

**MEDICAL COMPLICATIONS DURING A COMMUNITY-BASED  
MASS PARTICIPATION ENDURANCE RUNNING EVENT – AN  
INVESTIGATION OF THE EPIDEMIOLOGY AND RISK FACTORS  
ASSOCIATED WITH MEDICAL COMPLICATIONS,  
WITH RECOMMENDATIONS FOR RISK MITIGATION**

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by

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1. Schwabe K, Schwellnus M, Derman W, Swanevelder S, Jordaan E. Medical complications and deaths in 21 km and 56 km road race runners: a 4-year prospective study in 65 865 runners – SAFER study I. Br J Sports Med 2014 Jun;48(11):912-8. (Current Impact Factor: 11.645)
2. Schwabe K, Schwellnus M, Derman W, Swanevelder S, Jordaan E. Less experience and running pace are potential risk factors for medical complications during a 56 km road running race: a prospective study in 26 354 race starters – SAFER study II. Br J Sports Med 2014 Jun;48(11):905-11. (Current Impact Factor: 11.645)
3. Schwabe K, Schwellnus M, Derman W, Swanevelder S, Jordaan E. Older females are at higher risk for medical complications during 21 km road race running: a prospective study in 39 511 race starters -SAFER study III. Br J Sports Med 2014 Jun;48(11):891-7. (Current Impact Factor: 11.645)
4. Schwabe K, Schwellnus M, Swanevelder S, Jordaan E, Derman W, Bosch A. Leisure athletes at risk of medical complications: outcomes of pre-participation screening among 15778 endurance runners – SAFER VII. Physician and Sports Medicine 2018 Nov; 46:4,405-413. (Current Impact Factor 1.874)

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## LIST OF ABBREVIATIONS AND ACRONYMS

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am	ante meridiem
ACSM	American College of Sports Medicine
AHA	American Heart Association
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
AMAA	American Medical Athletic Association
AMJA	American Medical Joggers Association
AR	Absolute Risk
ARF	Acute Renal Failure
AVP	Arginine Vasopressin
BMI	Body mass Index
C	Celsius
°C	Degrees Celsius
Ca <sup>2+</sup>	Calcium
[Ca <sup>2+</sup> ]	Calcium Concentration
CABG	Coronary Artery Bypass Graft
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CARDIA	Coronary Artery Risk Development in Young Adults
CBF	cerebral blood flow
CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatine Kinase
CNS	Central Nervous System

CO <sub>2</sub>	carbon dioxide
CRP	C-Reactive Protein
CT	Computed Tomography
CVD	Cardiovascular Disease
CVA	Cerebrovascular Accident
CVR	cerebral vascular resistance
DBP	Diastolic Blood Pressure
EAC	Exercise-Associated Collapse
EACRP	European Association on Cardiovascular Prevention and Rehabilitation
EAH	Exercise-Associated Hyponatraemia
EAHE	Exercise-Associated Hyponatraemic Encephalopathy
EAMC	Exercise-Associated Muscle Cramps
EAPH	Exercise-Associated Postural Hypotension
ECG	Electrocardiogram
ED	Emergency Department
EIB	Exercise Induced Bronchospasm
EHS	Exertional Heatstroke
ePARMed-X+	Physical Activity Readiness Medical Examination
ESC	European Society of Cardiology
ER	Exertional Rhabdomyolysis
GIT	Gastrointestinal Tract
GPS	Global Positioning System
h	hour
hrs	hours
ICU	Intensive Care Unit

IgA	Immunoglobulin A
IFN	Interferon
IL-6	Interleukin-6
IMMDA	International Marathon Medical Directors Association
IR	Incidence rate
K <sup>+</sup>	Potassium
[K <sup>+</sup> ]	Potassium Concentration
Km	Kilometre
LBNP	Lower Body Negative Pressure
LDH	Lactate Dehydrogenase
[Mg <sup>2+</sup> ]	Magnesium
mg/dl	Milligram per Decilitre
MI	Myocardial Infarction
mmHg	Millimetres of Mercury
mmol/l	Millimoles per liter
MRI	Magnetic Resonance Imaging
Mg <sup>2+</sup>	Magnesium
MH	Malignant Hyperthermia
MSK	Musculoskeletal
N	Number
Na <sup>+</sup>	Sodium
[Na <sup>+</sup> ]	Sodium concentration
NCD	Non-communicable Disease
NS	Normal Sleep
NSAID	Non-steroidal Anti-inflammatory Drug

OA	Osteoarthritis
OI	Orthostatic Intolerance
OPRMSQ	Online pre-race medical screening Questionnaire
PAR-Q+	Canadian Physical Activity Readiness Questionnaire
PCC	Probiotic Lactobacillus Fermentum
PhD	Doctorandus Philosophiae/Doctor of Philosophy
Pm	post meridiem
PO43-	Phosphate
[PO43-]	Phosphate concentration
PSR	Partial Sleep Restriction
RACE	Registre des Accidents Cariaquers lors des courses d'Endurance
RCT	Randomised Controlled Trial
RIFLE	Risk, Injury, Failure, Loss, and End-stage renal disease
RYR1	Ryanodine Receptor
SAFER	Studies to Reduce Adverse Medical Events For the Exerciser
SBP	Systolic Blood Pressure
s-[CK]	serum Creatine Kinase Concentration
SCA	Sudden Cardiac Arrest
SCD	Sudden Cardiac Death
SICD	Sickle Cell Disease
SCT	Sickle Cell Trait
SD	Sudden Death
SD	Standard Deviation
SIADH	syndrome of inappropriate antidiuretic hormone secretion
Tb	Black Globe Temperature

Td	Ambient Temperature
Tx	Wet Bulb Temperature
sEAMC	serious-Exercise-Associated Muscle Cramps
UK	United Kingdom
URT	Upper Respiratory Tract
URTI	Upper Respiratory Tract Infection
US	United States
USA	United States of America
VO <sub>2</sub> max	The maximum capacity to utilise oxygen in a graded exercise test
WBGT	Wet Bulb Globe Temperature
WHO	World Health Organization

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## ABSTRACT

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Medical complications during a community-based mass participation endurance running event – an investigation of the epidemiology and risk factors associated with medical complications, with recommendations for risk mitigations.

**Background:** The epidemiology and risk factors associated with medical complications, including life-threatening complications during distance running events has not been well described. The aims of this research were to document the incidence of medical complications (study 1), determine risk factors associated with medical complications (studies 2 and 3), and develop and apply a pre-race medical screening tool to determine the prevalence of chronic disease in race entrants, using a risk stratification model (study 4).

**Design:** Prospective studies

**Setting:** Two Oceans Marathon races (2008-2011) (studies 1-3) and race entrants (2012)

**Participants:** Studies 1-3: 65 865 race starters; 21.1 km (n =39 511), 56 km runners (n=26 354). Study 4: 15 778 race entrants

**Methods:** Study 1: In all 4 years, race day medical complications were recorded and subdivided by severity (serious/life-threatening / death), organ system and final diagnosis. Studies 2 and 3: Independent risk factors associated with all medical complications, severity and organ system involvement were determined in 21.1 and 56 km runners, using multivariate modelling. Study 4: A pre-race medical screening tool was developed, based on international pre-exercise medical screening guidelines, and administered to all race entrants (2012). The prevalence (%) of runners with four risk categories was determined.

**Results:** The incidence (per 1000 race starters) of all and serious/life-threatening medical complications was 8.27 and 0.56 respectively (study 1). Risk factors associated with medical complications were less experience (56 km), slower running pace (56 km) and older females (21.1 km) (studies 2 and 3). 16.8% runners were identified as those that should undergo medical evaluation for suspected cardiac disease with 3.4% reporting existing CVD (very high risk) and 13.4% reporting multiple CVD risk factors (high risk) (study 4).

**Conclusion:** The incidence of all and serious/life-threatening medical complications in the 21.1 km and 56 km race is 1/121 and 1/1786 race starters respectively. Race experience, running pace and sex are risk factors for medical complications. 16.8% runners have underlying suspected cardiovascular disease. These data formed the basis for the implementation of a pre-race medical screening and risk stratification. The research lays the foundation for a future educational intervention programme to reduce the risk of medical complications in distance running and other endurance events.

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# **MEDICAL COMPLICATIONS DURING A COMMUNITY-BASED MASS PARTICIPATION ENDURANCE RUNNING EVENT – AN INVESTIGATION OF THE EPIDEMIOLOGY AND RISK FACTORS ASSOCIATED WITH MEDICAL COMPLICATIONS, WITH RECOMMENDATIONS FOR RISK MITIGATION**

## **CHAPTER 1**

### **INTRODUCTION AND SCOPE OF THE DISSERTATION**

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There is conclusive evidence that participation in regular physical activity has considerable and comprehensive health benefits. Regular physical activity is internationally recognised as an important lifestyle intervention for both primary and secondary prevention and management of non-communicable diseases. Specifically, moderate -to vigorous-intensity physical activity is associated with a lowering of all-cause mortality, including premature mortality, cardiovascular disease, cerebrovascular accidents (strokes), various malignancies, metabolic diseases such as diabetes mellitus and a number of other chronic diseases [1-3]. The recommended “dose” of physical activity is at least 150 minutes of moderate- to vigorous-intensity physical activity per week [3], and this supported by international organizations including the World Health Organization (WHO) [4], American College of Sports Medicine (ACSM), American Heart Association (AHA) [5] and European Association on Cardiovascular Prevention and Rehabilitation (EACPR) [6].

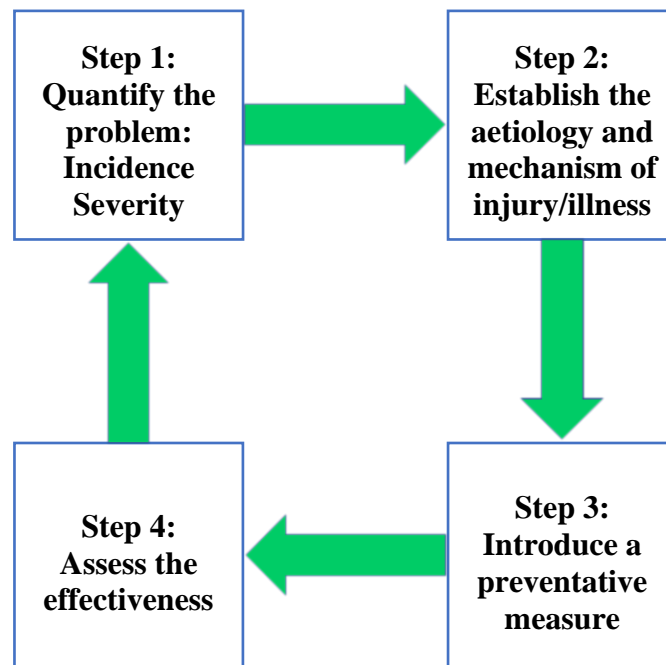
Recreational running has become an increasingly popular form of regular physical activity and participation in community based recreational distance running events (such as the 5 km, 10 km, 21.1 km, 42 km and ultra- marathon) has concomitantly increased [7, 8]. Annual reports from Running USA (<https://runningusa.org/annual-reports> -accessed on 1 March 2020) show a greater than 15-fold increase in overall participation in marathons since 1976 with estimated marathon race finishers, increasing from 25 000 in 1976 up to 500 000 in 2019. More noticeably, is the increase in female race finishers from 10% in 1976 to almost 60% in 2019 and an increase in race participants and finishers in older age categories (mean age of participants >40 years).

Despite the overwhelming health benefits of exercise, medical complications in a variety of organ systems can occur during moderate-to-high intensity exercise, such as distance running. This is a significant health problem because acute cardiac events, including myocardial

infarctions and potential lethal arrhythmias, potentially leading to sudden cardiac arrest (SCA) or sudden cardiac death (SCD) have been described in both older and younger runners [9-13].

Although there has been a considerable interest in determining the incidence and risk factors associated with SCA, SCD and sudden death (SD) in running races, there is a paucity of data related to other medical encounters during running. Although data describing the incidence of and risk factors associated with the development of medical encounters in distance running events dates back to over 15 years ago [14, 15], there are few data describing the broader health problem of medical encounters during exercise, including other non-cardiac related serious/life-threatening medical encounters such as exertional heatstroke, exercise-associated hyponatraemia and acute kidney injury.

In the area of sports injury and athlete health research there is a well-established stepwise circular model to systematically approach the investigation of a health problem. This model is known as Van Mechelen's Model of Injury Prevention, and is widely adopted by world-class research organizations (Figure 1.1) [16].



**Figure 1.1: Van Mechelen model for Sports Injury and Athlete Health research [16]**

In this model, the first step to address a health problem in sports injury and athlete health research is to accurately characterise the extent of the problem by determining incidence and

severity of the problem (Figure 1.1). This is then be followed by determining aetiology (risk factors) before preventative measures are introduced (Step 2).

Therefore, it is important to obtain accurate data on the risk of medical encounters and the risk factors associated with medical encounters as important first steps to:

- 1) adequately plan medical care of large community-based running events, and
- 2) introduce and assess the effectiveness of prevention programmes to reduce the risk of adverse medical encounters at running events.

The first objective of this dissertation is to address steps one and two of the research model by accurately determining the incidence of medical encounters in distance running events, and to identify risk factors associated with medical encounters. The second objective of the dissertation is to focus on step three of the model by developing and implementing a pre-race medical screening tool to risk stratify race entrants. This information can then form the basis of a future step four, which will be to implement a pre-race medical screening and educational intervention programme to reduce the risk of medical encounters at distance running events and make these races safer for participants.

In Chapter 2, a review of the available data on the incidence of medical encounters, including SCA, SD, serious/life-threatening and other medical encounters in distance running events will be presented. This will include a detailed review of the incidence of medical encounters per organ system and by specific diagnoses.

The first research study in this dissertation (Chapter 3) will describe the epidemiology of the medical encounters in two distance races (a 21.1 km and 56 km race) and report the incidence of medical encounters according to severity, organ system and specific diagnosis. In Chapter 4, the risk factors associated with the development of the medical encounters in distance running events will be reviewed. This will include a detailed review of the risk factors associated with medical encounters per organ system and by specific diagnoses. In Chapters 5 and 6, two research studies will be presented that identify novel independent risk factors associated with the development of all medical encounters, and medical encounters in specific organ systems, in 21.1 km and 56 km race starters respectively. The final research study in this dissertation (Chapter 7) describes the development of a pre-race medical screening tool to identify runners who, according to the current international guidelines for “risk self-

assessment” would be at higher risk of medical encounters during exercise i.e. be required to undergo a medical assessment prior to participation in a distance running event. This study will not only describe the novel risk stratification tool, based on the pre-race medical screening tool, but also report the prevalence of race entrants in each risk category (very high risk, high risk, intermediate risk and low risk).

The results of the research studies in this dissertation, which are summarised in Chapter 8, then formed the basis of the development and implementation of this pre-race screening tool. Future studies, leveraging epidemiologic and modelling work from this thesis, will seek to validate the capability of this tool to reduce the risk of medical encounters in distance running events.

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## CHAPTER 2

# A REVIEW OF THE INCIDENCE OF MEDICAL ENCOUNTERS DURING MASS PARTICIPATION COMMUNITY-BASED DISTANCE RUNNING EVENTS

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### 2.1. INTRODUCTION

The health benefits of regular participation in exercise are undisputed and regular physical activity is widely recommended as an important lifestyle intervention to prevent and manage non-communicable diseases (NCDs) [1-3]. Recreational distance running is a popular form of regular physical activity and in recent decades, the number of participants in community-based distance running events has increased, with more females and older individuals participating in these events [4]. A mass community-based endurance sports event is defined as “*a planned and organised endurance sports event, usually with >1000 entrants (recreational and/or elite), at a specific location, for a specific purpose, and for a defined period of time (single day/stage or multiple stages/several consecutive days)*” [5, 6]. These events are typically planned and organised by a community sports organisation, under the auspices of a regional or national sports federation. Organising committees for these events include a medical team.

The main function of the medical team is to protect the health of the athletes, because athletes participating in these events may develop medical complications, including serious/life-threatening medical complications and even death. In order for race medical directors and medical teams to adequately plan for these events, the incidence and types (by severity, organ system affected and specific diagnosis) of medical encounters need to be determined [7]. It is also important to compare incidence rates of medical encounters of events held at different geographical locations and climates around the world .

Until very recently, there has been no consensus on definitions and methods of data recording and reporting of medical encounters at mass participation community-based endurance sports events. In the first section of this review chapter the recent consensus on definitions and methods of data recording and reporting of medical encounters at mass participation community-based endurance sports events [8] will be introduced and the terminology, classification and definitions of medical encounters, using this consensus document, will be

briefly reviewed. The main body of this review will then focus on the incidence of medical encounters at mass participation community-based running events - firstly according to severity of medical encounters, and secondly by organ system and specific diagnosis. This chapter will conclude with a summary to highlight the need for further research to quantify the extent of health problems associated with mass participation community-based running events.

## **2.2. TERMINOLOGY, CLASSIFICATION AND DEFINITIONS**

### **2.2.1. Medical encounters versus medical complications**

Until very recently [8] (2019) there has been no consensus on definitions and methods of data recording and reporting at mass participation community-based endurance sports events. The original research studies that are reported in subsequent chapters of this dissertation (Chapter 3, 5, 6 and 7) [9-11] were all conducted prior to the publication of this consensus in 2019. In the original research studies, described in this dissertation, the term “medical complication” was used to describe a health problem that developed during a running event and reported to the medical team. However, in the 2019 consensus statement it was recommended that a health problem that develops during an endurance event is referred to as a “medical encounter”, which is defined as follows:

*“A reported medical problem that is an interaction between the medical team and a race participant requiring medical assistance or evaluation, taking place from the official start of the event, up to 24 hours after the official cut-off time of the event.”*

In order to be consistent with the 2019 international consensus statement, the terminology “medical encounter” instead of “medical complication” will be used consistently in this review chapter and in the remainder of this dissertation. The exceptions will be in Chapters 3, 5, 6 and 7, where the term “medical complications” was used in the original research papers that were published prior to the consensus in 2019.

## 2.2.2. Classification of medical encounters by severity

In the 2019 consensus statement, medical encounters are firstly classified by severity [8], and standard definitions of medical encounters by severity were adopted (Table 2.1.) . In this review chapter, and in the remainder of this dissertation, this classification of severity and the definitions will be used, unless otherwise indicated.

**Table 2.1.: Classification and definition of medical encounters in mass community-based endurance sports events by severity**

Classification by severity	Definition
Sudden death (SD)*	A medical encounter that resulted in sudden death from non-cardiac causes**, where the medical problem was: <ol style="list-style-type: none"> <li>1) deemed to be directly related to the event, and</li> <li>2) the onset of the medical problem occurred during the event of within 1-24 hours of the finish time</li> </ol>
Sudden cardiac death (SCD)*	A medical encounter that resulted in sudden cardiac death (SCD) from a SCA, where the medical problem resulting in SCD was: <ol style="list-style-type: none"> <li>1) deemed to be directly related to the event, <b>and</b></li> <li>2) the onset of the medical problem occurred during the event of within 1-24 hours of the finish time</li> </ol>
Sudden cardiac arrest (SCA)*	A medical encounter (cardiac arrest) that requires immediate cardiopulmonary resuscitation (including defibrillation), where the medical problem resulting in cardiac arrest was: <ol style="list-style-type: none"> <li>1) deemed to be directly related to the event, <b>and</b></li> <li>2) the onset of the medical problem occurred during the event of within 1-24 hours of the finish time</li> </ol>
Serious/life threatening medical encounters*	A medical encounter that is known to be life-threatening and requires immediate emergency medical treatment with: <ol style="list-style-type: none"> <li>1) either admission to a high-care (intensive care and observation) medical area at the event, <b>or</b></li> <li>2) transport (with or without admission) to a hospital</li> </ol>
Moderate medical encounter	<ol style="list-style-type: none"> <li>1) Is significant enough to result in withdrawel of the athlete from the event following assessment by the medical staff.</li> <li>2) Or is non-life threatening but requires medical assessment and admission to the event medical facilities with supervised medical care.</li> <li>3) Or is non-life threatening but requires referral of transfer to a hospital</li> </ol>
Minor medical encounter	<ol style="list-style-type: none"> <li>1) Is not significant enough to result in withdrawel of the athlete from the event following assessment by the medical staff.</li> <li>2) Or does not require admission and supervised medical care at race medical facilities or transfer to a hospital for supervised medical care.</li> </ol>

\*These are related to the event and are recorded up to 24 hours after finishing the event.

\*\*Non-cardiac causes include, but are not limited to Exertional Heatstroke (EHS), symptomatic hyponatraemia, acute renal failure and intracranial bleeds.

### 2.2.3. Classification and definitions of medical encounters by organ systems affected and specific diagnosis

In the 2019 consensus, medical encounters were also further classified by organ system and specific diagnosis (Table 2.2.) and this classification will be also used in this review chapter as well as in the dissertation, unless stated otherwise.

**Table 2.2.: Diagnostic categories of illness-related medical encounters by main organ system and more common specific types/ diagnosis of medical encounters**

Main organ system	Illness type / diagnosis
Multiple organ systems	Heat Illness
	Hypothermia
	Hyperthermia / exertional heatstroke
	Sunburn
	Rhabdomyolysis
	Fluid and electrolyte disorders
	Dehydration (mild: <5% body weight loss)
	(moderate: >5% to <7 % body weight loss)
	(severe: >7% body weight loss)
	Hyponatraemia
	Acid-base disorders
	Other electrolyte disorders
	Infection
	Systemic Infection (excluding pathogens localised to one area)
Cardiovascular system	Exercise-Associated Postural Hypotension (EAPH)
	Syncope (non-specific)
	Chest pain (non-specific)
	Ischaemic heart disease
	Acute coronary syndrome (myocardial infarction, angina)
	Stable angina
	Cardiac arrest
	Sudden cardiac death
	Cardiac arrest (successfully resuscitated)
	Conduction abnormality including arrhythmias
	Supraventricular tachycardia
	Ventricular tachycardia
	Frequent ventricular extra-systoles
	Other significant arrhythmia
	Other abnormality on ECG (including non-specific)
	Congestive heart failure
	Hypertrophic cardiomyopathy and other cardiomyopathies
	Other congenital/inherited cardiovascular disease
	Murmurs/ Valvular disease
	Acute myocarditis (viral)
	Acute pericarditis
	Venous disease
	Deep venous thrombosis
	Other venous disease including calf / ankle oedema, cause
	Peripheral vascular disease
	Other cardiovascular disease

**Table 2.2.: Diagnostic categories of illness-related medical encounters by main organ system and more common specific types/ diagnosis of medical encounters (continued)**

Respiratory disease and ENT (ear, nose / throat) systems	Respiratory tract infection (bacterial or viral)	
	Other upper respiratory tract infection	
	Other lower respiratory tract infection	
	Asthma and/or allergy	
	Allergy rhinitis/ sinusitis/ hay fever	
	Asthma - allergic	
	Asthma - exercise induced only	
	Pneumothorax	
	Acute pulmonary embolus	
	Vocal cord dysfunction	
	Other respiratory illness not otherwise specified	
	Central nervous system (CNS)	Exercise-Associated Muscle Cramps (EAMC)
		Mild EAMC (localised, no altered mental status, no systemic symptoms)
Severe EAMC (generalized, altered mental status or with systemic symptoms)		
Dizziness/nausea (non-specific)		
Coma (cause unknown)		
Confusion (non-specific)		
Stroke / Cerebrovascular Accident (CVA)		
Epilepsy		
Headaches		
Exercise related headache		
Migraine		
Cluster headaches		
Headache not otherwise specified		
Other neurological problem		
Generalised tight muscles/ spasticity		
Rheumatological system		Joint pain (non-specific)
	Joint infection - septic arthritis (excluding complications of surgery or perforating lacerations)	
	Infection of bone - osteomyelitis	
	Osteoarthritis (OA) - generalised (not isolated to one joint)	
	Gout	
	Pseudogout	
	Seronegative arthritis	
	Rheumatoid arthritis	
	Fibromyalgia/ multiple sore muscle areas	
	Rheumatological disease other/ undiagnosed	
	Gastrointestinal system	Nausea / vomiting (non-specific)
Abdominal pain (non-specific)		
Gastrointestinal infection		
Gastroenteritis (including food poisoning)		
Other gastrointestinal infection		
Gastritis		
Exercise-associated gastritis/ reflux		
Non-steroidal anti-inflammatory drug (NSAID) associated gastritis/ peptic ulceration		
Gastritis/ peptic ulceration - non exercise/ NSAID related		
Diarrhoea		
Runner's diarrhoea		
Gastrointestinal bleeding (upper gastrointestinal tract) including hematemesis		
Gastrointestinal bleeding (lower gastrointestinal tract) including melena		
Surgical bowel problem (acute bowel)		
Other gastrointestinal illness		

**Table 2.2.: Diagnostic categories of illness-related medical encounters by main organ system and more common specific types/ diagnosis of medical encounters (continued)**

Genitourinary system (excluding infections)	Genitourinary infection
	Cystitis
	Other genitourinary infection
	Acute kidney injury
	Acute renal failure
	Other urinary illness
	Haematuria
Haematological system and Nutritional Deficiencies	Pregnancy
	Anaemia
Endocrine / Metabolic system	Sickle-cell trait
	Thyroid disorder
	Hypothyroid
	Hyperthyroid
	Hypoglycaemia (non-specific)
	Diabetes mellitus
	Type I (insulin dependent)
	Type II (non-insulin dependent)
	Other endocrine disorder
Dermatological system (excluding infections, skin lesions/ tumours and sunburn)	Other endocrine disorder
	Sunburn
	Skin Infection/ Cellulitis/ Abscess/ Infected Bursa
	Skin chafing / blister
	Abrasion
	Laceration
	Urticaria
	Dermatitis
	Other rash not otherwise mentioned or undiagnosed
Ophthalmological system (excluding trauma)	
Dental illness	
Psychological / psychiatric illness	Anxiety/ panic disorder, including hyperventilation
	Other psychological/ psychiatric disorder not otherwise specified
Tumours / malignancies	
Drug use/ Overdose/ Poisoning	
Medical Illness (Other or undiagnosed)	Tired athlete (non-specific)
	Other medical illness

The incidence of medical encounters will now be reviewed, using the classification of medical encounters by: 1) severity (section 2.4.), and 2) organ systems and specific diagnosis (section 2.5.).

## **2.3. LITERATURE REVIEW FORMAT AND METHODS**

### **2.3.1. Search strategy**

A literature search was conducted to source published information on the incidence of medical encounters in distance runners by severity and by organ systems and specific diagnosis. The search strategy to obtain relevant peer reviewed publications was based on the

methodology employed in systematic reviews. A search was conducted on the PubMed and Google Scholar databases, using three levels with keywords in different combinations (Appendix A).

Only publications in English, and studies that involved human participants were included. The searches were conducted for publications in the following period: 1960 to 30 June 2020

### **2.3.2. Level of evidence**

Each publication was categorised and assessed using the 2011 Oxford Levels of Evidence criteria (<http://www.cebm.net/index.aspx?o=5653>) and the following were determined: type of study, level of evidence score (Levels I to V), and the strengths / limitations of each study.

### **2.3.3. Presentation of results**

In this review chapter, the results of the search strategy for each section will be summarised by presenting the main findings in tables using the following categories: study reference, type of study, number of participants, type of event, main findings (incidence), strengths of the study, limitations of the study, and the Oxford Level of Evidence (I to V).

## **2.4. A REVIEW OF THE INCIDENCE OF MEDICAL ENCOUNTERS IN MASS COMMUNITY-BASED DISTANCE RUNNING EVENTS BY SEVERITY**

Incidence is defined as “*the number of new cases of a disease that occur during a specified period in a population at risk for developing the disease [12]*”. For medical encounters at mass participation events, there are differences between studies in how incidence is expressed. The incidence of medical encounters has been expressed as medical encounters/1000 registrants, entrants, starters, finishers or participants. The consensus statement recommends that incidence be expressed as medical encounters/1000 starters [8] and in this chapter (and the dissertation) this is how incidence will be expressed. If this is reported differently in studies, this will be pointed out. In cases of rare medical encounters such as SD, SCD, SCA and serious/ life-threatening medical encounters, the incidence will be

expressed as the number of medical encounters per 100 000 starters (or documented denominator).

In the first section, the incidence of SD, SCD, SCA, serious/ life-threatening medical encounters and moderate medical encounters will be reviewed. A review of the incidence of minor medical encounters is not included in this dissertation due to the fact that by definition, they do not require admission to medical facilities [8].

#### **2.4.1. A review of the incidence of sudden death, sudden cardiac death and sudden cardiac arrest in distance running events**

On rare occasions, participating in long distance running may result in catastrophic events. In the literature, terminology to describe these catastrophic events have been variable and included terms such as sudden death (SD), sudden cardiac death (SCD) and sudden cardiac arrest (SCA). Differences in terminology and methods of data collection, including inconsistency of using race entrants, starters or finishers and timing of the incident make the interpretation of data and comparison of data between studies difficult.

In a comprehensive review of the literature pertaining to SD, SCD and SCA in distance running events, 11 main studies were identified. The results of these studies are summarised in Table 2.3. These studies were all published prior to the release of the 2019 international consensus document on definitions and methods of collecting the data. As a result, there are differences in data collection methods and reporting between studies, with some only recording SD, whilst others included SCD and/ or SCA. These 11 studies documented the incidence of SD, SCD and SCA in various distance running events from 1976 to date and represent studies from the United States of America (USA), United Kingdom (UK), Israel, France and Japan.

One of the first studies documenting SD in runners was a retrospective study (1976-1994) evaluating the risk of SCD associated with marathon running [13]. Of a total of 215 413 finishers in two races (Marine Corps and Twin Cities), four deaths were recorded, all of which were as a result of cardiac causes. In a subsequent study in the same two races (1995-2004), the SCD rate was 0.45/100 000 race finishers [14], which was lower than the SCD rate of 1.86/100 000 race finishers in the previous period (1976-1994).

In 2012, a retrospective study was conducted to determine the incidence of SCA in all marathons in the USA between 1976 - 2009[15]. In a total of 1 710 052 runners, 10 SD's, eight SCD's and 30 SCA's were recorded in this survey. The incidence of SD, SCD and SCA (per 100 000 participants) was 0.58, 0.47 and 1.75, respectively.

A further retrospective study was conducted on the runners of the London marathon over 25 years between 1981 and 2006 [16]. A total of 650 000 runners finished this race in the said period and there were 10 recorded SD's. The rates of SD, SCD and SCA was 1.5, 1.23 and 2.5/ 100 000 finishers, respectively.

The largest retrospective study to date was conducted on 10.9 million marathon and half-marathon runners in the USA over a decade (2000-2010) [17]. The SD and SCA rates were 0.39 and 0.54/ 100 000 registrants, respectively. Another retrospective study was conducted during the same time on 3 718 336 race participants from 2000-2009 in USA marathons [18]. The SD rate was reported as 0.7/100 000 finishers.

A retrospective study conducted in Tel Aviv, Israel evaluated 14 races (distances from 10 km to 42.4 km) over a period of 7 to 8 years (n=137 580) [19]. There were two documented deaths, resulting in a SD rate of 1.45/100 000 finishers. Of note in this paper is that both the deaths were as a result of exertional heatstroke (EHS), which differs from the other studies, where the main cause of SD was of cardiac origin. It is of interest that the authors suspected the cardiac arrhythmias may have occurred as a result of EHS.

The mortality rate in long-distance running races between 2007-2016 was reported in a recent Swedish retrospective study (n=834 412) [20]. There were only two documented deaths and both were due to cardiac causes. This equated to an incidence rate of 0.24/ 100 000 finishers, which is one of the lowest reported incidence rates.

One of the first prospective cohort studies reported the mortality rate in the Twin Cities marathon, USA, between 1983-1994 [21]. In 76 714 starters the SCA and SCD incidence rates were 1.2/100 000 starters. A more recent prospective cohort study was conducted in Paris, France between 2006 - 2012 among 511 880 runners participating in various distance running events [22]. These data were from the prospective RACE Paris Registry (Registre des

Accidents Cardiaques lors des courses d-Endurance). Two SCD's (rate: 0.39/ 100 000 runners) and nine SCA's (rate: 1.8/ 100 000 runners) were recorded in the study. Of interest in this study was that according to French legislation each participant required a medical examination and written approval issued by a physician. To our knowledge this was the only study where this was required from the runners. This same study also reported a meta-analysis on the data of 6 studies, [13] [14, 16, 17] and reported a SD rate of 0.5/ 100 000 participants.

