THE ALLERGY QUESTIONNAIRE FOR ATHLETES PROVIDES VALUE IN RULING-OUT EXERCISE-INDUCED BRONCHOCONSTRICTION

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Keywords: Allergy Questionnaire for Athletes (AQUA); Asthma; Exercise-induced bronchoconstriction (EIB); Diagnosis; Dyspnoea.

Word count: 1036.

To the Editor:

Exercise-induced bronchoconstriction (EIB) refers to a condition characterised by expiratory airflow limitation during physical activity and is one of the most common causes of exertional breathing difficulty in young athletic individuals [1]. Due to the limited value of a symptom-based approach to diagnosis [2] it is now widely recognised that EIB should be objectively confirmed via indirect bronchoprovocation testing before initiating treatment, with eucapnic voluntary hyperpnoea (EVH) often endorsed for this purpose [3]. Although the feasibility of EVH testing is well established, the practicalities and associated cost of assessment is substantial and therefore not widely available as part of routine diagnostic work-up across primary and secondary care. The development of simple yet robust clinical tools to aid the assessment of airway health in athletic individuals is therefore required.

The Allergy Questionnaire for Athletes (AQUA) was originally developed and validated as a reliable means to quantify the severity of allergic disease in athletes (specificity: 97.1% and sensitivity: 58.3%) [4]. Over the past decade, the relevant respiratory symptom components of AQUA have also been employed in studies evaluating perceived dyspnoea and respiratory tract infection [2,5] - leading to the suggestion that AQUA may offer value as a pre-screening tool for the assessment of airway health in susceptible or 'high-risk' athletic populations (e.g. elite level swimmers) [6]. Although utilising AQUA in this context is logical on the basis that airway hyper-responsiveness (AHR) and asthma are strongly associated with atopic disposition [7], the agreement with objective test outcome following indirect bronchoprovocation testing has yet to be determined. We therefore undertook this study to evaluate the predictive value of AQUA to confirm or refute evidence of EIB in a large cohort of screened athletes.

The study was conducted as a multi-site cross-sectional trial. Following approval from local research ethics committees (Ethics ID: 57144), one-hundred and eighty recreational athletes (male: n = 120) provided written informed consent (Table 1.). At study entry, exertional respiratory symptoms (i.e. cough, wheeze, chest tightness and dyspnoea) were evaluated via interview with all athletes completing AQUA followed by an EVH challenge. The EVH protocol consisted of breathing a dry compressed gas mixture (21% O_2, 5% CO_2, balance N_2) at a target ventilation equivalent to 85% maximum voluntary

ventilation (MVV) for a period of 6-min. To ensure test validity (i.e. avoid false-negative test outcome) all athletes were required to achieve ≥60% predicted MVV. Spirometry was performed in triplicate at baseline and in duplicate at 3, 5, 7, 10, and 15-min post EVH. A positive AQUA questionnaire was defined by a score ≥5 [4]. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated and evaluated against objective evidence of EIB in accordance with current committee guidance (-10% ΔFEV_1 at two consecutive time-points) [3] and a recently suggested revised EVH diagnostic cut-off (-15% ΔFEV_1 at one time-point) [8]. Diagnostic accuracy of AQUA was calculated using receiver operating characteristics area under the curve (ROC-AUC).

Almost all athletes (99%) had normal baseline lung function (FEV_1 % predicted ≥80%). Despite this, over half of the cohort (55%) reported at least one respiratory symptom during exercise. Over one-third (37%) of the cohort had a prior asthma diagnosis, however, of these, only thirty-one (46%) (-10% ΔFEV_1) and nineteen (28%) (-15% ΔFEV_1) presented with objective evidence of EIB. One hundred and twenty-nine athletes (72%) provided a positive AQUA score indicating a high likelihood of allergic disease. The prevalence of EIB for the entire cohort was 21% (-10% ΔFEV_1) and 14% (-15% ΔFEV_1). ROC-AUC for AQUA was 66% (-10% ΔFEV_1) and 69% (-15% ΔFEV_1), respectively. Irrespective of test outcome or asthma history, the majority of athletes (96%) experienced bronchoconstriction post EVH (average fall in FEV_1 -8.9 ± 10.1%). The predictive value of AQUA for the detection of EIB is presented in Table 2.

The present study highlights that a positive AQUA score (≥5) provides poor diagnostic specificity (32%) (i.e. ability to rule-in EIB). This finding supports the concept that AQUA and/or self-report respiratory symptoms should not be used to confirm a diagnosis in the absence of indirect bronchoprovocation testing [2]. Importantly, however, for the first time, our data indicate that a negative AQUA score (<5) offers excellent diagnostic sensitivity (i.e. ability to rule-out EIB). This was apparent when applying either current (92%) [3] or revised diagnostic thresholds (98%) [8]. Furthermore, in those with evidence of moderate to severe bronchoconstriction (i.e. ≥20% fall in FEV_1), a negative AQUA score ruled-out EIB in all cases. Of note, in the very few athletes with a negative AQUA score and evidence of EIB (2%), the majority provided a positive response to the relevant respiratory symptom components of the

questionnaire; i.e. Q10: “Did you ever feel tightness of your chest and/or wheeze” and Q13: “Have you ever had shortness of breath, cough and/or itching of the throat following exercise”.

