Manuscript title

Risk factors associated with gradual onset running-related injuries in 5770 ultramarathon race entrants – SAFER XXXII

Running title:

Risk factors for injuries in ultramarathoners

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ABSTRACT

Background: There is limited evidence available on contributing factors for gradual onset running-related injuries (GORRIs) in ultramarathon runners. The aim was to determine if selected risk factors were associated with a history of GORRIs in 90km ultramarathon race entrants.

Methods: Descriptive cross-sectional study**.** GORRI and medical data using an online pre-race medical screening tool was collected from 5770 consenting race entrants from the 2018 90km Comrades Marathon. Selected risk factors associated with 12-months history of GORRIs (age, sex, training, chronic diseases and allergies) were analysed using a multiple model (Poisson regression). Prevalence (%) and prevalence ratios (PR, 95%CIs) are reported.

Results: The overall 12-month prevalence of GORRIs was 11.6% (95%CI: 10.8-12.5) and this was higher in females vs males (PR=1.6; 1.4-1.9) ($p<0.0001$). Novel independent risk factors associated with a history of GORRIs were: history of chronic disease (PR=1.3; $p=0.0063$); history of allergies (PR=1.7 increased risk for every disease; $p<0.0001$); fewer training sessions/week (PR=0.8 decreased risk for every 2 additional training sessions per week; $p=0.0005$); and increased number of years as a recreational runner (PR=1.1 increased risk per 5 years of running; $p=0.0158$).

Conclusions: There is a complex interaction between the internal and external risk factors associated with GORRIs in 90km distance runners. These data can inform injury prevention programs targeted at subgroups of ultradistance runners.

KEYWORDS

Gradual onset running-related injuries, GORRIs, ultramarathon, ultra-distance, chronic diseases, allergies, females, training variables.

INTRODUCTION

Gradual onset running-related injuries (GORRIs) refer to injuries sustained from repetitive loading during running, combined with insufficient tissue recovery over time.[1] GORRIs can occur in various tissues, including muscles, tendons, bones, ligaments and joints.[2] Research focussing on the identification of risk factors that predict subgroups among long distance runners that are at higher risk for GORRIs has become increasingly important in recent years.[1, 3, 4] Risk factors associated with GORRIs may be internal or external. Internal risk factors include age, sex, body mass index, previous injuries, chronic diseases, medication, physical fitness, and psychological factors. External factors include characteristics of the training schedule (weekly training distance, frequency, intensity of the sessions), the training environment (hills or flat, stable or unstable running surfaces), and training gear such as footwear.[2, 5]

In a recent study, risk factors associated with a history GORRIs in 56km runners were identified as follows: female sex; history of allergies; chronic diseases; increased years of recreational running; decreased weekly running distance; and slower training running speed.[1] In a similar study among entrants of the Two Oceans Trail Run composing of 10km and 22km races[3] a higher chronic disease composite score and a history of allergies were associated with a higher 12-month prevalence of GORRIs.

The historic 90km Comrades Marathon is described as the world's greatest ultra-distance race, which tests the athletes' mental, physical and spiritual endurance. This race has been run since 1921 between the cities of Durban and Pietermaritzburg in South Africa, with >15 000 entrants annually.[6] Runners over the age of 20 qualify for entry if they are able to complete an officially recognized marathon (42.2km) in under five hours. There are data that

longer race distance is a risk factor associated with GORRIs[3] and thus the prevalence of GORRIs in 90km ultradistance runners may be high. The prevalence and risk factors associated with GORRIs in 90km ultramarathon race entrants have not yet been reported, and with such high participation rates, it is important to further investigate these injuries.

The aim of this study was to determine if selected risk factors (age, sex, training variables, chronic disease and allergies) are associated with a history of GORRIs in 90km ultramarathon race entrants.

METHODS

Study design

This was a cross-sectional analysis on data prospectively collected during the 2018 Comrades Marathon. Ethical clearance was obtained from the Research Ethics Committee of the University prior to the collection of data. This study is part of the larger SAFER (Strategies to reduce Adverse medical events For the ExerciseR) studies.[7]

Participants

All participants of the 2018 Comrades Marathon were invited to complete a voluntary online pre-race medical questionnaire 2-4 months prior to the race. Participants that consented to data being used for research were included in this study.

