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1 **Manuscript title**

2 Non Pharmacological Strategies to Manage Exercise Induced Bronchoconstriction

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4
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11
12 **Disclosure statement**

13 Authors have no conflicting interests.

14
15 **SYNOPSIS (100 words)**

16 Pharmacological management of exercise induced bronchoconstriction (EIB) is the mainstay
17 of preventative therapy. However, there are some non-pharmacological interventions that may
18 assist the management of EIB. In this review we will discuss these non-pharmacological
19 interventions and how they may be applied to patients and athletes with EIB.

20
21 **KEY WORDS (4-8):**

22 **Warm-Up, Face Mask, Asthma, Pollution, Avoidance, Athletes, Nutrition, Training**

26 **KEY POINTS:**

- 27 • There is emerging evidence that non-pharmacological strategies can be used to
28 supplement traditional therapy to reduce exercise-induced bronchoconstriction (EIB)
29 severity and lessen respiratory symptoms associated with exercise
- 30 • Most investigations into non-pharmacological have included non-athletes,
31 extrapolating towards athletes should be done with caution and studies in athletes with
32 EIB are encouraged.
- 33 • There is currently insufficient evidence to support the use of any non-pharmacological
34 EIB treatment strategy in the absence of regular pharmaceutical therapy for EIB.

35

36 **INTRODUCTION**

37 Exercise-induced bronchoconstriction (EIB) is an asthma-related condition, which occurs
38 during or following exercise as a result of large volumes of ‘unconditioned air’ entering the
39 lower airways to meet the increased ventilatory demands of exercise^{1,2}. In susceptible
40 individuals, EIB arises via multiple mechanisms that may involve dehydration of airway
41 surface liquid, mucosal cooling and epithelial damage (ref to pathophysiology paper in series),
42 which induces an airway inflammatory response (involving histamine, neuropeptides,
43 leukotrienes and prostaglandins) with resultant airway smooth muscle constriction³.
44 Management of EIB in athletes is almost exclusively based around pharmacological therapies
45 (ref to pharmacological paper in series), such as glucocorticoids and β_2 -Agonists^{1,2}. Although
46 clinical data on non-pharmacological therapies has been equivocal, there is emerging evidence
47 that non-pharmacological strategies could be used to supplement traditional therapy to reduce
48 EIB severity and lessen exercise respiratory symptoms (table 1). This paper reviews the
49 evidence and provides recommendations for the use of non-pharmacological strategies in the
50 management of EIB.

Table 1. Non-pharmacological strategies to manage EIB

Strategy	Intervention	Potential effect	Evidence level	Pitfalls	References
Pre-exercise warm up	Repetitive 30-s bouts close to VO_{2max}/HR_{max}	Reduces post-exercise fall in FEV1	Good	May accumulate peripheral fatigue prior to exertion	5
Face masks	HME face masks	Reduces post-exercise fall in FEV1	Insufficient	May affect ventilation and be associated with discomfort	9-12
Omega-3 fatty acid supplementation	3 g/d EPA and 2 g/d DHA	Reduces systemic inflammation	Medium	Side effects: Acid reflux, bloating, diarrhea and nausea	34-37,40
		Reduces airway inflammation	Insufficient		
		Reduces post-exercise fall in FEV1	Insufficient		
Caffeine	5-10 mg/kgbw	Induces bronchodilation	Good	Slow absorption	47-52, 55-56
		Reduces post-exercise fall in FEV1	Medium	Side effects: Muscle tremors, tachycardia	
		Improves respiratory muscle fatigue resilience	Medium		
		Counteracts exercise-induced hypoxemia	Insufficient		
Vitamins and anti-oxidants	1500 mg/d vitamin C	Reduces systemic inflammation	Medium	Side effects: Diarrhea, vomiting, headache, insomnia, nausea, kidney stones	57-68
	64 mg/d β -carotene	Scavenge ROS	Medium		
		Reduces post-exercise fall in FEV1	Insufficient		
Breathing control	See table 2	Reduces perception of respiratory symptoms	Insufficient		69-72
Respiratory muscle training	30 breaths x 2/d at 50% of MIP	Improves respiratory muscle fatigue resilience	Good	Time-consuming	73-88
		Reduces asthma severity	Insufficient		

52 FEV1: forced expired volume in 1 s, HME: heat and moisture exchange, HR_{max} : maximal heart rate, MIP: maximal

53 inspiratory pressure, ROS: reactive oxygen species, VO_{2max} : maximal oxygen consumption

54 **PRE-EXERCISE WARM UP**

55 In approximately half of those who suffer from EIB, high intensity pre-exercise warm up
56 effectively protects against subsequent bronchoconstriction³. A recent systematic review⁴
57 reported that intermittent high intensity pre-exercise warm up (repetitive sprints of ~30 s close
58 to peak oxygen consumption or maximal HR) provides about 10% reduction in the fall in FEV₁
59 post exercise, whereas neither low intensity nor continuous high intensity pre exercise warm up
60 provides significant protection in individuals with EIB.

