Patellofemoral Pain Syndrome Is Associated With Chronic Disease and Allergies in 60 997 Distance Runner Race Entrants: SAFER XXX Study

Tsungai Tirivashe Marandure, MD,*† Martin P. Schwellnus, MBBCh, MSc, MD,†‡§ Catharina Grant, PhD,* Audrey Jansen van Rensburg, PhD,* Esme` Jordaan, MSc,{‖ and Pieter Boer, PhD**

Abstract

Objective: Patellofemoral pain syndrome (PFPS) is a common running-related injury. Independent risk factors associated with PFPS have not been described in a large cohort of distance runners. Design: Descriptive, cross-sectional study. Setting: 21.1 and 56 km Two Oceans Marathon races (2012-2015). Participants: 60 997 race entrants. Assessment of risk factors: Participants completed a compulsory prerace medical screening questionnaire (history of PFPS in the past 12 months, n 5 362; no injury history, n 5 60 635). Selected risk factors associated with a history of PFPS were explored using univariate & multivariate analyses: demographics, training/running variables, history of chronic diseases (composite chronic disease score), and any allergy. Main Outcome Measures: Prevalence ratios (PRs, 95% confidence intervals). Results: Risk factors associated with PFPS (univariate analysis) were increased years of recreational running (PR 5 1.09; *P* 5 0.0107), older age (50 years), and chronic diseases (PR . 2): gastrointestinal disease (PR 5 5.06; *P* , 0.0001), cardiovascular disease (CVD) (PR 5 3.28; *P* , 0.0001), nervous system/psychiatric disease (PR 5 3.04; *P* , 0.0001), cancer (PR 5 2.83; *P* 5 0.0005), risk factors for CVD (PR 5 2.42; *P* , 0.0001), symptoms of CVD (PR 5 2.38; *P* 5 0.0397), and respiratory disease (PR 5 2.00; *P* , 0.0001). Independent risk factors (multivariate analysis) associated with PFPS (adjusted for age, sex, and race distance) were a higher chronic disease composite score (PR 5 2.68 increased risk for every 2 additional chronic diseases; *P* , 0.0001) and a history of allergies (PR 5 2.33; *P* , 0.0001). Conclusions: Novel independent risk factors associated with PFPS in distance runners are a history of multiple chronic diseases and a history of allergies. Identification of chronic diseases and allergies should be considered as part of the clinical assessment of a runner presenting with a history of PFPS.

Key Words: patellofemoral pain, endurance running, risk factors, chronic disease, ultramarathon, gradual onset running injury

INTRODUCTION

Regular exercise is recommended for the prevention and management of noncommunicable diseases.[1,2] In the past 3 decades, participation in mass community-based endurance sports events, including distance running events, has increased.[3] Running is associated with the risk of developing a gradual onset running-related injury (GORRI) with a reported annual incidence of lower limb injury in recreational runners of 11% to 85%.[4] Patellofemoral pain syndrome (PFPS) is one of the most common gradual onset injuries in runners training for and participating in longer distance endurance races[5] and accounts for up to 25% of running injuries.[6] Patellofemoral pain syndrome can be defined as pain "around or behind the patella which is aggravated by at least one activity that loads the patellofemoral joint during weight-bearing on a flexed knee."[7] To date, several biomechanical (kinetic and kinematic) risk factors possibly associated with PFPS in physically active individuals have been highlighted.[8] Intrinsic (age and sex)[9,10]

and extrinsic (training-related variables)[11] risk factors have been explored in some studies but are limited by the small number of participants/sample sizes and the inclusion of a limited number of possible risk factors. Few studies used multivariable analyses to identify independent risk factors.[9,12–14] We recently reported an association between both GORRI[15–17] and recurrent running-related injuries and chronic diseases or allergies.[18] More older runners enter distance running events, and these runners often have chronic conditions such as cardiovascular disease (CVD), diabetes, and other diseases. Patellofemoral pain syndrome is a common injury,[6,12] but chronic disease and allergies as possible risk factors associated with PFPS have not been investigated.

The aim of this study was to identify independent risk factors associated with a history of PFPS in a large cohort of distance runners (21.1 and 56 km). Risk factors included runner demographics (sex, age group, and race distance), training-related variables (years of recreational running, weekly running distance, and running speed), and history of chronic disease or allergies.

