

EXERCISE INDUCED ASTHMA

Prevalence of bronchoconstriction induced by eucapnic voluntary hyperpnoea in recreationally active individualsJ. Molphy, MSc¹, J. Dickinson, PhD², J. Hu, MSc¹, N. Chester, PhD¹, and G. Whyte, PhD¹¹Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK and ²Sports Therapy, Physical Activity and Health Research Group, School of Sport and Exercise Sciences, University of Kent, Chatham Maritime, UK**Abstract**

Objective: Exercise-induced bronchoconstriction (EIB) is more prevalent in elite athletes than in the general population. Many of these athletes provide a positive eucapnic voluntary hyperpnoea (EVH) challenge without previous diagnosis of EIB. It is unknown whether this is specific to elite athletes or whether the same risk applies to recreationally active individuals. The purpose of this study was to investigate the prevalence of a positive EVH challenge in a population of recreationally active individuals. **Methods:** 136 recreationally active individuals (Age: 21.9 ± 3.7 years; Height: 175 ± 9 cm; Weight: 70.9 ± 10.0 kg) without previous history of asthma or EIB, volunteered to take part in the study. All participants completed an EVH challenge, which was deemed positive if FEV₁ fell $\geq 10\%$ from baseline at two consecutive time points, and was reversible following inhalation of a short acting β_2 -agonist. **Results:** 18 of 136 (13.2%) participants had a positive EVH challenge. Of the 18 individuals, the fall in FEV₁ from baseline ranged from -12% to -50% . At baseline, percentage predicted FEV₁ ($97.5 \pm 12.5\%$ versus $104.9 \pm 10\%$; $p < 0.01$), FEV₁/FVC ratio ($79.5 \pm 6.9\%$ versus $87.8 \pm 5.5\%$; $p < 0.01$), FEF₂₅₋₇₅ (3.73 ± 1.00 versus 4.73 ± 1.00 l/s; $p < 0.01$) and predicted PEF ($89.4 \pm 8.8\%$ versus $97.5 \pm 13.6\%$; $p < 0.05$) values for EVH positive participants were significantly lower than EVH negative participants respectively. **Conclusions:** Overall, 13.2% of recreationally active individuals with no previous history of asthma presented with a positive EVH challenge. Individuals who are recreationally active may benefit from an objective bronchial provocation challenge, given that self-reported symptoms alone only provide a supportive role towards a valid EIB diagnosis.

Keywords

Asthma, bronchoprovocation, exercise-induced, objective, symptoms

History

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Introduction

Exercise-induced bronchoconstriction (EIB) is defined as a transient narrowing of the airways, which limits expiration and commonly occurs following a bout of exercise. EIB is reversible either spontaneously or via the inhalation of a short acting β_2 -agonist [1]. EIB has been estimated to occur in up to 90% of asthmatics [2], and also in around 10% of people without a known history of asthma [3]. Symptoms of EIB are very non-specific and can include: wheezing, dyspnoea, cough and chest tightness [2]. Given the lack of specificity, subjective symptoms are usually poorly correlated with objectively documented EIB [4,5], highlighting the importance of incorporating an objective bronchoprovocation challenge into the diagnosis of EIB.

Best practice in the diagnosis of EIB is achieved when an indirect airway challenge accompanies the practitioner's consultation with the patient [6]. The most exercise-specific indirect airway challenge is an exercise challenge, which incorporates measurement of maximal lung function

flow-volumes prior to and following a bout of exercise [1,6]. There are several issues with using exercise challenges in the diagnosis of EIB including the availability of equipment, the sensitivity of the challenge [7], the intensity of exercise, the specificity of the exercise modality, and the variability of the environment. Accordingly, challenges that use a surrogate for exercise may be more appropriate. The eucapnic voluntary hyperpnoea (EVH) challenge is a surrogate for exercise [8], that has proven to be specific and sensitive for the detection of EIB in athletes [9,10]. EVH challenges are the International Olympic Committee's preferred choice of indirect airway challenge to assist in the diagnosis of EIB in elite athletes [11]. In using objective tests such as EVH, studies have identified a large sub-group of athletes with no previous diagnosis of EIB, who exhibit a positive response to EVH [12]. When elite athletes are screened for EIB, via an EVH challenge, a large number (74%) of the positive challenges come from athletes with no previous history of asthma [12]. This finding can be explained by elite athletes not reporting symptoms or failing to relate exercise-related respiratory symptoms (e.g. post-exercise cough) with asthma/EIB.