61 The refractory period or refractory effect, that is induced after a first exercise bout, has
62 frequently been proposed to explain why high intensity warm-ups protect against EIB. It has
63 been proposed that the first exercise induces a variable period (called the refractory period)
64 during which (2-4 hours) subsequent exercise will not result in EIB or will result in decreased
65 fall in FEV₁. As discussed by XXXX (ref to refractory paper in this series), preceding exercise
66 may deplete constrictive mediators, induce secretion of protective mediators (particularly
67 prostaglandins) and cause desensitization of smooth muscle to bronchoconstrictive mediators³.
68 Regardless of the mechanism, there is good evidence to suggest a clinical benefit of warm ups
69 in protecting against EIB.

70

71 While high intensity exercise warm-ups may attenuate EIB³⁻⁴, the exercise intensity that is
72 required for the warm-up, may potentially cause perturbations in the exercising musculature
73 and compromise subsequent exercise performance⁵. However, emerging evidence suggests that
74 isolated respiratory warm-ups can provide similar bronchoprotective effects as whole-body
75 warm up⁶. Instead of using whole-body warm up, a recent study⁶ evaluated the effect of a
76 respiratory-only warm up on subsequent decline in FEV₁ induced by exhaustive cycling (\approx 14
77 min). In that study, subjects performed normocapnic hyperpnoea at different intensities (30-

78 80% of maximal voluntary ventilation). Notably, all hyperpnoea sessions attenuated post-
79 exercise decline in FEV₁ regardless of the intensity of the hyperpnoea session conducted and
80 without compromising cycling performance⁶. Perception of respiratory dyspnoea was also
81 reduced by preceding normocapnic hyperpnoea. Consequently, both pre-exercise whole body
82 and respiratory warm ups may be used to protect against EIB.

83

84 **AVOIDANCE OF TRIGGERS**

85 **Heat and Moisture Exchange Face Masks**

86 Exercise in dry and cold environments can be a significant trigger of bronchoconstriction (ref
87 to paper in series). The bronchoconstriction is thought to be caused by dehydration of the
88 airway surface liquid, which causes cell shrinkage, release of inflammatory mediators
89 precipitating airway smooth muscle constriction⁷. Repeated exposure of the airways to cold
90 dry air may also lead to airway epithelial cell damage, microvascular leakage and airway
91 remodelling, which may worsen asthma severity⁸. Given the increased risk of
92 bronchoconstriction in dry and cold environments, individuals with asthma may be advised to
93 avoid exercise outside. This places obvious constraints on athletes with asthma-related
94 conditions who have to train and complete in dry and cold environment and also the proportion
95 of individuals with asthma who engage in physical activity as part of their daily routines during
96 the winter months.

97

98 Face masks that incorporate a heat and moisture exchanger (HME) are a novel non-
99 pharmacological tool to counteract EIB in dry and cold environments. Although few studies
100 have investigated the efficacy of HME face masks in counteracting EIB, some studies have
101 demonstrated a protective effect as measured by an attenuation in post-exercise decline in
102 FEV₁⁹⁻¹². This suggests that individuals with asthma may use HME face masks to protect

103 against EIB when they engage in moderate to vigorous exercise in cold dry environments.
104 Currently, it is unknown whether the HME face masks reduce airway inflammation over acute
105 and multiple bouts of exercise. Nor is it known whether HME face masks reduce respiratory
106 symptoms and β_2 -Agonists usage over several weeks of engaging in exercise in dry cold
107 environments. If HME face masks are to be considered as part of a non-pharmaceutical therapy
108 plan, the design of the masks need to be considered, as individuals with asthma-related
109 conditions are unlikely to wear the masks if they find the masks large and cumbersome.
110 However, athletes may not see HME face masks as a viable strategy to prevent EIB as the
111 masks may not be practical wear to achieve optimal sporting performance or permitted by the
112 rules of the sport.

