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

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1 **SUBGROUP 4 - SYSTEMATIC REVIEW 7**

2

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

5

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29

30

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33 **ABSTRACT**

34 **Objective:** To report the prevalence of lower airway dysfunction in athletes and highlight risk factors
35 and susceptible groups. **Design:** Systematic review and meta-analysis **Data sources:** PubMed, EBSCO
36 Host and Web of Science (1st January 1990-31 July 2020). **Eligibility criteria:** Original full-text studies,
37 including male or female athletes/physically active individuals/military personnel (aged 15-65 years)
38 who had a prior asthma diagnosis and/or underwent screening for lower airway dysfunction via self-
39 report (i.e., patient recall or questionnaires) or objective testing (i.e., direct or indirect bronchial
40 provocation challenge). **Results:** In total, 1284 studies were identified. Of these, sixty-four studies (n =
41 37,643 athletes) from over 21 countries (81.3% European and North America) were included. The
42 prevalence of lower airway dysfunction was 21.8% (95% CI: 18.8-25.0%) and has remained stable over
43 the past 30-years. The highest prevalence was observed in elite endurance athletes 25.1% (CI: 20.0-
44 30.5%) (Q = 293, I² = 91%), those participating in aquatic (39.9%) (CI: 23.4-57.1) and winter-based
45 sports (29.5%) (CI: 22.5-36.8%). In studies that employed objective testing, the highest prevalence was
46 observed in studies utilising direct bronchial provocation (32.8%) (CI: 19.3-47.2%). A high degree of
47 heterogeneity was observed between studies (I² = 98%). **Conclusion:** Lower airway dysfunction affects
48 approximately one in five athletes, with the highest prevalence observed in those participating in elite
49 endurance, aquatic and winter-based sporting disciplines. Further longitudinal, multicentre studies
50 addressing causality (i.e., training status / dose-response relationship) and evaluating preventative
51 strategies to mitigate against the development of lower airway dysfunction remains an important
52 priority for future research.

53

54 PROSPERO registration: CRD42020167691

55

56

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

58 **SUMMARY BOX**

59 **What is already known?**

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

68

69 **What are the new findings?**

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

77

78

79 **INTRODUCTION**

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

87

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

93

94 To date, the best available data concerning the prevalence and epidemiological characteristics of lower
95 airway dysfunction in the athletic population primarily arises from cross-sectional studies in highly
96 selected cohorts (6-9). Moreover, prior studies have utilised a diverse range of diagnostic approaches,
97 including variable use of self-report and/or clinical or physician-based diagnosis and/or objective direct
98 bronchial provocation (i.e., histamine and methacholine) or indirect bronchial provocation (i.e.,
99 laboratory and field-based exercise challenge tests, eucapnic voluntary hyperpnoea (EVH) or inhaled
100 mannitol). Whilst it is now widely recommended that some form of objective testing is used to secure
101 a diagnosis (10, 11), it is common for studies to provide evidence detailing the prevalence of lower
102 airway dysfunction in elite athletes based on prior medication prescription data, often arising from
103 submitted therapeutic use exemption (TUE) requests prior to major competition (e.g., Olympic Games
104 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

130 1990 and 31st July 2020, in order to capture relevant contemporary literature concerning the diagnosis
131 of lower airway dysfunction in athletes. A combination of search terms was used to identify studies
132 focusing on the prevalence of lower airway dysfunction in athletes (e.g., exercise-induced asthma (EIA)
133 OR exercise-induced bronchoconstriction (EIB) OR exercise-induced bronchospasm OR asthma AND
134 athlete OR active population) and relevant exclusions. For the full search string for each database see
135 online supplementary file 1. The results of these searches were combined, and duplicate articles
136 removed. Any additional relevant articles identified by the authors or sourced from the reference list
137 of identified studies were included. All article screening and selection was undertaken using the online
138 tool CADIMA (15).

