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The Association Of Risk Markers And The Prevalence Of Exercise Associated Muscle Cramps In Distance Runners

Submitted in fulfillment of the requirements for the degree
MSc Sports Science

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DECLARATION

I, the undersigned, declare that the dissertation hereby submitted to the University of Pretoria for the degree MSc Sports Science and the work contained therein is my own original work and has not previously, in its entirety or in part, been submitted to any university for a degree.

Signed Izaan de Jager this 12th day of November 2020

DEDICATION

To my dad, Prof. Tiaan de Jager. Thank you for being my role model, always instilling hard work, determination, and ambition throughout my life.

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Finally, to the One above all, for being my hope, my life and my peace. May the work of my hands be honouring to You.

SYNOPSIS

Title: The Association Of Risk Markers And The Prevalence Of Exercise Associated Muscle Cramps In Distance Runners

Candidate: Izaan de Jager

Promoter: Prof. MP Schwellnus

Co-promoter: Dr. E Korkie

Degree: MSc Sports Science

Background: The epidemiology, clinical characteristics, severity and the risk markers associated with exercise associated muscle cramps (EAMC) in runners participating in different race distances have not been studied.

Aim of the study: To determine the lifetime prevalence, clinical characteristics, severity, preferred treatment and potential risk markers associated with EAMC in distance runners.

Design: Cross-sectional study.

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

Participants: 76654 consenting race entrants.

Methods: 106743 runners completed an online pre-race medical screening questionnaire as part of the entry for the 2012-2015 races. 76654 (71.8%) consenting entrants were included in this study (21.1km=47069; 56km=29585). The lifetime prevalence (%), retrospective annual incidence (%) and clinical characteristics (main muscle groups affected, timing of occurrence during a race, severity of EAMC, frequency of complex forms of EAMC, and preferred treatment of EAMC) were compared between 21.1km vs. 56km race entrants. Data are reported as frequency (%; adjusted for sex and age groups) and Risk Ratio (RR) with 95%CIs. Secondly, we apply a multivariate model to report independent risk markers associated with a history of EAMC (hEAMC) (sex, age, training variables, history of chronic disease, allergies, prescription medication use and running injuries) in all entrants and 21.1km and 56km entrants (prevalence risk ratios of hEAMC with 95%CI).

Results: The lifetime prevalence (%) of EAMC was significantly higher in the 56km (16.0; 15.5-16.5) compared to 21km race entrants (8.8; 8.5-9.1). The onset of EAMC (%) was significantly more frequent in the first quarter (4.9; 4.3-5.7), second quarter (3.7; 3.2-4.4) and after the race (29.5; 28.1-31.1) among 21.1km race entrants, while the onset in 56km race entrants was more frequent in the third (13.7; 12.7-14.8) and fourth quarter (47.2; 45.6-48.9). Serious EAMC (6.9; 6.2-7.8), EAMC associated with dark urine (2.9; 2.4-3.5) and whole body EAMC (4.1; 3.5-4.7) was reported more frequently in 56km race entrants. Specific independent risk markers associated with hEAMC in 21.1km and 56km runners were: history of GIT disease (PR; 21.1km=1.47, 56km=1.58), history of running injury in last 12 months (PR; 21.1km=1.44, 56km=1.45), history of CVD (PR; 21.1km=1.42, 56km=2.10), history of risk factor for CVD (PR; 21.1km=1.34, 56km=1.45), history of allergies (PR; 21.1km=1.21, 56km=1.40), average slower training speed in last 12 months (PR; 21.1km=1.06, 56km=1.03) and increase years of recreational running (PR; 21.1km=1.05, 56km=1.11).

Conclusion: More 56km race entrants report ever suffering from EAMC compared to 21.1km race entrants. The muscle groups affected, time of onset, severity (cramp duration), severity of serious EAMC and effective treatment modalities used to relieve acute muscle cramping differed between 21.1km vs. 56km race entrants. Independent risk markers associated with hEAMC identified in this study are male sex, older age, longer race distances runners, training variables, several chronic diseases, a history of allergies and the use of prescription medications for both 21.1km and 56km race entrants.

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

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LIST OF ABBREVIATIONS

AR	Absolute Risk
BMI	Body Mass Index
CI	Confidence Intervals
CK	Creatine Kinase
CTF	Cramp Threshold Frequency
CVD	Cardiovascular Disease
EAMC	Exercise Associated Muscle Cramp
EMG	Electromyogram
GIT	Gastrointestinal Tract
GTO	Golgi Tendon Organ
hEAMC	History of Exercise Associated Muscle Cramp
IR	Incidence Rate
km	Kilometres
km/h	Kilometres per hour
KT	Kinesio Tape
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OPRMSQ	Online pre-race medical screening questionnaire
PR	Prevalence Ratio
RR	Risk Ratio
SAFER	Strategies to reduce Adverse medical events For the ExerciseR
sEAMC	Serious Exercise Associated Muscle Cramp
TENS	Transcutaneous Electric Nerve Stimulation

CHAPTER 1

1 INTRODUCTION

1.1 BACKGROUND AND PROBLEM STATEMENT

Exercise Associated Muscle Cramps (EAMC) is a condition that regularly requires medical attention during or immediately after sports events. Medical attention includes a medical evaluation by a doctor, assistance from first aid stations and physiotherapy.[1] EAMC represents up to two-thirds of conditions complained about at endurance-related competitions, particularly ultra-marathon running and triathlons.[1-4] The lifetime prevalence of EAMC in marathon runners is found to be 39%.[1]

EAMC has been defined as "painful, spasmodic, and involuntary contractions of skeletal muscle that occur during or immediately after exercise" and have no underlying metabolic, neurological, or endocrine cause.[3] It may last one to three minutes and mainly occurs in muscles that cross two or more joints, usually while contracting in a shortened position. EAMC may vary in severity from mild discomfort, with minimal effects on physical performance, to extreme pain and debilitation.[3, 5]

The two main theories explaining the pathophysiology of EAMC are the dehydration and electrolyte imbalance theory and the altered neuromuscular control theory.[3]

The basis of the dehydration and electrolyte imbalance theory states that changes in the serum electrolyte concentrations, hydration status and metabolic abnormalities result in excessive sweating causing EAMC. Identification of environmental factors, such as hot and humid conditions, contributed to the belief of this theory.[6-9]

Concern was raised regarding the dehydration and electrolyte depletion theory after thorough review and analysis by different researchers. The main concern regarding the core of this theory was that no explanation could be found to explain how serum electrolyte imbalances could result in localised muscle cramping.[10-12]

In 1997 the first hypothesis to suggest that EAMC may be caused by altered neuromuscular control caused by muscle fatigue was published.[13] This was based on data reported from studies investigating EMG activity in runners with EAMC.[14] In this study, an increase in baseline EMG activity of a muscle cramping when compared to a muscle recovering from EAMC was reported and passive stretching also reduced EMG activity in muscles with a high EMG baseline. The theories related to the aetiology of EAMC will be discussed in the literature review chapter in this dissertation.

1.2 PROBLEM STATEMENT

EAMC is common during distance running and more research is needed to better understand the prevalence of EAMC, its clinical presentation and the potential risk markers associated with EAMC in distance runners. The epidemiology and clinical presentation of EAMC, as well as risk markers for EAMC, in distance runners entering in different race distances (21.1km vs. 56km), has not been investigated.

1.3 RESEARCH QUESTION

What is the lifetime prevalence, annual incidence, clinical characteristics, severity, preferred treatment and potential risk markers of EAMC in distance runners?

1.4 AIMS

The aim of the study is to determine the lifetime prevalence, annual incidence, clinical characteristics, severity, preferred treatment and potential risk markers of EAMC in distance runners.

1.5 OBJECTIVES

- To determine the epidemiology of EAMC (lifetime prevalence, retrospective annual incidence) and clinical characteristics (main muscle groups affected, timing of occurrence during a race, severity of EAMC, frequency of complex forms of EAMC, and preferred treatment of EAMC) in all runners and for sub-groups of 21.1km and 56km.

- To determine the potential risk markers associated with EAMC in distance runners in the following categories: demographics, training history and runner category, history of chronic diseases and medication use, and history of running injuries.

1.6 RESEARCH APPROACH

A quantitative research approach was used. Such a research approach focuses on what can be measured and involves collecting and analysing objective (often numerical) data that can be organised and analysed using statistics.[15] In this study, data were collected from distance runners who registered to participate in the 2012-2015 Two Oceans marathon races (21.1km and 56km), South Africa.

1.7 RESEARCH DESIGN

A cross-sectional prevalence survey design was used. A cross-sectional prevalence survey design is defined as a design that collects data from a variety of subjects at a given point in time, which examines the relationships of injury prevalence with other factors at one point in time in a defined population.[15] Data collected using a cross-sectional survey on distance runners participating in the 2012-2015 Two Oceans marathon races (21.1km and 56km), South Africa was used.

1.8 IMPORTANCE AND BENEFITS OF THE PROPOSED STUDY

The importance of this study is that it can assist in the development and implementation of prevention and management programs to reduce the risk of EAMC and improve management of EAMC in distance runners.

From the literature reviewed, this appears to be the largest study to determine the epidemiology, clinical characteristics and potential risk markers of EAMC. The dataset is representative of the population studied and reflects runners of all ages, sex and abilities.

1.9 DELIMITATIONS AND ASSUMPTIONS

1.9.1 Delimitations

The main limitation of this study is that the data is self-reported and that not all potential variables and risk markers are included in the online pre-race medical screening tool.

1.9.2 Assumptions

Participants who completed the online pre-race medical screening tool can read and comprehend English and were truthful in their responses.

1.10 DEFINITION OF KEY TERMS

- Distance runners: Long-distance running, or endurance running, is a form of continuous running over distances of at least eight kilometres (5 miles). In this study, the population of distance runners specifically refers to runners participating in a 21.1km or 56km Two Oceans Marathon (2012 to 2015).
- Muscle cramp: A sudden, uncomfortable squeezing or contraction of a muscle, lasting seconds to minutes, often with a palpable hard knot in the affected muscle.[16]
- Exercise associated muscle cramp: A painful, spasmodic, and involuntary contractions of skeletal muscle that occur during or immediately after exercise and have no underlying metabolic, neurological, or endocrine pathology.[3]
- Risk markers: A variable associated with an increased risk of disease or injury. In this study, it refers to variables associated with an increased risk of EAMC.
- Prevalence: Prevalence can be defined as the "overall proportion of a population who suffer from a disease".[1]
- Serious EAMC (sEAMC): Is defined as EAMC that 1) occurs together with other symptoms including confusion, dizziness, nausea and vomiting, diffuse cramping, or collapse or 2) is accompanied by dark urine, which may indicate rhabdomyolysis.[17]

1.11 FLOW OF DISSERTATION

In the next chapter (Chapter 2), the focus is on a literature review of the lifetime prevalence, clinical presentation, severity and self-reported treatment of EAMC in distance runners and the associated risk markers of EAMC. The first original research study is presented in Chapter 3 and describes the lifetime prevalence, clinical characteristics and self–reported treatment of EAMC and the differences between 21.1km and 56km race entrants. The second original research study is presented in Chapter 4, and in this study, independent risk factors associated with EAMC in distance runners were explored. In the final chapter (Chapter 5), the main findings of the dissertation will be summarised, limitations and strengths will be discussed and practical applications, as well as recommendations regarding future research, will be highlighted.

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CHAPTER 2

2 LITERATURE REVIEW

Running is one of the most popular types of exercise and participation in road races has increased over recent years.[18, 19] EAMC is a condition that regularly requires medical attention during or immediately after sports events.[1] In this chapter, the literature on the lifetime prevalence, clinical presentation and onset, severity, self-reported treatment and risk markers of EAMC in distance runners is reviewed.

The literature search was done using the PubMed database and the search strategy included the following keywords: cramp or cramps, muscle or skeletal muscle, exercise or physical activity or sport, incidence or prevalence, classification, pathophysiology or mechanism, aetiology or causes and risk factor or risk marker. The search was last completed on 12/11/2020 and yielded 41 results.

2.1 LIFETIME PREVALENCE OF EAMC IN DISTANCE RUNNERS

Muscle cramps affect 37% of healthy adults yearly and may be present in people with a history of neurological, endocrine or metabolic disorders but can also occur in generally healthy patients with no underlying pathology.[20-22] Muscle cramps are divided into different groups based on the aetiology.

The three main groups of muscle cramps, based on aetiology, are: the para-physiological group, idiopathic group and the group due to symptomatic causes.[1, 22] The idiopathic and symptomatic groups are well studied.[22] Para-physiological cramps are described as muscular cramps occurring in healthy subjects during specific conditions such as pregnancy or physical activity.[22] The focus of this literature review will be on the para-physiological category with special emphasis on EAMC in distance runners.

In this section, the lifetime prevalence of muscle cramps in distance runners will be reviewed. Muscle cramping linked to exercise was first reported almost a century ago in physical labourers.[23] Studies have found that between 30% to 50% of athletes in different sports such as running, triathlon, swimming, cycling, soccer and tennis have experienced muscle cramps in their lifetime.[21, 24-28] EAMC represents up to two-thirds of conditions complained about at endurance-related competitions, particularly ultra-marathon running and triathlons.[1-4]

Table 1 summarizes the seven international studies (1976-2016) reporting the incidence of EAMC in distance runners participating at events. To the knowledge of the authors, there were no new data published on the incidence of EAMC in distance runners after 2016. There are several cohort studies documenting the incidence of medical encounters at distance running events but EAMC were either classified under the musculoskeletal or heat-related illness section or not documented at all and were not included in this table [29-32]. The reasons for not recording EAMC in these studies are unknown; it may be that they were viewed as minor medical complications and not documented.

Table 1: The incidence of EAMC in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants [abc] (IR) and absolute risk (AR) of number of participants [abc]/1 incident)

Event and study reference	Type	N	Km	IR	AR	Strengths	Limitations	Level of evidence [41]
Sydney City-to-Surf fun run, Australia (1976-1979) [34]	Retrospective cohort	54 250 [a]	14	0.54 [a]	1 852	• Race starters used as denominator • First study	• Retrospective design • Shorter race distance	2b
Twin Cities Marathon, USA (1983-1994) [35]	Prospective cohort	69 043 [a]	42.2	1.30 [a]	775	• Prospective design • Study over longest period	• Possible underreporting	1b
Auckland Citibank Marathon, New Zealand (1993)[36]	Prospective cohort	1219 [a]	42.2	12.31 [a]	81	• Prospective design • Detailed data collection	• Single event	1b
Tsing Ma Bridge International (1997) Marathon, Hong Kong [37]	Prospective cohort	5 500 [c]	42.2 10	1.64 [c]	610	• Prospective design	• Single event • Physiotherapy EAMC data • Race run in heavy rain	1b
Army 10 miler, USA (1998-2004) [38]	Retrospective cohort	91 750 [a]	16	0.11 [a]	9 090	• Large cohort • Study period over six years	• Retrospective design • Shorter distance	2b
Splash 105.5FM/ICPC Marathon, Nigeria (2009-2010) [39]	Prospective cohort	920 [b]	42.2	70 [b]	14.3	• Prospective design	• Small number of participants • Data included physiotherapy data (inflating IR)	1b
Chicago Marathon, USA (2012-2016)[40]	Retrospective cohort	202 603 [b]	42.2	7.84 [b]	128	• Largest cohort • Digital data collection	• Retrospective design • Data collection errors • Missing transport data	2b

Type: Type of study
N: Number of participants
Km: Race distance
IR: Incidence rate of EAMC (rate/100 000 [abc])
AR: Absolute risk - no. of race participants [abc]/single incident)
[a]: per starters [b]: per participants [c]: per entrants

Table 1 shows that there is a broad range of reported incidence rates for EAMC during distance running events (ranging from 0.11 to 70/ 1000 participants).[35, 38] Factors that may lead to the wide range of reported incidence rates are race distance, use of various diagnostic criteria for EAMC, data collection errors, and differences in study design or varying environmental conditions.[34-40] The strengths and limitations of the studies summarised in Table 1 will be discussed.

The strengths of these studies include the study designs, time periods and the large cohort studies.[41] Four studies used a prospective design.[35-37, 39, 41] Prospective study designs reduce selection bias and determine the incidence rate and absolute risk of a specific characteristic. Prospective studies are essential in studying the risk markers for new diseases or conditions for which the data is not available and it aids in the effective management of the condition.[35-37, 39, 41] Five studies were done over two or more years and included data collected at more than one event.[34-36, 38-40] Four of the studies consisted of large cohorts ranging from 54, 250 – 202 603 entrants, participants or race starters.[34, 40]

Some of the limitations to the studies include retrospective study design, data collection errors, race distance, extreme environmental factors and included no South African studies. Retrospective studies are observational or historic in design; thus, selection biased may occur and the cohort may not be representative of the population being studied. Because of the historic design, all incidences and risk factors may not have been identified and subsequently documented.[42] Only one study had detailed data collection documented and several others reported missing data, possible overinflated or underreported incidence of EAMC.[35-37, 39, 40] Two studies included data from shorter 14km and 16km races and one race was run in heavy rain.[34, 37, 38]

Other and novel risk markers for EAMC not investigated in these studies could also have attributed to a wide range of incident rates, like exercise intensity, experience and duration. In the next section, the literature on the clinical presentation, onset and severity of EAMC in distance runners and the literature on the risk markers for EAMC are reviewed.

