Sex, training variables, history of chronic disease, and chronic injury are risk factors associated with a history of exercise-associated muscle cramping in 10,973 ultramarathon race entrants: a safer XXXVIII study

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ABSTRACT

BACKGROUND: The prevalence of a history of exercise-associated muscle cramping (hEAMC) among ultramarathon runners is high. While the Comrades is one of the most popular mass community-based participation ultramarathons (90 km) globally, research on the epidemiology, clinical characteristics, and risk factors of entrants' lifetime hEAMC are scarce. This research aimed to describe the epidemiology, clinical characteristics, and risk factors of hEAMC among Comrades Marathon entrants.

METHODS: This was a retrospective, cross-sectional study in which 10973 race entrants of the 2022 Comrades Marathon participated. Entrants completed a prerace medical screening questionnaire that included questions related to the lifetime prevalence (%; 95% CI), severity, treatment and risk factors (demographics, training/racing variables, chronic disease/allergies, injury) for EAMC.

RESULTS: One thousand five hundred eighty-two entrants reported hEAMC in their lifetime (14.4%; 95% CI: 13.77-15.09). There was a significantly (P<0.01) higher prevalence of male (16.10%; 95% CI:15.34-16.90) than female (8.31%; 95% CI: 7.27-9.50) entrants with hEAMC (PR=1.94; 95% CI:1.68-2.23). The prevalence of hEAMC was highest in entrants with a: 1) 1 disease increase in composite disease score (PR=1.31; 95% CI:1.25-1.39); 2) history of collapse (PR=1.87; 95% CI 1.47-2.38); 3) past chronic musculoskeletal (MSK) injury (PR=1.71; 95% CI 1.50-1.94); and 4) MSK injury in the previous 12 months (PR=2.38;95% CI: 2.05-2.77). Training-related risk factors included an increase of 10 km weekly running distance (PR=0.97; 95% CI:0.95-0.99) and a training pace increase of 1min/ km (slower) (PR=1.07; 95% CI:1.03-1.12).

CONCLUSIONS: Future research should investigate the causal relationship between risk factors identified and hEAMC in ultramarathon runners. Findings from this study could assist in effective anticipation and adequate planning for treating EAMC encounters during community-based mass participation events.

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KEY WORDS: Muscle cramp; Marathon running; Sports.

Ultramarathons are races comprising distances over 42.2 kilometers (km) on various terrains.[1-3] The 90 km Comrades Marathon is an annual community-based, road running race held in South Africa that attracts thousands of participants globally.[3, 4] Compared to similar events, the incidence of medical encounters among Com-

rades race starters is exceptionally high.[3] Like other mass-participation events, exercise-associated muscle cramping (EAMC) is one of the most common medical encounters at the Comrades Marathon.[3, 5] EAMC are painful, spasmodic, and involuntary contractions of skeletal muscle that occur during or immediately after exercise,[1, 5, 6] and are common among athletes participating in endurance events.[1, 3, 7] The Ironman triathlon includes a 42.2 km run, and over two years, almost 50% of entrants reported an history of EAMC (hEAMC).[7] The lifetime prevalence of hEAMC among runners competing in the Two Oceans road running race was significantly higher among the 56 km race entrants (16%) than the 21.1 km entrants (8.8%).[1] A 6-year longitudinal study investigating acute medical encounters at the Comrades Marathon reported a EAMC incidence rate of 3.2/1000 starters.[3] The exact pathophysiology of EAMC remains unclear. Although a triad of causes that include altered neuromuscular control with dehydration has been proposed, the most substantial evidence supports the neuromuscular etiology with a focus on muscle fatigue.[8, 9] Among endurance athletes, muscle overload and fatigue, due to training and racing volume and intensity, affects the balance between the excitatory drive from muscle spindles and the inhibitory drive from the Golgi tendon organs, resulting in a localized muscle cramp.[8, 9] Considering the aforementioned distance-related increase in EAMC prevalence, muscle fatigue-related neuromuscular etiology is plausible. The association between previous training-related muscle injury and EAMC suggests that previous muscle damage could result in a 'reflex muscle spasm' resulting in localized EAMC.[10] Although the exact causes remain debatable, efforts to identify EAMC-related risk factors remain empirical. Sex, age, a history of chronic diseases and allergies have been identified as independent risk factors for hEAMC among runners competing in 21.1 km, and 56 km races.[1] The incidence of hEAMC is higher among, Ironman triathletes,[7] and ultra-distance runners.[1, 11] A history of chronic musculoskeletal injury and several training variables, including training pace, weekly frequency, and distance, is also associated with a hEAMC among, triathletes,[7] and half-, and ultramarathon runners.[1, 11] Runners participating in the Comrades Marathon cover more than twice the distance of the Ironman run segment and is >35 km further than the Two Oceans ultramarathon. Considering the significant difference in race profile and that EAMC is one of the most common specific diagnoses among Comrades runners,[3] research investigating risk factors for hEAMC is warranted. This study aimed to identify selected risk factors associated with an hEAMC in Comrades Marathon entrants. Findings from this study can assist in the effective anticipation and adequate planning, in terms of necessary medical care and sufficient staff and facilities, for treating EAMC encounters on race day.

