Underlying chronic disease, medication use, history of running injuries and being a more experienced runner are independent factors associated with Exercise Associated Muscle Cramping (EAMC): A cross-sectional study in 15 778 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 Oceans races (21.1km, and 56km)

Participants: 15778 race entrants

Methods: Participants completed a pre-race 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 past history of EAMC (hEAMC group = 2997) and a control group (Control = 12781).

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), GIT 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; ultra-marathon; half-marathon; medical complications;epidemiology

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" [1-3] [4-6]. EAMC 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, in order 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 hyper excitability 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 pre-race 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 hyper-excitability [22].

It is well established that skeletal muscle cramping is also a clinical syndrome that is associated with a number of chronic diseases [16, 23, 24]. More specifically, skeletal muscle cramping is associated with chronic disease in a number of organ systems including cardiovascular disease, neurological disease, endocrine disease, renal disease, gastrointestinal disease [25], 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 [26-39]. 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 [23, 24][5].

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 if there is an association between a history of EAMC 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 [40], all race entrants from the Two Oceans 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 21.1km or 56km races completed the pre-race 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 if the participants in this study were indeed representative of all the race entrants. The profile [race type (21.1km vs. 56km runners), gender, and age] of all race entrants (n=25 455), and the final participants in this study (n=15 778) is presented in Table 1.

Table 1: The profile by race type, gender 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	21.1km	16 284	64.0	10 786	68.4
	56km	9 171	36.0	4 992	31.6
Gender	Males	14 775	58.0	8 916	56.5
	Females	10 680	42.0	6 862	43.5
Age groups	≤ 30 years	7 471	29.4*	4 951	31.4 *
	31–39 years	8 074	31.7#	4 499	28.5 *
	≥ 40 years	9 910	38.9^	6 328	40.1 *

*: Study participants significantly different from all race entrants ($p<0.05$)

In general, the profile of the participants in this study was very similar for race type and gender 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 ($\pm$ SD) of the 56km runners was 41.7 $\pm$ 9.4 years, and for the 21.1km runners was 35.6 $\pm$ 11.4 years. In the 56km runners, the largest proportion of runners was in the $\geq$ 40 year age category (56%), followed by 32% of 56km runners in the 31-39 year age category. In the 21.1km runners, the largest proportion of runners (40%) was in the < 30 year age category, followed by 33% of runners in the $\geq$ 40 year category.

Prior to 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 on-going analysis of the data presented in this manuscript.

Medical screening data

The on-line medical screening tool consisted of a series of questions that were specifically developed to provide clinical 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) [41]. 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: cardiovascular disease (CVD), risk factors for CVD, symptoms of CVD, respiratory disease, metabolic or hormonal disease, gastrointestinal 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 pre-race 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 (EAMC) 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 a past history of EAMC (hEAMC group = 2997, 21.1km = 1503, 56km = 1494). Therefore, the lifetime prevalence (%) of EAMC in the study participants was 19% (95% CI: 18.4-19.6), with the lifetime prevalence of EAMC in 56km runners (29.9%, 95% CI: 28.7- 31.2) being significantly higher than runners entering for the 21.1km (13.9%, 95% CI: 13.3-14.6).

Risk factors associated with a past history of EAMC (hEAMC) in runners

In this study, the following main categories of intrinsic risk factors associated with a past history of EAMC in distance runners were explored: 1) runner demographics (age, gender and race distance), 2) training history (years of recreational running, training sessions per week in the last 12 months, training speed in the last 12 months), 3) a history of existing chronic disease (cardiovascular disease - CVD), risk factors for CVD, symptoms of CVD, respiratory disease, endocrine disease, gastro-intestinal (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, 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 analysed using the SAS Enterprise Guide (V6.1) statistical program. Three training variables (years participating in distance races; times run/train/race per week; average training speed) were subjected to a Principal Components Analysis (PCA) to derive a linear composite variable of the three training variables. The first principal component from the PCA, explaining 46.6% of the variation, was then grouped into tertiles to reflect three runner categories: "novice" runners (on average few years of running, low number of weekly training sessions, slow training speed), "intermediate" runners (on average intermediate number of years of running, intermediate weekly number of training sessions, intermediate training speed) and "experienced" runners (on average high number of years of running, highest number of weekly training sessions, 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 a history of EAMC (hEAMC). Due to the cross-sectional nature of the study, we used log-binomial regression to directly estimate risk ratios (RR) 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 by using the Poisson regression model with a robust error variance [42]. 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.
Uni-variate regression models on all main category risk factors obtained the crude unadjusted risk ratio (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 gender, age category and race distance.

Results

Uni-variate logistic regression analysis of main categories of risk factors for hEAMC

Runner demographics

The frequency (%) and prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by age category, gender and race distance is depicted in Table 2.

