Males, older age, increased training, chronic diseases, allergies and history of injury are independent risk factors associated with a history of EAMC in distance runners in 76654 race entrants – SAFER XXIX

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ABSTRACT

Objective: To determine independent risk factors associated with a history of Exercise Associated Muscle Cramps (hEAMC) in distance runner race entrants in a community-based mass participation event.

Design: Cross-sectional study.

Setting: 2012-2015 Two Oceans marathon races (21.1km and 56km), South Africa.

Participants: 76654 consenting race entrants.

Assessment of Risk Factors: Entrants completed an online pre-race medical screening questionnaire as part of the entry process. In a multiple model sex, age, training variables, history of chronic disease, allergies, and running injuries were included as potential factors associated with hEAMC in 21.1km and 56km entrants.

Main Outcome Measures: Prevalence (%) and prevalence ratios (PR, 95%CIs) are reported.

Results: Males ($p<0.0001$) and older age (>40years, $p<0.0001$) were significantly associated with hEAMC. Therefore, the model was adjusted for sex and age group and run separately for

21.1km and 56km entrants. Specific independent risk factors associated with hEAMC in both 21.1km and 56km entrants were: a history of chronic diseases (21.1km: PR=1.9; 56km: PR=1.6; p<0.0001), running injury in the last 12 months (21.1km: PR=1.7; 56km: PR=1.4; p<0.0001), history of allergies (21.1km: PR=1.4; 56km: PR=1.2; p<0.0001), and various training variables (PR=1.0-1.1).

Conclusion: In both 21.1km and 56km race entrants, independent risk factors associated with hEAMC were males, older age, longer race distances, training variables, chronic diseases, history of allergies and history of a running injury in the past 12 months.

Keywords: EAMC, Muscle Cramps, Distance Runners, Risk Markers, Epidemiology, SAFER Study, Clinical Characteristics

INTRODUCTION

Exercise Associated Muscle Cramping (EAMC) is defined as a 'painful spasmodic involuntary contraction of skeletal muscle that occurs during or immediately after muscular exercise'.[1] EAMC presents clinically as a sudden onset of uncontrollable muscle contractions during or immediately after exercise, often accompanied by acute pain.[2,3] At community-based mass participation endurance sports events, including distance running events, EAMC is one of the most common reasons for admission and treatment at event medical facilities.[4-7] To prevent and manage EAMC in endurance athletes, it is important to identify possible risk factors associated with the development of EAMC. Despite EAMC being a common occurrence at endurance running events, there is limited research regarding risk factors associated with EAMC.

Historically, the two main aetiological factors explaining the pathophysiology of EAMC were dehydration and electrolyte imbalances, but more recently, factors associated with altered neuromuscular control as a result of muscle fatigue are reported.[5,8,9] Specifically, recent studies suggest that muscle fatigue and other potential risk markers that lead to muscle fatigue may alter the neuromuscular control and this is thought to be the common pathophysiological pathway resulting in EAMC.[6] Factors that can affect neuromuscular control during exercise, specifically the development of premature muscle fatigue, have not been explored in many studies. Because muscle fatigue contributes to the onset of EAMC, it might be important to explore the differences in the risk markers of EAMC in runners participating in varying race distances such as 21.1km vs. 56km runners.

Previous literature indicates that males are more likely to experience EAMC, as well as a higher incidence of EAMC in older males.[10] A review in 2016 reported conflicting results regarding age and EAMC, but several others reported no association between age and the incidence of EAMC.[5,11,12] A family and personal history of EAMC have also been investigated and found to be a risk factor.[3,4,13] Two studies found that marathons runners and triathletes with a family history of EAMC were more likely to develop EAMC compared to marathon runners and triathletes with no family history.[10,14] A previous personal history of EAMC was also found to be a risk factor for EAMC during an event in distance runners and triathletes.[10,15,16] Runners with a history of a soft tissue injury have also been associated with EAMC.[4]

In the largest cross-sectional study to date, novel independent risk factors associated with EAMC in 15778 distance runners were an underlying chronic disease, medication use, a history of running injuries, and experienced runners.[7] The study found that distance runners classed as either experienced or intermediate had a significantly higher prevalence ratio of a history of

EAMC when compared with novice runners. However, this study did not differentiate between risk factors associated with EAMC in 21.1km vs. 56km runners.[7]

Therefore, the aim of this study was to identify selected risk factors associated with a history of EAMC (hEAMC) in distance runners and to determine if risk factors differ between 21.1km and 56km runners.

