Underlying Chronic Disease, Medication Use, History of Running Injuries and Being a More Experienced Runner Are Independent Factors Associated With Exercise-Associated Muscle Cramping: A Cross-Sectional Study in 15778 Distance Runners

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Abstract

Background: Exercise-associated muscle cramping (EAMC) is a significant medical complication in distance runners, yet factors associated with EAMC are poorly documented. **Objective:** To document risk factors associated with EAMC in runners. **Design:** Cross-sectional study. **Setting:** Two ocean races (21.1 km, and 56 km). **Participants:** Fifteen thousand seven hundred seventy-eight race entrants. **Methods:** Participants completed a prerace medical history screening tool including: training, cardiovascular disease (CVD), risk factors for, and symptoms of CVD, history of diseases affecting major organ systems, cancer, allergies, medication use, and running injury. Runners were grouped as having a history of EAMC (hEAMC group = 2997) and a control group (Control = 12 781). **Results:** Independent factors associated with a higher prevalence ratio (PR) of hEAMC were any risk factor for CVD (PR = 1.16; $P = 0.0002$), symptoms of CVD (PR = 2.38; $P < 0.0001$), respiratory disease (PR = 1.33; $P < 0.0001$), gastrointestinal disease (PR = 1.86; $P < 0.0001$), nervous system or psychiatric disease (PR = 1.51; $P < 0.0001$), kidney or bladder disease, (PR = 1.60; $P < 0.0001$), haematological or immune disease (PR = 1.54; $P = 0.0048$), cancer (PR = 1.34; $P = 0.0031$), allergies (PR = 1.37; $P < 0.0001$), regular medication use (PR = 1.80; $P < 0.0001$), statin use (PR = 1.26; $P = 0.0127$), medication use during racing (PR = 1.88; $P < 0.0001$), running injury (PR = 1.66; $P < 0.0001$), muscle injury (PR = 1.82; $P < 0.0001$), tendon injury (PR = 1.62; $P < 0.0001$), and runners in the experienced category (PR = 1.22; $P < 0.0001$). **Conclusion:** Novel risk factors associated with EAMC in distance runners were underlying chronic disease, medication use, a history of running injuries, and experienced runners. These factors must be identified as possible associations, and therefore be considered in the diagnosis and treatment of EAMC.

Key Words: muscle cramping, endurance running, risk factors, chronic disease, medication, cross-sectional study, ultramarathon, half-marathon, medical complications, epidemiology

(*Clin J Sport Med* 2018;28:289–298)

Submitted for publication September 28, 2016; accepted May 9, 2017.

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Partial support from the IOC Research Centre funding (South Africa). South African Medical Research Council (partial funding, statistical analysis).

The authors report no conflicts of interest.

M. P. Schwellnus: responsible for the overall content as guarantor, study concept, study planning, data collection, data interpretation, manuscript (first draft), manuscript editing, facilitating funding. W. Derman: data collection, data interpretation, manuscript editing. S. Swanevelder: study planning, data analysis including statistical analysis, data interpretation, manuscript editing. E. Jordaan: study planning, data analysis including statistical analysis, data interpretation, manuscript editing. D. C. Janse Van Rensburg: data interpretation, manuscript editing.

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http://dx.doi.org/10.1097/JSM.0000000000000456

INTRODUCTION

Exercise-associated muscle cramping (EAMC) is a clinical syndrome defined as "painful, spasmodic, and involuntary contractions of skeletal muscle that occur during or immediately after exercise."[1–6] Exercise-associated muscle cramping is one of the most common complications that require medical attention during or immediately after sports events, in particular in endurance events such as distance running.[3,7–10] As a result of the high prevalence of EAMC in endurance athletes[11] (30%-50% in distance runners), it is important to determine the etiology and risk factors for EAMC, to implement prevention and management strategies.

Historically, dehydration and electrolyte depletion have been postulated as the causes of EAMC, but this has not been supported by data from prospective[12,13] and other studies.[14] Rather, there is now substantial evidence that EAMC is not a single disease entity but rather a clinical syndrome that occurs as a result of a common pathophysiological process that is characterized by a disturbance in neuromuscular control at the level of the spinal cord in the central nervous system.[2] In recently published extensive reviews of existing

experimental evidence, it was concluded that (1) evidence supporting a link between altered serum electrolyte concentrations and EAMC is poor,[15] (2) there is unambiguous proof that spinal (central nervous system) mechanisms are involved in the generation and development of muscle cramps during exercise,[16] and (3) that the "altered neuromuscular control theory" seems to be the most scientifically acceptable theory of EAMC.[17] Therefore, the focus to determine the etiology of EAMC now shifts to the identification of specific risk factors that may alter motor neuron hyperexcitability resulting from afferent synaptic inputs (and amplified by supra-spinal inputs) as this is the plausible common mechanism underlying a number of different types of cramp contractions, including EAMC.