**Table 2.3.: The incidence of SD, SCD and SCA in distance running events (by event and study reference, type of study, number of participants (n), race distance (km). Values are incidence/1000 participants (IR) and absolute risk (AR) of number of participants/1 incident**

Event and study reference	Type	N	Km	IR			AR			Strengths	Limitations	Level of evidence
				SD	SCD	SCA	SD	SCD	SCA			
USA marathons* (1995-2004) Marine Corps and Twin Cities [14]	Editorial	441 924 <sup>b</sup>	42.2	0.45 <sup>b</sup>	0.45 <sup>b</sup>	1.81 <sup>b</sup>	222 222 <sup>b</sup>	222 222 <sup>b</sup>	55 249 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Single race data</li> </ul>	<ul style="list-style-type: none"> <li>• Non-peer-reviewed editorial</li> </ul>	5
USA marathons (1976-1994) Marine Corps (1976-1994) Twin Cities (1982-1994) [13]	Retrospective	215 413 <sup>b</sup>	42.2	1.86 <sup>b</sup>	1.86 <sup>b</sup>	unknown	53 763 <sup>b</sup>	53 763 <sup>b</sup>	unknown	<ul style="list-style-type: none"> <li>• Long study period (30 years)</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective study</li> <li>• Data collection from telephone interviews and records, possible recall bias</li> <li>• Small sample size</li> <li>• SCA rate not known</li> <li>• Race starters not known</li> </ul>	2b
USA marathons (1976-2009) [15]	Retrospective	1 710 052 <sup>c</sup>	42.2	0.58 <sup>c</sup>	0.47 <sup>c</sup>	1.75 <sup>c</sup>	172 414 <sup>c</sup>	212 766 <sup>c</sup>	57 143 <sup>c</sup>	<ul style="list-style-type: none"> <li>• Large cohort</li> <li>• Long study period</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective study</li> <li>• Web-based survey to marathon directors</li> <li>• Low response rate (22%)</li> <li>• Possible recall bias</li> <li>• Possible missed cases</li> </ul>	2b
London Marathon (1981-2006) [16]	Retrospective	650 000 <sup>b</sup>	42.2	1.5 <sup>b</sup>	1.23 <sup>b</sup>	2.5 <sup>b</sup>	66 666 <sup>b</sup>	81 301 <sup>b</sup>	40 000 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Single race data over long period</li> <li>• Race medical director conducted studies and attended autopsies</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective study</li> <li>• Race finishers used as denominator</li> </ul>	2b

**Table 2.3.: The incidence of SD, SCD and SCA in distance running events (by event and study reference, type of study, number of participants (n), race distance (km). Values are incidence/1000 participants (IR) and absolute risk (AR) of number of participants/1 incident (continued)**

USA half-marathon and marathons (2000-2010) [17]	Retrospective	10 900 000 <sup>c</sup>	21.1 42.2	0.39 <sup>c</sup>	not reported	0.54 <sup>c</sup>	256 410 <sup>c</sup>	unknown	185 185 <sup>c</sup>	• Largest cohort to date	• Retrospective study • Data collection methods (internet search engines and outreach to race directors) – may have missed cases	2b
USA marathons (2000-2009) [18]	Retrospective	3 718 336 <sup>b</sup>	42.2	0.75 <sup>b</sup>	not reported	not reported	133 333 <sup>b</sup>	unknown	unknown	• Large cohort	• Retrospective study • Data collected from publicly available racing and news databases	2b
Japan races (2008-2013) [23]	Retrospective	459 479 <sup>c</sup>	42.2	unkno wn	unknown	2.18 <sup>c</sup>	unknown	unknown	45 872 <sup>c</sup>	• University medical records	• Retrospective study • SCA rate not known	2b
Tel Aviv, Israel races (2007-2013) [19]	Retrospective	137 580 <sup>c</sup>	10 21.1 42.2	1.45 <sup>c</sup>	0	Not reported	68 965 <sup>c</sup>	0	unknown	• Recognizing EHS as more common cause of SD	• Retrospective study • Race finishers used as denominator	2b
Swedish races (2007-2016) [20]	Retrospective	834 412 <sup>b</sup>	21.1 42.2	0.24 <sup>b</sup>	0.24 <sup>b</sup>	not studied	416 667 <sup>b</sup>	416 667 <sup>b</sup>	unknown	• Large cohort	• Retrospective study • Data collection- news and public databases • SCA rate not reported • Race finishers used as denominator	2b
Twin Cities, USA (1983-1994) [21]	Prospective	76 714 <sup>a</sup>	42.2	1.2	1.2	1.2	83 333 <sup>a</sup>	83 333 <sup>a</sup>	83 888 <sup>a</sup>	• Prospective study • Race starters known	• Smaller cohort	1b
Paris, France races (2006-2012) [22]	Prospective	511 880 <sup>d</sup>	Several 10 21.1 42.2	0.39 <sup>d</sup>	0.39 <sup>d</sup>	1.8 <sup>d</sup>	256 410 <sup>d</sup>	256 410 <sup>d</sup>	55 556 <sup>d</sup>	• Prospective study	• Race entrants used as denominator (not clear if all these runners started)	1b

Type: Type of study  
 N: Number of participants  
 Km: Race distance  
 SCD: Sudden cardiac death

SCA; Sudden cardiac arrest  
 IR: Incidence rate of sudden death, sudden cardiac death and sudden cardiac arrest (rate/100 000 participants<sup>abcd</sup>)  
 AR: Absolute risk - no. of race participants<sup>abcd</sup>/single incident<sup>a</sup>: per starters<sup>b</sup>: per finishers<sup>c</sup>: per participants<sup>d</sup>: per entrants

In summary, a number of studies reported the incidence of SD, SCD and SCA over the past 40 years. Despite the variation in methodology and quality of the studies, the main findings of this review are as follows:

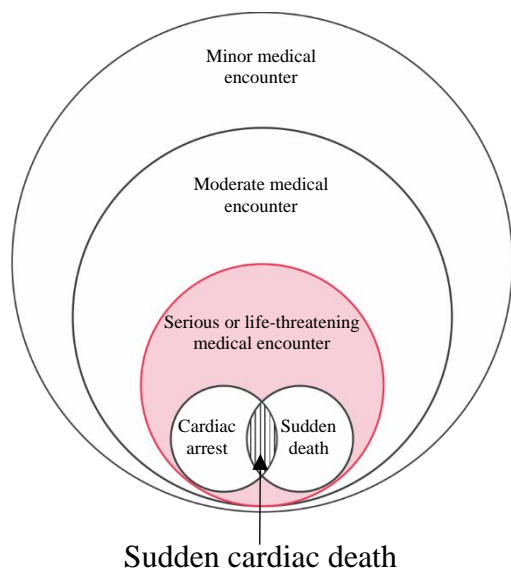
- the incidence of SD at distance running events varies between 0.24 - 1.86/ 100 000 participants [14, 20, 24] [19, 22] and this equates to 1 SD in 53 763 to 1 in 416 666 race participants,
- the incidence of SCD varies between 0 - 1.23/ 100 000 participants [16, 19], which equates to between 0 - 1 SCD in 81 300 participants
- the incidence of SCA varies between 0.54 - 2.5/ 100 000 race participants[16, 17].

In future, we recommend that studies record and report data according to the recent international consensus statement [8]. Data can then be compared more accurately between events and over time. Further research can be conducted to determine possible ways to reduce the incidence of SD, SCD and SCA and make distance running events safer.

SD, SCD and SCA represents only the apex of medical encounters in distance running events. Other medical encounters occur more frequently, and these also include other “non-cardiac”, but also serious and potentially life-threatening medical encounters.

#### **2.4.2. A review of the incidence of serious/ life-threatening medical encounters in distance running events**

In recent years, there has been a significant shift to not only document the incidence SD, SCD and SCA in distance running events, but also record the incidence of other “non-cardiac” serious/ life-threatening medical encounters. (Figure 2.1).



**Figure 2.1: Serious/ life-threatening medical encounters [8]**

Other “non-cardiac” serious/ life-threatening medical encounters include symptomatic hyponatraemia, exertional heatstroke, acute renal failure, subarachnoid bleeds, pulmonary oedema and ischaemic colitis. A detailed discussion on the aetiology of cardiac and “non-cardiac” serious medical encounters is beyond the scope of this chapter of the dissertation. Where relevant, the more common causes of other “non-cardiac” serious/life-threatening medical complications such as hyponatraemia, exertional heatstroke and acute renal failure will be briefly discussed. Numerous case studies related to “non-cardiac” serious/ life-threatening medical encounters have been documented in the literature [16, 25-31]. However, data on the incidence of other serious/ life-threatening medical encounters are generally limited.

Until recently the definition of serious/ life-threatening medical encounters was not consistent and not well characterized. This makes it difficult to compare the incidence rates of serious/ life-threatening medical encounters.

A comprehensive review of the literature identified eight studies (three retrospective and five prospective cohort studies) where the incidence of serious/ life-threatening medical encounters in distance running events was documented. These are summarised by study type and in chronological order in Table 2.4.

**Table 2.4.: The incidence of serious/life-threatening medical encounters in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants <sup>abcd</sup> (IR) and absolute risk (AR) of number of participants <sup>abcd</sup>/1 incident)**

<b>Event and study reference</b>	<b>Type</b>	<b>N</b>	<b>Km</b>	<b>IR</b>	<b>AR</b>	<b>Strengths</b>	<b>Limitations</b>	<b>Level of evidence [32]</b>
Tel Aviv races (2007-2013) [19]	Retrospective cohort	137 580 <sup>c</sup>	10 21.1 42.2	17 <sup>c</sup>	5988 <sup>c</sup>	<ul style="list-style-type: none"> <li>• Specific diagnosis of serious medical encounters</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
Gothenburg half-marathon (2013-2017) [33]	Retrospective cohort	230 501 <sup>a</sup>	21.1	154 <sup>a</sup>	649 <sup>s</sup>	<ul style="list-style-type: none"> <li>• Largest study to date</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• No specific diagnosis of serious cases</li> </ul>	2b
Chicago marathon (2012-2016) [34]	Retrospective cohort	202 603 <sup>c</sup>	42.2	100 <sup>c</sup>	1000 <sup>c</sup>	<ul style="list-style-type: none"> <li>• Digital data collection</li> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Data collection errors</li> <li>• Missing transport data</li> </ul>	2b
Twin Cities (1983-1994) [21]	Prospective cohort	76 149 <sup>a</sup>	42.2	35 <sup>a</sup>	2857 <sup>a</sup>	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Long study period</li> </ul>	<ul style="list-style-type: none"> <li>• Specific diagnosis not known</li> </ul>	1b
Baltimore marathon (2001) [35]	Prospective cohort	11 000 <sup>d</sup> 7 223 <sup>b</sup>	42.2 5 four-person marathon relay	155 <sup>d</sup> 235 <sup>b</sup>	645 <sup>d</sup> 425 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Smaller cohort</li> <li>• Single event</li> <li>• Three races</li> </ul>	1b

**Table 2.4.: The incidence of serious/life-threatening medical encounters in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants <sup>abcd</sup> (IR) and absolute risk (AR) of number of participants <sup>abcd</sup>/1 incident) (continued)**

Baltimore marathon (2002-2005) [36]	Prospective cohort	33 700 <sup>d</sup>	42.2 21.1 5 four-person marathon relay	48 <sup>d</sup>	2083 <sup>d</sup>	• Prospective design	• Four races • Potential underreporting	1b
Vancouver International marathon (2006-2011) [37]	Prospective cohort	67 402 <sup>c</sup>	42.2 21.1 8	53 <sup>c</sup>	1887 <sup>c</sup>	• Prospective design	• Data capturing problems • Spectator data included • Runners possibly also to alternative hospitals	1b
Singapore half-marathon (2010-2012) [38]	Prospective cohort	84 644 <sup>c</sup>	21.1 10	14 <sup>c</sup>	7142 <sup>c</sup>	• Prospective design	• Race registrants used as denominator • Shorter running distance • Included trained military recruits, possible explaining lower incidence	1b

Type: Type of study

N: Number of participants

Km: Race distance

IR: Incidence rate of serious/life-threatening medical encounters (rate/100 000 <sup>abcd</sup>)

AR: Absolute risk - no. of race participants <sup>abcd</sup>/single incident)

<sup>a</sup>: per starters <sup>b</sup>: per finishers <sup>c</sup>: per participants <sup>d</sup>: per entrants

The first retrospective study in runners of races in Tel Aviv over 7 years (n=137 580) reported an incidence of serious/life-threatening medical encounters of 17/100 000 participants (n=23). The main strength of the study was accurate documentation of the specific diagnosis of serious/life-threatening medical complications. The second retrospective study, from Sweden, was conducted among 230 501 participants in the Gothenburg half-marathon, also over 5 years [33] and is the largest study to date. The serious medical complication rate was 154/100 000 participants. The most recent retrospective study was conducted on the runners of the Chicago marathon (n=202 603), again over a period of 5 years [34]. The incidence of serious/life-threatening medical complications was 100/100 000 participants (n=204).

There were five large prospective cohort studies conducted over the past two decades, in which serious/life-threatening medical encounters were reported. The first of these was a 12-year prospective cohort study in the Twin Cities Marathon previously described (n=76 714) [21] (Table 2.3.). There were 27 documented cases of serious medical complications, with an incidence rate of 35/100 000 participants.

A second was a prospective cohort study conducted at the Vancouver International Marathon over a period of 6 years in a cohort of 67 402 runners [37], with race distances between eight km to a full 42 km marathon. The serious medical complication rate was 53/100 000 participants. The next two prospective studies were conducted over a 1 and 4 year period on the Baltimore marathon (n=11 000; 33 7000) [35, 36]. The incidence of serious/ life-threatening medical encounters was 155[35] and 48/100 000 [36] race entrants.

The final study referred to was a prospective study, in which participants in both 10 km and 21.1 km races at the Singapore half-marathon (n=84 644) were studied and the incidence of serious/ life-threatening medical complications found to be 14/100 000 participants [38]. This incidence was the lowest in all the studies and may be related to the inclusion of shorter running distances. However, future comparative studies are required to evaluate this.

## **Summary**

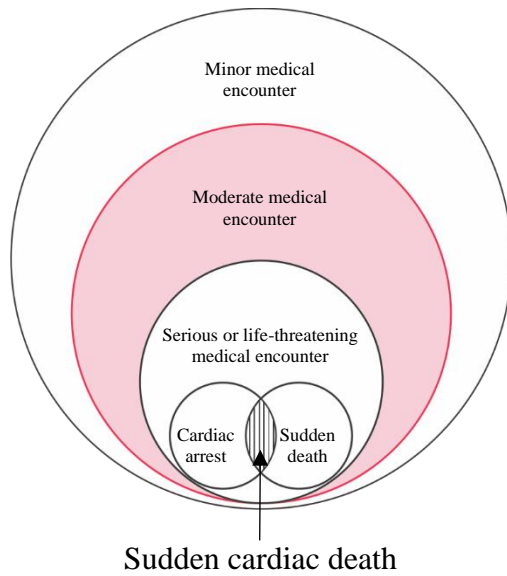
It is important to note that most of the studies were conducted prior to the release of the 2019 consensus statement. Therefore, there is no consistent use of a standardised definition of serious/ life-threatening medical encounters. Races also differed by location, climate, season

and race technicality. All these factors make comparisons between races difficult. The exact diagnosis of the serious/ life-threatening medical encounter, by organ system, was mostly not reported in the studies.

In summary, the incidence rate of serious/life-threatening medical encounters is between 14 - 235/100 000 participants. This equates to an absolute risk of 1 in 426 to 1 in 7000 participants. It is important to note that the incidence of serious/ life-threatening medical encounters is up to 100 times higher than the incidence of SD [8, 38, 39]. Therefore, accurate documentation of the incidence of serious/ life-threatening medical encounters is extremely important in order for race medical directors to properly plan and create a safer event. In future studies the use of a standardised definition of a serious/life-threatening medical complication, as stated in the consensus statement on medical encounters in endurance sports, as well as reporting of the specific diagnosis per organ system of each encounter, is encouraged.

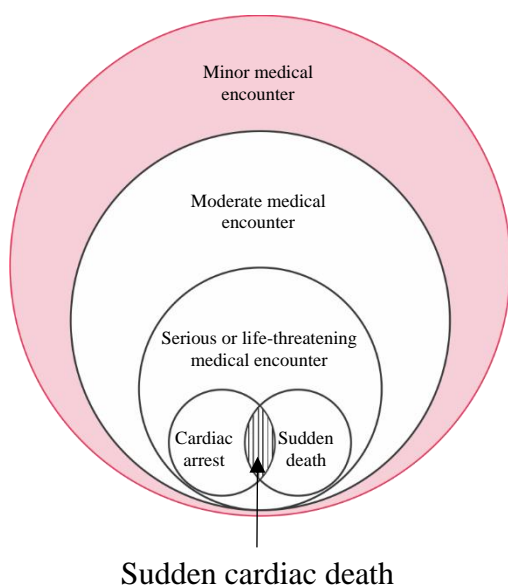
#### **2.4.3. A review of the incidence of moderate medical encounters in distance running events**

Moderate medical encounters account for the largest number of medical encounters (by severity) at events and the medical team at a race will spend the majority of their time and resources treating participants in this category (figure 2.2). These are not serious/life-threatening, but may result in significant morbidity of the participants. Some of these conditions may even deteriorate and become serious/ life-threatening if not managed appropriately.



**Figure 2.2.: Moderate medical encounters [8]**

To date, the data have not distinguished between minor and moderate medical encounters. It may be that only moderate medical encounters were documented, but it is not clear from the majority of the data. Secondly, some of the studies data documenting incidence excluded minor medical encounters, where others included those encounters thus affecting the reported rates. Minor medical encounters (figure 2.3) are usually of insufficient severity to adversely influence the health of the athlete and therefore not consistently and accurately documented in the literature.



**Figure 2.3: Minor medical encounters [8]**

Furthermore, there is paucity of data on specifically documenting the category of moderate medical encounters separately. Most of the data reports the overall incidence of medical encounters in distance running events. These data includes ALL the medical encounters which were documented in the different distance running events. It should be noted this overall incidence includes the SD, SCD, SCA and serious/ life-threatening medical encounters. The moderate incidence rate can be calculated from data where there are detailed data on SD, SCD, SCA and serious / life-threatening encounters, however, this is only possible in a small percentage of the known available data. Therefore, for consistency and comparative purposes the incidence of ALL medical encounters will now be discussed. As previously mentioned, it is important to note that there exists differences in the published data in documenting medical encounters per registrant, entrant, starter, participant and finisher. These will be documented according to the specific study.

### **Incidence of all medical encounters in distance running events**

The incidence rate of all medical encounters in distance running events are documented between 2.3 to 47/ 1000 participants (Table 2.5.).

**Table 2.5.: Incidence of all medical encounters in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants<sup>abcd</sup> (IR) and absolute risk (AR) of number of participants<sup>abcd</sup>/1 incident)**

Event and study reference	Type	N	Km	IR	AR	Strengths	Limitations	Level of evidence [32]
City-to-Surf (1976-1979) [40]	Retrospective cohort	54 250 <sup>a</sup>	14	15.5 <sup>a</sup>	65 <sup>a</sup>	• First study	• Retrospective design	2b
Houston Marathon (2000) [41]	Retrospective cohort	6 660 <sup>d</sup> 5082 <sup>b</sup>	42.2	36 <sup>d</sup> 47 <sup>b</sup>	28 <sup>d</sup> 21 <sup>b</sup>	• Dr/nurse: patient ratio small (1:4; 1:2), good records	• Retrospective design • Single event • Smaller cohort	2b
Army 10-miler (1998-2004) [42]	Retrospective cohort	91 750 <sup>a</sup> 72 100 <sup>b</sup>	16	3.8 <sup>a</sup> 4.7 <sup>b</sup>	263 <sup>a</sup> 213 <sup>b</sup>	• Large cohort • Study period over six years	• Retrospective design • Shorter distance	2b
Singapore Army Half-marathon (2010-2012) [38]	Retrospective cohort	84 644 <sup>d</sup>	21.1 10	2.3 <sup>d</sup>	435 <sup>d</sup>	• Large cohort	• Retrospective design • Race registrants used as denominator • Included trained military recruits, possible explaining lower incidence	2b

**Table 2.5.: Incidence of all medical encounters in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants<sup>abcd</sup> (IR) and absolute risk (AR) of number of participants<sup>abcd</sup>/1 incident) (continued)**

10-km Road races (2012-2017) [43]	Retrospective cohort	90 265 <sup>b</sup>	10	6.2 <sup>b</sup>	161 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Large cohort over two decades</li> <li>• Included 19 races</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Shorter distance</li> </ul>	2b
Twin Cities (1983-1994) [21]	Prospective cohort	76 714 <sup>d</sup> 69 043 <sup>a</sup> 57 246 <sup>b</sup>	42.2	19 <sup>d</sup> 21 <sup>a</sup> 25.4 <sup>b</sup>	53 <sup>d</sup> 48 <sup>a</sup> 39 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Study over longest period</li> </ul>	•	1b
Baltimore Marathon (2001) [35]	Prospective cohort	11 000 <sup>a</sup> 7223 <sup>b</sup>	42.2 5 four-person marathon relay	22.8 <sup>d</sup> 35 <sup>b</sup>	44 <sup>d</sup> 29 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Smaller cohort</li> <li>• Single event</li> <li>• Three different races</li> </ul>	1b
Baltimore Marathon (2002-2005) [36]	Prospective cohort	33 700 <sup>d</sup>	42.2 21.1 5 four-person marathon relay	34 <sup>d</sup>	29 <sup>d</sup>	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Four different races</li> <li>• Potential underreporting</li> </ul>	1b

**Table 2.5.: Incidence of all medical encounters in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants<sup>abcd</sup> (IR) and absolute risk (AR) of number of participants<sup>abcd</sup>/1 incident) (continued)**

London Marathon (2006) [44]	Prospective cohort	33 578 <sup>a</sup> 33 222 <sup>b</sup>	42.2	18 <sup>ab</sup>	56 <sup>ab</sup>	• Prospective design	• Single event • Race in wet, rainy conditions	1b
Vancouver International Marathon (2006-2011) [37]	Prospective cohort	67 402 <sup>c</sup>	21.1 42.2	45 <sup>c</sup>	22 <sup>c</sup>	• Prospective design	• Data capturing problems • Spectator data included • Runners possibly also to alternative hospitals	1b

Type: Type of study

N: Number of participants

Km: Race distance

IR: Incidence rate of any medical encounter (rate/1000<sup>abcd</sup>)

AR: Absolute risk - no. of race participants<sup>abcd</sup>/single incident)

<sup>a</sup>: per starters <sup>b</sup>: per finishers <sup>c</sup>: per participants <sup>d</sup>: per entrants

One of the first studies documenting the incidence of medical encounters in distance running events was a retrospective cohort study conducted on the runners of the 14 km City-to-Surf race in Sydney, Australia from 1976 to 1979[40]. During this time there were 54 250 race starters and 842 medical encounters documented. The incidence of medical encounters in this race was 15.5/ 1000 starters.

Following this, there were numerous further retrospective cohort studies conducted (Table 2.5.) [38, 41-43]. The incidence of medical encounters in these studies was documented between 2.3 – 47/ 1000 participants. The highest incidence was in the 2000 Houston marathon, USA [41]. This race was run in very warm conditions which may have affected the incidence.

In a number of well-conducted, large prospective cohort studies, the incidence of medical encounters was documented between 18 – 45/1000 participants [35-37, 44]. In these prospective studies the 2006 London marathon documented the lowest incidence and the Vancouver International Marathon (2006-2011) the highest incidence rate.

Caution should be applied when interpreting the data in Table 2.5., and drawing conclusions about the variation, as these data were collected prior to the recent consensus document.

## **Summary**

Following the analysis of the incidence data in the literature, it is again important to note that the medical team will spend the majority of their time taking care of non-serious medical encounters. This incidence data are important when a medical team/director plans and prepares for a mass-participation distance running event. In summary, the incidence of medical encounters in distance running events varies widely in the literature (2.3 to 47/ 1000 participants). However, these studies contribute to an important foundation for future research which should focus on the recent international consensus on definitions, data recording and reporting.

Following the recent international consensus document [8], the next section of this review will focus on a review of the incidence by organ systems affected and specific diagnosis.

## **2.5. A REVIEW OF THE INCIDENCE OF MEDICAL ENCOUNTERS BY ORGAN SYSTEM AND COMMON SPECIFIC DIAGNOSIS IN DISTANCE RUNNING EVENTS**

In this section of the literature review the focus will be on the incidence of the more common medical encounters per organ systems and specific diagnosis as per the consensus statement [8](Table 2.2.). Where applicable, this will include some of the more serious/life-threatening medical encounters. These will be discussed in their specific organ system (such as exertional heatstroke, exercise-associated hyponatraemia and acute kidney injury).

### **2.5.1. Incidence of medical encounters in multiple organ systems**

The more common specific diagnosis in multiple organ systems are:

- exertional heatstroke
- rhabdomyolysis
- fluid and electrolyte disorders including, dehydration, hyponatraemia, and other electrolyte disorders

#### **2.5.1.1. *Incidence of exertional heatstroke in distance running events***

##### ***Definitions and terminology***

Exertional heatstroke (EHS) is one of the important serious and potentially life-threatening medical encounters that can occur in distance running events. Heatstroke can be fatal [45] [46, 47] and can occur even in unexpectedly cool environmental conditions [48, 49]. It is important to distinguish EHS from other conditions such as hyperthermia and classic heatstroke. Hyperthermia is defined as “*an elevation of core body temperature above the normal diurnal range of 36 - 37.5 °C due to thermoregulatory failure of the anterior hypothalamus*” [50]. Hyperthermia is not synonymous with the more common sign of fever, which is induced by cytokine activation during inflammation and is regulated at the level of the hypothalamus [50]. Heatstroke is one of the causes of hyperthermia [50] and can be either exertional heatstroke or classic heatstroke.

Exertional heatstroke (EHS) is defined by the following criteria:

- A core temperature elevated above the highest mean temperatures (above 40.0-41.5° C) found in otherwise asymptomatic athletes [51-53]
- Altered cerebral function [54]
- Associated with exertion / exercise

Classic heatstroke has a similar definition to EHS, except that it results from exposure to high environmental temperatures, without being directly related to exertion / exercise {Bouchama, 2002 #971

It is also important to mention that in earlier epidemiological studies in running events, EHS has often been described together with heat exhaustion, heat fatigue or heat syncope [55-58]. EHS must also be distinguished from exercise-associated collapse, both clinically and for research purposes. Exercise-associated collapse will be reviewed in detail (section 2.5.2.1) presents as collapse after completion of a bout of exercise, whereas EHS is associated with collapse during exercise.

In summary, data from epidemiological studies that describe the incidence of EHS may not be accurate due to the fact that a number of other medical conditions, as mentioned above, may have been included in the definition of EHS and heat related deaths [19, 52]. For the purposes of this dissertation the definition of EHS, as described above, will be used.

### **Incidence of EHS in distance running events**

The first study discussed on the incidence of 'EHS' was a retrospective study from the 1970's and was conducted over five years at the City-to-Surf runs in Sydney, Australia. The incidence of 'heat exhaustion' was 1.70/ 1000 starters [40]. The definition of 'heat exhaustion' in this paper was a 'rectal temperature of >38° C associated with collapse', and this is different from the current definition of EHS, as stated above.

In a number of subsequent studies, the incidence of EHS has been documented and varied between 0.03 – 2.13/ 1000 participants. These studies included a case series [59], and a

number of retrospective cohort studies [19, 42, 60-62] and one prospective cohort study [21] (Table 2.6.).

In one of the first retrospective cohort studies at the 10 km Peachtree Road Race in Atlanta, USA (n = 17 632), an incidence of EHS was reported as 1.65/ 1000 race participants [60]. In other retrospective studies the incidence of EHS was as follows:

- 1.02/ 1000 race entrants at one of the world's biggest half-marathons, The Great North Run in the United Kingdom (n=54 000) [61]
- 0.15/ 1000 finishers in long distance races in Tel Aviv between 2007 and 2013 (n = 137 580) [19], and
- 2.13 /1000 race participants in the Falmouth Road 11 km road race over a period of 18 years (n=128 639). This race is held in the height of summer in Falmouth, Massachusetts, USA and the incidence of EHS in this race was the highest of all in the studies reviewed [62].

Finally, in one prospective cohort study over a 12-year period on the runners of the Twin Cities Marathon the incidence of EHS was 0.15/ 1000 starters [21].

**Table 2.6.: The incidence of EHS in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/ 1000 participants<sup>abcd</sup> (IR) and absolute risk (AR) of number of participants<sup>abcd</sup> per 1 incident)**

Event and study reference	Type	N	Km	IR	AR	Strengths	Limitations	Level of evidence [32]
Cincinnati Flying Pig Marathon, 2014-2016 [59]	Case-series	46 063 <sup>b</sup>	21.1 42.2	0.56 <sup>b</sup>	1786 <sup>b</sup>	<ul style="list-style-type: none"> <li>Detailed documentation</li> </ul>	<ul style="list-style-type: none"> <li>Limited to a case-series</li> </ul>	4
Peachtree Road Race 1979 [60]	Retrospective cohort	17 632 <sup>c</sup>	10	1.65 <sup>c</sup>	606 <sup>c</sup>	<ul style="list-style-type: none"> <li>One of first studies</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> <li>Single event</li> </ul>	2b
The Great North Run 2009 [61]	Retrospective cohort	54 000 <sup>d</sup>	21.1	1.02 <sup>d</sup>	980 <sup>d</sup>	<ul style="list-style-type: none"> <li>World's largest half marathon at the time</li> <li>Medical team with extensive EHS treatment experience</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> <li>Single event</li> </ul>	2b
Army 10-miler (1998 – 2004) [42]	Retrospective cohort	91 750 <sup>a</sup>	16	0.03 <sup>a</sup>	33 333 <sup>a</sup>	<ul style="list-style-type: none"> <li>Large cohort</li> <li>Long study period (6-yrs)</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> </ul>	2b
Tel Aviv races (2007 – 2013) [19]	Retrospective cohort	137 580 <sup>b</sup>	10 21.1 42.2	0.15 <sup>b</sup>	6536 <sup>b</sup>	<ul style="list-style-type: none"> <li>Large cohort</li> <li>Recognizing EHS as more common cause of SD</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> </ul>	2b
Falmouth Road Race* [62]	Retrospective cohort	128 639 <sup>b</sup>	11.26	2.13 <sup>b</sup>	470 <sup>b</sup>	<ul style="list-style-type: none"> <li>Long study period (18 years)</li> <li>Consistently high incidence</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> <li>Missing data reports</li> </ul>	2b
Twin Cities Marathon (1983-1994) [21]	Prospective cohort	69 043 <sup>a</sup>	42.2	0.15 <sup>a</sup>	6667 <sup>a</sup>	<ul style="list-style-type: none"> <li>Prospective design</li> <li>Study over longest period</li> <li>Detailed weather data</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>	1b

\*1984, 1989, 1992-1994, 1996-1998, 2001 and 2003-2011

Type: Type of study

N: Number of participants

Km: Race distance

IR: Incidence rate of EHS (rate/100 000<sup>abcd</sup>)

AR: Absolute risk - no. of race participants<sup>abcd</sup>/ single incident)

<sup>a</sup>: per starters <sup>b</sup>: per finishers <sup>c</sup>: per participants <sup>d</sup>: per entrants

In summary, the incidence of EHS in distance runners varies between 0.03 - 2.13/ 1000 race participants. Risk factors associated with EHS, that may explain the variation in the incidence of EHS between races, will be reviewed in chapter 4 of this dissertation. Further well-designed studies, using standardised definitions, are required to accurately determine the incidence of EHS in distance running.

### **2.5.1.2. Incidence of rhabdomyolysis in distance running events**

#### ***Definitions and terminology***

Rhabdomyolysis is a clinical syndrome of muscle pain, muscle swelling and weakness that is characterised by muscle cell injury resulting in the release of cellular components into the circulation [63]. Biochemically, it is characterised by marked elevation in serum creatine kinase (CK) activity. It is a syndrome that is caused by a variety of aetiologies [64] of which exercise is one [65].

Exertional rhabdomyolysis (ER) is defined as the rhabdomyolysis which is directly associated with strenuous physical exercise [66]. It ranges in severity from asymptomatic elevations in CK levels to life-threatening ER that can result in complications [31, 65, 67-69]. These complications can include electrolyte disorders [70], acute kidney injury [71], muscle ischaemia and death [70].

In addition to a clinical history and physical examination, the usual definition of ER is based on a rise in s-[CK] of five times the upper-limit of normal values or if s-[CK] exceeds 5000 units/L. However, after a recent systemic review regarding rhabdomyolysis diagnosis a diagnostic criterion for the diagnosis of ER was set at >1000 units/L [63].

#### **Incidence of exertional rhabdomyolysis in distance running events**

There are no accurate data on the true incidence of ER in distance running events because most studies are case reports [67, 72] or case series [68, 73]. In these case-series, clusters of ER and EAH have been described in ultra-distance events [68, 73]. In some studies only the biomarkers of ER in distance runners were measured, which were not of clinical relevance [74].

As mentioned, one of the more common serious medical complications of ER is AKI. The relationship between ER and acute kidney injury (AKI) in endurance sports was recently reviewed [75]. This review included 43 publications and a total of 813 of cases. Of these cases, 345 (43.5%) were diagnosed with ER (CK >5000 units/L) and 130 (16.39%) with ER and AKI (creatinine  $\geq$  1.85mg/dl). Endurance running was the cause in 36% of the ER cases and the cause of 97% of ER and AKI cases. From this review it was concluded that distance running is one of the more common causative endurance sports associated with ER and is more likely to lead to ARF (section 2.5.7.). The precise reasons for this is not known and further studies evaluating the incidence of ER, including ER and AKI, in distance running events are required. The incidence of AKI will be discussed in section 2.5.6. of this dissertation.