113

114 **Air pollution**

115 Air pollution has been shown to increase asthma severity and may have significant effects on
116 athletes due to the high ventilation rates they achieve and sustain during intense exercise¹³. Air
117 quality is inversely correlated with exercise-induced respiratory symptoms¹⁴. The risk is also
118 greater in those athletes who train on a regular basis in environments with poor air quality¹⁵.
119 Small particles, particularly ultra-fine ones (<100 nm diameter) like those from combustion
120 engines, have high lung deposition and may cause epithelial damage. These particles include
121 ozone (O₃), sulfur dioxide (SO₂), nitrogen oxides (NO_x) and particulate matter (PM_{2.5},
122 particles smaller than 2.5 mic diameter). Ice skaters are particularly exposed to combination of
123 cold dry air as well as PM₁ (PM < 1 mic diameter) in confined space of indoor ice arenas and
124 multiple ice-resurfacing by gas- or propane-powered machines. Particle inhalations have been
125 shown to induce oxidative stress, airway inflammation and airway remodelling. All these result
126 in higher prevalence of asthma symptoms, and great degree of small airway dysfunction¹⁶⁻¹⁹.

127

128 With regard to management, mechanical barriers, such as face masks, may help reduce the
129 effects of polluted particles⁹. Avoidance of training in low humidity conditions or during times
130 of high levels of atmospheric pollutants is advisable, yet its practical usage and scientific
131 benefit is still questionable. Similarly, whenever possible, it may be recommended to avoid
132 training close to busy major roadways or during rush hours or other times of elevated vehicular
133 congestion²⁰.

134

135 **Swimming**

136 The pathogenic mechanisms of EIB classically involve both osmolar and vascular changes in
137 the airways in addition to cooling of the airways^{2,7}. Increased minute ventilation during
138 exercise, requires significant warming and humidification of the inspired air. The resulting
139 respiratory heat and water loss from the airway mucosa into the inspired air may release
140 bronchoconstrictive mediators. In that respect, sports in warm humid environments, such as
141 indoor pools, are encouraged. Swimming has often been recommended as a less asthmogenic
142 trigger compared to other sports, because of the humid environment. Yet, a recent Cochrane
143 review concluded that there is insufficient evidence to suggest that aquatic-based exercise is
144 superior to comparative nonaquatic exercise in asthmatics²¹.

145

146 Chlorination is the most commonly used method for ensuring water hygiene in swimming
147 pools. Chlorine gas and its aerosol byproducts, (eg, trichloramine, hypochlorous acid, and
148 mono- and dichloramine), which float just above the water surface, may affect the nose,
149 pharynx, larynx trachea and bronchi with chronic exposure leading to structural epithelial
150 changes. During exercise, nasal breathing at rest shifts to oro-nasal breathing, thereby
151 significantly reducing the filtering effect of the nose. Aerosol particles travel and deposit
152 further into the lung. Trichloramine gas formed in chlorinated pools was suggested as a cause

153 for EIB in competitive swimmers and increased airway hyperreactivity (as measured by
154 methacholine or EVH challenge) has been demonstrated in swimmers where 43-68% of them
155 showed it²²⁻²⁴. Increasing evidence supports the notion that chronic repetitive swimming in
156 indoor pools may induce airway epithelial damage, inflammation, and remodelling²³⁻²⁵, and
157 increase the risk for atopy and asthma^{26,27}. A recent study found increased levels of 8-
158 isoprostane (8-IsoP) (as a marker of airway oxidative stress) in the exhale breath condensate of
159 competitive swimmers after a swimming session²⁷. Whenever possible, swimmers should train
160 in pools cleaned with non-chlorine water disinfection methods (such as copper/silver and
161 ozone) as well as in well ventilated pool environments. Yet, apart for some case reports²⁹, the
162 scientific evidence to support or refute many of these recommendations is lacking.

163

164 **DIETARY STRATEGIES**

165 **Omega-3 fatty acid supplementation**

166 It has been noted that populations who consume large quantities of oily fish have a lower
167 prevalence of asthma³⁰. Oily fish are rich in omega-3 fatty acids: eicosapentaenoic acid (EPA)
168 and docosahexaenoic acid (DHA). EPA and DHA are precursors to powerful agents involved
169 in the resolution of inflammation. Two mechanisms of action underpinning the anti-
170 inflammatory bio-actions include the ability of EPA to compete with arachidonic acid as a
171 substrate for cyclooxygenase (COX)-2 and 5-lipoxygenase (5-LO) enzymes and be converted
172 to less inflammatory leukotrienes and prostanoids³¹, and to generate the potent anti-
173 inflammatory E-series resolvins³¹. DHA may also alter gene transcription and translation via
174 direct or indirect actions on intracellular signalling pathways³³.