2.2 CLINICAL PRESENTATION, ONSET AND SEVERITY OF EAMC IN DISTANCE RUNNERS

EAMC is diagnosed using the medical history of the athlete as well as the clinical findings during a clinical examination during or after the onset of symptoms.[10] The typical clinical presentation of an athlete experiencing EAMC is that of gradual onset of pain and is accompanied by a visible muscle twitch resulting in a painful muscle contraction. This may last a few minutes to hours after exercise has stopped.[43] Myoelectric activity may be accompanied by either minor movements or forceful contractions. Acute pain is generally present with the onset of EAMC and discomfort may last for up to 72 hours after the termination of the contraction. Muscle contractions are largely isolated to a single muscle or portion of a muscle and occur whiles the muscle is in a shortened position. Swelling may also be visible.[16, 21] Passive muscle stretches usually alleviate the muscle contraction and an EAMC is followed by a period of relief. Muscles and muscle groups most commonly affected are the calf muscle complex, foot muscles, hamstring muscles, and quadriceps muscles.[4]

EAMC may vary in severity from mild discomfort, with minimal effects on physical performance, to extreme pain and debilitation.[3, 5] This may affect the performance, recovery and training of a runner. Serious EAMC (sEAMC) is defined as EAMC that occurs together with symptoms of confusion, dizziness, nausea and vomiting, diffuse cramping or collapse that requires an assessment by a medical doctor or hospitalization.[17] According to the SAFER I study, sEAMC accounted for 11% of all medical complications in distance runners.[17]

Special investigations, like blood tests and electromyographic examinations, should be used to exclude other possible causes like nervous system and muscular diseases. It is important to determine the possible causes of muscle cramps during or after sport to correctly diagnose and manage the underlying condition.[10]

This study aims to determine the epidemiology, clinical characteristics and potential risk markers for EAMC in distance runners. Therefore, the focus of this review of the literature on EAMC will only include a brief summary of the aetiology of EAMCC, focusing on the prevailing altered neuromuscular control theory.

A study on the aetiology of EAMC showed that muscle fatigue and risk markers resulting in muscle fatigue might alter the neuromuscular control that leads to EAMC. The basis of this altered neuromuscular control theory has been described as an abnormal neuromuscular reflex.[2]

In 2005, a laboratory-based exercise protocol study, specifically designed to cause premature fatigue of the calf muscles, brought about a higher incidence of muscle cramping during exercise compared to the control group.[44] The altered neuromuscular control theory is explained by a disparity between the inhibitory drive from the Golgi tendon organ's (GTO)'s and excitatory drive from the muscle spindles produced by muscle fatigue. The latter leads to a high excitatory drive to alpha motor neurons, which is responsible for the altered neuromuscular control and muscle contraction; thus, EAMC is classified as a central nervous system disorder.[3, 45] Electromyogram data recorded during bouts of acute cramping after performing fatiguing exercise confirmed this explanation and thereby supported the altered neuromuscular control theory.[4, 43]

To summarize, the clinical presentation of EAMC is experienced in varying degrees of intensity and duration by different athletes.[3, 5, 43] EAMC usually occurs in a single muscle, with the calf and foot muscles, hamstring muscles, and the quadriceps muscles the most common. EAMC is classified as a central nervous system disorder and sEAMC accounts for a significant portion of medical complications in distance runners.[1-4, 17]

2.3 SELF-REPORTED TREATMENT OF EAMC IN DISTANCE RUNNERS

Historically most treatment modalities and prevention strategies were circumstantial, self-reported and not supported by research.[5] Studies have investigated the following treatment modalities for EAMC; ingesting pickle juice, sports drinks, massage, compression garments, Kinesio tape, intravenous infusions of fluid and electrolytes, and transcutaneous electric nerve stimulation (TENS) therapy.[5, 46] Self-treatment includes passive stretches, the use of electrical stimulation, massage, rehydration, sports drinks and training aids. The first self-treatment to be reviewed is passive stretches. [3, 5, 47-51]

Passive stretching of the cramping muscle and rest have been proven to be the most effective in alleviating acute EAMC. Passive muscle stretches occur when a muscle is placed in the lengthen position while at rest.[47] This results in nearly instant relief from cramping by heightening the GTO tension, thereby stimulating inhibitory neurotransmitter release at the spinal cord level and decreasing EMG activity.[3, 5, 50] The inhibitory mechanism of heightened tension in the Golgi tendon organ results in increased afferent reflex inhibitory input to the alpha motor neurons.[48, 49] Stretching is the preferred treatment for acute EAMC.[51]

Two small studies have found that TENS therapy or electrically induced muscle cramp (EIMC) protocols assist in stabilizing the excitatory and inhibitory responses to the alpha neurons when compared to control groups and may prevent EAMC.[52, 53] The results were not statistically significant and inducing uncomfortable muscle cramps may not be an appropriate preventive measure for the majority of athletes.[3]

It has been proven that massage therapy techniques can alter the spinal reflex excitability and it is proposed that these neural changes may reduce EAMC, but no empirical or experimental data support this theory.[54, 55] Studies have found that massage reduces the spinal reflex excitability, but it is unclear how this will affect the disparity between the inhibitory drive from the GTO and excitatory drive from the muscle spindles produced by muscle fatigue.[56] Performing massage techniques immediately before or during an event and how this will influence the performance of a runner has not been studied.[3] Massage therapy is typically used as part of recovery strategies to manage post-exercise fatigue in distance runners.[57]

Dehydration has long been thought to be the cause of EAMC, but the concern was raised regarding the dehydration and electrolyte depletion theory after thorough review and analysis by different researchers. The main concern regarding the basis of this theory was that no explanation on how systemic serum electrolyte imbalances could result in localised muscle cramping.[10-12] The use of nutritional supplements such as sports drinks, magnesium and salt tablets to treat and prevent EACM remains common among athletes despite the absence of data supporting its efficacy in preventing or treating EAMC.[58]

Pickle juice or similar products containing high levels of salt and acetic acid are also being used by athletes and runners to treat EAMC.[58] Historically, it was thought that the pickle juice influences the plasma electrolyte concentrations based on the dehydration-electrolyte theory. The basis of the dehydration and electrolyte imbalance theory states that changes in the serum electrolyte concentrations, hydration status and metabolic abnormalities result in excessive sweating causing EAMC.[6-9] The main concern regarding the core of this theory was that no explanation could be found to explain how serum electrolyte imbalances could result in localised muscle cramping.[10-12] However, evidence suggests that ingesting pickle juice had no effect on electrolyte balance or plasma composition even though it did significantly shorten the cramp duration.[59]. A study by Milnet et al. (2010) found that the consumption of pickle juice increases the activity of the inhibitory neurotransmitters during acute EAMC, which may be a plausible explanation of why pickle juice consumption can treat EAMC.[46]

Training aids such as Kinesio tape and compression garments are commonly used by runners, but evidence supporting their efficacy in preventing and treating EAMC is lacking. It is suggested that these aids improve muscle activation by biomechanical or proprioceptive mechanisms and delay fatigue during physical activity.[40, 60, 61]

In summary, most historical treatment modalities for EAMC are circumstantial, self-reported and not supported by research. Passive stretches and rest have been proven to be the most effective in alleviating EAMC. Passive stretches and other successful treatment modalities were plausibly explained using the altered neuromuscular control theory.[46] Understanding the risk maskers associated with EAMC better may allow for improved management and prevention strategies.[5] In the next section, we will review the risk markers associated with EAMC.

2.4 RISK MARKERS OF EAMC IN DISTANCE RUNNERS

EAMC typically follows muscle fatigue caused by an increase in intensity and prolonged duration of exercise.[62] Figure 1 explains how risk markers leading to or associated with muscle fatigue, as well as other risk markers, can influence the development of EAMC.[3] In the next, section risk markers associated with EAMC will be discussed.

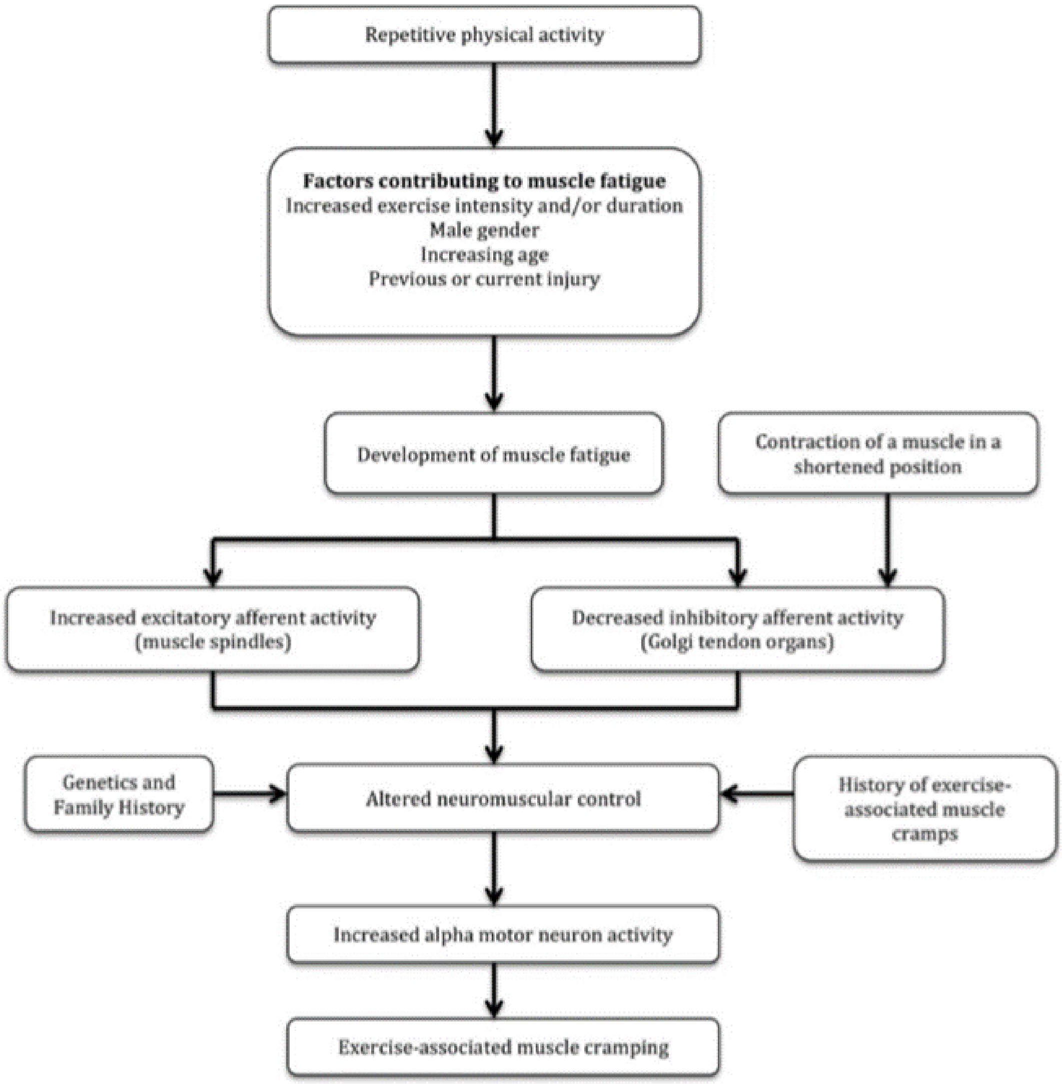

Figure 1: Risk markers associated with muscle fatigue EAMC [3]

To prevent and manage EAMC, it is important to be able to identify and consider the possible risk markers predisposing distance runners to developing EAMC and recurring EAMC. Several studies identified intrinsic and extrinsic risk markers that are associated with EAMC and these are summarised in Table 2.[12, 49, 63-66] First, the intrinsic factors are tabulated, followed by extrinsic factors. The studies included data from distance running events, triathlons, rugby, football and recreational athletes. In only a few studies, multivariate analyses identified independent risk markers associated with EAMC.[51, 64, 67, 68]

Table 2: Risk markers associated with EAMC in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence)

Risk factor	Study design and study reference	Main findings/s	Strengths	Limitations	Level of Evidence [41]
Intrinsic					
Age	Cross-sectional[68]	Increased age at higher risk (> 35 years)	• Included 3 different marathons	• Cross-sectional design • Low response rate (17%)	4
	Prospective cohort [51]	No effect	• Prospective design	• Small sample size	1b
Sex	Cross-sectional[68]	Males at higher risk Independent risk factor	• Included 3 different marathons	• Cross-sectional design • Low response rate (17%)	4
	Prospective cohort [51]	No effect	• Prospective design	• Small sample size	1b
Exercise intensity/pace	Case-control [67 a]	Increased risk with faster running pace Independent risk factor	• Large sample size	• Case-control • Possible recall bias • Study in triathletes	4
	Prospective cohort [51]	Increased risk with faster pace Independent risk factor	• Prospective design	• Small sample size	1b
	Prospective cohort [69]	Increased risk with faster pace	• Prospective design	• Study in triathletes • Small sample size	1b
Exercise duration	Cross-sectional[68]	Increase risk with longer exercise duration	• Included 3 different marathons	• Cross-sectional design • Low response rate (17%)	4
	Cross-sectional[70 b]	Increase risk with longer exercise duration		• Cross-sectional design • Rugby players	4
Running experience	Cross-sectional[64]	Increased risk with more running experience Independent risk factor	• Large sample size	• Cross-sectional design • Possible recall bias	4
	Cross-sectional[68]	Increased risk with more running experience Independent risk factor	• Included 3 different marathons	• Cross-sectional design • Low response rate (17%)	4
BMI	Cross-sectional[68]	Increased risk with a higher BMI (>30) Independent risk factor	• Included 3 different marathons	• Cross-sectional design • Low response rate (17%)	4
	Prospective cohort [69]	No effect	• Prospective design	• Study in triathletes	1b

Table 2: Risk markers associated with EAMC in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)

Risk factor	Study design and study reference	Main findings/s	Strengths	Limitations	Level of Evidence [41]
Height	Case-control [67 a]	Increased risk with increased heigh Independent risk factor	• Large sample size • Novel finding	• Case-control • Possible recall bias • Study in triathletes	4
Family history of EAMC	Case-control [67 a]	Increased risk with a positive family history of EAMC Independent risk factor	• Large sample size • Novel finding	• Case-control • Possible recall bias • Study in triathletes	4
	Cross-sectional[68]	Increased risk with a positive family history of EAMC Independent risk factor	• Included 3 different marathons	• Cross-sectional design • Low response rate (17%)	4
Previous history of EAMC	Case-control [67 a]	Increased risk with a previous history of EAMC Independent risk factor	• Large sample size	• Case-control • Possible recall bias • Study in triathletes	4
	Cross-sectional [12]	Increased risk with a previous history of EAMC Independent risk factor	• Large sample size	• Case-control • Possible recall bias	4
	Prospective cohort [69 a]	Increased risk with a previous history of EAMC Independent risk factor	• Prospective design • Novel finding	• Study in triathletes	1b
	Prospective cohort [51]	Increased risk with a previous history of EAMC Independent risk factor	• Prospective design	• Small sample size	1b
Dehydration	Case-control [25 a]	No effect		• Case-control • Study in triathletes • Small sample size	4
	Prospective cohort [27]	No effect	• Prospective design	• Small sample size	1b
	Prospective cohort[24]	No effect	• Prospective design	• Drinking patterns and fluid losses not analysed	1b
	Prospective cohort [69 a]	No effect	• Prospective design	• Study in triathletes	1b
NSAID use	Prospective cohort [71]	Decreased risk with the use of NSAID	• Prospective design	• Influence of possible confounders not analysed	1b

Table 2: Risk markers associated with EAMC in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)

Risk factor	Study design and study reference	Main findings/s	Strengths	Limitations	Level of Evidence [41]
Other medications use	Cross-sectional [64]	Increased risk with the use of medication (statins, any medication) Independent risk factor	• Large sample size • Only known study in distance runners to show this	• Cross-sectional design • Possible recall bias • No direct cause-effect relationship	4
	Retrospective cohort [72]	Increased risk with the use of medication (diuretics, statins, B-agonists) Independent risk factor	• Long study period	• Retrospective design • Study in general public	2b
	RCT [73]	Increased risk with the use of B-agonists	• RCT	• Small sample size • Study in general public	1c
History of underlying chronic disease	Cross-sectional [64]	Increased risk with a history of underlying chronic diseases Independent risk factor	• Large sample size • Novel finding	• Cross-sectional design • Possible recall bias • No direct cause-effect	4
Stretching	Cross-sectional [68]	Decreased risk with stretching Independent risk factor	• Included 3 different marathons	• Cross-sectional design • Low response rate (17%)	4
	Cross-sectional [65]	Decreased risk with stretching	• One of first studies	• Cross-sectional design	4
Muscle glycogen and energy stores	RCT [44]	Decreased risk in the onset of EAMC, but no difference in EAMC	• RCT	• Small sample size	1c
Pre-race/during race muscle damage	Prospective cohort [51]	Increased risk with pre-race/during race muscle damage	• Prospective design • Novel finding	• Small sample size	1b
	Cross-sectional [12]	Increased risk with pre-race/during race muscle damage Independent risk factor	• Large sample size	• Case-control • Blood tests only post-race	4

Table 2: Risk markers associated with EAMC in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)

Risk factor	Study design and study reference	Main findings/s	Strengths	Limitations	Level of Evidence [41]
Injury history	Cross-sectional [64]	Previous injury history at increased risk Independent risk factor	• Large sample size	• Cross-sectional design • Possible recall bias	4
	Case-control [67 a]	Previous injury history at increased risk Independent risk factor	• Large sample size • Novel finding	• Case-control • Possible recall bias • Timing relation to EAMC of past injury not recorded • Study in triathletes	4
Genetic markers	Retrospective case-control [74]	Increased risk with genetic marker (COL5A1CC)	• Novel finding with the COL5A1CC gene	• Retrospective case-control	2b
Extrinsic					
Increased environmental temperature and humidity	Retrospective cohort [66 c]	Increased risk with higher environmental temperatures and humidity	• Included data from 5 universities	• Retrospective design • Football players • Confounding variables (pre-season)	2b

[a] Triathlon
[b] Rugby
[c] Football

Studies have identified the following intrinsic risk markers for EAMC: age, sex, exercise intensity, exercise duration, exercise experience, BMI, height, previous history of EAMC, NSAID use, other medication use, history of underlying chronic diseases, muscle glycogen and energy stores, pre-race or during race muscle damage, injury history and genetic markers.[12, 44, 51, 64, 66-68, 74]. The extrinsic risk markers reviewed were increased environmental temperature and humidity.[66] The intrinsic risk markers will be reviewed first.