In a clinical setting, Brummel et al. [13] reported that most patients (81%) were able to attain the 60% maximal voluntary

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ventilation (MVV) cut-off value needed for a diagnostic test [14], suggesting that EVH challenges are a feasible modality to use with individuals who are not elite athletes. To date, however, little data exist on the prevalence of EIB in recreationally active individuals.

There is a greater prevalence of asthma/EIB in elite athletes when compared to the general population (21% versus 10%) [3,15,16]. Chronic exposure to high intensity exercise may lead to the development of asthma in elite athletes due to an increased exposure of inspired unconditioned air to the lower airways [17], leading to airway remodelling in susceptible individuals [18,19]. Consequently, the early diagnosis and treatment of EIB in athletic populations may be important in ameliorating the impact of chronic exercise on the lung and the progression of the disease.

Accordingly, the purpose of the present study was to examine the prevalence of EIB in recreationally active individuals through the use of an objective bronchoprovocation challenge in the form of an EVH test. Furthermore, the study set out to establish the sensitivity and specificity of self-reported symptoms compared against the EVH challenge result.

Methods

Following ethical approval from the Liverpool John Moores University research ethics committee, 92 males and 44 females (Mean $\pm$ SD: age, 21.9 ± 3.7 years; height, 175.6 ± 9.4 cm; body mass, 70.9 ± 10 kg) volunteered to participate in the study and provided their written informed consent. All participants were in good health, non-smokers and took part in recreational sport and fitness activities at least 3 hours per week. No participant had previously been diagnosed with asthma and/or EIB. No participant had completed a previous bronchodilator or bronchoprovocation challenge. All participants were free from chest infection for at least two weeks prior to testing.

In line with the methods of Dickinson et al. [12], each participant completed a questionnaire to report any respiratory symptoms they experienced either during or following exercise. Respiratory symptoms that participants were asked to comment on included: coughing, wheezing, chest tightness, difficult breathing (dyspnoea), or excess mucus production. Participants were asked if exposure to environmental conditions such as cold climate, low humidity, high pollen levels, high pollution or altitude, exacerbated or caused any reported symptoms.

Measurement of maximal flow-volume spirometry

Using a spirometer (Microlab ML3500, Cardinal Health, Basingstoke, UK), participants completed a forced maximal flow-volume manoeuvre. For each maximal flow-volume manoeuvre the following measurements were recorded: forced expiratory volume in one second (FEV_1); peak expiratory flow (PEF); forced vital capacity (FVC); forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}); and the FEV_1 :FVC ratio (FEV_1 /FVC). Individual maximal flow-volume loops were accepted in accordance with European Respiratory Society/American Thoracic Society criteria [20].

EVH Challenge

Participants were instructed to avoid exercise or caffeine consumption on the EVH challenge day. Baseline FEV_1 was recorded from the best of three maximal voluntary flow-volume manoeuvres. All participants had a baseline FEV_1 value greater than 70% of their predicted value (baseline FEV_1 predicted value range 71%–125%) [21]. Participants were asked to attain target minute ventilation ($\dot{V}_E$) of 85% (baseline $FEV_1 \times 30$) of their predicted maximal voluntary ventilation rate (MVV) for 6 minutes [8]. Inspired air during the EVH challenge consisted of 21% oxygen, 5% carbon dioxide and 74% nitrogen (inspired air temperature 19°C , humidity $<2\%$). The gas was delivered to each participant via a gas cylinder, reservoir and a two-way valve. $\dot{V}_E$ was recorded by calculating the volume of air passing through a dry gas meter every minute. After stopping the EVH challenge, maximal voluntary flow-volume loops were measured at 3, 5, 7, 10 and 15 minutes. Two flow-volume loops were collected at each time-point. The maximal flow-volume loop with the highest FEV_1 was recorded at each time-point. A test was deemed positive for EIB if the FEV_1 fell by at least 10% from baseline at two consecutive time-points following EVH. If the participant's FEV_1 fell greater than 10% of their baseline after the challenge they were given $200\mu\text{g}$ inhaled Salbutamol and asked to remain in the laboratory until their FEV_1 was within 10% of their baseline measurement. Positive participants were given written test reports and recommended to consult with their GP for further treatment.