139

140 **Inclusion and exclusion criteria**

141 Studies were required to meet the following criteria for inclusion: (1) study participants were male or
142 female athletes/physically active individuals/military personnel, aged 15 to 65 years; (2) participants
143 had received a prior clinical or physician-based asthma diagnosis or underwent screening for lower
144 airway dysfunction via self-report (i.e., patient recall or questionnaires) or objective testing (i.e., direct
145 or indirect bronchial provocation challenge); (3) original full-text studies (i.e., not research
146 correspondence or case studies) of observational, prospective, retrospective, cross-sectional,
147 longitudinal or intervention design, written in English. Animal or non-human studies were excluded.
148 Articles were also excluded if the study was a review article, expert opinion or consensus position
149 statement. The articles were screened independently by two reviewers (OP, JH) first by title/abstract
150 and then full text, and any conflicts resolved through discussion or via a third researcher (NS).

151

152 **Data extraction**

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

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

161

162 **Quality assessment and risk of bias**

163 A modified Downs and Black checklist was used to determine the quality of the articles (see online
164 supplementary file 2 for full checklist with relevant domains). Two reviewers (OP, JH) scored the
165 articles independently and reached consensus on the final score after discussion. A third reviewer (NS)
166 was consulted to resolve any inconsistencies. The Downs and Black checklist was adjusted to remove
167 questions pertaining to a randomised controlled trials (RCTs). The modified checklist included
168 components of reporting, external and internal validity (bias and selection bias) and yielded a final
169 score for each article out of a possible 13 points. The quality assessment score for each article was
170 determined against the following criteria: 11-13: Excellent; 9-10: Good; 7-8: Fair; ≤6: Poor. The level of
171 evidence was also determined using the 2009 Oxford Centre for Evidence Based Medicine Levels of
172 Evidence (OCEBM) (17). The OCEBM is a hierarchical system, grading studies on a scale of 1 (highest
173 level of evidence) to 5 (lowest level of evidence), including sub-sections for level 1, 2, and 3.

174

175 **Criteria and definitions of sub-categories and outcome measures**

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

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

189

190 **Data synthesis and analysis**

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

203

204 **RESULTS**

205 **Included studies and quality characteristics**

206 In total, 1284 studies were identified. Of these, sixty-four studies (6-9, 12, 13, 18-75), from over
207 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, I² = 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, I² = 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, I²
227 = 94%); 2001-2010 (21.6%; CI:16.9-26.6%) (Q = 1564, I² = 98%); 2011-2020 (21.0%; CI:17.2-25.0%) (Q
228 = 305, I² = 93%) (Figure 3). A high degree of heterogeneity was however observed between studies (Q
229 = 2711, I² = 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, I² =
231 89%), followed by EIB: 21.0% (CI: 15.4-27.0%) (Q = 1201, I² = 97%) and asthma: 17.8% (CI: 14.6-21.2%)
232 (Q = 831, I² = 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, I² = 98%),
242 followed by objective testing: 23.2% (CI: 19.1-27.5%) (Q = 606, I² = 92%), physician-diagnosed: 16.8%
243 (CI: 14.7-19.1%) (Q = 91, I² = 84%) and questionnaires: 14.9% (CI: 6.9-24.1%) (Q = 470, I² = 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, I² = 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, I² = 93%)
250 in comparison to indirect test methodology (i.e., exercise, EVH, inhaled mannitol): 22.3% (CI: 17.9-
251 26.9%) (Q = 472, I² = 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, I² = 93%), followed by
253 inhaled mannitol: 25.0% (CI: 0.0- 59.9%) (Q = 34, I² = 94%) and exercise: 16.8% (CI: 12.0-22.0%) (Q =
254 186, I² = 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

259 athletic groups partaking in individual sports: 27.5% (CI: 21.7-33.5%) (Q = 204, I² = 91%) when
260 compared with team sports: 17.3% (CI: 9.6-26.0%) (Q = 88, I² = 91%) (Figure S6).