### **2.5.1.3. *Incidence of fluid and electrolyte disorders in distance running events***

In this section, the incidence of following more common medical encounters in distance running events will be discussed:

- Dehydration
- Electrolyte disorders (exercise-associated hyponatraemia and other electrolyte disorders)

#### **a) Dehydration**

Dehydration is one of the most common medical encounters in distance runners. It is usually mild or moderate and therefore easily treated. However, severe dehydration may be associated with more serious/ life-threatening medical encounters such as EHS (section 2.5.1.1. of this chapter) and acute renal failure (section 2.5.6. of this chapter).

#### **Diagnosis and sub-classification of the severity of dehydration**

The diagnosis of dehydration in endurance runners can be a clinical diagnosis or by measuring the % body weight loss (post- versus pre-exercise). In most studies reporting the incidence of dehydration this was diagnosed clinically. In other studies, dehydration was diagnosed in runners if the % body weight loss was > 3% (post- versus pre-race). More

recently the severity of dehydration was defined, using % body weight loss, as mild (<5% body weight loss), moderate (>5% to <7% body weight loss) or severe (>7% body weight loss) [8]. However, it is important to point out a flaw in using an absolute body mass change for defining dehydration without considering the duration of the exercise [76]

### **Incidence of dehydration in distance running events**

There are limited data on the true incidence of dehydration in distance running events, mainly as a result of the variation in the criteria that were used to diagnose dehydration (clinical diagnosis versus % body weight loss). The incidence of dehydration in distance running events, using either clinical criteria or post- versus pre-body weight loss (>3% body weight loss) to assess hydration status, are summarised in Table 2.8.

Most of the data on the incidence of dehydration in mass participation distance running events are from studies using a clinical diagnosis. In these studies, the incidence of dehydration varied between 0.14 to 11/ 1000 participants [34-36, 42, 43](Table 2.8.).

In two studies, in ultramarathon events, dehydration was diagnosed using body weight loss of > 3% as the criteria. One prospective cohort study was conducted on 128 participants in a multistage desert ultramarathon race across four deserts on different continents (Gobi, Atacama and Jordan), and based on weight loss criteria the incidence of dehydration was 539/ 1000 finishers [77]. In a second prospective cohort study, conducted over five years on the participants (n=887) of a 161 km race in California, USA, the incidence of dehydration was 356/ 1000 finishers [78] (Table 2.8.). In summary, the reported incidence of dehydration in ultramarathon events, where weight loss > 3% body weight was used as diagnostic criteria, varied between 185 - 539/ 1000 participants [77-79] (Table 2.8.).

**Table 2.7.: The incidence of dehydration (a. diagnosed using % weight loss b. diagnosed using clinical criteria) in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants<sup>abcd</sup> (IR) and absolute risk (AR) of number of participants<sup>abcd</sup>/1 incident)**

Event and study reference	Type	N	Km	IR	AR	Strengths	Limitations	Level of evidence [32]
<b>a. Dehydration diagnosed using pre- versus post weight loss</b>								
Ironman Triathlon (2000,2001) (Cape Town South Africa) [79]	Cross-sectional	258 <sup>a</sup>	224	667 <sup>a</sup>	1.50 <sup>a</sup>	<ul style="list-style-type: none"> <li>• Actual weight loss measured</li> <li>• One of first ‘field’ studies evaluating weight loss as dehydration criteria</li> <li>• Inverse relationship found between weight loss and finishing time</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional</li> <li>• Triathlon</li> <li>• Weight loss criteria (&gt;3.5-4.5% and &gt;5% group versus &lt;3.5% group)</li> </ul>	3
8 endurance events and additional data reported in literature [80]	Retrospective cohort	2135 <sup>c</sup>	Various ultra-event distances	505 <sup>c</sup>	2 <sup>c</sup>	<ul style="list-style-type: none"> <li>• Large cohort</li> <li>• Actual weight loss measured</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Weight loss criteria &gt;3% (vs &gt;5%)</li> </ul>	2b

**Table 2.7.: The incidence of dehydration (a. diagnosed using % weight loss b. diagnosed using clinical criteria) in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants <sup>abcd</sup> (IR) and absolute risk (AR) of number of participants <sup>abcd</sup>/1 incident) (continued)**

161 km California races (2008-2012) (USA) [78]	Prospective cohort	887 <sup>b</sup>	161 <sup>b</sup>	185 <sup>b</sup>	5.41 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Five year data</li> <li>• Actual weight loss measured</li> </ul>	<ul style="list-style-type: none"> <li>• Weight loss criteria &gt;3% (vs &gt;5%)</li> </ul>	1b
4 Deserts Multistage Ultra-marathons (2012,2013) (Gobi, Atacama, Jordan deserts) [77]	Prospective cohort	128 <sup>b</sup>	250 <sup>b</sup>	539 <sup>b</sup>	1.86 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Cumulative effect shown</li> </ul>	<ul style="list-style-type: none"> <li>• Weight loss criteria &gt;3% (versus 5%)</li> <li>• Multistage, desert race – not always comparable</li> </ul>	1b
<b>b. Dehydration diagnosed using clinical criteria</b>								
Army 10-miler, (1998 – 2004) (Washington D.C., USA) [42]	Retrospective cohort	91 750 <sup>a</sup>	16	0.14 <sup>a</sup>	7 143 <sup>a</sup>	<ul style="list-style-type: none"> <li>• Large cohort</li> <li>• Six years data</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Shorter distance</li> <li>• Clinical diagnosis</li> </ul>	2b
Bank of America Chicago Marathon (2012-2016) (Chicago, USA) [34]	Retrospective cohort	205 788 <sup>c</sup>	42.2	3 <sup>c</sup>	333 <sup>c</sup>	<ul style="list-style-type: none"> <li>• Large cohort</li> <li>• Digital data collection</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Clinical diagnosis</li> <li>• Data collection errors</li> </ul>	2b

**Table 2.7.: The incidence of dehydration (a. diagnosed using % weight loss b. diagnosed using clinical criteria) in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants <sup>abcd</sup> (IR) and absolute risk (AR) of number of participants <sup>abcd</sup>/1 incident) (continued)**

10 km road races (2000 -2018) USA [43]	Retrospective cohort	90 265 <sup>b</sup>	10	5 <sup>b</sup>	200 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Large cohort over two decades</li> <li>• Included 19 races</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Shorter distance</li> <li>• Clinical diagnosis</li> </ul>	2b
Baltimore Marathon (2001) (Baltimore, USA)[35]	Prospective cohort	11 000 <sup>a</sup>	42.2 5 four- person marathon team relay	3.18 <sup>a</sup>	315 <sup>a</sup>	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical diagnosis</li> <li>• Single event</li> <li>• Smaller cohort</li> <li>• Three different races</li> </ul>	1b
Baltimore marathon (2002-2005) (Baltimore, USA) [36]	Prospective cohort	33 700 <sup>c</sup>	42.2 21.1 5 four- person marathon team relay	11 <sup>c</sup>	91 <sup>c</sup>	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical diagnosis</li> <li>• Four different races</li> <li>• Potential underreporting</li> </ul>	1b

Type: Type of study

N: Number of participants

Km: Race distance

IR: Incidence rate of dehydration (rate/100 000 <sup>abcd</sup>)

AR: Absolute risk - no. of race participants <sup>abcd</sup>/single incident)

<sup>a</sup>: per starters <sup>b</sup>: per finishers <sup>c</sup>: per participants <sup>d</sup>: per entrants

These data indicate that the incidence of dehydration based on clinical diagnosis only is much lower compared to the incidence if using weight loss is used as the diagnostic criteria. There is evidence that clinical signs of dehydration in distance runners correlate poorly with weight loss [81]. Also, of interest is that some large retrospective and prospective studies included dehydration in the exercise-associated collapse category [21, 33]. Further studies based on the weight loss criteria mentioned above are required to accurately determine the incidence of dehydration in distance running events.

## **b) Electrolyte disorders**

Prolonged endurance exercise, including distance running, can result in changes in serum electrolyte concentrations that may be of clinical relevance. These changes in serum electrolyte concentrations can either be asymptomatic and transient, or symptomatic. Symptomatic changes in serum electrolyte concentrations can include both less serious and serious/life-threatening encounters. The most frequent serum electrolyte disorder in endurance sports is hyponatraemia and the incidence of hyponatraemia will be reviewed. Abnormalities of other serum electrolyte disorders in endurance sports ( $Mg^{2+}$ ,  $Ca^{2+}$ ,  $K^+$ ,  $PO_4^-$ ) will only be mentioned briefly.

### **Hyponatraemia**

Hyponatraemia is the most common electrolyte disorder in distance running events. It is also a potentially serious/ life-threatening medical encounter.

#### ***Definitions***

Hyponatraemia is defined as a serum or plasma sodium concentration below the normal reference range of the laboratory performing the test, which in most laboratories is a serum sodium concentration of less than 135mmol/L. [82, 83].

Exercise-associated hyponatraemia (EAH) is the occurrence of hyponatraemia during or up to 24 hours following prolonged physical activity and there are two distinct forms of EAH. These are asymptomatic EAH and symptomatic EAH [84]. Asymptomatic EAH is defined as

*“a reduced serum sodium concentration of <135mmol/l without associated clinical symptoms and signs”*, while symptomatic EAH is defined as a *“reduced serum sodium concentration of <135mmol/l with associated clinical symptoms and signs”*.

### **Incidence of EAH in distance running events**

The incidence of asymptomatic EAH and symptomatic EAH in distance running events is summarised in Table 2.9. For the purposes of this dissertation and literature review, the emphasis will be on symptomatic EAH because athletes present to the medical facilities with symptoms and signs as a medical encounter.

The incidence of asymptomatic EAH in distance runners has been documented in a number of research studies where blood samples were taken from consenting athletes participating in events [44, 85-89]. These include cross-sectional, retrospective and prospective cohort studies. The incidence of asymptomatic EAH has been documented between 0 – 512/ 1000 participants in distance running events. The longer ultra-endurance races tend to have higher incidence rates when compared to a marathon [26, 85-88, 90, 91] (Table 2.9).

**Table 2.8.: The incidence of asymptomatic EAH in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/ 1000 participants (IR) and absolute risk (AR) of number of participants/1 incident)**

Event and study reference	Type	N	Km	IR	AR	Strengths	Limitations	Level of evidence [32]
Iditasport ultramarathon, USA [90]	Cross-sectional study	16	161	440	2	<ul style="list-style-type: none"> <li>• Study evaluated EAH in extreme cold</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Small cohort</li> <li>• Greater race distance</li> </ul>	4
Cali Half marathon, Columbia (2017) [88]	Cross-sectional study	81	21.1	0	0	<ul style="list-style-type: none"> <li>• 62% participation rate</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Small cohort</li> <li>• Shorter distance</li> </ul>	4
8 endurance events and additional data reported in literature [80]	Retrospective cohort study	2135	Various	58	37	<ul style="list-style-type: none"> <li>• Analysis of many endurance events and literature reports</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
Houston Marathon, USA (2000-2003) [87]	Retrospective cohort study	117	42.2	280	4	<ul style="list-style-type: none"> <li>• Three year study period</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
City of Christchurch Marathon, New Zealand (2002) [85]	Prospective cohort	185	42.2	0	0	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• ‘Ideal’ weather conditions</li> <li>• 52% participation</li> </ul>	<ul style="list-style-type: none"> <li>• No cases documented</li> </ul>	1b
Boston Marathon, USA (2002) [86]	Prospective cohort	488	42.2	127	8	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Largest cohort of studies evaluated</li> </ul>	<ul style="list-style-type: none"> <li>• 67% follow-up</li> <li>• Less follow-up in slower females –‘at risk’ population</li> <li>• No baseline [Na] pre-race</li> </ul>	1b

**Table 2.8.: The incidence of asymptomatic EAH in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/ 1000 participants (IR) and absolute risk (AR) of number of participants/1 incident) (continued)**

Zurich Marathon, Switzerland (2006) [26]	Prospective cohort	167	42.2	30	33	• Prospective design	• Low study participation rate	1b
Rio Del Lago 100 mile, USA (2008) [91]	Prospective cohort	45	161	512	2	• Prospective design	• Small cohort • Greater race distance	1b
Swiss ultra-endurance events, Switzerland [92]	Prospective cohort	200	Ultra-endurance events (running, mountain running, swimming and cycling)	60	17	• Prospective design	• Different endurance events	1b
Biel ultra-run, Switzerland (2007-2010) [93]	Prospective cohort	145	100	48	21	• Prospective design	• Greater distance	1b
London Marathon (2006) [44]	Prospective cohort study	88	42.2	125	8	• Prospective design • 80% follow-up	• Those not presenting for follow-up may have been slow runners ('at risk')	1b
Western States Endurance Run, USA (2009) [94]	Prospective cohort study	47	161	300	3.4	• Prospective design	• Greater distance • No pre-race [Na]	1b

Type: Type of study

N: Number of participants

Km: Race distance

IR: Incidence rate of asymptomatic EAH (rate/ 100 000)

AR: Absolute risk - no. of race participants/ single incident)

## **Clinical presentation of symptomatic EAH**

The initial clinical signs of EAH are non-specific, and can range from bloating, “puffiness”, nausea, vomiting and headache [41, 95-100]. As the severity of the condition progresses, more serious signs and symptoms of altered central nervous system (CNS) function can develop as a result of cerebral oedema. This includes alteration of mental status, seizures, respiratory distress (pulmonary oedema), obtundation, coma and death [97, 101, 102] [98, 103-105] [106-109] [99, 100, 110, 111].

An important sub-group of athletes with symptomatic EAH and CNS symptoms are considered to have EAHE (exercise-associated hyponatraemic encephalopathy). This is a very serious and life-threatening complication of EAH with a number of confirmed deaths have been documented due to EAHE [41, 44, 99, 108, 112-114].

The majority of participants with EAH will fortunately not develop EAHE, but just the initial symptoms as described, which if left untreated or incorrectly managed, could lead to EAHE. Therefore, it is important to recognize EAH and be knowledgeable of the incidence of EAH as discussed in the next section of this review.

## **Incidence of symptomatic EAH in distance running events**

In general, symptomatic EAH has been reported as isolated cases presenting to race medical facilities [44, 68, 73, 115] [111, 116-118]. Due to the nature of the studies and case reports the precise incidence of EAH cannot be determined accurately. Historical data on events documenting EAH are documented from 1966 [119-121]. The incidence of symptomatic EAH has been reported in various events, including marathons [41, 86], Ironman triathlons [79, 122-124] and cycling races [125]. In the marathon, the incidence of symptomatic EAH is generally below 1/ 1000 participants [41, 97].

An observational case series in the 2003 London marathon showed an incidence of symptomatic EAH as 0.43/ 1000 race finishers [126]. In a retrospective study during the 1998 and 1999 San Diego Marathon in North America there were 26 patients diagnosed with symptomatic EAH who presented to 14 Emergency Departments (EDs) [97]. The incidence of symptomatic EAH was 0.73/ 1000 participants. In two other studies in marathon runners,

incidence of symptomatic EAH was 3.15/ 1000 entrants (2000 Houston marathon) [41], and 0.94/ 1000 starters (2000 Pittsburgh marathon) [127].

The largest retrospective cohort to date, evaluated 2135 athletes in 8 different endurance events (including marathons, Ironman triathlons and 109 km cycle races). The overall incidence of symptomatic EAH was reported as 17/ 1000 participants [80]. A summary of the incidence of symptomatic EAH in five events is depicted in table 2.9.

**Table 2.9.: The incidence of symptomatic EAH in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants<sup>abcd</sup> (IR) and absolute risk (AR) of number of participants<sup>abcd</sup>/1 incident)**

Event and study reference	Type	N	Km	IR	AR	Strengths	Limitations	Level of evidence [32]
London, UK, 2003[126]	Observational case series	32 563 <sup>b</sup>	42.2	0.43 <sup>b</sup>	2326 <sup>b</sup>	<ul style="list-style-type: none"> <li>Detailed case data</li> </ul>	<ul style="list-style-type: none"> <li>Case-series</li> </ul>	4
San Diego, USA, 1998,1999 [97]	Retrospective cohort	35 572 <sup>c</sup>	42.2	0.73 <sup>c</sup>	1 370 <sup>c</sup>	<ul style="list-style-type: none"> <li>Largest cohort</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> <li>1998 data -14 EDs vs 1999 data one ED (prospective design)</li> </ul>	1b
Houston, USA, 2000[41]	Retrospective case-controlled	6660 <sup>d</sup>	42.2	3.15 <sup>d</sup>	318 <sup>d</sup>	<ul style="list-style-type: none"> <li>Rapid measurement of [Na]</li> <li>Good clinical records</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> </ul>	4
Different endurance events [80]	Retrospective cohort	2135 <sup>c</sup>	different endurance events	17 <sup>c</sup>	59 <sup>c</sup>	<ul style="list-style-type: none"> <li>Novel study</li> <li>All participants [Na] tested pre and post-race</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design, cannot be 100% sure all cases correctly diagnosed</li> <li>Included 'other' endurance races data</li> </ul>	2b
Pittsburgh, USA, 2000[127]	Prospective cohort	3200 <sup>a</sup>	42.2	0.94 <sup>a</sup>	1 063 <sup>a</sup>	<ul style="list-style-type: none"> <li>Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>Marathon on hot, humid day -representative?</li> <li>Runners transported from race course may have been missed</li> </ul>	1b

Type: Type of study

N: Number of participants

Km: Race distance

IR: Incidence rate of symptomatic EAH (rate/1000 participants<sup>abcd</sup>)

AR: Absolute risk - no. of race participants<sup>abcd</sup>/single incident) <sup>a</sup>: per starters <sup>b</sup>: per finishers <sup>c</sup>: per participants <sup>d</sup>: per entrants

## **Summary**

In summary, the overall incidence of asymptomatic EAH in endurance events has been documented as up to 510/1000 participants and in marathons specifically the incidence has been reported up to 280/1000 of runners. The incidence of symptomatic EAH in marathon runners is much lower at < 5/1000 participants, and is more common in other endurance events (up to 17/ 1000 participants in all endurance events). Notably, deaths due to EAH have been reported in the literature. The progression of asymptomatic to symptomatic cases of EAH is unknown and further studies are recommended to establish the true incidence.

## **Incidence of other less common serum electrolyte disorders in distance running**

To date most studies have focused on hyponatraemia, but there are other, less common, but potentially serious electrolyte disorders in distance running events. These include disturbances of the serum electrolyte concentration of magnesium, calcium, potassium and phosphate. The incidence of these less common serum electrolyte disorders associated with distance running events will be briefly reviewed.

### Magnesium disorders in distance running events

There are a number of cross-sectional, retrospective and prospective studies in distance running events that showed significant reductions in post-race serum magnesium concentration [ $\text{Mg}^{2+}$ ]. However, these reductions were of no clinical relevance [121, 128-132] and there are no reporting a direct relationship between changes in serum [ $\text{Mg}^{2+}$ ] and clinical symptoms in distance runners.

### Calcium disorders in distance running events

Post-race serum calcium concentrations [ $\text{Ca}^{2+}$ ] in distance running events have been studied. Post-race serum [ $\text{Ca}^{2+}$ ] vary and some prospective cohort studies in marathons and ultra-marathons reported hypocalcaemia [132-134], while other report no changes [135] or hypercalcaemia [136]. However, in none of these studies changes in serum [ $\text{Ca}^{2+}$ ] were of clinical relevance. In one retrospective study in the Boston marathon hypocalcaemia was

reported in collapsed runners with an incidence of 510/1000 [130]. It is not clear from this study, whether runners also had other associated electrolyte abnormalities i.e. combinations of electrolyte abnormalities were not documented.

#### Potassium disorders in distance running events

There are few data on changes in serum potassium concentrations [ $K^+$ ] in distance running events. Both hypokalaemia and hyperkalaemia are reported. In an observational cross-sectional study, the incidence of hypokalaemia was 5/1000 [137]. All cases were asymptomatic.

A review of the literature indicated that in most studies, [ $K^+$ ] tended to rise after distance running [121, 128, 138-142], whereas in other studies no change in [ $K^+$ ] were documented [83, 143]. None of the studies reported symptoms in any of the hyperkalaemic athletes.

Significant hyperkalaemia is a serious/life-threatening electrolyte disorder, but fortunately is rare. Hyperkalaemia above concentrations of 5.5 mmol/L can result in cardiac conduction disturbances, which can lead to cardiac arrest and death [144]. Earlier studies proposed that hyperkalaemia may indeed be the cause of unexplained cases of sudden cardiac death [145]. The precise incidence of hyperkalaemia resulting in cardiac associated medical encounters during distance running is unknown and further prospective studies are required.

#### Phosphate disorders in distance running events

Hypophosphataemia in endurance runners has rarely been described. Data on symptomatic hypophosphataemia are limited to a few case studies [146, 147] and a prospective cohort study [148]. In these cases, hypophosphataemia was often associated with EHS [147, 148], but the clinical relevance of hypophosphataemia in EHS is not known.

#### **Summary: other serum electrolyte disorders in distance running**

The majority of studies show that serum [ $Mg^{2+}$ ], [ $Ca^{2+}$ ], [ $K^+$ ] and [ $PO_4^{3-}$ ] may change immediately after distance running, but that these changes were small, mostly transitory and not of major clinical significance. These changes may be theoretically associated with certain

cardiac conduction disorders such as ventricular tachycardia and fibrillation when associated with other abnormalities. Furthermore, the role of hyperkalaemia in the pathogenesis of cardiac incidents during marathon running should be further elucidated.

## **2.5.2. Incidence of medical encounters in the cardiovascular system**

There are numerous cardiovascular conditions that can occur in runners in distance running events. These include conditions such as SCA, SCD (section 2.4.1.), arrhythmias, myocarditis, pericarditis and exercise-associated collapse (EAC). A further detailed discussion of all these conditions is beyond the scope of this dissertation and therefore the focus of the next section will be on the more common encounter, EAC.

### **2.5.2.1. *Exercise-Associated Collapse / Exercise-Associated Postural Hypotension***

The most common medical encounter in endurance running events is a clinical syndrome whereby a runner develops dizziness, feels faint or has syncope immediately after completion of a race. Typically, the runner develops these symptoms after the finish line and remains conscious.

#### Definitions

A number of clinical diagnostic terms have been used to describe this clinical syndrome. These include Exercise-Associated Collapse (EAC), Exercise-Associated Postural Hypotension (EAPH), and Orthostatic Intolerance (OI). In recent years, there has been some consensus and these terms have been defined as follows:

#### Exercise - Associated Collapse (EAC)

EAC is defined as “*collapse in an athlete who is conscious, but unable to stand/walk unaided as a result of dizziness, light-headedness or syncope causing a collapse that occurs after the completion of a bout of exercise or upon stopping exercise*” [149, 150]. It is considered a less serious medical complication of distance runners, because it is self-limiting and can be managed utilising the correct treatment protocols, which comprise positioning the runner in the Trendelenburg position and providing oral hydration [151]. It is important to note that

EAC should be differentiated from other potential serious causes of collapse, such as EHS, cardiac complications, serum electrolyte disorders and hypoglycaemia.

#### Exercise - Associated Postural Hypotension (EAPH)

EAPH is defined as “*a post-exercise drop in the systolic blood pressure (SBP) of at least 20 mmHg less than the supine values on assuming an upright position*” [150, 152]. It is important to note that EAPH can also be asymptomatic.

#### Orthostatic intolerance (OI)

Orthostatic intolerance (OI) is defined as “*a sustained reduction of SBP by at least 20 mmHg or diastolic blood pressure (DBP) of 10 mmHg within three minutes of standing or head-up tilt to at least 60 degrees on a tilt table*” [153].

EAC, EAPH and OI have all been associated with the clinical syndrome of post-exercise syncope or pre-syncope. However, EAC and EAPH are differentiated from OI, as these conditions are specifically associated with exercise. Furthermore, EAPH is differentiated from EAC in that it is used only when the actual blood pressures have been measured in both the supine and upright position and therefore fulfil the criteria of EAPH as described above.

In most epidemiological studies conducted in runners presenting with the clinical syndrome, supine and upright SBP were not measured routinely [21, 154, 155] and in other studies where both supine and upright SBP were measured, not all the runners were symptomatic [152, 156]. The focus of this section is on the incidence of medical encounters and hence only symptomatic runners were studied. Therefore, for the purposes of this section, and the dissertation, EAC will be the preferred term as it is the term that describes the clinical syndrome.

#### Pathophysiology of EAC

The pathophysiology of EAC is multifactorial and has been widely debated [157]. A detailed discussion of the pathophysiology of EAC is beyond the scope of this dissertation, but it is proposed that EAC is the result of transient postural hypotension, due to lower limb blood

pooling after completing exercise with added impairment of cardiac baroreflexes[150, 155, 158]. Therefore, EAPH is the likely mechanism that causes EAC in most of these runners.

#### Incidence of asymptomatic EAPH in distance running events

Although asymptomatic EAPH is not the focus of this dissertation, there are epidemiological data showing that asymptomatic post-exercise EAPH is very common in distance runners [152, 159, 160]. For example, in one cross-sectional study, in which the incidence of asymptomatic EAPH was investigated, a decrease in systolic blood pressure of  $\geq 20$ mmHg from supine to the upright position was documented in a group of 31 runners pre- and post an 80 km footrace. The results of this study showed that incidence of asymptomatic EAPH was 70/ 1000 runners pre -race and 680/ 1000 runners post-race [152]. As these were all asymptomatic, these data can therefore not be compared to those studies documenting EAC. However, the results do indicate that post-exercise decreases in systolic blood pressure in distance runners are very common.

#### Incidence of Exercise-Associated Collapse in distance running events

It has been reported in a number of case series and cross-sectional studies that the frequency of EAC (as a percentage of all medical encounters presenting to the medical facilities at the race) varies between 16-85% [21] [42, 152]. One of the first studies conducted was a retrospective cohort study during the 1998 New Zealand Ironman triathlon. In this study the frequency of EAC was 27% and the incidence of EAC was 49/1000 starters [161].

These figures are somewhat higher than those reported in another retrospective cohort study documented the medical encounters over a 6-year period at the Army Ten Miler (16.1 km) race. Of the 311 documented medical encounters, the frequency of EAC was 16.1%, with an incidence of 0.68/ 1000 race finishers [42]. In this study, EAC was the second most common medical complication after musculoskeletal conditions.

The true incidence of EAC in distance runners has, to our knowledge, only been documented in one large prospective cohort study on runners participating in the Twin Cities Marathon, USA over a 12-year period [21]. The incidence of EAC was 12.5 per 1000 race starters and the frequency of EAC (as a % of all medical encounters) was 59% [21].

## **Summary**

In summary, EAC is the most common illness-related medical encounter in distance runners and accounts for between 16-85% of all medical encounters in distance runners participating in a race. To our knowledge, there is only one prospective cohort study where the true incidence of EAC has been reported (12.5/ 1000 race starters). There is therefore a need for more accurate information regarding the true incidence of EAC in distance runners. It is suggested that well-conducted prospective cohort studies are required to determine the incidence and risk factors associated with this common medical encounter in distance runners.

### **2.5.3. Incidence of medical encounters in the respiratory system**

Respiratory conditions such as respiratory tract infections, asthma, exercise-induced bronchospasm (EIB), airway hyper responsiveness, respiratory allergies, vocal cord dysfunction, rhinitis, pulmonary oedema (of non-cardiac origin) and other respiratory medical encounters can occur in runners in distance running events. A comprehensive review of the literature revealed there are few data that accurately depict the incidence of these respiratory medical encounters in runners during events.

#### **2.5.3.1. *Incidence of all respiratory encounters in distance running events***

In one study, over a 12-year period the incidence of respiratory encounters was reported as 2.5/ 100 000 race entrants [21]. To our knowledge, there are no other studies that accurately reported all respiratory tract medical encounters during a race, therefore a true incidence rate of these encounters is not known.

### **2.5.3.2. *Incidence of asthma (acute exacerbation) in distance running events***

Asthma is one of the most common chronic respiratory conditions in athletes [162, 163]. Furthermore, it is well known that the prevalence of asthma is higher in distance runners than the general population [163]. Asthma may be therefore exacerbated on race-day [164].

In a single retrospective cohort study on runners participating in The Army Ten Miler, Washington, USA, the incidence of asthma was 0.04/ 1000 starters [42]. A limitation of this study may be that EIB presents similar to acute asthma, and some of these diagnosed cases may have been EIB.

EIB is a transient obstruction to airflow occurring five to 15 minutes after the onset of exercise, and peaking at about 10 minutes after exercise which typically lasts for 30 to 60 minutes [165]. This condition may occur in certain healthy individuals, only in the setting of exercise, and in the absence of any underlying asthma or other allergic disorders. EIB has a prevalence of 10 -15% [165]. This incidence is higher in elite athlete studies where the prevalence ranges from 10% to 50% [166]. It is postulated that continuous high intensity exercise including distance running, is more likely to cause EIB [167].

In summary, there are very limited data on the incidence of asthma and EIB in distance running events, and further research to determine the incidence of acute exacerbations of asthma or EIB is required.

### **2.5.3.3. *Incidence of immediate post-race respiratory tract infections in distance running events***

It is well known that respiratory infections commonly occur in distance runners both pre- and post-race [168-171]. The hypothesis that athletes are more susceptible to respiratory tract infections was first introduced in 1928 [172]. There are some studies that have documented the incidence of upper respiratory tract infections (URTI), upper respiratory tract (URT) symptoms in distance runners [163, 173, 174] in the period up to 14 days after a race. Most of these studies did not document the incidence of URTI during or immediately following the race. There are no data on the incidence of immediate post-race respiratory tract

infections in distance runners. A detailed discussion of the epidemiology of post-race UTRI in distance runners in the one to 14 day period after a race is beyond the scope of this dissertation.

#### **2.5.3.4. *Incidence of other acute respiratory conditions in distance running events***

##### Exercise-induced non-cardiogenic pulmonary oedema

In general, pulmonary oedema can result from either cardiogenic [175] or non-cardiogenic causes. Exercise-induced non-cardiogenic pulmonary oedema is a very rare but potential serious/ life-threatening condition in distance running events. The exact incidence of this condition in distance running is unknown, but there are some case reports describing this condition [28, 106].

Exercise-induced non-cardiogenic pulmonary oedema can be associated with severe concomitant hyponatraemia [106, 108, 117]. However, in these cases the primary diagnosis will be recorded as hyponatraemia (see section 2.5.1.3 of this dissertation).

##### Exercise-induced anaphylaxis

Although very rare, this condition is mentioned as it is also a potential cause of a life-threatening medical complication in distance running, as it can result in respiratory or vascular collapse [176, 177]. This condition is a physical urticarial reaction associated with athletic activity. The incidence of exercise-induced anaphylaxis in distance running events is not known.

### **Summary**

In summary, there is a paucity of accurate data on incidence of race day respiratory tract medical encounters, thus the epidemiology of respiratory medical encounters at running events requires further investigation.

#### **2.5.4. Incidence of medical encounters in the central nervous system**

In the 2019 consensus of reporting medical encounters, a number of conditions are classified as medical encounters relate to the central nervous system (CNS). These include exercise-associated muscle cramping (EAMC), dizziness/nausea, coma, confusion, strokes, epilepsy, headaches and other neurological problems. Of these conditions, EAMC is the most common CNS-related medical encounter. EAMC is defined as an involuntary, painful contraction of skeletal muscle during or immediately after exercise [178-180]. EAMC typically presents as a painful localized muscle cramp that can occur spasmodically in various muscle groups, of which the calf, hamstring and quadriceps are most commonly involved [181-183].

##### **2.5.4.1. *Exercise-associated muscle cramps***

Muscle cramping associated with physical activity was first reported in steamship and mine workers [184]. Muscle cramps are common in the general population and can present at rest, following strong sustained voluntary contraction, and during sport, sleep and pregnancy [185-188]. There are many causes of muscle cramps including use of certain medications and several pathologies and diseases such as myopathies, neuropathies, motor neuron diseases, metabolic disorders, hydro-electrolyte disorders, endocrine disorders and, inherited metabolic abnormalities [180, 189]. Exercise-associated muscle cramps (EAMC) has been reported in various different sports such as running, triathlon, swimming, cycling, soccer and tennis [135, 185, 190-192].

A detailed review of the aetiology and pathophysiology of EAMC is beyond the scope of this dissertation and has recently been reviewed [178, 183, 193-196]. Previously it was hypothesized that electrolyte derangements and dehydration were the causes of EAMC, but these data have not been supported by prospective studies [135], experimental design studies [197] and other studies [198, 199]. New evidence shows that EAMC is likely multifactorial and not a single disease entity. There is a common pathophysiological process, that is characterize by an imbalance between the excitatory drive from the muscle spindles and the inhibitory drive from the Golgi tendon organs to the alpha motor neurons [194]. The pathophysiology of EAMC is thought to be at the level of the spinal cord in the central nervous system [183], hence the classification of EAMC as a CNS disorder.