Procedures

Online pre-race medical questionnaire

The pre-race medical questionnaire for the 2018 Comrades Marathon was developed using guidelines from the European Association for Cardiovascular Prevention and Rehabilitation.[8] The questionnaire provides cardiovascular screening information for medical staff on race day, and has successfully been used in other studies.[9, 10] Questions included a specific question on gradual onset running-related injuries: "*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?"*. Injuries were included if "*the injury is/was severe enough to interfere with training/running or require treatment (e.g., use medication, or require you to seek medical advice from a health professional)?"*. Further questions regarding training history (years running, average number of training sessions per week, distance per week, average training speed for the past 12months), history of chronic diseases (history of cardiovascular disease (CVD), symptoms of CVD, risk factors for CVD, metabolic/endocrine disease, respiratory disease, gastrointestinal disease, nervous/psychiatric disease, kidney/bladder disease, haematological/immune disease and cancer) and history of allergies were also asked.

Main outcome and independent variables reported

The history of a GORRI among race entrants in the 12 months preceding the completion of the pre-race questionnaire was the main outcome variable of this study. Independent variables included were demographics (age and sex), training history, chronic diseases and a history of allergies. The ten chronic disease variables (previously mentioned and published) were combined to calculate a single chronic disease composite score.[1] Individual chronic diseases were not analysed due to small numbers.

Statistical analysis

Data analysis was conducted in conjunction with the Biostatistics Unit at the South African Medical Research Council (SAMRC). All data were analyzed using SAS 9.4 statistical program. The dependent variable in the model was the number of GORRI injuries for the entrant. Runners could report more than one GORRI, for example reporting both a knee and a foot injury. If a runner reported no injury in any of the GORRI related question, the response variable was given the value "0". If a runner reported 1 injury in any of the GORRI related question, the response variable was given the value "1". If a runner reported a second injury, the response variable was given the value "2". Poisson regression with a log link were used, and the various models included independent variables of interest. Univariate prevalences (% and 95% confidence interval [CIs]) and prevalence ratios (PR) were reported for sex and age, running experience and running training history, history of chronic disease, and history of any allergies. A multiple regression model was performed to determine independent risk factors predictive of GORRIs. Initially, the multiple regression model (adjusted for sex and age category) included all the significant univariate risk factors ($p<0.05$). The variable for the history of any allergies was entered into the model as categorical variables. Training variables and the chronic disease composite score were entered into the model as continuous variables. Prevalence ratios (95% CIs) and p-values were reported for the significant independent variables. The results for the final model only included the retained significant risk factors. Prevalence ratios (PR and 95% CI) were reported, and the statistical significance level was 5%.

RESULTS

Demographics

The age and sex of all entrants and consenting entrants of the 2018 Comrades Marathon are given in Table 1.

Table 1: The demographics of all entrants in 2018 compared to consenting entrants completing the full pre-race screening questionnaire

		All race entrants (n=23412)		Study population of consenting race entrants (n=5770)		p-value
		n	%	n	%	
Sex	Females	5276	22.5	1617	28.0	<0.0001
	Males	18136	77.5	4153	72.0	
Age category (years)	≤ 30	1795	7.7	461	8.0	0.8708
	31–40	8834	37.7	2175	37.7	
	41–50	8473	36.2	2073	35.9	
	> 50	4310	18.4	1061	18.4	

The distribution of all entrants and consenting entrants in the age categories was similar, but there was a higher percentage of female race entrants who completed the questionnaire (28.0%) compared to all entrants (22.5%) ($p<0.0001$).

Risk factors associated with a history of GORRIs

The number and unadjusted overall prevalence of a history of GORRIs in the previous 12 months among consenting race entrants was 614 (11.6%; 95% CI 10.8-12.5).

Demographic variables as risk factors

The number, prevalence and unadjusted prevalence ratio (PR) of race entrants with a history of GORRIs in the previous 12 months (by sex and age groups) is shown in Table 2.

Table 2: The number (n), prevalence (%; 95% CI) and unadjusted prevalence ratio (PR; 95% CI) of race entrants with a history of GORRIs (by sex and age groups) (univariate)

Runner demographics		Consenting race entrants (n=5770)	Number and prevalence of GORRIs (n=614)		PR (95% CI)	p-value
		n	n	Prevalence (%; 95% CI)		
Sex	Males	4153	373	9.9 (9.0-10.9)	1.6 (1.4-1.9)	<0.0001
	Females	1617	241	16.1 (14.3-18.2)		
Age groups (years)	≤30	461	52	11.9 (9.2-15.5)	-	0.3035
	31 to ≤40	2175	208	10.8 (9.5-12.2)	0.9 (0.8-1.1)	
	41 to ≤50	2073	228	11.7 (10.3-13.2)	0.8 (0.7-1.0)	
	>50	1061	126	13.2 (11.2-15.6)	1.1 (0.8-1.5)	

GORRI: gradual onset running-related injury
n: number
%: percentage race entrants with history of GORRI
PR: Prevalence Ratio
95% CI: 95% Confidence Intervals

The prevalence of GORRIs was higher in females compared to the males (PR=1.6; p<0.0001). The prevalence of GORRIs was not significantly different between age groups.

