History of multiple allergies and gradual onset running-related injuries in distance runners – SAFER XXXV

Short Title: Allergies and injuries in runners

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Abstract

Objective: To determine if any gradual onset running-related injury (GORRI) was associated with any allergies, multiple allergies (allergies to animals, plants, medication) and allergy medication use.

Design: cross-sectional descriptive study

Setting: Two Oceans Marathons (56km, 21.1km), South Africa

Participants: 76654 race entrants (2012-2015)

Independent Variables: The prevalence (%), and prevalence ratios (PR; 95%CIs) for history of: 1) any allergies 2) multiple allergies to broad categories of allergens (animal material, plant material, allergies to medication, and other allergies) and 3) allergy medication use.

Main Outcome Measures: Using a compulsory online screening questionnaire, the outcome was a history of any GORRIs, and subcategories of GORRIs (muscle, tendon) in the past 12 months. and history of GORRIs (and subtypes of GORRIs) were reported.

Results: In 68258 records with injury and allergy data, the following were significantly associated with reporting any GORRIs: a history of any allergy (PR=2.2; $p<0.0001$), a history of allergies to broad categories of allergens (animal, plant, medication allergy, other) ($p<0.0001$), and the use of allergy medication ($p<0.0001$). A history of any allergies (PR=2.4; $p<0.0001$), all broad categories of allergies, and allergy medication use were significantly associated with muscle ($p<0.0001$) and tendon injuries ($p<0.0001$). The risk of reporting a GORRI increased as the number of reported categories of allergies increased ($p<0.0001$).

Conclusions: A novel finding was the cumulative risk effect with a history of multiple allergies. Further studies should aim to determine the underlying mechanism relating allergies and GORRIs.

Keywords: allergies, epidemiology, overuse injuries, running, predictors

Introduction

Physical activity is an integral component of lifestyle intervention for the prevention and treatment of non-communicable disease.[1-5] Running is a popular form of physical activity, with a growing number of people participating in community-based endurance running events, such as the annual Two Ocean's Marathon held in South Africa.[6] Despite the numerous health benefits associated with running, long-distance running can also lead to medical complications and running-related injuries.[7-11] An injury is defined as any tissue damage or other derangement of normal physical function, resulting from rapid or repetitive transfer of kinetic energy. Injuries can be classified according to the mode of onset: acute – sudden onset, repetitive – sudden onset, repetitive – gradual onset or mixed.[12] Gradual onset running-related injuries (GORRIs) have a multifactorial etiology.[13] Independent risk factors associated with running injuries (including GORRIs) in marathon runners have been identified and include previous injury, weekly training distance, weekly training frequency, and previous race participation.[14,15] Whilst training history has been investigated as a risk factor for GORRIs, medical history not focusing on the musculoskeletal system has received less attention. The prevalence of allergies is higher in athletes than in the general population, particularly in athletes participating in outdoor endurance sports.[16,17] New evidence shows that a history of chronic disease and any allergies are independent risk factors associated with a history of GORRIs in ultramarathon runners, trail runners,[18,19] and cyclists.[20] In the general population, musculoskeletal pathology in adults and children is also associated with allergies. Adults with atopic dermatitis have a higher risk of any injury causing limitation, in comparison to adults without atopic dermatitis.[21,22] In one study, children with multiple allergies also have a higher risk of musculoskeletal problems in comparison to children without allergies.[23]

Currently it is not known if allergies to multiple allergens (e.g. plant material, animal material) or the use of chronic allergy medication is associated with a higher risk of running-related injuries. It is important to identify runners at the highest risk and to optimize medication used to treat allergies. Risk of injury in runners with any allergy may also be specific to the tissue (muscle, tendon, ligament or bone) affected by injury. By knowing if specific injuries, by tissue type, are more common in runners who have any allergy (as well as allergies to multiple allergens), targeted injury prevention strategies can be implemented.

The primary aim was to determine if a history of GORRIs in runners was associated with a history of any allergies, multiple allergies (allergies to multiple allergens) and allergy medication use. Additional aims were to determine if gradual onset injuries affecting two tissue types (muscle and tendon) were associated with a history of allergies to multiple broad categories of allergies and if the risk of a GORRI increased as the number of reported categories of allergies increased.

Methods

Study Design and Ethical Concerns:

This was a cross-sectional descriptive study of data collected prospectively over 4 years (2012-2015). The Research Ethics Committee of the University of Cape Town (REC 009/2011 and 030/2013) approved the protocol and the Faculty of Health Sciences of the University of Pretoria (REC 433/2015 and 292/2021) approved the ongoing analysis of the data.