It has already been shown that increased exercise intensity (running speed),[18,19] a history of a running injury,[18] a history of prerace muscle damage[19] or injury,[20] a history of muscle cramping,[18,19] and possible genetic factors[21] are etiological factors associated with EAMC in endurance athletes. Furthermore, we previously hypothesized that the final common pathway of these factors is that they can all be associated with increased motor neuron hyperexcitability.[2]

It is well established that skeletal muscle cramping is also a clinical syndrome that is associated with a number of chronic diseases.[16,22,23] More specifically, skeletal muscle cramping is associated with chronic disease in a number of organ systems including cardiovascular disease (CVD), neurological disease, endocrine disease, renal disease, gastrointestinal (GIT) disease,[24] metabolic diseases[16] and cancers. Skeletal muscle cramping, including nocturnal cramping, is also an unwanted side effect of a variety of medications that are used in the treatment of these chronic diseases.[25–38] Therefore, muscle cramping may occur as a clinical manifestation of many underlying medical conditions or can occur as a result of the use of a variety of medications to treat these conditions.[5,22,23]

Participation in regular physical activity is also part of the prevention and management of patients suffering from chronic diseases in these organ systems. As a result, an increasing number of individuals with risk factors for chronic diseases or known chronic disease participate in recreational endurance running events, where EAMC is a common clinical syndrome presenting to the medical staff during or after these events. We hypothesize that in a group of runners, EAMC may represent an "unmasking" of latent chronic disease or be associated with known underlying chronic diseases, medication use and underlying injury in athletes. However, to our knowledge, the association between EAMC in active individuals and underlying chronic disease, medication use and injury has not been investigated.

The objective of this study was to determine whether there is an association between a history of EAMC (hEAMC) in distance runners and underlying chronic diseases, risk factors for chronic diseases, medication use, underlying musculoskeletal injury and runner category (novice to experienced).

METHODS

Participants

In an ongoing series of studies to reduce adverse medical events during exercise,[39] all race entrants from the 2 ocean marathon races in 2012 were required to complete an online medical questionnaire at the time of registration. A total of 25 455 entrants who registered for the 21.1 or 56 km races completed the prerace medical questionnaire. Race entrants were given the opportunity to sign an informed consent form, giving permission that data may be used for research purposes, and 15 778 race entrants gave consent (62% response rate). This group was included as participants in this study.

Although the response rate was acceptable, a post hoc analysis was conducted to determine whether the participants in this study were indeed representative of all the race entrants. The profile [race type (21.1 vs 56 km runners), sex, and age] of all race entrants (n = 25 455) and the final participants in this study (n = 15 778) is presented in Table 1.

In general, the profile of the participants in this study was very similar for race type and sex to that of all race entrants, as well as all the runners who gave consent to be contacted for research. A notable exception was the age distributions, where significantly ($P < 0.05$) fewer runners in the middle age category (31-39 years) and significantly ($P < 0.05$) more in the younger and older age categories completed or consented to the study than expected from the number of runners who entered the race. In the study population, the mean (± SD) of the 56 km runners was 41.7 ± 9.4 years, and for the 21.1 km runners was 35.6 ± 11.4 years. In the 56 km runners, the largest proportion of runners was in the ≥40-year age category (56%), followed by 32% of 56-km runners in the 31 to 39-year age category. In the 21.1-km runners, the largest proportion of runners (40%) was in the <30-year age category, followed by 33% of runners in the ≥40-year category.

Before the onset of the study, the Research Ethics Committee of the University of Cape Town, Faculty of Health Sciences, approved the study (REC 009/2011). The Research Ethics Committee of the Faculty of Health Science at the University of Pretoria (433/2015) also approved the study, including the ongoing analysis of the data presented in this article.