METHODS

Study Design

This is a descriptive, cross-sectional study with analysis of data collected prospectively and forms part of the SAFER (Strategies to reduce Adverse medical events For the ExerciseR) studies.[19]

Participants and Demographics

All registered participants for the 21.1 and 56 km Two Oceans Marathon distances during 2012 to 2015 were included. In total, 106 743 runners entered the race over 4 years; of these, 76 654 (71.8%) entrants (44 042 males: 32 612 females) gave consent for their data to be used. Research ethics approval was received from the University of Cape Town (REC009/2011) and the University of Pretoria (Ref. 433/2015 and 613/2019) Ethics Committees before the onset of the study.

Online Prerace Medical Screening Questionnaire

The Two Oceans Marathon event organizers introduced a mandatory prerace medical screening questionnaire. We previously reported details on its development and contents.[20,21] The questionnaire was based on the European Society of Cardiology and the European Association of Cardiovascular Prevention and Rehabilitation guidelines for the pre-exercise evaluation of active persons.[22,23] In addition, training over the past 12 months, injury history, and history of chronic diseases or allergies were included.[20,21]

All entrants were requested to report demographics, training/running history (years of recreational running, average weekly training/running distance in the past 12 months, and average training/running speed), history of chronic disease (risk factors for CVD, history of CVD, symptoms of CVD, endocrine disease, respiratory disease, gastrointestinal disease, nervous system/psychiatric disease, kidney/bladder disease, hematological/immune disease, and cancer), and history of any allergies.[16]

Gradual onset injuries are classified as injuries resulting from cumulative stress-related changes to the involved anatomical structure or area.[24] Entrants answered the following specific question on running injuries: "Do you or did you suffer from any symptoms of a running injury (muscles, tendons, bones, ligaments, or joints) in the past 12 months or currently?" A "yes" response prompted further questions including the specific running injury and the treatment for the injury. Responses to these questions were used to define the study groups.

Definition of Study Groups

Control Group

Entrants who responded "no" to the question related to a running injury in the past 12 months, formed our noninjured control group. Of the 76 654 consenting entrants, 60 635 responded "no."

Patellofemoral Pain Syndrome Group

Entrants who responded "yes" to the question related to a running injury in the past 12 months, were required to specify any of the following common injuries: PFPS, iliotibial band, plantar fasciitis, Achilles tendon injury, lower back pain, hip muscle injury (including gluteus/buttock muscles), hamstring injury, quadriceps muscle injury, calf muscle injury, shin splints (bone), shin splints (muscle/tendon), lower leg compartment syndrome, foot pain, heel pain, or other injury. A total of 375 entrants indicated they had "patellofemoral pain" in the past 12 months and were considered for possible inclusion in the history of PFPS group. The accuracy of the self-reported diagnosis of injury was improved by the answers from a question on treatment. In the questionnaire, entrants specified the treatment methods for their selected injury from a list. The list included rest, tablets, stretches, cortisone injection, physiotherapy, other injection, surgery, orthotics, strengthening exercises, and equipment change. The only interventions that could be self-prescribed and self-applied were rest, stretches, and equipment change. If an entrant selected one or more interventions for PFPS injury that could only be prescribed or applied by a health care professional, the self-reported diagnosis was considered "verified." Of the 375 entrants who selected "patellofemoral pain," 362 entrants (96.5%) were in the category where the runner consulted a health care professional. In these cases, we considered the diagnosis of a history of PFPS to be "verified." These entrants were included in the PFPS group.

Main Outcome Variables

The primary outcome was a history of PFPS in the past 12 months among race entrants. The following main categories of risk factors associated with PFPS were explored in a multivariate model: (1) runner demographics, (2) training-related variables, and (3) history *of chronic disease* or *any allergies*. A chronic disease composite score was calculated by combining the 10 chronic disease variables (risk factors for CVD, history of CVD, symptoms of CVD, endocrine disease, respiratory disease, gastrointestinal disease, nervous system/psychiatric disease, kidney/bladder disease, hematological/immune disease, and cancer) to present a single score based on the risk of an increase in the number of chronic diseases.[16,25]

We acknowledge that reporting the above-listed variables as potential risk factors associated with PFPS, we cannot propose any causal inference. We use the term "associated with" to refer to the relationship between these potential risk predictors and PFPS, but the association does not imply a cause–effect relationship.[26]

Statistical Data Analysis

All race entrant data were entered into a database and analyzed using SAS statistical software (version 9.4, Cary, NC). Only data of consenting entrants were used for analysis. The dependent variable in the model was the binary-scaled response variable related to the question regarding PFPS. In some cases, modelling situations arose with convergence problems, and consequently, Poisson regression with robust standard errors was used and the various models included the specified independent variables of interest. Poisson regression using a log link was used for analysis. *P* values for Type 3 generalized estimating equation analysis were reported. A repeated statement was included to account for the exchangeable correlation structure as one runner could report more than one injury per year. In addition, the same entrant could have entered and started the race for each year or multiple years recorded in this period.