261

262 The highest prevalence of lower airway dysfunction was observed in athletes participating in aquatic
263 disciplines (39.9%) (CI: 23.4-57.1) (Q = 128, I² = 96%) (Figure S7) and winter-based sports (29.5%) (CI:
264 22.5-36.8%) (Q = 453, I² = 97%) (Figure S8). Likewise, when a single study of low numbers (<20) was
265 excluded, the prevalence of lower airway dysfunction was higher in endurance athletes 25.1% (CI:
266 20.0-30.5%) (Q = 293, I² = 91%) in comparison to those partaking in power-based sports (18.7%) (CI:
267 11.8-26.3%) (Q = 13, I² = 69%) (Figure S9). The prevalence also varied according to athletic standard
268 with lower airway dysfunction most commonly reported in elite level athletes 28.2% (CI: 22.4-34.3%)
269 (Q = 1032, I² = 97%) (Figure S10). A high degree of publication bias was observed for the overall analysis
270 when evaluating the DOI plots (and asymmetrical funnel plots), however this decreased when
271 accounting for the specific form of bronchial provocation test (i.e., the only sub-group analysis where
272 no asymmetry was observed) (supplementary file 4).

273

274 **DISCUSSION**

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

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

292

293 Our data indicate that the choice of diagnostic test significantly impacts prevalence estimates. For
294 example, in studies that employed a form of direct bronchial provocation testing (i.e., methacholine
295 or histamine) approximately one in three athletes were found to have evidence of lower airway
296 dysfunction. In contrast, in studies that utilised indirect bronchial provocation, the prevalence was
297 closer to one in five. Likewise, in studies that reported a physician or symptom-based approach to
298 diagnosis, the prevalence was closer to one in six. Importantly, even when comparing objective
299 methods, test selection appears to influence the reported prevalence. Specifically, studies that utilised
300 exercise testing (i.e., often considered the most intuitive approach to detect lower airway dysfunction
301 in athletes) (10, 11) actually resulted in the lowest prevalence (16.8%). Whilst this may appear
302 counterintuitive, exercise testing is recognised to be highly specific (i.e., ability to rule-in) but less
303 sensitive (i.e., ability to rule-out) given the type, duration and intensity of exercise and the temperature
304 and water content of inspired air are recognised to be important determinants of the airway response
305 (79, 80). For that reason, indirect 'surrogate' tests such as EVH and inhaled mannitol are often
306 recommended in an attempt to improve diagnostic sensitivity and specificity when screening athletes
307 (33, 81).

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

322

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

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

333

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

351

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

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

361

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

369

370 **Methodological limitations and future research**

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

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

383

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

391

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

401

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

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

407

408 A further consideration when evaluating the epidemiology of a condition is the availability of resources
409 to screen athletes (i.e., access to diagnostic tests), to ensure that best practice is upheld to rule-in/out
410 a diagnosis (i.e., adhering to established test protocols in accordance with international guidelines)
411 (10, 11). Despite the large number of athletes in our analysis, the majority of available data were
412 sourced from European countries (n = 36 studies) or North America (n = 16 studies), with a paucity of
413 evidence arising from other geographical areas, including developing nations. The reason(s) for this
414 remain to be fully established and thus further epidemiological research is required moving forward
415 to provide a globally inclusive prevalence estimate of lower airway dysfunction in athletes.

416

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

422

423 **Clinical implications and practical application**

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

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

431

432 **Conclusion**

433 In summary, lower airway dysfunction occurs in approximately one in five athletes, with a higher
434 prevalence in those participating in elite endurance, winter and aquatic disciplines. This estimate
435 appears to be unchanged over the past three decades, with studies consistently revealing that
436 objective testing results in a higher incidence in comparison to a physician or symptom-based
437 approach. Further longitudinal, multicentre studies addressing causality (i.e., training status / dose-
438 response relationship) and evaluating preventative strategies to mitigate against the development of
439 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
EZH	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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Competing interests

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

Analysis and interpretation: OP, NS, JH.

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

Guarantor statement

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

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