Materials and methods

Study design and ethical concerns

This was a retrospective, cross-sectional analysis of data prospectively collected during the 2022 Comrades Marathon. The Research Ethics Committee of the tertiary institution where the research was conducted (REC number 763/2019) granted ethical approval for the study. This study is part of the larger SAFER (Strategies to reduce Adverse medical events For the Exercise R) studies.[12]

Participants and demographics

All entrants of the 2022 Comrades Marathon were invited to complete a voluntary, online, prerace medical screening questionnaire two to four months before the race. Participants who completed the questionnaire (screened) and consented to data being used for research were included in this study. Entrants of the Comrades Marathon are required to qualify for the race.[13] Race entrants were defined as any runner registering for the race. The race rules stipulate that entrants must be 20 years or older.

Online prerace medical questionnaire

The online prerace medical screening questionnaire (*i.e.*, self-assessment of risk) administered to all race entrants were previously described[14] and used in studies with similar aims.[6, 15, 16] The online prerace medical questionnaire included a specific question related to the previous occurrence of EAMC, such as: "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)?" Race entrants who responded "yes" and "no" to this question were respectively grouped as those with and without (control group) a lifetime history of EAMC (hEAMC). Information related to the clinical characteristics of hEAMC included the main muscle groups affected, timing and onset of cramping during training and racing, severity, and treatment of cramping, and postcramping conditions, including dark urine and confusion. Seven broad individual categories of risk factors for hEAMC were explored in this study: 1) demographics; 2) training-related variables; 3) history of chronic diseases; 4) history of collapse; 5) his-

tory of prescription medication use; 6) history of allergies; and 7) history of injuries (never, past injury within the past 12 months, past injury >12 months prior). Demographic information included sex, age, and self-reported calculated body mass index (BMI) (athletes reported their height and mass). Training-related variables included years of recreational running, frequency of training per week, average training distance per week, and average self-reported training speed (min/ km). History of chronic disease variables included cardiovascular disease [CVD] risk factors, history of CVD, CVD symptoms, respiratory, gastrointestinal, nervous system/psychiatric, kidney/bladder, metabolic/endocrine, hematological/immune disease, and cancer. Furthermore, a composite chronic disease score was calculated as a continuous score out of 10 using these 10 variables. Each category was given a maximum of 1 point (if the participant reported a condition) and then summed.

Outcomes

The primary outcome of this study was a lifetime hEAMC amongst race entrants participating in the 2022 Comrades Marathon. Secondary outcomes were: 1) the epidemiology of hEAMC (lifetime and past 12-month prevalence); 2) the clinical characteristics of EAMC (including main muscle groups affected, timing of onset during racing/training and treatment of EAMC); and 3) the independent risk factors associated with hEAMC (demographics, running training/racing history, history of chronic disease, collapse, medication use, allergies, and running injuries). While the 12-month prevalence is reported, statistical modelling was performed on the lifetime prevalence.