Medical Screening Data

The online medical screening tool consisted of a series of questions that were specifically developed to provide clinical

TABLE 1. The Profile by Race Type, Sex, and Age Groups of All Race Entrants and Runners Who Participated in This Study

	All Race Entrants (n = 25 455)	Runners Participating in This Study (n = 15 778)
	N (%)	N (%)
Race type, km		
21.1	16 284 (64.0)	10 786 (68.4)
56	9171 (36.0)	4992 (31.6)
Sex		
Males	14 775 (58.0)	8916 (56.5)
Females	10 680 (42.0)	6862 (43.5)
Age groups, yrs		
≤30	7471 (29.4)	4951 (31.4)*
31-39	8074 (31.7)	4499 (28.5)*
≥40	9910 (38.9)	6328 (40.1)*

*Study participants significantly different from all race entrants ($P < 0.05$).

information for medical staff on race day. The main sections of the screening tool were based on the guidelines for cardiovascular evaluation of middle-aged/senior individuals engaged in leisure-time sport activities (Position stand from the European Association of Cardiovascular Prevention and Rehabilitation).[40] We added additional questions, specifically related to common medical complications encountered during running. Therefore, the final screening questions related to both training history and the following main categories of medical history: CVD, risk factors for CVD, symptoms of CVD, respiratory disease, metabolic or hormonal disease, GIT disease, nervous system disease, renal or bladder disease, haematological or immune system disease, cancer, allergies, general medication use, medication use during racing, and running injury (current or recent—last 12 months). If a runner answered "yes" to any of the main categories of questions, additional dropdown boxes appeared and runners were then required to add more specific details of the medical history in each main category. A pilot study to determine the feasibility and application of the questionnaire was conducted in 2011 during the prerace registration period and was on a voluntary basis. In this pilot study >6000 runners completed the screening questionnaire. Based on runner responses, the final questionnaire was developed. However, no specific validation study of the questionnaire was performed.

Exercise-Associated Muscle Cramping Group

In the medical screening tool, runners were specifically asked to answer the following question related to 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, runners were grouped as having hEAMC (hEAMC group = 2997, 21.1 km = 1503, 56 km = 1494). Therefore, the lifetime prevalence (%) of EAMC in the study participants was 19% [95% confidence interval (CI): 18.4-19.6], with the lifetime prevalence of EAMC in 56-km runners (29.9%, 95% CI: 28.7-31.2) being significantly higher than runners entering for the 21.1 km (13.9%, 95% CI: 13.3-14.6).

Risk Factors Associated With a History of EAMC in Runners

In this study, the following main categories of intrinsic risk factors associated with hEAMC in distance runners were explored: (1) runner demographics (age, sex, and race distance), (2) training history (years of recreational running, training sessions per week in the last 12 months, and training speed in the last 12 months), (3) a history of existing chronic disease (CVD), risk factors for CVD, symptoms of CVD, respiratory disease, endocrine disease, GIT disease, nervous system or psychiatric disease, kidney or bladder disease, hematological system disease, immune system disease, cancer, and allergies, (4) medication use (regular use of any medication and use of medication during racing), and (5) a history of running injuries (current and in the last 12 months).

Statistical Analysis

All data from the 2012 runner and medical screening database were entered into an Excel spread sheet (Microsoft 2010) and then analyzed using the SAS Enterprise Guide (V6.1) statistical program.

Three training variables (years participating in distance races; times run/train/race per week; and average training speed) were subjected to a Principal Component Analysis (PCA) to derive a linear composite variable of the 3 training variables. The first principal component from the PCA, explaining 46.6% of the variation, was then grouped into tertiles to reflect 3 runner categories: "novice" runners (on average few years of running, low number of weekly training sessions, and slow training speed), "intermediate" runners (on average intermediate number of years of running, intermediate weekly number of training sessions, and intermediate training speed) and "experienced" runners (on average high number of years of running, highest number of weekly training sessions, and faster training speed). This 3-level composite variable was also included in the subsequent regression analysis.

The binary-scaled response variable was the response to the question on hEAMC. Because of the cross-sectional nature of the study, we used log-binomial regression to directly estimate risk ratios (RRs) for the main category risk factors. However, convergence problems may arise with binomial regression models; in this case, they may fail to provide an estimate of the RR. To avoid this, we approximated the relative risk using the Poisson regression model with a robust error variance.[41] Risk ratios (95% CIs), also indicated as prevalence ratios (PRs), were reported for all the results. The statistical significance level was 5%, unless specified otherwise.

Univariate regression models on all main category risk factors obtained the crude unadjusted RR (PRs and 95% CIs) of hEAMC for each risk factor separately. The multiple regression models, by main categories of chronic disease or symptoms, medications use, injuries, training history, and runner category, adjusted the univariate PRs for sex, age category, and race distance.

RESULTS

Univariate Logistic Regression Analysis of Main Categories of Risk Factors for hEAMC

Runner Demographics

The frequency (%) and prevalence ratio (PR; with 95% CI) of runners with hEAMC by age category, sex, and race distance is depicted in Table 2.

