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SUBGROUP 4 - SYSTEMATIC REVIEW 7

Prevalence of lower airway dysfunction in athletes: a systematic review and meta-analysis by a sub-group of the IOC consensus group on "acute respiratory illness in the athlete"

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ABSTRACT

Objective: To report the prevalence of lower airway dysfunction in athletes and highlight risk factors and susceptible groups. **Design:** Systematic review and meta-analysis **Data sources:** PubMed, EBSCO Host and Web of Science (1st January 1990-31 July 2020). **Eligibility criteria:** Original full-text studies, including male or female athletes/physically active individuals/military personnel (aged 15-65 years) who had a prior asthma diagnosis and/or underwent screening for lower airway dysfunction via self-report (i.e., patient recall or questionnaires) or objective testing (i.e., direct or indirect bronchial provocation challenge). **Results:** In total, 1284 studies were identified. Of these, sixty-four studies (n = 37,643 athletes) from over 21 countries (81.3% European and North America) were included. The prevalence of lower airway dysfunction was 21.8% (95% CI: 18.8-25.0%) and has remained stable over the past 30-years. The highest prevalence was observed in elite endurance athletes 25.1% (CI: 20.0-30.5%) (Q = 293, I^2 = 91%), those participating in aquatic (39.9%) (CI: 23.4-57.1) and winter-based sports (29.5%) (CI: 22.5-36.8%). In studies that employed objective testing, the highest prevalence was observed in studies utilising direct bronchial provocation (32.8%) (CI: 19.3-47.2%). A high degree of heterogeneity was observed between studies (I^2 = 98%). **Conclusion:** Lower airway dysfunction affects approximately one in five athletes, with the highest prevalence observed in those participating in elite endurance, aquatic and winter-based sporting disciplines. Further longitudinal, multicentre studies addressing causality (i.e., training status / dose-response relationship) and evaluating preventative strategies to mitigate against the development of lower airway dysfunction remains an important priority for future research.

PROSPERO registration: CRD42020167691

Key words: Asthma, athlete, epidemiology, exercise-induced bronchoconstriction, prevalence, risk.

SUMMARY BOX

What is already known?

- Lower airway dysfunction (including asthma and/or exercise-induced bronchoconstriction [EIB] and/or airway hyper-responsiveness [AHR]) is often cited as the most common chronic medical condition in athletes.
- The reported prevalence data in athletes typically arises from cross-sectional studies in highly selected cohorts.
- A contemporary systematic appraisal of evidence is required to provide insight regarding the prevalence of lower airway dysfunction in athletes, associated risk factors and temporal change over the past 30 years.

What are the new findings?

- Lower airway dysfunction affects approximately one in five athletes across a broad range of sporting disciplines and abilities, with highest prevalence rates observed in those participating in elite endurance, aquatic and winter-based sporting disciplines.
- The prevalence of lower airway dysfunction in athletes has not changed significantly over the past thirty years.
- The majority of evidence arises from European countries or North American, with a paucity of evidence arising from other geographical areas, including developing nations.

INTRODUCTION

The respiratory tract is frequently affected by acute and chronic illness in athletic individuals (1) with disorders often classified by their involvement of the upper (i.e., laryngeal region), large central (i.e., trachea and main bronchi) and lower / small airways (2). It is now recognised that high-intensity exercise leads to a shift from nasal to predominantly oral breathing; thus 'bypassing' the upper airway (nasal and nasopharyngeal) structures and exposing the lower airways to significant physical, thermal and/or chemical stress (2). This can precipitate acute lower airway narrowing in susceptible individuals, leading to respiratory symptoms, such as cough, wheeze and dyspnoea (3).

Historically, various clinical definitions have been used to describe this condition, including exercise-induced asthma (EIA), exercise-induced bronchoconstriction (EIB) and/or airway hyper-responsiveness (AHR). Irrespective of the terminology or definitions employed, research published over the past fifty years indicates that some form of 'lower airway dysfunction' is an important and relevant issue in both elite and recreational athletes (4, 5).