Statistical analysis

Electronic data was exported and transferred to SAS 9.4 for analysis (SAS Institute, Cary, NC, USA). The data from all entrants who completed the screening and gave consent were used for analysis. The demographics (sex and age group) of all entrants and that of the study group were described using numbers and percentages. The binary response variable was the response to the question relating to the history of muscle cramping (hEAMC): "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)?" The clinical characteristics of hEAMC overall and by sex and age group were described (N.; %). A generalized linear model was used with a binomial distribution and log link to estimate the prevalence of lifetime and 12-month hEAMC prevalence overall, and by risk factors, sex and age group, training history, chronic disease, allergies, and chronic injuries. Prevalence ratios (PR) were provided as a measure of the association between hEAMC and the mentioned risk factors. A multiple model provided the independent risk factors. For the continuous factors in the model, estimates were given at the 1st quartile, median and 3rd quartile and PRs were given at an appropriate × number of units. The significance level was 1% throughout.

Results

There were 16 479 entrants, of which 13 259 (80.46%) completed the screening, and 10973 (62.00%) consented to be included in this study. There were significantly more male than female entrants (78.4% males; P<0.001). Most (N.=4599; 41.91%) consenting athletes were between 41-50 years. Notable differences between all entrants and the study group were in the age groups >50 (1.7% more in all entrants) and the 31-40 (1.4% less in all entrants).

Lifetime and 12-month prevalence of hEAMC

In our study, 1582 (14.4%; 95% CI: 13.77-15.09) entrants reported a lifetime hEAMC, while 995 (9.1%; 95% CI: 8.65-9.62) suffered from EAMC during the last 12 months.

Clinical characteristics of hEAMC

The muscle group most commonly affected was the calf (N.=593; 37.48%), and hEAMC was mostly reported during the race's fourth quarter (N.=800; 50.57%). Most cramping episodes lasted less than five minutes (N.=1067; 67.45%) and did not prevent entrants from finishing the race or training session. To relieve an acute cramp, entrants mainly stretched (N.=1402; 88.62%) and rested (81.04%). Whole body cramping was experienced by 90 (5.69%) entrants, however few entrants (N.=47; 2.97%) required hospitalization, had dark urine, or experienced confusion after an EAMC episode.

Risk factors associated with hEAMC (Univariate analysis)

Demographics (sex and age groups)

The number (N.), frequency (%; 95% CI), and prevalence ratio (PR; 95% CI) of runners with hEAMC by sex and age group are shown in Table I. There was a significantly higher prevalence of male (16.10%; 95% CI:15.34-16.90) than female (8.31%;95% CI:7.27-9.50) entrants with hEAMC (PR=1.94; 95% CI:1.68-2.23). There was no significant

TABLE I.—*The frequency (%; 95% CI) and prevalence ratio (PR; 95% CI) of Comrades Marathon (90 km) entrants with a hEAMC by sex and age groups (univariate analysis).*

Characteristics	Consenting race entrants (N.=10973)	Consenting race entrants with hEAMC (N.=1582)	% entrants per group with hEAMC (95% CI)	PR (95% CI)	P value
Sex					
Female	2371	197	8.31 (7.27-9.50)	Ref	P<0.0001
Male	8602	1385	16.10 (15.34-16.90)	1.94 (1.68-2.23)	
Age groups (years)					
<30	474	75	15.82 (12.86-19.47)	Ref	P=0.3668
31-40	3438	484	14.08 (12.96-15.30)	1.12 (0.89-1.41	
41-50	4599	646	14.05 (13.08-15.09)	1.13 (0.90-1.40)	
>50	2462	377	15.31 (13.95-16.80)	1.03 (0.82-1.30)	

EAMC: exercise-associated muscle cramping; hEAMC: history of EAMC; PR: prevalence ratio; Ref: reference category.

difference in the prevalence of hEAMC among entrants in the different age categories (P=0.3668).