Setting:

The Two Oceans Marathon races (21.1km and 56km) are held annually in Cape Town, South Africa. The half-marathon is open to any novice runner and the ultra-marathon requires a <5:00 42.2km qualifying time to enter. This study forms part of the SAFER studies (Strategies to Reduce Adverse Medical Events for the Exerciser), which are aimed at minimising the risk of an adverse medical event during exercise.[6]

Participants and Data Collection:

All runners who entered either of the Two Oceans Marathon events (21.1km or 56km) from 2012 to 2015 completed a compulsory pre-race medical screening questionnaire. Entrants who gave informed consent for their data to be used for research purposes were included in this study. The pre-race medical questionnaire was based on the European Association for Cardiovascular Prevention and Rehabilitation recommendations,[24] and was implemented as an initiative to prevent medical encounters on race day and improve the preparation of the medical staff and thus, medical care. The questionnaire consists of 20 questions, with different sub-questions, relating to illness and injury of the athlete (further details regarding the questionnaire have been published previously).[25] Injuries were defined as GORRIs based on the 2020 International Olympic Committee (IOC) consensus statement.[12] Specifically, entrants were asked the following question regarding a history of gradual onset running-related injuries (GORRIs): "*Do you or did you suffer from any symptoms of a CHRONIC running injury (muscles, tendons, bones, ligaments or joints) in the past 12 months or currently?*". An injury for inclusion was defined as "*an injury severe enough to interfere with running, or require treatment eg. use medication or require you to seek medical advice from a health professional*". Participants were asked to provide further information on their injury by indicating what anatomical area and type of structure was injured (muscle, ligament,

tendon, joint, nerve, bone) in a multi-select question. The medical questionnaire contained questions relating to the history of allergies, including subgroups of allergies and the use of chronic medication, including allergy medication. Entrants were asked the following questions pertaining to allergies and medication use: "*Do you suffer from any allergies including a past history of allergies to medication, plant material or animal material?*". If a race entrant answered "yes", they were asked to indicate the broad category/ies of allergy/ies they are allergic to, including allergy to animal material, plant material, medication, or 'other' (deemed multiple allergies if the participant ticked >1 category). Participants were asked if they use chronic medication to treat long-term medical conditions or injuries (multi-select question), which included using allergy medication. Further questions regarding training history (number of years as a recreational runner, average weekly running distance in the last 12 months (km/wk), average training running speed (km/hr)) and chronic disease history were asked. For chronic diseases, ten individual disease groups were asked (risk factors for cardiovascular disease [CVD], history of CVD, symptoms of CVD, endocrine disease, respiratory disease, gastrointestinal disease, nervous system/psychiatric disease, kidney/bladder disease, haematological/ immune disease, and cancer), and from this a chronic disease composite score (out of ten) was calculated.

Outcome Measures:

The main outcome of this study was a history of GORRIs in the past 12 months amongst race entrants. Secondary outcome variables were a history of specific GORRIs related to muscle and tendon (the two commonly injured structure type in this cohort). The following independent variables of interest associated with GORRIs were explored: a history of: 1) any allergies 2) four broad subcategories of allergies (animal material, plant material, allergies to medication, and other allergies) and 3) allergy medication use. A final outcome was the

number of allergies to the four broad categories of allergens (maximum of 4: animal, plant, medication, other) as independent variables to investigate the risk with multiple allergies investigating a "dose-response" relationship between allergies and GORRIs.

Statistical Analysis

Entry data of all entrants and consenting entrants were analyzed using SAS statistical software (version 9.4, Cary NC). The three dependent variables for the models were binary-scaled response variables that reported a history of GORRIs in the past year: (1) any running-related injury, (2) muscle injury, (3) tendon injury. Runners could report up to three injuries in the past year. For some outcomes, notably those with a relatively small number of positive outcomes, problematic modelling situations arise with convergence problems, therefore the Poisson regression model was used with robust standard errors, as well as an associated log link option. All 3 outcomes had the same number of entrants and came from the same control pool of entrants, however for the prevalence modelling of the number of injuries, the control groups differed. The Poisson distribution with the PROC GENMOD statement and an associated log link option were used for all analyses. A repeated statement was included to account for the exchangeable correlation structure as a runner could enter up to four times in either the Ultra marathon or the half-marathon in this 4-year period, also the runner could potentially report more than one injury per year. The three outcome variables for past year injuries were modeled with a history of allergies as independent variables: any allergy as well as specific broad categories of allergies by the following allergens: animal material, plant material, other allergen, allergy to any medication and being on allergy medication. After a runner indicated an allergy for a specific year of entry, the runner was flagged as having a history of this specific allergy for all subsequent entries. Prevalence (% and 95% confidence interval [CIs]), adjusted for sex, age group and race distance with p-values for Type 3

Generalized Estimating Equation-analysis were reported. Finally, as with all previous SAFER papers (specifically a previous paper on GORRIs among Ultra runners)[18] we include a multiple regression model to determine independent risk factors predictive of GORRIs. These independent risk factors included specific allergies, years being a recreational runner, average weekly training distance, average training running speed (km/h) and the chronic disease composite score. This model was again adjusted for sex, age group and race distance. Prevalence ratios (PR and 95% CI) were reported, and the statistical significance level was 0.05, unless otherwise specified.