To date, the best available data concerning the prevalence and epidemiological characteristics of lower airway dysfunction in the athletic population primarily arises from cross-sectional studies in highly selected cohorts (6-9). Moreover, prior studies have utilised a diverse range of diagnostic approaches, including variable use of self-report and/or clinical or physician-based diagnosis and/or objective direct bronchial provocation (i.e., histamine and methacholine) or indirect bronchial provocation (i.e., laboratory and field-based exercise challenge tests, eucapnic voluntary hyperpnoea (EVH) or inhaled mannitol). Whilst it is now widely recommended that some form of objective testing is used to secure a diagnosis (10, 11), it is common for studies to provide evidence detailing the prevalence of lower airway dysfunction in elite athletes based on prior medication prescription data, often arising from submitted therapeutic use exemption (TUE) requests prior to major competition (e.g., Olympic Games and World Championships) (12, 13). Overall, this broad range of methodological approaches, makes it

105 difficult to accurately quantify prevalence estimates and limits the ability to identify epidemiological
106 risk factors.

107

108 This acknowledged, in recent years there has been a significant number of additional studies
109 addressing this issue, published in both elite and recreational athletes. The primary aim of this
110 systematic review and meta-analysis was therefore to provide contemporary insight into the
111 prevalence of lower airway dysfunction in the athletic population and to characterise and describe
112 findings based on sex, test methodology, athletic standard, sporting discipline and geographic location.
113 A secondary aim was to highlight relevant risk factors and susceptible groups and to evaluate temporal
114 change over the study period (1990 to 2020).

115

116 **METHODOLOGY**

117 **Protocol and registration**

118 This systematic review was performed in accordance with the 2020 Preferred Reporting for Systematic
119 Reviews and Meta-Analyses (PRISMA) guidelines (14). The review was registered prospectively with
120 the PROSPERO database (registration number: CRD42020167691). In September 2019, an
121 International Olympic Committee (IOC) consensus statement core panel on 'acute respiratory illness
122 in athletes' was convened on behalf of the IOC Medical and Scientific Commission and chaired by MS.
123 A sub-group (number 4 out of 7) of this core panel, consisting of 10 members (OP, NS, MS, VB, TRN,
124 VB, LP, BC, KL, JH), focussed on lower airway dysfunction and was chaired by JH. The members of sub-
125 group 4 conducted this systematic review and meta-analysis.

126

127 **Study selection and eligibility criteria**

128 The search strategy was developed by members of IOC sub-group 4. PubMed, EBSCOhost and Web of
129 Science (core collection) databases were used to search for published articles between 1st January

1990 and 31st July 2020, in order to capture relevant contemporary literature concerning the diagnosis of lower airway dysfunction in athletes. A combination of search terms was used to identify studies focusing on the prevalence of lower airway dysfunction in athletes (e.g., exercise-induced asthma (EIA) OR exercise-induced bronchoconstriction (EIB) OR exercise-induced bronchospasm OR asthma AND athlete OR active population) and relevant exclusions. For the full search string for each database see online supplementary file 1. 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 (15).

Inclusion and exclusion criteria

Studies were required to meet the following criteria for inclusion: (1) study participants were male or female athletes/physically active individuals/military personnel, aged 15 to 65 years; (2) participants had received a prior clinical or physician-based asthma diagnosis or underwent screening for lower airway dysfunction via self-report (i.e., patient recall or questionnaires) or objective testing (i.e., direct or indirect bronchial provocation challenge); (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 a review article, expert opinion or consensus position statement. The articles were screened independently by two reviewers (OP, JH) first by title/abstract and then full text, and any conflicts resolved through discussion or via a third researcher (NS).