Prevalence ratios (PRs) were calculated as the measure of association. Univariate unadjusted prevalence (% and 95% confidence intervals [CIs]) and PR were reported for runner demographics, training/running history, history of chronic disease, and history of any allergies. Entrants reporting other specific injuries and nonverified PFPS injuries were excluded from the analyses, resulting in a sample of 60 997. Overall prevalence and the assessment of univariate risk factors were calculated using this sample. A multiple regression model was performed to identify independent factors associated with a history of PFPS. The demographic, chronic disease, and allergy history variables were entered into the model as categorical variables. The training and running variables were entered into the model as continuous variables, and the prevalence of a history of PFPS (% and 95% CIs) were reported at the first quartile, median, and third quartile for these variables. Initially, the multiple regression model included all the significant univariate risk factors (P , 0.01). The results for the final model only included the retained significant risk factors. The statistical significance level was 1%, and the marginal significance was between 1% and 5%.

RESULTS

Profile of Study Participants and All Entrants

Of the 106 743 race entrants, 76 654 (71.8%) gave consent to participate in this study and 60 997 were included in this study (Table 1). The demographics of all race entrants were compared with all consenting entrants in this study.

The sex and age profile of all consenting race entrants was similar to that of all race entrants. The number of consenting race entrants in the 21.1 km race was significantly more (P 5 0.0011) compared to all race entrants in the 56 km category.

Risk Factors Associated with a History of Patellofemoral Pain Syndrome (Univariate Analysis)

Runner Demographics (Sex, Age, and Race Distance)

A total of 337 individual race entrants reported 362 verified PFPS injuries. The period (12 months) prevalence of PFPS was 0.61% (95% CI, 0.54-0.68). The number (n), prevalence (%; with 95% CI), and PR (with 95% CI) of race entrants with a history of PFPS by sex, age group, and race distance are summarized in Table 2.

The prevalence of a history of PFPS in female versus male race entrants (PR 5 1.03; P 5 0.8177) and for the 56 km versus 21.1 km race distances (PR 5 1.24; P 5 0.0578) were not significantly different. There was a significantly lower prevalence of a history of PFPS in the #30 years, (PR 5 0.67, P 5 0.0158), 31 to 40 years (PR 5 0.71, P 5 0.0326), and 41 to 50 years (PR 5 0.51, P , 0.0001) age groups compared with the .50 years group.

Training-Related Variables (years of Recreational Running, Weekly Running Distance, and Running Speed)

The prevalence (%; with 95% CI) and unadjusted PR (with 95% CI) of entrants with a history of PFPS by training-related variables are summarized in Table 3.

TABLE 1. Profile of all Race Entrants, all Consenting Entrants, and Participants in This Study by Sex, Age Groups, and Race Distance

	All Race Entrants (n 5 106 743)		All Consenting Race Entrants (n 5 76 654)		Study Participants (n 5 60 997)		
	n	%	n	%	n	%	*P**
Sex							
Males	61 815	57.9	44 042	57.5	34 706	56.9	0.0520
Females	44 928	42.1	32 612	42.5	26 291	43.1	
Age groups, yrs							
#30	27 710	26.0	20 168	26.3	16 909	27.7	0.3643
31-40	35 049	32.8	25 045	32.7	20 011	32.8	
41-50	26 964	25.3	19 340	25.2	14 997	24.6	
.50	17 020	15.9	12 101	15.8	9080	14.9	
Race distance, km							
21.1	64 740	60.7	47 069	61.4	39 061	64.0	0.0011†
56	42 003	39.4	29 585	38.6	21 936	36.0	

** All race entrants versus all consenting race entrants.*

† Significance between all race entrants versus all consenting race entrants in the race distance categories.