The mean (±SD) age for 56 km runners in the hEAMC group was 42.7 ± 9.7 years and for 56-km runners in the control group was 41.3 ± 9.3 years. The mean (±SD) age for 21.1 km runners in the hEAMC group was 37.0 ± 12.3 years and for 21.1 km runners in the control group was 35.4 ± 11.2 years. Two-way interactions for race type, sex, and age were included in the analysis for runner demographics, resulting in a significant interaction between race type and age ($P < 0.0001$). The results indicated that a significant increase ($P < 0.0002$) in hEAMC risk for 21.1-km runners after the age of 40, while a significant increase in hEAMC risk for 56 km runners already occurred after the age of 30 ($P < 0.003$).

The crude unadjusted analysis showed that there was a significantly higher hEAMC prevalence ratio (PR) for runners in the 31 to 39-year category (18.4%, PR = 1.27; $P < 0.0001$) and the ≥40-year category (23.0%, PR = 1.59; P

TABLE 2. The Frequency (%) and Prevalence Ratio (PR; With 95% CI) of Runners With hEAMC by Age Category, Sex, and Race Distance

	% hEAMC	n	PR	95% CIs	*P*
Age categories, yrs					
≤30	14.5	4951			
31-39	18.4	4499	1.27	1.15-1.40	<0.0001
≥40	23.0	6328	1.59	1.46-1.73	<0.0001
Race, km					
21.1	13.9	10 786			
56	29.9	4992	2.15	2.02-2.29	<0.0001
Sex					
Female	12.2	6862			
Male	24.3	8916	1.99	1.84-2.16	<0.0001

% hEAMC, frequency (%) of runners with history of EAMC in each category; n, number of runners in study; P, P *value; PR, Prevalence ratio.*

< 0.0001) compared with runners in the younger (≤30 years) category (14.5%). Furthermore, the PR of hEAMC was significantly higher in male versus female runners (PR = 1.99; $P < 0.0001$) and runners competing in the 56-km versus the 21.1-km race (PR = 2.15; $P < 0.0001$).

Training History and Runner Category

The frequency (%) and prevalence ratio (PR; with 95% CI) of runners with hEAMC, by training history and runner category, is depicted in Table 3.

The crude unadjusted analysis showed that runners reporting >3 years of recreational running (PR = 1.80; 95% CI: 1.68-1.94; $P < 0.0001$) and those training >3 times per week (PR = 1.33; 95% CI: 1.25-1.42; $P < 0.0001$) had a significantly higher PR of hEAMC. Slower runners (>6 minutes per km running pace) had a significantly lower PR of hEAMC (PR = 0.77; 95% CI: 0.71-0.84; $P < 0.0001$). Furthermore, runners classified as either intermediate (PR = 1.34; 95% CI: 1.22-1.49; $P < 0.0001$) or experienced (PR = 1.97; 95% CI: 1.80-2.16; $P < 0.0001$) had a significantly higher PR of hEAMC compared with runners classified as novice.

History of Chronic Disease

The frequency (%) and prevalence ratio (PR; with 95% CI) of runners with hEAMC by a history of main categories of chronic disease is depicted in Table 4.

In the study population, the prevalence of a history of any CVD was 2.3% (95% CI: 2.0-2.5). The crude unadjusted analysis showed that the PR of hEAMC runners with a history of CVD was significantly higher compared with runners without CVD (PR = 1.31; $P = 0.0015$). In the study population, the prevalence for a history of any risk factors for CVD was 16.1% (95% CI: 15.5-16.7) and runners with a history of any risk factors for CVD had a significantly higher PR of hEAMC compared with runners without any risk factors for CVD (PR = 1.39; $P < 0.0001$). The prevalence for a history of any symptoms of CVD was 1.8% (95% CI: 1.6-2.0) and runners with a history of symptoms of CVD had a significantly higher PR of hEAMC

TABLE 3. The Frequency (%) and Prevalence Ratio (PR; With 95% CI) of Runners With hEAMC by Training History and Runner Category

	% hEAMC	n	PR	95% CIs	*P*
Recreational runner, yrs					
≤3	13.7	8101			
>3	24.6	7671	1.80	1.69-1.94	<0.0001
Last 12 mo, train and race (times a week)					
≤3	16.5	8301			
>3	21.9	7414	1.33	1.25-1.42	<0.0001
Last 12 mo, average training speed, min/km					
≤6	20.5	10 709			
>6	15.8	4784	0.77	0.71-0.83	<0.0001
Runner category (PCA)					
Novice	13.3	5119			
Intermediate	17.8	5126	1.34	1.22-1.49	<0.0001
Experienced	26.1	5145	1.97	1.80-2.16	<0.0001

% hEAMC, frequency (%) of runners with history of EAMC in each category; n, number of runners in study; P, P *value; PR, Prevalence ratio.*