Training/racing variables

The prevalence ratio (PR; 95% CI) of entrants with hEAMC by training/racing variables are shown in Table II. An increase in entrants' average weekly training frequency (PR=0.88 for every one session increase, P<0.0001) and distance (PR=0.96 for every 10 km increase, P<0.0001) in the last 12 months were associated with a decreased risk (12% and 4%) of hEAMC. Whilst a slower training speed increased the risk of hEAMC (PR=1.07 per 1 min/ km increase; P=0.0015). Notably, the prevalence (13.7%) for 75 km distance run per week is higher than training 6 sessions per week (12.1%). This indicates that the risk of hEAMC is lower if runners increase their weekly training frequency as opposed to weekly training distance.

History of chronic diseases, allergies, and chronic injury

The frequency and PR of entrants with a history of EAMC by BMI, history of composite chronic disease score, history of collapse, current prescription medication use, allergies, and chronic musculoskeletal (MSK) injury are shown in Table III. The prevalence of lifetime MSK injury and chronic MSK injury in the past 12 months among entrants were 8.38% (N.=920) and 2.82% (N.=309) respectively. 11.56% (N.=1269) of entrants used medication to treat MSK injury. The prevalence of hEAMC was higher in entrants with a 1 disease increase in composite disease score (PR=1.37; 95% CI:1.30-1.44) and a 2 unit increase in BMI (PR=1.01; 95% CI: 1.00-1.02). The PR of hEAMC was significantly higher (P<0.001) in entrants who reported a history of cardiovascular disease (CVD) risk factors (PR=1.66), CVD symptoms (PR=3.19), respiratory disease (PR=1.44), gastrointestinal disease (PR=1.99), blad-

TABLE II.—*The prevalence ratio (PR: 95% CI) of Comrades Marathon race entrants with a hEAMC by training history variables (univariate analysis).*

Training variables	Points in the continuous variable#	% Entrants with hEAMC (N.=1582) (95% CI)	PR (95% CI)	P value
Number of years as a recreational runner (years)*	6	14.4 (13.8-15.1)	3-year increase	0.5540
	10	14.4 (13.8-14.9)		
	15	14.3 (13.7-14.8)	1.00 (0.98-1.01)	
Number of years participating in distance running events >2 years	5	14.5 (13.8-15.2)	2-year increase	0.7477
	7	14.4 (13.9-15.0)		
	10	14.3 (13.6-15.1)	1.00 (0.97-1.02)	
Average weekly training frequency in the last 12 months (times per week)	4	15.6 (15.0-16.2)	1-session increase	<0.0001
	5	13.7 (13.2-14.3)		
	6	12.1 (11.4-12.8)	0.88 (0.86-0.91)	
Average weekly running distance in the last 12 months (km)	50	15.1 (14.5-15.8)	10-km increase	<0.0001
	60	14.5 (14.0-15.1)		
	75	13.7 (13.1-14.3)	0.96 (0.95-0.97)	
Average training speed (min/ km)	5:25	14.0 (13.5-14.6)	1-min/ km increase	0.0015
	5:75	14.5 (14.0-15.0)		
	6:25	15.0 (14.3-15.6)	1.07 (1.03-1.11)	

EAMC: exercise-associated muscle cramping; hEAMC: history of EAMC; PR: prevalence ratio.
#Points on the continuous variables (points are the 1st quartile, median, 3rd quartile); *254 missing values for this variable.