TABLE 2. Number (n), Prevalence (%; 95% CI), and PR (95% CI) of Participating Race Entrants (n 5 60 997) and Race Entrants With a History of PFPS (n 5 362) by Sex, Age Groups, and Race Distance

Characteristics	Participating Race Entrants (n 5 60 997)	History of PFPS Group (n 5 362)			
	n	n	Prevalence % (95% CI)	PR (95% CI)	*P*
Sex					
Male	34 706	200	0.60 (0.52-0.70)	1.03 (0.82-1.29)	0.8177*
Female	26 291	162	0.62 (0.52-0.73)		
Age groups, yrs					
#30	16 909	99	0.59 (0.48-0.72)	0.67 (0.49-0.93)	0.0158†
31-40	20 011	123	0.62 (0.52-0.75)	0.71 (0.52-0.97)	0.0326‡
41-50	14 997	62	0.45 (0.35-0.58)	0.51 (0.36-0.73)	0.0001§
.50	9080	78	0.87 (0.68-1.12)	Reference group	
Race distance, km					
21.1	39 061	216	0.56 (0.48-0.65)	1.24 (0.99-1.56)	0.0578
56	21 936	146	0.70 (0.58-0.83)		

** Comparing proportion of woman to man.*
† Significance between age groups .50 versus #30.
‡ Significance between age groups .50 versus 31-40.
§ Significance between age groups .50 versus 41-50.
%, % out of total; n, number of entrants in each category; P, P *value comparing the PFPS runners with the participating race entrants in sex, race distance, and age groups.*

An increased number of years of recreational running was associated with a higher prevalence of a history of PFPS (PR 5 1.09, a 9% increase in risk for every 5-year increase in running; *P* 5 0.0107). An increased running speed was associated with a marginal lower prevalence of a history of PFPS (PR 5 0.95, a 5% decrease in risk for every 1 km/h increase in running speed; *P* 5 0.0456). Average weekly running distance in the past 12 months was not associated with a history of PFPS (*P* 5 0.5150).

History of Underlying Chronic Disease and Allergies

The number (n), prevalence (%; with 95% CI), and unadjusted PR (with 95% CI) of entrants by history of chronic disease and allergies are summarized in Table 4.

Several specific chronic disease variables were significantly associated with an increased prevalence (PR . 2) of a history of PFPS in race entrants. These, in decreasing order of PR, include a history of any gastrointestinal disease (PR 5 5.06; *P* , 0.0001), any history of CVD (PR 5 3.28; *P* , 0.0001), any nervous system/psychiatric disease (PR 5 3.04; *P* , 0.0001), any cancer (PR 5 2.83; *P* 5 0.0005), any risk factors for CVD (PR 5 2.42; *P* , 0.0001), any symptoms for CVD (PR 5 2.38; *P* 5 0.0397), and any respiratory disease (PR 5 2.0; *P* , 0.0001). In addition to chronic disease, a history of any allergies (PR 5 3.02; *P* , 0.0001) was significantly associated with a higher prevalence of a history of PFPS in race entrants.

The relationship between an increasing number of chronic diseases (chronic disease composite score) and the prevalence

TABLE 3. Prevalence (%; 95% CI) and Unadjusted PR (95% CI) of Entrants With a History of PFPS by Training-Related Variables (Years of Recreational Running, Weekly Running Distance, and Running Speed)

Running, Training/Racing History	Points in the Continuous variable*	Consenting Race Entrants Reporting PFPS (n 5 362)		
		Prevalence % (95% CI)	PR (95% CI)	*P*
Years of recreational running (years)	3 yrs	0.54 (0.47-0.63)	1.09 (1.02-1.17)†	0.0107
	6 yrs	0.57 (0.51-0.65)		
	13 yrs	0.65 (0.58-0.74)		
Average weekly training/running distance in the past 12 months (km/wk)	20 km/wk	0.62 (0.55-0.71)	0.99 (0.97-1.01)‡	0.5150
	35 km/wk	0.61 (0.54-0.68)		
	50 km/wk	0.60 (0.52-0.68)		
Average training/running speed (km/h)	9 km/h	0.65 (0.57-0.74)	0.95 (0.91-1.00)§	0.0456
	10 km/h	0.62 (0.55-0.70)		
	11 km/h	0.59 (0.53-0.67)		

** Points on the continuous variables are the first quartile, median, and third quartile for each training variable.*
† Average increase in risk for every 5 years increase as a runner.
‡ Average decrease in risk for every 5 km increase in running distance per week.
§ Average decrease in risk for every 1 km/h increase in running speed.