TABLE 4. The Frequency (%) and Prevalence Ratio (PR; With 95% CI) of Runners With hEAMC by History of Main Category of Chronic Disease

	% hEAMC	n	PR	95% CIs	*P*
Any history of CVD					
No	18.9	15 418			
Yes	24.7	360	1.31	1.11-1.55	0.0015
Any risk factor for CVD					
No	17.9	13 234			
Yes	24.8	2544	1.39	1.29-1.49	<0.0001
Any symptoms of CVD					
No	18.6	15 494			
Yes	39.8	284	2.14	1.90-2.41	<0.0001
Any respiratory disease					
No	18.7	13 717			
Yes	21.3	2061	1.14	1.04-1.24	0.0034
Any endocrine disease					
No	19.0	15 226			
Yes	18.8	552	0.99	0.83-1.18	0.9254
Any GIT disease					
No	18.4	15 095			
Yes	32.4	683	1.76	1.60-1.94	<0.0001
Any nervous system/psychiatric disease					
No	18.8	15 185			
Yes	23.6	593	1.25	1.09-1.44	0.0012
Any kidney or bladder disease					
No	18.7	15 420			
Yes	30.2	358	1.61	1.40-1.85	<0.0001
Any hematological or immune disease					
No	19.0	15 640			
Yes	23.9	138	1.26	0.96-1.66	0.0981
Any cancer					
No	18.9	15 480			
Yes	25.5	298	1.35	1.13-1.61	0.0009
Any allergies					
No	18.4	13 589			
Yes	22.8	2189	1.24	1.15-1.35	<0.0001

% hEAMC, frequency (%) of runners with history of EAMC in each category; n, number of runners in study; P, P *value; PR, Prevalence ratio.*

compared with runners without symptoms of CVD (PR = 2.14; $P < 0.0001$).

The prevalence of a history of other chronic disease in this population was as follows: a history of respiratory disease was reported by 13.1% (95% CI: 12.5-13.6) and the crude unadjusted analysis showed that runners with a history of respiratory disease had a significantly higher PR of hEAMC compared with runners without respiratory disease (PR = 1.14; $P = 0.0034$). Endocrine disease was reported by 3.5% (95% CI: 3.2-3.8), and runners with a history of endocrine disease did not have a higher PR of hEAMC compared with runners without endocrine disease (PR = 0.83; $P = 0.9254$). Gastrointestinal disease was reported by 4.3% (95% CI: 4.0-4.6) of the study population, and runners with a history of GIT disease had a significantly higher PR of hEAMC compared with runners without GIT disease (PR = 1.76; $P < 0.0001$). In the study population, the prevalence of a history of nervous system/psychiatric disease was 3.8% (95% CI: 3.5-4.1), and the runners with a history of nervous system/psychiatric disease had a significantly higher PR of hEAMC compared with runners without nervous system/psychiatric disease (PR = 1.25; $P = 0.0012$). A history of kidney/bladder disease was reported by 2.3% (95% CI: 2.0-2.5) of runners, and these runners had a significantly higher PR of hEAMC compared with runners without kidney/bladder disease (PR = 1.61; $P < 0.0001$).

The prevalence of any haematological or immune system disease was 0.9% (95% CI: 0.7-1.0). The crude unadjusted analysis showed that runners with a history of haematological or an immune system disease did not have a higher PR of hEAMC compared with runners without haematological or an immune system disease (PR = 1.26; $P = 0.0981$). However,

TABLE 5. The Frequency (%) and Prevalence Ratio (PR; With 95% CI) of Runners With hEAMC by History of Regular Use of Any Medications, and Use of Medication During Racing

	% hEAMC	n	PR	95% CIs	*P*
Any regular medication use					
No	16.0	12 998			
Yes	33.0	2780	2.06	1.94-2.19	<0.0001
Any statin use					
No	16.0	12 998*			
Yes	23.8	403	1.49	1.27-1.74	<0.0001
Any medication use during racing					
No	16.8	14 078			
Yes	37.6	1700	2.24	2.11-2.39	<0.0001

** No regular medication use acted as the reference group.*
% hEAMC, frequency (%) of runners with history of EAMC in each category; n, number of runners in study; P, P *value; PR, Prevalence ratio.*

runners with a history of cancer (prevalence 1.9%; 95% CI: 1.7-2.1) had a higher PR of hEAMC compared with runners without a history of cancer (PR = 1.35; $P = 0.0009$). Finally, the reported prevalence of any allergies in runners was 13.9% (95% CI: 13.3-14.4), and runners with a history of any allergies had a significantly higher PR of hEAMC compared with runners without a history of any allergies (PR = 1.24; $P < 0.0001$).