175

176 The anti-inflammatory properties of EPA and DHA make a diet high in oily fish an attractive
177 addition to the therapy of an individual with EIB. Initial investigations demonstrated 10 weeks

178 dietary supplementation of 3.2 g/d EPA and 2.2 g/d DHA reduced leukotriene production by
179 50%, but not reduction in post-exercise decline in FEV₁ in asthmatics³⁴. However, using the
180 same EPA and DHA dietary supplementation over a three week period, Mickleborough and
181 co-workers reported significant reductions in airway inflammation, which was accompanied
182 by 64-80% reductions in FEV₁ fall post exercise in individuals with EIB^{35,36}. Notably, post-
183 exercise decline in FEV₁, whilst on EPA and DHA supplementation, was similar to those of
184 the non-EIB control group. In addition, 3.2 g/d EPA and 2 g/d DHA were observed to be as
185 favourably as 10 mg/d montelukast in reducing airway inflammation and hyperpnoea-induced
186 bronchoconstriction in participants with mild to moderate persistent asthma³⁷. However, there
187 appears to be no additional benefit of combining EPA and DHA supplementation with 10 mg
188 montelukast³⁷. Furthermore, a recent pilot study found no beneficial effect of vitamin D and
189 fish oil supplementation for 3 weeks on reduction in FEV₁ induced by EVH in recreational
190 athletes with EIB³⁸.

191

192 Recently, the marine lipid fraction of the New Zealand green-lipped mussel (*Perna canaliculus*)
193 PCSO-524, which is rich in omega-3 fatty acids, has been shown to produce similar reductions
194 in inflammation and bronchoconstriction (57% reduction of FEV₁ fall) following a eucapnic
195 voluntary hyperpnoea challenge³⁹. In this investigation the attenuation of airway inflammation
196 and bronchoconstriction cannot be explained entirely by the EPA and DHA content of PCSO-
197 524, since the amount of EPA and DHA consumed daily was only 72 mg and 48 mg
198 respectively. Therefore, it may be that the additional constituents of PCSO-524 act
199 synergistically with EPA and DHA to bring about the anti-inflammatory effect and reduction
200 in bronchoconstriction.

201

202 While a low intake of EPA and DHA does not appear to be a safety issue a few side effects can
203 occur, such as a fishy aftertaste, flatulence, acid reflux, bloating, diarrhoea, nausea and possibly
204 an increased risk of bleeding and immunosuppression with a high intake of omega-3 fatty
205 acids⁴⁰. The initial investigations provide promise for EPA and DHA dietary supplementation
206 to protect against EIB and associated airway inflammation. However, large-scale clinical
207 studies in individuals with EIB are required to determine the minimum effective dose, duration
208 required to observe the beneficial effect and compare the effect of combining omega-3 fatty
209 acid supplementation with prevention inhaler therapy (e.g. inhaled glucocorticoids).

210

211 **Caffeine**

212 Caffeine (1,3,7-trimethylxanthine) is among the most commonly used supplements by
213 athletes⁴¹. While formerly being subjected to anti-doping regulations, the restrictions towards
214 caffeine were lifted by the World Anti-Doping Agency (WADA) in 2004 and can as such be
215 used freely in and out of competition. Caffeine works as a non-selective competitive adenosine
216 receptor antagonist for all subtypes of the adenosine receptor^{42,43}, but may also act as a
217 phosphodiesterase inhibitor⁴⁴. Accordingly, caffeine induces intracellular cAMP-
218 dependent/protein kinase A signalling, which like β_2 -Agonists, causes smooth muscle
219 relaxation⁴⁵. Indeed, studies have shown dose-related bronchodilator effects of caffeine on
220 basal airway function⁴⁶. The interest in caffeine as a bronchoprotective agent started some 30
221 years ago when Becker and co-workers (1984) observed that 10 mg/kg_{bw} of orally ingested
222 caffeine had a similar bronchodilating effect as 5 mg/kg_{bw} oral theophylline in children with
223 asthma⁴⁷. Comparable bronchodilating effect was later shown in adult asthma patients after
224 ingestion of 5 mg/kg_{bw} caffeine⁴⁷ or 3 cups of coffee⁴⁹.