Statistical analysis

Participants were grouped according to whether they exhibited with a positive or a negative EVH challenge. One-way analysis of variance (ANOVA) was performed in order to compare baseline FEV_1 , PEF, FVC, FEF_{25-75} and FEV_1 /FVC ratio between EVH-positive (EVH +ve) and EVH-negative (EVH -ve) participants. Mixed model repeated measures ANOVA was used to compare FEV_1 at rest and at all time-points post-EVH challenge, between EVH +ve and EVH -ve groups. X^2 Analysis was used to evaluate the reported symptoms between EVH +ve and EVH -ve participants. Statistical significance was set at $p < 0.05$ for all analyses. All data were reported as mean $\pm$ SD unless otherwise stated. Statistical analysis was performed using the statistical package for the social sciences (SPSS, Chicago, IL).

Results

All 136 participants completed the EVH challenge, of which 18 (13.2%) were EVH +ve. Subject demographics are presented in Table 1.

Baseline spirometry

EVH +ve participants had a significantly lower baseline FEV_1 percentage predicted when compared with the EVH -ve participants ($p < 0.01$). EVH +ve participants also presented with a significantly lower FEV_1 /FVC ($p < 0.01$), and percentage predicted PEF ($p < 0.05$) at rest (Table 2).

Table 1. Mean ($\pm$ SD) Age, Height and Weight in EVH positive and negative males and females.

EVH	N	Gender	N	Age (yrs)	Height (cm)	Weight (kg)
Positive	18	Male	15	24($\pm$ 7)	177($\pm$ 6)	76($\pm$ 8)
		Female	3	23($\pm$ 1)	168($\pm$ 2)	61($\pm$ 6)
Negative	118	Male	77	21($\pm$ 3)	180($\pm$ 7)	75($\pm$ 8)
		Female	41	22($\pm$ 4)	166($\pm$ 5)	62($\pm$ 7)

EVH – Eucapnic voluntary hyperpnoea.

Table 2. Baseline spirometry.

	N	FEV ₁ (l)	Predicted FEV ₁ (%)	FVC(l)	Predicted FVC (%)	FEV ₁ /FVC	PEF (l/s)	Predicted PEF (%)
EVH Positive	18	4.15 $\pm$ 0.8	98 $\pm$ 13**	5.09 $\pm$ 1	104 $\pm$ 10	80 $\pm$ 7**	8.5 $\pm$ 1.1	89 $\pm$ 9*
EVH Negative	118	4.2 $\pm$ 0.8	105 $\pm$ 10	4.8 $\pm$ 1	102 $\pm$ 12	88 $\pm$ 6	8.7 $\pm$ 2.3	98 $\pm$ 14

Lung function predicted values = European Community for Coal and Steel predicted values.

*Significantly different from EVH negative participants ($p < 0.05$).**Significantly different from EVH negative participants ($p < 0.01$).EVH, eucapnic voluntary hyperpnoea; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

EVH challenge

Of the 18 EVH +ve individuals, the maximum fall in lung function ranged from -12% to -50% of baseline values (Figure 1). Ten participants presented with an FEV₁ fall from baseline of 10% at only one time point deeming them EVH –ve, yet interestingly two of these borderline negative individuals were unable to maintain $\dot{V}_E$ of $>60\%$ MVV. A total of 29 (21%) participants were unable to maintain $\dot{V}_E$ of $>60\%$ MVV. Despite this, two participants who were below this value still presented EVH +ve. Mean ($\pm$ SD) $\dot{V}_E$ during the EVH test between groups was 107 ($\pm$ 23) litres in the EVH +ve group and 101 ($\pm$ 22) litres in the EVH –ve group. The largest falls in FEV₁ were seen 3 minutes post-EVH challenge in both EVH +ve (FEV₁ 3.2 $\pm$ 0.7 litres) and EVH –ve (FEV₁ 4.0 $\pm$ 0.7 litres) groups.

