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ORIGINAL ARTICLE

Two distinct phenotypes of asthma in elite athletes identified by latent class analysis

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Abstract

Introduction: Clusters of asthma in athletes have been insufficiently studied. Therefore, the present study aimed to characterize asthma phenotypes in elite athletes using latent class analysis (LCA) and to evaluate its association with the type of sport practiced. **Methods:** In the present cross-sectional study, an analysis of athletes' records was carried out in databases of the Portuguese National Anti-Doping Committee and the Norwegian School of Sport Sciences. Athletes with asthma, diagnosed according to criteria given by the International Olympic Committee, were included for LCA. Sports practiced were categorized into *water*, *winter* and *other* sports. **Results:** Of 324 files screened, 150 files belonged to asthmatic athletes (91 Portuguese; 59 Norwegian). LCA retrieved two clusters: "*atopic asthma*" defined by allergic sensitization, rhinitis and allergic co-morbidities and increased exhaled nitric oxide levels; and "*sports asthma*", defined by exercise-induced respiratory symptoms and airway hyperresponsiveness without allergic features. The risk of developing the phenotype "*sports asthma*" was significantly increased in athletes practicing water (OR = 2.87; 95%CI [1.82–4.51]) and winter (OR = 8.65; 95%CI [2.67–28.03]) sports, when compared with other athletes. **Conclusion:** Two asthma phenotypes were identified in elite athletes: "*atopic asthma*" and "*sports asthma*". The type of sport practiced was associated with different phenotypes: water and winter sport athletes had three- and ninefold increased risk of "*sports asthma*". Recognizing different phenotypes is clinically relevant as it would lead to distinct targeted treatments.

Keywords

Asthma, athletes, clusters, exercise-induced bronchoconstriction, latent class analysis, phenotypes, sports, training environment

History

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Introduction

Exercise training improves asthma symptoms, quality of life, exercise capacity, bronchial hyperresponsiveness (BHR) and lung function in asthmatics [1,2]. Thus, physical activity should be recommended as a supplementary therapy to medication in asthmatic subjects [1]. However, although moderate exercise has proven to be beneficial, repeated high-intensity exercise performed by elite athletes seems to contribute to the development of asthma and BHR. In fact, it has been recognized that elite athletes have increased risk of developing asthma, especially those who practice endurance sports, such as swimming and running, or winter sports [3,4]. Nevertheless, asthma is a complex syndrome with variable clinical presentation, and different physiologic and pathologic

parameters. Characterization of this heterogeneity has promoted the concept of asthma consisting in multiple phenotypes or consistent groupings of characteristics [5].

Defining phenotypes of asthma has been a major objective in recent years, as it would facilitate research into etiology and pathophysiology, targeted treatment and preventive measures, and improve prediction of long-term outcomes [6]. Up to this moment, in what concerns athletes with asthma, there is no evidence to support clusters of grouping characteristics, although it is generally recognized that the asthmatic condition which develops in athletes during their sports career is not likely to be similar to what is usually considered to be asthma in clinical practice [7]. The hypothesis of different phenotypes of asthma occurring in athletes has only been approached once in the literature, in a review article. Haahtela et al. [8] suggested that there may be two different clinical phenotypes of asthma in elite athletes: "classical asthma" characterized by early onset childhood asthma, methacholine hyperresponsiveness, atopy and signs of

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eosinophilic airway inflammation reflected by increased exhaled nitric oxide levels (FE_{NO}); and another distinct phenotype with late onset of symptoms during sports career, airway responsiveness to eucapnic voluntary hyperpnoea (EVH) and a variable association with atopic markers and FE_{NO}. These phenotypes were described only in Finnish athletes, and have not been fully established so far.

Most recent efforts to describe phenotypes are based on cluster analysis. These multivariate statistical methods allow splitting the differences between patient group data into disease categories and clinically meaningful groups, therefore being less dependent on *a priori* assumptions. These methods have already been successfully applied within respiratory medicine [6,9–11] to identify asthma phenotypes that exhibited differences in clinical, physiological and inflammatory parameters as well as response to treatment [10,11]. However, such methods have not been applied to athletes with asthma.

The objectives of the present study were to identify and characterize asthma phenotypes in elite athletes using latent class analysis (LCA) and to assess a possible association with the type of sport practiced.