Data extraction

The data extracted from the studies were clustered into three groups: (1) quality assessment of the studies (modified Downs & Black score, and Oxford Level of Evidence, 2009) (16, 17); (2) descriptive characteristics of the studies (study design, cohort number, sex, sport, and level of participation), and

(3) study outcome measures (diagnostic method, test outcome and the prevalence of lower airway dysfunction in the cohort). For interventional studies (clinical, nutrition, pharmacological) only data from the control group(s) was extracted. The geographical location of each study was also recorded. All data were extracted by two reviewers independently (OP, JH) and checked by a third researcher during analysis (NS) until consensus was reached.

Quality assessment and risk of bias

A modified Downs and Black checklist was used to determine the quality of the articles (see online supplementary file 2 for full checklist with relevant domains). Two reviewers (OP, JH) scored the articles independently and reached consensus on the final score after discussion. A third reviewer (NS) was consulted to resolve any inconsistencies. The Downs and Black checklist was adjusted to remove questions pertaining to a randomised controlled trials (RCTs). The modified checklist included components of reporting, external and internal validity (bias and selection bias) and yielded a final score for each article out of a possible 13 points. The quality assessment score for each article 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) (17). The OCEBM is a hierarchical system, grading studies on a scale of 1 (highest level of evidence) to 5 (lowest level of evidence), including sub-sections for level 1, 2, and 3.

Criteria and definitions of sub-categories and outcome measures

The primary categorisation of the entities of lower airway dysfunction (EIB, asthma and AHR) was performed to determine the overall prevalence. The following outcomes were included in further sub-group analysis, and if multiple different domains were reported in sub-groups within a study, all were included in the analysis. The categories included: prevalence of lower airway dysfunction excluding studies rated as “poor”, decade of publication (1990-2000, 2001-2010, 2011-2020), diagnostic method (physician diagnosed, questionnaire only, bronchial provocation test, combination), type of

provocation test (methacholine, histamine, exercise, EVH, inhaled mannitol), provocation test (direct, indirect), athletic standard (Olympic, elite, or recreational), sex (males, females), sporting discipline (endurance, power; aquatic, non-aquatic; team, individual), season (summer, winter) and TUE studies. All studies that reported on these outcomes were included in the analysis. No direct contact was made with authors to determine if further data were available. If data were not differentiated for specific sub-groups, it was not included in the analysis (i.e., mixed data). For sex, the study had to include both sexes to be included in the analysis (i.e., male only studies were not included for this sub-analysis).

Data synthesis and analysis

The pooled prevalence of lower airway dysfunction was determined by dividing the number of cases of disease observed by the total number of athletes and was estimated using a DerSimonian Laird Random effects model to account for the heterogeneity in the cohorts (e.g., differences in diagnostic method and provocation test etc.) and weighting of studies. Heterogeneity was measured using I^2 and Cochran's Q statistics. Pooled prevalence analysis was performed using MetaXL 5.3 (Epigear International). Data are reported as prevalence (%) and 95% confidence intervals (95% CI). The latter were compared to determine significant differences between sub-groups for prevalence data (except sex) (i.e., 95% CIs were considered significantly different if they did not overlap). For the comparison of sex, these data were extracted from within studies, and analysed using a DerSimonian Laird Binary Random effects model using OpenMetanalyst (Metafor) to determine the Odds Ratio (OR; 95% CIs) of males having lower airway dysfunction in comparison to females ($P<0.05$ was considered statistically significant).

RESULTS

Included studies and quality characteristics

In total, 1284 studies were identified. Of these, sixty-four studies (6-9, 12, 13, 18-75), from over twenty-one countries were considered eligible for inclusion in the qualitative synthesis and meta-

208 analysis (none of the studies included in this review were RCTs) (Figures 1 and 2). Study characteristics
209 and sample sizes, according to sub-groups, are summarised in Tables 1 and S1. The Oxford Level of
210 Evidence ranged from 1b (n = 51) to 2b (n = 13) and included both prospective (n = 56) and
211 retrospective (n = 8) studies. Downs & Black Quality Assessment Scores ranged from 2-12 and studies
212 were rated as poor (n = 10); fair (n = 9); good (n = 21); excellent (n = 24) (Table S2 and supplementary
213 file 3).