Results

The total consenting race entrants (n=76654) were similar in age and sex to all race entrants (n=106743), however there were 0.8% more 21.1km entrants in the study population compared to all entrants (Supplementary Table 1).

Table 1: The number of entrants and prevalence (%: 95% CI) of a history of any GORRIs, muscle injuries and tendon injuries in all entrants with injury data (n=75401)

Injury	Total number of Entrants	Number of Entrants with injury (n; %)	Number of injuries	Unadjusted Prevalence of number of injuries % (95%CI)	Adjusted* Prevalence of number of injuries % (95%CI)
Any GORRI	75401	7281 (9.7)	7623	10.8 (10.5-11.1)	11.4 (11.1-11.7)
Muscle injury	75401	2942 (3.9)	2995	3.7 (3.6-3.9)	3.9 (3.7-4.0)
Tendon injury	75401	1965 (2.6)	1985	2.5 (2.4-2.6)	2.5 (2.4-2.6)

GORRI: gradual onset running related injury
*adjusted for sex, age group, race distance

The number of entrants and prevalence (%: 95% CI) of history of any GORRIs, muscle injuries and tendon injuries in all consenting entrants with injury data are shown in Table 1 (n=75401 entrants with and without injuries).

Other recorded structural injuries include ligament (n=978), other (n=591), bone (n=544) and joint (465). The overall unadjusted prevalence for history of GORRI's was 10.8% (95%CI: 10.5-11.1). There were significant differences in the prevalence of any GORRIs, muscle injuries and tendon injuries for race distance, age groups ($p<0.0001$) and to a lesser extent for sex ($p<0.02$) (details in Supplementary Tables 2a-2c). Therefore, all further models include sex, age group and race distance as confounders. The overall adjusted prevalence of GORRIs was 11.4% (95%CI: 11.1-11.7), prevalence of muscle injuries was 3.9% (95%CI: 3.7-4.0), and tendon injuries were 2.5% (2.4-2.6), adjusting for sex, age group and race distance.

Table 2: The number and prevalence (%; 95%CI) of any allergies, broad subcategories of allergies, and allergy medication use in all consenting entrants (n=76654)

Allergy	**Number n #**	**Prevalence (%; 95%CI)**
Any Allergy	9855	12.9 (12.6-13.1)
Broad subcategories of allergies #		
Animal	3648	4.8 (4.6-4.9)
Plant	4037	5.3 (5.1-5.4)
Medication	3463	4.5 (4.4-4.7)
Other Allergies	1784	2.3 (2.2-2.4)
Allergy Medication Use	1602	2.1 (2.0-2.2)

Medication: a reported allergy towards any medication; Allergy medication use: reported use of medication for the treatment of allergies
#Entrants could report more than 1 allergy

The number and prevalence (%; 95%CI) of any allergies, broad subcategories of allergies, and allergy medication use in all consenting entrants (n=76654) is shown in Table 2. The overall prevalence of history of any allergies was 12.9% (95%CI: 12.6-13.1). The prevalence by broad subcategories of allergies was highest for allergy to plants (5.3%; 95%CI: 5.1-5.4), however this was not significantly different to the prevalence of history of animal or medication allergies.

The number, prevalence (%; 95% CI) and PR of race entrants with a history of gradual onset running-related injuries (GORRIs) by any allergies, broad subcategories of allergies and

allergy medication use (adjusted for sex, age group and race distance) is shown in Table 3 (8738 missing data values; n=68258). There was a significantly higher prevalence of a history of GORRIs (PR=2.2; p<0.0001) in race entrants with a history of any allergy in comparison to runners not reporting any allergy. Similarly, race entrants reporting a history of allergy in any of the broad subcategories of allergies (animal material, plant material, and other) had a 2 times higher prevalence of a history of GORRIs (p<0.0001), and a slightly lower PR for allergy medication. There was also a significantly higher prevalence of any GORRI in race entrants who reported use of allergy medication (p<0.0001).

