 4 µmol to 9.47 µmol (15, 27, 35, 37, 38, 43), while papers using PC_{20} had a cut-off of 4 mg/mL methacholine (equivalent to accumulated 8 µmol methacholine) (17, 18, 32).

In the 16 papers describing EVH, target ventilation rate was described as 30 x FEV_1 (equivalent to 85% of maximum voluntary ventilation (MVV) (16-18, 21, 22, 26-28, 30-33, 37, 43, 44), while test duration time was either 6 (17, 18, 22, 26-28, 31-33, 44, 45) or 8 minutes (16, 21, 30, 37). The cut-off value for a diagnostic test was a single ≥10% fall in FEV_1 post challenge in the majority of studies (17, 18, 21, 26-28, 33), whilst some papers required a single ≥15% fall in FEV_1 post challenge or a ≥10% fall in FEV_1 at two consecutive time-points within 30 minutes post challenge (16-18, 21, 30, 32, 37, 44, 45).

Of the 13 papers including detail on ECTs, these reported various sport specific field-based ECTs in training or competition ranging in time from few minutes (speed skating races) to several hours (long-distance cross-country or triathlon competition), and in temperatures from +10 to -15°C (19, 22, 23, 25, 28, 29, 33-37, 42, 44). One study reported an ECT in a chlorinated pool (44). Three of the ECTs also included an indoor laboratory treadmill test (19, 22, 42). The cut-off value for a diagnostic test was a ≥10% fall in FEV_1 once post-challenge in all (19, 22, 23, 25, 28, 29, 33-37, 42), but one paper (44) requiring ≥10% reduction in FEV_1 at two consecutive time-points within 30 minutes post-challenge.

Diagnostic tests to confirm a symptom-based diagnosis of LAD

Figure 2 includes twelve studies comparing five BPT methodologies (methacholine BPT, AMP, Mannitol, ECT, EVH) with symptoms of LAD as the reference standard. Four of these studies included more than one BPT, allowing 15 cross BPT comparisons are to be included in the meta-analyses.

Overall, there was a poor level of agreement between BPT results and presence of LAD symptoms, with large discrepancies in the results from both indirect and direct BPTs to identify athletes with LAD; i.e. when symptoms of LAD were taken as the reference, the overall sensitivity of BPTs to identify athletes