Methods

Design and participants

In the present cross-sectional study, an analysis of elite athlete records kept in database files of two different countries was performed. Portuguese and Norwegian athletes training at high competitive levels (national, international or Olympic teams) were identified through existing institution databases. In Portugal, we used registries of elite athletes available at the Portuguese Anti-doping Authority and the Portuguese database of Olympic athletes; in Norway, we analyzed medical files from the respiratory medical team of the Norwegian School of Sport Sciences, including Olympic athletes participating in the 2008 summer and 2010 winter Olympic Games. Athletes were selected according with available information on symptoms, lung function and airway inflammation, BHR, and allergic sensitization. Healthy athletes and those with other conditions rather than asthma were excluded. From all reviewed files, 324 files had complete information available and informed consent for data use. Of these 324 athletes, 150 athletes fulfilled asthma criteria and were included for LCA.

The present study was conducted in accordance with Declaration of Helsinki for Medical Research Involving Human Subjects and was approved by Regional Medical Ethics Committees and Norwegian Data Inspectorate. All included subjects signed an informed consent for data usage.

Definitions

Asthma diagnosis was established by a medical doctor according to criteria set by the International Olympic Committee to document asthma in athletes [4,12], with objective evidence of either reversibility after bronchodilator administration or BHR after a bronchial provocation challenge. The demographic data obtained included age, gender, height, weight and sport practiced. The type of sport was

classified according to environmental training conditions into *water* sports (swimming and water polo), *winter* sports (cross-country skiing, biathlon, skeleton, alpine skiing and ski cross) and *other* sports (speed skating, curling, handball, judo, triathlon, football, cycling, beach volley, rowing, athletics, sailing, badminton, canoeing, curling, equestrian, taekwondo, auto-racing, billiards, paragliding, rugby, tennis, roller hockey, kickboxing, fencing, basketball or golf). Medical data collected included presence of respiratory symptoms, current use of asthma medication and presence of rhinitis or other allergic diseases (conjunctivitis, urticaria, eczema, anaphylaxis and drug, food and venom allergies). These data were sampled through allergy questionnaire for athletes (AQUA) questionnaire [13] at the time of the medical consultation. For statistical purposes, variables were categorized according to the definitions presented in Table 1. Spirometry was performed in agreement with the European Respiratory Society guidelines [14] and results (forced expiratory volume in first second – FEV₁ and forced vital capacity – FVC) were presented as both absolute and predicted values, according to published reference algorithms [15]. For both airflow obstruction and BHR, the first ever performed spirometry and the first ever performed bronchial provocation challenge, respectively, were considered.

Statistical analysis

Results are presented as mean values [95% confidence interval (CI)], mean $\pm$ standard deviation (SD), or medians $\pm$ interquartile range (IQR) in case of skewed distribution, or counts (*n*, %). Independent samples *t*-test was used for comparison of normally distributed continuous data, and Mann–Whitney test was used on data with skewed distribution. Categorical variables were compared by Chi-square or Fisher's exact tests. These analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp., Armonk, NY), considering a significance level of 0.05.

LCA was used to uncover distinct groups of individuals from a sample (patterns) homogeneous within the group, considering that the performance of an individual in a set of items is explained by a categorical latent variable with *K* classes, commonly called “latent classes”. Model interpretation was based on item profiles in each category and obtained from probabilities of endorsing each item response, conditional on class membership. In the present study, the number of latent classes was defined according to Bayesian Information Criterion (BIC). Starting from one single class and increasing one class at each step, the best solution was identified when the increase of number of classes did not lead to a decrease in BIC. LCA used nine variables important for asthma definition or relevant for differential diagnosis (Table 1). The selection of variables was based on the assumption of their clinical relevance for asthma definition. The Lo–Mendell–Rubin likelihood ratio test of model fit was used to quantify the likelihood that the data could be described by a model with one-less class. All LCA models were fitted using MPlus (V.5.2; Muthen & Muthen, Los Angeles, CA). Later, among asthmatic athletes, we estimated the risk associated with the sport training environment, by using regression

Table 1. Definitions of variables set for LCA.