History of Regular Use of Any Medications and Use of Medication During Racing

The frequency (%) and prevalence ratio (PR; with 95% CI) of runners with hEAMC by regular use of any medications, and medication use during racing is depicted in Table 5.

In the study population, the prevalence of regular use of any medications was 15.6% (95% CI: 15.0-16.2) and the use of any medication during racing was 10.8% (95% CI: 10.3-11.3). The crude unadjusted analysis showed that runners with a history of regular use of any medications had a significantly higher PR of hEAMC compared with runners not using any medications (PR = 2.06; $P < 0.0001$). In addition, runners reporting use of any statins (overall prevalence of use of 2.6%) had a significantly higher PR of hEAMC compared with runners not using any regular medication (PR = 1.49; $P < 0.0001$) and that runners using any medication during racing (prevalence 10.8%) had a significantly higher PR of hEAMC compared with runners not using any medication during racing (PR = 2.24; $P < 0.0001$).

History of Running Injuries

The frequency (%) and prevalence ratio (PR; with 95% CI) of runners with hEAMC by a history of any running injury and subgroups of any muscle or tendon injury are depicted in Table 6.

In the study population, the prevalence of a history of a running injury was 17.2% (95% CI: 16.6-17.8). The crude unadjusted analysis showed that runners with a history of any running injury had a significantly higher PR of hEAMC compared with runners with no history of a running injury (PR = 1.76; $P < 0.0001$). Furthermore, runners with a history of muscle injury (prevalence 7.2%; PR = 1.98; $P < 0.0001$) as well as runners with a history of a tendon injury (prevalence 4.9%; PR = 1.72; $P < 0.0001$) had a significantly higher PR of hEAMC compared with runners with no history of a running injury.

Multiple Regression Analysis of Main Categories of Risk Factors for hEAMC

The frequency (%) and adjusted prevalence ratio (PR; with 95% CI) of runners with hEAMC by main categories of

TABLE 6. The Frequency (%) and Prevalence Ratio (PR; With 95% CI) of Runners With hEAMC by History of Any Running Injuries

	% hEAMC	n	PR	95% CIs	*P*
Any running injury					
No	16.8	13 068			
Yes	29.6	2710	1.76	1.65-1.87	<0.0001
Any muscle injury					
No	16.8	13 068*			
Yes	33.3	1133	1.98	1.83-2.14	<0.0001
Any tendon injury					
No	16.8	13 068*			
Yes	28.9	776	1.72	1.55-1.90	<0.0001

** No running injury acted as the reference group.*
% hEAMC, frequency (%) of runners with history of EAMC in each category; n, number of runners in study; P, P *value; PR, Prevalence ratio.*

TABLE 7. The Adjusted* Frequency (%) and Prevalence Ratio (PR; With 95% CI) of Runners With hEAMC by Combined Main Categories of Risk Factors (History, Illness, Symptoms, Medications Use, Injuries, and Runner Category)

	% hEAMC	n	PR	95% CIs	*P*
Any history of CVD					
No	18.9	15 418			
Yes	24.7	360	1.18	0.99-1.41	0.0722
Any risk factor for CVD					
No	17.9	13 234			
Yes	24.8	2544	1.31	1.21-1.42	<0.0001
Any CVD symptoms					
No	18.6	15 494			
Yes	39.8	284	2.38	2.06-2.75	<0.0001
Any respiratory disease					
No	18.7	13 717			
Yes	21.3	2061	1.33	1.22-1.45	<0.0001
Any endocrine disease					
No	19.0	15 226			
Yes	18.8	552	1.18	0.99-1.39	0.0649
Any GIT disease					
No	18.4	15 095			
Yes	32.4	683	1.86	1.67-2.07	<0.0001
Any nervous system or psychiatric					
No	18.8	15 185			
Yes	23.6	593	1.51	1.30-1.75	<0.0001
Any kidney/bladder disease					
No	18.7	15 420			
Yes	30.2	358	1.60	1.37-1.88	<0.0001
Hematological/Immune disease					
No	19.0	15 640			
Yes	23.9	138	1.54	1.14-2.08	0.0048
Any cancer					
No	18.9	15 480			
Yes	25.5	298	1.34	1.10-1.62	0.0031
Any allergies					
No	18.4	13 589			
Yes	22.8	2189	1.37	1.26-1.49	<0.0001
Any regular medication use					
No	16.0	12 998			
Yes	33.0	2780	1.80	1.68-1.92	<0.0001
Any statin use					
No	16.0	12 998†			
Yes	23.8	403	1.26	1.05-1.51	0.0127
Any medication use during racing					
No	16.8	14 078			
Yes	37.6	1700	1.88	1.75-2.03	<0.0001
Any running injury					
No	16.8	13 068			
Yes	29.6	2710	1.66	1.55-1.78	<0.0001
Any muscle injury					
No	16.8	13 068‡			
Yes	33.3	1133	1.82	1.67-1.99	<0.0001