Symptom questionnaires

Of the 136 participants, 129 successfully completed the symptoms questionnaire. Of these, 16 were in the EVH +ve group. Seven (44%) of the sixteen EVH +ve participants reported having never experienced any previous asthma symptoms.

Results from the χ^2 analysis show that overall the occurrence of respiratory symptoms during exercise had no significant association with EVH challenge result ($p < 0.05$). Of these respiratory symptoms there was no association between the experience of coughing, tightness of chest, dyspnoea and excess mucus production during exercise, with EVH result ($p > 0.05$). However, there was a significant association between the experience of wheezing during exercise and EVH result ($p < 0.05$). When reporting the environmental conditions which have exacerbated respiratory symptoms there was no association between low humidity, high pollution, altitude and EVH result ($p > 0.05$). There was a significant association between the exacerbation of symptoms due to cold climate ($p < 0.05$) and high pollen ($p < 0.05$) with the EVH challenge result (Table 3).

The sensitivity and specificity of all respiratory symptoms with regard to a positive EVH challenge is presented in Table 4 [22]. Sensitivity values for all symptoms and

conditions ranged from 0% to 50%, well below the criterion value outlined by Rundell et al. [5] of at least 85%, and specificity values ranged from 86% to 91%, which are short of the required limit of 92% as recommended by Rundell et al. [5].

Discussion

This study examined the response of recreationally active individuals to an indirect bronchoprovocation challenge. Results highlighted 13.2% of the participants (18 of 136) presented with a positive response to the EVH challenge despite no previous diagnosis of asthma or EIB. This demonstrates, even without any previous history of asthma/EIB, recreationally active individuals may be at risk of EIB. Indeed, some of the participants included in our study presented with a fall in FEV₁ of up to 50% from baseline indicating that an individual with unrecognised history of asthma/EIB may potentially suffer from moderate to severe EIB. Recreationally active individuals could therefore benefit from greater awareness of EIB and from indirect airway challenge testing.

The number of participants who were EVH +ve in the present study is lower than the results of previous studies in athletic populations, where findings have been reported as high as 29% (59 of 198 athletes) of previously undiagnosed athletes in an elite population [12], and 38% (36 of 96 athletes) of previously undiagnosed athletes in a sub-elite population [4]. A number of studies have suggested that elite athletes are at a higher risk of developing asthma, EIB and airway hyper-responsiveness (AHR) when compared to the general population. With exercise hyperpnoea there is a loss of nasal breathing; inhaling large volumes of unconditioned air through the mouth can promote airway dehydration due to the requirement of the lower airways to both warm and humidify inspired air. Prolonged airway dehydration leads to an increase in mast cell inflammatory mediators such as Prostaglandin D₂, which over a period of time may result in an airway remodelling in susceptible individuals [18,19]. Our results show a lower prevalence in the recreationally active population compared with athletic populations, which