214

215

216 **Overall prevalence of lower airway dysfunction**

217 The sixty-four eligible studies resulted in a combined study population of n = 37,643: elite (n = 7,898)
218 (21.0%); recreational (n = 12,767) (33.9%); Olympic (n = 16,978) (45.1%) athletes. Detail regarding
219 athlete sex was available in 52 studies (n = 16,474 athletes) (43.8% of total athletes included in the
220 population) but revealed a slightly greater proportion of male athletes (62.3%). The overall mean
221 prevalence of lower airway dysfunction (i.e., those with confirmed EIB and/or asthma and/or AHR) for
222 all studies was 21.8% (95% CI: 18.8-25.0%) (Q = 2711, I^2 = 98%) (Figure S1). This remained unchanged
223 when (n = 10) "poor" studies were excluded from the analysis (23.0%; CI:19.1-27.1) (Q = 2254, I^2 = 98)
224 (Figure S2).

225

226 The prevalence remained similar over the study period: 1990-2000 (23.5%; CI:16.4-31.1%) (Q = 169, I^2
227 = 94%); 2001-2010 (21.6%; CI:16.9-26.6%) (Q = 1564, I^2 = 98%); 2011-2020 (21.0%; CI:17.2-25.0%) (Q
228 = 305, I^2 = 93%) (Figure 3). A high degree of heterogeneity was however observed between studies (Q
229 = 2711, I^2 = 98%). When stratified according to the original terminology reported in the respective
230 published paper, the highest prevalence was observed in AHR: 38.2% (CI: 26.9-49.8%) (Q = 92, I^2 =
231 89%), followed by EIB: 21.0% (CI: 15.4-27.0%) (Q = 1201, I^2 = 97%) and asthma: 17.8% (CI: 14.6-21.2%)
232 (Q = 831, I^2 = 97%) (Figure S3). In the twenty-three studies that compared sex, the prevalence of lower

233 airway dysfunction was significantly higher in females (15.5%) in comparison to males (11.5%) (OR:
234 0.75; CI: 0.62-0.91) (Q = 46, I2 = 52%) (P = 0.003).

235

236 **Prevalence analysis based on diagnostic methodology**

237 Thirty-six studies (56.3%) included at least one form of objective test methodology (i.e., bronchial
238 provocation test), twelve studies relied on a physician-based diagnosis (18.8%), nine studies utilised
239 questionnaires (14.1%) and nine employed combined methods (14.1%) (two studies employing
240 combined methods also included a bronchial provocation test). The prevalence of lower airway
241 dysfunction was highest when utilising combined methods: 25.8% (CI: 16.8-35.3%) (Q = 365, I^2 = 98%),
242 followed by objective testing: 23.2% (CI: 19.1-27.5%) (Q = 606, I^2 = 92%), physician-diagnosed: 16.8%
243 (CI: 14.7-19.1%) (Q = 91, I^2 = 84%) and questionnaires: 14.9% (CI: 6.9-24.1%) (Q = 470, I^2 = 98%) (Figure
244 4). Three studies reported the prevalence of lower airway dysfunction based on TUE application data
245 for Olympic competition (n = 13,869 athletes), revealing an overall prevalence estimate of 8.0% (CI:
246 3.6-13.8%) (Q = 136, I^2 = 99%).

