1 **Manuscript title**

2 Non Pharmacological Strategies to Manage Exercise Induced Bronchoconstriction

3 John Dickinson[1], PhD, Israel Amirav[2], MD, and Morten Hostrup[3,4], PhD

4

5   1. School of Sport and Exercise Sciences, University of Kent, UK

6   2. Department of Paediatrics, University of Alberta, Edmonton, Canada

7   3. Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark,

8   mail: mhostrup@nexs.ku.dk

9   4. Department of Respiratory Medicine, Bispebjerg University Hospital, Denmark, mail:

10   mhostrup@nexs.ku.dk

11

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

23

24

25

KEY POINTS:

- There is emerging evidence that non-pharmacological strategies can be used to supplement traditional therapy to reduce exercise-induced bronchoconstriction (EIB) severity and lessen respiratory symptoms associated with exercise

- Most investigations into non-pharmacological have included non-athletes, extrapolating towards athletes should be done with caution and studies in athletes with EIB are encouraged.

- There is currently insufficient evidence to support the use of any non-pharmacological EIB treatment strategy in the absence of regular pharmaceutical therapy for EIB.

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is an asthma-related condition, which occurs during or following exercise as a result of large volumes of 'unconditioned air' entering the lower airways to meet the increased ventilatory demands of exercise[1,2]. In susceptible individuals, EIB arises via multiple mechanisms that may involve dehydration of airway surface liquid, mucosal cooling and epithelial damage (*ref to pathophysiology paper in series*), which induces an airway inflammatory response (involving histamine, neuropeptides, leukotrienes and prostaglandins) with resultant airway smooth muscle constriction[3]. Management of EIB in athletes is almost exclusively based around pharmacological therapies (*ref to pharmacological paper in series*), such as glucocorticoids and β_2-Agonists[1,2]. Although clinical data on non-pharmacological therapies has been equivocal, there is emerging evidence that non-pharmacological strategies could be used to supplement traditional therapy to reduce EIB severity and lessen exercise respiratory symptoms (table 1). This paper reviews the evidence and provides recommendations for the use of non-pharmacological strategies in the management of EIB.

51

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

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

PRE-EXERCISE WARM UP

In approximately half of those who suffer from EIB, high intensity pre-exercise warm up effectively protects against subsequent bronchoconstriction[3]. A recent systematic review[4] reported that intermittent high intensity pre-exercise warm up (repetitive sprints of ~30 s close to peak oxygen consumption or maximal HR) provides about 10% reduction in the fall in FEV_1 post exercise, whereas neither low intensity nor continues high intensity pre exercise warm up provides significant protection in individuals with EIB.

The refractory period or refractory effect, that is induced after a first exercise bout, has frequency been proposed to explain why high intensity warm-ups protect against EIB. It has been proposed that the first exercise induces a variable period (called the refractory period) during which (2-4 hours) subsequent exercise will not result in EIB or will result in decreased fall in FEV_1. As discussed by XXXX (*ref to refractory paper in this series*), preceding exercise may deplete constrictive mediators, induce secretion of protective mediators (particularly prostaglandins) and cause desensitization of smooth muscle to bronchoconstrictive mediators[3]. Regardless of the mechanism, there is good evidence to suggest a clinical benefit of warm ups in protecting against EIB.

While high intensity exercise warm-ups may attenuate EIB[3-4], the exercise intensity that is required for the warm-up, may potentially cause perturbations in the exercising musculature and compromise subsequent exercise performance[5]. However, emerging evidence suggests that isolated respiratory warm-ups can provide similar bronchoprotective effects as whole-body warm up[6]. Instead of using whole-body warm up, a recent study[6] evaluated the effect of a respiratory-only warm up on subsequent decline in FEV_1 induced by exhaustive cycling ($\approx$ 14 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 FEV_1 regardless of the intensity of the hyperpnoea session conducted and

80 without compromising cycling performance[6]. 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 constriction[7]. 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 severity[8]. 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 FEV_1[9-12]. 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 exercise[13]. Air

117 quality is inversely correlated with exercise-induced respiratory symptoms[14]. The risk is also

118 greater in those athletes who train on a regular basis in environments with poor air quality[15].