## **Incidence of EAMC in distance running events**

The incidence of EAMC in distance runners during a race is not well documented. Of note, is that the severity of EAMC can differ. In some instances, EAMC will be severe enough for the runners to present to the medical facility seeking medical attention, while in other cases, mild EAMC could occur in runners but they did not seek medical help. In various retrospective and prospective studies, the incidence of EAMC has been reported [21 {Pasquina, 2013 #262, 34, 40, 42, 200-202} (Table 2.10.).

Of note is that there are numerous cohort studies, including a meta-analysis that documented the incidence of medical encounters. However, EAMC were either classified under the musculoskeletal (MSK) section or not documented at all and therefore were not included in this section [36] [35, 43, 203]. The reasons for not documenting EAMC in these studies are unclear, and it may be that they were also classified under the MSK section or seen as a minor medical complication and not documented.

**Table 2.10.: 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<sup>abc</sup> (IR) and absolute risk (AR) of number of participants<sup>abc</sup>/1 incident)**

Event and study reference	Type	N	Km	IR	AR	Strengths	Limitations	Level of evidence [32]
Sydney City-to-Surf fun run, Australia (1976-1979) [40]	Retrospective cohort	54 250 <sup>a</sup>	14	0.54 <sup>a</sup>	1 852	<ul style="list-style-type: none"> <li>• Race starters used as denominator</li> <li>• First study</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Shorter race distance</li> </ul>	2b
Army 10 miler, USA (1998-2004) [42]	Retrospective cohort	91 750 <sup>a</sup>	16	0.11 <sup>a</sup>	9 090	<ul style="list-style-type: none"> <li>• Large cohort</li> <li>• Study period over six years</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Shorter distance</li> </ul>	2b
Chicago Marathon, USA (2012-2016) [34]	Retrospective cohort	202 603 <sup>b</sup>	42.2	7.84 <sup>b</sup>	128	<ul style="list-style-type: none"> <li>• Largest cohort</li> <li>• Digital data collection</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Data collection errors</li> <li>• Missing transport data</li> </ul>	2b
Auckland Citibank Marathon, New Zealand (1993) [200]	Prospective cohort	1219 <sup>a</sup>	42.2	12.31 <sup>a</sup>	81	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Detailed data collection</li> </ul>	<ul style="list-style-type: none"> <li>• Single event</li> </ul>	1b
Tsing Ma Bridge International (1997) Marathon, Hong Kong [202]	Prospective cohort	5 500 <sup>c</sup>	42.2 10	1.64 <sup>c</sup>	610	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Single event</li> <li>• Physiotherapy EAMC data</li> <li>• Race run in heavy rain</li> </ul>	1b
Twin Cities Marathon, USA (1983-1994) [21]	Prospective cohort	69 043 <sup>a</sup>	42.2	1.30 <sup>a</sup>	775	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Study over longest period</li> </ul>	<ul style="list-style-type: none"> <li>• Possible underreporting</li> </ul>	1b
Splash 105.5FM/ICPC Marathon, Nigeria (2009-2010) [201]	Prospective cohort	920 <sup>b</sup>	42.2	70 <sup>b</sup>	14.3	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Small number of participants</li> <li>• Data included physiotherapy data (inflating IR)</li> </ul>	1b

Type: Type of study

N: Number of participants

Km: Race distance

IR: Incidence rate of EAMC (rate/100 000<sup>abc</sup>)

AR: Absolute risk - no. of race participants<sup>abc</sup>/single incident)

<sup>a</sup>: per starters <sup>b</sup>: per participants <sup>c</sup>: per entrants

The incidence of EAMC in marathons was documented between 1.3 to 70/ 1000 participants and in shorter races between 0.11 to 0.54/ 1000 participants. A retrospective cohort study of the 14 km Sydney City-to-Surf race in the 1970's was one of the first studies in which the incidence of EAMC in distance running was reported (previously described section 2.3.3.). The incidence of EAMC was 0.54/ 1000 starters [40]. Following this, the incidence of EAMC in retrospective studies was between 0.11 – 7.84/ 1000 participants [34, 42]. In prospective studies, the incidence of EAMC was documented between 1.30 – 70/ 1000 participants [21, 200-202].

In one of the largest prospective cohort studies to date, the incidence of EAMC in distance runners in the Twin Cities marathon, USA (n=69 043). In this study the incidence of EAMC was 1.3/ 1000 starters [21].

## **Summary**

In summary, there is a wide range of reported incidence rates for EAMC from 0.11 to 70/ 1000 participants. This wide range may be attributable to factors such as race distance, use of different diagnostic criteria, differing environmental conditions and whether the runners presented to the medical facilities with more serious EAMC and if the data also included the data on minor medical encounters. Future well-designed prospective cohort studies are required, particularly where the definition of EAMC is standardized and documented. Specifically, in such studies, more serious EAMC needing medical attention should be distinguished from less serious EAMC that do not require medical attention.

### **2.5.5. Incidence of medical encounters in the gastrointestinal system**

Gastrointestinal tract (GIT) physiology can be affected by distance running. It is well established that blood flow to the gut is reduced by as much as 80% during maximal exercise, regardless of the state of physical training [204]. The decrease in blood flow to the GIT system during exercise occurs as a result of physiological shunting due to splanchnic vasoconstriction. In addition, prolonged running can result in intestinal damage and increased intestinal permeability [205]. Both reduced blood flow and increased permeability to the GIT during exercise can occur, yet remain asymptomatic or compromise GIT function and lead to

GIT symptoms. Indeed, GIT symptoms and medical encounters are amongst the most common encounters reported in distance runners.

Symptomatic GIT medical encounters can be classified into less serious encounters such as nausea/vomiting, non-specific abdominal pain, gastro-intestinal infection, gastritis and diarrhoea or serious/life threatening medical encounters such as ischaemic colitis[206].

The most common GIT medical complication in distance runners is asymptomatic occult GIT bleeding. The proposed aetiology for GIT bleeding is mesenteric ischaemia and mechanical trauma to the GIT organs by repetitive impact during running [207, 208]. Studies to determine the precise incidence of occult GIT bleeding include case studies [209-211], retrospective cohort studies [212] and prospective cohort studies [213-215]. The incidence of occult GIT bleeding has been reported between 80 - 850/ 1000 runners in these studies.

The most common GIT symptoms in distance runners are bloating, regurgitation, abdominal cramps, side ache, nausea, vomiting, diarrhoea, urge to have a bowel movement and faecal incontinence [215-217]. In a recent cross-sectional study, runners participating in both the Liverpool (n=66) and Dublin (n=30) marathons completed an on-line questionnaire. Of these runners, 270/ 1000 participants reported GIT symptoms. The limitation to this study was the low response rate of 0.5% (n=96) [218]. A further limitation to this study may be potential selection bias.

A retrospective cohort study was conducted on 272 (71% of race entrants) of the ultra-marathon runners participating in the 161 km Western States Endurance run. A post-race questionnaire showed that 960/ 1000 runners reported GIT medical encounters [219].

Finally, to our knowledge, one of the largest studies on the incidence of GIT medical complaints was a retrospective cohort study that was conducted on distance runners (between 10 km – 42.2 km) in the Enschede Marathon in the Netherlands. An online questionnaire was sent out to all the participants post-race with a response rate of 62% (n=1281). Of these, 450/ 1000 race participants reported GIT medical encounters during the run [212].

In summary, to our knowledge there are no studies accurately documenting the incidence of GIT medical encounters, as most of the data have been based on post-race questionnaires, not

necessarily presented to the medical facilities. The incidence of the less serious symptomatic GIT encounters in distance runners is therefore high in these studies reviewed and documented between 270 to 960/ 1000 participants. Further well-designed prospective cohort studies are required to further understand the true incidence and nature of GIT encounters presenting to medical facilities.

As previously mentioned, whilst the majority of GIT medical encounters are not serious, some case studies of serious/ life-threatening encounters have been documented [206, 220, 221]. These have been classified into the following four major syndromes:

1. Acute mesenterial infarction – most serious and results from inadequate blood flow to the small intestine and right colon.
2. Chronic arterial or mesenteric ischemia
3. Mesenteric venous thrombosis
4. Colonic ischaemia – this is the most common form of intestinal ischaemia. The clinical presentation can range from reversible haemorrhagic colitis to stricture, gangrene and fulminant colitis.

The precise incidence of these four major syndromes is not known as only rare case reports have been documented in marathon runners in only the Boston marathon [210] [209, 211] and a few other marathons [221, 222].

GIT ischemia or ischemic bowel disease may be superimposed on dehydration, hyperthermia and exhaustion. Functional derangements result in symptoms such as nausea, vomiting, abdominal pain and (bloody) diarrhoea [223]. If the ischemia is severe enough, the damage becomes irreversible and variable degrees of necrosis will ensue. Post-exercise symptoms such as collapse, shivering, nausea and vomiting may be related to reperfusion damage and endotoxemia, a late result of GIT ischaemia [223].

GIT medical encounters are of the most common encounters in distance runners. Most symptomatic GIT medical encounters are not serious or life threatening. However, distance running can be associated with a significant increase in the risk of GIT bleeding. Whilst this is not symptomatic in most cases, individual case reports of

ischaemic colitis resulting in rectal bleeding have been reported. Risk factors associated with GIT medical encounters should be determined and these will be discussed in chapter four of this dissertation.

## **2.5.6. Incidence of medical encounters in the genitourinary system**

Distance running has been associated with some medical encounters that primarily affect the genitourinary system. These encounters include both less serious encounters (athletic ‘pseudonephritis’, haematuria and genitourinary infections), as well as serious/life-threatening encounters (acute kidney injury, renal artery dissection) [30, 224] [29, 31, 68, 225, 226]. To our knowledge, there are no accurate incidence data on the incidence of genitourinary infections in distance running events. Therefore, in this section, the main focus will be on the more serious/life-threatening renal (kidney) medical encounters (acute kidney injury/acute renal failure). Athletic ‘pseudonephritis’, haematuria and renal artery dissection will also be introduced firstly.

### **2.5.6.1. *Athletic pseudonephritis in distance running events***

To our knowledge, the first documentation of renal complications during prolonged distance running was documented in the 18<sup>th</sup> century [227].

In an observational study in 1899, the presence of albumin in the urine was analysed in the 17 runners participating in the Boston marathon. In this case series, albumin was present in the urine of 6/ 17 runners after the race (353/ 1000 runners). However, as these runners were asymptomatic, this phenomenon was termed ‘athletic *pseudonephritis*’ [228]. In 1902, the phenomenon of ‘athletic *pseudonephritis*’ was again reported in Boston marathon runners by analysing pre- and post-race urinary albumin [229]. Numerous further studies followed documenting proteinuria in distance runners with an incidence of up to 353/ 1000 participants [224, 230, 231]. These were asymptomatic.

### **2.5.6.2. *Haematuria in distance running events***

Influenced by war effort studies, “march hemoglobinuria” was studied in 1941 on Harvard freshman in distances ranging from 2.6 to 26.2 miles [232]. A raised plasma haemoglobin

concentration was found in 18 of the 22 marathon runners, of which four of the subjects also showed hemoglobinuria. The largest degree of hemoglobinuria was found following the marathon, when compared to the shorter distances.

In 1978 the first of many studies on different organ systems, were commenced on a group of runners of the American Medical Joggers Association (AMJA), later called the AMAA (American Medical Athletic Association) [233]. In one prospective cohort study in the 1978 Boston marathon, the urine of 50 runners was analysed before and two hours after the race, as well as for three successive days following the race. The incidence of gross haematuria was 1 in 50 (20/ 1000 runners), while 8/50 runners (160/ 1000 runners) developed microscopic haematuria after the race. Numerous studies followed documenting the incidence of haematuria in distance runners of up to 310/ 1000 participants [224, 234, 235]. The majority of cases of post-race haematuria were self-limiting and mostly asymptomatic.

#### **2.5.6.3. *Renal artery dissection***

Renal artery dissection as a potential serious/ life-threatening medical complication in distance runners is very rare, and to our knowledge only a single case has been described in the literature [30]. The precise incidence is therefore not known. Other cases of renal artery dissection have been described in other sports [236, 237].

#### **2.5.6.4. *Incidence of Acute Kidney Injury / Acute Renal Failure during or after distance running events***

Acute kidney injury (AKI), formerly known as acute renal failure (ARF) [238], is a syndrome that is characterized by the rapid loss of the kidney's excretory function and is typically diagnosed by the accumulation of end products of nitrogen metabolism (urea and creatinine), decreased urine output, or both [239]. The definition has evolved much since 2004 and the recent definition from the international Kidney Disease Improving Global Outcomes guidelines merged the definitions of Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) [239]. In this section, the term Acute Kidney Injury (AKI) will be used, even where the terminology ARF was used in a study.

The first cases of AKI (ARF) associated with distance running were reported in 1969 [240]. However, in the period from 1958 to 1965, AKI due to “heat injury” was documented on military recruits during basic exercise [241]. In subsequent years, a number of studies have documented that AKI can occur in distance runners [226, 242, 243] [72, 244-246] [29, 31, 68, 225, 247-249].

However, it is important to note that AKI is often present immediately after a race [248], but may remain asymptomatic or have a delayed presentation. Furthermore, the majority of AKI in distance runners resolve spontaneously, although it has the potential to progress and result in hospitalization and poorer outcomes. It is important to note that the biomarkers used to diagnose AKI mostly normalise after a few days [250]. The significance and long-term effect of the elevation of the biomarkers is not known.

The incidence of AKI during any sporting event is estimated at 20/ 1000 participants [251]. It is important to note that these incident values are meeting the diagnostic criteria for AKI rather than actually having or being treated for AKI. However, in distance running AKI is mainly reported in case control studies or case series [31, 68, 225, 226]. The incidence of AKI in distance running is reported between 0.24 [31] to 7.5/ 1000 participants [68].

There are limited data regarding the precise incidence of renal medical encounters during exercise. The available data indicate an estimated incidence (per 1000 runners) of renal encounters as follows: asymptomatic race proteinuria (353), asymptomatic post-race microscopic haematuria (310), post-race macroscopic haematuria (20) and AKI (between 0.24 and 7.5) [31, 224, 225, 234, 235, 248] . Of note is that the AKI data was documented pre-consensus on definition terminology and criteria. However, following this, more recent data from prospective cohort studies of AKI showed incidence rates immediately post- race (between 521 and 846) [252-255] .

In summary, there is a need to document the precise incidence of renal medical encounters during distance running events using standardized diagnostic criteria in larger prospective cohort studies with longer follow-up periods. There is minimal information that show no proof that prior AKI resulted in a greater dysfunction in subsequent endurance events [256]. Further evidence of long-term delirious effects of the transient development of AKI is lacking

and risk factors need to be identified so that preventative strategies can be implemented to reduce the risk of renal medical encounters in distance runners (Chapter 4).

### **2.5.7. Incidence of medical encounters in the dermatological system**

Disorders pertaining to the dermatological system are common medical encounters in distance running. The frequency of dermatological medical encounters range from 3.4% to 32.9% of the total medical encounters after races [21, 34, 38, 42, 43, 200] [35, 36]. In multiday ultra-marathon events, where there is increased exposure time and distance, dermatological medical encounters are very common and account for 74.3% of all medical encounters [257] while the frequency is less in shorter races, such as 10 km races, with shorter exposure times (3.4% of all medical encounters) [43]. In a number studies in distance runners, the dermatological system is the second most common system affected, after the musculoskeletal system [37, 38, 42] or exercise-associated collapse (EAC) [21].

The most common dermatological medical encounters are blisters, chafing and abrasions, with blisters being the most common specific condition [258].

The incidence of dermatological encounters in distance running events is well documented in a number of observational-, cross sectional, retrospective and prospective cohort studies. The incidence of dermatological medical encounters in distance running events varies between 0.22 to 9.57/ 1000 participants [21, 38, 40, 42, 43]. Blisters are the most common of all the dermatological encounters, with an incidence of 0.02-3.9/ 1000 participants [259] (Table 2.11.).

**Table 2.11.: Incidence of dermatological encounters in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants<sup>abc</sup> (IR) and absolute risk (AR) of number of participants<sup>abc</sup>/1 incident)**

Event and study reference	Type	N	Km	IR	AR	Strengths	Limitations	Level of evidence [32]
Sydney City-to-Surf, Australia (1976-1979) [40]	Retrospective cohort	54 250 <sup>a</sup>	14	9.57 <sup>a</sup>	105	<ul style="list-style-type: none"> <li>• First study</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
Army ten-miler Washington DC, USA (1998-2004) [42]	Retrospective cohort	91 750 <sup>a</sup>	16	0.91 <sup>a</sup>	1099	<ul style="list-style-type: none"> <li>• Large cohort</li> <li>• Study period over six years</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Shorter distance</li> </ul>	2b
Singapore Army Half-marathon (2010-2012) [38]	Retrospective cohort	84 644 <sup>c</sup>	21.1 10	0.77 <sup>c</sup>	1299	<ul style="list-style-type: none"> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Race registrants used as denominator</li> <li>• Included trained military recruits, possible explaining lower incidence</li> </ul>	2b
10 km races, USA (2016-2017) [43]	Retrospective review	90 265 <sup>b</sup>	10	0.22 <sup>b</sup>	4545	<ul style="list-style-type: none"> <li>• Large cohort over two decades</li> <li>• Included 19 races</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Shorter distance</li> </ul>	2b

**Table 2.11.: Incidence of dermatological encounters in distance running events (by event and study reference, type of study, number of participants (n), race distance (km), incidence/1000 participants<sup>abc</sup> (IR) and absolute risk (AR) of number of participants<sup>abc</sup>/1 incident) (continued)**

Baltimore marathon Maryland, USA (2001) ([35])	Prospective cohort	11 000 <sup>a</sup>	42.2 5 four-person marathon team relay	2.64 <sup>a</sup>	379	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Smaller cohort</li> <li>• Single event</li> <li>• Three different races</li> </ul>	1b
Baltimore marathon Maryland, USA (2002-2005) [36]	Prospective cohort	33 700 <sup>c</sup>	42.2 21.1 5 four-person marathon team relay	6.80	147	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Four different races</li> <li>• Potential underreporting</li> </ul>	2b
Twin Cities Marathon Minnesota, USA (1983-1994) [21]	Prospective cohort study	69 043 <sup>a</sup>	42.2	4.58 <sup>a</sup>	218	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Study over longest period</li> </ul>	<ul style="list-style-type: none"> <li>•</li> </ul>	1b

Type: Type of study

N: Number of participants

Km: Race distance

IR: Incidence rate of serious/ life-threatening medical encounters (rate/ 100 000<sup>abc</sup>)

AR: Absolute risk - no. of race participants<sup>abc</sup>/single incident)

<sup>a</sup>: per starters <sup>b</sup>: per finishers <sup>c</sup>: per participants

In summary, dermatological medical encounters in running are very common and account for 3.4 - 74% of all medical encounters reported to the medical facilities. The incidence of dermatological medical encounters varies between 0.22 to 9.75/ 1000 participants. The wide range in the incidence may be explained by the fact that some of the races were of shorter distance, therefore decreasing the exposure time [42, 43] to develop skin conditions, where in other studies the relative higher incidence may be related to the fact that the same runners could have presented to more than one medical point during the run [40]

Future well-designed prospective cohort studies are required to accurately document the incidence of dermatological encounters of distance running events. These studies need to further investigate the effects of different race distances and environmental conditions on the incidence of dermatological encounters.

#### **2.5.8. Incidence of medical encounters in other organ systems**

In the 2019 consensus, medical encounters were classified by organ system and specific diagnosis (Table 2.2.) [8] and this classification was used in this review chapter. The incidence of the more common medical encounters, by organ system, were reviewed. Medical encounters in the following organ systems are very uncommon and have not been included in this review chapter because there are insufficient data: haematological system, ophthalmological system, dental illness, psychological / psychiatric conditions, tumours / malignancies, drug use / overdose and other medical illness such as the tired athlete with (non-specific) fatigue. Future studies should focus on determining the incidence of medical encounters during distance running in these organ systems.

## 2.6. SUMMARY: INCIDENCE OF ILLNESS-RELATED MEDICAL ENCOUNTERS IN DISTANCE RUNNERS

The incidence of medical encounters in distance running events varies widely and is summarised by severity (Table 2.12.) and main organ system (Table 2.13.)

**Table 2.12.: Summary of the incidence of SD, SCD, SCA and serious / life-threatening medical encounters in distance running events (by severity and incidence/100 000 participants)**

Severity	Incidence/100 000 participants
Sudden death (SD)	0.24 – 1.86
Sudden cardiac death (SCD)	0.24 – 1.86
Sudden cardiac arrest (SCA)	0.54 – 2.50
Serious/life-threatening	14 - 235

**Table 2.13.: Summary of the incidence of medical encounters in distance running events (by main organ system and specific illness type / diagnosis)**

Main organ system	Specific illness type / diagnosis	Incidence/1000 participants
Overall medical encounters	All medical encounters	2.3 - 45
Multiple organ system	Exertional heatstroke (EHS)	0.03 – 2.13
	Rhabdomyolysis	No data
	Dehydration	0.14 – 11
	Asymptomatic Exercise-Associated Hyponatraemia (EAH)	0-512
	Symptomatic Exercise-Associated Hyponatraemia (EAH)	0.30 – 3.15
Cardiovascular system	Exercise-Associated Collapse (EAC)	0.68 – 12.5
Respiratory system	All respiratory system medical encounters	2.5
	Asthma	0.04
Central nervous system	Exercise-Associated Muscle Cramps (EAMC)	0.14 – 12.90
Gastrointestinal system	All gastrointestinal medical encounters	270 – 960
Genitourinary system	Acute renal failure /acute kidney injury	0.24 – 7.5
Dermatological system	All dermatological medical encounters	0.22 – 9.57

The incidence of SD, SCD and SCA is well documented and is generally low. However, there are little data available in the literature on the incidence of other serious/life-threatening medical encounters (Table 2.14.), but it appears that these are much more common, when

compared to SD, SCD and SCA. Future studies need to focus on accurately determining the incidence of other serious/life-threatening medical encounters.

Although the incidence of medical encounters rates per organ system and diagnosis have been reported (Table 2.15.), there are wide variations in the definitions used and methods applied to study these. Future studies need to apply the definitions and methods of data recording and reporting on the international consensus statement [8] so data can be compared more accurately.

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## CHAPTER 3

### STUDY 1: MEDICAL COMPLICATIONS AND DEATHS IN 21 KM AND 56 KM ROAD RACE RUNNERS: A 4-YEAR PROSPECTIVE STUDY IN 65 865 RUNNERS - SAFER STUDY I

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#### 3.1. ABSTRACT

**Background:** Cardiac arrest and sudden death during distance running events have been reported but other medical complications, including serious/life-threatening complications have not been well described.

**Objective:** To document the incidence and nature of medical complications during 21 km and 56 km running races.

**Design:** Prospective study

**Setting:** Two Oceans marathon races (21 km and 56 km races)

**Participants:** 65 865 race starters (39 511 21 km runners, 26 354 56 km runners)

**Methods:** Medical complications (defined as any runner requiring assessment by a doctor at the race medical facility or a local hospital on race day) were recorded in each of the 4 years of the study period. Complications were further sub-divided into serious (potentially life threatening) complications and deaths and were also analysed by system and final diagnosis.

**Results:** In the 4 years, 545 medical complications were recorded, resulting in an overall incidence (per 1000 race starters) of 8.27. The incidence of serious (potentially life threatening) medical complications was 0.56 (37 serious complications). Two deaths occurred in 21 km runners (incidence of 0.05). The most common specific medical complications were exercise-associated collapse (postural hypotension), dermatological conditions, musculoskeletal injuries and serious Exercise-Associated Muscle Cramping (sEAMC).

**Conclusion:** The incidence of medical complications was higher in 56 km runners but sudden cardiac deaths only occurred in 21 km runners. Serious medical complications were as common in 21 km as in 56 km runners. Risk factors for medical complications need to be determined in 21 km and 56 km runners to plan strategies to reduce the risk of adverse medical events in endurance runners.

### 3.2. INTRODUCTION

Regular participation in physical activity is well established as an important lifestyle intervention for primary and secondary prevention of chronic non-communicable disease [1, 2]. In this regard, recreational distance running as a form of regular physical activity has become popular globally. However, it is well documented that vigorous physical activity, such as distance running, may be associated with medical complications that can affect a variety of organ systems [3]. Of particular interest is that vigorous exercise may act as a trigger for acute myocardial infarction and sudden death, both in younger and older runners [4]. There is considerable interest to determine the risk of sudden death during exercise, in particular in distance running events such as the half-marathon (21 km) and the marathon (42 km) [5-11]. This information is important as it may identify risk factors for sudden death during running, and therefore point to possible measures to prevent sudden death and other adverse medical events in endurance runners.

Whilst sudden cardiac death has enjoyed the focus of a number of clinical studies, the incidence of other medical complications during running, including non-cardiac but serious/life-threatening medical complications, has not been well studied. Data are limited to a few studies [12], mostly dating back to over 10 years ago [13-15].

In one of the most comprehensive studies in marathon runners, the 12 year injury and illness data were reported for over 80 000 race entrants [15]. The main finding of this study was that the incidence of medical encounters (complications per 1000 race entrants) was 18.9, and the most common medical complications were exercise-associated collapse (11.3) followed by dermatological complications (4.1) and musculoskeletal complications (3.4). The incidence of cardiac arrest and sudden death was 1.2 per 100 000 runners (1 in 83 333 runners) [15]. In only one other study, medical complications were reported in a cohort of 396 ultra-marathon runners participating in a 7-day staged (240km) event [16]. These data show a very high medical complication rate of 3871 per 1000 runners, mostly affecting the skin and the musculoskeletal system. However, these data cannot be compared to a single day community-based distance running event.

There are few data describing the incidence and risk factors for some specific non-cardiac serious medical complications including hyponatraemia [17-20], acute renal failure [21] [21] and heatstroke [20, 22, 23].

Therefore, apart from the data reported in the single study on marathon runners [15], a detailed analysis of the incidence and nature of all medical complications during 21 km and 56 km (ultra-marathon) running, particularly in other organ systems has not been reported in the literature. This information is important to reduce the risk of any adverse medical events (deaths, serious and less serious) in endurance runners, and to plan medical care of large community-based endurance running events.

The Two Oceans Marathon races comprise a number of mass community-based running events that take place annually during late summer in Cape Town, South Africa. These races, which attract about 25 000 runners every year, comprise a short (5-8 km) fun-run, two trail runs (10 km and 22 km), a half marathon (21 km), and an ultra-marathon (56 km). The two main events that attract the majority of endurance runners are the 21 km race and the 56 km race. Entries to the 21 km race are open to novice runners and require no qualifying time, while the entry for the 56 km race requires completion of any one of the following qualifying times: a standard 42 km marathon in < 5 hours, 50 km in < 6 ½ hours, 56 km in < 7 hours, 90 km in < 12 hours, or a 100 km race in < 13 ½ hours.

The aim of this study was to document the incidence and nature of medical complications during the Two Oceans races (21 km and 56 km). In addition, we wanted to record the incidence of medical complications in different organ systems and by racing distance (21 km vs. 56 km). This is the first of a series of studies that are aimed at reducing the risk of an adverse medical event in endurance runners: the **SAFER** (Strategies to reduce Adverse medical events For the Exercise**R**) studies [24].

### **3.3. METHODS**

#### **3.3.1. Type of study**

This was a prospective study over 4 years.

#### **3.3.2. Participants and demographics**

All the participants of the Two Oceans Marathon races (includes a 21 km half-marathon and a 56 km ultra-marathon) over a 4-year period (2008 to 2011) were considered as participants. Information regarding registrants, starters and finishers was obtained, with permission, from the race organizers. These data, which include age, gender, previous participation (and number of completed races) in the Two Oceans races, are in the public domain and are obtainable from the race website. Registrations for these races typically open 3-5 months prior to the races. For purposes of conducting research on this population, this registry of runners has been approved by the Research Ethics Committee of the University of Cape Town (REC R030/2013) and specific permission to investigate the incidence and nature of medical complications during endurance running in the Two Oceans races was obtained from the Research Ethics Committee of the University of Cape Town (REC 009/2011).

During the 4-year study period, a total of 81 345 runners registered for the races. Of the total registrants, 65 865 runners started the races (81.1% of registrations), and only these runners were participants in this study. Whilst there is no upper age limit, entrants are required to be 16 years or older for the 21 km race and 20 years or older for the 56 km race. The demographics [by year of participation and gender] of all the race starters in the 4-year study period are depicted in Table 3.1. Our study cohort therefore consisted of 41 026 male starters and 24 839 female starters of the races. The starting times of the 21 km was staggered between 05h50-06h20 and the starting time for the 56 km was 06h40.

**Table 3.1.: Demographics of all race starters (by gender and year of participation)**

<b>Gender</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>2011</b>	<b>All runners</b>
<b>Males</b>	10142	10596	10708	9580	41026
<b>Females</b>	5600	6248	6650	6341	24839

### **3.3.3. Medical data collection (classification, medical complications, hospital admissions, deaths)**

A medical team, responsible for medical care on race day, is assembled 6-8 months prior to race day to prepare and plan for medical care on race day. Medical facilities on race day consisted of on-route medical stations, and a physical therapy and a medical facility at the finish. All runners with medical complications during or after the race underwent a triage by emergency medical staff and were then admitted for full assessment and management at either the medical or physiotherapy facilities. Runners with serious or life-threatening medical complications that occurred on route during the race were attended to by emergency response teams and these runners were immediately transported to the nearest local hospital if required. Emergency medical staff attended to serious/life threatening medical complications that occurred at the end of the race in the medical facility at the end of the race and these runners were then transported to local hospitals if required.

For the purposes of this study, a runner with a medical complication was defined as “any runner who required medical care on race day that was severe enough to warrant a medical assessment by a doctor, either in the medical facility at the end of the race, on route at the medical stations, or at one of the referral hospitals (for runners that were assessed by medical staff on the route)”. This definition is similar to that reported in one previous study [15], with the exception that minor medical encounters (not requiring an assessment by a medical doctor) were not included in our study. Examples of such encounters would be runners seeking assistance at first aid stations along the route, and admissions to the physical therapy section of the medical facility at the end of the race. Furthermore, not all runners with Exercise-Associated Muscle Cramps (EAMC) were included in the present study – only those with EAMC that required an assessment by a medical doctor because of EAMC together with associated symptoms (confusion, dizziness, nausea and vomiting, diffuse cramping or collapse). In this study, this group will be referred to as serious EAMC (sEAMC).

A serious/life-threatening complication was defined as “a medical complication that could result in death unless urgently diagnosed and treated”. The following serious medical complications (by organ system) were included in the study: cardiovascular (ischaemic heart disease, arrhythmias, myocarditis), renal (acute renal failure), fluid, electrolyte and acid base abnormalities (symptomatic hyponatraemia, metabolic acidosis, severe dehydration),

metabolic abnormalities (hypoglycaemic coma, diabetic coma), respiratory (severe asthma, pulmonary oedema), thermoregulatory abnormalities (heatstroke), and central nervous system (convulsions). Deaths that occurred during the 4-year period were also recorded.

Accurate and detailed clinical information of each medical complication was recorded by attending race physicians during the 4-year study period in a standardized format and included the system affected and the specific final diagnosis.

### **3.3.4. Data collection of environmental conditions on race days for each year**

Data concerning the environmental conditions between 6 AM and 12 PM on race day of each year including the temperature, humidity, rainfall, cloud cover, and wind speed were obtained from the database of the South African Weather Services and are depicted in Table 3.2. The Wet Bulb Globe Temperature (WBGT) Index was calculated from these data.

**Table 3.2.: Environmental conditions on race day for each year. Values are mean (SD).**

	<b>Temperature (°C)</b>	<b>Humidity (%)</b>	<b>Rainfall (mm)</b>	<b>Wind speed (knots)</b>	<b>WBGT index*</b>
<b>2008</b>	18.2 (1.9)	77 (8)	0	9.6 (2.4)	16.5 (2.4)
<b>2009</b>	17.1 (1.4)	83 (7)	0	7.8 (1.0)	15.4 (1.6)
<b>2010</b>	16.3 (0.8)	93 (3)	0	3.5 (0.6)	15.2 (1.4)
<b>2011</b>	11.5 (2.1)	87 (2)	0	1.5 (1.3)	13.5 (2.9)

\*: Wet Bulb Globe Temperature (WBGT) Index – calculated using temperature (°C), humidity, time of day and cloud cover data

### **3.3.5. Calculation of the incidence of all medical complications, serious/life-threatening medical complications and deaths**

For the purposes of this study, the incidence of all medical complications, serious/life-threatening medical complications and deaths were calculated as runners with medical complications/deaths per 1000 runners who started the races. We chose the denominator as the number of runners who started the race because most studies reporting deaths and medical complications report this denominator and we wanted to relate our findings to those of other studies. Data reported per 1000 starters are also important for medical staff to plan medical care at races such as these, as this format allows organizers to estimate the anticipated number

and nature of medical complications at races. Further analysis of the incidence was also conducted in sub-groups as follows: race type (21.1 km or 56 km race), year of observation (2008 to 2011) reflecting environmental conditions (Table 3.2.), organ system affected, and the final diagnosis for the more common medical complications. However, we were also able to document the number of finishers per race over the 4-year study period, and could also include some preliminary analyses on factors that could determine the ability to finish the race.