METHODOLOGY

Study design

This was an observational study with a cross-sectional analysis. The data were from the 2012-2015 Two Oceans race entrants (21.1km and 56km). The Research Ethics Committee of the Faculty of Health Sciences from both the University of Cape Town (REC 009/2011) and the University of Pretoria (433/2015) (028/2018) approved the ongoing analysis of the data. This study is also part of a series of ongoing SAFER (Strategies to reduce Adverse medical events For the ExerciseR) studies.[17]

Pre-race medical screening questionnaire

The details of the development of an online pre-race medical screening questionnaire or "self-assessment of risk" that was administered to all race entrants from 2012 to 2015 was previously described.[18] This questionnaire included the following categories of medical history: symptoms of cardiovascular disease (CVD), risk factors for CVD, and history of diagnosed chronic disease, general prescription medication use, medication use during racing, a past history of collapse during racing and previous running injuries. The online pre-race medical history screening tool

also included a specific question on EAMC "*Have you ever in your running career suffered from muscle cramping (painful, spontaneous, sustained spasm of a muscle) during or immediately (within 6 hours) after running (in training or competition)?*" In response to a "yes" answer to this question, race entrants were grouped as those reporting a history of EAMC (hEAMC) and a control group of participants with no history of EAMC.

Primary objective: risk factors for hEAMC

Four broad individual categories of risk markers for hEAMC that were explored in 21.1km and 56km race entrants (separately) in this study: 1) demographics, 2) training-related variables, 3) history of chronic diseases, allergies, and 4) history of injuries. More specifically, demographic variables included sex and age group. Training-related variables included years of recreational running (years), frequency of training per week, and average self-reported training speed (km/h). A history of chronic disease (history of CVD, CVD symptoms, CVD risk factors, other chronic diseases (metabolic/endocrine, respiratory, gastrointestinal, nervous system/psychiatric, kidney/bladder, haematological/immune, cancer), using the individual chronic disease categories mentioned above, a composite chronic disease score was calculated as a continuous score out of 10 (each category is given 1 point and then summed). A history of any allergy (including animal, plant, allergy to medication or other allergy) and a history of running injuries in the past 12 months was also included.

Statistical analysis

All questionnaire data were entered into an Excel spreadsheet (Microsoft 2010) and analysed using the SAS v9.4 statistical program. All data for consented race entrants was used for analysis (n=76 654). Although there were 76,654 entrants in the study, the same runner (individual) could have entered a race in more than one year, resulting in 47,784 unique runners that entered races over the 4 years. We had to account for the correlated data by reporting estimates from a Generalized Estimating Equation (GEE) analysis. This was obtained by including the repeated statement in the Poisson regression model which was used to model the risk factors for EAMC . We used an exchangeable correlation structure.

Demographics (sex, age group) were presented separately for 21.1km and 56km race distances. The overall lifetime prevalence (% and 95%CIs), as well as the lifetime prevalence by race distance (21.1km and 56km), of EAMC were reported. The Poisson regression model included an interaction term race distance x risk factor, to be able to report and compare estimates for the 21.1km and 56km. Prevalence ratios (PR: 95%CI), adjusted for age group and sex were reported as the measure of association. Prevalences (% and 95% CIs) and PR from the univariate model were reported for training history, history of chronic disease, history of any allergies and history of a running injury in the past 12 months. The multiple regression model reported the independent risk factors for EAMC. Initially, the multiple regression model included all the significant univariate risk factors for the 21.1km and 56km separately. The results for the final model only included the retained significant risk factors. The reported level of significance is 1%.

RESULTS

Demographics

There were a total of 106743 entrants, of which 76 654 gave consent to be included in this study. Details of all race entrants and race entrants who gave consent to participate in this study is shown in Supplementary Tables 1 and Table 2. There were significantly more male entrants in the 56km races (71.1%) compared to the 21.1km (48.9%) (p=0.0001), and 56km entrants were older than the 21.1km entrants (p=0.0001).

Lifetime prevalence and annual incidence of hEAMC

10614 race entrants indicated a history of EAMC (21.1km n=6233; 56km n=4381). The lifetime prevalence of hEAMC in the study population was 12.8% (95% CI: 12.6-13.1) and the lifetime prevalence of hEAMC was significantly higher in 56km (16.0%; 15.5-16.5) compared to 21.1km entrants (8.8%; 8.5-9.1) (p=0.0001) (adjusted for age group and sex). This difference in prevalence is the reason for exploring the risk factors for 21.1km and 56km entrants separately.

Risk markers associated with hEAMC (Univariate analysis)

Demographics (sex and age groups)

The frequency and prevalence ratio of entrants with hEAMC amongst 21.1km and 56km race entrants (by sex and age groups) are shown in Table 1.