225

226 Although caffeine shows promise as a bronchodilator, only a few studies have investigated its
227 potential to counteract EIB of which none have been performed in athletes. In non-athletes,
228 ingestion of caffeine was shown to have a post-exercise bronchoprotective effect compared to
229 placebo in individuals with EIB⁵⁰. While post-exercise decline in FEV₁ was 24% for placebo,
230 it was less than 1% after ingestion of 7 mg/kg_{bw} caffeine and 8% after 3 mg/kg_{bw} caffeine. In
231 accordance with this observation, Duffy & Phillips (1991) observed that ingestion of 10
232 mg/kg_{bw} caffeine reduced bronchoconstrictor response to EVH-provocation compared to
233 placebo in EVH-positive individuals⁵¹. When compared to inhalation of β_2 -Agonist salbutamol
234 (180 mg albuterol), ingestion of 9 mg/kg_{bw} caffeine was shown to be as effective as salbutamol
235 in attenuating post-exercise reduction in FEV₁ in asthmatics with EIB⁵².

236

237 Aside from its bronchoprotective effect, caffeine has a variety of other effects of relevance for
238 airway function during exercise. During submaximal exercise, as little as 3 mg/kg_{bw} oral
239 caffeine has been shown to modulate ventilatory dynamics by reducing the physiological dead
240 space ventilation/tidal volume ratio and breathing frequency, while concurrently increasing
241 tidal volume^{53,54}. In addition, caffeine may counteract exercise-induced hypoxemia
242 (desaturation) in elite athletes at submaximal intensities⁵⁵ and improve respiratory muscle
243 fatigue resilience⁵⁶.

244

245 Despite the small number of studies undertaken, there is some evidence to suggest that caffeine
246 has the potential to reduce EIB severity and improve ventilatory dynamics and respiratory
247 muscle fatigue resilience during exercise. The amount of orally ingested caffeine needed for
248 bronchoprotection is approximately 5-10 mg/kg_{bw}, which would be equivalent to 2-4 cups of
249 coffee. However, it appears that the bronchoprotective effect of caffeine is highly individual.
250 A limitation of caffeine is the slow absorption rate when ingested, giving rise to a

251 bronchodilator response 2 hours after ingestion. Future studies should investigate more
252 thoroughly the therapeutic efficacy of caffeine as a bronchoprotective substance during
253 exercise in athletes with EIB.

254

255 **Vitamins and anti-oxidants**

256 Supplementation with various vitamins and anti-oxidants has attracted some attention as means
257 to counteract EIB because of their ability to suppress proinflammatory signalling⁵⁷, to lower
258 levels of histamine^{58,59} and prostaglandin F_{2α}⁶⁰, and to scavenge reactive oxygen species
259 (ROS)^{61,62}. In practical terms, however, interpretation of the therapeutic efficacy of each
260 individual vitamin and anti-oxidant as bronchoprotective substances in EIB is limited by the
261 small number of studies that have been undertaken in individuals with EIB, especially in
262 athletes. Most convincing is the bronchoprotective effect of acute and chronic supplementation
263 with vitamin C on post-exercise decline in FEV₁ in individuals with EIB^{60,63-65}. In addition,
264 one week supplementation with β-carotene (64 mg), a provitamin A carotenoid, has been
265 shown to reduce post-exercise reduction in FEV₁⁶⁶. Conflicting results have been observed
266 after one week supplementation with the carotenoid lycopene (30 mg), in which a post-exercise
267 bronchoprotective effect was found in asthmatic individuals with EIB, whereas adolescent
268 athletes with EIB had no effect^{67,68}.

269

270 **STRATEGIES TO REDUCE PERCEPTION OF EXERTIONAL DYSPNOEA**

271 Above we have discussed strategies that may help control EIB. In addition, there may also be
272 a role for utilising breathing control and inspiratory muscle training in order enable athletes
273 with EIB to reduce perceptions of exertional dyspnoea.

274

275

276 **Breathing control**

277 A significant symptom of EIB is dyspnoea during and after exercise. There are a variety of
278 breathing exercises that may benefit individuals who experience asthma/EIB exacerbations that
279 include yogic breathing⁶⁹⁻⁷¹ and physiotherapist-supervised breathing training⁷². Although
280 these forms of breathing control exercises may not be able to reduce asthma severity they may
281 be able to reduce the perception of respiratory symptoms and increase perception of asthma
282 control⁶⁹. Moreover, breathing exercises have been shown to improve quality of life⁷⁰, reduce
283 use of relief medication⁷⁰, reduce the levels of anxiety and depression⁷² and airway
284 hyperresponsiveness⁷¹. Future research is required to understand the mechanisms behind these
285 observations in asthmatic individuals.