TABLE 4. Number (n), Prevalence (%; With 95% CI), and Unadjusted PR (With 95% CI) of Entrants With a History of PFPS by History of Chronic Disease and Allergies

Characteristics		All Consenting Entrants (n 5 60 997)	Consenting Race Entrants Reporting a History of PFPS (n 5 362)			
History of Chronic Disease		n	n	Prevalence (%) (95% CI)	PR (95% CI)	*P*
Chronic disease composite score (0-10)*	0 chronic diseases	N/A		0.46 (0.40-0.52)	3.15 (2.63-3.76)†	,0.0001
	2 chronic diseases			1.45 (1.23-1.70)		
	4 chronic diseases			4.56 (3.33-6.25)		
1. Any risk factor for CVD	Yes	6476	82	1.28 (1.02-1.61)	2.42 (1.88-3.13)	,0.0001
	No	54 521	280	0.53 (0.47-0.60)		
2. Any history of CVD	Yes	917	19	1.92 (1.18-3.14)	3.28 (1.98-5.41)	,0.0001
	No	60 080	343	0.59 (0.52-0.67)		
3. Any symptoms of CVD	Yes	538	9	1.43 (0.63-3.24)	2.38 (1.04-5.45)	0.0397
	No	60 459	353	0.60 (0.53-0.67)		
4. Any endocrine disease	Yes	1521	17	1.12 (0.67-1.88)	1.89 (1.11-3.21)	0.0184
	No	59 476	345	0.59 (0.53-0.67)		
5. Any respiratory disease	Yes	4758	54	1.13 (0.84-1.51)	2.00 (1.46-2.75)	,0.0001
	No	56 239	308	0.56 (0.50-0.64)		
6. Any GIT disease	Yes	1231	39	2.81 (1.95-4.06)	5.06 (3.45-7.42)	,0.0001
	No	59 766	323	0.56 (0.49-0.63)		
7. Any nervous system/psychiatric disease	Yes	1164	19	1.78 (1.17-2.69)	3.04 (1.98-4.67)	,0.0001
	No	59 833	343	0.58 (0.52-0.66)		
8. Any kidney/bladder disease	Yes	699	8	1.10 (0.50-2.38)	1.82 (0.83-3.99)	0.1342
	No	60 298	354	0.60 (0.54-0.67)		
9. Any hematological/immune disease	Yes	399	6	1.43 (0.58-3.55)	2.38 (0.95-5.93)	0.0632
	No	60 598	356	0.60 (0.54-0.67)		
10. Any cancer	Yes	859	14	1.68 (0.94-2.98)	2.83 (1.58-5.09)	0.0005
	No	60 138	348	0.59 (0.53-0.66)		
History of allergies						
Any allergies	Yes	5140	82	1.56 (1.24-1.97)	3.02 (2.32-3.92)	,0.0001
	No	55 857	280	0.52 (0.46-0.59)		

%, % out of total; GIT, gastrointestinal disease.
** Continuous variable, therefore, no number of participants in the groups.*
† Average increase in risk for every 2 additional chronic diseases.

of a history of PFPS is shown in Figure 1. For every 2 additional chronic diseases, the prevalence of a history of PFPS increases 3.2 times (P , 0.0001).

Independent Risk Factors Associated with a History of Patellofemoral Pain Syndrome (Multivariate Analysis)

In a multivariate analysis, the independent risk factors (adjusted for age, sex, and race distance) associated with a history of PFPS in the past 12 months in race entrants were a higher chronic disease composite score with a PR of 2.68 (95% CI, 2.22-3.24) times increased risk for every 2 additional chronic diseases; P , 0.0001) and a history of reporting any allergies (PR 5 2.33; 95% CI, 1.75-3.11 (P , 0.0001).

DISCUSSION

The aim of the study was to identify the independent risk factors associated with a history of PFPS in race entrants. The main findings of this study were (1) an increased number of years of recreational running and older age (older than 50 years) were associated with a history of PFPS and (2) a higher chronic disease composite score and a history of any allergies were 2 novel independent risk factors associated with a history of PFPS in distance runners.

Increased years of running was associated with a higher prevalence of a history of PFPS (PR 5 1.09 for every additional 5 years of recreational running), but this has not been reported in previous studies. Some studies analyzed the relationship between training load and PFPS with no positive association.[11] We demonstrate a 50% higher prevalence of a history of PFPS in runners older than 50 years compared with runners 30 years or younger. Older age as a risk factor associated with PFPS has not been widely published. One study reported that younger (18-35 years) inexperienced runners had a higher prevalence of PFPS compared with older, more experienced runners (36-55 years).[9] In that study, the sample size in the older age group (36-55 years) was small and