Table 1: The frequency (%) and prevalence ratio (PR: 95% CI) of 21.1km and 56km entrants with a history of EAMC (hEAMC) by sex and age groups (univariate analysis)

Race distance	Variable	Category	N	Entrants with hEAMC	% entrants with hEAMC* (95% CI)	PR (95% CI)	p-value
21.1km	Sex	Male	22998	2787	10.1 (9.6-10.6)	1.9 (1.8-2.1)	
		Female	24071	1594	5.3 (5.0-5.7)		<0.0001
	Age groups (yrs)	≤30	16594	1303	7.9 (7.4-8.3)		
		31-40	14290	1112	7.7 (7.2-8.2)	1.0 (0.9-1.1)	0.6323 **
		41-50	9262	956	9.9 (9.3-10.6)	1.3 (1.2-1.4)	<0.0001 **
		>50	6923	1010	13.5 (12.5-14.5)	1.7 (1.6-1.9)	<0.0001 **
56km	Sex	Male	21044	5157	21.4 (20.7-22.1)	2.0 (1.9-2.2)	
		Female	8541	1076	10.6 (9.8-11.4)		<0.0001
	Age groups (yrs)	≤30	3574	576	15.6 (14.4-16.9)		
		31-40	10755	2069	17.9 (17.1-18.7)	1.1 (1.0-1.3)	0.0047 **
		41-50	10078	2189	20.1 (19.2-21.0)	1.3 (1.2-1.4)	<0.0001**
		>50	5178	1399	24.4 (23.0-25.8)	1.6 (1.4-1.7)	<0.0001**

*: Model estimates
PR: Prevalence ratio
**compared to ≤30 age group

The PR of hEAMC is significantly higher in males and older age groups for both 21.1km and 56km race entrants (>40 years in 21.1km entrants, and >30 years in 56km entrants) (vs. younger age groups).

Training history

The frequency (%) and prevalence ratio of race entrants with a history of EAMC in 21.1km and 56km race entrants (by training history variables) are shown in Table 2.

The PR of hEAMC in both 21.1km and 56km race entrants was significantly higher as the years of recreational running increased, average weekly training frequency was reduced, and slower training speeds.

Table 2: The frequency (%) and prevalence ratio (PR: 95% CI) of 21.1km and 56km race entrants with a history of EAMC (hEAMC) by training history variables (adjusted for sex and age group) (univariate analysis)

Race distance	Training history variable	Points on the continuous variable	Predicted % of participants at specific points on the continuous variable (95% CI)	PR (95% CI)	p-value
21.1km	Years of recreational running (yrs)	3yrs	7.8 (7.5-8.1)	5 unit increase 1.11 (1.09-1.13)	<0.0001
		6yrs	8.3 (8.0-8.6)		
		13yrs	9.6 (9.3-9.9)		
	Average weekly training frequency in last 12 months (times a week)	3 / week	9.1 (8.8-9.4)	1 unit increase 0.96 (0.94-0.99)	0.0020
		4 / week	8.7 (8.4-9.1)		
	Average training speed in last 12 months (min/km)	5 min/km	8.4 (8.1-8.8)	1 unit decrease (1min/km slower) 1.05 (1.03-1.08)	<0.0001
		6 min/km	8.9 (8.6-9.2)		
		6.5 min/km	9.1 (8.8-9.5)		
56km	Years of recreational running (yrs)	3yrs	15.5 (14.9-16.2)	5 unit increase 1.05 (1.04-1.07)	<0.0001
		6yrs	16.0 (15.4-16.6)		
		13yrs	17.1 (16.6-17.6)		
	Average weekly training frequency in last 12 months (times a week)	3 / week	17.6 (16.9-18.3)	1 unit increase 0.96 (0.94-0.97)	<0.0001
		4 / week	16.8 (16.3-17.4)		
	Average training speed in last 12 months (min/km)	5 min/km	15.8 (15.2-16.4)	1 unit decrease (1min/km slower) 1.07 (1.05-1.10)	<0.0001
		6 min/km	16.9 (16.4-17.5)		
		6.5 min/km	17.6 (16.9 -18.2)		

PR: Prevalence ratio

History of chronic diseases and allergies

The frequency (%) and prevalence ratio of entrants with a history of EAMC in 21.1km and 56km race entrants (by history of composite chronic disease score and allergies) are shown in Table 3.

In both 21.1km and 56km race entrants, the PR of hEAMC was significantly higher in entrants who reported a history of chronic diseases in several categories (for every two categories of chronic diseases 21.1km PR=2.1; 56km PR=1.7) and allergies (21.1km PR=1.7; 56km PR=1.4) than in entrants without these conditions. For further details regarding the chronic diseases, see Supplementary Table 3.