247

248 In studies that employed bronchial provocation testing, a higher prevalence was observed in studies
249 utilising direct test (i.e., histamine or methacholine challenge): 32.8% (CI: 19.3-47.2%) (Q = 99, I^2 = 93%)
250 in comparison to indirect test methodology (i.e., exercise, EVH, inhaled mannitol): 22.3% (CI: 17.9-
251 26.9%) (Q = 472, I^2 = 92%) (Figure S4). Of the indirect tests, the highest prevalence of lower airway
252 dysfunction was observed in response to EVH: 29.2% (CI: 21.3-37.6%) (Q = 215, I^2 = 93%), followed by
253 inhaled mannitol: 25.0% (CI: 0.0- 59.9%) (Q = 34, I^2 = 94%) and exercise: 16.8% (CI: 12.0-22.0%) (Q =
254 186, I^2 = 89%) (Figure S5).

255

256 **Prevalence analysis based on sporting discipline and athletic standard**

257 The prevalence of lower airway dysfunction, classified according to sporting discipline and athletic
258 standard, is summarised in Figure 5. A higher prevalence of lower airway dysfunction was observed in

athletic groups partaking in individual sports: 27.5% (CI: 21.7-33.5%) (Q = 204, I^2 = 91%) when compared with team sports: 17.3% (CI: 9.6-26.0%) (Q = 88, I^2 = 91%) (Figure S6).

The highest prevalence of lower airway dysfunction was observed in athletes participating in aquatic disciplines (39.9%) (CI: 23.4-57.1) (Q = 128, I^2 = 96%) (Figure S7) and winter-based sports (29.5%) (CI: 22.5-36.8%) (Q = 453, I^2 =97%) (Figure S8). Likewise, when a single study of low numbers (<20) was excluded, the prevalence of lower airway dysfunction was higher in endurance athletes 25.1% (CI: 20.0-30.5%) (Q = 293, I^2 = 91%) in comparison to those partaking in power-based sports (18.7%) (CI: 11.8-26.3%) (Q = 13, I^2 = 69%) (Figure S9). The prevalence also varied according to athletic standard with lower airway dysfunction most commonly reported in elite level athletes 28.2% (CI: 22.4-34.3%) (Q = 1032, I^2 = 97%) (Figure S10). A high degree of publication bias was observed for the overall analysis when evaluating the DOI plots (and asymmetrical funnel plots), however this decreased when accounting for the specific form of bronchial provocation test (i.e., the only sub-group analysis where no asymmetry was observed) (supplementary file 4).

DISCUSSION

It has long been reported that lower airway dysfunction is the most common chronic medical condition encountered in elite and recreational athletes (1, 76). In this comprehensive, systematic review and meta-analysis, that included data from over thirty-seven thousand individuals and from over twenty-one countries, we confirm that approximately one in five athletes are affected by lower airway dysfunction (including asthma and/or EIB and/or AHR). In-keeping with asthma prevalence estimates from the general population in developed countries (77), the high prevalence of lower airway dysfunction in athletes has remained relatively stable over the past thirty years and appears particularly common in elite endurance athletes and those partaking in aquatic and winter-based sporting disciplines.

The evaluation of the epidemiology or prevalence of a clinical condition depends on several key factors including definitions, diagnostic methodology, test protocols and cut-off criteria employed (78). In this respect, it is apparent that a broad range of diagnostic approaches have been used to assess the prevalence of lower airway dysfunction in the athletic population over the past three decades. It is widely recommended that a form of objective testing should be conducted to secure a diagnosis of lower airway dysfunction in athletes (10, 11, 76). However, this approach was only employed in approximately half of the studies (n = 36) included in this review, with a large number (n = 28) relying solely on either physician diagnosis and/or symptom-based questionnaires.