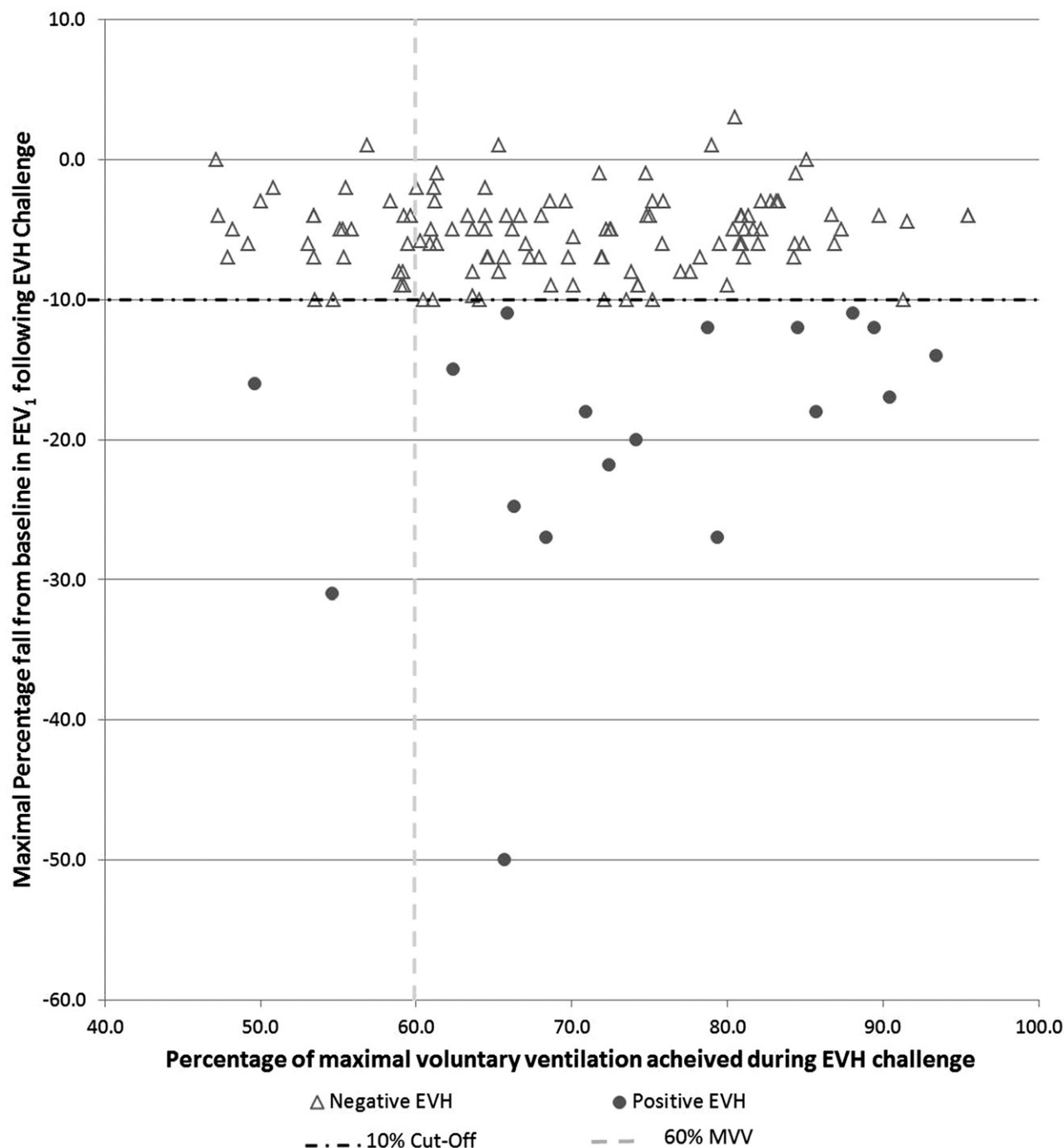


Figure 1. Maximal fall in FEV₁ post EVH challenge showing tests that attained 60% MVV and tests that were above and below the 10% drop in FEV₁ cut-off value for a positive test.

may be associated with lower ventilatory demands for recreational activity. It is possible that recreationally active individuals have a reduced exposure to cold, dry or polluted air when compared to their elite counterparts, which may result in reduced stimulation of airway inflammatory mediators. Furthermore, it may also be possible that moderate exercise provides a protective effect against the lung cell inflammatory processes [23,24].

A small number of studies have reported a higher prevalence of EIB in sub-elite and clinical populations. Mannix et al. [25] reported a 29% (18 of 62) prevalence of EIB in high-school athletes and 19% (41 of 212) in previously undiagnosed individuals attending a fitness centre [26].