Table 3: The number, prevalence (%; 95% CI) and prevalence ratio of race entrants with a history of any gradual onset running-related injuries (GORRIs) by history of any allergies, broad subcategories of allergies and allergy medication use (adjusted for sex, age group and race distance) (n=68258) (entrants with injury and allergy data, 8738 missing values)

History of Allergy		History of any GORRIs		PR (95% CI)	p-value
		n (7623)#	Prevalence % (95% CI)		
Any Allergy	yes	1740	22.0 (21.0 – 23.1)	2.2 (2.1-2.3)	<0.0001
	no	5883	10.0 (9.7 – 10.3)		
Broad subcategories of allergies					
Animal	yes	694	24.3 (22.5 – 26.2)	2.2 (2.1-2.4)	<0.0001
	no	6929	10.9 (10.6 – 11.1)		
Plant	yes	800	25.3 (23.6 – 27.1)	2.3 (2.2-2.5)	<0.0001
	no	6823	10.8 (10.5 – 11.0)		
Medication	yes	571	19.5 (17.8 – 21.2)	1.8 (1.6-1.9)	<0.0001
	no	7052	11.0 (10.7 – 11.3)		
Other Allergies	yes	377	23.9 (21.3 – 26.7)	2.1 (1.9-2.4)	<0.0001
	no	7246	11.1 (10.8 – 11.4)		
Allergy Medication Use	yes	356	21.7 (19.2 – 24.5)	1.9 (1.7-2.2)	<0.0001
	no	7267	11.2 (10.9 – 11.5)		

Medication: a reported allergy towards any medication; Allergy medication use: reported use of medication for allergies

Number of GORRIs with allergy types are greater than number of entrants with allergy types as entrants could report more than 1 GORRI and report more than 1 allergen subcategory

PR: Prevalence ratio

8738 missing values

Table 4: The number, prevalence (%; 95% CI) and prevalence ratio of race entrants with a history of muscle injuries (n=63630) and tendon injuries (n=62620) by history of any allergies, broad subcategories of allergies and allergy medication use (adjusted for sex, age group and race distance)

History of Allergy		History of Muscle Injuries		PR (95% CI)	p-value
		n (2995)#	Prevalence % (95% CI)		
Any Allergy	yes	681	10.5 (9.7-11.4)	2.4 (2.2 – 2.7)	<0.0001
	no	2314	4.3 (4.2-4.5)		
Broad subcategories of allergies					
Animal	yes	257	11.3 (10.0-12.8)	2.4 (2.1 – 2.7)	<0.0001
	no	2738	4.8 (4.6-5.0)		
Plant	yes	288	11.7 (10.4-13.2)	2.5 (2.2 – 2.8)	<0.0001
	no	2707	4.7 (4.5-4.9)		
Medication	yes	232	9.6 (8.4-11.0)	2.0 (1.7 – 2.3)	<0.0001
	no	2763	4.8 (4.6- 5.0)		
Other Allergies	yes	156	12.6 (10.6 – 14.9)	2.6 (2.2 – 3.1)	<0.0001
	no	2839	4.9 (4.7-5.1)		
Allergy Medication Use	yes	149	12.3 (10.3 – 14.8)	2.5 (2.1 – 3.0)	<0.0001
	no	2846	4.9 (4.7 – 5.1)		
History of Allergy		**History of Tendon Injuries**		**PR (95% CI)**	**p-value**
		n (1985)#	**Prevalence % (95% CI)**		
Any Allergy	yes	462	7.3 (6.6 - 8.0)	2.5 (2.3 – 2.8)	<0.0001
	no	1523	2.9 (2.7 – 3.0)		
Broad subcategories of allergies					
Animal	yes	185	8.4 (7.2 – 9.7)	2.7 (2.3 – 3.1)	<0.0001
	no	1800	3.1 (3.0 – 3.3)		
Plant	yes	231	9.3 (8.2 – 10.7)	3.0 (2.6 – 3.5)	<0.0001
	no	1754	3.1 (2.9 – 3.3)		
Medication	yes	148	6.4 (5.4 – 7.5)	2.0 (1.7 – 2.4)	<0.0001
	no	1837	3.2 (3.0 – 3.4)		
Other Allergies	yes	82	7.6 (6.1 – 9.5)	2.3 (1.9 – 2.9)	<0.0001
	no	1903	3.3 (3.1 – 3.4)		
Allergy Medication Use	yes	71	7.0 (5.4 -8.9)	2.1 (1.6 – 2.7)	<0.0001
	no	1914	3.3 (3.1 – 3.4)		

Medication: a reported allergy towards any medication; Allergy medication use: reported use of medication for allergies
Number of Muscle injuries with allergy types are greater than number of entrants with allergy types as entrants could report more than 1 muscle or tendon injury and report more than 1 allergen subcategory
PR: Prevalence ratio
13366 missing values for muscle injuries
14376 missing values for tendon injuries

The number, prevalence (%; 95% CI) and prevalence ratio of race entrants with a history of muscle and tendon injuries by history of any allergies, broad subcategories of allergies and allergy medication use (adjusted for sex, age group and race distance) is shown in Table 4.