286

287 It is currently unknown how these forms of breathing control exercises may be beneficial for
288 athletes with EIB, whose main symptoms are experienced during exercise. However, the use
289 of breathing training incorporating, inspiratory muscle training and breathing technique
290 training (table 2), has been shown to be helpful in reducing the perception of breathing in an
291 athlete with non-asthmatic exercise respiratory conditions⁷³. Future research is required to
292 investigate how athletes with EIB respond to using breathing exercises. Furthermore, the
293 current breathing control methods may need to be adapted to replicate respiratory control
294 during exercise rather than focusing on breathing control at rest.

295

296

297

298

299

300

301 Table 2: Summary of breathing training for athletes

Breathing Control Methods	Overview
Breathing Technique	Encourage initiation of inspiration from the lower rib cage. Inspiratory manoeuvre should be smooth with little tension through the shoulders and neck. Aids such as elastic strap or hands placed on sides of torso over lower ribs can be used to help athletes. Athlete can begin to attempt to practice this technique in functional sport specific positions
Inspiratory Muscle Training (IMT)	Ensure breathing technique is addressed before initiating IMT. Athletes with poor breathing technique, who proceed directly to IMT, may experience exacerbation of their symptoms. IMT should incorporate forceful inspiratory manoeuvres through a hand-held device providing resistance to the inspired airflow. Focus during the IMT should be on good breathing technique (as described above). An IMT session should comprise of 30 continuous forced inspiratory efforts at the equivalent of 30 breath repetition maximum, with relaxed expiration.

302 Adapted from Dickinson, J. McConnell A. Ross E. Brown, P. Hull, J. Assessment and
 303 Management of Non-Asthma Related Breathing Problems in Athletes. The Sport and Exercise
 304 Scientist. 2015; 45: 8-9

305

306 **Respiratory Muscle Training**

307 Respiratory muscle training is an easy and cheap way to enhance both inspiratory and
 308 expiratory muscle strength⁷⁴, and has also been associated with improvements in exercise

309 performance during various exercise protocols in healthy individuals^{75,76}. However, despite
310 decades of research into the applications of respiratory muscle training, the area is still
311 controversial and subject to scientific debate⁷⁷⁻⁷⁹. Respiratory muscle training has shown some
312 promise in the management of chronic obstructive pulmonary disease⁸⁰, inspiratory stridor⁷³
313 and exercise-induced vocal cord dysfunction^{81,82}. However, although studies also have shown
314 that respiratory muscle training may have beneficial effects on asthma severity and beta₂-
315 agonist usage⁸³⁻⁸⁵, a recent cochrane review, based on 113 asthmatics, concluded that there is
316 no conclusive evidence to support or refute the therapeutic efficacy of inspiratory muscle
317 training in asthma⁸⁶. Nevertheless, given individuals with EIB may experience airway
318 obstruction and airflow limitation during intense exercise⁸⁷, which potentially puts a larger
319 work load on respiratory muscles^{3,88}, it could be speculated that respiratory muscle training
320 may be beneficial for athletes with EIB. However, to our knowledge, no studies have
321 investigated the effectiveness of respiratory muscle training on EIB severity⁸⁹.

322

323 **SUMMARY AND FUTURE CONSIDERATIONS**

324 There are numerous non-pharmacological strategies that can be utilised to support the treatment
325 of EIB, however the evidence is inconclusive and future studies are encouraged before any
326 recommendations are implemented. There is currently insufficient evidence to support the use
327 of any non-pharmacological EIB treatment strategy in the absence of regular pharmaceutical
328 therapy for EIB. While there is some encouraging findings with regards to nutritional
329 supplementation and respiratory muscle training, future studies are encouraged, especially in
330 athletes. Most studies have included non-athletes and extrapolation towards athletes should
331 therefore be done with caution. Furthermore, data on other commonly used supplements by
332 athletes, such as beta-alanine and creatine are lacking in relation to EIB. For instance, beta-

333 alanine supplementation increases intracellular content of carnosine, which among other
334 factors⁹⁰, may affect nitric oxide production and modulate inflammation^{91,92}, both of which
335 could affect EIB severity. In addition, creatine supplementation has been shown to exacerbate
336 airway inflammation, increase airway hyperresponsiveness and induce smooth muscle
337 thickening in mice⁹³. However, no studies, have to our knowledge, investigated the effect of
338 creatine supplementation on EIB severity in athletes. Consequently, there are numerous non-
339 pharmacological strategies yet to be studied in athletes with EIB.

340

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