TABLE III.—*The frequency (95% CI) and prevalence ratio (PR: 95% CI) of Comrades Marathon race entrants with hEAMC by BMI, history of chronic disease, collapse, allergies, and chronic musculoskeletal injury (univariate analysis).*

Characteristics	Race entrants with hEAMC (N.=1582)		PR (95% CI)	P value
	N.	Prevalence % (95% CI)		
Anthropometric characteristics				
BMI[#]	-			
22.2		14.21 (13.63-14.82)	2-unit increase	0.1718
24.2	-	14.34 (13.82-14.89)		
26.6	-	14.50 (13.96-15.06)	1.01 (1.00-1.02)	
History of chronic disease				
Composite chronic disease score				
0	-	13.26 (12.73-13.81)	1 disease increase	<0.0001
2	-	24.75 (22.49-27.24)	1.37 (1.30-1.44)	
4	-	46.21 (37.90-56.34)		
History of collapse				
Yes	117	31.62 (24.86-40.22)	2.22 (1.74-2.83)	<0.0001
No	80	14.23 (13.71-14.77)		
Medication use				
Current prescription medication use				
Yes	185	14.2 (13.7-14.8)	1.13 (1.01-1.26)	0.043
No	1397	16.0 (14.4-17.9)		
History of allergies				
Any allergies				
Yes	111	20.56 (17.89-23.62)	1.5 (1.3-1.7)	<0.0001
No	1471	14.10 (13.57-14.65)		
History of injury				
Chronic musculoskeletal injury				
Never	1341	13.34 (12.82-13.88)		<0.0001
Past >12 months ago	141	23.08 (20.42-26.08)	1.73 (1.52-1.97)^	
Past 12* months	100	32.36 (27.98-37.43)	2.43 (2.09-2.82)[§]	

EAMC: exercise-associated muscle cramping; hEAMC: history of EAMC; PR: prevalence ratio; CVD: cardiovascular disease; BMI: Body Mass Index.
[#]Points on the continuous variables (points are the 1st quartile, median, 3rd quartile); *of the 309 with injuries in the past 12 months, 274 (89%) reported that EAMC occurred after the chronic injury; ^PR past>12months *vs*. never; [§]PR past <12 months *vs*. never.

der or kidney disease (PR=1.83), blood or immune disease (PR=1.76), cancer (PR=1.61) allergies (PR=1.5), collapse that required medical attention (PR=2.22) and chronic musculoskeletal injury (past >12months [PR=1.73] and current <12months [PR=2.43]).

Independent risk factors associated with hEAMC (multiple model)

The independent risk factors (adjusted for sex) associated with hEAMC are summarized in Table IV. The prevalence of hEAMC was higher in entrants with a 1 disease increase in composite disease score (PR=1.31; 95% CI:1.25-1.39). An increase in 10 km average weekly training distance was associated with a lower risk of hEAMC (PR=0.97). Slower average running speed was associated with increased PRs for hEAMC among males and females (PR=1.07). There was an interaction between sex and running pace and the effect on the risk of hEAMC. Figure 1 shows the difference between the prevalence increase in hEAMC as the running pace increases. The risk of hEAMC for males running at faster paces was higher than that of females up to a speed of under 7.5 min/ km, after which the risk for males and females is similar.

Discussion

This is one of few studies describing the characteristics of hEAMC among ultramarathon runners and adds to the growing body of evidence related to risk factors for hEAMC among endurance athletes. The main findings were: 1) male sex; 2) certain chronic diseases, symptoms, and risk factors; 3) chronic musculoskeletal injury; and 4) average weekly training distance and speed were associated with hEAMC among Comrades Marathon runners.

Lifetime prevalence of hEAMC among Comrades Marathon entrants

In our study, 14.42% of entrants had a lifetime prevalence of hEAMC, which is lower than runners who participated in a 56 km ultramarathon (16%), endurance cyclists

TABLE IV.—*Independent risk factors (training, chronic disease, allergies, chronic musculoskeletal injury) associated with hEAMC in race entrants (multiple model, adjusted for sex).*

Risk factors	PR (95% CI)	P value
Running training/racing variables		
Average weekly running distance (km per week)*	10 km increase 0.97 (0.96-0.99)	0.0004
Average training speed (min/ km)*	1min/ km increase (slower) 1.07 (1.03-1.12)	0.0008
History of chronic disease		
Composite chronic disease score	1 disease increase 1.31 (1.25-1.39)	<0.0001
History of collapse (yes *vs*. no)	1.87 (1.47-2.38)	<0.0001
History of injury		
Chronic musculoskeletal injury		
Past# *vs*. never	1.71 (1.50-1.94)	<0.0001
Past 12 months *vs*. never	2.38 (2.05-2.77)	

Data were adjusted for sex.
EAMC: exercise-associated muscle cramping; PR: prevalence ratio.
*Continuous variable; #past chronic injury does not include chronic injury in the last 12 months.