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 (O_3), sulfur dioxide (SO_2), nitrogen oxides (NOx) and particulate matter (PM2.5,

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 dysfunction[16-19].

127

128 With regard to management, mechanical barriers, such as face masks, may help reduce the

129 effects of polluted particles[9]. 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 congestion[20].

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 asthmatics[21].

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

for EIB in competitive swimmers and increased airway hyperreactivity (as measured by methacholine or EVH challenge) has been demonstrated in swimmers where 43-68% of them showed it[22-24]. Increasing evidence supports the notion that chronic repetitive swimming in indoor pools may induce airway epithelial damage, inflammation, and remodelling[23-25], and increase the risk for atopy and asthma[26,27]. A recent study found increased levels of 8-isoprostane (8-IsoP) (as a marker of airway oxidative stress) in the exhale breath condensate of competitive swimmers after a swimming session[27]. Whenever possible, swimmers should train in pools cleaned with non-chlorine water disinfection methods (such as copper/silver and ozone) as well as in well ventilated pool environments. Yet, apart for some case reports[29], the scientific evidence to support or refute many of these recommendations is lacking.

DIETARY STRATEGIES

Omega-3 fatty acid supplementation

It has been noted that populations who consume large quantities of oily fish have a lower prevalence of asthma[30]. Oily fish are rich in omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are precursors to powerful agents involved in the resolution of inflammation. Two mechanisms of action underpinning the anti-inflammatory bio-actions include the ability of EPA to compete with arachidonic acid as a substrate for cyclooxygenase (COX)-2 and 5-lipoxygenase (5-LO) enzymes and be converted to less inflammatory leukotrienes and prostanoids[31], and to generate the potent anti-inflammatory E-series resolvins[31]. DHA may also alter gene transcription and translation via direct or indirect actions on intracellular signalling pathways[33].

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

dietary supplementation of 3.2 g/d EPA and 2.2 g/d DHA reduced leukotriene production by 50%, but not reduction in post-exercise decline in FEV_1 in asthmatics[34]. However, using the same EPA and DHA dietary supplementation over a three week period, Mickleborough and co-workers reported significant reductions in airway inflammation, which was accompanied by 64-80% reductions in FEV_1 fall post exercise in individuals with EIB[35,36]. Notably, post-exercise decline in FEV_1, whilst on EPA and DHA supplementation, was similar to those of the non-EIB control group. In addition, 3.2 g/d EPA and 2 g/d DHA were observed to be as favourably as 10 mg/d montelukast in reducing airway inflammation and hyperpnoea-induced bronchoconstriction in participants with mild to moderate persistent asthma37. However, there appears to be no additional benefit of combining EPA and DHA supplementation with 10 mg montelukast[37]. Furthermore, a recent pilot study found no beneficial effect of vitamin D and fish oil supplementation for 3 weeks on reduction in FEV_1 induced by EVH in recreational athletes with EIB[38].

Recently, the marine lipid fraction of the New Zealand green-lipped mussel (Perna canaliculus) PCSO-524, which is rich in omega-3 fatty acids, has been shown to produce similar reductions in inflammation and bronchoconstriction (57% reduction of FEV_1 fall) following a eucapnic voluntary hyperpnoea challenge[39]. In this investigation the attenuation of airway inflammation and bronchoconstriction cannot be explained entirely by the EPA and DHA content of PCSO-524, since the amount of EPA and DHA consumed daily was only 72 mg and 48 mg respectively. Therefore, it may be that the additional constituents of PCSO-524 act synergistically with EPA and DHA to bring about the anti-inflammatory effect and reduction in bronchoconstriction.

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 acids[40].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 athletes[41]. 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 inhibitor[44]. Accordingly, caffeine induces intracellular cAMP-

218 dependent/protein kinase A signalling, which like β_2-Agonists, causes smooth muscle

219 relaxation[45]. Indeed, studies have shown dose-related bronchodilator effects of caffeine on

220 basal airway function[46]. 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 asthma[47]. Comparable bronchodilating effect was later shown in adult asthma patients after

224 ingestion of 5 mg/kg$_{bw}$ caffeine[47] or 3 cups of coffee[49].