Care is warranted in the interpretation of these results; however, as it is unclear if the authors accounted for any previous diagnosis prior to the inclusion in the study. It is also possible that as the test was voluntary, people with respiratory symptoms during exercise may have been more likely to volunteer, allowing for a bias population sample. In a clinical setting, Brummel et al. [13] reported an EIB prevalence of 28% (50 of 178 patients) in previously undiagnosed patients.

It is important to recognise that EIB is extremely variable and that symptoms are poorly correlated with EIB diagnosis [12,13]. It is interesting to note that 15.2% (11 of 72) symptomatic individuals were EVH +ve and 8.7% (5 of 57) asymptomatic individuals were also EVH +ve. The results

Table 3. χ^2 analysis examining the association between exercise-induced bronchoconstriction and previous experience of respiratory symptoms during exercise along with environmental conditions which have exacerbated symptoms.

	<i>N</i>	Number of participants reporting at least one symptom	Coughing	Wheezing	Tight chest	Dyspnoea	Excess mucus production
Respiratory symptoms							
EVH Positive	16	11 (69%)	1 (6%)	2 (13%)	1 (6%)	1 (6%)	2 (13%)
EVH Negative	113	61 (54%)	10 (9%)	2 (2%)	5 (4%)	2 (2%)	5 (4%)
Total	129	72 (56%)	11 (8.5%)	4 (3%)	6 (5%)	3 (2%)	7 (5%)
χ^2	<i>p</i> =	0.27	0.73	0.02	0.75	0.27	0.18
	<i>N</i>	Number of participants reporting at least one symptom	Cold climate	Low humidity	High pollen	High pollution	Altitude
Environmental conditions							
EVH Positive	16	11 (69%)	8 (50%)	1 (6%)	3 (19%)	0 (0%)	1 (6%)
EVH Negative	113	61 (54%)	29 (26%)	21 (19%)	6 (5%)	8 (7%)	6 (5%)
Total	129	72 (56%)	37 (29%)	22 (17%)	9 (7%)	8 (6%)	7 (5%)
χ^2	<i>p</i> =	0.27	0.04	0.22	0.05	0.27	0.88

Table 4. The efficacy of self-reported symptoms in terms of true identification, sensitivity and specificity.

	Number of participants reporting at least one symptom	Coughing	Wheezing	Tight chest	Dyspnoea	Excess mucus production
Respiratory Symptoms						
Proportion of True identification	49%	81%	88%	84%	87%	86%
Sensitivity	15%	9%	50%	17%	33%	29%
Specificity	91%	87%	89%	88%	88%	89%
	Number of participants reporting at least one symptom	Cold climate	Low humidity	High pollen	High pollution	Altitude
Environmental conditions						
Proportion of True identification	49%	71%	72%	85%	81%	84%
Sensitivity	15%	22%	5%	33%	0%	14%
Specificity	91%	91%	86%	89%	87%	87%

The proportion of true identification (Those whose reported symptoms matched the EVH result).

Sensitivity (The proportion of symptom positives that test positive).

Specificity (The proportion of symptom negatives that test negative).

from the questionnaire detailing previous experience of respiratory symptoms and environmental influences upon these symptoms indicate that in this group of participants, wheezing after exercise was the main symptom associated with an EVH +ve challenge ($p < 0.05$), yet this occurred in only two of the 18 positive individuals and two of the 118 negative individuals, indicating that although it is significant between groups, it is not necessarily frequent amongst either group. Our study found that the most common self-reported symptom was coughing. This is also found in elite athletes [5,12], yet this was also the least sensitive (9%) and least specific (87%) symptom to identify EVH +ve. When assessing subjective symptoms in a population of elite Olympic athletes, Rundell et al. [5] found that even when subjective symptoms are associated with EIB they are deemed not to be sensitive or specific enough to fully identify true positives and cannot exclude true negatives. The present study supports this finding with a sensitivity of only 50% and a specificity of 89% for wheezing and EVH +ve, where 85% sensitivity and 92% specificity are required for accurate correlation between a reported symptom and the test outcome [5]. The main environmental factors associated with EVH +ve were cold climate and high pollen ($p < 0.05$). The sensitivity was only 22% for cold

climate and only 33% for exposure to high pollen levels, with specificities of 91% and 89%, respectively. This demonstrates that although associations can be made between certain symptoms and presentation of EIB, they do not allow for a conclusive diagnosis, highlighting the need for objective bronchial provocation tests for accurate diagnosis of EIB.