Variable	Definition
Airflow obstruction	FEV ₁ /FVC ratio lower than 0.70
Reversibility	Increase of at least 200 mL and 12% in FEV ₁
Rhinitis ^a	Positive answer to the question “Did any doctor diagnose you an allergic disease?” AND “Rhinitis” OR Positive answer to the question “Do you frequently sneeze, have a running, itchy nose (apart from colds)?”
Any other allergic disease ^a	Positive answer to the question “Did any doctor diagnose you an allergic disease?” (except rhinitis) OR Positive answer to the question “Have you frequently red eyes with tearing and itching?” OR Positive answer to the question “Have you ever had severe allergic or anaphylactic reactions?” OR Positive answer to the question “Have you ever had allergic reactions to foods?” OR Positive answer to the question “Have you ever had allergic reactions to drugs?”
Respiratory symptoms ^a	Self-reported recurrent breathlessness, cough, wheezing, chest tightness and/or phlegm production OR Positive answer to the question “Did any doctor diagnose you an allergic disease?” AND “Asthma” OR Positive answer to the question “Have you ever had shortness of breath, cough and/or itching of the throat following exercise?”
Asthma treatment	Current or recent treatment with ICS and/or Beta ₂ -agonists
Airway hyperresponsiveness ^b	A fall in FEV ₁ ≥10% from baseline with exercise or EVH OR A fall in FEV ₁ ≥15% from baseline after inhaling 22.5 ml of 4.5 g% NaCl or ≤635 mg of mannitol OR A fall in FEV ₁ ≥20% from baseline with methacholine: PC ₂₀ ≤4 mg/ml, or PD ₂₀ ≤400 µg (cumulative dose) or ≤200 µg (noncumulative dose) in those not taking ICS, and PC ₂₀ ≤16 mg/ml or PD ₂₀ ≤1600 µg (cumulative dose) or ≤800 µg (noncumulative dose) in those taking ICS for at least 1 month
Eosinophilic inflammation	The presence of FE _{NO} levels above 25 ppb
Allergic sensitization	The presence of at least one positive (mean of largest and perpendicular diameter of the wheal ≥3 mm for each allergen and controls showing adequate reactions) skin prick test or the presence of positive specific IgE (≥0.35 kU/L) for at least one common aeroallergen in the local geographic area

EVH, eucapnic voluntary hyperpnoea; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; ICS, inhaled corticosteroids; FE_{NO}, exhaled nitric oxide; PD₂₀, provocative dose of methacholine causing a 20% decrease in FEV₁; PC₂₀, provocative concentration of methacholine causing a 20% decrease in FEV₁.

^aConsidering the AQUA questionnaire.

^bAccording to International Olympic Committee Medical Commission to diagnose asthma in athletes.

analysis to predict the odds of having a specific asthma pattern (phenotype), having “other sports” as reference.

Results

Included subjects

From 324 files reviewed, 150 files belonged to athletes who fulfilled asthma criteria (91 Portuguese; 59 Norwegian). Forty-five athletes were diagnosed with asthma based on positive bronchodilation (the mean ± SD of FEV₁ increase was 450 mL ± 292 and 13% ± 9.4), and 105 by presenting airway responsiveness after a provocation challenge: 1 positive challenge to mannitol, 3 positive challenges with exercise and the remaining 101 positive challenges with methacholine (7 reporting PC₂₀: mean 3.9 mg/mL; 94 reporting PD₂₀: mean 6.8 µg). The remaining athletes were healthy ($n = 129$) or had other pathologic conditions ($n = 45$). Asthmatic subjects included in the present study presented airflow limitation, more reversibility to salbutamol, more BHR, atopy, rhinitis and airway inflammation assessed by FE_{NO} (Table 2).

LCA model

Relying on asthma defining variables, the increase in likelihood values leveled off when increasing from one to

two classes, and BIC reached its optimum value at two classes (Online Table). This result was confirmed by Lo–Mendell–Rubin likelihood ratio test.

Class 1 was characterized by allergic sensitization, rhinitis and other allergic co-morbidities, and increased FE_{NO} levels (“*Atopic asthma*”); while class 2 was characterized by the occurrence of respiratory symptoms and BHR, in the absence of atopic features (“*Sports asthma*”) (Table 3 and Figure 1).

Subject’s differences between classes

The athletes which were assigned to “atopic asthma” presented higher values of FE_{NO} than those in “sports asthma” (32.2 vs. 15.7, $p = 0.002$). In “atopic asthma”, 28 athletes presented increased values of FE_{NO}, compared to only 7 among those in “sports asthma”.

Allergic diseases were evident in 60.7% of athletes in “atopic asthma”, and in 12.5% of those assigned to “sports asthma”, namely: conjunctivitis (48% of athletes in “atopic asthma” and none in “sports asthma”), atopic eczema (12% of athletes in “atopic asthma” and none in “sports asthma”), and food allergy (31% of athletes in “atopic asthma” and none in “sports asthma”). Hymenoptera venom allergy, drug allergy and anaphylaxis had a similar prevalence in both

Table 2. Features of athletes screened at Portuguese National Anti-Doping Organization and at Norwegian School of Sports Sciences databases.