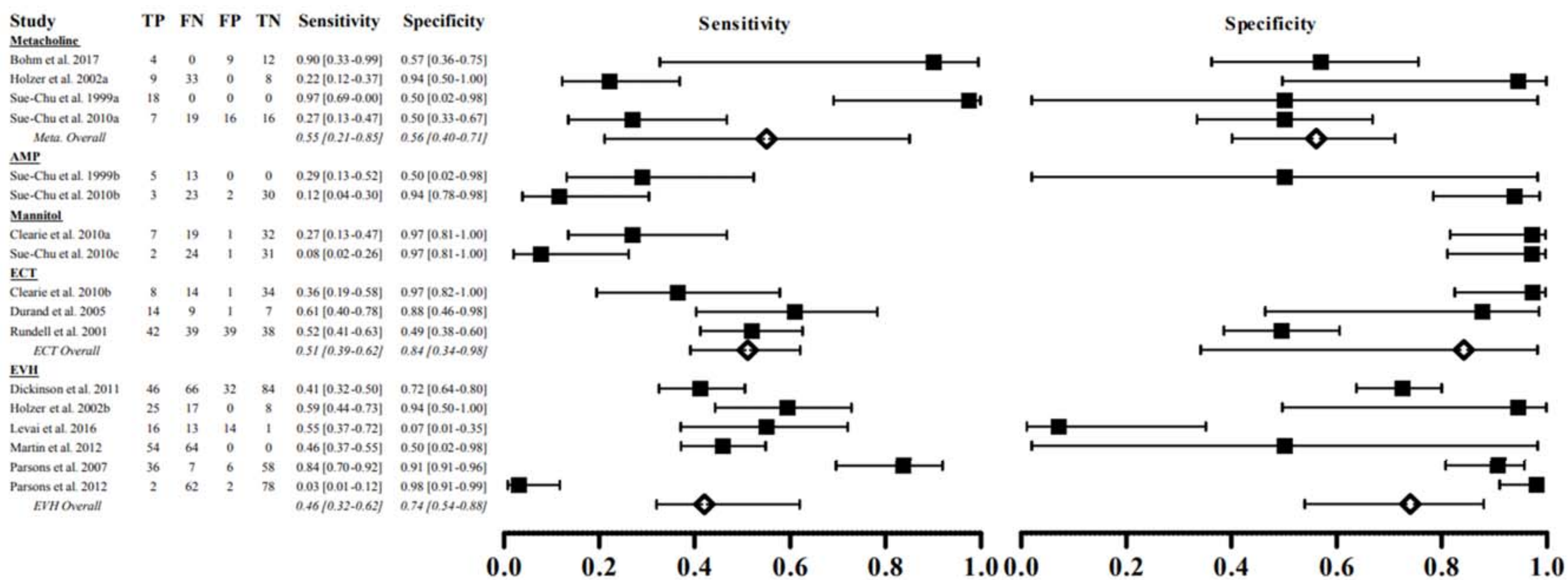

Figure 2. Bronchoprovocation tests compared to the reference standard of previously reported lower airway dysfunction symptoms. Overall sensitivity: 39.6% [29.5-50.7] p=0.066, I^2=83.1; overall specificity: 81.6% [68.6-89.9] p<0.001, I^2=82.7 Abbreviations:

TN – test negative

FN – false negative

FP – false positive

TP – test positive

AMP - adenosine 5'-monophosphate; ECT - exercise challenge test; EVH - eucapnic voluntary hyperpnoea with LAD was 40% (95% CI: 30-51%). In contrast, the agreement between a negative BPT result and absence of respiratory symptoms was more consistent with a specificity of 82% (95% CI: 69-90%). Studies evaluating EVH demonstrated an overall 46% sensitivity (95% CI: 32-62%) and 74% specificity (95% CI: 54-88%) for a symptom-based LAD diagnosis. The ECTs included in the meta-analyses were all field-based and sport specific (Figure 2 and Table 2) and demonstrated a similar specificity (84%, 95% CI: 34-98%) due to similar means and wide variance, with a somewhat higher sensitivity (51%, 95% CI: 39-62%). Figure 2 demonstrates that the ECTs performed in colder weather, higher altitudes and higher intensities, demonstrated the highest sensitivities for the LAD diagnosis (23, 34). Studies evaluating methacholine BPT demonstrated a lower overall test performance for a symptom-based diagnosis, with a 55% (95% CI: 21–85%) and 56% (95% CI: 40-71%) sensitivity and specificity, respectively.

Diagnostic tests to detect LAD regardless of symptoms in athletes, i.e. screening for LAD

Eucapnic voluntary hyperpnoea (EVH) as the reference standard

Figure 3 details findings from eleven studies comparing respiratory symptoms and BPT methodologies, with EVH as the reference standard. Athletes with symptoms of LAD demonstrated 78% sensitivity (95% CI: 57-90%) and 45% specificity (95% CI: 26-66%) for a positive EVH, while a positive ECT was 42% sensitive (95% CI: 27-59%) and 82% specific (95% CI: 66-91%) for a positive EVH.

Exercise challenge testing (ECT) as the reference standard

Figure 4 includes ten comparisons in the meta-analyses comparing respiratory symptoms and BPT methodologies with ECT as the reference standard (n = 9 studies; 1 multiple comparisons). Athletes with symptoms of LAD demonstrated 80% sensitivity (95% CI: 38-96%) and 56% (95% CI: 39-71%) specificity for a positive ECT, while a positive EVH was 65% sensitive (95% CI: 34-87%) and 65% specific (95% CI: –47-79%) for a positive ECT.