The clinical relevance of our findings are perhaps most applicable in a primary care setting where it is commonplace to encounter athletic individuals reporting breathing difficulty during exercise. Indeed, when faced with this clinical presentation, athletes are most frequently prescribed a course of inhaler therapy (in the absence of objective assessment) for presumed EIB. This is despite increasing recognition that a broad differential diagnosis exists for breathing difficulty in athletes; i.e. not all wheeze is asthma [9]. Accordingly, utilising AQUA as an initial form of assessment, particularly in susceptible athletes who train and compete in irritant-laden environments (e.g. high aeroallergen) offers a reliable and time-efficient approach to aid clinical decision-making; i.e. inform referral for specialist objective testing and/or consider differential diagnosis. For example, exercise-induced laryngeal obstruction (EILO); a condition characterised by closure of the upper airway (i.e. laryngeal structures) during exercise is highly prevalent in young athletes (~5-10%) yet frequently overlooked [9]. Similarly, incorporating AQUA in the context of widespread screening (e.g. sports teams or squads) offers a practical and cost-effective approach to ensure airway health is optimised and maintained.

In summary, AQUA is a simple tool that provides value in the assessment of EIB in athletes and should be utilised as a ‘first-step’ to rule-out the condition during diagnostic work-up. The development and validation of an athlete specific questionnaire and risk prediction algorithms to confirm (i.e. rule-in) EIB remains an important avenue for future research.

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Table 1. Study population clinical characteristics.

Variables	Distribution	Mean (± SD)	Median (IQR)
Age (years)	Non-normal	33 ± 10	31 (16)
Height (cm)	Normal	175 ± 9	175 (13)
Weight (kg)	Non-normal	73 ± 13	73 (15)
BMI ($kg \bullet m^{-2}$)	Non-normal	24 ± 3	23 (4)
Training ($hrs \bullet wk^{-1}$)	Non-normal	7 ± 3	6 (3)
FEV_1 (L)	Normal	3.92 ± 0.73	3.84 (1.12)
FEV_1 % predicted	Non-normal	102 ± 12	100 (16)
FVC (L)	Normal	4.84 ± 0.89	4.85 (1.40)
FVC % predicted	Non-normal	106 ± 12	105 (15)
FEV_1/FVC (%)	Normal	82 ± 7	82 (10)
AQUA score	Non-normal	9 ± 7	9 (12)
Eucapnic voluntary hyperpnoea			
Average fall in FEV_1 (%)	Non-normal	-8.9 ± 10.1	-5.5 (6.3)
Target ventilation (L)	Normal	118 ± 22	115 (34)
Achieved ventilation (L)	Normal	97 ± 24	99 (32)
Predicted ventilation (%)	Non-normal	78 ± 23	83 (21)
		Ratio (percentage)	
Sporting discipline			
Endurance		151/180 (84%)	
Intermittent		21/180 (12%)	
Sprint/power		8/180 (4%)	
Physician diagnosed asthma		67/180 (37%)	
EIB positive (-10% ΔFEV_1)		31/67 (46%)	
EIB negative (-10% ΔFEV_1)		36/67 (54%)	
EIB positive (-15% ΔFEV_1)		19/67 (28%)	
EIB negative (-15% ΔFEV_1)		48/67 (72%)	
Inhaler medication			
Reliever therapy		27/67 (40%)	
Reliever + maintenance therapy		40/67 (60%)	

Table 2. AQUA sensitivity, specificity, PPV and NPV value for the detection of EIB.

Population: n = 180						
Prevalence (-10% ΔFEV_1): 21%						
Prevalence (-15% ΔFEV_1): 14%						
		EVH				
		-10% ΔFEV_1			-15% ΔFEV_1	
		+	-		+	-
AQUA score	+	33	96	+	24	105
	-	4	47	-	1	50
		AQUA score				
		-10% ΔFEV_1			-15% ΔFEV_1	
Sensitivity (%)		89			96	
Specificity (%)		32			32	
PPV (%)		26			19	
NPV (%)		92			98	

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ACKNOWLEDGEMENTS

Nil.

FUNDING STATEMENT

Nil relevant.

CONFLICT OF INTEREST

The authors have no real or perceived conflict of interest in respect of this manuscript.

CONTRIBUTION STATEMENT

Conception and design: HA, JH, LD, OP; Analysis and interpretation: HA, OP; Drafting the manuscript for important intellectual content: HA, JH, SB, TC, LD, OP.

GUARANTOR STATEMENT

OP confirms full responsibility for the content of the manuscript.