Table 3: The frequency (%) and prevalence ratio (PR: 95% CI) of 21.1km and 56km race entrants with hEAMC by history of chronic disease and allergies (adjusted for sex and age group) (univariate analysis)

Race distance	History of chronic disease and allergies		n	Number with hEAMC	% hEAMC (95%CI)	PR (95% CI)	p-value
21.1km	Composite Chronic Disease Score*		0	-	7.3 (7.0-7.6)	2 unit increase 2.1 (2.0-2.3)	<0.0001
			2	-	15.6 (14.8-16.3)		
			4	-	33.2 (30.1-36.6)		
	Any allergies	No	41847	3572	8.4 (8.1-8.7)		
		Yes	5222	809	14.2 (13.1-15.3)	1.7 (1.6-1.8)	<0.0001
56km	Composite Chronic Disease Score*		0	-	14.9 (14.3-15.4)	2 unit increase 1.7 (1.7-1.8)	<0.0001
			2	-	26.0 (24.7-27.3)		
			4	-	45.4 (41.2-50.0)		
	Any allergies	No	27040	5470	16.0 (15.4-16.5)		
		Yes	2545	763	22.8 (21.3-24.4)	1.4 (1.3-1.5)	<0.0001

*Continuous variable
PR: Prevalence ratio

History of running injuries

The frequency (%) and prevalence ratio of entrants with a history of EAMC by history of any running injury (in the last 12 months) are shown in Supplementary Table 4 (21.1km and 56km race entrants). The PR of hEAMC was significantly higher in entrants with a history of a running injury for both 21.1km (PR=1.9; 95%CI: 1.8-2.1) and 56km race entrants (PR=1.5; 95%CI: 1.5-1.6) ($p<0.001$).

Independent risk factors associated with hEAMC (Multiple model)

The independent risk factors (adjusted for sex and age groups) associated with hEAMC in 21.1km and 56km race entrants are depicted in Table 4.

Table 4: Independent risk factors (training, chronic disease, allergies, running injury) associated with hEAMC in race entrants (multiple model, adjusted for sex and age groups)

Race distance	Category of variables	Variable		PR (95% CI)	p-value
21.1km	**Training variables**	Years of recreational running (yrs)	For every 5 yrs increase	1.1 (1.1-1.1)	<0.0001
		Average weekly training frequency in last 12 months (times a week)	For an increase of 1 weekly training session	1.0 (0.9-1.0)	0.0041
		Average training speed in last 12 months (min/km)	For every 1 min / km slower training speed	1.0 (1.0-1.1)	0.0153
	History of chronic disease	Composite chronic disease score	For every increase of 2 chronic diseases	1.9 (1.8-2.0)	<0.0001
	Any allergies	Any history of allergies	No		
			Yes	1.4 (1.3-1.5)	<0.0001
	Running injury history	Any running injury (past 12 months)	No		
			Yes	1.7 (1.5-1.8)	<0.0001
56km	**Training variables**	Years of recreational running (yrs)	For every 5 yrs increase	1.0 (1.0-1.1)	<0.0001
		Average weekly training frequency in last 12 months (times a week)	For an increase of 3 weekly training sessions	1.0 (0.9-1.0)	0.0004
		Average training speed in last 12 months (min/km)	For every 1 min / km slower training speed	1.1 (1.0-1.1)	<0.0001
	History of chronic disease	Composite chronic disease score	For every increase of 2 chronic diseases	1.6 (1.5-1.7)	<0.0001
	Any allergies	Any history of allergies	No		
			Yes	1.2 (1.1-1.3)	<0.0001
	Running injury history	Any running injury (past 12 months)	No		
			Yes	1.4 (1.4-1.5)	<0.0001

PR: Prevalence ratio

The independent risk factors associated with hEAMC were similar in 21.1km and 56km race entrants. Specific independent risk factors associated with hEAMC were: a history of chronic diseases (21.1km: PR=1.9; 56km: PR=1.6), running injury in the last 12 months (21.1km: PR=1.7; 56km: PR=1.4), history of allergies (21.1km: PR=1.4; 56km: PR=1.2), and various training variables (PR=1.0-1.1).

DISCUSSION

As far as we are aware, this is the largest study to determine risk factors associated with a history of EAMC using a multiple model. The first main observation was that increased race distance (56km vs. 21.1km), male sex and older age were risk factors for hEAMC. In the subsequent analyses, we therefore explored independent risk factors separately for 21.1km and 56km race entrants and adjusted for sex and age. In both 21.1km and 56km race entrants, independent risk factors for hEAMC were related to training variables, history of chronic disease, allergies and a history of running injuries in the last 12 months.