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 EIB[50]. While post-exercise decline in FEV_1 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 individuals[51]. 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 EIB[52].

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 intensities[55] and improve respiratory muscle

243 fatigue resilience[56].

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 signalling[57], to lower

258 levels of histamine[58,59] and prostaglandin F2α[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 FEV_1 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 FEV_1[66]. 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

Breathing control

A significant symptom of EIB is dyspnoea during and after exercise. There are a variety of breathing exercises that may benefit individuals who experience asthma/EIB exacerbations that include yogic breathing[69-71] and physiotherapist-supervised breathing training[72]. Although these forms of breathing control exercises may not be able to reduce asthma severity they may be able to reduce the perception of respiratory symptoms and increase perception of asthma control[69]. Moreover, breathing exercises have been shown to improve quality of life[70], reduce use of relief medication[70], reduce the levels of anxiety and depression[72] and airway hyperresponsiveness[71]. Future research is required to understand the mechanisms behind these observations in asthmatic individuals.

It is currently unknown how these forms of breathing control exercises may be beneficial for athletes with EIB, whose main symptoms are experienced during exercise. However, the use of breathing training incorporating, inspiratory muscle training and breathing technique training (table 2), has been shown to be helpful in reducing the perception of breathing in an athlete with non-asthmatic exercise respiratory conditions[73]. Future research is required to investigate how athletes with EIB respond to using breathing exercises. Furthermore, the current breathing control methods may need to be adapted to replicate respiratory control during exercise rather than focusing on breathing control at rest.

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 strength[74], 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 debate[77-79]. Respiratory muscle training has shown some

312 promise in the management of chronic obstructive pulmonary disease[80], inspiratory stridor[73]

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 $beta_2$-

315 agonist usage[83-85], 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 asthma[86]. Nevertheless, given individuals with EIB may experience airway

318 obstruction and airflow limitation during intense exercise[87], 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 severity[89].

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-

alanine supplementation increases intracellular content of carnosine, which among other factors[90], may affect nitric oxide production and modulate inflammation[91,92], both of which could affect EIB severity. In addition, creatine supplementation has been shown to exacerbate airway inflammation, increase airway hyperresponsiveness and induce smooth muscle thickening in mice[93]. However, no studies, have to our knowledge, investigated the effect of creatine supplementation on EIB severity in athletes. Consequently, there are numerous non-pharmacological strategies yet to be studied in athletes with EIB.

REFERENCES

1. Fitch KD, Sue-Chu M, Anderson SD, Boulet LP, Hancox RJ, McKenzie DC, Backer V, Rundell KW, Alonso JM, Kippelen P, Cummiskey JM, Garnier A, Ljungqvist A. Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22-24, 2008. J Allergy Clin Immunol. 2008; 122(2):254-60

2. Price OJ, Hull JH, Backer V, Hostrup M, Ansley L. The impact of exercise-induced bronchoconstriction on athletic performance: a systematic review. Sports Med. 2014 ; 44(12):1749-61.

3. Larsson J, Anderson SD, Dahlén SE, Dahlén B. Refractoriness to exercise challenge: a review of the mechanisms old and new. Immunol Allergy Clin North Am. 2013; 33(3): 329-5.

Stickland MK, Rowe BH, Spooner CH, Vandermeer B, Dryden DM. Effect of warm-up exercise on exercise-induced bronchoconstriction. Med Sci Sports Exerc. 2012; 44(3): 383-91.

5. Hostrup M, Bangsbo J. Limitations in intense exercise performance of athletes - effect of speed endurance training on ion handling and fatigue development. J Physiol. 2017; 595(9): 2897-2913.

6. Eichenberger PA, Scherer TA, Spengler CM. Pre-Exercise Hyperpnea Attenuates Exercise-Induced Bronchoconstriction Without Affecting Performance. Loukides S, ed. *PLoS ONE*. 2016; 11(11): e0167318. doi:10.1371/journal.pone.0167318.

359   7. Anderson SD, Kippelen P. Airway injury as a mechanism for exercise-induced
360   bronchoconstriction in elite athletes. J Allergy Clin Immunol. 2008 Aug; 122(2): 225-35.