2.4.1. <u>Intrinsic risk markers associated with EAMC</u>

The first intrinsic risk marker reviewed is age. Research on age as a risk marker is contradicting. A cross-sectional study that included data from three different marathons found that runners older than 35 years are at a higher risk for EAMC. Some limitations to this study were the cross-sectional study design and response rate of only 17%.[68] A prospective cohort study with a small sample size found that age had no effect on the incidence of EAMC.[51] A narrative review in 2016 concluded that there is no association between age and the incidence EAMC.[3, 67, 75-77]

The same cross-sectional study by Manjta et al. (1996) found that being male is an independent risk marker for developing EAMC. [68] However, the prospective cohort study found that the sex of runners was related to the incidence of EAMC.[51, 68] The mechanism of how the sex of a distance runner affects EAMC risk is still unclear, but a review suggested that the skeletal muscles of males have a greater number of fast-twitch muscle fibres when compared to females. Fast-twitch muscle fibres have fewer capillary and mitochondrial concentrations and may therefore, be more prone to muscle fatigue and consequently, males are generally more likely to experience EAMC.[3, 67]

A faster running pace was also found to be an independent risk marker for EAMC in a study investigating risk markers associated with a self-reported history of EAMC in 433 triathletes. The limitations of this study were the case-control design and the possibility of recall bias.[67] A prospective cohort study also reported that triathletes competing at a higher intensity and faster pace are at increased risk for EAMC.[78] A limitation of the study was the small sample size of 210 triathletes. Ultra-distance runners were also found to be at higher risk of developing EAMC when running at a faster pace during the early stages of a race.[51] These prospective cohort studies on ultra-distance runners and triathletes made use of multivariate analyses to identify faster pace as an independent risk marker associated with EAMC. It is proposed that the onset of muscle fatigue predisposes runners to EAMC based on the altered-neuromuscular control theory. The theory states that the heightened α motor neuron activity, caused by lowered afferent Golgi tendon organ activity and heightened afferent muscle spindle activity, may lead to EAMC.[13, 45, 79] Performing exercise at a higher relative exercise intensity or duration in comparison to normal training load will add to the cramp susceptibility. Cramp susceptibility is associated with an individual's cramp threshold frequency (CTF). CTF is defined as "the minimum electrical stimulation required to evoke a muscle cramp".[5]

Two cross-sectional studies found that there is an increased risk for EAMC with longer exercised duration.[68, 70] The longer the duration of physical activity, the higher the likelihood of muscle fatigue, which may explain why the longer exercise duration leads to EAMC. One of the studies was done on rugby players and as mentioned previously, the second study included data from three marathons but had a low response rate, which were limitations of the studies.[68, 70]

Manjra et al. (1996) also concluded that more running experience is an independent risk marker for EAMC.[68] An exploratory cross-sectional study on 15 778 distance runners reported a higher incidence of self-reported history of EAMC in more experienced runners. The study found that distance runners classed as either experienced or intermediate had a significantly higher prevalence ratio of a history of EAMC when compared with novice runners. The main strength of this study was its large sample size of distance runners, but the authors did acknowledge that the data is self-reported and that there is a possible lack of accuracy and reliability. Because of the cross-sectional design, no cause-effect can be established and there could also have been recall bias.[80] These studies could not explain why experienced distance runners are at a higher risk of EAMC but did suggest that exercise duration, frequency and intensity might play a role.[68, 80]

Another independent risk marker for EAMC is a BMI higher than 30 kg/m^2.[68] A study by Shang et al. (2011) found that triathletes with a history of EAMC were significantly taller than those with no history of EAMC.[67] The study identified increased height as a novel independent risk marker for EAMC, but as mentioned earlier, limitations to this study included the case-control study design and the possibility of recall bias. Shang et al. (2011) could not explain why height was a risk factor for EAMC but suggested that biomechanical differences linked to height may play a role.[67] However, in a prospective cohort study by Schwellnus et al. (2011), no association between EAMC and higher BMI or height was found.[51]

Both Shang et al. (2011) and Schwellnus et al. (2011) identified positive family history of EAMC as an independent risk marker for EAMC.[67, 68] Studies investigating the association between family history and EAMC were reviewed in 2016, and a family history of EMAC was considered as a main risk marker for EAMC.[3, 4, 21]

A previous history of EAMC was also found to be an independent risk marker for EAMC by four studies in distance runners and triathletes, of which two are prospective cohort studies and the other two are cross-sectional studies.[12, 51, 67, 69] It was found that athletes with a history of EAMC had a considerably lower CTF compared to those with no history of EAMC, which may explain why distance runners with a history of EAMC are more prone to developing EAMC during or after an event.[46]

The use of NSAID before a distance running event has been associated with a decreased risk of EAMC. A prospective non-interventional cohort study surveyed 3913 marathon runners after an event, but the influence of possible confounders was not analysed in this study.[71]

A history of the use of other medications has also been studied. A recent cross-sectional study by Schwellnus et al. (2018) reported an increased risk for EAMC with the use of medications such as statins.[1] This is the only study in distance runners to show that medication use is an independent risk marker for EAMC. The limitations of the study were that there could be possible recall bias and the authors did not identify a direct cause-effect relationship.[64] Two other studies also found that medications use is a risk marker for skeletal muscle cramps and nocturnal cramps in the general public.[72, 73]

The history of underlying chronic disease was found to be a novel independent risk for EAMC by Schwellnus et al. (2018).[1] The chronic diseases investigated included cancer, allergies and chronic diseases in organ systems, particularly cardiovascular, respiratory, GIT, nervous system or psychiatric, hematological or immune, and renal. The limitations to the study were the possible recall bias and there was no direct cause-effect identified between EAMC and specific diseases because the sample size was too small.[64]

Another independent risk marker for EAMC is inadequate stretching. Two cross-sectional studies concluded that there is a decreased risk for EAMC in runners with a history of stretching.[65, 68] As discussed earlier, stretching is also a preferred method of treatment for EAMC because stretching results in nearly instant relief from cramping by decreasing EMG activity and heightening the GTO tension.[51]

A previous injury is another independent risk marker for EAMC in distance runners and triathletes.[64, 67] Shang et al. (2011) explained that an increased reflex alpha motor activity caused by the soft tissue injury could result in EAMC.[67] A previous injury may also contribute to the muscle fatiguing prematurely due to localised muscle weakness.[64, 67]

Pre-race and during race muscle damage was identified as an independent risk factor for EAMC by a cross-sectional study in 280 distance runners.[12] The extent of muscle injury was measured using serum creatine kinase (CK) concentration. A post-race blood draw was done on 181 race finishers to determine their blood CK concentrations and the association of EAMC. The study found that EAMC was most common in runners with greater muscle damage. A limitation of this study was that blood samples were only collected after the race and the study's cross-sectional design.[12] A prospective cohort study by Schwellnus et al. (2011) with a small sample size of 49 distance runners also identified pre-race and during race muscle damage as a novel risk marker for EAMC.[51]

The final intrinsic risk marker for EAMC was a novel genetic marker called the COL5A1CC gene.[74] The gene was identified in a retrospective genetic case-control association study using genotyping for selected variants. The COL5A1CC genotype was significantly over-represented with the group with no self-reported history of EAMC when compared with the EAMC group. No significant genotype differences were found for the other variants. The main limitation of this study was the participants included in this study were not representative of all distance runners.[74]

2.4.2 Extrinsic risk markers associated with EAMC

Extrinsic risk markers associated with an increased incidence of EAMC are higher environmental temperatures and increased humidity.[66] The retrospective study on football players from five universities recorded wet bulb globe temperatures at the beginning, middle, and end of each practice session. These recordings were correlated with the rate of heat-related medical encounters. Muscle cramps were reported most often and were commonly associated with a lack of acclimatization or conditioning. The limitations of this study included the retrospective study design and confounding variables.[66] Extrinsic or environmental risk markers such as higher temperatures and humidity may contribute to the onset of EAMC.[6-9, 43]

2.4.3. Independent risk markers associated with EAMC

In several studies reviewed in the previous section, multiple logistic regression analyses were done and the following independent risk markers associated with EAMC were identified: Male sex, increased exercise intensity, more running experience, increased BMI, increased height, a family history of EAMC, a previous history of EAMC, a history of the use of medication, previous injury history, pre-race muscle damage, existing chronic disease and positive genetic markers (COL5A1CC gene).

Although previous studies have identified some risk markers for EAMC, more research is needed to determine potential risk markers associated with EAMC in distance runners. The incidence, clinical characteristics, and treatment modalities and potential risk markers associated with EAMC may differ between runners entering for a 21.1km compared with ultramarathon (56km) race entrants, and as far as we are aware, this has not been explored. In Chapter 3 we aim to determine if the lifetime prevalence, annual incidence, clinical characteristics, severity, and preferred treatment of EAMC differ between road runners entering a 21.1km vs. a 56km race. In Chapter 4 we aim to determine the independent risk markers associated with a history of EAMC.

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CHAPTER 3

3 ORIGINAL RESEARCH PAPER 1

In preparation for submission to the Clinical Journal of Sport Medicine

Title: The Lifetime Prevalence, Clinical Characteristics And Self–Reported Treatment Of Exercise Associated Muscle Cramping (EAMC) Differs Between 21.1km And 56km Race Entrants - A Cross-Sectional SAFER Study in 76654 Race Entrants

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The authors declare that there are no competing interests

3.1 ABSTRACT

Background: The epidemiology, clinical characteristics and severity of exercise associated muscle cramps (EAMC) in runners participating in different race distances has not been studied.

Aim of the study: To determine if the lifetime prevalence, annual incidence, clinical characteristics, severity, and preferred treatment of EAMC differs between road runners entering a 21.1km vs. a 56km race.

Design: Cross-sectional study.

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

Participants: 76654 consenting race entrants.

Methods: 106743 runners completed an online pre-race medical screening questionnaire as part of the entry for the 2012-2015 races and 76654 consenting race entrants (71.8%) were included in this study (21.1km=47069; 56km=29585). We compared the lifetime prevalence (%), retrospective annual incidence (%) and clinical characteristics (main muscle groups affected, timing of occurrence during a race, severity of EAMC, frequency of complex forms of EAMC, and preferred treatment of EAMC) between 21.1km vs. 56km race entrants. Data are reported as frequency (%; adjusted for sex and age groups) and Risk Ratio (RR) with 95%CIs.

Results: The lifetime prevalence (%) of EAMC was significantly higher in the 56km (16.0; 15.5-16.5) compared to 21.1km race entrants (8.8; 8.5-9.1). Among 21.1km race entrants, the calves (61.1; 60.0-63.2) and foot muscles (7.9; 7.1-8.8) were significantly more affected. Hamstring (20.1; 18.8-21.5) and quadriceps muscles (16.9;15.7-18.2) were most affected among 56km race entrants. The onset of EAMC was significantly more frequent in the first quarter (4.9; 4.3-5.7), second quarter (3.7; 3.2-4.4) and after the race (29.5; 28.1-31.1) among 21.1km race entrants, while the onset in 56km race entrants was more frequent in the third (13.7; 12.7-14.8) and fourth quarter (47.2; 45.6-48.9). Mild EAMC (65.0; 63.5-66.6:) was significantly more frequent in the 21km compared to 56km race entrants. Serious EAMC (6.9; 6.2-7.8), EAMC associated with dark urine (2.9; 2.4-3.5) and whole body EAMC (4.1; 3.5-4.7) was reported more frequently in 56km race entrants. Significant differences in treatment modalities used to relieve EAMC between 21.1km and 56km race entrants are also reported.

Conclusion: More 56km race entrants report ever suffering from EAMC compared to 21.1km race entrants. The muscle groups affected, time of onset, severity (cramp duration), severity of serious

EAMC and effective treatment modalities used to relieve acute muscle cramping also differed between 56km vs. 21.1km race entrants. These data suggest that independent risk factors associated with EAMC may differ between race entrants and need to be explored in future studies.

3.2 INTRODUCTION

Exercise Associated Muscle Cramping (EAMC) is defined as 'painful spasmodic involuntary contraction of skeletal muscle that occurs during or immediately after muscular exercise'.[13] EAMC is one of the most common clinical presentations that require medical attention during or immediately after distance running events.[2, 80] EAMC presents as sudden onset of uncontrollable muscle contractions, is accompanied by acute pain, and usually occurs while the muscle is in the shortened position. The most common muscle groups affected are the calf muscles, hamstring muscles, and quadriceps muscles.[16, 21, 81] The lifetime prevalence of EAMC in marathon runners was reported to be 39%.[81]

Historically it was believed that dehydration and electrolyte depletion results in EAMC.[8, 9] However, in an alternate hypothesis, it was suggested that muscle fatigue and possible risk markers that lead to muscle fatigue might alter the neuromuscular control and result in EAMC.[43] Muscle fatigue caused by an increase in intensity and prolonged duration of exercise is associated with EAMC.[43] Evidence from a number of recent reviews suggests that the "neuromuscular fatigue" hypothesis prevails over the initial hypothesis of the dehydration or electrolyte imbalances as the common pathophysiological pathway for the development of EAMC.[3, 82-84] Current evidence, therefore, suggests EAMC is multifactorial in nature and that EAMC occurs in endurance athletes because of underlying risk markers, which, combined with prolonged, high-intensity exercise, can lead to premature neuromuscular fatigue and EAMC.

However, risk markers for EAMC, exercise duration and exercise intensity may differ between endurance athletes that participate in races with different distances. For example, 21.1km races generally attract less experienced runners, 21.1km runners may run at a faster average race pace and the overall exercise duration is shorter compared with ultramarathon runners.[85] As premature muscle fatigue contributes to EAMC, the risk markers associated with EAMC may differ among 21.1km and 56km runners. In one cross-sectional study of 15778 runners, researchers showed that there was a significantly higher lifetime prevalence of EAMC in 56km compared to 21.1km runners and that there was a higher incidence of serious EAMC (sEAMC) in 56km compared to 21.1km runners.[80] Serious EAMC (sEAMC) is defined as EAMC that 1) occurs together with other symptoms including confusion, dizziness, nausea and vomiting, diffuse cramping, or collapse or 2) is accompanied by dark urine, which may indicate rhabdomyolysis.[17] The incidence of sEAMC in distance runners has been reported as 0.91/1000 race starters and accounted for 11% of all reported medical encounters.[86] The prevalence of sEAMC may also differ between 21.1km and 56km race entrants but has not been reported.

The incidence, clinical characteristics, and treatment modalities of EAMC may differ between runners entering for a 21.1km compared with ultramarathon (56km) race entrants, and as far as we are aware, this has not been explored. Therefore, the aim of the study was to compare the lifetime prevalence, retrospective annual incidence, and clinical characteristics of EAMC (muscle groups affected by EAMC, onset of EAMC during races, severity of EAMC, and efficacy of treatment modalities) in 21.1km vs. 56km race entrants.

3.3 METHODOLOGY

Study design

This study formed part of a series of ongoing SAFER (Strategies to reduce Adverse medical events For the ExerciseR) studies and was an observational cross-sectional analysis of data collected prospectively over a four-year period.[17, 86, 87] We conducted a secondary analysis of data from an existing database. Data collection was through an online pre-race medical screening questionnaire that was administered to all entrants at the time of registration 3-4 months prior to the 2012-2015 Two Oceans races (21.1km and 56km) over the four-year period and this has been previously described.[17, 86, 87] Ethical approval to conduct the study was obtained from the Research Ethics Committees of the Faculties of Health Sciences from both the University of Cape Town (REC009/2011) and the University of Pretoria (Ref. 433/2015) (Ref. 28/2018).

Study participants

A total of 106 743 runners entered and 76 654 entrants gave consent to be included in this study, as seen in Table 3.1.. Entrants (n=10614) who indicated a history of EAMC were included in the study.

Table 3.1: The profile (race distance, sex and age groups) of all race entrants and race entrants who gave consent to participate in this study

		All race entrants (n=106743)		Consenting race entrants participating in this study (n=76654)		p value
		N	%	N	%	P
Race distance	21.1km	64740	60.7	47069	61.4	
	56km	42003	39.4	29585	38.6	p= 0.001*
Sex	Males	61815	57.9	44042	57.5	
	Females	44928	42.1	32612	42.5	p=0.052
Age groups	≤ 30 years	27710	26	20168	26.3	
	31–40 years	35049	32.8	25045	32.7	
	41–50 years	26964	25.3	19340	25.2	
	≥ 51 years	17020	15.9	12101	15.8	p= 0.364

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

Study participants did not differ from all race entrants by age group (p=0.364) and sex (p=0.052), but we note that there was a small but significantly higher percentage of 21.1km vs. 56km consenting race entrants compared with all race entrants (p=0.001).

Demographic information was obtained from race entrants and included their age, sex, and race distance. The demographics (sex, age groups) of all the consenting entrants and the sub-groups (21.1km and 56km) are shown in Table 3.2. The mean age ($\pm$SD) for all entrants was 38.7 years (11.1) and the mean age of the 56km runners (41.5 $\pm$ 9.4) was significantly higher than the 21.1km race entrants (36.9 $\pm$ 11.7) (p=0.0001).

Table 3.2: The demographics (sex, age groups) of all the consenting race entrants and the sub-groups (21.1km and 56km)

		All entrants		56km entrants		21.1.km entrants		p value
		n	%	N	%	N	%	
All race entrants		76654	100	29585	38.6	47069	61.4	
Sex	Males	44042	57.5	21044	71.1	22998	48.9	
	Females	32612	42.5	8541	28.9	24071	51.1	0.0001 *
Age	≤30 years	20168	26.3	3574	12.1	16594	35.3	
	31-40 years	25045	32.7	10755	36.4	14290	30.4	
	41-50 years	19340	25.2	10078	34.1	9262	19.7	
	≥51 years	12101	15.8	5178	17.5	6923	14.7	0.0001 *

*: Significant p values for comparison of 21.1km and 56km races

We note that significantly more males entered in the 56km races (71.1%) compared to females (28.9%) (p=0.0001), and 56km entrants were significantly older compared with the 21.1km entrants (p=0.001).