	Asthmatic athletes (n = 150)	Non-asthmatic athletes (n = 174)	p
Male, n (%)	107 (71)	89 (51)	<0.001 ^e
Age, years	25 (14–40)	26 (16–38)	0.251 ^d
BMI, kg/m ²	23 [23;24]	23 [22;23]	0.06 ^c
Physician reported rhinitis, n (%)	54 (36)	33 (19)	0.003^e
Other allergic disease, n (%)	20 (13)	26 (15)	0.750 ^e
Atopy, n (%)	89 (59)	58 (33)	<0.001 ^e
Respiratory symptoms, n (%) [*]	138 (92)	89 (51)	<0.001 ^e
Dyspnea/heavy breathing	48 (32)	20 (11)	<0.001 ^e
Chest tightness	12 (8)	11 (6)	0.379 ^e
Wheezing	42 (28)	15 (9)	<0.001 ^e
Cough	44 (29)	33 (19)	0.002^e
Tiredness	1 (0.7)	1 (0.6)	0.427 ^f
Phlegm	18 (12)	15 (9)	<0.001 ^e
Asthma treatment, n (%)			<0.001 ^f
Inhaled steroids alone	9 (6)	1 (0.6)	
Beta-2-agonists alone	13 (9)	2 (1)	
Inhaled steroids + β 2-agonists	96 (64)	13 (8)	
Airway obstruction ^a , n (%)	43 (29)	21 (12)	<0.001 ^e
FVC			
L	5.4 [5.1;5.7]	5.2 [5.0;5.4]	0.41 ^c
% of predicted	114 [110;117]	112 [109;116]	0.60 ^c
FEV ₁			
L	4.1 [3.9;4.4]	4.3 [4.1;4.4]	0.06 ^c
% of predicted	101 [96;106]	109 [106;111]	0.001^c
FEV ₁ /FVC	69 [65;74]	76 [72;80]	0.012^c
Reversibility ^b , n (%)	26 (17)	1 (0.6)	0.037^f
Airway hyperresponsiveness, n (%)	126 (84)	51 (29)	<0.001 ^e
FE _{NO} , ppb	33 (6–213)	19 (4–70)	0.01^d

Bold values indicate $p < 0.05$.

Data presented as mean (95% confidence interval) except for age and FE_{NO} which are presented as median (min–max).

BMI, body mass index; FE_{NO}, exhaled fraction of nitric oxide; L, liters; FVC, forced vital capacity; FEV₁, forced expiratory volume in one second.

^aDefined as a FEV₁/FVC ratio <0.70.

^bDefined as an increase in FEV₁ ≥ 200 mL and $\geq 12\%$.

^cIndependent samples *t*-test.

^dIndependent samples Mann–Whitney *U* test.

^eChi-square test.

^fFisher's exact test.

classes (4% of athletes for both diseases). Male gender was predominant in “sports asthma”.

Regarding therapeutic, 92.5% of those athletes with “atopic asthma” and 78% of those with “sports asthma” were under anti-asthmatic drugs. Thirteen asthmatic athletes were using only short-acting β 2-agonists as therapeutic – 9 (8%) among the “atopic asthma” and 4 (8%) among the “sports asthma” phenotype; the remaining athletes were on inhaled corticosteroids (ICS) alone or combined with long-acting β 2-agonists.

Risk factors for each class

A 2.87 (95%CI: 1.82–4.51) and 8.65 (95%CI: 2.67–28.03) fold increase for risk of “sports asthma” was observed in athletes practicing water sports and winter sports, respectively, when compared to other sports (Figure 2).

Discussion

Using LCA, this present study identifies two distinct phenotypes of asthma in athletes: “atopic asthma” defined by the occurrence of atopy, increased levels of FE_{NO}, rhinitis and other allergic co-morbidities; and “sports asthma”, defined by the presence of exercise-induced respiratory symptoms and

BHR in the absence of allergic features. Moreover, specific training and environmental conditions are associated with an increased risk of developing “sports asthma”, as athletes practicing water and winter sports had, respectively, a three- and ninefold increase in their risk of “sports asthma”, when compared with others.

This study allows for hypothesis generation and has several strengths. Its major strength is the new type of statistical models used to pool and characterize different clusters. This methodological approach makes this study especially useful by retrieving a clear view on asthma phenotypes in athletes. Replication of results in other datasets is important when using these exploratory statistical techniques; and the two asthma patterns obtained in this study are remarkably in accordance with the only previous report, a study relying on different study design and an *a priori* list of selected variables for statistical analysis [8]. Another strength of the present study is its multicentric nature, allowing the inclusion of a large sample of elite athletes, all competing at top levels, some of which are among the world's best in their discipline with several winners of Olympic Gold medals.