Training variables as risk factors

The prevalence and unadjusted prevalence ratio (PR) of race entrants with a history of GORRIs in the previous 12 months (by running training/racing history) is presented in Table 3.

Table 3: The prevalence (% and 95%CI) and unadjusted prevalence ratio (PR; with 95%CI) of race entrants with a history of GORRIs (by running training/racing history) (univariate)

Running training/racing history	Points in the continuous variable#	Prevalence of race entrants with a GORRI (%; 95% CI)	PR (95% CI)	p-value
Number of years as a recreational runner (years)	3	10.6 (9.6-11.7)	5-unit increase: 1.06 (1.02-1.10)	0.0032
	6	10.9 (10.0-11.9)		
	13	11.8 (11.0-12.8)		
Average weekly training/ running frequency in the last 12 months (times per week)	2	14.5 (12.3-17.2)	2-unit increase: 0.83 (0.73-0.95)	0.0044
	3	13.3 (11.8-14.9)		
	4	12.1 (11.2-13.1)		
Average weekly training/running distance in the last 12 months (km)	15	15.0 (12.8-17.6)	10-unit increase: 0.94 (0.90-0.97)	0.0004
	25	14.1 (12.4-16.0)		
	40	12.8 (11.7-14.0)		
Average training speed (km/hr)	9	14.6 (11.5-18.5)	1-unit increase: 1.08 (1.00-1.16)	0.1912
	11	16.9 (11.5-24.9)		
	13	19.6 (11.5-33.5)		

GORRI: gradual onset running-related injury
#points on the continuous variables
PR: Prevalence Ratio

Increased number of running years was associated with a higher prevalence of a history of GORRIs (PR=1.1; p=0.0032). Increased weekly training frequency (PR=0.8) and increased weekly training/running distance (an increase of 10km had an average 6% decrease in risk, PR=0.9) were associated with a lower prevalence of history of GORRIs. The average training speed was not significantly associated with GORRIs.

History of chronic disease and allergies as risk factors

The number, prevalence and unadjusted prevalence ratio (PR) of race entrants with a history of GORRIs (by history of any chronic disease and a history of allergies) are presented in Table 4. Details by types of chronic diseases are presented in Supplementary Table S1.

Table 4: The number (n), prevalence (%; 95% CI) and unadjusted prevalence ratio (PR; 95% CI) of race entrants with a history of GORRIs (by history of any chronic disease and a history of allergies) (univariate)

Variable		Consenting race entrants (n=5770)	Number and prevalence of GORRIs (n=671)	Prevalence of race entrants with a GORRI (%; 95% CI)	PR (95% CI)	p-value
Composite Chronic Disease Score (0-10)*	0 chronic diseases	-	-	11.1 (10.2-12.0)	1 unit increase 1.4 (1.2-1.7)	0.0001
	2 chronic diseases	-	-	23.2 (16.7-32.4)		
Any allergies	Yes	587	121	20.6 (17.2-24.6)	1.9 (1.6-2.4)	0.0001
	No	5183	550	10.6 (9.8-11.5)		

GORRI: gradual onset running-related injury
n: number
%: percentage race entrants with history of GORRI
PR: Prevalence ratio
95% CI: 95% Confidence Intervals
*points on continuous variable

A total of 510 (8.7%) runners reported a history of one or more chronic diseases. A history of chronic diseases (for an increase of 1 more chronic disease PR=1.4; p=0.0001) and a history of allergies (PR=1.9; p=0.0001) were associated with a history of GORRIs.

Independent risk factors associated with history of GORRIs

Independent risk factors (adjusted for age and sex) associated with a history of GORRIs in the previous 12 months (multiple regression) are presented in Table 5.