When performing the EVH test, there were 29 (21%) individuals who did not reach the minimum required percentage maximal voluntary ventilation (MVV) of 60%; outlined as a criterion for the acceptance of a valid test [13,14,27]. Brummel et al. [13] state that females were less likely to attain the cut-off value, this was not apparent in the current study where only 9 of the 29 individuals unable to reach the cut-off were female. The EVH challenge was able to identify positive responders even though they failed to reach the 60% criterion. However, the individuals who were borderline (FEV_1 fall between 6%–9% from baseline) may have presented with an EVH +ve result had they achieved $>60\%$ MVV during the EVH challenge. Amongst the individuals who failed to reach the cut-off, two were borderline positive with falls of 10% on only one occasion. Whilst Rundell et al. [28] suggest that a target of 85% MVV should be attained when assessing elite athletes, Brummel

et al. [13] reported that MVV rarely exceeds 60% when assessing healthy non-elite athletes yet also highlighted that the proportion of EVH positive challenges were the same regardless of whether individuals attained the 60% cut-off for MVV. However, the present study has identified that two (7%) of the 29 participants who did not reach 60% MVV were EVH +ve and that 16 (15%) of the 107 participants who were over 60% MVV were EVH +ve. As the percentage is much lower in the group below the cut-off value this raises questions towards the validity of these tests with 27 individuals presenting EVH –ve yet also failing to reach 60% MVV. Care is warranted in those individuals who present EVH –ve whilst failing to reach the 60% cut-off for a valid test. A repeat test may be required in which they are aggressively encouraged to reach the 60% cut-off. Alternatively a different indirect airway challenge, such as a Mannitol challenge [29], could be used to rule out EIB in low-performing individuals who also present with co-existing indications of EIB, i.e. wheezing, cough or environmental triggers.

Limitations

The EVH challenge is a very provocative test with a high degree of sensitivity. Given that the air is around 2% humidity there may be individuals who exhibit AHR only with this unique trigger, which may not be typical of their exercise environment. This may reduce the relevance of the test and, therefore, there may be a need to adjust the cut-off threshold for a positive test or to supplement the test with some form of sport-specific exercise challenge in order to provide a more ecologically valid test result. The challenges in the current study were also not supported by any measures of airway inflammation; therefore, it is difficult to state conclusively what is triggering the EIB, reducing the specificity of the treatment that can be given to the individual [27]. The supporting data for a valid diagnosis in the current study would have also benefited from the inclusion of additional supporting tests such as: fractional exhaled nitric oxide (FeNO); allergy identification via skin prick test; specific airway inflammation biomarker identification in urine, i.e. leukotriene E₄ and 9 α , 11 β prostaglandin F₂ [30]; and induced sputum cell counts.

Conclusions

In conclusion, 13.2% of recreationally active individuals with no previous EIB diagnosis presented EVH +ve. This value is lower than previous studies which have looked at high-level athletes and non-athletes in a clinical setting and also lower than other studies looking at similar populations [4,12,19,25,26]. The current study agrees with previous work suggesting diagnosis of EIB should not be made using only symptoms or baseline measures of lung function and that objective bronchial provocation challenges should be incorporated to support an accurate identification of EIB. One in five participants could not achieve the 60% MVV minimum target. Therefore, other indirect airway challenges, such as mannitol, may be considered in which recreationally active individuals are more likely to achieve an acceptable level of performance in the test [29].

Declaration of interest

The authors would like to state that there were no conflicts of interest during the preparation of this manuscript.

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