Pre-race medical screening questionnaire

The details of the development of an online pre-race medical screening questionnaire (OPRMSQ) or "self-assessment of risk" that was administered to all race entrants from 2012 to 2015 was previously described.[17, 86, 87] This questionnaire included the following categories of medical history: symptoms of cardiovascular disease (CVD), risk factors for CVD, and history of diagnosed chronic disease (CVD, respiratory, metabolic or hormonal, gastrointestinal, nervous system, renal or bladder, hematological or immune system, cancer, allergies), general prescription medication use, medication use during racing, and a past history of collapse during racing. These factors are all associated with a possible increased risk of acute medical complications in moderate- to high-intensity exercise such as distance running, including EAMC.[88]

In the medical screening tool, race entrants 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, race entrants were grouped as those reporting a history of EAMC (All = 10614, 21.1 km = 6233, 56 km = 4381) and were also asked to complete additional questions related to their history of EAMC.

Specific questions related to the history of EAMC included clinical characteristics of EAMC as follows: main muscle groups affected, timing of occurrence during a race, severity of EAMC, history of serious EAMC, and preferred treatment of EAMC. The severity of EAMC was graded from mild to severe based on the duration (min) of muscle cramping. Serious EAMC referred to EAMC that is either 1) combined with symptoms (confusion, dizziness, nausea and vomiting, diffuse cramping, or collapse), or 2) EAMC associated with dark urine, indicative of exertional rhabdomyolysis.[75]

Main outcome variables

We report the following main outcome variables for all entrants and we compare these variables between 21.1km and 56km race entrants:

1. Epidemiological variables - lifetime prevalence (%), retrospective annual incidence (%) of EAMC
2. Clinical characteristics - muscle groups affected, onset of EAMC during a race, EAMC severity by cramp duration, prevalence of serious EAMC (sEAMC)
3. Successful self-reported treatment modalities for EAMC

Statistical analysis of data

The lifetime prevalence, annual incidence, clinical characteristics (muscle groups affected, onset during a race, cramp duration, sEAMC, and self–reported treatment for EAMC) were adjusted for age and sex compared (%; 95%CI) and compared between the 56km and 21.1km race entrants. The data were analysed using standard descriptive statistical analysis.

3.4 RESULTS

3.4.1 Epidemiology of EAMC

Lifetime prevalence of EAMC

The lifetime prevalence (adjusted for sex and age groups) of EAMC in the study population was 12.8% (95% CI 12.6-13.1). The lifetime prevalence of EAMC was significantly higher in 56km (16.0%; 15.5-16.5) compared to 21.1km race entrants (8.8%; 8.5-9.1) (p=0.0001).

Retrospective annual incidence of EAMC

The retrospective annual incidence (adjusted for sex and age groups) of EAMC in the study population was 7.8% (95% CI 7.6-8.0). The retrospective annual incidence of EAMC was significantly higher in 56km (10.5%; 10.1-11.0) compared with 21.1km race entrants (5.2%; 4.9-5.4) (p=0.0001).

3.4.2 Clinical characteristics of EAMC

Muscles groups affected by EAMC

The frequency (%) and Risk Ratio (RR) (adjusted for sex and age groups) of muscle groups affected in race entrants with a history with EAMC (21.1km and 56km) is shown in Table 3.3.

Table 3.3: The frequency (%) and Risk Ratio (RR), adjusted for sex and age groups, of muscle groups affected in race entrants with a history with EAMC (21.1km and 56km)

	All entrants		**21.1km entrants**		**56km entrants**		**RR (95%CI) #**	**p value**
	(n=10567) **		**(n=4362)**		**(n=6205)**			
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)		
Calves	5629	53.1 (52.1-54.2)	2680	61.6 (60.0-63.2)	2949	48.5 (47.0-50.1)	0.8 (0.7-0.8)	0.0001 *
Hamstrings	2215	20.9 (20.0-21.7)	620	12.6 (11.6-13.8)	1595	20.1 (18.8-21.5)	1.6 (1.5-1.7)	0.0001 *
Quadriceps	1746	16.3 (15.5-17.1)	559	11.8 (10.8-12.9)	1187	16.9 (15.7-18.2)	1.4 (1.3-1.6)	0.0001 *
Foot	631	6.2 (5.7-6.7)	345	7.9 (7.1-8.8)	286	6.1 (5.4-6.9)	0.8 (0.7-0.9)	0.003 *
Buttocks	68	0.7 (0.5-0.8)	34	0.8 (0.6-1.1)	34	0.7 (0.5-1.0)	0.9 (0.5-1.5)	0.591
Upper body	87	0.8 (0.7-1.0)	43	0.9 (0.6-1.2)	44	0.9 (0.6-1.2)	1.0 (0.6-1.6)	0.932
Other	191	2.0 (1.7-2.3)	81	1.9 (1.6-2.4)	110	2.2 (1.7-2.7)	1.1 (0.8-1.5)	0.508

*: Significant p values for comparison of 21.1km and 56km races

**: Data missing from 47 race entrants

#: Risk ratio in 56km vs. 21.1km race entrants

The first main observation from Table 3.3 is that the muscle groups most frequently affected by EAMC in all race entrants were the calf muscles followed by the hamstrings and the quadriceps muscles. The second observation is that the muscle groups affected by EAMC differed between 21.1km and 56km race entrants. The calf (21.1km = 61.1%; 60.0-63.2: 56km = 48.5%; 47.0-50.1) (p=0.0001) and foot muscles (21.1km = 7.9%; 7.1-8.8: 56km = 6.1%; 5.4-5.9) (p=0.003) were more frequently affected in 21.1km race entrants, while the hamstring (21.1km = 12.6%; 11.6-18.8: 56km = 20.1%; 18.8-21.5) (p=0.0001) and quadriceps muscle (21.1km = 11.8; 10.8-12.9: 56km = 16.9%; 15.7-18.2) (p=0.0001) were more frequently affected in 56km race entrants.

Onset of EAMC during a race

The frequency (%) (adjusted for sex and age groups) of reported onset of EAMC during the race in race entrants with a history with EAMC (21.1km and 56km) is shown in Table 3.4.

Table 3.4: The frequency (%) of reported onset of EAMC during the race, adjusted for sex and age groups, in race entrants with a history with EAMC (21.1km and 56km)

	All entrants		21.1km entrants		56km entrants		RR (95%CI) #	p value
	(n=10559) **		(n=4354)		(n=6205)			
	N	% (95% CI)	N	% (95% CI)	n	% (95% CI)		
First quarter	287	2.8 (2.5-3.2)	209	4.9 (4.3-5.7)	78	1.6 (1.2-2.0)	0.3 (0.2-0.4)	0.0001*
Second quarter	298	2.9 (2.6-3.2)	157	3.7 (3.2-4.4)	141	2.7 (2.3-3.2)	0.7 (0.6-0.9)	0.013*
Third quarter	1258	11.9 (11.2-12.6)	403	9.3 (8.4-10.2)	855	13.7 (12.7-14.8)	1.5 (1.3-1.7)	0.0001*
Fourth quarter	5044	46.4 (45.4-47.5)	1654	35.1 (33.6-36.6)	3390	47.2 (45.6-48.9)	1.3 (1.2-1.4)	0.0001*
After the race	2297	22.3 (21.4-23.2)	1242	29.5 (28.1-31.1)	1055	18.6 (17.5-19.8)	0.6 (0.5-0.7)	0.0001*
No pattern	1159	11.3 (10.7-12.0)	608	14.2 (13.2-15.4)	551	10.4 (9.5-11.3)	0.7 (0.6-0.8)	0.0001*

*: Significant p values for comparison of 21.1km and 56km races

**: Data missing from 271 race entrants

#: Risk ratio in 56km vs. 21.1km race entrants

Among all race entrants, the majority reported the onset of EAMC in the fourth quarter of a race (All = 46.4%; 45.4-47.5: 56km = 35.1%; 33.6-36.6; 21.1km = 47.2%; 45.6-48.9) followed by after the race (All = 22.3%; 21.4-23.2: 56km = 29.5%; 28.1-31.1: 21.1km = 18.6%; 17.5-19.8).

However, the onset of EAMC during a race differed between 21.1km and 56km entrants. A higher % of 21.1km race entrants reported the onset of EAMC in the first quarter (21.1km = 4.9%; 4.3-5.7: 56km = 1.6%; 1.2-2.0) (p=0.0001), second quarter (21.1km = 3.7%; 3.2-4.4: 56km = 2.7%; 2.3-3.2) (p=0.013) and after the race (21.1km = 29.5%; 28.1-31.1: 56km = 18.6%; 17.5-19.8) (p=0.0001), while a higher % of 56km race entrants reported the onset of EAMC in the third quarter (21.1km =9.3%; 8.4-10.2: 56km = 13.7%; 12.7-14.8) (p=0.0001) and fourth quarter (21.1km = 35.1%; 33.6-36.6: 56km = 47.2%; 45.6-48.9) of the race (p=0.0001).

EAMC severity by cramp duration

The severity grading (adjusted for sex and age groups) of EAMC by cramp duration in race entrants with a history of EAMC (21.1km and 56km) is shown in Table 3.5.

Table 3.5: The severity grading of EAMC by cramp duration, adjusted for sex and age groups, in race entrants with a history of EAMC (21.1km and 56km)

	All entrants		**21.1km entrants**		**56km entrants**		**RR (95%CI) #**	**p value**
	(n=10569) **		**(n=4359)**		**(n=6210)**			
	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)		
Mild: Less than 5 minutes and able to continue exercising	6778	65.2 (64.2-66.2)	2853	65.0 (63.5-66.6)	3925	62.8 (61.3-64.3)	1.0 (0.9-1.0)	0.025*
Moderate: 5-15 minutes and able to continue exercising	3228	29.9 (29.0-30.9)	1293	30.1 (28.7-31.6)	1935	31.7 (30.3-33.2)	1.1 (1.0-1.1)	0.104
Severe: More than 15 minutes or have to STOP exercising	563	5.0 (4.6-5.5)	213	4.8 (4.2-5.6)	350	5.4 (4.7-6.2)	1.1 (0.9-1.3)	0.26

*: Significant p-value for comparison of 21.1km and 56km races

**: Data missing from 45 race entrants

#: Risk ratio in 56km vs. 21.1km

In all race entrants, mild EAMC (short duration) is common and accounts for over 65% of all EAMC. However, the severity of EAMC by cramp duration differed between 21.1km and 56km race entrants. Mild EAMC (21.1km = 65.0%; 63.5-66.6: 56km = 62.8%; 61.3-64.3) (p=0.025) was significantly more frequent in the 21.1km compared to 56km race entrants while moderate (21.1km = 30.1%; 28.7-31.6: 56km = 31.7%; 30.3-33.2) (p=0.104) and severe EAMC (21.1km = 4.8%; 4.2-5.6: 56km = 5.4%; 4.7-6.2) (p=0.26) was similar in 21.1km and 56km race entrants.

Prevalence of serious EAMC (sEAMC)

The prevalence (%) of sEAMC, adjusted for age and sex, in race entrants with a history of EAMC (21.1km and 56km) is shown in Table 3.6.

Table 3.6: The prevalence (%) of sEAMC, adjusted for age and sex, in race entrants with a history of EAMC (21.1km and 56km)

	All entrants		**21.1km entrants**		**56km entrants**		**RR (95%CI) #**	**p value**
	(n=10614)		**(n=4381)**		**(n=6233)**			
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)		
All serious (combined)	**766**	**6.3 (5.8-6.8)**	**205**	**4.6 (3.9-5.4)**	**561**	**6.9 (6.2-7.8)**	**1.5 (1.3-1.8)**	**0.0001***
Whole body EAMC	460	3.7 (3.4-4.2)	120	2.8 (2.3-3.4)	340	4.1 (3.5-4.7)	1.4 (1.2-1.8)	0.002*
EAMC associated with dark urine	321	2.6 (2.3-3.0)	86	1.8 (1.4-2.3)	235	2.9 (2.4-3.5)	1.7 (1.3-2.2)	0.0001*
Hospital admission for EAMC	35	0.3 (0.2-0.5)	13	0.3 (0.2-0.6)	22	0.3 (0.2-0.5)	1.1 (0.6-2.2)	0.763
EAMC associated with confusion / coma **	15	0.1 (0.1-0.2)	4	-	11		-	0.217

*: Significant p value for comparison of 21,1km and 56km races

**: Numbers to small to calculate 95%CI

#: Risk ratio in 56km vs. 21.1km race entrants

The prevalence of all sEAMC differed between 21.1km and 56km race entrants (21.1km = 4.6%; 3.9-5.4: 56km = 6.9%; 6.2-7.8) (p=0.0001). Specific sub-categories of sEAMC also differed between 21.1km and 56km race entrants. EAMC associated with dark urine (21.1km = 1.8%; 1.4-2.3: 56km = 2.9%; 2.4-3.5) (p=0.0001) and whole body EAMC (21.1km = 2.8%; 2.3-3.4: 56km = 4.1%; 3.5-4.7) was more frequently reported by 56km compared to 21.1km race entrants (p=0.002).

Successful self-reported treatment modalities for EAMC

The frequency (%) (adjusted for age and sex) of self-reported treatment modalities to relieve an acute EAMC in race entrants with a history of EAMC (21.1km and 56km) is shown in Table 3.7.

Table 3.7: Frequency (%) (adjusted for age and sex) of self-reported treatment modalities to relieve an acute EAMC in race entrants with a history of EAMC (21.1km and 56km)

	All entrants		**21.1km entrants**		**56km entrants**		**RR (95%CI) #**	**p value**
	(n=10614)		**(n=4381)**		**(n=6233)**			
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)		
Stretching	7399	70.2 (69.2-71.1)	3328	74.8 (73.4-76.2)	4071	66.2 (64.8-67.6)	0.9 (0.8-0.9)	0.0001*
Resting	4014	37.9 (36.9-38.9)	1828	39.9 (38.3-41.5)	2186	33.8 (32.4-35.3)	0.8 (0.8-0.9)	0.0001*
Massage	4013	37.9 (37.0-39.0)	1753	40.5 (38.9-42.1)	2260	38.4 (36.9-39.9)	0.9 (0.8-1.0)	0.049*
Drinking fluid	3509	33.3 (32.4-34.3)	1516	33.0 (31.5-34.6)	1993	30.4 (29.0-31.8)	0.9 (0.8-0.9)	0.005*
Magnesium	3169	29.4 (28.5-30.4)	1241	29.1 (27.7-30.6)	1928	31.9 (30.5-33.4)	1.1 (1.0-1.2)	0.006*
Salt (tablets or solution)	2492	23.2 (22.3-24.1)	737	16.6 (15.4-17.8)	1756	27.6 (26.2-29.1)	1.7 (1.5-1.8)	0.0001*
Ice application	2185	20.5 (19.6-21.3)	751	17.3 (16.2-18.6)	1434	22.5 (21.3-23.9)	1.3 (1.2-1.4)	0.0001*
Other	687	6.3 (5.8-6.8)	243	5.7 (5.0-6.5)	444	7.0 (6.2-7.8)	1.2 (1.0-1.5)	0.011*

*: Significant p value for comparison of 21.1km and 56km races

#: Risk ratio in 56km vs. 21.1km race entrants

In general, the most successful self-reported treatment modality to relieve EAMC in all race entrants was stretching, followed by resting and massage. However, the most successful self-reported treatments to relieve EAMC differed between 21.1km and 56km race entrants. Stretching (21.1km = 74.8%; 73.4-76.2: 56km = 66.2%; 64.8-67.6) (p=0.0001), resting (21.1km = 39.9%; 38.3-41.5: 56km = 33.8%; 32.4-35.3) (p=0.0001), drinking fluids (21.1km = 33.0%: 31.5-34.6: 56km = 30.4%; 29.0-31.8) (p=0.005) and massage (21.1km = 40.5%: 38.9-42.1: 56km = 38.4%; 36.9-39.9) (p=0.049) were more frequently reported as successful treatment modalities in 21.1km compared to the 56km race entrants.

Among 56km race entrants the use of salt (21.1km =16.6%; 15.4-17.8: 56km = 27.6%; 26.2-29.1) (p=0.0001), application of ice (21.1km =17.3%; 16.2-18.6: 56km = 22.5%; 21.3-23.9) (p=0.0001) and magnesium (21.1km = 29.1%; 27.7-30.6: 56km = 31.9%; 30.5-33.4) (p=0,006) were more frequently reported as successful treatment modalities.

3.5 DISCUSSION

As far as we are aware, this is the largest study to report the epidemiology and clinical characteristics (muscle groups affected by EAMC, onset of EAMC during races, severity of EAMC, and efficacy of self-reported treatment modalities) of EAMC in distance runners. We show that 12.8% of recreational runners in our cohort reported ever suffering from EAMC. This is considerably lower than the lifetime prevalence of EAMC reported in previous studies in marathon runners (42.2km) (39%), cyclists (60%) and triathletes (67%).[10] The most likely reason for this observation is that in previous descriptive studies, there were low response rates to questionnaires that could introduce a selection bias in the samples reported in previous studies. A study reporting the incidence of EAMC in marathon runners only recorded runners who presented with injuries to the medical tent in route or at the finish line.[39] In our study, we had a high response rate (71.8%), and we show that our study participants were representative (for age and sex) of all entrants in the races.