TABLE 7. The Adjusted* Frequency (%) and Prevalence Ratio (PR; With 95% CI) of Runners With hEAMC by Combined Main Categories of Risk Factors (History, Illness, Symptoms, Medications Use, Injuries, and Runner Category) *(Continued)*

	% hEAMC	n	PR	95% CIs	P
Any tendon injury					
No	16.8	13 068‡			
Yes	28.9	776	1.62	1.44-1.82	<0.0001
Runner category (PCA)					
Novice	13.3	5119			
Intermediate	17.8	5126	1.07	0.97-1.17	0.1814
Experienced	26.1	5145	1.22	1.11-1.34	<0.0001

** No regular medication use acted as the reference group.*
† No running injury acted as the reference group.
‡ Analysis conducted separately for each factor and adjusted for sex, age group and race distance.
% hEAMC, frequency (%) of runners with history of EAMC in each categor; n, number of runners in study; P, P *value; PR, Prevalence ratio.*

chronic disease or symptoms, medications use, injuries, training history, and runner category is depicted in Table 7.

In the adjusted analysis (adjusting for sex, age group, and race distance), the independent factors associated with a higher PR of hEAMC compared with runners with no history of these factors were as follows: any risk factor for CVD (PR = 1.31; 95% CI: 1.21-1.42; $P < 0.0001$), any CVD symptoms (PR = 2.38; 95% CI: 2.06-2.75; $P < 0.0001$), any respiratory disease (PR = 1.33; 95% CI: 1.22-1.45; $P < 0.0001$), any GIT disease (PR = 1.86; 95% CI: 1.67-2.07; $P < 0.0001$), any nervous system or psychiatric disease (PR = 1.51; 95% CI: 1.30-1.75; $P < 0.0001$), any kidney or bladder disease (PR = 1.60; 95% CI: 1.37-1.88; $P < 0.0001$), any haematological or immune disease (PR = 1.54; 95% CI: 1.14-2.08; $P = 0.0048$), any cancer (PR = 1.34; 95% CI: 1.10-1.62; $P = 0.0031$), any allergies (PR = 1.37; 95% CI: 1.26-1.49; $P < 0.0001$), any regular medication use (PR = 1.80; 95% CI: 1.68-1.92; $P < 0.0001$), any statin use (PR = 1.26; 95% CI: 1.05-1.51; $P = 0.0127$), any medication use during racing (PR = 1.88; 95% CI: 1.75-2.03; $P < 0.0001$), any running injury (PR = 1.66; 95% CI: 1.55-1.78; $P < 0.0001$), any muscle injury (PR = 1.82; 95% CI: 1.67-1.99; $P < 0.0001$), any tendon injury (PR = 1.62; 95% CI: 1.44-1.82; $P < 0.0001$), and runners in the experienced category (PR = 1.22; 95% CI: 1.11-1.34; $P < 0.0001$).

DISCUSSION

Exercise-associated muscle cramping is a clinical syndrome that has a high prevalence in athletes participating in endurance sports such as distance running (19%; 95% CI: 18.4-19.6). However, there is also a known association between skeletal muscle cramping and underlying chronic medical conditions, including medications that are used in the treatment of chronic medical conditions.[22] We therefore hypothesized that risk factors for chronic disease, underlying chronic medical conditions and drugs used to treat these conditions may increase the risk of EAMC. This is, to our knowledge, the first study to explore an association between EAMC in distance runners and a history of underlying chronic diseases, risk factors for chronic diseases, and medication use.

The main findings of this cross-sectional study are that the following independent intrinsic factors are associated with a self-reported history of EAMC in distance runners: a history of any risk factor for CVD (this was also the most prevalent risk factor, reported by 16% of all runners), a history of any symptoms of CVD, a history of respiratory disease, a history of any GIT disease, a history of nervous system or psychiatric disease, a history of any kidney or bladder disease, a history of haematological or immune system disease, a history of cancer, a history of any allergies, and the regular use of any medication, use of statin drugs, and use of medication use during racing. We also showed a significant independent association between EAMC and a history of a running injury, specifically history of a muscle or tendon injury. Finally, we also found a higher risk of a history of EAMC in more experienced runners.