Table 2: The frequency (%) and prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by age category, gender and race distance

		% hEAMC	n	PR	95% CI's	p
Age categories (years)	≤ 30	14.5	4 951			
	31-39	18.4	4 499	1.27	1.15; 1.40	<0.0001
	≥ 40	23.0	6 328	1.59	1.46; 1.73	<0.0001
Race	21.1km	13.9	10 786			
	56km	29.9	4 992	2.15	2.02; 2.29	<0.0001
Gender	Female	12.2	6 862			
	Male	24.3	8 916	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

PR: Prevalence risk

p: p-value

The mean (± SD) age for 56km runners in the hEAMC group was 42.7 ± 9.7 years and for 56km runners in the control group was 41.3 ± 9.3 years. The mean (± SD) age for 21.1km runners in the hEAMC group was 37.0 ± 12.3 years and for 21.1km runners in the control group was 35.4 ± 11.2 years. Two-way interactions for race type, gender 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 21.1km runners after the age of 40, while a significant increase in hEAMC risk for 56km runners already occurred after the age of 30 ($p<0.003$).

The crude unadjusted analysis showed that there was a significantly higher hEAMC prevalence risk (PR) for runners in the 31-39 years category (18.4%, PR=1.27; $p<0.0001$) and the $\geq$ 40 years category (23.0%, PR=1.59; $p<0.0001$) compared with runners in the younger ($\leq$ 30 years) category (14.5%). Furthermore, the PR of hEAMC was significantly higher in male vs. female runners (PR=1.99; $p<0.0001$) and runners competing in the 56km vs. the 21.1km race (PR=2.15; $p<0.0001$).

Table 3: The frequency (%) and prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by training history and runner category

		% hEAMC	n	PR	95% CI's	p
Recreational runner (years)	≤3 years	13.7	8 101			
	>3 years	24.6	7 671	1.80	1.69; 1.94	<0.0001
Last 12 months, train and race (times a week)	≤ 3 times/ week	16.5	8 301			
	>3 times/ week	21.9	7 414	1.33	1.25; 1.42	<0.0001
Last 12 months, average training speed (min/km)	≤6 min/km	20.5	10 709			
	>6 min/km	15.8	4 784	0.77	0.71; 0.83	<0.0001
Runner category (PCA)	Novice	13.3	5 119			
	Intermediate	17.8	5 126	1.34	1.22; 1.49	<0.0001
	Experienced	26.1	5 145	1.97	1.80; 2.16	<0.0001

PCA: Principle Component Analysis

% hEAMC: frequency (%) of runners with history of EAMC in each category

n: number of runners in study

PR: Prevalence risk

p: p-value

Training history and runner category

The frequency (%) and prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (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 (>6min 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 risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by 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 to 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 to 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 compared to runners without symptoms of CVD (PR=2.14; p<0.0001).

Table 4: The frequency (%) and prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by history of main category of chronic disease

		% hEAMC	n	PR	95% CI's	p
Any history of CVD	no	18.9	15418			
	yes	24.7	360	1.31	1.11; 1.55	0.0015
Any risk factor for CVD	no	17.9	13234			
	yes	24.8	2544	1.39	1.29; 1.49	<0.0001
Any symptoms of CVD	no	18.6	15494			
	yes	39.8	284	2.14	1.90; 2.41	<0.0001
Any respiratory disease	no	18.7	13717			
	yes	21.3	2061	1.14	1.04; 1.24	0.0034
Any endocrine disease	no	19.0	15226			
	yes	18.8	552	0.99	0.83; 1.18	0.9254
Any GIT disease	no	18.4	15095			
	yes	32.4	683	1.76	1.60; 1.94	<0.0001
Any nervous system / psychiatric disease	no	18.8	15185			
	yes	23.6	593	1.25	1.09; 1.44	0.0012
Any kidney or bladder disease	no	18.7	15420			
	yes	30.2	358	1.61	1.40; 1.85	<0.0001
Any hematological or immune disease	no	19.0	15640			
	yes	23.9	138	1.26	0.96; 1.66	0.0981
Any cancer	no	18.9	15480			
	yes	25.5	298	1.35	1.13; 1.61	0.0009
Any allergies	no	18.4	13589			
	yes	22.8	2189	1.24	1.15; 1.35	<0.0001

CVD: Cardiovascular disease

GIT: Gastrointestinal

% hEAMC: frequency (%) of runners with history of EAMC in each category

n: number of runners in study

PR: Prevalence risk

p: p-value

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 to 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 to runners without endocrine disease (PR=0.83; p=0.9254). GIT 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 to 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 to 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 to 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 to runners without haematological or an immune system disease (PR=1.26; p=0.0981). However, runners with a history of cancer (prevalence 1.9%; 95% CI: 1.7-2.1) had a higher PR of hEAMC compared to 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 to 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 risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by regular use of any medications, and medication use during racing is depicted in Table 5.

Table 5: The frequency (%) and prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by history of regular use of any medications, and use of medication during racing

		% hEAMC	n	PR	95% CI's	p
Any regular medication use	no	16.0	12 998			
	yes	33.0	2 780	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	1 700	2.24	2.11; 2.39	<0.0001

% hEAMC: frequency (%) of runners with history of EAMC in each category

n: number of runners in study

*: No regular medication use acted as the reference group

PR: Prevalence risk

p: p-value

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 to 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 to 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 to runners not using any medication during racing (PR=2.24; p<0.0001).