In a previous study, we showed that the lifetime prevalence of hEAMC was significantly higher in 56km compared to 21.1km entrants.[19] Longer race distances imply longer exercise duration, inducing muscle fatigue, which may lead to EAMC based on the altered-neuromuscular control theory.[1,6,20] A cross-sectional study that included data from three marathons also reported an increased risk for EAMC with longer exercise duration.[14] However, the other factors that contribute to an increased risk of hEAMC are key to further understanding EAMC in distance runners.

The first novel finding were the demographic risk factors (males and older age) associated with a higher prevalence of hEAMC. The PR of hEAMC was 2 times higher in males for both 21.1km and 56km race entrants. Another study also identified males as an independent risk factor for developing EAMC,[14] however, one cohort study with a small sample size found that sex had no effect on the incidence of EAMC.[16] Older age was also a significant risk factor of hEAMC in both 21.1km and 56km race entrants. Previous studies have shown that runners older than 35 years are at a higher risk for EAMC.[14] A review in 2016 reported that two studies found older

athletes more likely to develop EAMC, but several others reported no association between age and hEAMC.[5,11,12] Seeing as demographic risk factors are still disputed in the literature, further research is needed in this regard.

A second novel finding was that training variables were independent risk factors associated with hEAMC. Specifically, an increased number of years of running, reduced number of weekly training sessions and slower average weekly training speed were independent risk factors for hEAMC in 21.1km and 56km race entrants. A longer history of running has previously been described as a risk factor for marathon runners and EAMC,[14] supporting our finding of increased number of running years. However, the same study did not find training speed to be a risk factor.[14] It must be cautioned that the training speed in our study was self-reported and therefore not an objective measure of training speed. A hEAMC may either cause or result from a reduction in weekly training sessions and training speed and this relationship should be explored in future causal studies.

A third novel finding was that several chronic diseases and a history of allergies were independent risk factors associated with hEAMC. Entrants with self-reported chronic diseases had a >1.5 times increased chance of hEAMC, whilst those with allergies had an increased chance of >1.2 times. No other studies (other than those conducted by our author group on this Two Oceans database) have explored allergies and chronic diseases in respect to hEAMC. In a recent review, the authors quote the Schwellnus papers, and the only other risk factor that has been reported was that of weather conditions.[21] The lack of evidence in this area leaves much room for investigation and hypotheses regarding the mechanism resulting in the association between chronic diseases / allergies and hEAMC. There are numerous studies showing an association between gradual onset injuries and chronic diseases and allergies, and these studies

have hypothesised the mechanism is related to potential medication use (due to the conditions) and the low grade inflammation related to allergies.[22-24] However, at present these are all hypothesis driven and require further studies to confirm.

Finally, we also show that the risk of hEAMC was about 1.7 times higher in 21.1km and 1.4 times higher in 56km race entrants with a history of a running injury in the past 12 months. This is supported by data from a previous study where previous/current injuries were associated with a hEAMC.[10] Previous injuries may result in localised muscle weakness, and therefore contribute to the development of abnormal neuromuscular control and muscle fatigue during distance running. Furthermore, acute local injury can result in an increased reflex alpha motor activity, which acts as a trigger for the development of EAMC. However, these relationships should be explored in future studies.

Strengths and Limitations

The strengths of this study were the large sample size, a high response rate, and minimal differences between consenting race entrants and all race entrants. As far as we could determine, this is the first study to report independent risk factors associated with hEAMC in 21.1km and 56km entrants. We recognise the following limitations of our study: 1) all data are self-reported with a potential of recall bias, but this would likely be similar in 21.1km and 56km entrants; and 2) this was a cross-sectional study, therefore cause-effect relationships between hEAMC and independent risk factors should therefore be explored in future studies, 3) the data are from a single race, representing a homogenous sample and, 4) the chronic disease composite score is not yet validated and should be interpreted with caution.

SUMMARY AND CONCLUSION

In summary, this study found significant differences in the lifetime prevalence of hEAMC in male, older and longer race distance runners. A second novel finding was that the training variables were independent risk factors for hEAMC, specifically reduced number of weekly training sessions and slower average weekly training speed in all race entrants. Finally, chronic diseases, a history of allergies and a history of a running injury in the past 12 months were independent risk factors associated with hEAMC. We suggest that independent risk factors associated with hEAMC should be explored in future studies, along with potential prevention strategies.

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