361   8. Karjalainen, E., Laitinen, A., Sue-Chu, M., Altraja, A., Bjermer, L. & Laitinen, L. Evidence
362   of airway inflammation and remodeling in ski athletes with and without bronchial
363   hyperresponsiveness to methacholine. Am J Respir Crit Care Med. 2000. 161, 2086-91.

364   9. Beuther DA, Martin RJ. Efficacy of a heat exchanger mask in cold exercise-induced asthma.
365   Chest. 2006; 129(5): 1188-93.

366   10. Brenner, A., Weiser, P., Krogh, L. & Loren, M. (1980) Effectiveness of a portable face
367   mask in attenuating exercise-induced asthma. *JAMA*. *1980;* 244: 2196-8.

368   11. Millqvist E., Bengtsson U. Löwhagen O. Combining a beta2-agonist with a face mask to
369   prevent exercise-induced bronchoconstriction. Allergy. 2000; 55: 672-5.

370   12. Nisar M. Spence D. West D. Haycock J. Jones Y. Walshaw M. Earis J. Calverley P. Pearson
371   M. A mask to modify inspired air temperature and humidity and its effect on exercise induced
372   asthma. Thorax. 1992; 47: 446-50.

373   13. Guarnieri M. Balmes J. Outdoor air pollution and asthma. The Lancet. 2014; 383: 1581-
374   1592

375   14. Rundell KW, Spiering BA, Judelson DA, Wilson MH. Bronchoconstriction during cross-
376   country skiing: is there really a refractory period? Med Sci Sports Exerc. 2003; 35(1): 18-26.

377   15. Bernard A, Nickmilder M, Voisin C. Outdoor swimming pools and the risks of asthma and
378   allergies during adolescence. Eur Respir J. 2008; 32(4): 979-88.

379   16. Lumme A, Haahtela T, Ounap J, Rytilä P, Obase Y, Helenius M, Remes V, Helenius I.
380   Airway inflammation, bronchial hyperresponsiveness and asthma in elite ice hockey players.
381   Eur Respir J. 2003; 22(1): 113-7.

382   17. Rundell KW, Spiering BA, Evans TM, Baumann JM. Baseline lung function, exercise-
383   induced bronchoconstriction, and asthma-like symptoms in elite women ice hockey players.
384   Med Sci Sports Exerc. 2004; 36(3): 405-10.

385   18. Rundell KW, Im J, Mayers LB, Wilber RL, Szmedra L, Schmitz HR. Self-reported

386   symptoms and exercise-induced asthma in the elite athlete. Med Sci Sports Exerc. 2001; 33(2):

387   208-13.

388   19. Rundell KW, Caviston R, Hollenbach AM, Murphy K. Vehicular air pollution,

389   playgrounds, and youth athletic fields. Inhal Toxicol. 2006; 18(8): 541-7

390   20. Cutrufello PT, Smoliga JM, Rundell KW. Small things make a big difference: particulate

391   matter and exercise. Sports Med. 2012; 42(12): 1041-58.

392   21. Silva GAJ, Andriolo BNG, Riera R, Parra SA, Peccin MS. Water-based exercise for adults

393   with asthma (review) Cochrane Database Syst Rev. 2014;7:CD003316, 1–36.

394   22. Levai IK, Hull JH, Loosemore M, Greenwell J, Whyte G, Dickinson JW.Environmental

395   influence on the prevalence and pattern of airway dysfunction in elite athletes. Respirology.

396   2016; 21(8): 1391-1396.

397   23. Bougault V, Boulet LP. Is there a potential link between indoor chlorinated pool

398   environment and airway remodeling/inflammation in swimmers? Expert Rev Respir Med.

399   2012; 6(5): 469-71.

400   24. Bougault V, Loubaki L, Joubert P, Turmel J, Couture C, Laviolette M, Chakir J, Boulet

401   LP. Airway remodeling and inflammation in competitive swimmers training in indoor

402   chlorinated swimming pools. J Allergy Clin Immunol. 2012; 129(2): 351-8.

403   25. Sue-Chu M. Winter sports athletes: long-term effects of cold air exposure. Br J Sports Med.