A second finding is that we also show that the muscle groups most frequently affected by EAMC in all entrants were the calf (53.1%), hamstring (20.9%) and quadriceps muscles (16.3%), which supports the findings of previous studies.[4, 81] Most entrants experienced EAMC either in the fourth quarter (46.4%) or after the race (22.3%). The severity of EAMC (by duration) was mild in most cases (65.2 % of EAMC), which supports the notion that EAMC typically lasts one to three minutes.[3, 5, 17] The most successful self-reported treatment to relieve an acute muscle cramp in all race entrants was stretching (70.2%) followed by rest (37.9%) and massage (37.9%). This is supported by studies examining the inhibitory mechanism of heightened tension in the Golgi tendon organ resulting in increased afferent reflex inhibitory input to the alpha motor neurons.[3, 5, 48-50]

A third main finding and a novel aspect of our study is that we report differences in the lifetime prevalence, clinical characteristics (muscle groups affected by EAMC, onset of EAMC during races, severity of EAMC, and efficacy of self-reported treatment modalities) in EAMC between runners entering for a 21.1km vs. a 56km race. As far as we are aware, this is the first study to report such differences between race entrants.

The lifetime prevalence of EAMC (adjusted for age and sex) was almost two times higher in 56km (16.0%), compared to the 21.1km race entrants (8.8%). The pattern of muscle groups affected by EAMC differed between 21.1km and 56km entrants, with 21.1km entrants reporting significantly more frequent EAMC in their calf and foot muscles compared to the 56km race entrants, reporting EAMC more frequently in the hamstrings and quadriceps muscles. Other differences in the clinical characteristics of EAMC in 21.1km compared to 56km race entrants were as follows: in 21.1km runners, the onset of EAMC was more frequently reported in the first quarter, second quarter and after the race, while 56km race entrants reported the onset of EAMC in the third quarter and fourth quarter of the race. EAMC was less severe (by the duration of EAMC, and serious EAMC associated with dark urine and whole body EAMC was reported less frequently) in the 21.1km entrants.

In general, the most successful self-reported treatment modality to relieve an acute EAMC in all race entrants was stretching, followed by resting and massage. In 21.1km entrants, stretching, resting, drinking fluids and massage were more frequently reported as successful treatment modalities compared to the 56km race entrants. Among the 56km race entrants, the use of salt, ice application and magnesium were more frequently reported as successful treatment modalities. Currently, most treatment modalities for EAMC are not supported by experimental research, and a number of treatment modalities for EAMC are suggested, including ingesting pickle juice, sports drinks, cryotherapy, thermotherapy, massage, compression garments, Kinesio tape, intravenous infusion, and transcutaneous electric nerve stimulation (TENS) therapy.[5] However, stretching has been proven to be the most effective in alleviating EAMC and this is confirmed by the results of our study.[51]

Our study was not designed to address specific reasons for the observed differences in EAMC between 21.1km and 56km race entrants. At this stage, we can only speculate about possible reasons for the observations. An obvious difference between these race entrants is the exercise duration and intensity of the events, with the 21.1km race being of shorter duration but is on average run at a faster pace. Other factors that could account for the observed differences are race experience, years of running, training history and prevalence of underlying chronic medical conditions and medication use and differences in the prevalence of these risk markers in 21.1km vs. 56km race entrants could perhaps be related to the observed differences in EAMC risk and clinical characteristics between race distances. It is tempting to speculate that 21.1km race entrants may, in general, be less experienced, train less but run at a faster pace, and have a higher prevalence of underlying chronic medical conditions. In other words, 21.1km race entrants may have more risk markers associated with EAMC but run at a faster pace that may result in muscle fatigue and subsequent EAMC patterns that differ from ultramarathon (56km) runners. However, it is clear that more research is needed to explore reasons for the differences in lifetime prevalence, clinical characteristics (muscle groups affected by EAMC, onset of EAMC during races, severity of EAMC) and efficacy of self-reported treatment modalities in 56km vs. 21.1km runners. More specifically, studies are needed to identify independent risk markers for EAMC in distance runners that consider race experience, years of running, training history, and prevalence of underlying chronic medical conditions and medication use.

The strengths of this study are the large sample size, a high response rate among participants that gave consent, and minimal differences between consenting race entrants and all race entrants. We recognise the following limitations of our study. All the data are self-reported with a potential of recall bias, but this would likely be similar in 21.1km and 56km entrants. We also acknowledge that we did not explore the precise reasons for the observed differences but suggest that future studies should explore different independent risk markers associated with EAMC in different endurance events and race distances using multivariate models.

3.6 SUMMARY AND CONCLUSION

In summary, this study shows that there are significant differences in EAMC risk and clinical characteristics between 21.1km and 56km race entrants. We suggest that independent risk markers associated with EAMC, which could account for these observed differences be explored in future studies.

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CHAPTER 4

4 ORIGINAL RESEARCH PAPER 2

In preparation for submission to the Clinical Journal of Sport Medicine

Title: Males, Older Age, Increased Training, Chronic Disease, Allergies And History Of Injury Are Independent Risk Markers Associated With A History Of EAMC In Distance Runners: A Cross-Sectional Study In 76654 Race Entrants – SAFER study

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The authors declare that there are no competing interests.

4.1 ABSTRACT

Background: There are few data on the risk markers associated with exercise associated muscle cramping (EAMC) in distance runners.

Aim of the study: To determine independent risk markers associated with a history of EAMC (hEaMC) in a large cohort of distance runner race entrants in a community-based mass participation event.

Design: Cross-sectional study.

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

Participants: 76654 consenting race entrants.

Methods: 106743 runners completed an online pre-race medical screening questionnaire as part of the entry for the 2012-2015 races. 76654 (71.8%) consenting entrants were included in this study (21.1km=47069; 56km=29585). We apply a multivariate model to report independent risk markers associated with hEAMC (sex, age, training variables, history of chronic disease, allergies, prescription medication use and running injuries) in all entrants and 21.1km and 56km entrants (prevalence risk ratios of hEAMC with 95%CI).

Results: Specific independent risk markers associated with hEAMC in 21.1km runners were: history of GIT disease (PR=1.47), history of running injury in the last 12 months (PR=1.44), history of CVD (PR=1.42), history of risk factor for CVD (PR=1.34), history of allergies (PR=1.21), average slower training speed in last 12 months (PR=1.06) and increase years of recreational running (PR=1.05). Specific independent risk markers associated with hEAMC in 56km runners were: any symptoms of CVD (PR=2.10), history of GIT disease (PR=1.58), history of running injury in the last 12 months (PR=1.45), history of risk factor for CVD (PR=1.45), history of allergies (PR=1.40), history of nervous system or psychiatric diseases (PR=1.36) and increase years of recreational running (PR=1.11).

Conclusion: Independent risk markers associated with hEAMC identified in this study are male sex, older age, longer race distances runners, training variables, several chronic diseases, a history of allergies and the use of prescription medications for both 21.1km and 56km race entrants.

4.2 INTRODUCTION

Exercise Associated Muscle Cramping (EAMC) is defined as a 'painful spasmodic involuntary contraction of skeletal muscle that occurs during or immediately after muscular exercise'.[13] EAMC presents clinically as a sudden onset of uncontrollable muscle contractions during or immediately after exercise, often accompanied by acute pain.[16, 21] At community-based mass participation endurance sports events, including distance running events, EAMC is one of the most common reasons for admission and treatment at event medical facilities.[1-4]

To prevent and manage EAMC in endurance athletes, it is important to identify possible intrinsic and extrinsic risk markers associated with the development of EAMC and recurring EAMC. Despite the fact that EAMC is common at endurance running events, there is limited research to specifically identify intrinsic risk markers associated with EAMC in distance runners. Potential intrinsic risk markers include sex, age, family history of EAMC, previous history of EAMC, history of soft tissue injury, running experience and history of underlying chronic disease.[12, 49, 63-65]

In general, males are more likely to experience EAMC and there is a higher incidence of EAMC in older males.[67] A review in 2016 reported that two studies indicated that older athletes are more likely to develop EAMC, but several others reported no association between age and the incidence of EAMC.[3, 75-77] A recent study on distance runners found that males older than 51years were more likely ($p = 0.0007$) to develop EAMC compared to runners in the 41-50- year group.[75]

A family history of EAMC was also considered as an intrinsic risk marker.[4, 21] Studies investigating the association between family history and EAMC were reviewed in 2016 and a family history of EMAC was considered a main risk marker for EAMC.[3, 4, 21] Two studies found that marathons runners and triathletes with a family history of EAMC were more likely to develop EAMC compared to marathon runners and triathletes with no family history.[67, 68]

A previous history of EAMC was also found to be an independent risk marker for EAMC by four studies in distance runners and triathletes.[12, 51, 67, 69] Athletes with a history of EAMC had a considerably lower CTF compared to those with no history of EAMC, which may explain why distance runner with a history of EAMC are more prone to developing EAMC during or after an event.[46] One observational study with a population of 157 distance runners compared the characteristics of those with and without cramps.[4] EAMC was most commonly found in runners with a previous history of EAMC and runners with a history of a soft tissue injury.[4]

The association between previous and current soft tissue injuries and the history of EAMC was also documented in another study.[67] The study suggested that increased reflex alpha motor activity caused by the soft tissue injury could result in EAMC. A previous injury may also contribute to the muscle fatiguing prematurely due to localized muscle weakness.[67]

In the largest cross-sectional study to date, novel independent risk factors associated with EAMC in 15778 distance runners were an underlying chronic disease, medication use, a history of running injuries, and experienced runners.[80] The study found that distance runners classed as either experienced or intermediate had a significantly higher prevalence ratio of a history of EAMC when compared with novice runners. However, this study did not differentiate between risk markers associated with EAMC in 21.1km vs. 56km runners.[80]

Historically the two main aetiological factors explaining the pathophysiology of EAMC were dehydration and electrolyte imbalances, but more recently, factors associated with altered neuromuscular control as a result of muscle fatigue are reported.[3, 8, 9] Specifically, recent studies suggest that muscle fatigue and other potential risk markers that lead to muscle fatigue may alter the neuromuscular control and this is thought to be the common pathophysiological pathway resulting in EAMC.[43] Factors that can affect neuromuscular control during exercise, specifically the development of premature muscle fatigue, have not been explored in many studies. Because muscle fatigue contributes to the onset of EAMC, it might be important to explore the differences in the risk markers of EAMC in runners participating in varying race distances such as 21.1km vs. 56km runners.

The aim of this study was to identify selected intrinsic risk markers associated with a history of EAMC (hEAMC) in a large sample of distance runners and to determine if risk markers for EAMC differ between 21.1.km and 56km runners. The following specific risk markers associated with hEAMC will be explored using multivariate analysis: runner demographics (age group and sex), running training/racing history, a history of existing chronic disease, and prescription medication usage.

4.3 METHODOLOGY

Study design

This was an observational study with a cross-sectional analysis of data collected prospectively over four years. We utilized the secondary data from an existing database that was collected prospectively using an online pre-race medical screening tool prior to the 2012-2015 Two Oceans races (21.1km and 56km) over the four-year period. Prior to the onset of the study, the Research Ethics Committee of the Faculty of Health Sciences from both the University of Cape Town (REC009/2011) and the University of Pretoria (Ref. 433/2015) (Ref. 28/2018). This study is also part of a series of ongoing SAFER (Strategies to reduce Adverse medical events For the ExerciseR) studies, for which data collection is ongoing.[89]

Study participants

A total of 106743 runners entered and 76 654 entrants gave consent to be included in this study. Entrants (n=10614) who indicated a history of EAMC was included in the study. A small but significantly higher proportion of 21.1km vs. 56km entrants participated in this study compared with all race entrants (p=0.001). However, study participants did not differ from all race entrants by age group (p=0.364) and sex (p=0.052), as seen in Table 4.1.

Pre-race medical screening questionnaire

The details of the development of an online pre-race medical screening questionnaire (OPRMSQ) or "self-assessment of risk" that was administered to all race entrants from 2012 to 2015 was previously described.[17, 86, 87] This questionnaire included the following categories of medical history: symptoms of cardiovascular disease (CVD), risk factors for CVD, and history of diagnosed chronic disease (CVD, respiratory, metabolic or hormonal, gastrointestinal, nervous system, renal or bladder, hematological or immune system, cancer, allergies), general prescription medication use, medication use during racing, and a past history of collapse during racing. These factors are all associated with a possible increased risk of acute medical complications in moderate- to high-intensity exercise such as distance running, including EAMC.[88] The online pre-race medical history screening tool also included a specific question on EAMC "*Have you ever in your running career suffered from muscle cramping (painful, spontaneous, sustained spasm of a muscle) during or immediately (within 6 hours) after running (in training or competition)?*" In response to a "yes" answer to this question, race entrants were grouped as those reporting a history of EAMC (hEAMC = 10614, 21.1 km = 6233, 56 km = 4381) and a control group of participants with no history of EAMC.

Primary objective: Intrinsic risk markers of hEAMC

Four broad individual categories of risk markers for hEAMC that were explored in 21.1km and 56km race entrants (using the data from the pre-race medical screening questionnaire) in this study were: 1) demographics, 2) training-related variables, 3) history of chronic diseases/allergies, medication use, and 4) history of injuries. More specifically, demographic variables included sex, age group and race distance (21.1km or 56km). Training-related variables included years of recreational running (years), frequency of training per week, and average self-reported training speed (km/h). A history of chronic disease, allergies and injuries was obtained from the pre-race medical screening variables: history of CVD, CVD symptoms, CVD risk factors, other chronic diseases (metabolic/endocrine, respiratory, GIT, nervous system/psychiatric, kidney/bladder, hematological/immune, cancer) and allergies. The history of running injuries was also obtained from the pre-race medical screening questionnaire. The potential risk markers were in univariate and multivariate models for both 21.1km and 56km race entrants.

Statistical analysis of data

The data were analysed using the SAS 9.4 statistical program (SAS Institute Inc, Cary, North Carolina).

4.4 RESULTS

4.4.1 Demographics

The profile by race distance, sex and age groups of all race entrants and race entrants who gave consent to participate in this study is shown in Table 4.1.

Table 4: The profile by race distance, sex and age groups of all race entrants and race entrants who gave consent to participate in this study

		All race entrants (n=106743)		**Consenting race entrants (n=76654)**		**p value**
		N	%	N	%	P
Race distance	21.1km	64740	60.7	47069	61.4	*p= 0.001
	56km	42003	39.4	29585	38.6	
Sex	Males	61815	57.9	44042	57.5	p=0.052
	Females	44928	42.1	32612	42.5	
Age groups	≤ 30 years	27710	26.0	20168	26.3	p= 0.364
	31–40 years	35049	32.8	25045	32.7	
	41–50 years	26964	25.3	19340	25.2	
	≥ 51 years	17020	15.9	12101	15.8	

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

The profile by race distance, sex and age groups of the study population and the sub-group of 56km and 21.1km entrants are shown in Table 4.2. The mean (±SD) age for all entrants was 38.7±11.1 years.

Table 4.2: The demographics (sex, age groups) of all the consenting race entrants and the sub-groups (21.1km, 56km) over the 4-year period

		All entrants		56km entrants		21.1.km entrants		p value*
		N	%	N	%	N	%	p
All race entrants		76654	100	29585	38.6	47069	61.4	
Sex	Males	44042	57.5	21044	71.1	22998	48.9	
	Females	32612	42.5	8541	28.9	24071	51.1	0.0001
Age	≤30 years	20168	26.3	3574	12.1	16594	35.3	
	31-40 years	25045	32.7	10755	36.4	14290	30.4	
	41-50 years	19340	25.2	10078	34.1	9262	19.7	
	≥51 years	12101	15.8	5178	17.5	6923	14.7	0.0001

There were significantly more male entrants in the 56km races (71.1%) compared to females (28.9%) (p=0.0001), and 56km entrants were significantly older compared with the 21.1km entrants (p=0.0001). A greater % entrants in the 56km race were in the older age categories compared to the 21.1km entrants (p=0.0001).

4.4.2 Lifetime prevalence and annual incidence of hEAMC

The lifetime prevalence of hEAMC in the study population was 12.8% (95% CI 12.6-13.1) and the lifetime prevalence of hEAMC was significantly higher in 56km (16.0%;15.5-16.5) compared to 21.1km entrants (8.8%; 8.5-9.1) (p=0.0001) (adjusted for age and sex). The annual incidence of EAMC in the study population was 7.8% (95% CI 7.6-8.0). The annual incidence of EAMC was significantly higher in 56km (10.5%; 10.1-11.0) compared with 21.1km entrants (5.2%; 4.9-5.4) (p=0.0001) (adjusted for age and sex). Because the lifetime prevalence and annual incidence of EAMC were significantly different in the 21.1km vs. the 56km race entrants, risk markers associated with hEAMC will be explored separately for 21.1km and 56km race entrants.

4.4.3 Risk markers associated with hEAMC (Univariate model)

Demographics (sex and age groups)

The frequency and prevalence risk ratio of entrants with hEAMC amongst 21.1km and 56km race entrants (by sex and age groups) are shown in Table 4.3.

Table 4.3: The frequency (%) and prevalence risk ratio (PR; with 95% confidence intervals - CI) of 21.1km and 56km entrants with a history of EAMC (hEAMC) by sex and age groups

Race distance	Variable	Category	N	Number with hEAMC	% participants with hEAMC * (95% CI)	PR (95% CI)	p value
21.1km	All entrants**		47069	4381	9.0 (8.7-9.3)		
	Sex	Male	22998	2787	10.1 (9.6-10.6)		
		Female	24071	1594	5.3 (5.0-5.7)	1.9 (1.8-2.1)	0.0001
	Age groups (yrs)	≤30 yrs	16594	1303	7.9 (7.4-8.3)		
		31-40 yrs	14290	1112	7.7 (7.2-8.2)	0.98 (0.90-1.1)	0.6323 ***
		41-50 yrs	9262	956	9.9 (9.2-10.6)	1.3 (1.2-1.4)	0.0001 ***
		≥51 yrs	6923	1010	13.5 (12.6-14.4)	1.7 (1.6-1.9)	0.0001 ***
56km	All entrants**		29585	6233	19.3 (18.7-19.8)		
	Sex	Male	21044	5157	21.4 (20.7-22.1)		
		Female	8541	1076	10.1 (9.8-11.4)	2.0 (1.9-2.2)	0.0001
	Age groups (yrs)	≤30 yrs	3574	576	15.6 (14.3-16.9)		
		31-40 yrs	10755	2069	17.8 (17.0-18.7)	1.1 (1.0-1.3)	0.005 ***
		41-50 yrs	10078	2189	20.1 (19.2-21.0)	1.3 (1.2-1.4)	0.0001***
		≥51 yrs	5178	1399	24.4 (23.0-25.8)	1.6 (1.4-1.7)	0.0001***

*: Model estimates
**: Unadjusted
PR: Prevalence Risk ratio
***: Pairwise differences compared to youngest age group

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

Training history

The frequency (%) and prevalence risk ratio of race entrants with a history of EAMC in 21.1km and 56km race entrants (by training history variables) are shown in Table 4.4.