The overall prevalence of any allergy for those with muscle injuries was 10.5%. There was a significantly higher prevalence of a history of muscle injuries in race entrants with any allergies (PR=2.4; p<0.000; 95%CI: 9.7-11.4), including all broad subcategories of allergies and those reported using allergy medication (p<0.0001). The overall prevalence for any allergies for those with tendon injuries was 7.3%. There was a significantly higher prevalence of a history of tendon injuries in race entrants with any allergies (PR=2.5; p<0.0001; 95%CI: 2.7–3.0), including all broad categories of allergies and those reported using allergy medication (p<0.0001).

Prevalence of history of GORRIs and multiple allergies

The prevalence of a history of any GORRI (%; 95% CI) by the number of allergies reported by entrants is presented in Table 5. (Supplementary Table 3 reports further results on the distribution of the number of Allergies in those with GORRIs) The main observation is that as the number of allergies increased, so did the risk of reporting a GORRI (p<0.0001) compared to race entrants who reported no allergies.

Table 5: The prevalence of a history of any GORRI (%; 95% CI) by the number of allergies reported by entrants (adjusted for sex, age group and race distance) (n=68258)

Number of allergies by subcategory of allergies#	Total Number of Entrants (n=68258)	Number of entrants with history of GORRIs (n=7623)	Prevalence of GORRIs % (95%CI)	PR (95%CI)	p-value
0	54310	5935	10.1 (9.8-10.4)	-	
1	4648	1079	19.9 (18.8-21.2)	2.0 (1.9-2.1)	
2	1410	483	26.4 (24.2-28.8)	2.6 (2.4-2.9)	
3 or more	267	128	32.5 (27.8-38.0)	3.2 (2.8-3.8)	<0.0001

#combination of allergy to multiple allergens (animal material, plant material, medication) and other allergy
Number of allergies by subcategory of allergens: 2 vs 1 PR=1.3 p<0.0001; 3-4 vs 1 PR=1.6 p<0.0001; 3-4 vs 2 PR=1.2 p=0.0184;
8738 missing values
PR: Prevalence ratio

Discussion

The main aim of the study was to determine if a history of GORRI in runners was associated with any allergy, multiple broad categories of allergies (plant, animal, medication allergy, other allergy) and allergy medication use. Additional aims were to determine if injuries affecting two tissue types (muscle and tendon) were associated with a history of allergies and if the risk of a GORRI increased as the number of reported categories of allergies increased**.** The main findings of the study were: 1) race entrants who reported any allergy were more likely to report a GORRI (PR=2.2); 2) entrants who reported an allergy to any broad subcategory of allergies were also more likely to report a GORRI (animals; PR=2.2, plants; PR=2.3, allergy to medication; PR=1.8, other allergies PR=2.1), 3) race entrants who reported any allergy and broad categories of allergies were also more likely to report muscle injuries (any allergy PR=2.4); and tendon injuries (any allergies PR=2.5). Finally, we show that there was a "dose-response" relationship between a history of any GORRI and a history of multiple allergies - as the number of allergies increased, so did the risk of reporting a history of any GORRI.

Our first finding is that race entrants who reported any allergies were more likely to report a history of any GORRI. This is in keeping with results from previous studies in trail runners, ultramarathon running race entrants[18,19] and recreational road cyclists,[20] where a history of any GORRI was associated with a history of allergies. We must note that the race distance was controlled for, as the 56km entrants had a higher prevalence of GORRIs compared to 21.1km entrants, most likely due to the larger training and running volume the 56km entrants are exposed to. In this study we report three novel findings: 1) the higher prevalence of any GORRI in running race entrants is associated with a history of subcategories of reported

allergies by allergens (animal, plant, other allergens and medications, minimal difference between subcategories), 2) allergies and subcategories of allergies are associated with muscle and tendon injuries, and 3) we observed "dose-response" relationship between a history of GORRI and multiple allergies in subcategories by allergies (animal material, plant material, medication allergy and other). As the number of reported allergies increased, the risk of a history of GORRI also increased. These findings raise several important questions.

Is there any evidence that allergies are related to musculoskeletal injury in the non-athletic population? Our finding that gradual onset injuries are associated with allergies in the athletic population correlates with reports of higher risk of injuries and musculoskeletal complaints amongst atopic adults and children in the general population.[21,22] Studies show that adults with atopic dermatitis have a higher risk of any injury causing limitation, in comparison to adults without atopic dermatitis.[21,22] In a study looking at self-reported allergic diseases in children and musculoskeletal problems, children with allergies had an increased risk of musculoskeletal problems in comparison to children without allergies, and this association was strengthened by the allergy severity.[23] This is important as it shows allergies are associated with musculoskeletal compromise amongst children and adults, which could translate to GORRIs in athletes.