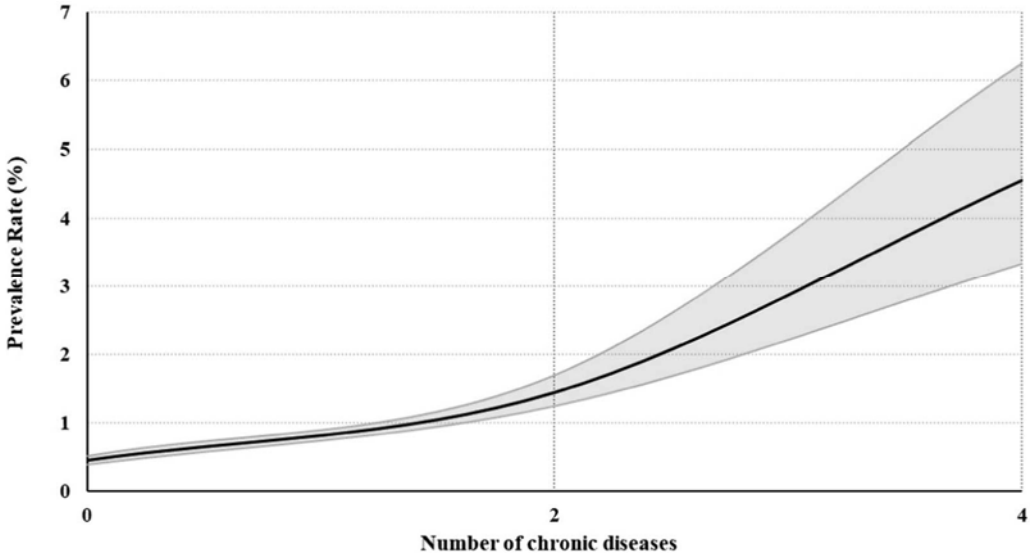

Figure 1. Relationship between prevalence of a history of PFPS and the number of chronic diseases (chronic disease composite score) (shaded area is 95% CI).

no runners older than 55 years were included. Older age and increased years of running may be related to increased frequency of loading the patellofemoral joint, causing injury.

A novel finding of our study was the strong association between a history of chronic diseases and a history of PFPS in race entrants. This finding is in agreement with data we recently published showing an association between all GORRIs and a history of multiple chronic diseases in several cohorts of endurance athletes, including ultramarathon runners,[16] trail runners,[15] and recreational road cyclists.[27] We also reported an association between chronic disease history and one specific running injury, medial tibial stress syndrome (MTSS).[17] From our univariate analysis, specific chronic disease variables are associated with an increased prevalence of a history of PFPS in distance runners. We hypothesize that several potential mechanisms could account for this observation. The first possibility is that increased risk is related to the disease/s process itself. There is a well-documented association between specific chronic disease entities and pathology in tissues such as tendons, ligaments, and muscles. For example, metabolic syndrome, characterized by a prediabetic state, is associated with chronic low-grade inflammation in tissues and is directly linked to tendinopathy.[28,29] Less frequently occurring metabolic disorders such as alkaptonuria have also been associated with tendinopathies.[30] Other direct disease links include cancer-associated idiopathic inflammatory myopathies.[31,32]

A second possible mechanism is related to the medication/s used in the treatment of chronic diseases. For example, a key therapeutic agent in the management of gastroesophageal reflux is a proton pump inhibitor (PPI). PPIs have a negative effect on bone remodelling and mineralization[33] and this may increase the risk of bone stress injuries and fractures,[33] particularly in physically active individuals. Similarly, other drugs used to manage chronic conditions can have a systemic effect on the musculoskeletal system contributing to an increased risk of injury. Other examples include myopathy related to corticosteroid use for chronic respiratory conditions,[34] and statins, which are commonly prescribed for hypercholesterolemia, are associated with myopathy or tendinopathy.[35,36]

A second novel finding of our study was the strong association between a history of allergies and a history of PFPS in race entrants. This correlates with data we recently published showing an association between all GORRI and a history of allergies in several cohorts of endurance athletes including ultramarathon runners,[16] trail runners,[15] and recreational road cyclists.[27] We also reported an association between a history of allergies and MTSS.[17] Allergic reactions are fundamentally an inflammatory response by the body, and the multicellular, multisystemic nature of this reaction may lead to arthralgia and myalgia. Inflammation also stimulates sensory nerves, producing the symptom of pain.[37]

Allergic inflammation involves epithelial and fibroblast cells, some of which make up joint surfaces. These cells become sources of inflammatory mediators such as cytokines, propagating the inflammatory response. Inflammation of surfaces within the patellofemoral joint compromise its anatomy and alter how it handles the repetitive loading associated with running, and its adaptive capability, thus predisposing the athlete to pathology such as PFPS.[38] In addition, endogenous anti-inflammatory mechanisms may be defective in allergic disease perpetuating the inflammatory process.[38] Repetitive exposure to allergens therefore results in chronic allergic inflammation, increasing the risk of aggravating gradual onset injuries such as PFPS. Finally, there has been considerable interest in the role of histamine during acute exercise and adaptation to exercise training.[39–41] Histamine receptor blockers that are used in the management of allergies can influence recovery and may be associated with increased risk of gradual onset injury.