Athletes in this study are all competing in an elite level and, therefore, all are more prone to negative consequences of exercise “injuring” airways due to prolonged and repeated

Table 3. Characteristics of asthmatic athletes according with their asthma phenotype and variables in each assigned latent class.

	Total	Atopic asthma, <i>n</i> = 104	Sports asthma, <i>n</i> = 46	<i>p</i>
Male, <i>n</i> (%)	107	81 (78)	26 (57)	0.008^c
Age, median ± IQR in years	–	23.0 ± 12	24.5 ± 8	0.522 ^f
Height, mean ± SD in cm	–	175.4 ± 8.7	176.5 ± 8.7	0.530 ^g
Weight, mean ± SD in kg	–	70.9 ± 11.5	71.4 ± 10.3	0.815 ^g
BMI, mean ± SD in kg/m ²	–	23.0 ± 2.6	22.8 ± 1.9	0.741 ^g
FEV ₁ , mean ± SD in L	–	4.0 ± 0.9	4.1 ± 0.7	0.221 ^g
FEV ₁ , mean ± SD in % predicted	–	98.1 ± 20.4	99.7 ± 21.1	0.640 ^g
FVC, mean ± SD in L	–	5.1 ± 1.0	5.3 ± 1.1	0.413 ^g
FVC, mean ± SD in % predicted	–	108.0 ± 15.4	113.4 ± 15.0	0.084 ^g
FEV ₁ /FVC, mean ± SD	–	77.9 ± 8.9	78.7 ± 11.1	0.649 ^g
<i>Variables used in LCA</i>				
Airflow obstruction ^a				0.036
No	80.5	85.3	69.4	
Yes	19.5	14.7	30.6	
Reversibility ^b				0.023
No	23.4	19.0	39.7	
Yes	76.6	81.0	60.3	
Rhinitis				<0.001
No	64.0	51.5	90.9	
Yes	36.0	48.5	9.1	
Any other allergic disease ^c				<0.001
No	61.5	39.3	87.5	
Yes	38.5	60.7	12.5	
Respiratory symptoms				0.133
No	6.1	4.0	10.7	
Yes	93.9	96.0	89.3	
Asthma treatment				0.017
No	11.9	7.5	22.0	
Yes	88.1	92.5	78.0	
Airway hyperresponsiveness				0.834
No	25.7	25.0	26.9	
Yes	74.3	75.0	73.1	
FE _{NO} ^d				<0.001
Normal	62.8	44.8	84.5	
Increased	37.2	55.2	15.5	
Atopy				<0.001
No	31.0	0	100	
Yes	69.0	100	0	

Bold values indicate *p* < 0.05.

Data presented as percentage of total, except otherwise stated. BMI, body mass index; FE_{NO}, exhaled fraction of nitric oxide; L, liters; FVC, forced vital capacity; FEV₁, forced expiratory volume in one second.

^aDefined as a FEV₁/FVC ratio < 0.70.

^bDefined as an increase in FEV₁ ≥ 200 mL and ≥ 12%.

^cOther allergic diseases include conjunctivitis, urticaria, eczema, anaphylaxis and drug, food and venom allergies, sampled through AQUA questionnaire.

^dDefined as increased if above 25 ppb.

+Chi-square test.

^fMann–Whitney *U* test.

hyperpnoea. For athletes practicing water and winter sports, in addition to frequent episodes of prolonged hyperpnoea, their “occupation” demands exposure to potentially noxious stimuli, such as sport-specific environmental exposures [16]. Keeping in mind the close relation to environmental conditions, one could speculate whether “*sports asthma*” should be classified as a variant of occupational asthma, as recently suggested [16]. This designation could help improve the general idea of this concept of asthma dependent upon environmental factors which are part of an athlete’s occupation. The “*sports asthma*” phenotype is similar to the late-onset phenotype identified among “normal” asthmatics. In many cases, the late-onset phenotype appears to be more severe, less responsive to standard therapy and more related to environmental risk factors [17]. However, “*sports asthma*” tends to improve after cessation of sport participation, in what

concerns airway inflammation and hyperresponsiveness [18,19].

In athletes, atopy has been long recognized to be positively associated with asthma and BHR [20,21]. Moreover, training in cold air [21] and swimming [20] were identified as risk factors for asthma. In both swimmers and cross-country skiers, the prevalence of asthma is known to increase with age [22–24], which is consistent with the hypothesis of “*sports asthma*” occurring throughout the sport career and being induced by cumulative years of exposure to environmental training conditions. The results of our study contribute to confirm that different risk factors, such as atopy and environmental training conditions, result in different patterns of asthma. The effect of these risk factors on determining different underlying mechanisms of asthma should be considered.