Our data indicate that the choice of diagnostic test significantly impacts prevalence estimates. For example, in studies that employed a form of direct bronchial provocation testing (i.e., methacholine or histamine) approximately one in three athletes were found to have evidence of lower airway dysfunction. In contrast, in studies that utilised indirect bronchial provocation, the prevalence was closer to one in five. Likewise, in studies that reported a physician or symptom-based approach to diagnosis, the prevalence was closer to one in six. Importantly, even when comparing objective methods, test selection appears to influence the reported prevalence. Specifically, studies that utilised exercise testing (i.e., often considered the most intuitive approach to detect lower airway dysfunction in athletes) (10, 11) actually resulted in the lowest prevalence (16.8%). Whilst this may appear counterintuitive, exercise testing is recognised to be highly specific (i.e., ability to rule-in) but less sensitive (i.e., ability to rule-out) given the type, duration and intensity of exercise and the temperature and water content of inspired air are recognised to be important determinants of the airway response (79, 80). For that reason, indirect 'surrogate' tests such as EVH and inhaled mannitol are often recommended in an attempt to improve diagnostic sensitivity and specificity when screening athletes (33, 81).

It is important to note, that from an epidemiological perspective, it does not appear to be appropriate to use objective methods interchangeably, given a higher prevalence of lower airway dysfunction was observed when utilising surrogate tests (EVH: 29.2%; inhaled mannitol: 25.0%) in comparison to exercise. This observation is in-keeping with studies conducted over the past two decades that consistently reveal poor diagnostic agreement when directly comparing exercise, EVH and/or inhaled mannitol (27, 33, 82-84). Accordingly, whilst surrogate tests may reduce the risk of underdiagnosis (i.e., false-negative outcome), there remains concern regarding the potential for overdiagnosis (i.e., false-positive outcome) (85). Indeed, recent studies have questioned the suitability of current diagnostic thresholds when utilising surrogate tests in this setting. Specifically, Price et al. (86) has previously observed a greater reduction in lung function post EVH in 'healthy' (defined as entirely asymptomatic, with no prior history of asthma or inhaler medication use) elite vs. recreational athletes, indicating that the 'normative' airway response may differ according to the athletic population tested. This also presents challenges with respect to the most appropriate diagnostic 'cut-off' value according to the form of bronchial provocation challenge employed (85, 86).

Historically, many studies that report the prevalence of lower airway dysfunction in Olympic athletes have arisen from mandatory evidence of inhaled beta-2 agonist use when TUE certificates were required for this type of medication (for review see Allen et al. (87)). Indeed, large retrospective studies in this area reveal a consistent prevalence of lower airway dysfunction (i.e., asthma medication use) of approximately 8% in Olympic level athletes, over sequential major competitions (1996-2004) (12, 13). The reason this figure is lower than the overall prevalence in our analysis is unclear, but certainly challenges the widely held supposition that many athletes report 'asthma symptoms' or use inhalers to potentially enhance performance (87-89); i.e., studies objectively confirming lower airway

dysfunction actually suggest that a greater number of athletes should be using inhaler therapy to optimise and maintain their respiratory health.

A secondary aim of this meta-analysis was to evaluate 'risk' factors and highlight susceptible groups. To achieve this objective, we sub-classified athlete populations according to sporting discipline and athletic standard. It has long been recognised that endurance sport is associated with the highest prevalence of AHR and our systematic review substantiates this, with a higher incidence observed in endurance (25.1%) vs. power athletes (18.7%), aquatic (39.9%) vs. non-aquatic disciplines (20.7%) and winter (29.5%) vs. summer sports (19.6%). The pathophysiological mechanism(s) underpinning this remains to be fully determined, however it has been proposed that high-intensity repeated periods of hyperpnoea particularly when conducted in noxious environments (e.g., high aeroallergen, exposure to chlorine derivatives, cold dry air, particulate matter etc.) may act to sensitise or potentially damage the small airways, akin to an airway injury, thus driving a predisposition to AHR (5, 90, 91). This theory is supported by the finding that discontinuing exercise is associated with a fairly rapid resolution of heightened AHR on discontinuing vigorous training (92). In support of this concept, Helenius et al. (93) previously observed a reduction in airway inflammation and attenuation or disappearance of AHR in elite swimmers who stopped high-level training. The fact environmental exposure appears to be relevant in terms of aetiology, yet the prevalence has remained unchanged over time, supports a need for closer scrutiny regarding this issue and development of effective preventative strategies moving forward.