Study	TP	FN	FP	TN	Sensitivity	Specificity
Mannitol						
Holzer et al. 2003	24	1	2	23	0.96 [0.77-0.99]	0.92 [0.73-0.98]
Symptoms						
Dickinson et al. 2011	46	32	66	84	0.59 [0.48-0.69]	0.56 [0.48-0.64]
Holzer et al. 2002b	25	0	17	8	0.98 [0.76-1.00]	0.33 [0.18-0.52]
Levai et al. 2016	16	14	13	1	0.53 [0.36-0.70]	0.07 [0.01-0.37]
Martin et al. 2012	54	0	64	0	0.99 [0.87-1.00]	0.01 [0.00-0.11]
Parsons et al. 2007	36	6	7	58	0.86 [0.72-0.93]	0.89 [0.79-0.95]
Parsons et al. 2012	2	2	62	78	0.50 [0.12-0.88]	0.56 [0.47-0.64]
Symp. Overall					*0.78 [0.57-0.90]*	*0.45 [0.26-0.66]*
ECT						
Dickinson et al. 2006a	3	7	0	4	0.32 [0.12-0.62]	0.90 [0.33-0.99]
Kennedy et al. 2019	2	3	4	7	0.40 [0.10-0.80]	0.64 [0.34-0.86]
Leahy et al. 2020	1	3	1	10	0.25 [0.03-0.76]	0.91 [0.56-0.99]
Rundell et al. 2004	9	8	2	19	0.53 [0.30-0.75]	0.91 [0.67-0.98]
ECT Overall					*0.42 [0.27-0.59]*	*0.82 [0.66-0.91]*

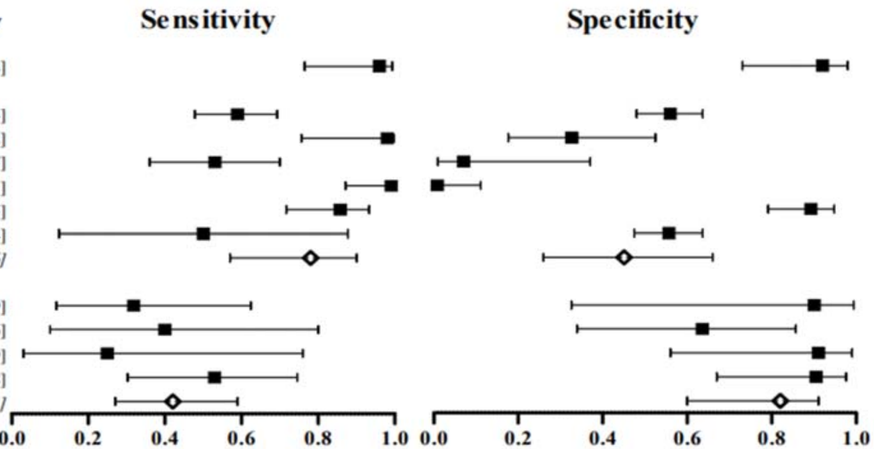

Figure 3. Symptoms and bronchoprovocation tests compared to the reference standard of an eucapnic voluntary hyperpnoea test.

Overall sensitivity: 68.0% (50.8-81.4) p=0.041 I^2=74.3; overall specificity: 63.6% (46.4-77.9) p=0.118 I^2=85.3

Abbreviations:

TN – test negative

FN – false negative

FP – false positive

TP – test positive

ECT - exercise challenge test

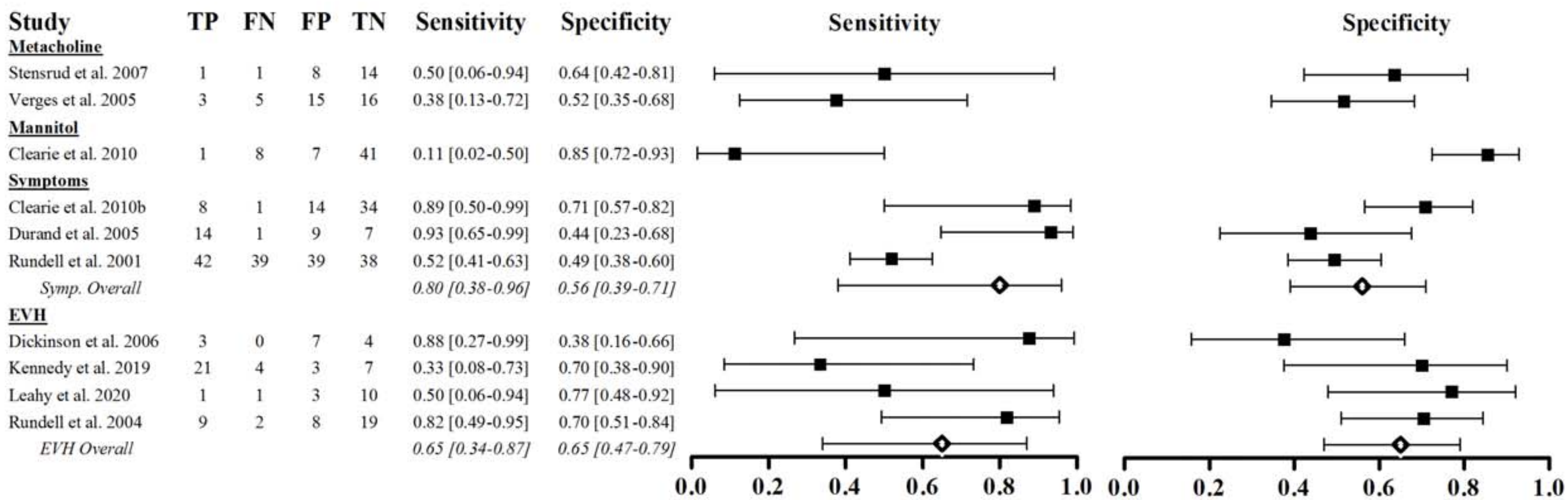

Figure 4. Symptoms and bronchoprovocation tests compared to the reference standard of an exercise challenge test.

Overall sensitivity: 59.8% (40.4-76.5) p=0.324 I^2=54.5; overall specificity: 62.9% (52.3-72.4) p=0.018 I^2=64.0

Abbreviations:

TN – test negative

FN – false negative

FP – false positive

TP – test positive

EVH - eucapnic voluntary hyperpnoea

DISCUSSION

In this systematic review and meta-analysis, we evaluated studies conducted over the past thirty years that characterise the diagnostic techniques and approaches used in the assessment of LAD in athletes. Our qualitative analyses included thirty-one studies that describe diagnostic assessments of LAD in approximately 3000 athletes. Out of these, 26 studies included sufficient data to perform a quantitative meta-analysis, comparing diagnostic test modalities for the diagnosis of LAD in approximately 2500 athletes. This analysis revealed that there is a heterogeneous approach in both the test protocols and diagnostic cut-off values employed, however the key findings from our analysis indicate that: 1) when the aim for a sport and exercise medicine clinician is to confirm a diagnosis based on the presence of LAD symptoms, EVH and ECTs demonstrated moderate and similar specificity for a diagnosis, given the similar overall mean and variance estimates, 2) in athletes with symptoms of LAD, methacholine BPT demonstrated a lower overall test performance for the diagnosis of LAD, and 3) when screening athletes regardless of the presence of symptoms of LAD, a field-based sport specific ECT at a high intensity level performed in a cold environment may be more sensitive than EVH in the assessment of LAD.

A key difficulty encountered when comparing BPTs to confirm LAD in athletes, is determining what should be considered the gold standard or comparator test. In the context of other diagnostic tests, an assessment algorithm employing tests with the highest sensitivity is preferable, to ensure early detection and thus initiation of appropriate treatment. However, the negative effects of misclassification need to be considered in any diagnostic appraisal, including the potential long-term side effects and risks of prescribing unnecessary medications, including associated healthcare costs and psychological implications (47). Hence, clinicians need to be aware of the sensitivity and specificity of any given diagnostic test, in order to successfully apply this test when evaluating symptoms (48). In the diagnostic assessment of athletes with respiratory problems, ultimately the diagnosis will arise following a synthesis between the presence of compatible symptoms and diagnostic tests that support the evidence of LAD. The likelihood of a correct diagnosis is increased if the pre-test probability of a diagnosis is high, and the test performance is high quality (48). In contrast, if the pre-test probability is low, test result needs to be interpreted with caution (48).