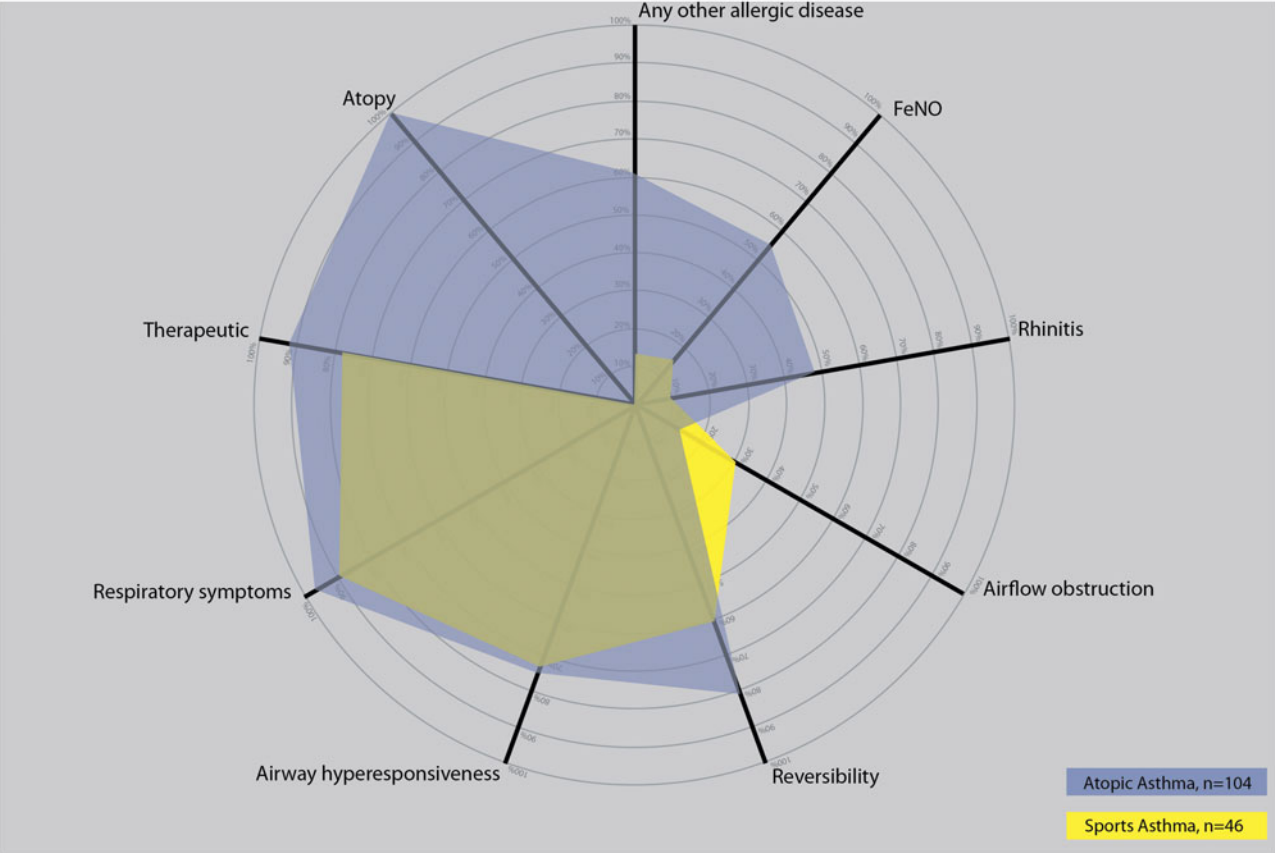


Figure 1. Percent of athletes presenting each of the variables included for LCA.

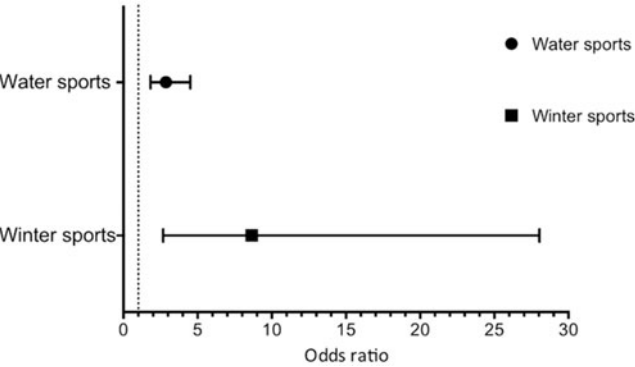


Figure 2. Risk of presenting the “sports asthma” phenotype of athletes practicing water and winter sports, considering other sports as reference.