404   2012; 46(6): 397-401.

405   26. Bernard A, Carbonnelle S, de Burbure C, Michel O, Nickmilder M. Chlorinated pool

406   attendance, atopy, and the risk of asthma during childhood. Environ Health Perspect. 2006;

407   114(10): 1567-73.

408   27. Bernard A, Carbonnelle S, Michel O, Higuet S, De Burbure C, Buchet JP, Hermans C,

409   Dumont X, Doyle I. Lung hyperpermeability and asthma prevalence in schoolchildren:

410   unexpected associations with the attendance at indoor chlorinated swimming pools. Occup

411   Environ Med. 2003; 60(6): 385-94.

412 28. Morissette MC, Murray N, Turmel J, Milot J, Boulet LP, Bougault V. Increased exhaled
413 breath condensate 8-isoprostane after a swimming session in competitive swimmers. Eur J
414 Sport Sci. 2016; 16(5): 569-576.

415 29. Beretta S, Vivaldo T, Morelli M, Carlucci P, Zuccotti GV. Swimming pool-induced asthma.
416 J Investig Allergol Clin Immunol. 2011; 21(3): 240-1.

417 30. Horrobin D. Low prevalences of coronary heart disease (CHD), psoriasis, asthma and
418 rheumatoid arthritis in Eskimos: are they caused by high dietary intake of eicosapentaenoic
419 acid (EPA), a genetic variation of essential fatty acid (EFA) metabolism or a combination of
420 both? Med Hypotheses. 1987; 22(4): 421-8

421 31. Thien F, Hallsworth M, Soh C, Lee T. Effects of exogenous eicosapentaenoic acid on
422 generation of leukotriene C4 and leukotriene C5 by calcium ionophore-activated human
423 eosinophils in vitro. J Immunol. 1993; 150: 3546-52.

424 32. Serhan CN, Yang R, Martinod K, Kasuga K, Pillai PS, Porter TF, Oh SF, Spite M.
425 Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions.
426 J Exp Med. 2009;206(1): 15-23.

427 33. Weldon S, Mullen A, Loscher C, Hurley L, Roche H. Docosahexaenoic acid induces an
428 anti-inflammatory profile in lipopolysaccharide-stimulated human THP-1 macrophages more
429 effectively than eicosapentaenoic acid. J Nutr Biochem. 2007; 18(4): 250-8.

430 34. Arm JP, Horton CE, Mencia-Huerta JM, House F, Eiser NM, Clark TJ, Spur BW, Lee TH.
431 Effect of dietary supplementation with fish oil lipids on mild asthma. Thorax. 1988; 43(2): 84-
432 92.

433 35. Mickleborough TD, Murray RL, Ionescu AA, Lindley MR. Fish oil supplementation
434 reduces severity of exercise-induced bronchoconstriction in elite athletes. Am J Respir Crit
435 Care Med. 2003; 168(10): 1181-9.

436 36. Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil
437 supplementation on exercise-induced bronchoconstriction in asthma. Chest. 2006; 129(1): 39-
438 49.

439 37. Tecklenburg-Lund S, Mickleborough TD, Turner LA, Fly AD, Stager JM, Montgomery

440 GS. Randomized controlled trial of fish oil and montelukast and their combination on airway

441 inflammation and hyperpnea-induced bronchoconstriction. PLoS One. 2010; 5(10): e13487.

442 38. Price OJ, Hull JH, Howatson G, Robson-Ansley P, Ansley L. Vitamin D and omega-3

443 polyunsaturated fatty acid supplementation in athletes with exercise-induced

444 bronchoconstriction: a pilot study. Expert Rev Respir Med. 2015; 9(3): 369-78

445 39. Mickleborough TD, Vaughn CL, Shei RJ, Davis EM, Wilhite DP. Marine lipid fraction

446 PCSO-524 (lyprinol/omega XL) of the New Zealand green lipped mussel attenuates

447 hyperpnea-induced bronchoconstriction in asthma. Respir Med. 2013; 107(8): 1152-63.

448 40. Mickleborough TD, Lindley MR. Omega-3 fatty acids: a potential future treatment for

449 asthma? Expert Rev Respir Med. 2013; 7(6): 577-80.