Table 4.4: The frequency (%) and prevalence risk ratio (PR; with 95% CI's; adjusted for sex and age group) of 21.1km and 56km race entrants with a history of EAMC (hEAMC) by training history variables

Race distance	Training history variable	Points in the continuous variable	Predicted % of participants at specific points in the continuous variable (95% CI)	PR (95% CI)	p value
21.1km	Years of recreational running (yrs)	3yrs	7.8 (7.5-8.1)		
		6yrs	8.3 (8.0-8.6)		
		13yrs	9.6 (9.3-9.9)	1.11 (1.09-1.13) *	0.0001
	Average weekly training frequency in last 12 months (times a week)	3 / week	9.1 (8.8-9.4)		
		4 / week	8.7 (8.4-9.1)	0.96 (0.94-0.99) **	0.002
	Average training speed in last 12 months (min/km)	5 min/km	8.4 (8.1-8.9)		
		6 min/km	8.9 (8.6-9.2)		
		6.5 min/km	9.1 (8.8-9.5)	1.05 (1.03-1.08) ***	0.0001
56km	Years of recreational running (yrs)	3yrs	15.85(14.9-16.2)		
		6yrs	16.0 (15.4-16.6)		
		13yrs	17.1 (15.7-16.9)	1.1 (1.04-1.07)	0.0001
	Average weekly training frequency in last 12 months (times a week)	3 / week	17.6 (16.9-18.3)		
		4 / week	16.8 (16.3-17.4)	0.96 (0.94-0.97)	0.0001
	Average training speed in last 12 months (min/km)	5 min/km	15.8 (15.2-16.4)		
		6 min/km	16.9 (16.4-17.5)		
		6.5 min/km	17.6 (16.9 -18.2)	1.07 (1.05-1.10)	0.0001

PR: Prevalence Risk ratio

*: PR for every 5yrs of additional running

**: PR for every 1 more training times per week

***: PR for every 1 min/km decrease in speed

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

History of chronic diseases and allergies

The frequency (%) and prevalence risk ratio of entrants with a history of EAMC in 21.1km and 56km race entrants (by history of main category of chronic disease and allergies) are shown in Table 4.5.

Table 4.5: The frequency (%) and prevalence risk ratio (PR; With 95% CI's; adjusted for sex and age group) of 21.1km and 56km race entrants with hEAMC by history of chronic disease and allergies

Race distance	History of chronic disease variable and regular prescription medication use		n	Number with hEAMC	% hEAMC	PR (95% CI)	p value
21.1km	Any history of CVD	No	46208	4218	8.9 (8.6-9.2)		
		Yes	861	163	14.6 (12.5-17.1)	1.6 (1.4-1.9)	<0.001
	Any risk factor for CVD	No	41154	3361	8.1 (7.8-8.4)		
		Yes	5915	1020	14.3 (13.4-15.3)	1.8 (1.6-1.9)	<0.001
	Any symptoms of CVD	No	46496	4180	8.7 (8.4-9.0)		
		Yes	573	201	25.7 (21.7-30.4)	2.9 (2.4-3.5)	<0.001
	Any respiratory disease	No	42073	3630	8.4 (8.1-8.7)		
		Yes	4996	751	14.0 (12.9-15.1)	1.7 (1.5-1.8)	<0.001
	Any endocrine disease	No	45620	4205	8.9 (8.6-9.2)		
		Yes	1449	176	12.5 (10.7-14.6)	1.4 (1.2-1.7)	<0.001
	Any GIT disease	No	45759	4082	8.7 (8.4-9.0)		
		Yes	1310	299	19.8 (17.5-22.3)	2.3 (2.0-2.6)	<0.001
	Any nervous system / psychiatric disease	No	45782	4155	8.7 (8.4-9.0)		
		Yes	1287	226	17.5 (15.3-20.1)	2.0 (1.7-2.3)	<0.001
	Any kidney / bladder disease	No	46400	4228	8.8 (8,5-9.1)		
		Yes	669	153	17.5 (14.8-20.7)	2.0 (1.7-2.3)	<0.001
	Any hematologica / immune disease	No	46666	4305	8.9 (8.6-9.2)		
		Yes	403	76	18.9 (14.8-24.2)	2.1 (1.7-2.7)	<0.001
	Any cancer	No	46290	4258	8.9 (8.6-9.2)		
		Yes	779	123	13.5 (11.3-16.2)	1.5 (1.3-1.8)	<0.001
	Any allergies	No	41847	3572	8.4 (8.1-8.7)		
		Yes	5222	809	14.2 (13.1-15.3)	1.7 (1.6-1.8)	<0.001
	Any regular prescription medication use	No	40430 [a]	3404	8.3 (8.0-8.6)		
		Yes	6639	977	12.6 (11.8-13.5)	1.5 (1.4-1.6)	<0.001
56km	Any history of CVD	No	29036	6047	16.5 (16.0-17.0)		
		Yes	549	186	23.5 (20.3-27.1)	1.4 (1.2-1.6)	<0.001
	Any risk factor for CVD	no	26179	5090	15.8 (15,3-16.3)		
		yes	3406	1143	24.2 (22.8-25.6)	1.5 (1.4-1.6)	<0.001
	Any symptoms of CVD	no	29305	6101	16.4 (15.9-17.0)		
		yes	280	132	30.3 (25.7-35.7)	1.8 (1.6-2.2)	<0.001
	Any respiratory disease	no	27500	5633	16.0 (15.5-16.6)		
		yes	2085	600	23.1 (21.4-25.0)	1.4 (1.3-1.6)	<0.001
	Any endocrine disease	no	28923	6052	16.4 (15.9-17.0)		
		yes	662	181	22.5 (19.4-26.1)	1.4 (1.2-1.6)	<0.001
	Any GIT disease	no	28838	5930	16.3 (15.8-16.8)		
		yes	747	303	30.0 (27.1-33.0)	1.8 (1.7-2.0)	<0.001
	Any nervous system / psychiatric disease	no	29012	6075	16.4 (15.9-16.9)		
		yes	573	158	23.9 (20.7-27.5)	1.5 (1.3-1.7)	<0.001
	Any kidney / bladder disease	no	29133	6067	16.4 (15.9-17.0)		
		yes	452	166	26.6 (23.1-30.7)	1.6 (1.4-1.9)	<0.001
	Any hematologica / immune disease	no	29395	6192	16.5 (16.0-17.1)		
		yes	190	41	25.5 (19.1-34.0)	1.5 (1.2-2.1)	0.0034
	Any cancer	no	29156	6115	16.5 (16.0-17.1)		
		yes	429	118	20.1 (16.6-24.3)	1.2 (1.0-1.5)	0.048

Table 4.5: The frequency (%) and prevalence risk ratio (PR; With 95% CI's; adjusted for sex and age group) of 21.1km and 56km race entrants with hEAMC by history of chronic disease and allergies (continued)

Race distance	History of chronic disease variable and regular prescription medication use		n	Number with hEAMC	% hEAMC	PR (95% CI)	p value
56km	Any allergies	no	27040	5470	16.0 (15.4-16.5)		
		yes	2545	763	22.8 (21.3-24.4)	1.4 (1.3-1.5)	<0.001
	Any regular prescription medication use	no	26036	5249	16.0 (15.5-16.6)		
		yes	3549	984	21.0 (19.7-22.4)	1.3 (1.2-1.4)	<0.001

PR: Prevalence Risk ratio
CVD: cardiovascular
GIT: gastrointestinal

In both 21.1km and 56km race entrants, the PR of hEAMC was significantly higher in entrants who reported CVD risk factors, CVD symptoms and a history of a number of chronic diseases (CVD, respiratory, GIT, endocrine, nervous system / psychiatric, kidney / bladder, hematologica / immune, cancer) and allergies than in entrants with no hEAMC.

History of running injuries

The frequency (%) and prevalence risk ratio of entrants with a history of EAMC by history of any running injury are shown in Table 4.6 (21.1km and 56km race entrants).

Table 4.6: The Frequency (%) and prevalence risk ratio (PR; With 95% CI's; adjusted for sex and age group) of 21.1km and 56km race entrants with hEAMC by history of any running injury

Race distance	Running injury		n	Number with hEAMC	% hEAMC (95%CI)	PR (95% CI)	p value
21.1km	Any running injury	No	42632	3493	8.2 (7.9-8.5)		
		yes	4437	888	15.7 (14.6-16.9)	1.9 (1.8-2.1)	<0.001
56km	Any running injury	No	25691	4875	15.5 (14.9-16.0)		
		yes	3894	1358	24.6 (23.3-25.9)	1.6 (1.5-1.7)	<0.001

PR: Prevalence Risk ratio

The PR of hEAMC was significantly higher in entrants with a history of a running injury for both 21.1km (PR=1.9) and 56km race entrants (PR=1.6).

4.4.4 Independent risk markers associated with hEAMC (Multivariate model)

The independent risk markers (adjusted for sex and age groups) associated with hEAMC in 21.1km and 56km race entrants are depicted in Table 4.7.

Table 4.7: Independent risk markers (training, chronic disease, running injury) associated with hEAMC in 21.1km race entrants (multivariate model, adjusted for sex and age groups)

Race distance	Category of variables	Variable		PR (95% CI)	p value
21.1km	**Training variables**	Years of recreational running (yrs)	For every 5 yrs increase	1.05 (1.04-1.07)	<0.0001
		Average weekly training frequency in last 12 months (times a week)	For every increase in one weekly training frequency	0.97 (0.95-0.99)	0.0008
		Average training speed in last 12 months (min/km)	For every 1 min / km slower training speed	1.06 (1.03-1.08)	<0.0001
	History of chronic disease	Any risk factor for CVD	no		
			yes	1.34 (1.26-1.43)	<0.0001
		Any symptoms of CVD	no		
			yes	1.42 (1.21-1.67)	<0.0001
		Any respiratory disease	no		
			yes	1.17 (1.08-1.28)	0.0002
		Any GIT disease	no		
			yes	1.47 (1.33-1.63)	<0.0001
		Any kidney or bladder disease	no		
			yes	1.30 (1.12-1.50)	0.0004
		Any allergies	no		
			yes	1.21 (1.12-1.30)	<0.0001
	Running injury history	Any running injury (past 12 months)	no		
			yes	1.44 (1.36-1.52)	<0.0001
56km	**Training variables**	Years of recreational running (yrs)	For every 5 yrs increase	1.11 (1.10-1.13)	<0.0001
		Average weekly training frequency in last 12 months (times a week)	For every increase in one weekly training frequency	0.97 (0.94-0.99)	0.0066
		Average training speed in last 12 months (min/km)	For every 1 min / km slower training speed	1.03 (1.01-1.06)	0.0171
	History of chronic disease	Any risk factor for CVD	no		
			yes	1.45 (1.33-1.57)	<0.0001
		Any symptoms of CVD	no		
			yes	2.01 (1.70-2.36)	<0.0001
		Any respiratory disease	no		
			yes	1.22 (1.12-1.34)	0.0002
		Any GIT disease	no		
			yes	1.58 (1.40-1.79)	<0.0001

Table 4.7: Independent risk markers (training, chronic disease, running injury) associated with hEAMC in 21.1km race entrants (multivariate model, adjusted for sex and age groups) (continued)

Race distance	Category of variables	Variable		PR (95% CI)	p value
56km	History of chronic disease	Any nervous system / psychiatric disease	No		
			yes	1.36 (1.19-1.57)	<0.0001
		Any kidney or bladder disease	No		
			yes	1.37 (1.15-1.63)	0.0004
		Any hematologica / immune disease	No		
			yes	1.45 (1.16-1.81)	0.0038
		Any allergies	No		
			yes	1.40 (1.29-1.53)	<0.0001
	Running injury history	Any running injury (past 12 months)	No		
			yes	1.45 (1.34-1.57)	<0.0001

CVD: cardiovascular
GIT: gastrointestinal
PR: Prevalence Risk ratio
*: PR for every 5yrs of additional running
**: PR for every 1 more training times per week
***: PR for every 1 min/km increase in speed

In general, the independent risk markers associated with hEAMC were similar in 21.1km and 56km race entrants. Specific independent risk markers associated with hEAMC in 21.1km runners were: a history of GIT disease (PR=1.47), history of running injury in the last 12 months (PR=1.44), history of CVD (PR=1.42), history of risk factor for CVD (PR=1.34), history of allergies (PR=1.21), average slower training speed in last 12 months (PR=1.06) and increase in years of recreational running (PR=1.05).

Specific independent risk markers associated with hEAMC in 56km runners were: any symptoms of CVD (PR=2.10), history of GIT disease (PR=1.58), history of running injury in last 12 months (PR=1.45), history of risk factor for CVD (PR=1.45), history of allergies (PR=1.40), history of nervous system or psychiatric diseases (PR=1.36) and increase in years of recreational running (PR=1.11).

4.5 DISCUSSION

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

The first novel finding in our study was that the lifetime prevalence of hEAMC was significantly higher in 56km (16.0%;15.5-16.5) compared to 21.1km entrants (8.8%; 8.5-9.1) (p=0.0001) (adjusted for age and sex). Longer race distances imply longer exercise duration, which has been found to cause muscle fatigue, which may lead to EAMC based on the altered-neuromuscular control theory.[13, 45, 79] A cross-sectional study that included data from three marathons also reported an increased risk for EAMC with longer exercise duration.[68]

We show that male sex and older age are risk markers associated with hEAMC. The PR of hEAMC was about 2 times higher in males for both 21.1km (PR=1.9) and 56km (PR=2.0) race entrants. Manjta et al. (1996) also found that being male is an independent risk marker for developing EAMC. However, a previous prospective cohort study with a small sample size found that the sex of runners had no effect on the incidence of EAMC.[51] Based on the data from our analyses we conclude that male sex is a significant risk marker associated with hEAMC (p=0.0001).

Older age (>40 years) was also a significant intrinsic risk marker of hEAMC in both 21.1km and 56km race entrants. Previous studies have shown that runners older than 35 years are at a higher risk for EAMC. Some limitations to this study were the cross-sectional study design and response rate of 17%.[68] A review in 2016 reported that two studies indicated that older athletes are more likely to develop EAMC, but several others reported no association between age and the incidence EAMC.[3, 75-77]. We conclusively found that hEAMC in both 21.1km (PR=1.7) (p=0.0001) entrants and 56km entrants (PR=1.6)(p=0.0001) is associated with older age.

A second novel finding was that training variables are independent risk markers for hEAMC in both 21.1km and 56km race entrants. Specifically, an increased number of years of running, reduced number of weekly training sessions and slower average weekly training speed were independent risk markers for hEAMC in both 21.1km and 56km race entrants. In this study, we did not explore the specific reasons why these training variables are associated with hEAMC. It is tempting to speculate that inadequate race preparation (fewer weekly training sessions at a slow speed) could lead to premature muscle fatigue on race day, and this is a common pathophysiological pathway leading to EAMC. However, we acknowledge that this a cross-sectional study and we cannot determine a cause-effect relationship. A hEAMC may either cause or result from a reduction in weekly training sessions and training speed and this relationship should be explored in future studies.

A third novel observation was that several chronic diseases, a history of allergies and the use of prescription medications are independent risk markers associated with hEAMC and this holds for both 21.1km and 56km race entrants. These associated risk markers differ between 21.1km and 56km race entrants with respect to a history of nervous system disease (only for 56km race entrants) and the relative risk - PR is highest for GIT disease in 21.1km and for history of CVD in 56km race entrants. This study does not provide any explanation of why there is an association between hEAMC and these risk markers, but we speculate that there might be a relationship between several chronic diseases, a history of allergies and the use of prescription medications and the altered-neuromuscular control theory. These findings are of significance for health care providers who consult with distance runners with hEAMC to explore and assess various possible underlying causes of EAMC. Again, we acknowledge that we cannot determine a cause-effect relationship in this cross-sectional study and the relationship with these risk markers should be explored in future studies.

Finally, we also show that the PR of hEAMC was about 1.45 times higher in both 21.1km and 56km race entrants with a history of a running injury. This confirms data from one previous study where previous and current injuries were associated with a history of EAMC.[67] We did not study the precise reasons for this observation but can speculate that a previous injury may result in localised muscle weakness and therefore contribute to the development of abnormal neuromuscular control and muscle fatigue during distance running. Furthermore, acute local injury can result in an increased reflex alpha motor activity, which acts as a trigger for the development of EAMC. However, these relationships need to be explored in future studies.

The strengths of this study are the large sample size, a high response rate among participants that gave consent, and minimal differences between consenting race entrants and all race entrants. As far as we could determine, we were the first study to apply a multivariate model to report independent risk markers associated with hEAMC in 21.1km and 56km entrants. We recognise the following limitations of our study. All the data are self-reported with a potential of recall bias, but this would likely be similar in 21.1km and 56km entrants. We also acknowledge that this a cross-sectional study and we cannot determine a cause-effect relationship between hEAMC and independent risk markers should therefore be explored in future studies.

4.6 SUMMARY AND CONCLUSION

In summary, this study shows that there are significant differences in the lifetime prevalence of hEAMC in male sex, older age and longer race distances runners. A second novel finding was that the training variables are independent risk markers for hEAMC, specifically reduced number of weekly training sessions and slower average weekly training speed in both 21.1km and 56km race entrants. A third novel observation was that several chronic diseases, a history of allergies and the use of prescription medications are independent risk markers associated with hEAMC and this holds for both 21.1km and 56km race entrants. Finally, we also show that the PR of hEAMC was about 1.45 times higher in both 21.1km and 56km race entrants with a history of a running injury. We suggest that independent risk markers associated with EAMC that could account for these observed differences be explored in future studies.

