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1 **TITLE**

2 ENVIRONMENTAL INFLUENCE IN THE PREVALENCE AND PATTERN OF
3 AIRWAY DYSFUNCTION IN ELITE ATHLETES

4

5 **CORRESPONDING AUTHOR**

6 **Dr Irisz Karolina Levai**, MD; School of Sport and Exercise Sciences, University of Kent,
7 Medway Building (M0-27), Chatham Maritime, Kent, UK, ME4 4AG; email:
8 ikl3@kent.ac.uk; telephone: +44(0) 1634 888903

9

10 **CO-AUTHORS**

11 **Dr James H Hull**, MBBS, FRCP; Department of Respiratory Medicine, Royal Brompton
12 Hospital, London, UK

13 **Dr Mike Loosemore**, MBBS, DCH, MRCPG, MSc, FFSEM, PGCME; The Institute of
14 Sport, Exercise and Health, University College London, London, UK

15 **Dr Jon Greenwell**, MBBS MRCP FFSEM MSc; British Swimming, Pool and Marathon
16 Swimming, Loughborough, UK

17 **Prof Greg Whyte**, OBE, PhD, DSc, FBASES, FACSM; Research Institute for Sport and
18 Exercise Sciences (RISES), Liverpool John Moores University, Liverpool, UK

19 **Dr John W Dickinson**, PhD; School of Sport and Exercise Sciences, University of Kent,
20 Chatham Maritime, UK

21

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24

25

1 SUMMARY AT GLANCE

2 This is the first study to screen the entire elite GB Swimming and Boxing teams using an
3 EVH challenge. The findings support the notion that athletes who train and compete in
4 provocative environments at a sustained high ventilation have an increased susceptibility to
5 airway dysfunction.

6

7 ABSTRACT

8 **Background and objective:** Elite swimming and boxing require athletes to achieve
9 relatively high minute ventilation. The combination of a sustained high ventilation and
10 provocative training environment may impact the susceptibility of athletes to Exercise-
11 induced bronchoconstriction (EIB). The purpose of the study was to evaluate the prevalence
12 of EIB in elite Great British (GB) Boxers and Swimmers.

13 **Methods:** Athletes from Boxing (n=38, Mean age: 22.1±3.1 yrs.) and Swimming (n=44,
14 Mean age: 21.1±2.6 yrs.) volunteered. Athletes completed an exercise-induced respiratory
15 symptoms questionnaire, baseline assessment of exhaled Nitric Oxide (FeNO), maximal
16 spirometry manoeuvres and a Eucapnic Voluntary Hyperpnoea (EVH) challenge. EIB was
17 confirmed if FEV₁ reduced by ≥10% from baseline at two time points post-EVH challenge.

18 **Results:** The prevalence of EIB was greater in elite swimmers (30 of 44; 68%) than boxers
19 (3 of 38; 8%) (p<0.001). 22 out of the 33 (67%) EVH-positive athletes had no prior diagnosis
20 of asthma/EIB. Moreover, 12% (6 of 49) of the EVH-negative athletes had a previous
21 diagnosis of asthma/EIB. We found a correlation between FeNO and FEV₁ change in lung
22 function post-EVH challenge in swimmers (r= -0.32; p=0.04), but not in boxers (r= -0.24;
23 p=0.15).

24 **Conclusions:** The prevalence of EIB was nine fold greater in swimmers when compared with
25 boxers. Athletes who train and compete in provocative environments at sustained high

1 ventilation may have an increased susceptibility to EIB. It is not entirely clear whether
2 increased susceptibility to EIB affects elite sporting performance and long-term airway health
3 in elite athletes.