450 41. Del Coso J, Muñoz G, Muñoz-Guerra J. Prevalence of caffeine use in elite athletes

451 following its removal from the World Anti-Doping Agency list of banned substances. Appl

452 Physiol Nutr Metab. 2011;36(4): 555-61.

453 42. Evoniuk G, Jacobson KA, Shamim MT, Daly JW, Wurtman RJ.A1- and A2-selective

454 adenosine antagonists: in vivo characterization of cardiovascular effects. J Pharmacol Exp

455 Ther. 1987; 242(3): 882-7.

456 43. Snyder SH, Katims JJ, Annau Z, Bruns RF, Daly JW. Adenosine receptors and behavioral

457 actions of methylxanthines. Proc Natl Acad Sci U S A. 1981; 78(5): 3260-4.

458 44. Rivedal E, Sanner T. Caffeine and other phosphodiesterase inhibitors are potent inhibitors

459 of the promotional effect of TPA on morphological transformation of hamster embryo cells.

460 Cancer Lett. 1985; 28(1): 9-17.

461 45. Niewoehner DE, Campe H, Duane S, McGowan T, Montgomery MR. Mechanisms of

462 airway smooth muscle response to isoproterenol and theophylline. J Appl Physiol Respir

463 Environ Exerc Physiol. 1979; 47(2): 330-6.

464 46. Welsh EJ, Bara A, Barley E, Cates CJ. Caffeine for asthma. Cochrane Database Syst Rev.

465 2010; (1): CD001112.

466 47. Becker AB, Simons KJ, Gillespie CA, Simons FER. The bronchodilator effects and
467 pharmacokinetics of caffeine in asthma. N Eng J Med 1984; 310:743-46.

468 48. Bukowskyj M, Nakatsu K. The bronchodilator effect of caffeine in adult asthmatics. Am
469 Rev Respir Dis. 1987; 135(1): 173-5.

470 49. Gong H Jr, Simmons MS, Tashkin DP, Hui KK, Lee EY. Bronchodilator effects of caffeine
471 in coffee. Chest. 1986; 89: 335-42.

472 50. Kivity S, Ben Aharon Y, Man A, Topilsky M. The effect of caffeine on exercise-induced
473 bronchoconstriction. Chest. 1990; 97(5): 1083-5.

474 51. Duffy P, Phillips YY. Caffeine consumption decreases the response to bronchoprovocation
475 challenge with dry gas hyperventilation. Chest. 1991; 99(6): 1374-7.

476 52. VanHaitsma TA, Mickleborough T, Stager JM, Koceja DM, Lindley MR, Chapman R.
477 Comparative effects of caffeine and albuterol on the bronchoconstrictor response to exercise
478 in asthmatic athletes. Int J Sports Med. 2010; 31(4): 231-6.

479 53. Birnbaum LJ, Herbst JD. Physiologic effects of caffeine on cross-country runners. J
480 Strength Cond Res. 2004; 18(3): 463-5.

481 54. Brown DD, Knowlton RG, Sullivan JJ, Sanjabi PB. Effect of caffeine ingestion on alveolar
482 ventilation during moderate exercise. Aviat Space Environ Med. 1991; 62(9 Pt 1): 860-4.

483 55. Chapman RF, Stager JM. Caffeine stimulates ventilation in athletes with exercise-induced
484 hypoxemia. Med Sci Sports Exerc. 2008; 40(6): 1080-6.

485 56. Supinski GS, Levin S, Kelsen SG. Caffeine effect on respiratory muscle endurance and
486 sense of effort during loaded breathing. J Appl Physiol. 1986; 60(6): 2040-7.

487 57. Jiang Q. Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory
488 activities and their role in disease prevention and therapy. Free Radic Biol Med. 2014; 72: 76-
489 90.

490 58. Johnston CS, Retrum KR, Srilakshmi JC. Antihistamine effects and complications of
491 supplemental vitamin C. J Am Diet Assoc. 1992; 92(8): 988-9.

492 59. Johnston CS, Solomon RE, Corte C. Vitamin C depletion is associated with alterations in
493 blood histamine and plasma free carnitine in adults. J Am Coll Nutr. 1996; 15(6): 586-91.