Table 5: Independent risk factors (adjusted for age and sex) associated with a history of GORRIs in the previous 12 months (multiple regression)

Independent risk factors	PR (95% CI)	p-value
Number of years as a recreational runner (years) [a]	1.06 (1.01 – 1.10)	0.0158
Average weekly training/running frequency in the last 12 months [b]	0.79 (0.69 – 0.91)	0.0005
Chronic Disease [c]	1.30 (1.09 – 1.56)	0.0063
Allergies (yes vs. no)	1.69 (1.38 – 2.06)	<0.0001

GORRI: gradual onset running-related injury
PR: Prevalence Ratio
[a] Average risk for every 5 years of running
[b] Average risk for every 2 additional training sessions per week
[c] Average risk for reporting 1 more chronic disease

Independent risk factors associated with a history of GORRIs in the previous 12 months were numbers of years as a recreational runner, a history of chronic diseases (an increase of 1 more chronic disease PR=1.3) and a history of allergies (PR=1.7). Increased average weekly training/running frequency in the last 12 months was associated with a lower prevalence of a history of GORRIs (PR=0.8 for every additional 2 sessions per week).

DISCUSSION

The aim of this study was to determine if selected risk factors (age, sex, training variables, chronic disease, and allergies) were associated with a history of GORRIs in 90km ultramarathon race entrants. The main findings in this study were: 1) the overall 12-month period prevalence of GORRIs in 90km race entrants was 11.6%; 2) independent risk factors associated with a history of GORRIs in race entrants were: being female, training variables (increased number of years of training, reduced weekly training frequency), history of chronic diseases, and a history of allergies.

In our study, female sex was associated with a 60% higher chance of reporting a history of GORRIs. Our finding is not consistent with data reported in two reviews that concluded that males distance runners are at a slightly higher risk for GORRIs.[11] [12] In another recent systematic review (2020), runners were divided into short- (<20km/week; <10km/event) and long distance (>20km/week;>10km/event) groups. Males in the short-distance group had a higher risk for GORRIs compared to females, and there was no significant difference between males and females in the-long distance group.[12] However, females were reported to be at higher risk of GORRIs in another review on this topic.[13] Our data are also consistent with findings in another study among 56km running race entrants, where females had a 24% higher risk of reporting a GORRI in 12 months.[1] It must be noted that this was a self-selected sample and there is a chance that a higher proportion of females with GORRIs decided to complete the questionnaire. In summary, there is some evidence that female ultramarathon runners may be at higher risk of GORRIs, but this needs further investigation. It is important for clinicians to identify runners at higher risk for GORRIs to better target specific prevention strategies reducing the risk of GORRIs.

We identified training-related variables that are associated with a higher risk of GORRIs in race entrants. The first training-related variable significantly associated with GORRIs was increasing number of running years (a proxy for greater running experience), and this in keeping with findings in some previous studies.[1, 4] This finding is not supported by data from two systematic reviews, where one concluded that <3 years running experience, and another that <5 years running experience is a risk factor associated with GORRIs.[13, 14] Another systematic review concluded that there is no significant association between running experience and injury risk,[11] and another suggested limited evidence that more running

experience was a risk factor for injuries.[12] In summary, there is no conclusive evidence that years of running is associated with an increased risk of GORRI and more research is needed.

In our study, two additional training variables were associated with an increased risk of GORRIs. These were reduced number of weekly training sessions and reduced weekly kilometres. These findings are consistent with those reported in one study[15] but data from systematic reviews remain mainly inconclusive about the risk/benefit from increased weekly training.[11, 16] The inconsistency in the literature may be related to the fact that either the injury itself reduces the ability to train, or that reduced training is associated with an increased risk of injury. Further studies, using a randomised controlled trial study design, are required to clarify this inconsistency. It has been suggested that a minimum of 30km weekly training is protective against GORRIs in marathon runners, but that there is no further protection of injury risk when weekly training distances exceed this.[15, 17] It is worth noting that these weekly training distances are very different to the 186.6km/week that elite ultra-marathon runners average.[18] Time-to event-analysis for training load on sports injuries remains an intricate topic, and prospective studies might better our current understanding on this relationship.[19]

The long-term effects of ultra-endurance distance running on the body may negatively impact the cardiovascular-, renal-, respiratory- and musculoskeletal systems.[20] Whether these effects lead to chronic diseases remains a topic of research, but in this study the reverse effect of chronic disease on musculoskeletal injury was observed and found to be significant. An independent association between a history of chronic disease, and an increased prevalence of history of GORRIs with a 1.3-fold increase per 1 additional chronic disease was reported (adjusted for age and sex). This finding is in keeping with similar results reported in several