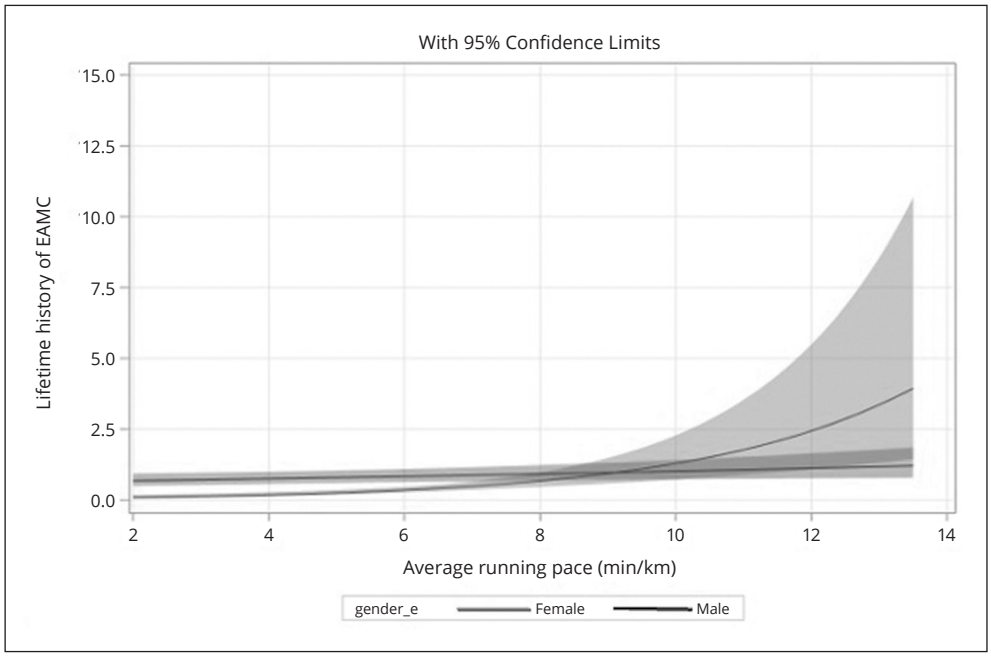

Figure 1.—The association between running pace and history of exercise-associated muscle cramping (prevalence; %) in multi-variate models that respectively include injury in the past 12 months.
MSK: musculoskeletal.
*The values at which the risk was calculated for an individual with the following: running 60 km per week, chronic disease score of 1, a history of collapse, and history of MSK injury in the past 12 months.

(60%)[17] and triathletes (57.4%-67.0%),[7, 17] but higher than 21.1 km runners (8.8%).[1] When interpreting these results, the differences in response rates, the number of participants, and individual and collective participant hEAMC risk profiles, especially regarding sex and age group, should be considered. The percentage of male entrants was higher in the Comrades Marathon (78%) compared to the 21.1 km (51%) and 56 km (71%) races. Age group composition also differed between races. The percentage of runners younger than 30 was much less for the Comrades Marathon (4%) than the 21.1 km (12%) and 56 km (35%) races, but higher for the age group 41-50 (21 km 20%, 56 km 34%, 90 km 42%). To make direct comparisons between the three races, future analysis will have to combine data from the three races or align sex and age profiles. As male sex was a risk factor for hEAMC in our study, subsequent analysis of independent risk factors was adjusted for sex. The differences in nature and physiological demands of the different sports should also be considered.[17] Further investigations to identify possible

reasons for differences in entrants' lifetime hEAMC between races are necessary.