### **3.3.6. Statistical analysis of data**

All the data from the runner and medical complications database were entered into an Excel spread sheet (Microsoft 2010) and then analysed using the SAS Enterprise Guide (V6.1) statistical programme. If included, log linear modelling was applied to model the starter characteristics. A logistic regression was used to model the non-finisher characteristics, separately for 21 km and 56 km runners. The association between finishers/non-finishers and runner characteristics (race type, gender, and age) were explored. Crude incidence rates are reported overall and by year, race type, organ system and final diagnosis. Categorical data analyses comparing 21 km and 56 km races used the Fisher Exact and Chi Square tests. Statistical significance was accepted at  $p < 0.05$ .

## **3.4. RESULTS**

### **3.4.1. Race finishers**

Of the runners who started the races, 64 420 finished their race within the required cut-off times (97.8% runners) (Table 3.3.). In the 21 km race, 39 111 of the 39 511 starters finished the races (99.0%), and in the 56 km race 25 309 of the 26 354 starters finished the races (96.0%).

**Table 3.3.: Demographics of participation (starters and finishers) by year of the race and type of race participation**

	<b>Race type</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>2011</b>	<b>All (2008-2011)</b>
Total starters	All	15742	16844	17358	15921	65865
	21 km	9723	10696	9550	9542	39511
	56 km	6019	6148	7808	6379	26354
Total finishers	All	15541	16635	17071	15173	64420
	21 km	9714	10689	9539	9169	39111
	56 km	5827	5946	7532	6004	25309

In a logistic regression analysis (data not shown) gender and age were two factors that were significantly associated with non-finishing. In both race types, the odds for a female not to finish was higher than for a male not to finish ( $OR_{56\text{ km}} = 1.31$ ;  $OR_{21\text{ km}} = 2.82$ ). In the 21 km race for every 10-year increase in age, the odds for not finishing increased by 35% ( $OR_{21\text{ km}} = 1.35$ ), and in the 56 km race for every 10-year increase in age the odds for not finishing increased by only 15% ( $OR_{56\text{ km}} = 1.15$ ).

### **3.4.2. Incidence of deaths**

In the 4-year period, 2 deaths were documented. Both deaths occurred in 21 km runners and therefore the incidence of deaths in 21 km runners was 0.05 per 1000 21 km runners (1 in 20 000 21 km runners starting the race).

### **3.4.3. Incidence of medical complications (all complications and the sub-group of serious/life-threatening medical complications), by race type and year of observation**

The incidences of all (serious and less-serious) medical complications and the sub-group of serious/life-threatening medical complications in each year of the study and race type are depicted in Table 3.4.

**Table 3.4.: Incidences (per 1000 runners starting the race: 95% CI) of any medical complications and serious medical complications by race type in the 4 years of study**

		2008	2009	2010	2011	All years
All	All	7.11 (5.91-8.56)	8.43 (7.15-9.94)	7.55 (6.36-8.96)	10.05 (8.61-11.73)	8.27 (7.61-9.00)
	Serious	0.57 (0.30-1.10)	0.42 (0.20-0.87)	0.63 (0.35-1.14)	0.63 (0.34-1.17)	0.56 (0.41-0.78)
21 km	All	4.73 (3.54-6.32)	3.93 (2.90-5.31)	5.03 (3.79-6.67)	7.02 (5.53-8.92)	5.14 (4.48-5.90)
	Serious	0.51 (0.21-1.24)	0.47 (0.19-1.12)	0.63 (0.28-1.40)	0.42 (0.16-1.12)	0.51 (0.33-0.78)
56 km	All	10.97 (8.61-12.93)	16.27 (13.37-19.79)	10.63 (8.57-13.18)	14.58 (11.90- 17.86)	12.98 (11.67-14.43)
	Serious	0.66 (0.25-1.39)	0.33 (0.08-1.30)	0.64 (0.27-1.54)	0.94 (0.42-2.09)	0.65 (0.40-1.04)

#### Incidence of all medical complications

In the 4-year observation period, a total of 545 medical complications (serious and less serious) were documented in 65 865 runners starting the races (0.827 % of all runners starting the races). Therefore, the incidence of any medical complications was 8.27 per 1000 runners (95% Confidence Intervals; 95% CI = 7.61- 9.00) (1 in 121 race starters). Of the 545 medical complications, 203 were documented in the 39 511 21 km runners (5.14 per 1000 runners; 95% CI = 4.48–5.90) (1 in 195 race starters) and 342 were documented in the 26 354 56 km runners (12.98 per 1000 runners; 95% CI = 11.67–14.43) (1 in 77 race starters). Thus, the incidence of medical complications (per 1000 runners) was higher in 56 km runners compared with 21 km runners ( $p < 0.0001$ ).

#### Incidence of all serious/ life-threatening medical complications

In the 4-year observation period, a sub-group of 37 medical complications were classified as serious/life threatening (0.056% of all runners starting the races). The serious/life-threatening complications included the following: ischaemic heart disease (n=3) (including successfully resuscitated sudden cardiac arrest), myocarditis (n=2), serious cardiac arrhythmias (n=2), symptomatic hyponatraemia (n=9), serious metabolic complications (n=5), serious heat related disorders (hyperthermia=6, hypothermia=1)(n=7), pulmonary oedema (n=2), serious fluid, electrolyte or acid base abnormalities (hyperkalaemia=1, metabolic acidosis=1, significant dehydration=2)(n=4), bronchospasm (n=2) and convulsions (n=1). The incidence of all serious medical complications was 0.56 per 1000 runners (95% Confidence Intervals; 95% CI = 0.41–0.78) (1 in 1 786 race starters). Of the 37 serious medical complications, 20

were documented in the 21 km runners (0.51 per 1000 runners; 95% CI = 0.33–0.78) (1 in 1 961 race starters) and 17 were documented in the 56 km runners (0.65 per 1000 runners; 95% CI = 0.40–1.04) (1 in 1 538 race starters). There was no significant difference in the incidence of serious medical complications between 56 km and 21 km runners ( $p=0.4612$ ).

#### **3.4.4. The incidence of medical complications by organ system affected and final diagnosis**

The incidence of specific medical complications in all the runners (per 1000 runners) by the organ system affected, and by the final diagnosis is depicted in Table 3.5a.

**Table 3.5a.: Incidences of specific medical complications by organ system affected and by final diagnosis in all runners and all years**

System		All runners		
		Incidence per 1000	95% CI	
<b>Cardiovascular</b>		<b>1.93</b>	<b>1.62</b>	<b>2.29</b>
Serious cardiac	All serious cardiac	0.12	0.06	0.24
	Ischemic Heart Disease	0.05	0.01	0.14
	Arrhythmia	0.03	0.01	0.12
	Myocarditis	0.05	0.01	0.14
Postural hypotension		1.75	1.45	2.10
Other cardiovascular		0.06	0.02	0.16
<b>Musculoskeletal</b>		<b>1.31</b>	<b>1.06</b>	<b>1.61</b>
<b>Dermatological</b>		<b>1.37</b>	<b>1.11</b>	<b>1.68</b>
<b>Serious Exercise -Associated Muscle Cramps</b>		<b>0.91</b>	<b>0.71</b>	<b>1.17</b>
<b>Gastrointestinal</b>		<b>0.88</b>	<b>0.68</b>	<b>1.14</b>
<b>Respiratory</b>		<b>0.53</b>	<b>0.38</b>	<b>0.74</b>
Asthma		0.18	0.10	0.32
Infection		0.21	0.13	0.36
Pulmonary oedema		0.03	0.01	0.12
Respiratory Other		0.11	0.05	0.22
<b>Fluid, electrolyte and acid base</b>		<b>0.43</b>	<b>0.29</b>	<b>0.62</b>
Hyponatraemia		0.23	0.14	0.38
Dehydration		0.18	0.10	0.32
Acidosis		0.02	0.00	0.11
<b>Metabolic</b>		<b>0.24</b>	<b>0.15</b>	<b>0.40</b>
<b>Fatigue</b>		<b>0.26</b>	<b>0.16</b>	<b>0.42</b>
<b>Central nervous system</b>		<b>0.14</b>	<b>0.07</b>	<b>0.26</b>
Convulsions		0.02	0.00	0.11
Confusion		0.02	0.00	0.11
Other collapse		0.03	0.01	0.12
Concussion		0.05	0.01	0.14
CNS Other		0.03	0.01	0.12
<b>Temperature regulation</b>		<b>0.14</b>	<b>0.07</b>	<b>0.26</b>
Hyperthermia		0.09	0.04	0.20
Hypothermia		0.05	0.01	0.14
<b>Renal</b>		<b>0.05</b>	<b>0.01</b>	<b>0.14</b>
<b>Other</b>		<b>0.11</b>	<b>0.05</b>	<b>0.22</b>

The incidence of specific medical complications in 21 km and 56 km runners (per 1000 runners) by the organ system affected, and by the final diagnosis is depicted in Table 3.5b.

**Table 3.5b.: Incidences of medical complications by organ system affected and by final diagnosis in 21 km and 56 km runners**

System and final diagnosis		21 km race			56 km race			p value
		Incidence	95% CI		Incidence	95% CI		
<b>Cardiovascular</b>		<b>1.21</b>	<b>0.92</b>	<b>1.61</b>	<b>3.00</b>	<b>2.40</b>	<b>3.74</b>	<b>&lt;0.0001 *</b>
Serious cardiac	All serious cardiac	0.13	0.05	0.30	0.11	0.04	0.35	1.0000
	Ischemic Heart Disease	0.05	0.01	0.20	0.04	0.01	0.27	1.0000
	Arrhythmia	0.03	0.00	0.18	0.04	0.01	0.27	1.0000
	Myocarditis	0.05	0.01	0.20	0.04	0.01	0.27	1.0000
Postural hypotension		1.06	0.79	1.44	2.77	2.20	3.48	<0.0001 *
Other cardiovascular		0.03	0.00	0.18	0.11	0.04	0.35	0.3088
<b>Musculoskeletal</b>		<b>0.96</b>	<b>0.70</b>	<b>1.32</b>	<b>1.82</b>	<b>1.37</b>	<b>2.42</b>	<b>0.0028 *</b>
<b>Dermatological</b>		<b>1.29</b>	<b>0.98</b>	<b>1.70</b>	<b>1.48</b>	<b>1.08</b>	<b>2.03</b>	<b>0.5199</b>
<b>Serious Exercise-Associated Muscle Cramps</b>		<b>0.25</b>	<b>0.14</b>	<b>0.47</b>	<b>1.90</b>	<b>1.44</b>	<b>2.50</b>	<b>&lt;0.0001 *</b>
<b>Gastrointestinal</b>		<b>0.23</b>	<b>0.12</b>	<b>0.44</b>	<b>1.86</b>	<b>1.41</b>	<b>2.46</b>	<b>&lt;0.0001 *</b>
<b>Respiratory</b>		<b>0.35</b>	<b>0.21</b>	<b>0.60</b>	<b>0.80</b>	<b>0.52</b>	<b>1.22</b>	<b>0.0158 *</b>
Asthma		0.15	0.07	0.34	0.23	0.10	0.51	0.5602
Infection		0.13	0.05	0.30	0.34	0.18	0.66	0.0637
Pulmonary oedema		-	-	-	0.08	0.02	0.30	-
Respiratory Other		0.08	0.02	0.24	0.15	0.06	0.40	0.4485
<b>Fluid, electrolyte and acid base</b>		<b>0.33</b>	<b>0.19</b>	<b>0.57</b>	<b>0.57</b>	<b>0.34</b>	<b>0.94</b>	<b>0.1430</b>
Hyponatraemia		0.23	0.12	0.44	0.23	0.10	0.51	0.9992
Dehydration		0.10	0.04	0.27	0.30	0.15	0.61	0.0769
Acidosis		-	-	-	0.04	0.01	0.27	-
<b>Metabolic</b>		<b>0.08</b>	<b>0.02</b>	<b>0.24</b>	<b>0.49</b>	<b>0.29</b>	<b>0.85</b>	<b>0.0008 *</b>
<b>Fatigue</b>		<b>0.10</b>	<b>0.04</b>	<b>0.27</b>	<b>0.49</b>	<b>0.29</b>	<b>0.85</b>	<b>0.0022 *</b>
<b>Central nervous system</b>		<b>0.13</b>	<b>0.05</b>	<b>0.30</b>	<b>0.15</b>	<b>0.06</b>	<b>0.40</b>	<b>1.0000</b>
Convulsions		0.03	0.00	0.18	-	-	-	-
Confusion		0.03	0.00	0.18	-	-	-	-
Other collapse		0.03	0.00	0.18	0.04	0.01	0.27	1.0000
Concussion		-	-	-	0.11	0.04	0.35	-
CNS Other		0.05	0.01	0.20	-	-	-	-
<b>Temperature regulation</b>		<b>0.15</b>	<b>0.07</b>	<b>0.34</b>	<b>0.11</b>	<b>0.04</b>	<b>0.35</b>	<b>0.7491</b>
Hyperthermia		0.10	0.04	0.27	0.08	0.02	0.30	1.0000
Hypothermia		0.05	0.01	0.20	0.04	0.01	0.27	1.0000
<b>Renal</b>		-	-	-	<b>0.11</b>	<b>0.04</b>	<b>0.35</b>	-
<b>Other</b>		<b>0.05</b>	<b>0.01</b>	<b>0.20</b>	<b>0.19</b>	<b>0.08</b>	<b>0.46</b>	<b>0.1243</b>

\*: Indicates a significant difference between 56 km and 21 km race (p<0.05)

The incidence of cardiovascular, musculoskeletal, metabolic, gastrointestinal and respiratory complications was significantly higher in 56 km runners compared with 21 km runners (Table

3.5b). For specific diagnoses, the incidence of postural hypotension, serious exercise-associated muscle cramping (sEAMC), and severe fatigue was higher in 56 km runners compared with 21 km runners (Table 3.5b). It is important to note that the incidence of serious cardiac conditions was not significantly different between the two races.

### **3.5. DISCUSSION**

To our knowledge, this is the largest and most comprehensive prospective study documenting the incidence and nature of medical complications (including deaths, serious/life-threatening medical complications, and complications by the system affected) during 21 km and 56 km distance running. The first main finding of this study is that incidence of death in 21 km runners was 0.05/1000 runners (1 in 20 000 runners starting the race). Secondly, the incidence of serious/life-threatening medical complications in both races combined was 0.56 (1 in 1 785 runners starting the race), and this was similar in the 21 km runners (0.51) and 56 km runners (0.65). Thirdly, the common medical complications in distance runners (per 1000 runners) by organ system affected, and by final diagnosis, were as follows: postural hypotension (1.75), followed by dermatological complaints (1.37), musculoskeletal complaints (1.31), serious exercise-associated muscle cramping (sEAMC) (0.91), and gastrointestinal complaints (0.88). Fourthly, we show that the overall incidence of medical complications is significantly higher in 56 km runners compared with 21 km runners, and that the incidence of specific medical complications by organ system affected, and the clinical profile of the final diagnosis differs between the two race types. Finally, our data show female runners and older runners are less likely to complete an endurance race (21 km and 56 km race).

In our study, both deaths occurred in 21 km runners. Therefore, we can only compare our observed death rate to other studies in 21 km runners. Our observed death rate of 5/100 000 runners is about 18 times higher than the death rate (0.27/100 000) reported in only one other study in 21 km runners in the USA [8]. The high death rate in 21 km runners in our study is of great concern and is not well explained. However, there are a number of possible reasons for our observed high death rate. Firstly, there are significant methodological differences in the data collection procedures between our study and that conducted by Kim et al [8]. We prospectively followed all runners who entered the race over the 4-year period and this is in contrast to retrospective data obtained in the US study, which was from the race medical data

and press reports. Therefore, it is possible that under-reporting could have occurred in the previous study. However, the total number of races and therefore runners studied was substantially higher in the study by Kim et al [8]. Finally, from the data described in the US study, it is not clear if any screening took place prior to races, and whether there were any specific entry requirements.

In our study, apart from age ( $\geq 16$  years) there are no other restrictions to participate in the 21 km race. Therefore, the race may attract runners of all ages that do not necessarily perform regular exercise, runners that are not necessarily well prepared and have not undergone any pre-race medical screening. In addition, runners may have risk factors for cardiovascular disease, or may have other chronic medical conditions. Our data, from both races, indicate that about 30% of runners are older than 40 years (data not shown). Although older age is a well-established risk factor for cardiovascular disease, this is not likely to explain the increased risk of sudden death in 21 km runners in our study. However, it is possible that the prevalence of other risk factors for cardiovascular disease may be higher in 21 km compared with 56 km runners. In our population there are no data on cardiovascular risk factors, and no pre-exercise screening was conducted. Data concerning other possible risk factors for underlying chronic disease in this group would also be important to obtain and will be the focus of future studies.

The second main finding in our study was that we documented an overall incidence of serious/life-threatening complications in 0.56/1000 runners starting the race. Notably, this was similar in the 21 km (0.51) and 56 km (0.65) races. There are very few published data documenting serious/life-threatening complications during distance running. In one study, an incidence of more serious medical complications was reported as 0.03/1000 marathon runners entering a race. We can only compare the results of our study in 21 km and 56 km runners to that reported in Roberts's study. The present study indicate that the incidence of serious medical complications during the 56 km race was more than 21 times higher than that reported in this one study in 42 km (marathon) runners [15]. Besides the obvious longer race distance (56 km vs. 42 km), other reasons for this finding are not clear. Firstly, the definition of what constitutes a serious complication in the two studies is different and there may have been under-reporting. Although environmental conditions may explain differences in these two studies, we do note that there was a large variation in the environmental conditions in the Roberts's study, whereas the annual variation in the WBGT indices during our 4-year study

was minimal (variation between 13.5 and 16.5). The WBGT indices in the 4-year period were always in the “low risk” category [25]. We strongly suggest that race medical directors take note of this and encourage further research in this area.

There are however more data for some specific serious medical complications during marathon and ultra-marathon running, such as hyponatraemia. In our study, the incidence of symptomatic hyponatraemia in 56 km runners was 0.23/1000. This incidence is lower compared to some studies (0.31) [17] and 0.6 [26], and higher than that reported in other studies (0.05) [27]; (0.001) [19]. There is no obvious explanation for this wide discrepancy in the reported incidences of hyponatraemia. However, factors that may be related to these differences are 1) the definition of hyponatraemia (clinical vs. biochemical), 2) different protocols for pre-race runner education on fluid intake, 3) different environmental conditions, including heat stress, 4) different events, and 5) differences in the availability of water stations on route. Further studies are required to determine the precise incidence and risk factors for hyponatraemia in distance running.

In our study, we report an overall incidence of medical complications of 8.27 per 1000 runners (5.14 in 21 km runners; 12.98 in 56 km runners). This is lower when compared to the 18.9 per 1000 42 km (marathon) runners that have been reported in one other study [15]. As these are different races, the data may not be comparable. Furthermore, in the study by Roberts et al., all medical complications were documented, whereas we only reported medical complications that were of sufficient severity to require assessment by a medical doctor, and this could be another factor explaining the different incidences. We suggest that standardized definitions and procedures be developed to report medical complications data so that the results of future studies can be compared.

To our knowledge, the profile of other less serious medical complications in marathon runners has only been reported in two studies [15, 16]. In a 12-year period, the profile of medical injury and illness for the Twin Cities marathon was reported [15]. Exercise-associated collapse (59% of medical complications) skin complications (21%) and musculoskeletal accounted for the majority of less serious medical complications reported in that study. In our study, the most common complication was also exercise-associated collapse (postural hypotension) (21%), followed by dermatological complications (17%), and musculoskeletal complications (16%). More serious exercise-associated muscle cramps (sEAMC) and gastro-

intestinal complications each accounted for 11% of all complications. Our data are therefore similar to that previously reported in marathon runners. Although we cannot strictly compare our data to the profile of medical complications reported in the multi-staged ultra-marathon race, we do note similarities with respect to dermatological and musculoskeletal complaints being very common [16].

To our knowledge, the incidence of medical complications (per 1000 race starters) in 56 km ultra-marathon runners compared to 21 km runners has not been studied. In our study, the overall incidence of medical complications (per 1000 runners starting the race) was significantly higher in the 56 km race (12.89) compared with the 21 km race (5.14). However, it is important to note that the incidence of serious medical complications was not significantly different in the 56 km race (0.65) compared to the 21 km race (0.51). This highlights that there are differences in the nature of medical complications between the races. In 56 km runners, the incidence of exercise-associated postural hypotension ( $p<0.0001$ ), sEAMC ( $p<0.0001$ ), gastro-intestinal complications ( $p<0.0001$ ), musculoskeletal complications ( $p<0.0028$ ) and fatigue ( $p<0.0022$ ) were significantly higher than in the 21 km runners. The most likely explanation for these observations is likely to be the difference in the overall duration of these races, but this would require further study. However, for the race organizer and the medical staff the practical clinical message is that a runner is more likely to develop any medical complication, and some specific medical complications during the longer 56 km compared with a 21 km race. It is also important to note that the risk factors for medical complications in 56 km races and 21 km races may be different, and these factors should be explored in future studies. We suggest that an analysis should be conducted to identify independent risk factors for medical complications associated with distance running, and that these analyses should be done separately in the 21 km and 56 km races.

Finally, in our study, we showed that female runners and older runners are less likely to complete an endurance race (21 km or 56 km). We are not aware of any other study where this has been reported, and the precise reason/s for not finishing the races is/are not clear and need further study. We recognize that the development of medical complications during a race could be one possible reason for not finishing a race. Therefore, we suggest that the relationship between gender and age as potential risk factors associated with medical complications during 21 km and 56 km running be explored in further studies.

This study has a number of strengths, and also some limitations. To our knowledge, this is one of the largest prospective studies documenting not only deaths, but also serious/life threatening and other medical complications during endurance races. Other strengths of the study are that the medical data were comprehensive, and were collected by physicians using a standardized method of collection and classification. Precise definitions for what constitute a medical complication and a serious medical complication were reported. Also, we collected data on medical complications that developed either during the race, or at completion of the race. Finally, we had not only accurate data on race starters (as most previous studies) but also had novel data on race finishers. One of the main limitations of our data relate to the small absolute number of deaths and the relatively small number of runners in the analysis of the mortality data. In comparison to other studies documenting sudden cardiac deaths in distance runners, our data on sudden death are therefore limited and should be interpreted with caution. However, our data on serious/life-threatening medical complications are very accurate and this has not been reported in studies on sudden cardiac deaths in runners. We aim to continue our surveillance of deaths and medical complications in these races over the next years.

### **3.6. SUMMARY AND CONCLUSIONS**

In our study, sudden cardiac death and serious medical complications are higher in 21 km runners while the incidence of overall medical complications is higher in 56 km runners. The most common medical complications are postural hypotension, followed by dermatological and musculoskeletal complications but the incidence of these complications differs in 21 km compared with 56 km runners. In order to reduce the risk of medical complications during distance running, the next step is to determine the risk factors for any medical complications and specific complications during distance running. Thereafter, strategies to reduce the risk of these adverse medical events in endurance runners can be implemented and then re-assessed.

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## **CHAPTER 4:**

### **A REVIEW OF THE RISK FACTORS ASSOCIATED WITH MEDICAL ENCOUNTERS IN COMMUNITY-BASED DISTANCE RUNNING EVENTS**

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#### **4.1. INTRODUCTION**

In sports injury and athlete health research there is a well-established stepwise circular model to systematically approach the investigation of a health problem (Chapter 1). This thesis focuses on medical encounters in community-based distance running events and follows that model (known as the Van Mechelen's Model of Injury Prevention), because it is widely adopted by world-class research organisations [1].

The first objective of this dissertation was to address step 1 of the model by accurately determining the incidence of medical encounters during distance running events (Chapters 2 and 3). The next step in the process is to determine risk factors associated with medical encounters during community-based distance running events.

Knowledge of the risk factors is vital to 1) design prevention programmes and thereby reduce the risk of medical encounters in distance running events and 2) plan optimal medical care for an event. Race participants can have either intrinsic (internal) risk factors or be exposed to extrinsic (external) risk factors on race day, which predispose them to increased risk of a medical encounter on race day.

The aim of Chapter 4 is to review the literature on the risk factors (both intrinsic and extrinsic), associated with more common medical encounters in distance running events. As in Chapter 2 of this dissertation, risk factors associated with medical encounters will be reviewed firstly by severity of medical encounters and then by medical encounters in organ systems and by specific diagnosis, where applicable.

## **4.2. LITERATURE REVIEW FORMAT AND METHODS**

### **4.2.1. Search strategy**

A similar literature search strategy as described in Chapter 2 was adopted. The literature search was conducted to source published information on the risk factors associated with medical encounters in distance runners by severity and by organ systems and specific diagnosis. As in Chapter 2, the search strategy to obtain relevant peer-reviewed publications was based on the methodology employed in conducting systematic reviews. A search was conducted on the PubMed and Google Scholar databases, using three levels with keywords in different combinations (Appendix A).

Only publications in English, and studies that involved human participants were included. The searches were conducted for publications between the periods 1960 to 30 June 2020

### **4.2.2. Level of evidence**

As in Chapter 2, each publication was categorised and assessed using the 2011 Oxford Levels of Evidence criteria (<http://www.cebm.net/index.aspx?o=5653>) and the following were determined: type of study, level of evidence score (Levels I to V), and the strengths / limitations of each study.

### **4.2.3. Presentation of results**

The results of the search strategy for each section will be summarised by presenting the main findings in tables in a standardised format using the following categories: risk factors, study design, study references, description, main findings, strengths of the study, limitations of the study, and the Oxford Levels of Evidence (I to V).

## **4.3. DEFINITIONS: INTRINSIC AND EXTRINSIC FACTORS**

Risk factors can be classified as either intrinsic or extrinsic risk factors [2-4]. Alternative terminology that has been used is “internal” or “external” risk factors [5] [6]. In this

dissertation the terminology intrinsic and extrinsic risk factors will be used, as this is the terminology that is more frequently used in recent publications.

*Intrinsic risk factors* are defined as factors that are within the body [2-4]. Examples of these are age, sex, race, Body Mass Index (BMI), ethnicity, running experience, level of fitness, running pace, use of medication and supplements, underlying acute and chronic diseases and hydration status. It is important to note that some of these factors can change, for example level of fitness, acute medical disease and short-term medication use. Furthermore, some of these risk factors are modifiable and include (but are not limited to) runner education, hydration status, level of fitness and running pace.

*Extrinsic risk factors* are defined as factors which are outside of the body [2-4]. Examples of extrinsic risk factors are environmental conditions, race distance, participant number, course terrain / technicality and runner education. Again, some of these risk factors may change, such as course technicality, environmental conditions and participant number, among others.

#### **4.4. A REVIEW OF THE RISK FACTORS ASSOCIATED WITH SUDDEN CARDIAC ARREST AND SUDDEN CARDIAC DEATH (SCA / SCD) IN DISTANCE RUNNING EVENTS**

In this section, the risk factors associated with sudden cardiac arrest (SCA) and sudden cardiac death (SCD) in distance runners will be reviewed. The risk factors associated with other potential “non-cardiac” causes of sudden death (SD) will be discussed where relevant under the heading of specific medical encounters in an organ system. These include, but are not limited to: exertional heatstroke (EHS), exercise-associated hyponatraemia (EAH) and acute renal failure.

The causes of acute cardiovascular events resulting from physical exercise have been extensively reviewed in both the younger (< 35 years) and older (≥ 35 years) exercising populations [7-11]. This Chapter focusses on risk factors, therefore a detailed review of the causes of SCD / SCA is beyond the scope of this Chapter. In summary, coronary atherosclerosis is the main underlying cause of SCA / SCD, and therefore also the main known risk factor associated with SCD / SCA in the older athlete (≥ 35 yrs.). Hypertrophic

cardiomyopathy, coronary anomalies and arrhythmogenic right ventricular cardiomyopathy are the more common causes of SCA / SCD in the younger athlete (<35 yrs.) [12, 13]. Any runner may have various intrinsic risk factors or be exposed to a range of extrinsic risk factors that can potentially predispose them to SCD / SCA [14].

The literature search revealed several studies where intrinsic and extrinsic risk factors associated with SCA / SCD during distance running were identified. Data from these studies (by risk factor, study design and study reference, description, finding, strengths, limitations and level of evidence) are summarised in Table 4.1.