studies in runners, cyclists and trail runners.[1, 3, 21] Chronic disease as a risk factor associated with GORRIs could either be due to the direct detrimental effect of the specific disease on the body, or the treatment modalities used. Examples of direct effects of chronic disease and injury risk are: obesity that can be associated with mechanical lower back pain,[22] dyslipidaemia which can lead to tendinopathies and oligoarthritis,[23, 24] hypertension is associated with reduced muscle glucose uptake,[25] and there is an association between diabetes and rheumatological complaints.[26] Medications used in the treatment of chronic diseases can also affect the musculoskeletal system negatively. For example, antihypertensives might reduce muscle strength and increase fatiguability,[27] up to 10% of statin users develop associated myopathy,[28] anti-epileptic drugs increase the risk for osteoporosis,[29] and newer antihyperglycemics can negatively affect bone metabolism.[30] There appears to be a complex interaction between disease, treatment goals, medication, physical activity and risk of musculoskeletal injury. Our findings highlight this complexity and illustrate the necessity for specialist, individualised patient management. This complex interaction needs to be considered when prescribing exercise as a medicine for individuals with chronic diseases.

A final significant finding from this study was the independent association between a history of allergies and a history of GORRIs in runners. There was a 1.7-fold increase (adjusted for age and sex) in the prevalence of GORRIs when entrants reported a history of allergies. In other SAFER studies this same independent association was reported and varied between a 1.7- to a 2.8-fold increase in risk.[1, 3, 4] The precise reasons for this association are not known, and similar to chronic diseases, there could be the effect of the allergy, or the effect of medications used. Outdoor sports, such as distance running, are associated with greater exposure to environmental factors. Recurrent exposure to specific allergens can lead to

chronic allergic inflammation.[31] Chronic inflammation negatively affects the complex interaction of osteopontin, periostin, histamines, interleukins, Vit D and autophagy, which can all affect bone health and can lead to chronic injuries.[32] Several dietary supplementations have been studied as an alternative to nonsteroidal anti-inflammatory (NSAID) medications. These include Omega 3 polyunsaturated fatty acids (PUFA), White Willow Bark, Curcumin, Green Tea, Maritime Pine Bark, Frankincense, Cat's Claw, Capsaicin, Ginger and Cinnamon. [33] The clinical advantage of these factors remains debatable and the 2018 International Olympic Committee statement on dietary supplementation concluded that there is limited support in athletes for these findings.[34] The presence/absence of these supplements was not taken into account for this study and may be of value in future research. Anti-histamines used in the management of allergic conditions may inhibit the nociceptive effects of delayed onset muscle soreness in endurance athletes, with raised CK blood levels compared to placebo groups indicating more severe exertional rhabdomyolysis.[35] In addition to this, antihistamines prolong the recovery end remodelling process of exercise adaptation. The combination of these two factors may predispose ultra-marathon athletes with allergies to chronic overuse injuries.[36] Another factor that may explain the high rate of GORRIs is the use of corticosteroids in allergic conditions. Corticosteroid use side-effects include osteopenia, muscle/tendon breakdown and aseptic joint necrosis among others.[37] All of these conditions can contribute to gradual onset injuries like osteoarthritis, muscle strains and tendinopathies. The use of systemic corticosteroid therapy has been disadvised for all common allergic conditions due to the poor risk-benefit ratio when considering side effects. This finding emphasizes the importance of a holistic approach to athletes with a history of GORRIs that includes aggressive allergy control.

Strengths and Limitations

The strengths of this study are the large sample size, and the ability to explore risk factors in a multiple model. Limitations include selection bias (self-selected sample) because of the higher percentage of female responders (22.5% entrants vs 28% consenting) in our sample compared to the whole population and this could lead to selection bias when reporting. Whilst there was a large sample, a study using a larger sample, where the questionnaire is mandatory should be performed to confirm the results. It also appears this was a sub population that reported fewer chronic diseases, indicating a bias in the sub population (reporting a maximum of 3 chronic diseases compared to 0-10 in other populations). We also acknowledge that all the data are self-reported, which can introduce recall bias.

CONCLUSION

Independent risk factors associated with a history of GORRIs in 90km ultra-distance runners were female sex, increased years as a runner, decreased weekly training days, and the presence of chronic diseases and allergies. These findings highlight a triad of novel factors associated with GORRIs (chronic diseases, allergies, and potentially the medication to treat chronic disease or allergies) and this requires further investigation to determine cause-effect and identify underlying mechanisms. Sport and Exercise Medicine (SEM) clinicians can possibly use this information for future development of injury prevention programmes for GORRIs in distance runners.

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Highlights

- Females, history of chronic disease, allergies are risk factors for GORRIs
- There is a complex interaction of a triad of novel factors associated with GORRIs
- Clinicians can use this information to develop prevention programmes