494 60. Tecklenburg SL, Mickleborough TD, Fly AD, Bai Y, Stager JM. Ascorbic acid
495 supplementation attenuates exercise-induced bronchoconstriction in patients with asthma.
496 Respir Med. 2007; 101(8): 1770-8.

497 61. Traber MG, Stevens JF; Stevens. Vitamins C and E: Beneficial effects from a mechanistic
498 perspective. Free Radical Bio Med 2011; 51 (5): 1000–13.

499 62. Ashton T, Young IS, Peters JR, Jones E, Jackson SK, Davies B, Rowlands CC. Electron
500 spin resonance spectroscopy, exercise, and oxidative stress: an ascorbic acid intervention study.
501 J Appl Physiol. 1999; 87(6): 2032-6.

502 63. Schachter EN, Schlesinger A. The attenuation of exercise-induced bronchospasm by
503 ascorbic acid. Ann Allergy. 1982; 49(3): 146-51.

504 64. Cohen HA, Neuman I, Nahum H. Blocking effect of vitamin C in exercise-induced asthma.
505 Arch Pediatr Adolesc Med. 1997; 151(4): 367-70.

506 65. Hemilä H. The effect of vitamin C on bronchoconstriction and respiratory symptoms caused
507 by exercise: a review and statistical analysis. Allergy Asthma Clin Immunol. 2014; 10(1): 58.

508 66. Neuman I, Nahum H, Ben-Amotz A. Prevention of exercise-induced asthma by a natural
509 isomer mixture of beta-carotene. Ann Allergy Asthma Immunol. 1999; 82(6): 549-53.

510 67. Neuman I, Nahum H, Ben-Amotz A. Reduction of exercise-induced asthma oxidative stress
511 by lycopene, a natural antioxidant. Allergy. 2000; 55(12): 1184-9.

512 68. Falk B, Gorev R, Zigel L, Ben-Amotz A, Neuman I. Effect of lycopene supplementation
513 on lung function after exercise in young athletes who complain of exercise-induced
514 bronchoconstriction symptoms. Ann Allergy Asthma Immunol. 2005; 94(4): 480-5.

515 69. Karam M, Kaur B, Baptist A. A modified breathing exercise program for asthma is easy to
516 perform and effective. J Asthma. 2017; 54(2): 217-222

517   70. Vempati R, Bijlani RL, Deepak KK. The efficacy of a comprehensive lifestyle modification

518   programme based on yoga in the management of bronchial asthma: a randomized controlled

519   trial. BMC Pulm Med. 2009; 9: 37.

520   71. Manocha R, Marks G, Kenchington P, Peters D, Salome C. Sahaja yoga in the management

521   of moderate to severe asthma: a randomised controlled trial. Thorax. 2002; 57(2): 110-5.

522   72. Thomas M, McKinley RK, Mellor S, Watkin G, Holloway E, Scullion J, Shaw DE,

523   Wardlaw A, Price D, Pavord I. Breathing exercises for asthma: a randomised controlled trial.

524   Thorax. 2009; 64(1): 55-61.

525   73. Dickinson J, Whyte G, McConnell A. Inspiratory muscle training: a simple cost-effective

526   treatment for inspiratory stridor. Br J Sports Med. 2007; 41(10): 694-5.

527   74. Romer LM, McConnell AK. Specificity and reversibility of inspiratory muscle training.

528   Med Sci Sports Exerc. 2003; 35(2): 237-44.

529   75. Kilding AE, Brown S, McConnell AK. Inspiratory muscle training improves 100 and 200

530   m swimming performance. Eur J Appl Physiol. 2010; 108(3): 505-11.

531   76. Illi SK, Held U, Frank I, Spengler CM. Effect of respiratory muscle training on exercise

532   performance in healthy individuals: a systematic review and meta-analysis. Sports Med. 2012;

533   42(8): 707-24.

534   77. McConnell AK. CrossTalk opposing view: respiratory muscle training does improve

535   exercise tolerance. J Physiol. 2012; 590(15): 3397-8.