This is a large study where multiple risk factors associated with a history of PFPS were explored in a multivariate model. There was a high (71.81%) consent rate, and our sample was representative of all race entrants. However, a limitation is that injury and training data are self-reported, potentially introducing recall bias. Furthermore, injury diagnosis was not confirmed by a health professional. We addressed this

limitation by only including entrants in the PFPS group if their treatment was administered by a health care professional. Finally, we recognize that this is a cross-sectional study and we cannot establish a cause–effect relationship between any of the identified risk factors and PFPS. The cause–effect relationship needs to be explored in future studies.

SUMMARY AND CONCLUSIONS

The main independent risk factors associated with a history of PFPS in race entrants were a higher chronic disease composite score and a history of any allergies. We acknowledge that the risk factors associated with a history of PFPS are multifactorial and that the cause–effect relationship need to be explored in future studies. Of clinical importance is that physicians take note of the potential association between a history of PFPS injuries and certain chronic diseases and allergies when managing athletes with PFPS or when recommending running injury prevention programs. We do recommend that a medical evaluation to identify chronic diseases and allergies should be considered as part of the clinical assessment of a runner presenting with a history of PFPS. In addition, in patients with a chronic disease who are advised to start a walk/jog program, specific injury prevention strategies to reduce the risk of PFPS should be implemented. This is particularly relevant in patients with a history of chronic disease because they benefit greatly from regular physical activities such as running.[1]

ACKNOWLEDGMENTS

The authors thank the Two Oceans medical staff, the Two Oceans Marathon organizers, and all the race entrants participating in this study.