What are possible pathophysiological mechanisms that can explain the association between allergies and GORRIs in athletes? To date the underlying pathophysiological mechanism/s that could explain the association between allergies and GORRIs are not yet established. Broadly, we believe this may be due to the disease process itself such as the chronic low-grade inflammatory state or the medication used to treat allergies (e.g. antihistamines and corticosteroids) or perhaps a combination of these.

In this study we show that injuries in soft tissues (muscle and tendon) are associated with a history of allergies. Approximately 2% of Achilles tendinopathies are due to inflammatory joint disorders such as Rheumatoid Arthritis resulting from persistent systemic inflammation, which may be low grade and subclinical.[26] A chronic low grade inflammatory state, as seen in other conditions associated with tendinopathies, may therefore be one possible mechanisms to explain the increased risk of sustaining a GORRI in individuals with allergies. In another study, respondents with a history of any allergy or allergic reaction had a 43% greater odds of having low-back pain alone.[27] In this study it has been suggested that the mechanism may be related, at least in part, by alterations in the hypothalamic-pituitary-adrenal (HPA) axis function through the action of cytokines and/or other immune factors. It was suggested that variation in HPA-axis responsiveness could be a factor in the development of chronic pain.[27] Therefore, although speculative, chronic low grade inflammation may be a mechanism to explain our finding that a history of multiple allergies is associated with a higher risk of GORRI.

The potential effect of medications that are used in the treatment of allergies and increased risk of GORRI deserves discussion. Firstly, use of antihistamine medication may be associated with increased risk of GORRI. Histamine is released within skeletal muscle during exercise, resulting in increased local blood flow for several hours post-exercise.[28,29] A recent study showed that taking combined histamine H1 and H2 receptor antagonists had a significant negative effect on time-to-completion of a 10km time-trial in competitive cyclists.[30] This suggests that exercise-induced increases of histamine in skeletal muscle plays an important role in endurance exercise capacity.[30] Histamine blockade may not only have a negative effect on endurance capacity, it may also contribute to an increased risk of gradual onset injuries by potentially influencing blood flow and nutrient delivery to skeletal muscle.

Secondly, use of corticosteroids may also increase risk of GORRIs. Different formulations of corticosteroids (inhaled, intranasal and systemic) are used to treat allergic rhinitis and asthma.[31] Although systemic side effects of non-systemic preparations of corticosteroids are not well documented, when used frequently for a prolonged period, they potentially have the same adverse effects.[32] Glucocorticoid-induced myopathy is an adverse effect of corticosteroid use and is due to decreased protein synthesis and an increased rate of protein catabolism resulting in muscle atrophy.[33] The catabolic effect of corticosteroids on muscle may be a factor to consider for the link between medication used to treat allergies and risk of GORRI's such as muscle injuries. Further studies need to be conducted to determine the cause-effect of the risk factors identified and the underlying mechanism for the relationship between allergies, subgroups of allergies and GORRIs.

Strengths of this study includes a large sample size and high consent rate, making independent risk factor analysis possible using a multivariate risk prediction model. Runners were asked about specific subcategories of allergies in an online questionnaire, allowing further analysis to be conducted and establishing a novel risk factor for GORRIs. The main limitations of this study are that all data are self-reported and both the diagnosis of allergies as well as injuries that could not be verified. The information provided in the medical questionnaire was self-reported and therefore the extent of recall accuracy cannot be determined. Furthermore, this is a cross-sectional study, and we cannot establish a cause-effect relationship between the risk factors identified, as well as the underlying mechanism leading to the association between GORRIs and allergies.

Summary and Conclusions

In a large population size of runners completing 21.1km and 56km races over a 4-year period, we have established that there is an association between a history of GORRIs and self-reported allergies in athletes. We also show that this association holds for subgroups of allergies (animals, plants, medication, other), for specific injuries (muscle and tendon), and that the risk of GORRIs is higher in athletes with multiple allergies. The mechanism behind this association is unknown, it may be due to the underlying inflammatory state in atopic individuals, or due to the medication used over prolonged periods of time to treat allergies. The main clinical implication of the findings in our study are: 1) we identified a subcategory of runners with a history of allergies that are at higher risk of GORRIs, which may require a different approach when advice on increasing training load is given, 2) we recommend obtaining a comprehensive medical history, including a history of allergies and medications used to treat allergies when evaluating a runner presenting with a GORRI, and 3) carefully consider the possibility that chronic low-grade inflammation resulting from allergies and the medications that are used to treat allergies in runners may be associated with an increased risk of GORRI. Our findings may also be used to implement programs to prevent muscle and tendon injuries in runners with a history of allergies. Further causative studies should be conducted to establish a better understanding of this mechanism.