Ideally, it would have been informative to assess biological risk factors in our analysis, such as the impact of allergenic profiling. Indeed, prior studies have shown that AHR and asthma are strongly associated with atopic disposition in athletes (30, 31). However, our ability to analyse this type of data

was limited on the basis that few studies completed skin prick testing and/or included specific statistics with respect to sub-group prevalence. Accordingly, logistic regression or odds ratios are often not reported and therefore this does not permit extraction of true prevalence data which limited our ability to analyse atopic vs. non-atopic athletes. Similarly, differentiating between type-2 and non-type-2 'asthma' was not possible in this analysis. Likewise, there is also limited data available regarding relevant biomarkers of airway inflammation such as fractional exhaled nitric oxide.

It is also important to highlight that very few studies have reported the prevalence of acute lower airway dysfunction ('asthmatic' events) and thus we did not systematically evaluate the literature to address this issue. It is recognised that acute respiratory illness is highly prevalent in athletes and the most common reason an athlete seeks acute medical attention during major competition (94). It is likely that a proportion of these acute events are exacerbations of lower airway dysfunction, and a four-year prospective study found an incidence of 0.18 per 1000 athletes required treatment for acute asthma (94).

Methodological limitations and future research

Several methodological limitations are worthy of consideration. Firstly, we recognise that the nomenclature pertaining to 'asthma in athletes' remains debated, and thus we opted to use the term 'lower airway dysfunction' to encompass and capture all relevant prevalence-based studies in athletes. Furthermore, as with any epidemiological evaluation, a true prevalence estimate is dependent on appropriate and robust capture of the population of interest. It is important that, as close as possible, the whole population is included, to provide an accurate denominator (i.e., asymptomatic and symptomatic athletes). Despite our best efforts to exclude studies with potential biased-inclusion criteria, it seems likely that in most of the studies there is inadequate capture of the whole study population. Specifically, the nature of any study with a self-report or questionnaire-based approach

response will be associated with a degree of self-selection bias; i.e., it is likely that symptomatic individuals may be preferentially included thus potentially artificially increasing prevalence rates in some studies.

The wide range of diagnostic methods employed over the past thirty years resulted in a high level of heterogeneity between studies included in this review (I^2 = 98%), (even when accounting for sub-groups analysis). The publication bias was also high (major asymmetry in all analyses except for the specific form of bronchial provocation test sub-group analysis), and therefore all prevalence estimates should be interpreted with caution. Furthermore, the risk of bias failed to account for the observed heterogeneity (i.e., when analysing the data excluding "poor" studies, the asymmetry was still present, and the prevalence was not significantly different).

It is also important to acknowledge that whilst some groups have previously reported good test re-test repeatability following objective testing in athletes (95, 96), others have highlighted that a single bronchial provocation challenge (i.e., exercise and EVH) has the potential to result in misdiagnosis (particularly in athletes with mild severity disease or a borderline diagnosis) (97, 98). In this respect, none of the included studies performed multiple assessments (i.e., in / out of season testing) in the same athlete to confirm or refute a diagnosis. Whilst repeat assessment is not a current requirement, it is important to note that airway calibre fluctuates over short-term periods (99) and thus any change in training status or environmental exposure (e.g., seasonal variation due to high aeroallergen etc.) has the potential to impact test outcome.

In addition, the lack of longitudinal studies limits the ability to draw robust conclusions concerning the development of lower airway dysfunction (i.e., training status / dose-response relationship) over the course of a sporting career. Also, a key deficiency in the field is the paucity of data with respect to

racial differences in prevalence figures and individuals participating in Paralympic sport which remains an important avenue for future research.