Defining these distinct phenotypes could lead not only to further understanding the underlying mechanisms of asthma in elite athletes, but also, and most important from a practical point of view, to recognizing that potentially different treatments specifically targeted for defined phenotypic groups are needed. Optimal asthma treatment is a prerequisite for asthmatic athletes because of potential implications in performance, since airway narrowing during exercise could compromise ventilatory capacity and efficiency. However, it has been recognized that the natural course of asthma in athletes is difficult to change by “normal” anti-inflammatory treatment [25]. This highlights the need for a different therapeutic approach in these subjects, which leads us to the

clinical implications of our study. Differences in airway response to bronchodilating drugs have been reported in the literature, and whether athletes with asthma occurring during sports career respond to anti-asthmatic drugs similarly to subjects with classic allergic or with nonallergic asthma has not been extensively studied [7] and needs further research. Most recent guidelines for treatment of exercise-induced bronchoconstriction (EIB) state a strong recommendation for using a short-acting β_2 -agonist before exercise in *all* patients with EIB [26]. However, we have recently shown that elite skiers with asthma respond better to anticholinergic treatment as compared with β_2 -agonists [27]. Differences in parasympathetic bronchial tone were suggested as a possible explanation to why some subjects are responders and other non-responders to anticholinergic drugs [28,29]. It seems, therefore, that the approach of “one treatment fits all” is *insufficient* to comply with the needs of asthmatic athletes.

Despite its several strengths, our study also has some limitations that must be pointed out. The first is the use of different methods (both direct and indirect challenges) to assess BHR in athletes. In the present study, information was collected from medical files, so there was no possibility to homogenize tests performed by athletes in two centers. In any case, final diagnosis was made according to IOC criteria. Another weakness to be noted is the absence of information about age of asthma onset; this limits the extent of our conclusions as we cannot be aware of whether the previous presence of asthma would influence the type of sport chosen. However, based on previous literature, it does not seem to be

the case as the prevalence of asthma is known to increase with age both in swimmers and skiers [22–24]. The interpretation of our results is also limited by the cross-sectional design, which is not able to identify causality; however, it is suitable for hypothesis generation. Thus, the present study should be succeeded by new prospective studies following youth athletes from adolescence until adulthood. Moreover, although motivating, results provided by this exploratory analysis have to be interpreted in context of future work, addressing whether the two phenotypes are relevant from a clinical perspective. Potential phenotypes require prospective validation with clinical interventional trials. A recent trial showed that Norwegian competitive endurance winter athletes respond with a higher reversibility to ipratropium bromide than to inhaled β_2 -agonists [27], helping research in this field to move forward and toward a new direction.

Conclusion

Using LCA on a large sample of top elite athletes from two national databases we were able to identify two patterns of asthma aggregation features based on findings routinely collected in clinical practice: “*atopic asthma*”, defined by the presence of allergic sensitization, rhinitis and other allergic co-morbidities and increased FE_{NO} ; and “*sports asthma*”, defined by the presence of exercise-induced respiratory symptoms and BHR in the absence of allergic features. Moreover, exposure to particular environmental conditions of training and competition was associated with increased risk to develop “*sports asthma*” phenotype: water sports increased the risk by almost three times, whereas in winter sports the risk increased by almost nine times. Recognizing different phenotypes as a result of probable different underlying mechanisms related to environmental exposures highlights the need for distinct targeted treatments. These potential phenotypes require prospective validation by larger clinical interventional trials. If confirmed by other studies, such a model could be useful for the standardization of clinical diagnosis and future treatment of asthmatic athletes.