**Table 4.1.: Intrinsic and extrinsic risk factors associated with SCA and SCD 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 finding/s	Strengths	Limitations	Level of Evidence [15]
Intrinsic					
Sex	Narrative review [16]	Males at higher risk	<ul style="list-style-type: none"> <li>Comprehensive</li> </ul>	<ul style="list-style-type: none"> <li>Review</li> </ul>	5
	Retrospective cohort [17]	Males at higher risk	<ul style="list-style-type: none"> <li>Largest cohort to date</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective study</li> <li>Data collection methods (internet search engines and outreach to race directors) – may have missed cases</li> </ul>	2b
	Retrospective cohort [18]	Males at higher risk	<ul style="list-style-type: none"> <li>Long study period (28 years)</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective study</li> <li>Small number of events-reduces statistical power</li> <li>Possible underreporting</li> </ul>	2b
	Retrospective cohort [19]	Males at higher risk	<ul style="list-style-type: none"> <li>University medical records</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective study</li> <li>SCA rate not known</li> </ul>	2b
	Prospective cohort [20]	Males at higher risk	<ul style="list-style-type: none"> <li>Prospective study</li> </ul>	<ul style="list-style-type: none"> <li>Race entrants used as denominator (not clear if all these runners started)</li> </ul>	1b
	Review [16]	>35 years group at higher risk	<ul style="list-style-type: none"> <li>Comprehensive</li> </ul>	<ul style="list-style-type: none"> <li>Review</li> </ul>	5
Age	Retrospective cohort [17]	>35 years group at higher risk	<ul style="list-style-type: none"> <li>As above</li> </ul>	<ul style="list-style-type: none"> <li>As above</li> </ul>	2b
	Retrospective cohort [18]	>35 years group at higher risk	<ul style="list-style-type: none"> <li>Long study period (28 years)</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective study</li> <li>Small number of events-reduces statistical power</li> <li>Possible underreporting</li> </ul>	2b
	Prospective cohort [20]	>35 years group at higher risk	<ul style="list-style-type: none"> <li>As above</li> </ul>	<ul style="list-style-type: none"> <li>As above</li> </ul>	1b
	Systematic review [21]	Older age (between 30-50 years) at higher risk	<ul style="list-style-type: none"> <li>Systematic review</li> <li>Over 34 years</li> </ul>	<ul style="list-style-type: none"> <li>Lack of central registrar</li> <li>Some studies included registrants vs participants</li> <li>Differences in SCD definition</li> </ul>	1a

**Table 4.1.: Intrinsic and extrinsic risk factors associated with SCA and SCD in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)**

Ethnicity	Position paper [22]	African-Americans <sup>a</sup> at higher risk	<ul style="list-style-type: none"> <li>• Comprehensive outline of registry</li> </ul>	<ul style="list-style-type: none"> <li>• Position paper</li> </ul>	5
	Retrospective cohort [23]	African-Americans <sup>a</sup> at higher risk	<ul style="list-style-type: none"> <li>• Long study period</li> <li>• Large number of SCD's (64)</li> <li>• &gt;5x in African-Americans</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• U.S. college athletes</li> </ul>	2b
Level of fitness	Review [16]	Individuals with a sedentary lifestyle, are at higher risk	<ul style="list-style-type: none"> <li>• Comprehensive</li> </ul>	<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
	Review [24]	Individuals with a sedentary lifestyle, are at higher risk	<ul style="list-style-type: none"> <li>• Comprehensive</li> </ul>	<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
	Retrospective cohort [25]	Individuals with a sedentary lifestyle, are at higher risk	<ul style="list-style-type: none"> <li>• One of first studies</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Possible recall bias (from spouses)</li> </ul>	2b
	Retrospective cohort [26]	Individuals with a sedentary lifestyle are at higher risk	<ul style="list-style-type: none"> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Possible recall bias</li> </ul>	2b
	Prospective cohort [27]	Individuals with a sedentary lifestyle are at higher risk	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Large cohort/ Physician's health study</li> </ul>	<ul style="list-style-type: none"> <li>• Study included only male physicians</li> <li>• Baseline data on vigorous exercise frequency not updated in study period</li> </ul>	1b
	Systematic review [28]	Individuals with a sedentary lifestyle are at higher risk	<ul style="list-style-type: none"> <li>• One of largest systematic reviews</li> </ul>	<ul style="list-style-type: none"> <li>• Study included all physical activity, not only distance running</li> </ul>	1a
Exercise intensity	Position statement [29]	Increased exercise intensity	<ul style="list-style-type: none"> <li>• Evidence informed model</li> </ul>	<ul style="list-style-type: none"> <li>• Position statement</li> </ul>	5
	Retrospective cohort [30]	Increased exercise intensity	<ul style="list-style-type: none"> <li>• One of first studies</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Possible recall bias (from spouses)</li> </ul>	2b
	Prospective cohort [27]	Increased exercise intensity	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Large cohort/ Physician's health study</li> </ul>	<ul style="list-style-type: none"> <li>• Study included only male physicians</li> <li>• Baseline data on vigorous exercise frequency not updated in study period</li> </ul>	1b
Running experience	Retrospective cohort [17]	<p>More running experience at lower risk</p> <p>Independent risk factor</p>	<ul style="list-style-type: none"> <li>• As above</li> </ul>	<ul style="list-style-type: none"> <li>• As above</li> </ul>	2b

**Table 4.1.: Intrinsic and extrinsic risk factors associated with SCA and SCD in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)**

Co-morbid medical conditions (Hypertension, diabetes, ↑ LDL-cholesterol, ↓ HDL cholesterol, ↑ BMI, chronic inflammation)	Review [16]	Existing co-morbid conditions at higher risk	<ul style="list-style-type: none"> <li>Comprehensive review</li> </ul>	<ul style="list-style-type: none"> <li>Review</li> </ul>	5
	Review [31]	Existing co-morbid conditions at higher risk	<ul style="list-style-type: none"> <li>Comprehensive review related to chronic inflammation</li> </ul>	<ul style="list-style-type: none"> <li>Review</li> </ul>	5
	Review [32]	Existing co-morbid conditions at higher risk  Independent risk factors	<ul style="list-style-type: none"> <li>Comprehensive summary of data</li> </ul>	<ul style="list-style-type: none"> <li>Review</li> </ul>	5
	Retrospective cohort [17]	Existing co-morbid conditions at higher risk	<ul style="list-style-type: none"> <li>As above</li> </ul>	<ul style="list-style-type: none"> <li>As above</li> </ul>	2b
	Prospective cohort [33]	Existing co-morbid conditions at higher risk	<ul style="list-style-type: none"> <li>Prospective study</li> <li>Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>Study limited to Asian population</li> <li>Hospital data accuracy is uncertain</li> </ul>	1b
	Systematic review/meta-analysis [34]	Existing co-morbid conditions at higher risk  Independent risk factors	<ul style="list-style-type: none"> <li>Systematic review</li> <li>Included 27 studies</li> </ul>	<ul style="list-style-type: none"> <li>May have missed relevant studies for inclusion</li> </ul>	1a
Presence of risk factors associated with CVD (↑ Smoking, dyslipidaemia, increased BMI, family history of premature CVD: males <50 years and females <60 years, hypertension, diabetes mellitus)	Review [32]	Increased risk with CVD risk factors	<ul style="list-style-type: none"> <li>Comprehensive summary of data</li> </ul>	<ul style="list-style-type: none"> <li>Review</li> </ul>	5
	Retrospective cohort [35]	Increased risk with CVD risk factors  Independent risk factors	<ul style="list-style-type: none"> <li>Independent modifiable risk factors identified</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> <li>Small sample</li> <li>Single medical centre</li> <li>Subjects mainly Caucasian males</li> </ul>	2b
	Prospective cohort [33]	Increased risk with CVD risk factors  Independent risk factors	<ul style="list-style-type: none"> <li>Prospective study</li> <li>Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>Study limited to Asian population</li> <li>Hospital data accuracy is uncertain</li> </ul>	1b
	Systematic review/meta-analysis [34]	Increased risk with CVD risk factors	<ul style="list-style-type: none"> <li>Systematic review</li> <li>Included 27 studies</li> </ul>	<ul style="list-style-type: none"> <li>May have missed relevant studies for inclusion</li> </ul>	1a

**Table 4.1.: Intrinsic and extrinsic risk factors associated with SCA and SCD in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)**

Symptoms of CVD (↑ with symptoms such as chest pain (including referred pain to jaw, arms or neck), dyspnoea at rest or with minimal exertion, orthopnoea, paroxysmal nocturnal dyspnoea, syncope or near-syncope, pitting ankle oedema, palpitations, claudication and fatigue <sup>b)</sup> )	Review/Position paper [36]	Experiencing symptoms of CVD, is a higher risk.		• Review/Position paper	5
	Position paper [29]		• Evidence informed model	• Position paper	5
	Systematic review [28]		• One of largest systematic reviews	• Study included all physical activity, not only distance running	1a
Acute illness	Case study [37]	Acute illness at higher risk	• Detailed documentation in Olympic marathon runner	• Case study	4
	Case study [38]	Acute illness at higher risk	• Detailed documentation	• Case study	4
Drugs and medication use	Editorial [39]	Decreased risk with the use of aspirin	•	• Editorial	5
	Position paper/review [40]	Increased risk with the use of performance enhancing substances	• Good review of evidence	• Review	5
	RCT [41]	Decreased risk with the use of aspirin	• RCT • Large sample size		1b
Coronary Artery Calcium Score	Prospective cohort [42]	Increased risk with CAC	• Prospective study	• Possible selection bias • Small event number	1b
	Prospective cohort [43] <sup>d)</sup>	Increased risk with CAC  Independent risk factor	• Prospective study • Large sample size	• Relatively small number of events	1b
Myocardial fibrosis	Prospective cohort [42]	Increased risk with myocardial fibrosis	• Prospective study	• Possible selection bias • Small event number	1b
Nutrition	RCT [44]	Decreased risk with intake of polyphenol rich juice due	• RCT	• Small sample size • Possible 'other' nutritional interference	1b
Race distance <sup>c)</sup>	Retrospective cohort [17]	Increased risk running the marathon vs half marathon	• As above	• As above	2b
	Retrospective cohort [45]	Increased risk running the marathon vs half marathon	• Long study period • Large sample size	• Retrospective study	2b
	Retrospective cohort [19]	Decreased risk running the marathon vs half marathon	• University medical records	• Retrospective study •	2b
	Retrospective cohort [46]	Decreased risk running shorter race distances	• Large sample size • 62 races	• Retrospective study • Small event number	2b

**Table 4.1.: Intrinsic and extrinsic risk factors associated with SCA and SCD in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)**

Education and mental preparedness	Descriptive [47]	Decreased risk with education and mental preparedness	<ul style="list-style-type: none"> <li>• Novel study</li> <li>• Large cohort</li> <li>• Long study period</li> </ul>	<ul style="list-style-type: none"> <li>• Descriptive design</li> <li>• Low response rate (36%)</li> <li>• Included only collapsed runners</li> </ul>	4
	Retrospective cohort [48]	Decreased risk with education and mental preparedness	<ul style="list-style-type: none"> <li>• Novel data</li> <li>• Largest half marathon over multi-years</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective study</li> <li>• Definition limitations</li> <li>• Low event number</li> </ul>	2b

<sup>a</sup> evidence in general athletic population only

<sup>b</sup> examples of symptoms of CVD, not only limited to these

<sup>c</sup> conflicting evidence

<sup>d</sup> general population

#### **4.4.1. Intrinsic risk factors associated with SCA / SCD in distance running events**

##### *a. Sex*

There is good evidence that the incidence of SCA / SCD during distance running events is higher in males compared to females [17-20]. This is consistent with reports in other athletic populations [49-51]. Historically, females have a lower participation rate in distance running events, but in the past decade female participation has increased and currently up to 60% of the running field are woman (<https://running usa.org/annual-reports-accessed on 18 February 2020>). Females also have a delayed CAD onset when compared to males [28] and this may be related to a difference in the prevalence of the pathological substrate for SCA / SCD [52]. The main findings from retrospective [17, 18] [19] and prospective studies [20] comparing incidence of SCA / SDC by sex will be briefly reviewed.

In a study over a prolonged time period, marathon-related cardiac arrest in males and females was evaluated in a retrospective cohort study in the USA over a period of 28 years (n=548 092) [18]. In this period, there were 14 SCA's of which 13 were male. The SCA rate for males was 3.4 / 100 000 runners compared to 0.6 / 100 000 female runners. In a more recent retrospective cohort study on participants (n=459 479) in half-marathons and full marathons in Japan over a period of five years, a total of 10 SCA cases occurred and all were in males (incidence of SCA in males = 2.18 / 100 000 runners) [19].

In a prospective study, conducted in France (n = 511 880) over a six-year period [20], 13 major cardiovascular events were documented and all were in male athletes (100%) (incidence of SCA in males = 2.5 / 100 000 runners). Lastly, one of the largest retrospective studies reported cardiac arrests in USA distance running events over a decade (n=10.9 million). There was a significantly higher incidence of SCA in males (0.90 / 100 000 runners) compared to females (0.16 / 100 000 runners). In summary, all the data show an increased risk of SCA / SCD in male compared with female runners. Being male is therefore a significant risk factor for SCA / SCD in distance runners.

#### *b. Age*

The majority of SCA / SCD in distance running events occur in the older population [21] [16] [18]. The mean age of distance runners with SCA, in a retrospective cohort conducted over 28 years, was  $48 \pm 10$  years (mean + SD) [18] and the average age of SCA a retrospective Japanese study in marathon and half-marathon races, was  $46 \pm 18$  years (mean + SD) [19]. Similarly, in a large USA-based retrospective study conducted over a decade in distance running events, the average SCA age was  $42 \pm 13$  years (mean + SD)[17]. Finally, the mean age of SCA in the prospective RACER study was  $43 \pm 10$  years(mean + SD) [20]. In summary, there is consistent evidence of SCA / SCD occurring in the older age group (> 40 years), which is also the group where CAD is the most prevalent [16].

#### *c. Ethnicity*

In the general athletic population, African-American athletes have a higher incidence of SCA / SCD compared to Caucasian athletes [23] [22]. In USA collegiate athletes, for example, African-American athletes have a three-five times higher risk of SCD compared to their

Caucasian counterparts [53]. To our knowledge, ethnicity as a risk factor associated with SCA / SCD in distance runners has not been reported and this should be investigated in future studies.

#### *d. Level of fitness*

The greatest benefits of exercise are in the sedentary individuals that become physically active [16] [28] [24]. However, in this group there is an increased risk (up to 56 times higher) of SCA / SCD during exercise [30]. There is good evidence that the relative risk of developing SCA / SCD during exercise is higher in those who exercise on fewer occasions per week [26] and this was shown in both retrospective [25] and prospective studies [27]. To our knowledge, long-term prospective studies in distance runners to analyse the association between training history and SCA / SCD have not been conducted.

#### *e. Known cardiovascular disease*

Distance runners are not exempt from CVD and SCA / SCD can be the first presentation of occult cardiovascular disease in distance runners. The aetiology and pathophysiology of SCA / SCD during exercise has been reviewed [54] [55] [56] and it is known that the majority of SCA / SCD in distance running events are secondary to acute complications of atherosclerotic CAD [17] [57] [20] [50]. Therefore, known coronary artery disease is an important risk factor of SCA / SCD is [16].

#### *f. Use of medication*

There are numerous medications, performance-enhancing substances and social drugs that are potentially arrhythmogenic and may be associated with SCA / SCD during exercise [40]. These have not been specifically studied in the running population and a detailed discussion of all these drugs is beyond the scope of this review. The relationship between medications, performance-enhancing substances and social drugs and the risk of SCA / SCD during exercise is an area that requires further study.

It is noteworthy that there has been a recent interest in the possible prophylactic use of pre-race aspirin to reduce the incidence of SCA / SCD during exercise [39]. The International Marathon Medical Directors Association (IMMDA) (<https://immda.org/wp-content/uploads/2015>, accessed 20 February 2020), recently recommended pre-race aspirin for males over 40 years with approval by their physicians (considering related risks such as

allergy and GIT bleeding). This recommendation is based on the understanding that there is a haemostatic imbalance with prothrombotic effects that includes in vivo platelet activation during the race. Pre-race low-dose aspirin use is prudent to protect susceptible runners from a high, if transient, risk for cardiac arrest during races as evidence-based to prevent first myocardial infarctions in same-aged healthy men [41] [58]. However, there are no RCT studies to prove this and further research is needed.

*g. Other risk factors*

There has recently been an increased interest in the following cardiovascular novel risk factors associated with SCA / SCD during exercise. These factors include coronary artery calcium, cardiac fibrosis and polyphenol-containing substances, and these will be briefly discussed.

*i. Coronary artery calcium*

It has been shown that the coronary artery calcium (CAC) score independently predicts CAD and SCD in males between the age of 32 to 46 years old [43]. The Coronary Artery Risk Development in Young Adults (CARDIA) study is a prospective community-based study that recruited 5115 African American and Caucasian participants [43] who have been under surveillance for 30 years, with CAC measured 15, 20 and 25 years after recruitment. The outcomes showed that any amount of CAC resulted in a five-fold increase of coronary heart disease (CHD) events. In summary, adults younger than 50 years with any measurable CAC are at increased risk for CHD, SCA and SCD.

There have been recent cross-sectional and prospective cohort studies evaluating CAC in distance runners [59] [42]. In a cross-sectional study the prevalence of CAC in middle-aged, male marathon runners (n=50) was almost 50% [59]. However, only a minority had obstructive CAD and treadmill testing failed to detect this in any of these patients. Based on these results, cardiac CT may help identify runners with elevated risk for coronary events in the future, especially those with a positive family history. A further prospective cohort study collected baseline data in 108 German marathon runners (with age/age-risk-matched controls) [42]. Their coronary event rates and all-cause mortality was determined after  $6 \pm 1$  years. Of these, 74 marathon runners were evaluated for potential predictors of coronary events including CAC, the presence of myocardial fibrosis (as measured by cardiac MRI with contrast), and the Framingham risk score. The results showed that increasing CAC scores and

prevalence of myocardial fibrosis were associated with higher coronary events in distance runners [42]. In future, larger studies with longer follow-up periods are required to confirm these findings. In summary, the CAC score may be more widely used in the future to identify high-risk runners with ‘silent’ cardiovascular disease.

#### *ii. Cardiac fibrosis*

Recently there has been an increased interest in the potential harmful effects of chronic endurance exercise. A detailed discussion of cardiac fibrosis in athletes is beyond the scope of this dissertation, but this has been reviewed recently [60] [61] [62]. A potential link between endurance exercise and the development of cardiac fibrosis has been shown, where the patchy myocardial fibrosis may potentially create a substrate for arrhythmias. In the section discussing CAC above, the risk of additional cardiac fibrosis in association with CAC has been discussed [42].

#### *iii. Polyphenol-containing substances*

It is known that significant activation of the coagulation system and platelet activation occurs during exercise, and more specifically during distance running [63]. An interesting recent novel study examined the effect of pre-race ingestion of Aronia juice, a polyphenol-rich juice, on platelet function. Polyphenols may exert a cardioprotective effect by positively influencing platelet function. In this regard, an RCT was conducted on 10 healthy male runners who ingested 200 ml of Aronia juice in the morning before the race vs. a placebo group [44]. Blood analysis post-race showed a significant lowering of platelet aggregation markers and platelet-neutrophil aggregates in the Aronia group after the race when compared to the placebo group. These results suggest that pre-race Aronia consumption may counteract the distance running race-induced changes in platelet function. Future well-designed studies in larger cohorts, as well as well-conducted RCT’s are needed to assess repeatability of these results.

### **4.4.2. Extrinsic risk factors associated with SCA / SCD in distance running events**

#### *a) Environmental conditions*

Environmental conditions as potential risk factors have not been specifically documented in association with SCA / SCD. However, these factors have been explored as risk factors associated with other serious medical encounters such as EHS (Section 4.7.1.1.) and EAH

(Section 4.7.1.2.) and these factors will be discussed under the heading of those relevant sections (Section 4.7.). Future studies should evaluate the association of environmental conditions and SCA / SCD.

*b) Race distance*

There is conflicting evidence that longer race distances are associated with increased risk of SCA / SCD. Most data show an increased incidence of SCA / SCD in the marathon when compared to the shorter half-marathon or other shorter races [17] [10] [45]. In one study, reporting on data over a decade in USA races, there was a significantly higher incidence of SCA in the marathon (1.01 / 100 000 runners) compared with the half-marathon (0.27 / 100 000 runners) [17]. However, other data report higher incidences of SCA / SCD in half-marathons and shorter distances [46]. In a study on Japanese races the incidence of SCA / SCD was 2.5 / 100 000 runners in the half-marathon compared to 2 / 100 000 runners in the full marathon [19]. Another retrospective study documented the incidence of SCD in 62 of the largest races in the USA (race distances between 10 -21.1 km) [46]. Of the 5 SCD's among 1,636 720 runners, 4 occurred in the 10 km race and only 1 in the 21.1 km. The overall incidence of SCD was documented as 0.3 / 100 000 runners.

In summary, it is not clear if the incidence of SCA / SCD is higher in shorter or longer races. It is possible that in the longer races a runner is exposed to risk for a longer time, therefore the incidence may be higher. However, it is also possible that the race starter populations differ and that the average marathon runner is already self-selected to have a lower risk for SCA / SCD because they are healthier or better conditioned compared to the half-marathon runner. A further consideration is that many marathons have minimal entry requirements (including qualifying races), which is not usually the case with half-marathons and shorter races. Future well-designed studies are needed to further evaluate race distance with differing and starter populations as a risk factor associated with SCA / SCD during running.

*c) Runner pre-race education*

A recent descriptive study was conducted on runners that collapsed during the Gothenburg half-marathon in the period 2010 to 2017 [47]. The collapse was not specifically SCA / SCD related, but collapse may be the first sign of a serious underlying cardiac condition. Certain individual characteristics were evaluated in the collapsed runners, using a post-race questionnaire and interview. This study showed that unique individual traits and mental

characteristics may point to a specific profile for runners that collapse and that runner pre-race education may influence this. However, further studies are needed.

## **Summary**

In summary, there is consistent good evidence that being male and of older age are risk factors associated with the increased risk of SCA / SCD in distance running events. Race distance, runner pre-race education, the use of medication, CAC score and cardiac fibrosis are other possible risk factors associated with SCA / SCD in distance runners. Evidence of risk factors associated with SCA / SCD in other exercising groups include ethnicity, level of fitness, exercise intensity, exercise duration, underlying chronic diseases and risk factors associated with CVD. These risk factors should be specifically evaluated in well- designed long-term studies in distance runners.

A few important points to consider are that firstly, caution is necessary when comparing data from past distance running events to current race data, as it is known that there has been a change in the demographics of the participants over the past few decades. Secondly, care should be taken not to ignore the risk to woman, especially with the numbers of female participants rising. Thirdly, there are greater numbers of runners in the ‘high-risk’ age group participating in distance running events than in the past. Therefore, these data need to be reviewed on a regular basis.

Finally, it is important to note that the most common cause of SCA / SCD during distance running is coronary artery disease. Therefore, the pre-race risk profile of race entrants, specifically risk factors associated with coronary artery disease, is a key consideration in the quest to reduce the incidence of SCA / SCD in distance runners. Future recommendations include the need for well-designed prospective cohort studies, that also control for age, sex, race distance and environmental conditions. The role of CAC score and cardiac fibrosis as risk factors in distance runners for SCA / SCD should be further investigated in larger studies.

#### **4.5. A REVIEW OF THE RISK FACTORS ASSOCIATED WITH SERIOUS/LIFE-THREATENING MEDICAL ENCOUNTERS IN DISTANCE RUNNING EVENTS**

These risk factors have not been separately discussed here (as in Chapter 2) as the risk factors vary per serious/life-threatening condition and will be discussed under the specific organ system/diagnosis further in this chapter.

#### **4.6. A REVIEW OF THE RISK FACTORS ASSOCIATED WITH ANY MEDICAL ENCOUNTER IN DISTANCE RUNNING EVENTS**

In this section, the literature was reviewed related to risk factors associated with any collective medical encounter, irrespective of severity or cause, during distance running events. There are limited data related to risk factors associated with the overall presentation of medical encounters in comparison to the data related to specific medical encounters. The data related to specific medical conditions and organ systems will be discussed in section 4.4. of this chapter.

To date, the most extensive summary in the literature regarding risk factors was documented in the Vancouver International Marathon publication [64] in which the authors discussed variables influencing patient presentation rates at marathon events. Following this publication, there have been several studies reporting risk factors related to the development of any medical complication in distance running events (Table 4.2.). The extrinsic and intrinsic risk factors associated with ‘any’ /overall medical encounters rate will be briefly discussed.

**Table 4.2.: Intrinsic and extrinsic risk factors associated with medical encounters in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence)**

Intrinsic					
Risk factor	Study design study reference	Main finding/s	Strengths	Limitations	Level of Evidence [15]
Running experience	Cross-sectional [65]	Increased risk with more experience	<ul style="list-style-type: none"> <li>• One of first studies</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional</li> <li>• 57% response rate</li> <li>• Possible recall bias</li> </ul>	4
	Cross-sectional [66]	Increased risk with more experience	<ul style="list-style-type: none"> <li>• 87% response rate</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional</li> <li>• Related to injuries only</li> </ul>	4
	Retrospective cohort [67]	Increased risk with less experience  Independent risk factor		<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Injuries only</li> </ul>	2b
Running speed	Cross-sectional [66]	Increased risk with faster pace	<ul style="list-style-type: none"> <li>• 87% response rate</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional</li> <li>• Related to injuries only</li> </ul>	4
	Retrospective cohort [68]	Increased risk in the fastest and slowest runners (front and back of pack)	<ul style="list-style-type: none"> <li>• Large cohort</li> <li>• 19 races</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
Psychological factors	Review [69]	Both increased and decreased risk with different personality traits, runner mental preparation, runner motivation	<ul style="list-style-type: none"> <li>• Comprehensive review</li> </ul>	<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
	Review [70]	Both increased and decreased risk with different personality traits, runner mental preparation, and runner motivation	<ul style="list-style-type: none"> <li>• Comprehensive review</li> </ul>	<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
	Case-series [71]	Increased risk with hypnotic susceptibility and cognitive dissociation	<ul style="list-style-type: none"> <li>• Novel</li> </ul>	<ul style="list-style-type: none"> <li>• Case-series</li> </ul>	4
	Descriptive [47]	Increased risk in dissociating runners	<ul style="list-style-type: none"> <li>• Novel study</li> <li>• Large cohort</li> <li>• Long study period</li> </ul>	<ul style="list-style-type: none"> <li>• Descriptive design</li> <li>• Low response rate (36%)</li> <li>• Included only collapsed runners</li> </ul>	4

**Table 4.2.: Intrinsic and extrinsic risk factors associated with medical encounters in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)**

Extrinsic					
Environmental condition - warm	Review [72]	Increased risk in warmer conditions	<ul style="list-style-type: none"> <li>• One of first</li> </ul>	<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
	Review [73]	Increased risk in warmer conditions	<ul style="list-style-type: none"> <li>• Comprehensive</li> </ul>	<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
	Review [69]	Increased risk in warmer conditions		<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
	Retrospective review [74]	Increased risk in warmer conditions	<ul style="list-style-type: none"> <li>• Data from various marathons</li> <li>• Developed calculation of a WBGT 'do not start' number</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
	Retrospective cohort [75]	Increased risk in warmer conditions  Independent risk factor	<ul style="list-style-type: none"> <li>• Detailed weather records</li> <li>• Multiple linear regression analysis</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
	Retrospective cohort [76]	Increased risk in warmer conditions  Independent risk factor	<ul style="list-style-type: none"> <li>• 7 years data</li> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
Environmental condition - cold	Position statement [77]	Increased risk in colder conditions	<ul style="list-style-type: none"> <li>• Comprehensive review of data</li> </ul>	<ul style="list-style-type: none"> <li>• Position statement</li> </ul>	5
	Review [73]	Increased risk in colder conditions	<ul style="list-style-type: none"> <li>• Comprehensive review of race data</li> </ul>	<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
	Review [69]	Increased risk in colder conditions		<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
Participant number	Retrospective cohort [68]	Increased risk with increasing participant numbers	<ul style="list-style-type: none"> <li>• Large cohort</li> <li>• 19 races</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
Course geography	Cross-sectional study [78]	Increased risk towards end of race and uphill	<ul style="list-style-type: none"> <li>• Simple way of identifying 'clusters'</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Datasets from different years</li> <li>• Convenience sampling method</li> </ul>	4
	Retrospective cohort [76]	Increased risk with steep gradients, longest climbs and towards the finish line	<ul style="list-style-type: none"> <li>• 7 years data</li> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
Runner education	Descriptive [47]	Decreased risk in educated runners	<ul style="list-style-type: none"> <li>• Novel study</li> <li>• Large cohort</li> <li>• Long study period</li> </ul>	<ul style="list-style-type: none"> <li>• Descriptive design</li> <li>• Low response rate (36%)</li> <li>• Included only collapsed runners</li> </ul>	4

#### **4.6.1. Intrinsic risk factors associated with any medical encounter in distance running events**

##### *a. Running speed*

It has been shown that both the faster (front) and slower (back) runners in the race are more likely to present to the medical facilities with a medical encounter [68]. The front runners are generally more motivated with definite achievement goals for various reasons and may be more likely to ignore early warning signs of medical conditions such as EAC. It has been proposed that there may be a failure of psychological and physiological regulatory mechanisms in these runners, associated with a strong psychological drive to override them, which can potentially lead to a medical complication [70]. In contrast to the aforesaid, the slowest runners are exposed to a longer ongoing risk and may potentially be less trained, may have underlying chronic disease or risk factors and be less experienced. These are important potential risk factors for any medical encounters and need to be explored in future studies.

##### *b. Running experience*

There are some studies reporting that more experienced runners are more likely to present with a medical complication [65] [79]. Conversely, there are also data to support the hypothesis that show that less-experienced runners are more likely to develop a medical complication [80] [67].

##### *c. Psychological factors*

It is well-known that most medical encounters occur at or close to the finish line [79] [81] [78]. There are numerous proposed reasons for this. A potential reason is that the runner's motivation to finish the race may result in them ignoring the sensory feedback from their body until after the finish line [71]. Various proposed theories have been discussed, more specifically related to EAC and the psychological reasons behind this. However, one can argue that these factors may be related to any medical complication, especially at or near the finish line [70].

More recently a descriptive study, over 8 years, was conducted on runners participating in a Swedish marathon which focused on collapsed runners. The aim of the study was to find a perceived risk profile among these runners [47]. The study was conducted by way of questionnaires completed by each individual runner who collapsed. The findings showed that

the affected runners lacked an ability to decide whether to withdraw from the race, despite adverse symptoms. The runners involved were unable to adjust their pacing and put meaning to their symptoms. These varying mental traits may indicate a distinctive profile for a collapsing athlete and possibly also for other athletes presenting with medical encounters, especially at the finish line. It is recommended that these factors are explored in future well-designed studies.

#### **4.6.2. Extrinsic risk factors associated with any medical encounter in distance running events**

##### *a. Environmental conditions*

The incidence of medical encounters tends to increase in “extreme” environmental conditions that are not limited to only heat and humidity, but also extends to cold and rainy conditions [69, 73, 82]. The incidence of medical encounters increases in both warmer and cool conditions and the most beneficial environmental conditions appear to be when the WBGT range is in the range of 4-15 °C [73]. It is important to note that an increase in medical encounters has been related to the warmest temperature during the race and not only the temperature at the start of the race. Heat-and-cold-related medical encounters have been well documented in distance running events. The risk factors associated with the development of specific heat- and cold-related illness medical encounters will be explored separately and discussed in section 4.4.1. of this chapter.

##### *i) Heat*

The relationship between the incidence of injury, illness and environmental conditions in distance running events has been widely recognised [75, 83]. One of the initial studies related to ambient temperature was conducted on the runners participating in the 14 km Sydney City-to-Surf run [75]. The results showed that in successive runs, the injury and illness pattern correlated with the ambient temperatures. In a further recent study conducted in Australia, it was shown that there was a significant positive linear association between the ambient temperature and the overall incidence of medical encounters, specifically heat and physical exhaustion casualties [76]. Furthermore, this study showed a significant relationship between type of medical encounter and meteorological conditions. On cooler days only 30% of medical encounters are related to exhaustion, and this increases up to 70% on warmer days.

WBGT has been considered a better indicator of heat stress than temperature alone. Thus, a retrospective cohort study was conducted on the effect of WBGT Wet Bulb Globe Temperature (WBGT) and marathon finishing times in seven marathons across the USA and Canada and is of particular interest [84].

Definition:  $WBGT = (0.7T_w + 0.2T_b + 0.1T_d)$

$T_w$ : wet bulb temperature

$T_b$ : black globe temperature

$T_d$ : ambient temperature

The results of a multiple regression analysis showed significantly slower finishing times as the WBGT increased, and this was more profound in the slower runners. One of the strengths of this study was that the slower runners were also included, compared to previous studies that only evaluated elite male runners [85, 86]. It is therefore suggested that slower runners are exposed to risk for a longer period, with a potential increase in the incidence of medical encounters.

In a retrospective review it has been shown that the number of medical encounters and runners whom did not finish a race increased as the WBGT (both the starting WBGT and incident WBGT) increased [74]. This has often led to a race cancellation. Based on this knowledge, the authors proposed a do-not-start temperature of  $> 20.5\text{ }^{\circ}\text{C}$  in their respective races [74]. This recommendation is different for various race organisations and it has been suggested that each race should have their own ‘do-not-start’ WBGT based on previous experience and race data [74].

#### *ii) Cold*

It is known from the literature that there is an increased runner dropout rate in cold conditions. In both wet and cold conditions, the medical encounter rate also increases [73, 77], specifically for cold-related illnesses [69, 82, 87].

### *b. Running distance and course location*

There are data to show that longer races are associated with a higher overall medical encounter rate. The medical encounter rate is consistently higher in longer races, such as the Twin Cities Marathon [88], the Boston Marathon [89], the Vancouver International Marathon [64], the Baltimore Marathon [90] and the London Marathon [91] when compared to the shorter distances such as the Sydney City-to-Surf races [92], the Army 10-miler [93] and the recently documented 10 km USA races [68]. However, these races are all conducted in different conditions and among varying running populations. Further studies are required on this topic, preferably when races of different distances are conducted under the same conditions (race day). Furthermore, there are studies in ultramarathons documenting course location where medical encounters occurred [94, 95].

### *c. Participant number (race size)*

The results of recent review of 10 km road races in the USA showed an increased event rate of 0.36 / 1000 runners for each additional 500 finishers [68]. To our knowledge, this is one of the first studies evaluating race size as a risk factor associated with medical encounters. It is suggested that future studies should include races of increasing distances to establish whether this event rate will concurrently increase with increasing distances. However, it was pointed out by the author that the possibility exists that larger races may have more substantial budgets for provision of medical care (regardless of race distance). This may result in medical facilities that are potentially be more accessible, better marked and advertised to runners and with greater number of volunteer staff, thus increasing the capacity of staff to see medical encounters. To the best of our knowledge this was only documented in one study and requires to be explored further in future well designed studies.

### *d. Course geography*

A novel study was recently conducted in the world's largest 14 km fun run. The aim of the study was to characterise patterns of medical encounters linked to the geographical location across the course and to further evaluate the type of medical encounter with location and meteorological conditions [76]. This retrospective study was conducted over a period of seven years. A cluster of cardiovascular events was found at the top of the longest climb of the race ("heartbreak hill") and a cluster of musculoskeletal medical encounters emerged at the parts of course with the steepest negative gradients.

*e. Runner education and perception of race difficulty by geographical areas*

There are limited data from literature suggesting that educating runners regarding certain factors may reduce the risk of developing a medical encounter. These include educating runners on factors such as fluid intake, the danger of running with possible infections, the risk factors associated with chronic disease and numerous other relevant issues [67, 69, 77].

Of interest are data from a recent study where 237 half-marathon runners were interviewed post-race. Runners found the race to be most exhausting in certain areas on the course that were then identified with GPS position. The aim of this was to possibly correlate these areas with ambulance pick-up points [78]. There was a high level of agreement between geographical points identified by runners and the points where ambulance transfers were needed. Runner perception of race course difficulty and risk of medical encounters needs further investigation.

## **Summary**

There are several intrinsic and extrinsic risk factors associated with medical encounters in distance running events and these have been summarised (Table 4.2.).

Knowledge of the risk factors associated with any medical complication is important for race medical directors to plan medical care at a mass participation distance running event. Preventative strategies can be designed and implemented to reduce the risk of medical encounters in runners. These strategies could include planning related to environmental conditions (season in the year), time of day, participant numbers and race technicality.

It is of note studies relating a do-not-start temperature to incidence of medical encounters were mainly from races in the Northern hemisphere. It is therefore recommended that future well designed studies also focus on distance running races in the Southern hemisphere where the runners may be differently acclimatised. Educating the runner is also a key important factor. These include information about training pre-race, pacing in the race and knowledge related to their own health risk factors. More recent studies show that the psychological profile of the runners is related to the risk of developing medical complications. Therefore, pre-race educational initiatives aimed at the mental preparedness of runners should be explored in future studies [47]. In the future, well-designed prospective cohort studies are

required to identify independent risk factors associated with any medical complication in distance running events.

#### **4.7. A REVIEW OF THE RISK FACTORS ASSOCIATED WITH MEDICAL ENCOUNTERS BY ORGAN SYSTEM**

In this section the risk factors associated with medical encounters by organ system will be reviewed per organ system. As in the Chapter 2 review, this section will follow the classification of medical encounters by organ systems, as described in the recently published international consensus document [96].