A further consideration when evaluating the epidemiology of a condition is the availability of resources to screen athletes (i.e., access to diagnostic tests), to ensure that best practice is upheld to rule-in/out a diagnosis (i.e., adhering to established test protocols in accordance with international guidelines) (10, 11). Despite the large number of athletes in our analysis, the majority of available data were sourced from European countries (n = 36 studies) or North America (n = 16 studies), with a paucity of evidence arising from other geographical areas, including developing nations. The reason(s) for this remain to be fully established and thus further epidemiological research is required moving forward to provide a globally inclusive prevalence estimate of lower airway dysfunction in athletes.

Finally, despite conducting a robust and comprehensive search strategy, there is vast literature on this topic, and thus it is possible that some studies may not have been identified in the initial search. Irrespective of this potential limitation, the current analysis included a combined study population of over thirty-seven thousand athletes and thus we feel that this analysis provides a reliable representation of the current epidemiological characteristics of the condition within this population.

Clinical implications and practical application

The clinical implications and practical application of our findings can be considered two-fold. Firstly, improved epidemiological insight enables sport and exercise medicine clinicians and support personnel to conduct targeted screening and assessment in high-risk athletic cohorts (e.g., elite endurance, aquatic and winter-based sports) moving forward. Secondly, the ability to identify susceptible groups provides the opportunity to conduct focussed longitudinal research to establish the

underpinning pathophysiological mechanism(s) associated with disease onset and progression and to evaluate the efficacy of preventative strategies to protect and maintain airway health.

Conclusion

In summary, lower airway dysfunction occurs in approximately one in five athletes, with a higher prevalence in those participating in elite endurance, winter and aquatic disciplines. This estimate appears to be unchanged over the past three decades, with studies consistently revealing that objective testing results in a higher incidence in comparison to a physician or symptom-based approach. Further longitudinal, multicentre studies addressing causality (i.e., training status / dose-response relationship) and evaluating preventative strategies to mitigate against the development of lower airway dysfunction remains an important priority for future research.

Table 1. Summary of key study variables, athlete characteristics and prevalence statistics.

	*Athlete breakdown (%)	Lower airway dysfunction (%)
Standard		
Elite	21.0	28.2
Recreational	33.9	16.7
Olympian	45.1	16.1
Sex		
Male	60.9	11.5
Female	39.1	15.5
Diagnostic method		
Bronchial provocation	13.7	23.2
Physician-diagnosed	38.8	16.8
Questionnaire	12.3	14.9
Combined	35.2	25.8
Type of bronchial provocation		
Direct challenge	14.2	32.8
Indirect challenge	85.8	22.3
Direct challenge		
Methacholine	64.0	32.8
Histamine	36.0	
Indirect challenge		
Exercise	54.9	16.8
EVH	41.8	29.2
Inhaled mannitol	3.3	25.0
Sporting discipline		
Endurance	96.8	25.1
Power	3.2	18.7
Aquatic	5.5	39.9
Non-aquatic	94.5	20.7
Team	7.7	17.3
Individual	92.3	27.5
Season		
Summer	70.1	19.6
Winter	29.9	29.5
	Studies (n)	**Studies (%)**
Geographical location		
Europe	36	56.3
North America	16	25.0
South America	1	1.6
Africa	2	3.1
Asia	3	4.7
Australasia	2	3.1
Global	4	6.3

*percentage breakdown presented according to available data reported in studies.

Figure 1. PRISMA flowchart representing search results.

Figure 2. Prevalence of studies according to geographical location (size of red circles denotes number of studies per country).

Figure 3. Prevalence of lower airway dysfunction in athletes between 1990-2020.

Figure 4. Prevalence of lower airway dysfunction according to diagnostic method.

Figure 5. Prevalence of lower airway dysfunction according to athletic standard and sporting discipline. TUE: Therapeutic use exemption.

Supplementary file 1. Full search string for each database.

Supplementary file 2. Downs and Black assessment checklist with relevant domains.

Supplementary file 3. Downs and Black assessment checklist scores.

Supplementary file 4. Publication bias statistics, funnel and DOI plots.

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

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Guarantor statement

OP and JH confirm full responsibility for the content of the manuscript.

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