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Declaration of interest

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References

- Eichenberger PA, Diener SN, Kofmehl R, Spengler CM. Effects of exercise training on airway hyperreactivity in asthma: a systematic review and meta-analysis. *Sports Med* 2013;43:1157–1170.
- Avallone KM, McLeish AC. Asthma and aerobic exercise: a review of the empirical literature. *J Asthma* 2013;50:109–116.
- Fitch K. An overview of asthma and airway hyper-responsiveness in Olympic athletes. *Br J Sports Med* 2012;46:413–416.
- Carlsen K-H, Anderson S, Bjermer L, Bonini S, Brusasco V, Canonica W, Cummiskey J, et al. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. *Allergy* 2008;63:387–403.
- Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012;18:716–725.
- Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: are they real? *Clin Exp Allergy* 2010;40:1130–1141.
- Larsson K, Carlsen K-H, Bonini S. Antiasthmatic drugs: treatment of athletes and exercise-induced bronchoconstriction. European respiratory society monograph: diagnosis, prevention and treatment of exercise-related asthma, respiratory and allergic disorders in sports. *European Respiratory Society*; 2005:73–88. doi: 10.1183/1025448x.00033-008.
- Haahtela T, Malmberg P, Moreira A. Mechanisms of asthma in Olympic athletes – practical implications. *Allergy* 2008;63:685–694.
- Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, Strachan DP, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974–980.
- Haldar P, Pavord I, Shaw D, Berry M, Thomas M, Brightling C, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–224.
- Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D’Agostino R Jr, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med* 2010;181:315–323.
- Medical Commission of the International Olympic Committee. IOC’s medical code. Lausanne: International Olympic Committee; 2002.
- Bonini M, Braido F, Baiardini I, Del Giacco S, Gramiccioni C, Manara M, Tagliapietra G, et al. AQUA: allergy questionnaire for athletes. Development and validation. *Med Sci Sports Exerc* 2009;41:1034–1041.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
- Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, et al. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med* 2008;177:253–260.
- Price OJ, Ansley L, Menzies-Gow A, Cullinan P, Hull JH. Airway dysfunction in elite athletes – an occupational lung disease? *Allergy* 2013;68:1343–1352.
- Peters SP. Asthma phenotypes: nonallergic (intrinsic) asthma. *J Allergy Clin Immunol Pract* 2014;2:650–652.
- Couto M, Andrade P, Pereira M, Araújo J, Moreira P, Delgado L, Moreira A. Effect of competitive swimming on airway inflammation: a 3-yr longitudinal study. *Pediatr Allergy Immunol* 2014;25:193–195.
- Helenius I, Ryttilä P, Sarna S, Lumme A, Helenius M, Remes V, Haahtela T. Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: a 5-year prospective follow-up study of 42 highly trained swimmers. *J Allergy Clin Immunol* 2002;109:962–968.
- Helenius I, Tikkanen H, Sarna S, Haahtela T. Asthma and increased bronchial responsiveness in elite athletes: atopy and sport event as risk factors. *J Allergy Clin Immunol* 1998;101:646–652.
- Helenius I, Tikkanen H, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *Br J Sports Med* 1998;32:125–129.
- Bougault V, Boulet LP. Airway dysfunction in swimmers. *Br J Sports Med* 2012;46:402–406.
- Pedersen L, Lund TK, Barnes PJ, Kharitonov SA, Backer V. Airway responsiveness and inflammation in adolescent elite swimmers. *J Allergy Clin Immunol* 2008;122:322–327.

24. Stensrud T, Mykland KV, Gabrielsen K, Carlsen KH. Bronchial hyperresponsiveness in skiers: field test versus methacholine provocation? *Med Sci Sports Exerc* 2007;39:1681–1686.
25. Helenius I, Lumme A, Haahtela T. Asthma, airway inflammation and treatment in elite athletes. *Sports Med* 2005;35: 565–574.
26. Parsons JP, Hallstrand TS, Mastrorarde JG, Kaminsky DA, Rundell KW, Hull JH, Storms WW, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013;187:1016–1027.
27. Stang J, Couto M, Carlsen K-H, Stensrud T. Increased bronchial parasympathetic tone in elite cross-country and biathlon skiers: a randomised crossover study. *Br J Sports Med* 2015;49:56–61.
28. Knöpfli BH, Bar-Or O, Araújo CGS. Effect of Ipratropium Bromide on EIB in children depends on vagal activity. *Med Sci Sports Exerc* 2005;37:354–359.
29. Knöpfli BH, Luke-Zeitoun M, von Duvillard SP, Burki A, Bachlechner C, Keller H. High incidence of exercise-induced bronchoconstriction in triathletes of the Swiss national team. *Br J Sports Med* 2007;41:486–491.

Supplementary material available online

Online Table: Latent class analysis for asthma features in the elite athlete population.

Number of Classes ^a	Asthma			
	Log L	Number of parameters	BIC	p ^b
1	-503.304	9	1051	
2	-472.636	19	1040	<0.001
3	-457.683	29	1060	0.0614

BIC: Bayesian information criteria; **Log L:** log likelihood; ^a The bold font denotes the best models according to lowest BIC; ^b Lo-Mendell-Rubin likelihood ratio test of model fit to quantify the likelihood that the data can be described by a model with one-less class.