Clinical characteristics of lifetime hEAMC in Comrades Marathon entrants

Muscle groups affected by hEAMC

In our study, the calf (37.48%) and hamstring (33.69%) muscle groups were affected mainly by EAMC. Similarly, among race entrants of a 56 km ultramarathon, the calves (47.5%) and hamstrings (21%) were most frequently affected by EAMC.[1] Among endurance cyclists, the quadriceps muscle group was the most affected by EAMC (47.7%), followed by the calf muscles (27.8%) and the hamstring muscles (20.4%). EAMC usually occurs in multi-joint muscle groups,[2] and is confined to muscle groups primarily used during an athletic event.[2, 17] During the push-off phase in running, the calf muscles are primarily responsible for ankle plantar flexion and assist in knee flexion, while the hamstring muscle group primarily flexes the knee and assists in hip extension. This could explain why EAMC mainly occurred in runners' calf and hamstring muscles. In cycling, however, the knee extensor group (quadriceps) are prime movers during the downstroke phase of cycling, while the hamstring, calf, and hip flexor muscles are responsible for the upward pull.[18] The extent and way different muscle groups are recruited during different activities could explain the differences in the distribution of EAMC.

Timing of onset of EAMC during racing/training

Entrants in this study (50.6%) and those participating in 56 km Ultramarathon (47.0%)[1]nand triathletes (57.4%)[7] all reported that EAMC mainly occurred in the final quarter of the race or training session. This consistent finding highlights the trend that prolonged exercise is associated with a higher risk of experiencing EAMC and supports the continued research focus on fatigue-related neuromuscular etiology for EAMC.[5, 8, 17]

Risk factors associated with lifetime hEAMC in Comrades Marathon entrants

Sex

Similar to the findings of studies that investigate 21.1 km (PR=1.9) and 56 km (PR=2.0) race entrants[15, 19] and triathletes,[7] the prevalence ratio (PR=1.94) of hEAMC was significantly higher among male than female Comrades entrants. The prevalence of hEAMC among male runners is, therefore twice (rounded) that of female runners. These findings confirm that sex is significantly associated with hEAMC among distance runners. Sex-related physiological and anatomical differences result in profound differences in fatigability between sexes.[20] Although the exact mechanisms and functional consequences are not fully understood, females are usually less fatigable than males.[20] In the context of the proposed muscle fatigue-related etiology of hEAMC,[8, 17, 21] this might provide a plausible explanation for this finding.

Training variables

An increase of 10 km average weekly training distance was associated with a lower risk of hEAMC. While average weekly training distance was not an independent hEAMC risk factor among runners in a 21.1 km and 56 km races,[19] an increase in weekly training frequency was. Increased training frequency might be associated with increased distances, depending on the distance covered per training session, explaining these similarities. Slower running speed was associated with a higher risk of hEAMC among runners in our study as well as those participating in 21.1 km and 56 km races.[19] Slower running paces leads to longer race duration and, in turn, increased levels of neuromuscular fatigue. These results once again support the muscle fatigue hypothesis related to muscle cramping.[8, 17, 21] Training speed was also not associated with hEAMC among marathon runners.[22] It should be noted that training speed in our, and all studies referenced above, was self-reported and not measured objectively. These results should therefore be interpreted with caution. Due to the cross-sectional nature of the above studies and differences among study participants, direct insight into the underlying reasons for the difference in findings amongst studies are unclear.