What are the new findings?

- There is a higher prevalence of a history of GORRIs in runners with allergies and any subcategories of allergies (animal, plant, allergy to medication, other allergies)
- There is a higher prevalence of a history of muscle and tendon injuries in runners with allergies and any subcategories of allergies (animal, plant, allergy to medication, other allergies)

- There is a higher prevalence of a history of GORRIs in runners with multiple allergies

Practical Implications

- Runners with allergies represent a subgroup with a higher risk of GORRIs
- Clinicians can consider including a comprehensive history, including all allergies, when evaluating an athlete presenting with a GORRI
- Clinicians should carefully consider the possibility that chronic low-grade inflammation resulting from allergies as well as medications that are used to treat allergies in runners may be associated with an increased risk of GORRI
- More studies should be done focusing on the underlying mechanism relating allergies and GORRIs

References

1. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports. 2015;25(S3):1-72. doi:10.1111/sms.12581
2. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circula. 2007;116(9):1081-93.
3. Khan KM, Thompson AM, Blair SN, et al. Sport and exercise as contributors to the health of nations. Lancet. 2012;380(9836):59-64. doi:10.1016/S0140-6736(12)60865-4
4. Warburton DER, Bredin SSD. Reflections on Physical Activity and Health: What Should We Recommend? Canadian J Cardiol. 2016;32(4):495-504. doi:10.1016/j.cjca.2016.01.024
5. Kohl HW, 3rd, Alkandari JR, Craig CL, et al. The pandemic of physical inactivity: global action for public health. Lancet. 2012;380(9838):294-305. doi:10.1016/S0140-6736(12)60898-8
6. Schwellnus M, Derman W. The quest to reduce the risk of adverse medical events in exercising individuals: Introducing the SAFER (Strategies to reduce Adverse medical events for the ExerciseR) studies. Br J Sports Med. 2014;48(11):869-870. doi:10.1136/bjsports-2014-093606
7. Schwabe K, Schwellnus M, Derman W, Swanevelder S, Jordaan E. Medical complications and deaths in 21 and 56 km road race runners: a 4-year prospective study in 65 865 runners--SAFER study I. Br J Sports Med. 2014;48(11):912-8. doi:10.1136/bjsports-2014-093470

8. Schwabe K, Schwellnus M, Swanevelder S, Jordaan E, Derman W, Bosch A. Leisure athletes at risk of medical complications: outcomes of pre-participation screening among 15,778 endurance runners - SAFER VII. Physician Sportsmed. 2018;46(4):405-413. doi:10.1080/00913847.2018.1505569
9. Schwellnus MP. Premarathon evaluations: is there a role for runner prerace medical screening and education to reduce the risk of medical complications? Curr Sports Med Rep. 2017;16(3):129-136. doi:10.1249/JSR.0000000000000366
10. Fokkema T, Burggraaff R, Hartgens F, et al. Prognosis and prognostic factors of running-related injuries in novice runners: A prospective cohort study. J Sci Med Sport. 2019;22(3):259-263.
11. Fokkema T, van Damme A, Fornerod MWJ, de Vos RJ, Bierma-Zeinstra SMA, van Middelkoop M. Training for a (half-)marathon: Training volume and longest endurance run related to performance and running injuries. Scand J Med Sci Sports. 2020;30(9):1692-1704. doi:10.1111/sms.13725
12. Bahr R, Clarsen B, Derman W, et al. International Olympic Committee consensus statement: methods for recording and reporting of epidemiological data on injury and illness in sport 2020 (including STROBE Extension for Sport Injury and Illness Surveillance (STROBE-SIIS)). Br J Sports Med. 2020;54(7):372-389. doi:10.1136/bjsports-2019-101969
13. Ferber R, Hreljac A, Kendall K. Suspected mechanisms in the cause of overuse running injuries: a clinical review. Sports Health. 2009;1(3):242-246.
14. Besomi M, Leppe J, Mauri-Stecca MV, Hooper TL, Sizer PS. Training volume and previous injury as associated factors for running-related injuries by race distance: A cross-sectional study. J Human Sport Exer. 2019;14(3)doi:10.14198/jhse.2019.143.06
15. Rasmussen CH, Nielsen RO, Juul MS, Rasmussen S. Weekly running volume and risk of running-related injuries among marathon runners. Int J Sports Phys Ther. 2013;8(2):111-20.
16. Thomas S, Wolfarth B, Wittmer C, Nowak D, Radon K, study-Team GAL-O. Self-reported asthma and allergies in top athletes compared to the general population - results of the German part of the GA2LEN-Olympic study 2008. Allerg Asthma Clin Immunol. 2010;6(1):31. doi:10.1186/1710-1492-6-31
17. Perrotta F, Simeon V, Bonini M, et al. Evaluation of allergic diseases, symptom control, and relation to infections in a group of italian elite mountain bikers. Clin J Sport Med. 2020;30(5):465-469.
18. Mokwena PL, Schwellnus MP, Van Rensburg AJ, et al. Chronic disease, allergies, and increased years of running are risk factors predicting gradual onset running-related injuries in ultramarathon runners-SAFER XIX Study in 29 585 Race Entrants. Clin J Sport Med. 2021;doi:10.1097/JSM.0000000000000949
19. Viljoen CT, Sewry N, Schwellnus MP, Janse van Rensburg DC, Swanevelder S, Jordaan E. Independent Risk Factors Predicting Gradual Onset Injury in 2824 Trail Running Race Entrants: SAFER XVIII Study. Wilderness Environ Med. 2021;32(3):293-301. doi:10.1016/j.wem.2021.04.002
20. Du Toit F, Schwellnus M, Wood P, Swanevelder S, Killops J, Jordaan E. History of chronic disease is a novel intrinsic risk factor associated with gradual onset injuries in recreational road cyclists: A cross-sectional study in 21,824 cyclists-SAFER XIV. Phys Therap Sport. 2020;46:137-144.
21. Silverberg JI. Selected comorbidities of atopic dermatitis: Atopy, neuropsychiatric, and musculoskeletal disorders. Clin Dermatol. 2017;35(4):360-366. doi:10.1016/j.clindermatol.2017.03.008