Diagnostic tests to confirm a symptom-based diagnosis of LAD

In the meta-analyses, we show that both the EVH and field-based ECTs have reasonable test performance characteristics, if viewed from the perspective of a sport and exercise medicine clinician trying to confirm a diagnosis of LAD in a symptomatic athlete. The overall value of EVH as a diagnostic test for LAD in athletes, is that it mimics the pathophysiology of LAD (49). The key pathophysiological mechanism behind LAD is hyperpnoea-induced evaporative water loss from the airway surface which induces release of local mediators with subsequent bronchoconstriction (50, 51). The process is amplified by dry and cold air, air pollution (52), and inhalation allergies (51). Hence, the EVH is a highly potent stimulus as it involves a high ventilation rate of dry gas mixture, reported to result in a low false-negative rate for the diagnosis of EIB (49). However, our meta-analysis demonstrated EVH to have an overall moderate specificity (74%) and low sensitivity (46%) to confirm a symptom-based LAD-diagnosis. In contrast to the moderate specificity, Levai et al. demonstrated an overall low specificity which may be impacted by the very high prevalence of LAD in the elite aquatic population study and the nature of the study design (45). The low sensitivity of EVH in our meta-analysis was influenced by one study by Parsons et al (31), which may have been influenced by the inclusion of mostly soccer/lacrosse sports at a sub-elite level, and thus associated with a lower prevalence of LAD (1, 53). However, most studies in this meta-analysis show that EVH has a moderate sensitivity. This finding aligns with previous guideline documents, recommending EVH as the 'gold standard' to identify EIB in athletes (10, 54, 55). There does remain some debate regarding the test-retest repeatability, with some studies reporting relatively poor short-term repeatability, especially in the context of mild or borderline EIB (54, 56), whilst others have shown better short- and long-term test-retest validity for EVH (57, 58).

A moderate specificity of EVH may increase the false-positive rate. In a study on n = 224 asymptomatic athletes (53), as many as 20% had a positive EVH when >10% fall in FEV_1 post-challenge was employed as the diagnostic cut-off. The fall in FEV_1 following EVH was also more pronounced in elite level, when compared with recreational athletes. To reduce the risk of false positives, some researchers have suggested use of a more conservative cut-off value (e.g. >15% fall in FEV_1) (4). However, one cannot rule out the possibility that athletes whom are reportedly asymptomatic, may be misattributing the perception of dyspnoea as their normal exercise response (59-61). In our meta-analyses, variations in EVH results may also have been influenced both by different diagnostic cut-off values as well as variations in test duration time.

Our findings indicate that field-based sport specific ECTs also demonstrate a moderate performance in the confirmation of a symptom-based LAD in athletes, in line with previously published studies (22, 59, 62). Standardisation is the main challenge with sport specific ECTs in this context. Reports indicate that exercise load and intensity during sport specific ECTs most certainly have an impact on occurrence of EIB (62). Furthermore, ambient conditions also have a great impact increasing both specificity and sensitivity of sport specific ECTs if performed in cold weather (23, 34) or in chlorinated swimming pools (20, 44), whereas humid air may blunt propensity to development of EIB (63). In this meta-analysis, we found that studies reporting ECT in colder ambient temperatures appear to report a higher sensitivity result (19, 23, 25, 28, 33), which is in line with previous reports demonstrating that inspiring cold dry air enhances the risk of EIB and inversely, inhaling warm humid air is a weaker stimulus and may even prevent EIB (4, 5, 64). The sensitivity of an ECT would also be increased by reducing the cut-off of the % fall in FEV_1 of ECT from the baseline value to diagnose EIB, from 10 to 6.5% as some authors suggested (25).

In this meta-analysis, direct BPTs, mainly methacholine BPT, appear to be less specific compared with indirect BPTs in confirming a diagnosis of LAD. This finding is in line with a previous study that reported low sensitivity (<40%) and a low negative predictive value of methacholine BPT in the elite athlete (27). This indicates that the methacholine BPT is a less favourable diagnostic test for athletes in the work-up of LAD compared with indirect BPTs (65). Our meta-analysis highlights the variability of the techniques and devices used worldwide to deliver methacholine, making it difficult to be precise about dose/concentration equivalents, especially when concentration is mostly cited in guidelines (66). The question of the cut-off values of methacholine responsible for 20% fall in FEV_1 used to diagnose airway obstruction is also crucial. In this meta-analysis, we note that cut-off levels for a positive PD_{20} varied from 4 μmol to 9.47 μmol administered cumulated methacholine (27, 35), clearly contributing to the results. Furthermore, one study also performed a methacholine BPT after an EVH on the same day (18). Performing two bronchial provocation challenges on the same day is not advised, since the first challenge may affect the outcome of the latter, resulting in a possible false positive test (67).