4

5 **KEYWORDS**

6 Asthma, Athlete's care, Exercise-induced bronchoconstriction, Sport, Training environment

7

8 **SHORT TITLE**

9 EIB in elite boxers and swimmers

10

11 **LIST OF ABBREVIATIONS**

12 Dx, previous diagnosis; EIB, exercise-induced bronchoconstriction; GB, Great British; EVH,
13 eucapnic voluntary hyperpnoea; FeNO, fraction of exhaled nitric oxide; FEV₁, forced
14 expiratory volume in one second; PEF, peak expiratory flow; FVC, forced vital capacity;
15 FEV₁/FVC, FEV₁:FVC ratio; MVV, maximal voluntary ventilation

16

17 **MAIN TEXT**

18 **INTRODUCTION**

19 Exercise-induced bronchoconstriction (EIB) has been shown to be highly prevalent in
20 certain groups of elite athletes (e.g. swimmers, cyclists, cross country skiers);¹⁻³ our group
21 previously reported that approximately a quarter of the Great British Olympic Team have
22 asthma/EIB,⁴ i.e. more than double the national prevalence of asthma.⁵

23

24 This heightened prevalence is thought to arise due to a combination of the deleterious impact
25 of training and competition environmental exposures (e.g. pollution, swimming pool

1 chemicals), coupled with the repeatedly high ventilatory requirements, necessitated by
2 participation in elite level sport.⁶ This combination may result in airway injury,⁷ leading to
3 a greater propensity to bronchoconstriction, during or following vigorous exercise.⁸

4
5 Elite level swimmers, appear to have an alarmingly high prevalence of EIB (41% - 55%).⁴
6⁹ This heightened airway hyper-reactivity appears to resolve in retirement from competitive
7 swimming.¹⁰ It has been proposed that repeated exposure to airborne irritants and sensitizing
8 agents (e.g. halocetic acids and trihalomethanes) may drive a sensitisation process and
9 induce airway inflammation, that increases a propensity to EIB.⁸ Despite this, a clear
10 relationship between EIB and airway inflammation has not been determined; with some
11 studies demonstrating no difference in markers of eosinophilic inflammation between pool
12 and non-pool athletes.¹¹

13
14 In contrast, very little information is currently available on exercise associated respiratory
15 problems in elite level boxing.^{12, 13} Although not intuitive, both sports necessitate that
16 athletes reach a similar peak heart rate and minute ventilation¹⁴, however both the training
17 environment and the duration athletes are exposed to these physiological demands differ
18 significantly.^{6, 12, 14}

19
20 We therefore undertook this study with the aim of firstly providing an ‘up-to-date’
21 evaluation of the prevalence of EIB in the Great British (GB) elite swimming squad but also,
22 for the first time, establish the prevalence of EIB in a cohort of screened elite-level boxers.
23 A secondary aim was to compare the Eucapnic Voluntary Hyperpnoea (EVH) challenge
24 response and baseline exhaled nitric oxide (FeNO), as a surrogate of airway inflammation,

1 between two sports with similar peak ventilatory demands, but with differing training
2 environments.

3

4 **METHODS**

5 *Study design and participants*

6 Adult members (Age >18 years) of the elite GB Boxing and GB Swimming squads,
7 competing regularly in international competition were recruited, as part of a screening study,
8 to assess their airway health. Participants attended the laboratory on a single occasion at
9 various locations between July 2013 and September 2015. Participants were invited to take
10 part in the testing regardless of previous diagnosis (Dx) of asthma/EIB.

11

12 Athletes were excluded if they had a chest infection within 4 weeks, did not withdraw from
13 using their prescribed asthma medications or they had a current FEV₁ value of ≤70%
14 predicted. The study was approved by the University Ethics Committee (Reference Number:
15 Prop74_2012_13 and Prop82_2013_14) and all participants provided written informed
16 consent.

17

18 *Training environment*

19 The boxing squad trained indoors in gymnasiums with moderate temperatures (19-21°C) and
20 relative humidity (40-50%) levels. In contrast, the swimming squad trained in indoor pools
21 with air temperatures of 29°C with relative humidity above 60%. All pools that swimmers
22 trained in followed WHO Guidelines ¹⁵ for use of chlorine-based disinfectants. The free
23 chlorine levels were maintained at 1mg/l or below. Combined chlorine (chloramines) levels
24 were never more than half the free chlorine, and never more than 1mg/l.

25

1 *Study measurements*

2 Participants initially completed a questionnaire, addressing exercise respiratory symptoms
3 and environmental triggers. They then completed measurements of FeNO and spirometry,
4 followed by an EVH challenge. Participants were requested to avoid high intensity exercise
5 and caffeine for four hours prior to the study. Participants with a Dx of asthma/EIB were
6 required to withhold inhaled asthma medications according to recommendations. ¹⁶

7

8 *Fraction of Exhaled Nitric Oxide (FeNO)*

9 A NIOX analyser (NIOX MINO[®], Aerocrine AB, Sweden) was used to measure FeNO in
10 the exhaled breath at rest at a flow rate of 50 ml/min. ¹⁷ FeNO was performed prior to
11 spirometry manoeuvres ¹⁸ and taken as the mean of duplicate measures.