22. Garg N, Silverberg JI. Association between eczema and increased fracture and bone or joint injury in adults: a US population-based study. JAMA Dermatol. 2015;151(1):33-41. doi:10.1001/jamadermatol.2014.2098
23. Barrick BJ, Jalan S, Tollefson MM, et al. Associations of self-reported allergic diseases and musculoskeletal problems in children: A US population-based study. Ann Allerg Asthma Immunol. 2017;119(2):170-176. doi:10.1016/j.anai.2017.06.002
24. Borjesson M, Urhausen A, Kouidi E, et al. Cardiovascular evaluation of middle-aged/ senior individuals engaged in leisure-time sport activities: position stand from the sections of exercise physiology and sports cardiology of the European Association of Cardiovascular Prevention and Rehabilitation. Euro J Cardiovasc Prev Rehabil. 2011;18(3):446-58. doi:10.1097/HJR.0b013e32833bo969
25. Schwellnus M, Swanevelder S, Derman W, Borjesson M, Schwabe K, Jordaan E. Prerace medical screening and education reduce medical encounters in distance road races: SAFER VIII study in 153 208 race starters. Br J Sports Med. 2019;53(10):634-639. doi:10.1136/bjsports-2018-099275
26. Kabore C, Salier Q, Geerts P, Kaux JF. Management of systemic risk factors for chronic tendinopathy. Science et Sports. 2021;36(1):5-15. doi:10.1016/j.scispo.2020.12.003
27. Hurwitz EL, Morgenstern H. Cross-sectional associations of asthma, hay fever, and other allergies with major depression and low-back pain among adults aged 20–39 years in the United States. Am J Epidemiol. 1999;150(10):1107-1116.
28. Romero SA, McCord JL, Ely MR, et al. Mast cell degranulation and de novo histamine formation contribute to sustained postexercise vasodilation in humans. J Appl Physiol. 2017;122(3):603-610. doi:10.1152/japplphysiol.00633.2016
29. McCord JL, Halliwill JR. H1 and H2 receptors mediate postexercise hyperemia in sedentary and endurance exercise-trained men and women. J Appl Physiol. 2006;101(6):1693-701.
30. Ely MR, Sieck DC, Mangum JE, et al. Histamine-Receptor Antagonists Slow 10-km Cycling Performance in Competitive Cyclists. Med Sci Sports Exerc. 2019;51(7):1487-1497. doi:10.1249/MSS.0000000000001911
31. Parle-Pechera S, Powers L, St Anna L. Intranasal steroids vs antihistamines: Which is better for seasonal allergies and conjunctivitis? J Fam Pract. 2012;61(7):429-431.
32. Gupta R, Fonacier LS. Adverse Effects of Nonsystemic Steroids (Inhaled, Intranasal, and Cutaneous): a Review of the Literature and Suggested Monitoring Tool. Curr Allergy Asthma Rep. 2016;16(6):44. doi:10.1007/s11882-016-0620-y
33. Pereira RMR, Freire de Carvalho J. Glucocorticoid-induced myopathy. Joint Bone Spine. 2011;78(1):41-4. doi:10.1016/j.jbspin.2010.02.025