The main novel finding of our study is the association between a history of EAMC and chronic diseases in some organ systems (notably cardiovascular, respiratory, GIT, nervous system or psychiatric, haematological or immune, and renal), cancer, allergies, or regular medication use. The association between muscle cramps (including nocturnal muscle cramps) and a number of chronic diseases in several organ systems including the cardiovascular system (arterial and venous disease, heart disease, and hypertension), endocrine-metabolic disease, GIT system (cirrhosis), central and peripheral nervous system disease, diseases associated with altered fluid and electrolyte status such as kidney disease, psychiatric disease, and muscle diseases has been reported.[22] In addition, a number of classes of chronic medication have been associated with muscle cramps β2 stimulants[32,42–44], β-blockers with intrinsic sympathomimetic activity,[25–27] angiotensin receptor blockers,[28] angiotensin-converting enzyme inhibitors,[29] calcium channel blockers,[30] diuretics[32,45], lipid lowering agents (statin drugs[31,32] and fibrates,[33–35] proton pump inhibitors[36]), and anticancer drugs.[37,38] Therefore, our study confirms an association between EAMC and underlying medical conditions and use of regular medications.[5,22,23] However, this study design does not confirm any direct cause–effect relationship between EAMC and chronic diseases or medication, neither does it provide any information about specific pathophysiologic mechanisms for EAMC in these chronic diseases. We were also not able to determine the association between EAMC and specific risk factors, specific diseases within organ systems, or specific medications because the sample size was too small for this analysis. The exception is that our data confirm an association between

statin use and a history of EAMC.[31,32] In future, we will report data from a larger sample size where subanalyses will be done for specific risk factors, disease, and medications. In future, large prospective cohort studies are also required to determine a cause–effect relationship between EAMC and these novel factors.

Our second main finding was that a past or current running injury and both a muscle or tendon injury was associated with a history of EAMC. These findings are in keeping with previous studies from our group where we reported that a history of a running injury[18] and a history of prerace muscle damage[19] are associated with EAMC. A history of any past injury,[20] previous muscle cramping,[18,19] and possible genetic factors[21] have also been identified as risk factors associated with EAMC in endurance athletes. Again, a limitation of our study design is that we cannot confirm a cause–effect relationship between any injury or a muscle/tendon injury and EAMC. In future, large prospective cohort studies are required to confirm a cause–effect relationship. Similarly, our study did not allow us to determine the pathophysiological mechanism by which previous injury and EAMC are linked. However, possible mechanisms are either an exaggerated myotatic reflex as a result of a soft tissue injury or premature muscle fatigue during exercise after a muscle or tendon injury, both of which are associated with muscle cramping.

Finally, we documented that the more "experienced" runners category is more likely to have a history of EAMC. This runner category represents a group of runners who reported running for a greater number of years, run greater weekly distances, and run at a faster running pace. Although we have previously shown that both increased running speed[18,19] and participating in longer distance races[46] are risk factors for EAMC, the precise reason why this profile of runner is at higher risk of EAMC is not clear from this study. This would have to be explored in future studies, in which we could potentially include additional training variables with an acceptable response rate in the PCA analysis to improve the % of the variance explained by the linear component.

The main strengths of this study are the large sample size and that it is the first study investigating underlying chronic disease, medication use and a history of a running injury as independent factors associated with EAMC. We do acknowledge that the study is based on self-reported data, there is possible lack of accuracy and reliability as data could not be validated, and that subanalyses need to be performed to determine the relationship between EAMC and specific chronic conditions or medications. In addition, we recognize that we did not include exposure data in our analysis because we could not accurately collect these data. We do plan to explore this in future studies.

In summary, in this exploratory study, we identified novel independent factors that are associated with a history of EAMC. More specifically, we show an association between EAMC and a history of chronic disease (any risk factor for CVD, a history of cardiovascular, respiratory, GIT, nervous system or psychiatric, haematological or immune, and renal), cancer, allergies), and the regular use of any medication (specifically statin use and the use of medication during racing). These findings are important for the clinician who consults with endurance athletes complaining of regular EAMC. We encourage clinicians to consider EAMC not as a single diagnosis, but rather a more complex clinical syndrome that requires careful and methodical clinical assessment. We suggest that clinicians explore the possibility that the syndrome of EAMC may, in some cases, indicate underlying chronic disease in these athletes, underlying muscle or tendon injury, or be an unwanted side effect of medications that are used by these individuals. Finally, we acknowledge that future research is required to validate the screening questionnaire that we used, determine the cause–effect relationship between EAMC and the factors we identified, and also explore possible pathophysiological mechanisms that may link EAMC to underlying chronic disease and medication use. This includes investigating more complex (direct and indirect) relationships between intrinsic, extrinsic factors and hEAMC.

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