12

13 *Spirometry*

14 Using digital spirometers (Spiro-USB[™] and MicroLab[™], CareFusion, Germany),
15 participants completed a minimum of three forced maximal flow-volume manoeuvres. ¹⁹ For
16 each maximal flow-volume manoeuvre the following measurements were recorded in
17 accordance to ATS/ERS 2005 Guidelines ¹⁹: forced expiratory volume in one second (FEV₁);
18 peak expiratory flow (PEF); forced vital capacity (FVC) and FEV₁:FVC ratio (FEV₁/FVC).

19

20 *EVH Challenge*

21 EVH challenge was conducted in accordance to methods outlined by Anderson et al. ²⁰.
22 Briefly, participants were asked to attain a target minute ventilation of 85% of their predicted
23 maximal voluntary ventilation (MVV) rate for 6 minutes and maximal voluntary flow-
24 volume loops were measured at 3, 5, 7, 10 and 15 minutes. ²¹ The test was deemed positive
25 if the FEV₁ fell by at least 10% from baseline at two consecutive time points. ²¹

1 *Statistical Analysis*

2 Normally distributed data were expressed as mean \pm SD unless otherwise stated. One-way
3 analysis of variance (ANOVA) was performed to compare baseline spirometric indices
4 between EVH-positive and EVH-negative participants. Chi-squared (X^2) analysis was used
5 to evaluate the reported symptoms between EVH-positive and EVH-negative participants.
6 To assess the efficacy of self-reported symptoms, sensitivity, specificity and diagnostic
7 accuracy were calculated.²² Assumptions of normal distribution of FeNO data could not be
8 made therefore Spearman's correlation was used to demonstrate the strength and the direction
9 of the relationship between mean FeNO values and the maximal fall in FEV₁ post-EVH
10 challenge. The results were considered significant if $p \leq 0.05$. Statistical analysis was
11 performed using statistical package for social sciences (SPSS, Version 22, IBM).

12

13 **RESULTS**

14 *Participants' characteristics*

15 Participant characteristics are shown in Table 1. Thirty-eight boxers (5 females; 26
16 Caucasians) and forty-four swimmers (19 females; 44 Caucasians) completed the study. Ten
17 participants (12%) were excluded (n=6, under age of 18; n=3 resting airflow obstruction;
18 n=1, equipment failure during testing).

19

20 Seventeen (21%) of the participants had a Dx of asthma/EIB. Of these, all were prescribed
21 short-acting β_2 -agonist for use pre-exercise, however in addition four (24%) were prescribed
22 inhaled corticosteroid, six (35%) were prescribed an inhaled corticosteroid/long-acting β_2 -
23 agonist combination. One participant (6%) was not using any regular asthma medication.

24

1 At baseline, when compared against swimmers, boxers had lower baseline FEV₁, percentage
2 predicted FEV₁, FVC, percentage predicted FVC and FEV₁/FVC (Table 1).

3
4 *Airway response to EVH Challenge and Dx of asthma/EIB*

5 Eighty-two participants completed the EVH challenge, of which thirty-three (40%) had a
6 positive EVH challenge. Twenty-two (67%) of these subjects (three boxers and nineteen
7 swimmers) had no Dx of asthma/EIB. In contrast, six (12%) participants with Dx of
8 asthma/EIB had a negative EVH result.

9
10 Six (12%) EVH-negative athletes (six swimmers) and ten (30%) EVH-positive athletes (ten
11 swimmers) reported having previously been diagnosed with asthma/EIB and were using one
12 or a combination of short-acting β_2 -agonists, long-acting inhaled β_2 -agonists and inhaled
13 corticosteroids.