##### **4.7.1. A review of the risk factors associated with medical encounters in multiple organ systems in distance running events**

The common specific medical conditions that classified as “multiple organ medical encounters” are exertional heatstroke and fluid and electrolyte disorders [96]. The risk factors associated with these two common medical encounters follows.

###### **4.7.1.1. *A review of the risk factors associated with exertional heatstroke in distance running events***

Exertional heatstroke (EHS) is one of the most serious medical encounters than can occur in distance running and is potentially life-threatening. This condition occurs when excess heat, generated by muscular exercise, exceeds the body’s heat dissipation rate resulting in an elevated core body temperature that damages body tissues, leading to potentially fatal multiple organ failure [97]. The fatality rate from heatstroke is about 5%, therefore it is very important to identify possible risk factors associated with EHS [98, 99].

EHS is by and large a preventable medical complication. It is widely accepted that EHS occurs when exercising at high intensity in hot, humid environments, combined with a lack of heat acclimatisation and poor physical fitness.

The intrinsic and extrinsic risk factors associated with EHS are summarised and will be discussed. Of note is that athletes and military recruits largely share the same risk factors

associated with EHS, therefore in this section reference is made to the relevant studies in military populations.

### **a. Intrinsic risk factors associated with exertional heatstroke in distance running events**

#### *i. Male sex*

Recent reports show that the incidence of classic heatstroke presenting to USA Emergency Departments over two years is 2.8 times higher in males (1.99 visits / 100 000; 95% CI = 1.81-2.16) compared to females (0.71 visits / 100 000; 95% CI =0.63-0.79) [100]. There are also other reports showing that EHS may have a higher incidence in males compared with females [101]. However, males are more exposed in EHS prone situations (e.g. military, American Football), therefore case reports and case series of EHS may simply be as a result of activities where more males participate in races or military training [102, 103] [104, 105]. On the other hand, males may be predisposed to develop EHS due to morphological (i.e. muscle mass, body surface area-to-mass ratio), sex specific hormonal or psychological differences. As the percentage of female participants in distance running increased over the past decade, distance races may constitute a more accurate study population to study the true incidence of EHS in males and females [18].

An analysis of incidence differences between male and female runners was addressed in a recent retrospective cohort study. The study population included the participants of the Flying Pig Cincinnati Marathon (n=11 593 finishers) and half-marathon (n=34 470 finishers) over a 3-year period (n=46 063 finishers) [106]. The results showed a significantly higher incidence of EHS in males (2 / 1000 finishers) compared to the female marathon runners (0.4 / 1000 finishers). There was, however, no difference in the incidence of EHS in male and female half-marathon runners (0.3 / 1000 finishers for both male and females). The limitation of this study is the possibility of underreporting cases that occurred before the end of the race. Further well-conducted prospective cohort studies are required to establish the true incidence of EHS in male and female race starters.

#### *ii. Extremes of age*

It has been suggested that extremes of age (<15 years or >65 years) are at increased risk of classic heatstroke [107-109]. However, to our knowledge, no similar direct association has been found for EHS.

### *iii. Increased Body Mass Index*

A body mass index (BMI) of 18.5 to 25 is considered normal and a BMI above 25 is considered overweight. An increased BMI is associated with a relatively smaller body surface area needed for heat dissipation through evaporation. Therefore, with an increase in body weight, the metabolic heat production increases and heat dissipation decreases [110]. In one case series conducted in the Israeli Defence Force all cases of EHS during exercise over a 20-year period were documented. Of the 134 cases of EHS, 64% were classified as being overweight [97]. These findings are in agreement with those of a case-control study conducted on EHS to determine possible risk factors. In this study, male Marine Corps recruits in basic training were observed over a four-year period. The results showed that a higher BMI (BMI >26 compared to BMI <22) was an independent risk factor for heatstroke [111]. An increased risk of EHS in overweight athletes or military recruits is well documented in other studies [110, 112-114]. In summary, there is good evidence that a higher BMI is an independent risk factor for EHS.

### *iv. Dehydration*

Dehydration (of more than three percent) is associated with reduced endurance exercise performance, decreased time to exhaustion and increased heat storage [101, 115-118]. However, heatstroke also occurs in shorter distances, where dehydration often does not develop [68]. To date there are no well-conducted prospective cohort studies to confirm dehydration as an independent risk factor for EHS.

### *v. Recent or current acute illness*

A history of recent or current acute respiratory, gastrointestinal or other infections has been associated with EHS [92, 97, 119]. In an early retrospective cohort study on the City to Surf race, 23% of the 179 heatstroke cases reported a recent acute illness [92]. Further case-control and case series also showed this association, such as a case series in a military population, in which 20% of all the cases identified with EHS over a 20-year period were documented as having an underlying acute illness [97]. Therefore, there are some data to suggest a possible relationship between recent or current acute illness and EHS. However, this remains to be confirmed in well-conducted prospective studies.

#### *vi. Sickle cell trait*

Sickle cell disease (SICD) or sickle cell trait (SCT) is a condition where an individual has an abnormal haemoglobin (haemoglobin S) that is unstable and can cause red blood cells to sickle during times of physiological stress. If an individual inherits two haemoglobin S genes, they have a sickle cell disorder [120]. Patients with the sickle cell disorder have a higher likelihood of a significant painful crises related to the sickling of their red blood cells when they participate in exercise.

The SCT refers to individuals, (including athletes) that carry only one haemoglobin S genes. In African-Americans the prevalence of SCT is eight percent [120]. These athletes are predisposed to sickling during times of stress with exercise. There are several reports linking sudden cardiac death (SCD) to the SCT and it is important to note that some of these deaths have been associated with EHS [121, 122]. However, data directly linking SCT to EHS are limited and are mostly from published case-studies or case series.

A retrospective case series documented all deaths that occurred during military training in the U.S. Air Force over a 30-year period [123]. A total of 85 deaths occurred during exertion - seven of these cases were SCT-positive. This study concluded that the relative risk for non-traumatic deaths between SCT-positive and non-SCT-positive was 23.53 [123]. The literature regarding the risk of EHS and SCT remains inconclusive, however, emphasising the need for further well-conducted prospective cohort studies.

#### *vii. Malignant hyperthermia*

Malignant hyperthermia (MH) is an autosomal dominant, potential life-threatening condition. It is triggered in susceptible individuals by exposure to potent inhalational anaesthetic agents and the muscle relaxant, suxamethonium. More than 50% of families with MH have mutations in the gene coding of ryanodine receptor (RYR1) [124]. The clinical characteristics of MH may have similarities to that of EHS [125] and may be considered a stress syndrome, of which heatstroke is one manifestation. Further studies are required to explore the association between a genetic predisposition for MH and EHS.

#### *viii. Comorbid medical conditions*

A history of underlying chronic diseases has been associated with a higher incidence of classic heatstroke in a large national retrospective cohort study [100]. Results showed that

patients with a comorbid medical condition may have a weakened cardiovascular response to heat and the associated use of medication for the comorbid conditions may reduce sweating and impair thermoregulation [126]. The risk of EHS in runners may therefore also be related to underlying chronic diseases, [127] but more specific studies are required to study this relationship.

*ix. Previous history of heatstroke*

There are case reports of recurrent EHS in individuals [128]. Recurrence of EHS may be related to an underlying genetic disorder such as SCT, MH or Fabry's disease [122, 124, 129]. Furthermore, recurrent EHS can be associated with the use of certain medication [130]. Thus, there are a variety of potential primary risk factors that may predispose a runner to recurrent EHS, and this requires further study.

*x. Heat acclimatization*

There is some evidence that there are more cases of EHS at the start of the season when athletes are not acclimatised to heat [101, 105, 131]. In one retrospective cohort study the incidence of EHS was documented in two separate Melbourne triathlons, one at the start of the triathlon season and the second three months later. The geographical location and environmental conditions were similar. Of the 1884 participants in the first triathlon, 15 presented with EHS, whereas in the second triathlon with 2000 participants, three months later, there were no documented cases of EHS [131]. These results suggest that at the start of the season, when athletes were less likely to be acclimatised they were more likely to develop EHS in similar environmental conditions. Further studies are required to confirm such an association.

*xi. Level of physical fitness*

Sporting events and physical training may cause athletes and military personnel to undertake tasks that exceed their physical capacity. Individuals with the lowest maximal aerobic capacity (i.e.  $VO_2\text{max} \leq 40\text{ml/kg/min}$ ) are often less heat tolerant [119, 132, 133]. Less fit individuals are often required to function at a higher exercise capacity to maintain pace when running in a group. Poorly-conditioned athletes are more likely to have a higher rectal temperature on completing the run versus individuals with a higher  $VO_2\text{max}$  [101]. A case series reported data of 10 runners with EHS and showed an association with a slower running pace and EHS [119]. In a further case series conducted over 20 years in the Israeli Defence

force, 57% of the 134 EHS cases had low levels of physical fitness [97]. Further well-conducted prospective studies are required to explore the association between level of physical fitness and the risk of developing EHS.

#### *xii. Sleep deprivation*

Sleep deprivation has also been suggested as a risk factor for EHS. In one case series from Israel, 44% of all the EHS cases suffered from sleep deprivation [97] and reported a higher incidence of deaths among the EHS cases related to sleep deprivation. This was studied in a laboratory-based observational study which explored the relationship between sleep deprivation and EHS. Fourteen healthy participants were studied by walking for 40 minutes in a hot room after a night of normal sleep (NS) and a night of partial sleep restriction (PSR). Results showed a significant increase in rectal temperature in the PSR group during walking compared with the NS group [134]. The exact mechanism by which sleep deprivation can affect EHS risk is not known. However, it is suggested that changes in serum cortisol and growth hormone concentrations may play a role, as these hormones are known to affect temperature regulation [135]. This indicates the need for further research to determine the relationship between sleep deprivation and EHS.

#### *xiii. Over motivation*

In a case series of EHS events in the Israeli army, more than 50% of cases were identified during the initial six months of service [136]. The desire to push physical limits and over-motivation was often linked to EHS. Further studies are required to evaluate this as a risk factor for EHS.

#### *xiv. The use of medication and other substances*

Various medications and substances from different classes have been associated with an increased risk of EHS [137, 138]. Medications may increase the risk of EHS by the following possible mechanisms: 1) negatively affecting heat dissipation by various mechanisms such as reduction of sweat production (e.g. antihistamines, anticholinergics), alteration of skin blood flow (e.g. calcium channel blockers, female reproductive hormones, capsaicin), reduction of cardiac contractility (e.g. B-adrenergic or calcium channel blockers), 2) increase heat production, or 3) alteration (elevation) of the hypothalamic set point (e.g. amphetamines, salicylates, dopamine and noradrenaline reuptake inhibitors) [138-140]. The use of specific medication classes that may predispose to EHS have been described [127]. Further well-

conducted studies are needed to study the association between the different medication and medication classes and the development of EHS.

## **b. Extrinsic risk factors associated with exertional heatstroke in distance running events**

### *i. Hot, humid environmental conditions*

It is widely accepted the incidence of that heatstroke increases in hot and humid environmental conditions [141-144][145]. The incidence of EHS in distance running races is much higher when races are conducted in hot and humid conditions, rather than during cooler environments [141-144, 146][145]. However, there are also reports that EHS can occur in cool conditions [98, 119, 147]. EHS mostly occurs in higher temperatures. One of the races with the highest incidence of EHS is the 11 km Falmouth Road race in Massachusetts (USA), which takes place in the height of summer. Over an 18-year period, the incidence of EHS was 213 / 100 000 runners [148], which is substantially higher than an incidence of about 100 / 100 000 runners at the Twin Cities Marathon, the Chicago Marathon and the Marine Corps Marathon (over two years, based on 30 cases) [146]. Further studies directly linking the risk of EHS to a measure of environmental conditions, the WBGT, will now be reviewed.

### *ii. Wet bulb globe temperature/Physiological equivalent temperature*

The risk of EHS is higher if the WBGT is  $>15^{\circ}\text{C}$  [146] and the greatest risk for EHS exists when the WBGT exceeds  $28^{\circ}\text{C}$  [128, 149]. However, in a review on WBGT, it was confirmed that humans cope well in extreme environments (e.g. fire fighting in the Australian bush), by modifying their behaviours. WBGT is of value when used in defined populations and circumstances, but the WBGT underestimated the stress of low wind movement and high humidity, both of which add to the restriction of heat loss by evaporation [150].

In a recent novel study, other rational indices, such as the physiological equivalent temperature (PET) index and Universal Thermal Climate index (UTCI) were evaluated against the WBGT [151]. This study was conducted over an 8-year period in the Gothenburg Marathon. During this period associations between these 3 indices and both the rate of ambulance required assistance and collapses were evaluated. The PET index showed the strongest correlation with both of these, followed by the UTCI [151]. In summary, the WBGT and possibly the PET score in future could be used as a guide to determine the risk of developing EHS.

### *iii. Increased intensity of exercise*

High intensity exercise (heart rate > 80% of maximum capacity) is one of the leading risk factors of developing EHS [97, 152, 153]. This is indicated in a prospective cohort study investigating the relationship between running pace and post-race rectal temperatures, in 30 recreational runners participating in a marathon in South Africa. Post-race rectal temperature was significantly related to total metabolic rate for the 42.2 km and during the last 6 km of the race [152]. Of note is that increases in rectal temperature were not clinically significant in any of the participants. Therefore, this is not an independent risk factor for EHS, but merely for elevated post-race rectal temperature.

### *iv. Shorter race distance*

It has been suggested that shorter race distances are associated with an increased incidence of exertional heatstroke when compared with longer race distances [74, 88] due to the higher exercise intensity [148, 154]. The shorter Falmouth 11 km road race has up to 10-fold increase in the incidence of EHS compared to longer marathons [74, 88]. Future studies should the incidence of EHS in races of different distances, but in similar environmental conditions.

### *v. Clothing and protective gear*

Evaporative heat loss is a critical factor in thermoregulation for the athlete [127]. Wearing of clothing and uniforms that restrict evaporative heat loss have been associated with EHS [127, 155]. These studies were limited to sporting activities other than distance running and future well-designed studies to evaluate a possible association between clothing and protective gear as a potential risk factor for EHS in distance running are required.

### *vi. Cumulative effect of heat exposure*

The cumulative effect of heat exposure resulting from multiple days of exercising in the heat may be associated with an increased risk of developing EHS [119]. A case study on a male soldier illustrated this phenomenon. The soldier took part in a multiday high-intensity monitored exercise regimen at 41.2° C. At day three he was asymptomatic with rectal temperatures of 38.3-38.9° C and by day five he lost 5.4 kg body weight and the baseline temperature increased to 39.6°C. However, on day eight he developed EHS [116]. Compared to the other 13 recruits in this study who maintained their weight and completed the protocol without incident. It can be postulated that the accumulative heat, in association with

dehydration, affected his heat tolerance ability. This is elucidated in a case-crossover study which was conducted to determine whether cumulative daily average WBGT index, over one or two preceding days, is a predictor for EHS. The study was conducted on the recruits in basic training at Marine Corps, USA. Environmental data were obtained for 2069 cases of EHS and randomly selected control periods before and after each EHI episode [156]. The results of the study showed evidence for a cumulative effect of previous day's heat exposure on EHS risk.

#### *vii. Combined risk factors*

It is hypothesised that an accumulation of predisposing factors is associated with heatstroke. In one study, a combination of predisposing risk factors impaired heat tolerance [111] while a combination of risk factors was found to be associated with poorer survival outcomes of EHS [97]. The effect of multiple risk factors on the risk of EHS requires investigation in future studies.

### **Summary**

There are several studies showing a causal relationship between heatstroke and certain risk factors, but well-conducted prospective cohort studies are required to identify independent risk factors associated with EHS. In this review the only independent risk factor for EHS was a higher BMI. Heatstroke is a serious life-threatening and potentially fatal medical condition in distance running and other sports and these further stresses the need for future research in this area.

In conclusion, over the past 10 years the incidence of EHS, specifically deaths, remains high, with incidences in some countries being the highest ever recorded [157]. In future studies, the phenomenon of global warming and how this relates to EHS would be of interest.

#### **4.7.1.2. *A review of the risk factors associated with electrolyte disorders in distance running events***

##### **Exercise-associated hyponatraemia**

The most common and well-documented electrolyte disorder in distance running events is exercise-associated hyponatraemia (EAH). The risk factors associated with EAH will now be reviewed.

##### **Risk factors associated with EAH in distance running events**

A number of case control, cross-sectional studies, retrospective cohort studies, prospective cohort studies and randomised controlled trials reported possible risk factors associated with EAH (Table 4.3.) The following have been identified as potential risk factors associated with EAH in distance runners: female sex, longer finishing times, higher ambient temperature, increased body weight during the race, body mass index extremes, use of medication, excessive water or fluid intake, composition of fluid ingested, syndrome of inappropriate antidiuretic hormone secretion (SIADH), increased AVP, rhabdomyolysis and IL-6 release from muscles. Some of the risk factors may be modifiable. The evidence that these risk factors are associated with EAH in distance runners will now be discussed (Table 4.3.).

**Table 4.3.: Intrinsic and extrinsic risk factors associated with EAH in distance running events (by risk factors, study design and study reference, main finding/s, strengths, limitations and level of evidence)**

Risk factor	Study design and study reference	Main finding/s	Strengths	Limitations	Level of Evidence [15]
<b>Intrinsic</b>					
Sex	Case series [158]	Females at higher risk	<ul style="list-style-type: none"> <li>• Good follow-up/outcome</li> </ul>	<ul style="list-style-type: none"> <li>• Case-series</li> <li>• Hikers</li> <li>• Small sample size</li> </ul>	4
	Case series [159]	Females at higher risk	<ul style="list-style-type: none"> <li>• ICU details known</li> </ul>	<ul style="list-style-type: none"> <li>• Case-series</li> <li>• Small sample size</li> </ul>	4
	Case-control [160]	No difference in risk between males and females	<ul style="list-style-type: none"> <li>• Larger sample size</li> <li>• Single race</li> </ul>	<ul style="list-style-type: none"> <li>• Case-control</li> </ul>	4
	Retrospective cohort [161]	Females at higher risk Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> <li>• 2 years data from same race</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective study</li> </ul>	2b
	Prospective cohort [162]	Females at higher risk Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective study</li> <li>• Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>• Triathletes</li> <li>• Asymptomatic EAH</li> </ul>	1b
	Prospective cohort [163]	No difference between males and females	<ul style="list-style-type: none"> <li>• Prospective cohort</li> <li>• Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>• 67% follow-up - less likely in females</li> </ul>	4
BMI extremes	Prospective cohort [163]	Increased risk with a low BMI (<20) Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective cohort</li> <li>• Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>• Runners self-report of fluid intake</li> </ul>	4
Weight changes	Retrospective cohort [164]	Increased risk with weight gain Independent risk factor	<ul style="list-style-type: none"> <li>• Largest cohort to date (n=2135)</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Also included other endurance races</li> </ul>	2b
	Prospective cohort [162]	Increased risk with weight gain Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Triathletes</li> <li>• Asymptomatic EAH</li> </ul>	1b
	Prospective cohort [163]	Increased risk with weight gain Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective cohort</li> <li>• Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>• 67% follow-up</li> </ul>	4
	Prospective cohort [165]	Increased risk with weight loss	<ul style="list-style-type: none"> <li>• Prospective cohort</li> <li>• One of few studies showing contrast in results to weight gain</li> </ul>	<ul style="list-style-type: none"> <li>• No pre-race [Na] examined</li> <li>• 45% of the consenting runners finished race</li> </ul>	

**Table 4.3.: Intrinsic and extrinsic risk factors associated with EAH in distance running events (by risk factors, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)**

Runner experience	Prospective cohort [166]	Increased risk with less experience	• Prospective study design	• Small sample size	1b
	Prospective cohort [165]	Increased risk with less experience	• Prospective study design	• No pre-race [Na] examined • Only 45% of consenting participants finished race	1b
	Prospective cohort [167]	Increased risk with less experience	• Prospective study design	• Small % of finishers developed EAH(6%)	1b
Serum-CK level	Prospective cohort [166]	Increased risk with higher s-CK levels	• Prospective study design	• Small sample size	1b
	Prospective cohort [167]	Increased risk with higher s-CK levels	• Prospective study design	• Small % of finishers developed EAH(6%)	1b
Rhabdomyolysis	Case report [168]	Increased risk with rhabdomyolysis	• Of first reported cases	• Case report	4
	Case report [169]	Increased risk with rhabdomyolysis		• Case report	4
	Case-control [170]	Increased risk with rhabdomyolysis	• Detailed blood analysis	• Case-control • Included ultra-runners and cyclists • No follow-up >1 day	4
	Retrospective cohort [171]	Increased risk with rhabdomyolysis	• One of first 'cluster' reports	• Retrospective cohort • Small sample size	2b
Use of medication (NSAIDs)	Case series [159]	Increased risk with rhabdomyolysis	• All 7 runners used NSAIDs	• Case-series • Small sample size	4
	Case-control [172]	Increased risk with rhabdomyolysis	• Single race	• Case-control • Recall bias	4
	Retrospective cohort [161]	Increased risk with rhabdomyolysis	• Large sample size • 2 years data from same race	• Retrospective design	2b
	Prospective cohort [163]	No effect	• Prospective cohort • Large sample size	• 67% follow-up	1b
	Prospective cohort [173]	Increased risk with rhabdomyolysis	• Prospective design	• Small sample size • Haematocrit and haemoglobin not measured (volume)	1b
Failure to suppress AVP	Case-control [174]	Increased risk with failure to suppress AVP	• One of first studies	• Case-control • Small sample size	4
	Cross-sectional [175]	Increased risk with failure to suppress AVP	• Large sample size	• Cross-sectional design	4
	Prospective cohort [173]	Increased risk with failure to suppress AVP	• Prospective design	• Small sample size	1b
IL-6	Case-control [174]	Increased risk with IL-6 elevation	• One of first studies	• Case-control • Small sample size	4
	Prospective cohort [173]	Increased risk with IL-6 elevation	• Prospective cohort	• Small sample size	1b

**Table 4.3.: Intrinsic and extrinsic risk factors associated with EAH in distance running events (by risk factors, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)**

Risk factor	Study design and study reference	Main finding/s	Strengths	Limitations	Level of Evidence [15]
<b>Extrinsic</b>					
Excessive fluid intake	Review [176]	Increase risk with excessive fluid intake	<ul style="list-style-type: none"> <li>Comprehensive summary</li> </ul>	<ul style="list-style-type: none"> <li>Editorial review</li> </ul>	5
	Case report [177]	Increase risk with excessive fluid intake		<ul style="list-style-type: none"> <li>Case report</li> <li>Triathlete</li> </ul>	4
	Case series [178]	Increase risk with excessive fluid intake	<ul style="list-style-type: none"> <li>Prospective case-series</li> </ul>	<ul style="list-style-type: none"> <li>Triathletes</li> </ul>	4
	Case-control [160]	Increase risk with excessive fluid intake  Independent risk factor	<ul style="list-style-type: none"> <li>Larger sample size</li> <li>Single race</li> </ul>	<ul style="list-style-type: none"> <li>Case-control</li> </ul>	4
	Retrospective cohort [164]	Increase risk with excessive fluid intake  Independent risk factor	<ul style="list-style-type: none"> <li>Largest cohort to date (n=2135)</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> <li>Also included other endurance races</li> </ul>	2b
	Retrospective cohort [166]	Independent risk factor	<ul style="list-style-type: none"> <li>Large cohort</li> <li>5 years data re-analyzed</li> </ul>	<ul style="list-style-type: none"> <li>Lower rates of EAH in last 2 years possibly due to runner education</li> </ul>	2b
	Prospective cohort [162]	Increase risk with excessive fluid intake  Independent risk factor	<ul style="list-style-type: none"> <li>Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>Triathletes</li> <li>Asymptomatic EAH</li> </ul>	1b
	Prospective cohort [163]	Increase risk with excessive fluid intake  Independent risk factor	<ul style="list-style-type: none"> <li>Prospective cohort</li> <li>Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>67% follow-up</li> </ul>	4
Fluid composition	RCT [179]	No effect	<ul style="list-style-type: none"> <li>RCT</li> </ul>	<ul style="list-style-type: none"> <li>Triathletes</li> </ul>	1c
	Prospective cohort [163]	No effect	<ul style="list-style-type: none"> <li>Prospective cohort</li> <li>Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>67% follow-up</li> </ul>	1b
	Prospective cohort [180]	No effect	<ul style="list-style-type: none"> <li>Prospective cohort</li> </ul>	<ul style="list-style-type: none"> <li>Bloodwork only at finish line</li> <li>Post-race questionnaire subject to recall bias</li> </ul>	1b
Higher ambient temperature	Case report [181]	Increased risk with higher ambient temperatures		<ul style="list-style-type: none"> <li>Case report</li> </ul>	4
	Case series [182]	Increased risk with higher ambient temperatures	<ul style="list-style-type: none"> <li>One of first case-series</li> </ul>	<ul style="list-style-type: none"> <li>Case-series</li> </ul>	4
	Case series [158]	Increased risk with higher ambient temperatures	<ul style="list-style-type: none"> <li>Good follow-up/outcome</li> </ul>	<ul style="list-style-type: none"> <li>Case-series</li> <li>Hikers</li> </ul>	4
	Retrospective cohort [166]	Significant positive relationship with higher ambient temperatures	<ul style="list-style-type: none"> <li>Large cohort</li> <li>5 years data re-analyzed</li> </ul>	<ul style="list-style-type: none"> <li>Lower rates of EAH in last 2 years possibly due to runner education</li> </ul>	2b
	Prospective cohort [183]	Increased risk with higher ambient temperatures  Independent risk factor	<ul style="list-style-type: none"> <li>Prospective cohort</li> <li>Multisite</li> <li>First study to show hot climates as independent risk factor</li> </ul>	<ul style="list-style-type: none"> <li>Possible referral bias as only English-speaking runners included (of 25 countries)</li> </ul>	1b

**Table 4.3.: Intrinsic and extrinsic risk factors associated with EAH in distance running events (by risk factors, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)**

Finishing time	Case-control [160]	Increased risk with a longer finishing time Independent risk factor	<ul style="list-style-type: none"> <li>• Larger sample size</li> <li>• Single race</li> </ul>	<ul style="list-style-type: none"> <li>• Case-control</li> <li>•</li> </ul>	4
	Retrospective cohort [161]	Increased risk with a longer finishing time Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> <li>• 2 years data from same race</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> </ul>	2b
	Prospective cohort [163]	Increased risk with a longer finishing time Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective cohort study</li> </ul>	<ul style="list-style-type: none"> <li>• 67% follow-up</li> </ul>	1b

## **a. Intrinsic risk factors associated with EAH in distance running events**

### *i. Female sex*

Most case studies on hyponatraemia report an apparently disproportionate number of females compared with males [158, 159, 161, 162, 184]. Therefore, female sex has been proposed to be a risk factor for EAH [161].

However, not all studies have shown this; in a retrospective case-control series conducted at the 2000 Houston marathon, the incidence of EAH was similar in males and females (5/ 1000 in females and 4/ 1000 in males) [160]. In a further prospective cohort study, conducted at the 2002 Boston marathon, hyponatraemia developed in more female than male runners but female sex was not an independent risk factor associated with EAH [163].

Therefore, being a female runner may be a risk associated with EAH, but this may be attributable to other factors such as body size and longer racing time, rather than sex per se. In summary, sex, specifically the female sex, has not consistently been shown to be an independent risk factor associated with EAH.

### *ii. Excessive fluid consumption, fluid overload and body weight gain*

There is strong evidence that fluid overload is the main cause of EAH [133, 158, 160-162, 178, 181, 182, 185-189]. There is good evidence that EAH is predominantly a dilutional hyponatraemia caused by an increase in total body water relative to the amount of total exchangeable [Na<sup>+</sup>][158, 160, 161, 163, 181, 182, 186, 190-194] [162, 164, 177, 195-200].

The primary etiological factor in cases of EAH that have been well studied is consumption of fluids (water or sports drinks) more than total body fluid losses resulting from insensible (transcutaneous, respiratory and gastrointestinal) sweat and urine losses [176, 184, 201]. In summary, excessive fluid intake has been shown to be an independent risk factor for the development of EAH [160, 162-164].

There is also strong evidence to suggest that runners who consume excessive fluid during exercise gain weight during exercise and that this is a risk factor for EAH [163, 164, 202]. Body weight gain was found to be an independent risk factor in the multivariate analysis in a prospective cohort study conducted at the 2002 Boston marathon [163]. In the largest

retrospective review to date in 2135 athletes participating in eight different endurance races, it was estimated that athletes who gained more than four percent of body weight during exercise had an 85% probability of developing EAH [164]. However, not all athletes who develop EAH gained weight during exercise, and this suggests that while excessive consumption of fluids is a clear risk factor for EAH, it is not the only risk factor. However, runners that lose weight during an event, rarely develop EAH, more specifically severe EAH [160].

*iii. Body mass index (BMI)*

In one prospective cohort study at the Boston marathon, a low body mass (BMI <20) was found to be an independent risk factor for EAH [163].

*iv. Rhabdomyolysis*

Various studies and case reports have suggested a bilateral association between EAH and rhabdomyolysis [168, 169, 171]. An observational study investigated this association in seven different ultra-endurance races and sports (i.e. multi-stage mountain biking, 24-h mountain biking, 24-h ultra-running and 100 km ultra-running) [170]. The results showed that hyponatraemic athletes tended to develop exercise-induced rhabdomyolysis more frequently than the normonatraemic athletes. In a further observational study on 15 participants of a 104 km run, serial bloods samples were taken for serum sodium and creatine kinase before, during and after the race [203]. The results supported the possibility that transient hyponatraemia preceded a significant higher elevation in creatine kinase during the race. This association needs to be investigated further with level 1 and level 2 studies.

*v. Failure to suppress arginine vasopressin (AVP) during exercise*

It has been suggested that in some individuals, there is an inability to maximally suppress AVP secretion during exercise and this may contribute to the pathogenesis of EAH if voluntary fluid intake were to exceed fluid output. Evidence in support of this hypothesis originates from several studies [173-175] and the mechanism may be related to interleukin-6 and inflammatory markers.

vi. *Interleukin-6*

It is proposed that AVP may be stimulated by the release of inflammatory markers, especially interleukin-6 (IL-6). IL-6 has been shown to increase during exercise in both a physiological (where it is involved in the mobilisation of energy stores) and a pathological (secondary to inflammation of muscle breakdown) manner, and that this increase may act as a trigger for AVP production [201].

In one study, conducted on runners in the 2001 Boston marathon, it was suggested that IL-6 release from damaged muscles may play a role in the non-osmotic secretion of arginine vasopressin, thereby linking rhabdomyolysis to the pathogenesis of EAH [174]. In a further study, 15 participants in ultra-marathons were evaluated and a significant association between AVP and IL-6 was found ( $p < 0.05$ ) [173].

In summary there is evidence that failure to suppress AVP during exercise may be associated with EAH and that IL-6 release from damaged muscles may play a role in this. Further well-conducted level 1 and level 2 studies are required.

**b. Extrinsic risk factors associated with EAH in distance running events**

*i. Longer finishing times*

There is evidence to suggest that runners with longer finishing times have a higher fluid intake and therefore a higher potential to develop EAH. In a retrospective cohort study conducted during the 1998 and 1999 San Diego marathons, a longer finishing time was suggested as a risk factor for EAH [161]. There was also a significant inverse linear relationship between both longer finishing times and lower serum sodium levels in a retrospective case-control study in the 2000 Houston marathon, [160]. Finally, in a prospective cohort study during the 2002 Boston marathon, a longer finishing time was reported as an independent risk factor associated with EAH [163]. In conclusion, there is good evidence that a longer finishing time is an independent risk factor associated with EAH.

*ii. Higher ambient temperature*

It is well known that there is an association between ambient environmental conditions and certain medical conditions during running, including EHS, hypothermia and EAC. In most cases where EAH has been reported in marathon runners, high ambient temperatures have

been documented [158, 161, 181, 182]. It has been suggested that the runners reduce their running speed in the heat, and furthermore that there is a perception that ‘fatigue’ is associated with ‘dehydration’. This may encourage slower runners to actively rehydrate more than what is required to maintain fluid balance. Hence, the tendency to overhydrate because of the heat may explain a relationship between higher ambient temperatures and the risk of developing hyponatraemia [160].

However, the relationship between higher ambient temperatures and increased incidence of EAH has not been reported consistently. The incidence of “asymptomatic” hyponatraemia was documented in three races covering 161 km (100 miles) in North America. Two of the said races took place in high ambient temperatures of up to 37° C [204] [165] and the incidence of EAH ranged between 300 - 512 / 1000 finishers. In the other 161 km race, ambient temperatures ranged between 8° C and 4° C, and an incidence of EAH of 440 / 1000 finishers was reported [205]. Despite these differences in ambient temperatures, the incidence of EAH was similar in these races.