History of running injuries

The frequency (%) and prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by history of any running injury, and subgroups of any muscle or tendon injury is depicted in Table 6.

Table 6: The frequency (%) and prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by history of any running injuries

		% hEAMC	n	PR	95% CI's	p
Any running injury	no	16.8	13068			
	yes	29.6	2710	1.76	1.65; 1.87	<0.0001
Any muscle injury	no	16.8	13068 *			
	yes	33.3	1133	1.98	1.83; 2.14	<0.0001
Any tendon injury	no	16.8	13068 *			
	yes	28.9	776	1.72	1.55; 1.90	<0.0001

% hEAMC: frequency (%) of runners with history of EAMC in each category

n: number of runners in study

*: No running injury acted as the reference group

PR: Prevalence risk

p: p-value

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 to 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 to runners with no history of a running injury.

Multiple regression analysis of main categories of risk factors for hEAMC

The frequency (%) and adjusted prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by main categories of chronic disease or symptoms, medications use, injuries, training history and runner category is depicted in Table 7.

Table 7: The adjusted* frequency (%) and prevalence risk (PR; with 95% confidence intervals - CI) of runners with a history of EAMC (hEAMC) by combined main categories of risk factors (history, illness, symptoms, medications use, injuries and runner category)**

		% hEAMC	n	PR	95% CI's	p
Any history of CVD	no	18.9	15418			
	yes	24.7	360	1.18	0.99; 1.41	0.0722
Any risk factor for CVD	no	17.9	13234			
	yes	24.8	2544	1.31	1.21; 1.42	<0.0001
Any CVD symptoms	no	18.6	15494			
	yes	39.8	284	2.38	2.06; 2.75	<0.0001
Any respiratory disease	no	18.7	13717			
	yes	21.3	2061	1.33	1.22; 1.45	<0.0001
Any endocrine disease	no	19.0	15226			
	yes	18.8	552	1.18	0.99; 1.39	0.0649
Any GIT disease	no	18.4	15095			
	yes	32.4	683	1.86	1.67; 2.07	<0.0001
Any nervous system or psychiatric	no	18.8	15185			
	yes	23.6	593	1.51	1.30; 1.75	<0.0001
Any kidney/bladder disease	no	18.7	15420			
	yes	30.2	358	1.60	1.37; 1.88	<0.0001
Hematological/Immune disease	no	19.0	15640			

	yes	23.9	138	1.54	1.14; 2.08	0.0048
Any cancer	no	18.9	15480			
	yes	25.5	298	1.34	1.10; 1.62	0.0031
Any allergies	no	18.4	13589			
	yes	22.8	2189	1.37	1.26; 1.49	<0.0001
Any regular medication use	no	16.0	12 998			
	yes	33.0	2 780	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	1 700	1.88	1.75; 2.03	<0.0001
Any running injury	no	16.8	13068			
	yes	29.6	2710	1.66	1.55; 1.78	<0.0001
Any muscle injury	no	16.8	13068 **			
	yes	33.3	1133	1.82	1.67; 1.99	<0.0001
Any tendon injury	no	16.8	13068 **			
	yes	28.9	776	1.62	1.44; 1.82	<0.0001
Runner category (PCA)	Novice	13.3	5 119			
	Intermediate	17.8	5 126	1.07	0.97; 1.17	0.1814
	Experienced	26.1	5 145	1.22	1.11; 1.34	<0.0001

CVD: Cardiovascular disease

GIT: Gastrointestinal

PCA: Principle Component Analysis

% hEAMC: frequency (%) of runners with history of EAMC in each category

n: number of runners in study

PR: Prevalence risk

p: p-value

*: 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 gender, age group and race distance

In the adjusted analysis (adjusting for gender, age group and race distance), the independent factors associated with a higher PR of hEAMC compared to 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

EAMC 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 [23]. 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, gastrointestinal, 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, gastro-intestinal 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 [23]. In addition, a number of classes of chronic medication have been associated with muscle cramps β2 stimulants [33, 43-45]), β-blockers with intrinsic sympathomimetic activity [26-28], angiotensin receptor blockers (ARBs) [29], angiotensin converting enzyme inhibitors [30], calcium channel blockers [31], diuretics [33, 46]), lipid lowering agents (statin drugs [32, 33]and fibrates [34-36], proton pump inhibitors [37]) and anti-cancer drugs[38, 39]. Therefore, our study confirms an association between EAMC and underlying medical conditions and use of regular medications [23, 24] [5]. 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 [32, 33]. In future, we will report on data from a larger sample size where sub-analyses 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 pre-race 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 following 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 [47] 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 sub-analyses need to be performed to determine the relationship between EAMC and specific chronic conditions or medications. In addition, we recognise 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, gastrointestinal, 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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