14
15 The maximum fall in FEV₁ from baseline ranged from -11.6% to -21.3% in EVH-positive
16 boxers and from -12.4% to -56.1% in EVH-positive swimmers. Two boxers and one
17 swimmer presented with a FEV₁ fall from baseline of >10% (-10.1% and -10.5% for the
18 boxers and -10.1% for the swimmer) at only one time point, deeming them EVH-negative.
19 Of the thirty-three positive EVH challenges three (7.9%) were elite boxers and thirty (68.2%)
20 were elite swimmers (Figure 1). There was no difference in anthropometric characteristics
21 between EVH-positive and EVH-negative participants (Table 1).

1 *Symptoms*

2 Of the EVH-positive participants, fourteen (43%; all swimmers) reported no exercise-
3 associated respiratory symptoms. However, thirteen (93%) of the fourteen EVH-negative
4 swimmers reported at least one exercise respiratory symptom.

5
6 There was an inverse relationship between the maximal fall in lung function following EVH
7 challenge and self-report of exercise-associated chest tightness ($r = -0.25$; $p = 0.02$) and
8 wheezing ($r = -0.25$; $p = 0.02$) in EVH-positive participants. There was also an inverse
9 relationship between the maximal fall in FEV₁ and reports that high pollen content increased
10 severity of symptoms ($r = -0.35$; $p = 0.04$).

11
12 Ten (23%) swimmers reported increased respiratory symptoms due to “bad pool air and/or
13 high chlorine concentrations” and three (7%) swimmers reported exacerbation of respiratory
14 symptoms due to “hot, humid climate”. There was no difference in likelihood of a positive
15 EVH between these groups; i.e. five were EVH-positive and eight EVH-negative. Thus
16 overall, the precision of symptoms for a positive EVH test in swimmers was poor; specificity
17 values ranging from 19.2% (cough) to 29.4% (breathing difficulty).

18

19 *Fraction of Exhaled Nitric Oxide (FeNO)*

20 Resting mean FeNO was similar between boxers and swimmers, 40.7 ± 40.9 ppb vs. 28.1 ± 21.9
21 ppb; $p = 0.08$, respectively. EVH-positive boxers had greater FeNO values when compared to
22 their negative counterparts (99.0 ± 86.5 vs. 35.7 ± 32.5 ; $p = 0.01$). **There was no difference in**
23 **FeNO values between EVH-positive and -negative swimmers** (32.0 ± 25.0 vs. 19.6 ± 8.7 ;
24 $p = 0.08$). There was a correlation between mean FeNO values and the maximal fall in FEV₁
25 post-EVH challenge in swimmers ($r_s = 0.32$; $p = 0.04$), but not in boxers ($r_s = 0.24$; $p = 0.15$).

1 **DISCUSSION**

2 It is proposed that the combination of training and performing in noxious environments
3 makes certain groups of elite athletes highly susceptible to the development of airway
4 dysfunction.²³ The findings from our study supports this notion, confirming the very high
5 prevalence of airway hyper-reactivity in elite level swimmers. Indeed, to our knowledge,
6 this is the highest prevalence (68%) of airway dysfunction reported in an elite
7 internationally-competitive squad of athletes, screened using an indirect stimulus for
8 bronchial provocation. In contrast, in a cohort of athletes, who are not exposed to the
9 environmental stress of the pool environment (i.e. boxers), the prevalence of airway
10 dysfunction was found to be nine fold lower (8%).

11

12 The training and competition environment that elite swimmers are exposed to clearly differs
13 from that of elite boxers. In this respect, boxers train indoors in gymnasiums with relatively
14 low levels of airborne irritants (e.g. allergens (5-10 μ m) and ultrafine particles (<0.1 μ m))²⁴,
15 moderate temperatures and moderate humidity levels. In contrast, the elite swimmers we
16 studied trained in high temperature and humidity. Previous studies²⁵⁻²⁸ suggest that athletes
17 who regularly attend indoor swimming pools are acutely and repeatedly exposed to high
18 concentrations of inhaled surface irritants such as chlorine gas derivatives. Repeated
19 exposure to airborne irritants and sensitizing agents can induce an airway inflammation and
20 remodelling process that may lead to the development of asthma/EIB.^{8, 29} It has been
21 suggested that the increased occurrence of EIB in swimmers may be caused by the combined
22 effects of the inhalation of by-products arising from disinfection and high number of training
23 hours.³⁰ Our cohort may have had even greater exposure to triggers, as they were part of an
24 elite squad, in contrast to other studies that have only tested well-trained and/or sub-elite
25 athletes^{16, 31, 32}. Indeed, the prevalence of EVH-positive elite swimmers and boxers is