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CHAPTER 5

FINDINGS, LIMITATIONS, STRENGTHS, CONCLUSION AND RECOMMENDATIONS

5.1 PRIMARY FINDINGS

As far as we are aware, this is the largest study to report the epidemiology and clinical characteristics of EAMC in distance runners and also the largest study to determine intrinsic risk markers associated with a history of EAMC using a multivariable model.

The first main finding is that 12.8% of recreational runners in our cohort reported ever suffering from EAMC. This is considerably lower than the lifetime prevalence of EAMC reported in previous studies in marathon runners (42.2km) (39%), cyclists (60%) and triathletes (67%).[10]

A second main finding is the muscle groups most frequently affected by EAMC in all entrants were the calf (53.1%), hamstring (20.9%) and quadriceps muscles (16.3%), which supports the findings of previous studies.[4, 81] Most entrants experienced EAMC either in the fourth quarter (46.4%) or after the race (22.3%). The severity of EAMC (by duration) was mild in most cases (65.2 % of EAMC), which supports the notion that EAMC typically lasts one to three minutes.[3, 5, 17] The most successful self-reported treatment to relieve an acute muscle cramp in all race entrants was stretching (70.2%) followed by rest (37.9%) and massage (37.9%).

A third main finding and a particularly novel aspect of our study is that we report differences in the lifetime prevalence, clinical characteristics (muscle groups affected by EAMC, onset of EAMC during races, severity of EAMC, and efficacy of self-reported treatment modalities) in EAMC between runners entering for a 21.1km vs. a 56km race. As far as we are aware, this is the first study to report such differences between race entrants.

The lifetime prevalence of EAMC (adjusted for age and sex) was almost two times higher in 56km (16.0%), compared to the 21.1km race entrants (8.8%). The pattern of muscle groups affected by EAMC differed between 21.1km and 56km entrants, with 21km entrants reporting significantly more frequent EAMC in their calf and foot muscles compared to the 56km race entrants, reporting EAMC more frequently in the hamstrings and quadriceps muscles. Other differences noted were the onset and the severity of EAMC. In 21km entrant, the onset of EAMC was more frequently reported in the first quarter, second quarter and after the race, EAMC was less severe (by duration of EAMC and serious EAMC associated with dark urine and whole body EAMC was reported less frequently). Stretching has been found to be the most effective self-reported treatment modality in 21.1km and the 56km race entrants.

The fourth main series of findings relate to the multivariable model we used to determine intrinsic risk markers associated with hEAMC. We first showed that increased race distance (56km vs. 21.1km), male sex and older age were risk markers for hEAMC. More specifically, we showed that the lifetime prevalence of hEAMC was significantly higher in 56km entrants compared to 21.1km entrants (adjusted for age and sex). We also show that the PR of hEAMC for males is about 2 times higher for all race entrants. Older age (>40 years) was also a significant intrinsic risk marker of hEAMC in both 21.1km and 56km race entrants.

In the subsequent analyses, we therefore explored independent risk markers separately for 21.1km and 56km race entrants and adjusted for sex and age.

In both 21.1km and 56km race entrants, independent risk markers for hEAMC were related to training variables, history of chronic disease and history of running injury.

Training variables are independent risk markers for hEAMC in both 21.1km and 56km race entrants, specifically, an increased number of years of running, reduced number of weekly training sessions and slower average weekly training speed. These were independent risk markers for hEAMC in both 21.1km and 56km race entrants. In this study, we did not explore the specific reasons why these training variables are associated with hEAMC.

A specific novel finding, and possibly the most important scientific contribution of this research is that several chronic diseases, a history of allergies and use of prescription medications are independent risk markers associated with hEAMC and this also holds for both 21.1km and 56km race entrants (observations from the multivariable analysis). Finally, we also show that the PR of hEAMC was about 1.45 times higher in both 21.1km and 56km race entrants with a history of a running injury. We did not study the precise reasons for these findings and suggest that these are especially important areas for future research studies.

5.2 LIMITATIONS

The main limitation of this study is that the data is self-reported and that not all potential variables and risk markers could be included in the online pre-race medical screening tool. We recognize that self-reported data has the potential of recall bias, but this would likely be similar in 21.1km and 56km entrants. We also acknowledge that this a cross-sectional study and we cannot determine a cause-effect relationship between hEAMC and independent risk markers. A cause-effect relationship could be explored in future studies.

5.3 STRENGTHS

As far as we are aware, this is the largest study to report the epidemiology and clinical characteristics of EAMC in distance runners. The strengths of this study are the large sample size, a high response rate among participants that gave consent, and minimal differences between consenting race entrants and all race entrants. As far as we are aware, this is the first study to apply a multivariate model to report independent risk markers associated with hEAMC in 21.1km and 56km entrants.

5.4 CONCLUSION

In summary, the findings from this dissertation are: 1)there are significant differences in EAMC risk and clinical characteristics between 21.1km and 56km race entrants, 2) there are significant differences in the lifetime prevalence of hEAMC in the male sex, older age and longer race distances runners, 3) training variables are independent risk markers for hEAMC specifically reduced number of weekly training sessions and slower average weekly training speed in both 21.1km and 56km race entrants, 4) several chronic diseases, a history of allergies and use of prescription medications are independent risk markers associated with hEAMC and this holds for both 21.1km and 56km race entrants, and 5) the prevalence risk of hEAMC was about 1.45 times higher in both 21.1km and 56km race entrants with a history of a running injury.

5.5 RECOMMENDATIONS

We recommend that future studies are conducted to explore the cause-effect relationship between hEAMC and the risk markers identified in this dissertation, including the following: training variables, chronic diseases, a history of allergies, use of prescription medications and a history of running injury.

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APPENDIX A: PERMISSION TO USE DATA

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Professor Martin Schwellnus
MBBCh, MSc (Med), MD, FACSM, FFIMS
Director: Sport, Exercise Medicine and Lifestyle Institute (SEMLI)
Director: IOC Research Center, South Africa
Faculty of Health Sciences
University of Pretoria
South Africa

7 November 2017

To: Chair: Masters Committee / Research Ethics Committee
University of Pretoria

Letter of permission to access data for research

This letter is to confirm that Prof Martin Schwellnus of the University of Pretoria is the principle investigator of the project with the title **"Medical consequences in endurance sports. Two Oceans marathon longitudinal study: 2009-2015**". This study has Research Ethics clearance from the Faculty of Health Sciences Research Ethics Committee at the University of Pretoria (REC reference number: 433/2015).

A master's student, Ms Izaan De Jager (Student#: 28068824), will be conducting a study, in fulfillment of an "MSc Sport Science" degree at the University of Pretoria, on a sub-component of the study above. The focus of her study will be **"Risk markers associated with Exercise Associated Muscle Cramps in distance runners"**.

I hereby give permission that the student can conduct novel research on the raw dataset, and therefore can access the data that were collected for the study.

Please feel free to contact me if any further information is required.

Yours sincerely

Prof. Martin Schwellnus (MBBCh, MSc(Med), MD, FACSM. FFIMS)
Full Professor: Sport and Exercise Medicine
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: Gesondheidswetenskappe
ha la Disaense tša Maphelo

APPENDIX B: UNIVERSITY OF PRETORIA ETHICS APPROVAL

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
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Faculty of Health Sciences Research Ethics Committee

1/10/2015

Approval Certificate
New Application

Ethics Reference No.: 433/2015

Title: MEDICAL CONSEQUENCES IN ENDURANCE SPORTS. TWO OCEANS MARATHON LONGITUDINAL STUDY: 2009-2015

Dear Martin Schwellnus

The **New Application** as supported by documents specified in your cover letter dated 27/08/2015 for your research received on the 31/08/2015, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 30/09/2015.

Please note the following about your ethics approval:

- Ethics Approval is valid for 5 years
- Please remember to use your protocol number (**433/2015**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:

- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, H W Snyman South Building, Room 2.33 / 2.34.*

Dr R Sommers; MBChB; MMed (Int); MPharMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

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The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

• FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.

• IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

09-Feb-2018

Approval Certificate

New Application

Ethics Reference No.: 28/2018

Title: THE ASSOCIATION OF RISK MARKERS AND THE PREVALENCE OF EXERCISE ASSOCIATED MUSCLE CRAMPS IN DISTANCE RUNNERS

Dear Miss Izaan de Jager

The **New Application** as supported by documents specified in your cover letter for your research received on the , was approved by the Faculty of Health Sciences Research Ethics Committee on the 31-Jan-2018.

Please note the following about your ethics approval:

- Ethics Approval is valid from to .
- Please remember to use your protocol number (28/2018) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:

- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

Additional Conditions:

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed(Int) MPharMed
Deputy Chairperson: Faculty of Health Sciences Research Ethics Committee

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

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APPENDIX C: PARTICIPANT INFORMATION AND INFORMED CONSENT

MEDICAL CONSEQUENCES IN ENDURANCE SPORTS

TWO OCEANS MARATHON LONGITUDINAL STUDY: 2013-2015

PARTICIPANT INFORMATION AND INFORMED CONSENT (COMPONENT 1)

PRE-RACE MEDICAL QUESTIONNAIRES

Dear Athlete,

Medical questionnaire information for safety on race day

As part on ongoing commitment to making your race experience as safe as possible, and to provide the best medical care we can on race day, the organizers and the medical team are including online medical questionnaires as part of the registration and entry to the race. There are two parts in this process:

a. The completion of an online medical questionnaire (part 1) when you enter for the race
b. The completion of a short medical questionnaire (part 2) in the few days before race registration

The main purpose for this is that the information will allow the medical team to plan medical care for the event and to address important medical consequences and injuries associated with participation in the event. In the interests of your health and safety, the medical team may contact you before or after the event for further information about any medical conditions or injuries you may report in these questionnaires. This information will be of an informative nature to improve race safety.

Medical and scientific research

You do also have the opportunity to volunteer that the information on these medical questionnaires can be used for ongoing medical and scientific research to improve race safety and medical care.

The Clinical Sport and Exercise Medicine Research Group of the UCT/MRC Research Unit for Exercise Science and Sports Medicine based at the Sports Science Institute of South Africa, in collaboration with the race organizers and the medical team conducts ongoing research to improve race safety (protecting the health of the athlete and reducing injury risk). Your participation in this research effort is to improve safety and is entirely voluntary. Please read through the Participant information and then you will be given the opportunity to consent that your information in the medical questionnaires can be included in research studies, and that you can be contacted about participating in other components of the research project that relate to muscle cramps and injuries.

Participant information of the research studies:

The main aim of these studies is to determine if there are any factors that can be identified before the race that will predict whether an athlete is likely to develop a medical problem (including cramps and injuries) during or after the race. The details of the studies are as follows:

- At the race entry and registration, a web-based (or a paper-based) questionnaire detailing personal particulars and medical information, will be completed as part of the race entry and race registration requirements.
- The completion of a questionnaire is not associated with any risk. Questionnaire and other clinical data (paper and electronic) will be kept confidential, will be kept secure, and will not be made available to any party other than the medical and research team without the consent of the individual participant.
- You may be contacted before or after the race (by telephone or email), for further information, advice and participation in research related to injuries or a medical condition (such as cramps) that you developed before, during or after the race.
- Volunteering to make medical information available for ongoing research has no direct benefit to an individual athlete. However, the long term anticipated benefits of this research are to identify factors that may predispose an increased risk of medical consequences and injury in endurance athletes. This information will eventually assist athletes in decreasing their risk of medical complications and injuries during racing and training.

Consent to participate in the research study

- I understand that I am free to volunteer to participate in the study on pre-race predictors (including medical history, medication use, and injuries) of medical complications that may occur in runners before, during and immediately after the race
- I understand that my participation in this research project may have no direct benefits to me during the race. However, I understand that my participation in the research project will advance the medical and scientific knowledge related to endurance sports. Therefore, information gathered through my participation in this project could advance the future medical care, training advice and performance of endurance athletes.
- I have read the participant information and am satisfied that the procedures and concepts have been explained to me in full.
- I agree that all the questionnaire information, my performance during the race, together with all the other data collected from the various components of this study may be used to answer scientific questions about the medical conditions, injuries, physiological responses and measures of performance associated with the preparation, participation in and completion of a race.

- I have been informed that the individual data derived from my participation will remain confidential
- I understand that the data obtained from this study may be used for the research components of higher degrees at the University of Cape Town.
- I understand that the Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town has approved the protocol for this research study (REC number XXXXXX).
- I understand that this research study will be covered by a liability insurance policy with the University of Cape Town, but that this cover only applies to illness and injury as a result of the research study and not as a result of participating in the race.
- I understand that each of the medical practitioners involved in the research study on athletes will have up to date professional medical insurance.
- I understand that I can contact members of the research team should I have any questions related to the study. Contact details of the research team are as follows: +27 21 650 4567
- I hereby consent to participate in this study, and that I can be contacted for information about research studies on injuries and muscle cramping.
- I understand that I may withdraw from this study at any time without further question.

Consent to allow medical information in this questionnaire to be used in ongoing research

Yes, I give consent that the information from the medical questionnaire can be used in ongoing research

No, I do not give consent that the information form the medical questionnaire can be used in ongoing research

Prof Martin Schwellnus

APPENDIX D: DATA COLLECTION INSTRUMENTS

MEDICAL CONSEQUENCES IN ENDURANCE SPORTS

TWO OCEANS MARATHON LONGITUDINAL STUDY: 2013-2015

PRE-RACE MEDICAL QUESTIONNAIRES

Dear Runner,

<u>Medical information required during race entry process</u>

In 2012, the Old Mutual Two Oceans Marathon Medical Team conducted an online medical questionnaire that was completed by approximately 25 000 participants. Every year, more than 700 runners receive medical care at the medical facilities – both on the route, as well as at the medical tent at the finish. By reviewing the results of the completed pre-race online questionnaires, we were able to pre-plan for the necessary medical care and ensure sufficient staff and facilities were available in 2012.

<u>The preliminary results from the 2012 race show that there were significant reductions in the incidence of all medial admissions to our medical facility. More importantly, there was a very significant decrease in serious life-threatening medical complications during the 2012 event.</u>

Following this success, we have upgraded our goal and the present focus is to further prevent as many medical events as possible in order to make this not only the most beautiful but also the safest race on the running calendar!

Due to the successful implementation of the questionnaire and the information it yielded in 2012, the Medical Team in conjunction with the event organisers decided to continue making this medical questionnaire a part of the registration process for 2013. The questionnaire is therefore included in the online registration process for completion by all runners.

The medical questionnaire consists of a series of yes/no questions relating to your medical history, previous medical complications during races or training and common running injuries. If you are healthy and have no injuries, it will take approximately 5 minutes to complete (a bit longer if there are medical details you need to enter). In the interests of your health and safety, the medical team may contact you before or after the race for further information about any medical conditions or injuries you may have.

<u>Please take the necessary time and care to complete this section of the entry form as accurately as possible. In addition, at the end of this questionnaire, we will also ask you to consider that the medical information be used for on-going medical research so that we can continue with our effort to improve medical care and race safety.</u>

Prof. Martin Schwellnus, Prof. Wayne Derman, and the rest of the Medical Team

General running information

*** Please start by completing the following general running information**

Please note that we require you to provide answers to all the questions.

For how many years have you been a recreational runner?*		years
For how many years have you participated in distance races?*		years
In the last 12 months, on average, how many times a week do you run (train and race)?*		per week
In the last 12 months, what is your average weekly training distance?*		km/week
In the last 12 months, what is your average training speed? (please use a decimal point for fractions of a minute) (Examples: 5min 30sec per km should be entered as 5.5)*		min/km
In the past 12 months, please indicate the average percentage time that you run/train on a treadmill?		% time on treadmill
In the past 12 months, please indicate the average percentage time that you run/train on tar roads?		% time on tar roads
In the past 12 months, please indicate the average percentage time that you run/train on concrete surfaces e.g. pavements?		% time on concrete
In the past 12 months, please indicate the average percentage time that you run/train on gravel roads (e.g. jeep tracks)?		% time on gravel roads
In the past 12 months, please indicate the average percentage time that you run/train on footpaths/single tracks?		% time on footpaths / single tracks
What is your current body weight?*		kg
What is your height?*		cm

*** You will now be guided through a series of 17 questions that relate to your medical history. These are all in a yes/no format and should take you only a few minutes to complete, unless you have medical conditions in which case you will be directed to provide more information. Please read these questions carefully and complete the information as accurately as possible.**

Question 1 of 17

Are you aware or have you ever been diagnosed with any risk factors for heart or blood vessel disease, including high blood cholesterol, a family member with heart disease, cigarette smoking, lack of physical activity, high blood pressure, being overweight or having diabetes mellitus (sugar sickness)?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from

You may tick more than one box if needed

- [ ] High blood pressure
- [ ] High blood cholesterol
- [ ] Cigarette smoking
- [ ] Obesity (overweight)
- [ ] Diabetes mellitus
- [ ] Family history of heart disease (< 50 years)

*** Question 2 of 17**

Have you ever suffered from any heart or blood vessel conditions, including heart attack, undiagnosed chest pain, coronary artery bypass operation, angioplasty (balloon), heart failure, heart transplant, cardiac arrhythmia (abnormal heart beat), rheumatic fever, heart murmur, use of a pacemaker or inherited heart defect?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from (you may tick more than one box if needed)

- [ ] Myocardial infarct (heart attack)
- [ ] Chest pain that has been diagnosed as "angina"
- [ ] Coronary artery bypass graft (CABG)
- [ ] Angioplasty (no stent)
- [ ] Angioplasty (with stent)
- [ ] Heart failure
- [ ] Heart transplant
- [ ] Arrhythmia
- [ ] Rheumatic fever
- [ ] Heart murmur
- [ ] Use of a pacemaker
- [ ] Inherited conditions of the heart or blood vessels
- [ ] Any other form of heart or blood vessel disease (please specify)

*** Question 3 of 17**

Do you currently suffer from any symptoms of heart or blood vessel disease including swollen ankles, abnormal shortness of breath (with exercise), chronic dry cough, palpitations, chest pain, pain (or discomfort) in the neck, jaw, or arms at rest or during exercise, dizziness, fainting spells, and/or calf pain when running/walking?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from (you may tick more than one box if needed)

- ☐ Swollen ankles
- ☐ Water retention
- ☐ Shortness of breath when sitting or lying down
- ☐ Shortness of breath with mild exercise
- ☐ Waking up with shortness of breath at night
- ☐ Palpitations with no dizziness
- ☐ Palpitations that make you dizzy
- ☐ Chest pain when sitting
- ☐ Chest pain when performing exercise
- ☐ Chest pain when you are emotionally stressed
- ☐ Pain (or discomfort) in the neck, jaw, arms at rest or during exercise
- ☐ Dizziness during exercise
- ☐ Fainting spells
- ☐ Chronic dry cough
- ☐ Painful calves when walking

*** Question 4 of 17**

Have you ever collapsed (fell down not because of an accident, needing medical attention) during, at the finish or after a race or training session?