536   78. Mickleborough TD, Stager JM, Chatham K, Lindley MR, Ionescu AA. Pulmonary

537   adaptations to swim and inspiratory muscle training. Eur J Appl Physiol. 2008; 103(6): 635-

538   46.

539   79. Patel MS, Hart N, Polkey MI. CrossTalk proposal: training the respiratory muscles does

540   not improve exercise tolerance. J Physiol. 2012; 590(15): 3393-5.

541   80. Geddes EL, O'Brien K, Reid WD, Brooks D, Crowe J. Inspiratory muscle training in adults

542   with chronic obstructive pulmonary disease: an update of a systematic review. Respir Med.

543   2008; 102(12): 1715-29.

544   81. Mathers-Schmidt BA, Brilla LR. Inspiratory muscle training in exercise-induced
545   paradoxical vocal fold motion. J Voice. 2005; 19(4): 635-44.

546   82. Ruddy BH, Davenport P, Baylor J, Lehman J, Baker S, Sapienza C. Inspiratory muscle
547   strength training with behavioral therapy in a case of a rower with presumed exercise-induced
548   paradoxical vocal-fold dysfunction. Int J Pediatr Otorhinolaryngol. 2004; 68(10): 1327-32.

549   83. Turner LA, Mickleborough TD, McConnell AK, Stager JM, Tecklenburg-Lund S, Lindley
550   MR. Effect of inspiratory muscle training on exercise tolerance in asthmatic individuals. Med
551   Sci Sports Exerc. 2011; 43(11): 2031-8.

552   84. Weiner P, Azgad Y, Ganam R, Weiner M. Inspiratory muscle training in patients with
553   bronchial asthma. Chest. 1992; 102(5): 1357-61.

554   85. Weiner P, Berar-Yanay N, Davidovich A, Magadle R, Weiner M. Specific inspiratory
555   muscle training in patients with mild asthma with high consumption of inhaled beta(2)-
556   agonists. Chest. 2000; 117(3): 722-7.

557   86. Silva IS, Fregonezi GA, Dias FA, Ribeiro CT, Guerra RO, Ferreira GM. Inspiratory muscle
558   training for asthma. Cochrane Database Syst Rev. 2013; (9):CD003792.

559   87. Johnson BD, Scanlon PD, Beck KC. Regulation of ventilatory capacity during exercise in
560   asthmatics. J Appl Physiol. 1995; 79(3): 892-901.

561   88. Kosmas EN, Milic-Emili J, Polychronaki A, Dimitroulis I, Retsou S, Gaga M, Koutsoukou
562   A, Roussos Ch, Koulouris NG. Exercise-induced flow limitation, dynamic hyperinflation and
563   exercise capacity in patients with bronchial asthma. Eur Respir J. 2004; 24(3): 378-84.

564   89. Shei RJ, Paris HL, Wilhite DP, Chapman RF, Mickleborough TD. The role of inspiratory
565   muscle training in the management of asthma and exercise-induced bronchoconstriction. Phys
566   Sportsmed. 2016; 44(4): 327-334.

567   90. Hostrup M, Bangsbo J. Improving beta-alanine supplementation strategy to enhance
568   exercise performance in athletes. J Physiol. 2016; 594(17): 4701-2.

569   91. Severina IS, Bussygina OG, Pyatakova NV. Carnosine as a regulator of soluble guanylate
570   cyclase. Biochemistry (Mosc). 2000; 65(7): 783-8.

571 92. Caruso G, Fresta CG, Martinez-Becerra F, Antonio L, Johnson RT, de Campos RP, Siegel

572 JM, Wijesinghe MB, Lazzarino G, Lunte SM. Carnosine modulates nitric oxide in stimulated

573 murine RAW 264.7 macrophages. Mol Cell Biochem. 2017 Mar 13. doi: 10.1007/s11010-017-

574 2991-3.

575 93. Vieira RP, Duarte AC, Claudino RC, Perini A, Santos AB, Moriya HT, Arantes-Costa FM,

576 Martins MA, Carvalho CR, Dolhnikoff M. Creatine supplementation exacerbates allergic lung

577 inflammation and airway remodeling in mice. Am J Respir Cell Mol Biol. 2007; 37(6): 660-7.