1 notably greater than the only previous report of the prevalence of asthma and EIB in GB
2 Olympic Swimmers (41%).⁴ Although Dickinson et al.⁴ used similar methods to confirm
3 asthma/EIB, they did not screen the entire 2004 GB Olympic Team, but only conducted
4 indirect bronchoprovocation challenges with athletes who had a Dx of asthma/EIB or at the
5 request of a team medical officer.

6
7 In the entire athletic cohort, we found no significant relationship between FeNO values and
8 the maximal fall in FEV₁ post-EVH challenge. This is in keeping with prior publications³³,
9³⁴ and indicates that FeNO is a poor predictor of airway hyper-reactivity and clinical asthma
10 in elite athletes. However, when this association was evaluated in swimmers alone, there
11 was a correlation between FeNO and the maximal fall in FEV₁ post-EVH challenge,
12 indicating that baseline airway inflammation may predict more severe response to EVH.

13
14 In total, 22 out of 33 (67%) EVH-positive athletes had no Dx of asthma/EIB. **Sixty-three**
15 **percent** (19 of 30) of the EVH-positive swimmers had no previous history of EIB, whilst
16 none of the EVH-positive boxers had a Dx of asthma/EIB. Moreover, reports of exercise-
17 associated respiratory symptoms were not predictive for the presence of a positive EVH test.
18 Taken together these findings continue to confirm and underline the complex relationship
19 between respiratory symptoms in athletes and presence or indeed lack of airway dysfunction.
20³⁵ Conditions such as exercise-induced laryngeal obstruction are commonly misdiagnosed
21 as EIB due to inappropriate initial diagnosis.³⁶

22
23 There were six swimmers who had a Dx of EIB who did not have a positive EVH challenge.
24 Of these six athletes, four were using Salbutamol inhaler exclusively, one was also prescribed
25 inhaled corticosteroid and one was prescribed an inhaled corticosteroid/long-acting β_2 -

1 agonist combination. Although athletes stopped using inhaler therapy prior to the EVH
2 challenge,¹⁵ this may not have been adequate and athlete may still have received some
3 protection from inhalers. Furthermore, a negative indirect airway challenge does not confirm
4 the absence of EIB. An alternate test, such as Mannitol or sport specific exercise, may be
5 appropriate to confirm or reject diagnosis of EIB.

6
7 The best approach to manage an asymptomatic aquatic athlete with a positive EVH challenge
8 remains to be determined. There is a lack of data to indicate whether initiating treatment in
9 this context has a beneficial impact for health and performance³⁷ and indeed the relationship
10 between a positive EVH result and ‘in the field’ airway dysfunction is not straightforward.⁹
11 Castricum et al.⁹ reported a discrepancy between different bronchial provocation tests when
12 they were compared to field based exercise challenge tests in the diagnosis of EIB in
13 swimmers. At the current time initiation of treatment in asymptomatic EVH-positive athletes
14 with no previous history of EIB must be taken on a case-by-case basis. The transient nature
15 of EVH positivity can be reduced and/or normalised in swimmers when intense training has
16 ceased for a period of at least 15 days³⁸. These observations suggest that the results of
17 bronchial challenges in swimmers may be dependent on training and resting periods.

18

19 **METHODOLOGICAL CONSIDERATIONS / STUDY LIMITATIONS**

20 Seven athletes (one boxer and six swimmers) did not attain the minimum required percentage
21 of Maximal Voluntary Ventilation (MVV) (60%) during the EVH challenge. Despite this,
22 four had a significant fall in FEV₁ post EVH challenge confirming EIB. Those who did not
23 provide a positive challenge should be offered another opportunity to complete the EVH
24 challenge and achieve >60% MVV. Alternatively, a different indirect challenge or exercise
25 may be preferred.