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;25:1–72.
2. *Global Action Plan on Physical Activity 2018–2030: More Active People for a Healthier World*. Geneva: World Health Organisation; 2018; Available at: https://www.who.int/publications/i/item/9789241514187. Accessed February 3, 2022.
3. Murphy N, Lane A, Bauman A. Leveraging mass participation events for sustainable health legacy. *Leis Stud*. 2015;34:758–766.
4. Nielsen RO, Buist I, Sørensen H, et al. Training errors and running related injuries: a systematic review. *Int J Sports Phys Ther*. 2012;7:58–75.
5. Fredericson M, Misra AK. Epidemiology and aetiology of marathon running injuries. *Sports Med*. 2007;37:437–439.
6. Mullaney MJ, Fukunaga T. Current concepts and treatment of patellofemoral compressive issues. *Int J Sports Phys Ther*. 2016;11:891–902.
7. Crossley KM, Stefanik JJ, Selfe J, et al. 2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 1: terminology, definitions, clinical examination, natural history, patellofemoral osteoarthritis and patient-reported outcome measures. *Br J Sports Med*. 2016;50:839–843.
8. Halabchi F, Abolhasani M, Mirshahi M, et al. Patellofemoral pain in athletes: clinical perspectives. *Open Access J Sports Med*. 2017;8: 189–203.
9. Kunene SH, Ramklass S, Taukobong NP. Anterior knee pain and its intrinsic risk factors among runners in under-resourced communities in Ekurhuleni, Gauteng. *South Afr J Physiother*. 2018;74:452.
10. Francis P, Whatman C, Sheerin K, et al. The proportion of lower limb running injuries by gender, anatomical location and specific pathology: a systematic review. *J Sports Sci Med*. 2019;18:21–31.
11. Fredette MA, Roy J-S, Esculier J-FO, et al. Most military runners report recent changes in running parameters before lower limb injury onset. *Mil Med*. 2021;186:e1140–e1148.
12. Bonacci J, Hall M, Fox A, et al. The influence of cadence and shoes on patellofemoral joint kinetics in runners with patellofemoral pain. *J Sci Med Sport*. 2018;21:574–578.
13. Esculier JF, Roy JS, Bouyer LJ. Lower limb control and strength in runners with and without patellofemoral pain syndrome. *Gait Posture*. 2015;41:813–819.
14. Noehren B, Pohl MB, Sanchez Z, et al. Proximal and distal kinematics in female runners with patellofemoral pain. *Clin Biomech*. 2012;27:366–371.
15. Viljoen CT, Sewry N, Schwellnus MP, et al. Independent risk factors predicting gradual onset injury in 2824 trail running race entrants: SAFER XVIII study. *Wilderness Environ Med*. 2021;32:293–301.
16. Mokwena PL, Schwellnus MP, Jansen van Rensburg A, 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*. 2022;32:e422–429.
17. Boer P-H, Schwellnus MP, Jordaan E. Chronic diseases and allergies are risk factors predictive of a history of Medial Tibial Stress Syndrome (MTSS) in distance runners: SAFER study XXIV. *Phys Sportsmed*. 2022;51:166–174.
18. Swanevelder S, Sewry N, Schwellnus M, et al. Predictors of multiple injuries in individual distance runners: a retrospective study of 75,401 entrants in 4 annual races–SAFER XX. *J Sport Health Sci*. 2022;11:339–346.
19. 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;48:869–870.
20. Schwabe K, Schwellnus M, Swanevelder S, et al. Leisure athletes at risk of medical complications: outcomes of pre-participation screening among 15,778 endurance runners-SAFER VII. *Phys Sportsmed*. 2018;46: 405–413.
21. Schwellnus M, Swanevelder S, Derman W, et al. 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;53:634–639.
22. Perk J, De Backer G, Gohlke H, et al. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012): the fifth joint task force of the European society of cardiology and other Societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635–1701.
23. Corrado DSC, Schmied C, Basso C, et al. Risk of sports: do we need a pre-participation screening for competitive and leisure athletes? *Eur Heart J*. 2011;32:934–944.
24. 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 sports 2020 (including the STROBE extension for sports injury and illness surveillance (STROBE-SIIS)). *Orthopaedic J Sports Med*. 2020;8:1–33.
25. Viljoen CT, Janse van Rensburg DC, Verhagen E, et al. Epidemiology of injury and illness among trail runners: a systematic review. *Sports Med*. 2021;51:917–943.
26. Nielsen RO, Simonsen NS, Casals M, et al. Methods matter and the 'too much, too soon' theory (part 2): what is the goal of your sports injury research? Are you describing, predicting or drawing a causal inference? *Br J Sports Med*. 2020;54:1307–1309.
27. Du Toit F, Schwellnus M, Wood P, et al. 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 Ther Sport*. 2020;46:137–144.
28. Nichols AEC, Oh I, Loiselle AE. Effects of Type II diabetes mellitus on tendon homeostasis and healing. *J Orthop Res*. 2020;38:13–22.
29. Burne G, Mansfield M, Gaida JE, et al. Is there an association between metabolic syndrome and rotator cuff-related shoulder pain? A systematic review. *BMJ Open Sport Exerc Med*. 2019;5:e000544.
30. Abate M, Schiavone C, Salini V, et al. Occurrence of tendon pathologies in metabolic disorders. *Rheumatology (Oxford)*. 2013; 52:599–608.
31. Zampieri S, Valente M, Adami N, et al. Polymyositis, dermatomyositis and malignancy: a further intriguing link. *Autoimmun Rev*. 2010;9: 449–453.
32. Ungprasert P, Bethina NK, Jones CH. Malignancy and idiopathic inflammatory myopathies. *North Am J Med Sci*. 2013;5:569–572.
33. Thong BKS, Ima-Nirwana S, Chin K-Y. Proton pump inhibitors and fracture risk: a review of current evidence and mechanisms involved. *Int J Environ Res Public Health*. 2019;16:1571.

34. Levin OS, Polunina AG, Demyanova MA, et al. Steroid myopathy in patients with chronic respiratory diseases. *J Neurol Sci*. 2014;338: 96–101.
35. Mammen AL. Statin-associated autoimmune myopathy. *N Engl J Med*. 2016;374:664–669.
36. Marie I, Delafene ̂tre H, Massy N, et al. Tendinous disorders attributed to statins: a study on ninety-six spontaneous reports in the period 1990–2005 and review of the literature. *Arthritis Rheum*. 2008;59: 367–372.
37. Barnes PJ. Pathophysiology of allergic inflammation. *Immunol Rev*. 2011; 242:31–50.
38. Waryasz GR, McDermott AY. Patellofemoral pain syndrome (PFPS): a systematic review of anatomy and potential risk factors. *Dynamic Med*. 2008;7:9.
39. Van der Stede T, Blancquaert L, Stassen F, et al. Histamine H1 and H2 receptors are essential transducers of the integrative exercise training response in humans. *Sci Adv*. 2021;7:eabf2856.
40. Ely MR, Sieck DC, Mangum JE, et al. Histamine-receptor antagonists slow 10-km cycling performance in competitive cyclists. *Med Sci Sports Exerc*. 2019;51:1487–1497.
41. Luttrell MJ, Halliwill JR. The intriguing role of histamine in exercise responses. *Exerc Sport Sci Rev*. 2017;45:16–23.