To summarise, we have found in this meta-analysis, that EVH and ECTs have similar specificity and are the most precise methods for confirming a symptom-based diagnosis, whilst ECTs may be more sensitive than EVH. In contrast, direct BPT are less specific in this setting. The same appears to be true in the work-up of LAD in the general population (8).

Diagnostic tests to detect LAD regardless of symptoms in athletes, i.e. screening for LAD

The second aim of this systematic review and meta-analysis was to compare the performance of different BPTs in a 'screening-type' context, to inform decision making. When screening, we search for both a high sensitivity and a high specificity. In our meta-analysis, EVH and ECTs demonstrated a similar and moderate specificity due to similar means and a wide range. Regarding sensitivity however, the meta-analysis demonstrated that ECTs were more sensitive than EVH, particularly if performed in colder weather, higher altitudes and higher intensities.

Hence, for field-based sport specific ECTs performed at colder temperatures, there was a high agreement between the presence of LAD symptoms and a positive test. These findings are in contrast to included studies reporting no association between respiratory symptoms and a positive BPT (4, 23, 27, 28, 30, 32, 34, 68). The discrepancy between symptoms and BPT results may be explained by 1) athletes under-reporting symptoms since respiratory symptoms are expected to increase with exercise load (59-61), 2) co-existing conditions that mimic LAD, such as EILO (2), 3) long time interval between presence of LAD symptoms and the BPT, as BPT results can normalise in some cases after a few week's rest (17, 25), and 4) use of direct BPTs rather than indirect BPTs in the assessment of LAD in athletes, which in this systematic review has been well demonstrated may lead to under-diagnosis.

To summarise, EVH and field-based sport specific ECTs demonstrate a similar and moderate specificity, even though only EVH were significantly specific in detecting LAD by screening athletes regardless of symptoms. However, ECTs may be more sensitive than EVH in this context.

Methodological considerations and future research

Several methodological limitations were evident from the systematic review process. Firstly, there is marked heterogeneity between studies with differences in BPT methods, protocols, sport-types and clinical definitions of LAD and asthma, limiting the ability to make direct and conclusive comparisons between studies. Additionally, the minimal data we have at present may also have resulted in the wide variance in confidence intervals with imprecise results. These factors highlight the need for caution when interpreting the overall mean values from the synthesis and meta-analysis of data sources, and may be the reason why a similar precision for ECTs and EVH were observed. It also highlights a need for future work in this field to adhere to recognised protocols, based upon international guidelines for the performance and interpretation of BPT (4, 67). Secondly, it would be preferable with more high-quality data describing other phenotypic features and/or a robust characterisation of asthma-related morbidity (e.g. exacerbations or marker of type 2 inflammation such as blood eosinophils and/or fractional exhaled nitric oxide [FENO]). In the general population, this level of detail is now recognised as central in a process that informs best management. Thirdly, the included studies largely include male subjects and from centres in the United States of America and Northern Europe and thus, there remains very limited insight from more diverse geographical regions and/or low resource countries. And finally, restricting the literature search to English language, may also have resulted in a selection bias.

CONCLUSION

In conclusion, the best available data indicates that EVH and ECTs had similar test performance due to their wide confidence intervals in the diagnostic assessment of LAD in symptomatic athletes. A field-based sport specific ECT performed in a dry air environment appears to be more sensitive than EVH. In contrast, direct BPTs appear to have lower test performance characteristics for the diagnosis of LAD in athletes. Future work should focus on improved overall characterisation of LAD in athletes with comparison to other features, such as airway inflammation and in different sporting types. Studies should also include data from low resource countries, to provide a globally inclusive perspective concerning the best way to assess and diagnose LAD in athletes.

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TRN, NS, BC, VB, KL, OP, LP, VB, MS, JH have no real or perceived conflict of interest in respect of this manuscript.

Contribution statement

Conception and design: TRN, NS, BC, VB, KL, OP, LP, VB, MS, JH

Analysis and interpretation: TRN, NS

Drafting the manuscript for important intellectual content: TRN, NS, BC, VB, KL, OP, LP, VB, MS, JH

Guarantor statement

TRN takes full responsibility for the content of the manuscript.

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