1 It is also possible that some athletes, with a positive EVH test on the day of testing, could
2 have a negative EVH result on a subsequent or second test. This acknowledged, the majority
3 of the athletes tested positive had a fall in FEV₁ >15% (n=24; 73%) and in prior studies, test
4 repeatability is improved in those with a fall of this severity or above.³⁹

5
6 The athletes that demonstrated higher FeNO values were tested during summer time. This
7 seasonal variation in FeNO levels could be explained by the variation of ambient pollution
8 or outdoor allergens. FeNO can also be influenced by nitrate intake and anti-inflammatory
9 agents. Future studies would be methodologically strengthened by the inclusion of additional
10 supporting tests such as skin prick test to characterise atopic status, other measures of airway
11 inflammation (e.g. sputum analysis) and data on athlete's nitrate supplementation.

12 13 **CONCLUSION**

14 Our results demonstrate a very high prevalence of airway dysfunction in elite swimmers and
15 overall a nine-fold greater prevalence than elite boxers. The findings support the notion that
16 athletes who train and compete, for prolonged periods, in provocative environments have an
17 increased susceptibility to airway dysfunction. Future research should investigate whether
18 increased exposure to provocative environments allied with certain biochemical and genetic
19 components has a long-term health impact in elite athletes and what can be done to
20 ameliorate this risk.

21 22 **ACKNOWLEDGEMENTS**

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TABLES

Table 1 Participant characteristics

	N	GB Boxing			GB Swimming		
		Total	EVH-positive	EVH-negative	Total	EVH-positive	EVH-negative
		38	3	35	44	30	14
Gender	Males	33 (86.8%)	3 (100%)	30 (85.7%)	25 (56.8%)	19 (63.3%)	6 (42.9%)
	Females	5 (13.2%)	-	5 (14.3%)	19 (43.2%)	11 (36.7%)	8 (57.1%)
Age (yrs.)		22.1(±3.1)	25.7(±2.1)	21.8(±3.0)	21.1(±2.6)	21.2(±3.0)	20.7(±1.7)
Height (cm)		179.8(±11.5)	183.3(±12.1)	179.5(±11.6)	180.4(±8.6)	180.8(±7.4)	179.7(±11.0)
Weight (kg)		70.9(±16.1)	74.7(±14.4)	70.6(±16.4)	74.5(±10.1)	73.7(±9.4)	76.2(±11.5)
FeNO (ppb)		40.7(±40.9)	99.0(±86.5) ^a	35.7(±32.5)	28.1(±21.9)	32.0(±25.0)	19.6(±8.7)
FEV₁ (L)		4.3(±0.7) ^b	4.5(±1.0)	4.3(±0.7)	4.8(±0.9)	4.8(±1.0)	4.9(±0.7)
FEV₁ (% of predicted)		100.9(±13.6) ^c	102.3(±9.9)	100.7(±14.0)	112.9(±15.5)	110.5(±15.4)	118.1(±14.7)
FVC (L)		5.1(±0.9) ^c	5.3(±1.2)	5.1(±0.9)	6.2(±1.1)	6.2(±1.1)	6.2(±1.1)
FVC (% of predicted)		101.8(±11.9) ^c	102.7(±9.7)	101.7(±12.2)	123.7(±12.2)	121.8(±12.9)	127.6(±10.0)
FEV₁/FVC (%)		83.4(±7.0) ^c	82.7(±2.5)	83.5(±7.3)	77.2(±6.4)	76.5(±5.7)	78.7(±7.6)

^a Different from EVH-negative boxers (p<0.05); ^b Different from GB Swimmers (p<0.05); ^c Different from GB Swimmers (p<0.001); EVH - Eucapnic Voluntary Hyperpnoea; FeNO – Fraction of Exhaled Nitric Oxide; FEV₁ - Forced Expiratory Volume in 1 second; FVC – Forced Vital Capacity

1 **FIGURE LEGENDS**

2 **Figure 1** Maximal fall in FEV₁ post-EVH challenge showing tests that attained 60% MVV
3 (vertical line) and tests, that were above and below the 10% fall in FEV₁ cut-off value
4 (horizontal line) for a positive test. *Panel A* represents GB Boxing and *Panel B* represents
5 GB Swimming. EVH - Eucapnic Voluntary Hyperpnoea; FEV₁ - Forced Expiratory Volume
6 in 1 second; MVV - Maximal Voluntary Ventilation; Dx - Previous Asthma/EIB Diagnosis
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