Chronic diseases and history of allergies

A hEAMC has been associated with a two-disease increase in composite chronic disease score among runners participating in 21.1 km (PR=1.9) and 56 km (PR=1.6) races.[15, 19] Similarly, among Comrades race entrants, a one-disease increase in composite chronic disease score was associated with increased hEAMC risk (PR=1.31). We also investigated chronic diseases and chronic disease risk factors individually as an individual analysis provides more details regarding the association between specific chronic diseases and hEAMC. An hEAMC was significantly higher ($P<0.004$) among entrants with CVD risk factors (PR=1.42), CVD symptoms (PR=2.38), gastrointestinal disease (PR=1.62), blood and immune disease

(PR=1.75), and previous collapse requiring medical attention (PR=1.98), and a history of allergies (PR=1.26). It should be noted that the composite disease scores reported have not been validated. Like race entrants of 21.1 km (PR=1.4) and 56 km (PR=1.2) running races,[19] allergies were associated with hEAMC among Comrades Marathon entrants (PR=1.26). Runners with various underlying chronic diseases and allergies have a significantly higher risk of medication use,[16] Studies have therefore hypothesized that the mechanism of EAMC might be related to the underlying chronic condition or medications used to treat these conditions and allergies.[9, 15, 17] The findings of this study, therefore, reiterates the need for further investigation to explore this hypothesis.

Chronic musculoskeletal injury

The prevalence of hEAMC was higher among entrants with a history of chronic injury (PR=1.69). Similarly, chronic musculoskeletal injury was also identified as an hEAMC risk factor among Ironman triathletes,[7] and 21.1 km and 56 km race entrants.[15, 16, 19] The altered neuromuscular control theory suggests that EAMC results from a combination of factors, including fatigue, inadequate conditioning, and muscle damage, ultimately increasing alpha motor neuron excitability.[17, 23] Our findings support this theory as previously injured soft tissue structures may be vulnerable to fatigue due to weakness if treatment and rehabilitation of the injury are ineffective at the time of injury.

Limitations of the study

Strengths of this paper are the large sample size (N.=10973) and that it is one of few studies reporting on the association between independent risk factors and hEAMC in ultramarathon entrants. Although the study sample attempted to include all entrants, there was a difference between the consenting and all race entrants by age group and sex. Limitations of the study are the following: 1) due to the cross-sectional nature of the study, a cause-effect relationship between any of the identified risk factors and hEAMC could not be determined; 2) all EAMC, training, and chronic disease data were self-reported, which is subject to recall bias; 3) data were collected from a single race, representing a homogenous sample; and 4) the composite disease scores reported have not been validated. Future studies are needed to explore the causal relationship between the risk factors identified and EAMC in runners. The consistency in findings among endurance athletes, specifically ultramarathon runners, warrants further investigation into the direct causal relationship between sex, history of chronic diseases, and hEAMC. Not all entrants completed the screening questionnaire upon entry and consented for their data to be used for analysis (10,973/16 479=66.6%), and there was a difference in the rate for age groups (highest in the age group 31-40 69.6% and lowest in the age group 51+62%) between entrants and consenters.

Conclusions

Male sex, training-related factors, chronic diseases, history of allergies, and chronic musculoskeletal injury were identified as risk factors for hEAMC among Comrades Marathon entrants. Future research should investigate the causal relationship between the risk factors identified and hEAMC in ultramarathon runners. The results of this study could assist medical professionals involved in mass community-based participation events in the effective anticipation and adequate planning, in terms of necessary medical care and sufficient staff and facilities, for treating EAMC encounters on race day.

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Conflicts of interest

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Authors' contributions

Candice MacMillan, Martin Schwellnus, Marlise Dyer and Esme Jordaan have given substantial contributions to the data interpretation; Candice MacMillan and Martin Schwellnus contributed to the manuscript first draft; Candice MacMillan, Nicola Sewry, Martin Schwellnus, Marlise Dyer and Esme Jordaan contributed to the manuscript editing; Nicola Sewry and Martin Schwellnus contributed to the manuscript critical revision for important intellectual content; Martin Schwellnus, Jeremy Boulter and Esme Jordaan contributed to the study design; Martin Schwellnus and Jeremy Boulter contributed to the study conception and to the data collection; Marlise Dyer and Esme Jordaan contributed to the data analysis and interpretation. All authors read and approved the final version of the manuscript.

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