- ○ Yes
- ○ No

Have you ever collapsed during training or racing?

- Training
- Racing
- Training and racing

How many times have you collapsed in training session or races during the last five years?

races:

training session:

How many times have you collapsed in training session or races during the last 12 months (1 year)?

When you collapse, does it mostly occur before or after the finish line / completion of the training session?

- Before the finish
- After the finish

What is the cause of your collapse?

- Dehydration
- Heat illness
- Hyponatraemia
- Low blood pressure
- Low blood sugar
- Other condition, please specify

*** Question 5 of 17**

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)?

- ○ Yes
- ○ No

For how many years have you suffered from cramping?

[ ]

Did you suffer from cramping during or after running in the last 12 months?

- ○ Yes
- ○ No

In the last 10 races or training sessions, how many times have you experienced cramping?

Races /10: [ ]

Training sessions /10: [ ]

What treatment/s have you had that successfully relieved an acute cramp?

You can tick more than one

- ☐ Stretching
- ☐ Resting
- ☐ Drinking fluid
- ☐ Ice application
- ☐ Massage
- ☐ Magnesium
- ☐ Salt (tablets or solution)
- ☐ Other, please specify

[ ]

At what point in the race or training run do you usually first experience cramping?

- ☐ First quarter
- ☐ Second quarter
- ☐ Third quarter
- ☐ Fourth quarter
- ☐ After the race
- ☐ No pattern
- ☐ Other, please specify

In which muscle do you usually cramp?

Please tick the muscle in which cramps most frequently occur

- ☐ Calves
- ☐ Hamstrings
- ☐ Quadriceps (thigh)
- ☐ Foot muscles
- ☐ Other, please specify

Have you ever suffered from cramping in your whole body (arms and legs)?

- ○ Yes
- ○ No

Have you ever been admitted to hospital following cramping?

- ○ Yes
- ○ No

Have you ever been confused or in a coma during or after a cramping episode?

- ○ Yes
- ○ No

Have you ever had "dark urine" in the 3 days following a cramping episode?

- ○ Yes
- ○ No

If you cramp, how severe is the cramp usually?

Please tick one box

- ○ Mild: < 5 minutes and you are able to continue exercising
- ○ Moderate: 5-15 minutes and you are able to continue exercising
- ○ Severe: >15 minutes or if you have to STOP exercising

*** Question 6 of 17**

Do you currently suffer from any metabolic or hormonal disease including diabetes mellitus, thyroid gland disorders, hypoglycaemia (low blood sugar), hyperglycaemia (high blood sugar), or heat intolerance?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from

You may tick more than one box if needed

- ☐ Hyperglycaemia (high blood sugar) (Pre-diabetes)
- ☐ Type 1: Insulin dependent (Diabetes Mellitus)
- ☐ Type 2: Non insulin dependent (Diabetes Mellitus)
- ☐ Underactive thyroid (hypothyroidism)
- ☐ Overactive thyroid (hyperthyroidism)
- ☐ Hypoglycaemia (low blood sugar)
- ☐ Heat intolerance

*** Question 7 of 17**

Do you suffer from any respiratory (lung) disease including asthma, emphysema (COPD), wheezing, cough, postnasal drip, hay fever, or repeated flu like illness?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from

You may tick more than one box if needed

- ☐ Asthma (Non exercise-induced)
- ☐ Asthma (Exercise-induced)
- ☐ Wheezing during exercise
- ☐ Cough during exercise
- ☐ Post nasal drip
- ☐ Allergies/hay fever (ear, nose, throat)
- ☐ Repeated infections in respiratory tract
- ☐ Previous lung complaints
- ☐ COPD (Chronic obstructive pulmonary disease)
- ☐ Interstitial lung disease
- ☐ Cystic fibrosis
- ☐ Other respiratory complaints

*** Question 8 of 17**

Do you suffer from any gastrointestinal disease including heartburn, nausea, vomiting, abdominal pain, weight loss or gain (> 5kg), a change in bowel habits, chronic diarrhoea, blood in the stools, or past history of liver or gallbladder disease?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from

You may tick more than one box if needed

- ☐ Heartburn
- ☐ Nausea/vomiting
- ☐ Abdominal pain
- ☐ Weight loss (>5kg) in the last 2 years
- ☐ Weight gain (>5kg) in the last 2 years
- ☐ A change in bowel habits over the last year
- ☐ Chronic diarrhoea

- [ ] Blood in stool
- [ ] Abdominal complaints during exercise
- [ ] Liver/gallbladder disease
- [ ] Other gastrointestinal complaints

*** Question 9 of 17**

Do you suffer from any diseases of the nervous system including past history of stroke or transient ischaemic attack (TIA), frequent headaches, epilepsy, depression, anxiety attacks, muscle weakness, nerve tingling, loss of sensation, or chronic fatigue?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from

You may tick more than one box if needed

- [ ] Stroke or transient ischaemic attack
- [ ] Frequent headaches
- [ ] Epilepsy
- [ ] Depression
- [ ] Anxiety attacks
- [ ] Other psychological/psychiatric conditions
- [ ] Muscle weakness
- [ ] Nerve tingling/loss of sensation
- [ ] Chronic fatigue
- [ ] Other nervous system complaints

*** Question 10 of 17**

Do you suffer from any disease of the kidney or bladder including past history of kidney or bladder disease, blood in the urine, loin pain, kidney stones, frequent urination, or burning during urination?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from

You may tick more than one box if needed

- ☐ Past history of kidney disease
- ☐ Past history of bladder disease
- ☐ History of blood in the urine
- ☐ Chronic loin pain
- ☐ History of kidney stones
- ☐ Frequent urination
- ☐ Burning during urination

*** Question 11 of 17**

Do you suffer from any disease of the blood or immune system including anaemia, recurrent infections, HIV/AIDS, leukaemia, or are you using any immunosuppressive medication?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from

You may tick more than one box if needed

- ☐ Past history of anaemia
- ☐ Past history of cancer of the blood cells (leukaemia)
- ☐ Past history of cancer of the lymphatic system (lymphoma)
- ☐ Past history of blood disorders
- ☐ History of HIV/AIDS
- ☐ History of a depressed immune system

*** Question 12 of 17**

Do you suffer from any growths or cancer including a past history of cancer?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from

You may tick more than one box if needed

- ☐ Past history of cancer
- ☐ Current undiagnosed growth

*** Question 13 of 17**

Do you suffer from any allergies including a past history of allergies to medication, plant material or animal material?

- ○ Yes
- ○ No

Please tick the appropriate condition/s that you suffer/ed from

You may tick more than one box if needed

- ☐ Past history of allergies to medication
- ☐ Past history of allergies to plant material
- ☐ Past history of allergies to animal material
- ☐ History of any other allergies

*** Question 14 of 17**

At the moment, do you use any prescribed medication on a daily, weekly or monthly basis to treat chronic (long-term) medical conditions or injuries?

- ○ Yes
- ○ No

Pease provide a list of the medication in the table below:

*** Question 15 of 17**

Have you ever in your running career used medicines to treat injuries in the week before or during a race – including anti-inflammatory drugs, cortisone (pills, or injection), or pain killers?

- Yes
- No

Which of the following medicines have you used in the past to treat an injury in the week just BEFORE a race?

- Paracetamol (e.g. Panado, Tylenol)
- Non-steroidal anti-inflammatories (e.g. Voltaren, Cataflam)
- Cortisone (pills)
- Cortisone injection
- Codeine
- Anti-inflammatory gels/creams/patches
- Any other pain killers

Which of the following medicines have you used in the past to treat an injury DURING a race?

- Paracetamol (e.g. Panado, Tylenol)
- Non-steroidal anti-inflammatories (e.g. Voltaren, Cataflam)
- Cortisone (pills)
- Cortisone injection
- Codeine
- Anti-inflammatory gels/creams/patches
- Any other pain killers

*** Question 16 of 17**

Do you or did you suffer from any symptoms of a running injury (muscles, tendons, bones, ligaments or joints) in the past 12 months or currently?

(NB: Only if an injury is/was severe enough to interfere with running, or require treatment e.g. use medication, or require you to seek medical advice from a health professional)

- ○ Yes
- ○ No

Injury 1

Pease tick if past or current:

- ○ Past
- ○ Current

How long ago did you first become aware of the injury? (months)

[ ]

Please indicate which side of your body is injured (if applicable)

- ○ Right
- ○ Left
- ○ Both

Please indicate which anatomical area is/was injured

- ☐ Head
- ☐ Neck
- ☐ Face
- ☐ Front chest
- ☐ Back chest
- ☐ Shoulder
- ☐ Upper arm
- ☐ Elbow
- ☐ Forearm

- ☐ Wrist
- ☐ Finger
- ☐ Lower back
- ☐ Hip
- ☐ Groin muscle
- ☐ Hip muscle
- ☐ Hamstring muscle
- ☐ Quadriceps muscle
- ☐ Calf muscle
- ☐ Knee
- ☐ Shin
- ☐ Achilles
- ☐ Ankle
- ☐ Foot
- ☐ Other, please specify

Please indicate the type of structure that was injured

- ☐ Muscle (e.g. strain)
- ☐ Ligament (e.g. sprain)
- ☐ Tendon
- ☐ Joint (e.g. arthritis)
- ☐ Bone (e.g. bruise or stress fracture)
- ☐ Other, please specify

Please indicate if your injury was any of the following common running injuries

- ☐ Patellofemoral pain
- ☐ Iliotibial band (ITB)
- ☐ Plantar fasciitis
- ☐ Achilles tendon injury
- ☐ Lower back pain

- ☐ Hip muscle injury
- ☐ Hamstring injury
- ☐ Quadriceps muscle injury
- ☐ Calf muscle injury
- ☐ Shin splints (bone)
- ☐ Shin splints (muscle/tendon)
- ☐ Foot pain
- ☐ Heel pain
- ☐ Other, please specify

Please indicate the severity of the injury

- ○ I only experience symptoms after exercise
- ○ I experience symptoms during exercise, but it does not interfere with exercise
- ○ I experience symptoms during exercise that may interfere with my training/ competition
- ○ I am so painful that I may not be able to train or compete

Please indicate how your injury was treated to date (you can tick more than one)?

- ☐ Rest
- ☐ Tablets
- ☐ Stretches
- ☐ Cortisone injection
- ☐ Physiotherapy
- ☐ Other injection
- ☐ Surgery
- ☐ Orthotics
- ☐ Strengthening exercises
- ☐ Equipment change

Would you like to list another important injury?

- ○ Yes
- ○ No

(At this point, there is an option to complete details for more than one injury using the same data capture procedure for the first injury)

*** Question 17 of 17**

Have you consulted with a medical doctor in the last 12 months to obtain medical clearance that you can safely participate in endurance running?

- ○ Yes
- ○ No

If yes, please indicate which of the following procedure formed part of the medical assessment for clearance to participate in endurance running? (you may tick more than one box if needed)

- ☐ Your doctor spoke to you only (medical history but no physical examination)
- ☐ Your doctor spoke to you and examined you physically (medical history and a physical examination)
- ☐ You performed an exercise test but no ECG (electrical leads attached to your chest to measure the hearts response to exercise)
- ☐ You performed an exercise test with an ECG (electrical leads attached to your chest to measure the hearts response to exercise)
- ☐ You had an echocardiogram (a sonar of the heart to examine the structure of the heart)
- ☐ You had blood tests for cholesterol
- ☐ You had other blood tests
- ☐ You had other tests (please specify)

If yes, did your medical practitioner clear you with any specific advice for participating in endurance running?

- ○ My doctor did not give clearance for me to run
- ○ My doctor did give clearance for me to run but with some restrictions and guidelines on safe participation
- ○ My doctor did give clearance to run with no restrictions

APPENDIX E: LETTER FROM STATISTICIAN

BIOSTATISTICS

Date: 7 November 2017

LETTER OF STATISTICAL SUPPORT

This letter is to confirm that Prof Martin Schwellnus of the University of Pretoria discussed statistical support for a research project, entitled "**Medical consequences in endurance sports. Two Oceans marathon longitudinal study: 2009-2015**", with me

A master's student, Ms. I. De Jager (Student#: 28068824), will be conducting a study, in partial fulfillment of an MSc (Sport Science) degree at the University of Pretoria, on a sub-component of the study above. The focus of her study will be **"Risk Markers Associated with Exercise Associated Muscle Cramps in Distance Runners"**.

I hereby confirm that I am aware of the project and undertake to assist with the statistical analysis of the data generated from the project. In summary, the race entrant demographic data, pre-screening medical data, race participation data, and medical complications data on approximately 44 000 runners, who entered and then participated in the Two Oceans Marathon races between 2012 and 2015, will be entered into an Excel spread sheet (Microsoft 2010) and then analysed using the SAS Enterprise Guide (V7.13) statistical program.

The main outcomes will be 1) the prevalence of Exercise Associated Muscle Cramps (EAMC), and 2) risk factors associated with EAMC.

The binary-scaled response variable for EAMC will be created from the question on injury history. Due to the cross-sectional nature of the study, we will use a 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 will approximate the relative risk by using the Poisson regression model with a robust error variance. Risk ratios (95% CIs), also indicated as prevalence ratios (PR), will be reported for all the results. The statistical significance level is 5%, unless specified otherwise.
Univariate regression models on all main category risk factors will obtain the crude unadjusted risk ratio (PRs and 95% CIs) of EAMC 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, are adjusted univariate PRs, by adjusting for gender, age category and race distance.

Ms. Sonja Swanevelder
Biostatistics Unit
Medical Research Council
Telephone: 021-9380927

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APPENDIX F: LETTER OF SUPPORT FOR FUNDING

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Professor Martin Schwellnus
MBBCh, MSc (Med), MD, FACSM, FFIMS
Director: Sport, Exercise Medicine and Lifestyle Institute (SEMLI)
Director: IOC Research Center, South Africa
Faculty of Health Sciences
University of Pretoria
South Africa

7 November 2017

To: Chair: Masters Committee / Research Ethics Committee
University of Pretoria

Sufficient funding for research study

This letter is to confirm that Prof Martin Schwellnus of the University of Pretoria is the principle investigator of the project with the title "**Medical consequences in endurance sports. Two Oceans marathon longitudinal study: 2009-2015**". This study has Research Ethics clearance from the Faculty of Health Sciences Research Ethics Committee at the University of Pretoria (REC reference number: 433/2015). This study is funded by the IOC Research Centre grant.

A master's student, Ms. Izaan De Jager (Student#: 28068824), will be conducting a study, in fulfillment of an MSc (Sport Science) degree at the University of Pretoria, on a sub-component of the study above. The focus of her study will be **"Risk markers associated with Exercise Associated Muscle Cramps in distance runners"**.

I hereby certify that there are sufficient funds for the proposed study by Ms. Izaan De Jager (Student#: 28068824).

Please feel free to contact me if any further information is required.

Yours sincerely

Prof. Martin Schwellnus (MBBCh, MSc(Med), MD, FACSM. FFIMS)
Full Professor: Sport and Exercise Medicine
Faculty of Health Sciences
University of Pretoria
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: Gesondheidswetenskappe
ha la Disaense tša Maphelo

APPENDIX G: DECLARATION BY INVESTIGATOR

DECLARATION BY PRINCIPAL INVESTIGATOR AND SUB-INVESTIGATOR

Name: Izaan de Jager

Trial: Secondary data from 2012-2015 Two Oceans Marathon

Brief Study Title: Risk Markers Associated with Exercise Associated Muscle Cramps in Distance Runner

Study Number: 28068824

Site: University of Pretoria

1. I have read and understood item 1.5.5 on page 5 and section 3 (pages 14-20) "Responsibility of the Principal Investigator (PI) and participating investigators of the *Clinical Trials Guidelines of the Department of Health: 2000*
2. I have notified the South African regulatory authority of any aspects of the above guidelines with which I do not / unable to comply (If applicable, this may be attached to this declaration).
3. I have thoroughly read, understood, and critically analysed (in terms of the South African context) the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent forms(s).
4. I will conduct the trial as specified in the protocol.
5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time period.
6. I will not commence with my role in the trial before written authorizations from the relevant ethics committee (s) as well as the South African Medicines Control Council (MCC) have been obtained.
7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.
8. I will ensure that every participant (or other involved persons, such as relatives), shall at all times be treated in a dignified manner and with respect.
9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.
   *Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence(bias) his orher actions)**
   *Modified from: Davidhoff F, et al. Sponsorship, Authorship and Accountability.
   (Editorial) JAMA Volume 286 number 10 (September 12, 2001)
10. I have not previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice.
11. I have not previously been the principal investigator at a site which has been closed due to failure to comply with Good Clinical Practise (*Attach details)
12. I will submit all required reports within the stipulated time-frames.

Signature: ____________________ Date: 7 / 11 / 2017

Witness: ____________________ Date: 7 / 11 / 2017