A very recent prospective cohort study was conducted on the runners of the 2017-2018 “RacingThePlanet” races to evaluate the effect of hot environmental conditions on serum sodium concentration [183]. A total of 266 runners enrolled and post-race bloods for serum sodium were collected in 171 runners (76%). A total of 98 of the runners ran in hot race environmental conditions. The results from a multilinear regression analysis showed significantly lower serum sodium concentrations for those runners running with higher temperatures. The novelty of this study was that it was the first study to show that hot environmental conditions are an independent risk factor for EAH. Further studies to reproduce these findings are needed.

### *iii. Use of medication*

It is well established that athletes ingest NSAID before and during an event [172, 206, 207]. There is some evidence to suggest that endurance athletes who consume NSAIDs during exercise may have a higher risk of developing EAH.

Initial evidence came from observations in case reports and a retrospective study [159, 161]. In a further prospective cohort study, conducted during the New Zealand Ironman, pre and post-race blood markers showed a significantly lower post-race serum sodium concentration

in a group of athletes taking NSAIDs. However, the documented EAH was not symptomatic EAH [200]. In contrast, data from another prospective study, conducted at the Boston marathon, show that NSAID use was not an independent risk factor for EAH [163].

Finally, a recent prospective cohort study was conducted on 28 participants of a UK marathon where investigators evaluated the use of NSAID on serum sodium concentration [172]. The results show a significant reduction ( $p=0.0039$ ) in serum sodium concentration over the course of the marathon in participants who used NSAIDs, while athletes who did not use NSAIDs had an increase in serum sodium concentration. However, a multiple linear regression analysis of these data did not show a significant difference. This study confirmed the findings of previous studies of an association between the use of NSAID and EAH, but NSAID use was not an independent risk factor for EAH.

In summary, it is not clear whether the relationship between NSAID use and EAH is causal. The possibility that NSAIDs increase the risk for EAH because they increase the activity of arginine vasopressin (AVP) requires further investigation. There is a need for further well-conducted level 1 and 2 studies.

#### *iv. Composition of fluid ingested*

It has been suggested that the composition of fluid ingestion, particularly fluids containing sodium, can reduce the risk of EAH, but this is not supported by a number of studies [163, 179, 208]. These studies include prospective cohort studies [163, 208] and an RCT [179]. In an RCT conducted during the 2001 Cape Town Iron Man, South Africa, there was no difference in the serum  $[Na^+]$  of those athletes who ingested salt tablets vs those ingesting placebo tablets [179].

In summary, well conducted (level 1 and level 2) studies show that the composition of ingested fluid is not an independent risk factor associated with EAH. In addition to these data, it has, however, been shown that longer term reduction in dietary sodium intake can result in plasma sodium reductions both pre-race and during exercise when fluid losses and consumption are large and this may potentially have adverse influences on the physiology during exercise [209, 210]. This requires further investigation in well-designed long-term studies.

Hyponatraemia associated with distance running and other endurance exercise, [158, 182, 192, 195, 211] appears to be a preventable condition. The primary risk factors associated with EAH are excessive fluid intake and failure to suppress AVP. The failure to suppress AVP can markedly reduce the ability of the kidneys to excrete a water load. Other independent risk factors associated with EAH that were identified in this review are longer finishing times, body weight gain during exercise, high BMI and running in hot environmental conditions. Additional possible risk factors, not shown in multivariate regression analyses to be independent risk factors, include the use of certain medication, exertional rhabdomyolysis, IL-6 elevation and female sex. Data from well-conducted randomised controlled trials showed that the composition of the fluid ingested is not an independent risk factor associated with EAH.

## **4.7.2. Cardiovascular system**

### **4.7.2.1. Exercise-associated collapse (EAC)**

EAC is currently thought to be primarily the result of transient postural hypotension caused by lower extremity pooling of blood when the runner stops running and the concomitant impairment of cardiac baroreflexes [133, 212]. In this literature review, where the terminology orthostatic intolerance (OI) or exercise-associated postural hypotension (EAPH) was used to describe this condition, this will be referred to as EAC (as discussed in chapter 2).

### **Risk factors associated with EAC in distance running events**

EAC has been associated with intrinsic and extrinsic factors and these will be discussed in this section.

#### **a. Intrinsic risk factors associated with EAC in distance running events**

##### *i. Heat and dehydration*

It has been postulated that dehydration leading to hyperthermia is a risk factor for EAC [213-215]. Heat stress has been shown to reduce baroreflex control in response to an orthostatic challenge [216]. Furthermore, heat stress and dehydration have been suggested to impair aerobic performance due to cardiovascular strain and reduction of  $\text{VO}_2$  max [217].

The effect of heat stress on cerebral blood flow (CBF) and cerebral vascular resistance (CVR) was investigated in 15 athletes in a laboratory setting. A subset of eight athletes was also exposed to lower body negative pressure (LBNP) in both normothermic and heat stressed conditions. The data showed a significant reduction in CBF and increase in CVR in heat stress and that the reduction in the CBF for a given orthostatic challenge is significantly greater in heat stress [218]. Therefore, it was suggested that increase in whole body heating, in association with even greater increases in CVR during orthostasis and heat stress, likely contribute to EAC. Results from two laboratory studies suggest that laboratory-induced hypovolemia changes baroreflex control of blood pressure. The limitations of these studies were that both had only a small number of athletes as participants [219, 220].

In contrast, results from a larger study in 31 runners completing an 80 km ultra-marathon showed that collapsed runners did not have a higher body temperature compared to those runners that did not collapse. Although all the runners were dehydrated, the level of dehydration was not related to the degree of postural hypotension on completion of the run [221]. Therefore, there are no data to show that either heat or dehydration are independent risk factors associated with EAC and there are no level 1 or level 2 studies to support these as risk factors for EAC in endurance athletes [222]. Further well-designed studies are required to evaluate both heat and dehydration and their combined effect as a potential risk factor for EAC.

#### *ii. Baroreflex modulation*

Pooling of blood in the lower extremities upon termination of exercise has been suggested as the main pathophysiological mechanism for EAC. If an increase in systemic vascular resistance, which is reduced by exercise, is not triggered by an intact baroreflex after stopping exercise, a LBNP develops and postural hypotension may occur [223]. A detailed review of the pathophysiology of baroreflex modulation is beyond the scope of this dissertation but in summary, there is good evidence from level 2 studies supporting an attenuated baroreflex response as the principle mechanism responsible of EAC. [219, 224-227].

#### *iii. Sex*

Data from several studies show that females have an increased incidence of EAC [228-232]. In a laboratory-controlled trial, conducted on 10 woman and 13 men, EAC in females was associated with decreased cardiac filling rather than decreased vascular resistance [225]. It

has also been shown that females have less responsiveness in mechanisms that underlie blood pressure regulation under orthostatic challenge [228] which has been confirmed in a number of studies conducted in outer space [229, 230, 232]. In summary, there is good evidence suggesting that females, compared with males, are at increased risk of EAC, based on differences in cardiac responsiveness.

#### *iv. Hypoglycaemia*

Data from laboratory clinical trials show that hypoglycaemia decreases baroreflex sensitivity due to impaired autonomic function [233]. This may be of importance, as serum glucose concentrations can decrease as the duration of exercise increases, which may predispose endurance athletes to EAC [223]. However, this has not been investigated and further level 1 and level 2 studies are required to determine if hypoglycaemia as an independent risk factor for EAC.

#### *v. Hypo- and hypercapnia*

Breathing carbon dioxide (CO<sub>2</sub>) is well known to induce hypercapnic acidosis and to affect the chemoreceptor regulation of the cardiovascular system. The effects of breathing CO<sub>2</sub> upon tolerance to orthostatic stress was investigated in a laboratory-based clinical trial in 9 athletes. The results showed that during hypercapnic conditions, as compared to normocapnia, there was a significant increase in orthostatic tolerance during LBNP [234]. In another clinical trial, 9 men completed a 24-hour exercise trial and were compared with a 24-hour sedentary control group. The results showed that during prolonged exercise, postural hypotension and hypocapnia exacerbate cerebral hypoperfusion and facilitate syncope [235]. The clinical relevance of these studies is that hyperventilation resulting in hypocapnia may be a risk factor for EAC in runners. However, this hypothesis requires further investigation.

#### *vi. Use of medications*

There is evidence that several medications may cause postural hypotension. It is well established that many cardiovascular medications including beta-blockers, ACE inhibitors, diuretics, angiotensin 2 receptor blockers, calcium channel blockers, alpha-2 receptor agonists and combined alpha and beta-blockers affect the cardiovascular response to exercise [236] and these medications will not be reviewed. However, other classes of medication that are also commonly prescribed may also cause postural hypotension. For the purpose of this

dissertation, the possible role of these other commonly used non-cardiac medications, which are also used by runners, in causing postural hypotension will be briefly discussed.

### *1. Antidepressants*

There is evidence from case series studies that the use of antidepressant medication is associated with postural hypotension [237, 238]. The results of studies show that there was a significant impairment of all cardiovascular responses in patients using antidepressant medication, and that both cholinergic and adrenergic blockade are affected by such agents [238-240]. In summary, postural hypotension is associated with the use of antidepressant medication and is caused largely by failure of reflex peripheral vasoconstriction.

### *2. H<sub>1</sub> and H<sub>2</sub> receptor antagonists*

There is data from RCTs that both H<sub>1</sub> and H<sub>2</sub> receptor antagonists affect post-exercise hypotension [241, 242]. Two RCTs were conducted testing both H<sub>1</sub> (n=14) [241] and H<sub>2</sub> (n=10) receptor antagonists [242] to determine their potential contribution to post-exercise hypotension [241]. In both these RCTs, healthy normotensive men and woman were observed before and through to 90 min after 60 min bout of cycling at 60%. The findings showed a marked reduction in post-exercise hypotension in the H<sub>1</sub> and H<sub>2</sub> receptor antagonist groups versus the placebo groups [241]. H<sub>1</sub> and H<sub>2</sub> receptor antagonists may be protective or used as prophylaxis in the high risk EAC group. This association between the intake of H<sub>1</sub> and H<sub>2</sub> antagonist and the reduction of post-exercise hypotension requires further study in larger cohorts.

### *vii. Pacing strategies and psychological factors*

In a recent review it was proposed that pacing strategies may relate to risk of developing EAC [70]. A higher psychological drive may be associated with an increased risk of EAC. The hypothesis is that there may be a diminished sensitivity to interoceptive feedback, situational appraisal or even very high motivational drive which could potentially increase the risk of EAC. Factors postulated to be responsible are the finding that athletes collapse at or near the finish line, near cut-off times for medals and near race closure times, which may implicate the psychological drive [243-245]. Further well-designed studies are required to evaluate pacing and to explain psychological drives as potential risk factors.

## Summary

In conclusion, EAC is one of the most common medical encounters presenting to the medical tent following distance running and other endurance events. It is characterised by collapse following a race in the absence of CNS, biochemical or hyperthermic abnormalities. The current evidence supports that EAC and postural hypotension is primarily caused by an attenuated baroreflex response, which results in the pooling of blood in the lower extremities. There is limited evidence that EAC is caused primarily by dehydration or heatstroke. There may be contributory factors that alter the baroreflex response including the use of certain medications, hypoglycaemia and hypocapnia associated with hyperventilation. Further evidence shows that females are at higher risk to develop EAC due to a decrease in cardiac filling, rather than baroreflex modulation. The role of pacing and psychological factors as potential risk factors associated with EAC require further investigation.

### 4.7.3. Respiratory system

In general, respiratory tract medical complications are common in distance runners [246-251]. Athletes, and more specifically, distance runners, are at increased risk to develop upper and lower airway dysfunction [252], particularly infections. Numerous epidemiological studies, including observational and case series, have supported the “J” curve relationship between exercise load (intensity and duration) and the risk of upper respiratory tract infections [246, 247, 253]. The “J” curve model suggests that a moderate exercise “load” improves immune function compared to sedentary individuals, whereas prolonged high intensity exercise may impair the immune system [254] in recreational athletes. This does not necessarily apply to elite athletes, where the relationship between exercise “load” and risk of respiratory tract infections resembles more an “S shaped” curve [248, 255, 256] with a lower risk of infection at high training loads. The general relationship between risk of respiratory tract infections and training / competition load was recently reviewed [246, 256] and a further discussion on the relationship between exercise, the immune system and the general respiratory infection risk in athletes is beyond the scope of this dissertation.

Respiratory illness related medical encounters in period after an endurance running event are common. One of the first studies investigating the occurrence of symptoms of URTI associated with completing a distance race was conducted in 1983. In a prospective cohort

study, 150 participants were randomly selected from entrants in the 56 km Two Oceans Marathon, Cape Town, South Africa. Symptoms of post-race URTI occurred in 33,3% (0.03/ 1000) of runners compared to 15.3% (0.02/ 1000) of non-running age matched controls. The results suggested a relationship between acute stress and susceptibility to symptoms of URTI [251]. Similarly, a cross-sectional epidemiological study was conducted to analyse the relationship between self-reported symptoms of URTI and 42 km marathon participation. The runners included a randomly selected group of 4926 of the 12 200 entrants of the Los Angeles marathon. Seven days post-race, questionnaires were sent out to these pre-identified runners, and 2311 runners responded. There was a significant increase in symptoms of URTI following the marathon [247]. In contrast, no increased symptoms of infection post marathon were found in a prospective cohort study where participants of the Stockholm marathon were randomly selected to participate in a pre- and post-marathon questionnaire related to symptoms of infection [248]. The group consisted of 1694 participants (17% of race finishers). The pre-race incidence of symptoms of infection was 17% and the post-race incidence was 19%. In this specific study there was no evidence of increased symptoms of infection rate post long-distance running [248]. Risk factors associated with post-race respiratory tract infections will not be reviewed because the focus of this dissertation is on medical encounters on race day.

### **Risk factors associated with respiratory tract infections during distance running events**

The most common respiratory medical encounter during distance running events is infection, although in comparison to other medical encounters, including EAMC, EAC, GIT and dermatological medical encounters, the risk is low. There are limited data documenting risk factors associated with respiratory medical encounters in distance runners during an event with only a few studies on intrinsic and extrinsic risk factors associated with respiratory tract infections. The majority of studies only report symptoms of respiratory tract infection which were not confirmed either clinically or documented with laboratory tests. In the studies reviewed below, it will be mentioned which studies only reported symptoms and which have actual documented infection.

#### **4.7.3.1 *Intrinsic risk factors associated with respiratory tract infections during distance running events***

##### *a. Age*

In a prospective cohort study on marathon runners, younger age was shown to be an independent risk factor for symptoms of a post-race infectious episode [248].

##### *b. Pre-race symptoms of infections*

A longitudinal observational field study on 14 runners participating in the 86.5 km Comrades ultra-marathon in South Africa was conducted to investigate the association between symptoms of pre-race upper respiratory tract infections (URTI) and the occurrence of symptoms of post-race URTI. In this group, 10 runners had symptoms of self-reported URTI in the four weeks pre-race, and eight of these reported symptoms of URTI two weeks following the race. The results of the study may indicate reactivation of pre-race viral infections that then explain post-race infectious symptoms when runners were exposed to the stress of a distance running race [257]. The limitations of this study were the small sample size, athlete self-reporting of symptoms and the fact that the diagnosis of infections was not confirmed. In a prospective cohort study on a much larger number of participants (n=1694; 17% of finishers) in the Stockholm marathon, possible risk factors associated with post-race symptoms of possible infection were determined. Pre-race symptoms of infection were found to be an independent risk factor for post-race symptoms of infections [248].

##### *c. Pre-race salivary IgA*

In a prospective study, the effect of a 12-week endurance training intervention on salivary proteins and symptoms of URTI was studied in 25 young men (age 34.6 years) [258]. Thirteen of the men developed symptoms of URTI and 12 remained asymptomatic. Basal salivary IgA concentrations were significantly higher ( $p < 0.05$ ) in the asymptomatic group in both the pre- and post- training period. Limitations of this study included the small study sample size, the fact that it was training data and not event data, and only symptoms and not actual confirmed URTI was measured. Future well-conducted studies are thus required to study the relationship between pre-race salivary IgA and the development of URTIs.

##### *d. Probiotic use*

A double-blind, placebo-controlled, crossover trial was conducted to evaluate the ability of a probiotic *Lactobacillus fermentum* (PCC) to enhance mucosal immunity in elite distance runners. Over a period of four months, 20 male distance runners were given a daily dose of PCC and another group received a placebo. The results showed that prophylactic PCC was associated with a significant reduction in days and severity of respiratory symptoms of illness in these trained distance runners. The results may be explained by maintenance of interferon (IFN)gamma levels [259]. The limitation to this study was again that it was related to training data and not specifically for an endurance event.

*e. Other nutritional interventions*

Other nutritional interventions may also affect risk of developing respiratory tract infections during a race. A pilot study was conducted to evaluate the effect of Montmorency cherry juice on parameters of exercise-induced stress and symptoms of URTI following a marathon run [260]. Twenty recreational runners consumed either cherry juice or placebo before and after a marathon. In the placebo group, the incidence and severity of symptoms of URTI was significantly higher at 24 hrs and 48 hrs after the race (vs. baseline), and was also higher than the cherry juice group ( $p < 0.05$ ). None of the runners in the cherry juice group reported any symptoms while 50% of the placebo group developed symptoms. The post-race increases in blood CRP, measured at 24 hours and 48 hours post-race, was significantly lower in the cherry juice group vs. the placebo group.

Similar results were shown in another double-blind trial in 27 trained endurance runners, in which the effect of a short-term supplementation of a powdered tart cherry supplement before and after a half-marathon on markers of inflammation and oxidative stress was determined [261]. Participants ingested the supplementation for 10 days before the race, on race day and 48 hours post-race. The results showed that in the powdered tart cherry supplementation group, there was a 47% lower concentration of inflammatory markers and a linear increase in antioxidant activity at 24 hours and 48 hours of recovery.

There is also evidence from an RCT that the ingestion of carbohydrate containing beverages during a marathon, was effective in attenuating increases in plasma cytokines and stress hormones [262, 263]. Further studies are required to evaluate if nutritional interventions can reduce the risk of developing respiratory tract infections during a race.

#### *f. Menstrual status*

The effects of amenorrhea on mucosal immune function and susceptibility to symptoms of URTI in female elite distance runners was studied in a retrospective case-control study [264]. A group of 20 runners were divided into two groups, based on their status during past year of either eumenorrhea (n=8) or amenorrhoea (n=13). Participants reported symptoms of URTI during the past month and this was correlated to salivary IgA and oestradiol and progesterone concentrations in the blood. The salivary IgA and oestradiol were significantly lower ( $p < 0.05$ ) in the amenorrhoea group than the eumenorrhea group and a higher frequency of symptoms of URTI was reported in the amenorrhoea group. The results suggested that athletes with amenorrhoea and lower oestrogen have a downregulation of salivary immune function which may enhance the susceptibility for symptoms of URTI. Future well-designed studies to further evaluate evidence for this risk factor are required, specifically related to endurance running events.

#### **4.7.3.2. *Extrinsic risk factors associated with respiratory tract infections during distance running events***

##### *a. Training distance*

The association between weekly training distance and symptoms of URTI was investigated in a cross-sectional study on the participants of the Los Angeles Marathon. The results of this study showed an increased weekly training distance of  $\geq 97$  km/week (vs. less than 32 km/week) to be an independent risk factor for self-reported symptoms of URT infections [247]. The limitations to this study are that the data regarding symptoms were self-reported and was limited to training data, and no diagnosis of infection was confirmed. It is well known that a large percentage of perceived infection may be allergy-related [265-268]. A further prospective cohort study also investigated the effect of training distance on the occurrence of symptoms of infection during a race. This study was conducted on 1694 randomly selected runners in the Stockholm marathon-and found no relation between training distance and symptoms of an infection [248].

##### *b. Cold*

In a recent study the effect on selected immunological, biochemical and haematological parameters was investigated in a group of 15 runners during a 100 km ultramarathon in extreme cold ( $-1^{\circ}\text{C}$  to  $+1^{\circ}\text{C}$ ) [269]. This study found an association between the markers of

acute inflammation (i.e. neutrophils, immature neutrophils, platelets and monocytes) and the markers of muscle damage (i.e. platelets, CK and LDH) under cold conditions with severe stress on the body. Limitations to this study were that there was no control group running in warmer conditions. The effects of environmental conditions, particularly exposure to cold dry air, as an independent risk factor for respiratory tract illness medical encounters during a race requires further investigation.

## **Summary**

In summary, there is some evidence that younger age and pre-race respiratory symptoms of URTI are independent risk factors associated with race symptoms of URTI. However, there is conflicting evidence if training distance is associated with an increased occurrence of symptoms of URTI during a race. The administration of certain probiotics is associated with a significant reduction in the incidence and severity of symptoms of respiratory tract infections. Running in cold environments affects the markers of inflammation and further studies to correlate this with symptoms of URTI are required. Furthermore, it is possible that a non-infectious inflammatory response is responsible for the increase in specific symptoms of URTI in runners [270]. This suggestion is further supported by the fact that local anti-inflammatory nasal sprays have been shown to reduce symptoms of URTI [271]. This coupled with the fact that there are limited data regarding risk factors associated with developing other respiratory medical encounters in distance running, stresses the need for further research in this area.

### **4.7.4. Central nervous system**

#### **4.7.4.1. *Exercise-Associated Muscle Cramps***

According to the recent consensus statement, Exercise-associated muscle cramps (EAMC) are classified as a central nervous system medical encounter. EAMC is one of the most common medical encounters in distance running events and the risk factors associated with EAMC in distance runners will be summarised.

### **Risk factors associated with EAMC in distance running events**

Various studies identified intrinsic and extrinsic risk factors that are associated with EAMC and these are summarised in Table 4.4. [209, 272-276]. In a few studies, multivariate analyses identified independent risk factors associated with EAMC [274, 277-279].

**Table 4.4.: Risk factors 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 [15]
<b>Intrinsic</b>					
Age	Cross-sectional [279]	Increased age at higher risk (> 35 years)	<ul style="list-style-type: none"> <li>Included 3 different marathons</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> <li>Low response rate (17%)</li> </ul>	4
	Prospective cohort [277]	No effect	<ul style="list-style-type: none"> <li>Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>Small sample size</li> </ul>	1b
Sex	Cross-sectional [279]	Males at higher risk  Independent risk factor	<ul style="list-style-type: none"> <li>Included 3 different marathons</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> <li>Low response rate (17%)</li> </ul>	4
	Prospective cohort [277]	No effect	<ul style="list-style-type: none"> <li>Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>Small sample size</li> </ul>	1b
Exercise intensity/pace	Case-control [278] <sup>a</sup>	Increased risk with faster running pace  Independent risk factor	<ul style="list-style-type: none"> <li>Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>Case-control</li> <li>Possible recall bias</li> <li>Study in triathletes</li> </ul>	4
	Prospective cohort [277]	Increased risk with faster pace  Independent risk factor	<ul style="list-style-type: none"> <li>Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>Small sample size</li> </ul>	1b
	Prospective cohort [280]	No effect	<ul style="list-style-type: none"> <li>Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>Study in triathletes</li> </ul>	1b
Exercise duration	Cross-sectional [279]	Increase risk with longer exercise duration	<ul style="list-style-type: none"> <li>Included 3 different marathons</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> <li>Low response rate (17%)</li> </ul>	4
	Cross-sectional [281] <sup>b</sup>	Increase risk with longer exercise duration		<ul style="list-style-type: none"> <li>Cross-sectional design</li> <li>Rugby players</li> </ul>	4
Running experience	Cross-sectional [274]	Increased risk with more running experience  Independent risk factor	<ul style="list-style-type: none"> <li>Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> <li>Possible recall bias</li> </ul>	4
	Cross-sectional [279]	Increased risk with more running experience  Independent risk factor	<ul style="list-style-type: none"> <li>Included 3 different marathons</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> <li>Low response rate (17%)</li> </ul>	4
BMI	Cross-sectional [279]	Increased risk with a higher BMI (>30)  Independent risk factor	<ul style="list-style-type: none"> <li>Included 3 different marathons</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> <li>Low response rate (17%)</li> </ul>	4
	Prospective cohort [280]	No effect	<ul style="list-style-type: none"> <li>Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>Study in triathletes</li> </ul>	1b

**Table 4.4.: Risk factors 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)**

Height	Case-control [278] <sup>a</sup>	Increased risk with increased height  Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> <li>• Novel finding</li> </ul>	<ul style="list-style-type: none"> <li>• Case-control</li> <li>• Possible recall bias</li> <li>• Study in triathletes</li> </ul>	4
Family history of EAMC	Case-control [278] <sup>a</sup>	Increased risk with a positive family history of EAMC  Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> <li>• Novel finding</li> </ul>	<ul style="list-style-type: none"> <li>• Case-control</li> <li>• Possible recall bias</li> <li>• Study in triathletes</li> </ul>	4
	Cross-sectional [279]	Increased risk with a positive family history of EAMC  Independent risk factor	<ul style="list-style-type: none"> <li>• Included 3 different marathons</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Low response rate (17%)</li> </ul>	4
Previous history of EAMC	Case-control [278] <sup>a</sup>	Increased risk with a previous history of EAMC  Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>• Case-control</li> <li>• Possible recall bias</li> <li>• Study in triathletes</li> </ul>	4
	Cross-sectional [209]	Increased risk with a previous history of EAMC  Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>• Case-control</li> <li>• Possible recall bias</li> </ul>	4
	Prospective cohort [280] <sup>a</sup>	Increased risk with a previous history of EAMC  Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Novel finding</li> </ul>	<ul style="list-style-type: none"> <li>• Study in triathletes</li> </ul>	1b
	Prospective cohort [277]	Increased risk with a previous history of EAMC  Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Small sample size</li> </ul>	1b
Dehydration	Case-control [282] <sup>a</sup>	No effect		<ul style="list-style-type: none"> <li>• Case-control</li> <li>• Study in triathletes</li> <li>• Small sample size</li> </ul>	4
	Prospective cohort [283]	No effect	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Small sample size</li> </ul>	1b
	Prospective cohort [284]	No effect	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Drinking patterns and fluid losses not analyzed</li> </ul>	1b
	Prospective cohort [280] <sup>a</sup>	No effect	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Study in triathletes</li> </ul>	1b
NSAID use	Prospective cohort [285]	Decreased risk with the use of NSAID	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Influence of possible confounders not analyzed</li> </ul>	1b

**Table 4.4.: Risk factors 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)**

Other medications use	Cross-sectional [274]	Increased risk with the use of medication (statins, any medication)  Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> <li>• Only known study in distance runners to show this</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Possible recall bias</li> <li>• No direct cause-effect relationship</li> </ul>	4
	Retrospective cohort [286]	Increased risk with the use of medication (diuretics, statins, B-agonists)  Independent risk factor	<ul style="list-style-type: none"> <li>• Long study period</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Study in general public</li> </ul>	2b
	RCT [287]	Increased risk with the use of B-agonists	<ul style="list-style-type: none"> <li>• RCT</li> </ul>	<ul style="list-style-type: none"> <li>• Small sample size</li> <li>• Study in general public</li> </ul>	1c
History of underlying chronic disease	Cross-sectional [274]	Increased risk with a history of underlying chronic diseases  Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> <li>• Novel finding</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Possible recall bias</li> <li>• No direct cause-effect</li> </ul>	4
Stretching	Cross-sectional [279]	Decreased risk with stretching  Independent risk factor	<ul style="list-style-type: none"> <li>• Included 3 different marathons</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Low response rate (17%)</li> </ul>	4
	Cross-sectional [275]	Decreased risk with stretching	<ul style="list-style-type: none"> <li>• One of first studies</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> </ul>	4
Muscle glycogen and energy stores	RCT [288]	Decreased risk in the onset of EAMC, but no difference in EAMC	<ul style="list-style-type: none"> <li>• RCT</li> </ul>	<ul style="list-style-type: none"> <li>• Small sample size</li> </ul>	1c
Pre-race/during race muscle damage	Prospective cohort [277]	Increased risk with pre-race/during race muscle damage	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Novel finding</li> </ul>	<ul style="list-style-type: none"> <li>• Small sample size</li> </ul>	1b
	Cross-sectional [209]	Increased risk with pre-race/during race muscle damage  Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>• Case-control</li> <li>• Blood tests only post-race</li> </ul>	4

**Table 4.4.: Risk factors 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)**

Injury history	Cross-sectional [274]	Previous injury history at increased risk  Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Possible recall bias</li> </ul>	4
	Case-control [278] <sup>a</sup>	Previous injury history at increased risk  Independent risk factor	<ul style="list-style-type: none"> <li>• Large sample size</li> <li>• Novel finding</li> </ul>	<ul style="list-style-type: none"> <li>• Case-control</li> <li>• Possible recall bias</li> <li>• Timing relation to EAMC of past injury not recorded</li> <li>• Study in triathletes</li> </ul>	4
Genetic markers	Retrospective case-control [289]	Increased risk with genetic marker (COL5A1CC)	<ul style="list-style-type: none"> <li>• Novel finding with the COL5A1CC gene</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective case-control</li> </ul>	2b
Extrinsic					
Increased environmental temperature and humidity	Retrospective cohort [276] <sup>c</sup>	Increased risk with higher environmental temperatures and humidity	<ul style="list-style-type: none"> <li>• Included data from 5 universities</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Football players</li> <li>• Confounding variables (pre-season)</li> </ul>	2b

<sup>a</sup> Triathlon

<sup>b</sup> Rugby

<sup>c</sup> Football

There is good evidence from several prospective cohort studies that both dehydration and electrolyte disturbances are not risk factors associated with EAMC [280, 283, 284]. There is limited/weak evidence from case-control and cross-sectional studies that EAMC is associated with the following risk factors: increased age [279], increased exercise duration [281], both shorter and irregular daily stretching [275, 279], and increased environmental temperature and humidity [276].

In several studies, where multiple logistic regression analyses were done, the following independent risk factors associated with EAMC were identified:

1. Male sex
2. Increased exercise intensity/ faster pace
3. More running experience
4. Increased BMI
5. Increased height
6. A positive family history of EAMC
7. A previous history of EAMC

8. A history of the use of medication
9. Previous injury history
10. Pre-race muscle damage
11. Existing chronic disease
12. Positive genetic markers (COL5A1CC gene)

To date there are no meta-analysis reviews regarding the risk factors associated with EAMC [290] and future studies should focus on this.

#### **4.7.5. Gastrointestinal system**

Gastrointestinal tract (GIT) medical encounters in distance runners on race day are common (Chapter 2, section 2.5.5.). The occurrence of GIT encounters may limit exercise performance and participation [291-293].

#### **Risk factors associated with gastrointestinal tract encounters in distance running events**

There are various risk factors associated with GIT encounters. A review of the literature identified several intrinsic and extrinsic risk factors associated with GIT medical encounters and symptoms and these are shown in Table 4.5. Most of the risk factors described in the literature associated with GIT encounters in distance runners are identified from univariate analyses and in only a few studies, independent risk factors have been identified using multivariate models. Some of these risk factors may be modifiable. Of note is that some of the studies refer to GIT encounters in distance running in general and are not limited to a distance runner's race data or race participants presenting to medical facilities.

**Table 4.5.: Risk factors associated with GIT medical encounters in distance running events (by risk factor, study design and study reference, main finding/s and level of evidence)**

Risk factor	Study design and study reference	Main finding/s	Strengths	Limitations	Level of Evidence [15]
<b>Intrinsic</b>					
Use of analgesics	Prospective cohort [285]	Increased risk with use of analgesics  Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• 55% response rate</li> </ul>	<ul style="list-style-type: none"> <li>• Single race</li> </ul>	1b
Age	Cross-sectional [294]	Younger age at increased risk  Independent risk factor	<ul style="list-style-type: none"> <li>• Multilinear regression analysis</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Included training data</li> <li>• Response rate not available</li> <li>• Shorter races (5 km ;10 km)</li> </ul>	4
	Cross-sectional [295]	Younger age at increased risk  Independent risk factor	<ul style="list-style-type: none"> <li>• Response rate 62%</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Possible selection bias</li> </ul>	4
	Cross-sectional [296]	Younger age at increased risk  Independent risk factor	<ul style="list-style-type: none"> <li>•</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• 27% response rate</li> <li>• Included training data</li> </ul>	4
	Case-control [297]	Younger age at increased risk (<20 years)  Independent risk factor	<ul style="list-style-type: none"> <li>• One of first studies</li> </ul>	<ul style="list-style-type: none"> <li>• Study design</li> <li>• Cross-sectional design</li> <li>• 41.6% response rate</li> <li>• Possible selection bias</li> </ul>	4
Sex	Cross-sectional [295]	Females at higher risk  Independent risk factor	<ul style="list-style-type: none"> <li>• 62% response rate</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> </ul>	4
	Cross-sectional [296]	Females at higher risk		<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Included training data</li> <li>• Low response rate</li> </ul>	4
	Case-control [298]	No effect	<ul style="list-style-type: none"> <li>• Included intestinal permeability tests</li> </ul>	<ul style="list-style-type: none"> <li>• Study design</li> <li>• Small study size (n=24)</li> </ul>	4
BMI	Cross-sectional [294]	Increased risk with a higher BMI  Independent risk factor	<ul style="list-style-type: none"> <li>• Multilinear regression analysis</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional design</li> <li>• Included training data</li> </ul>	4
Less running experience	Cross-sectional [294]	Increased risk with less experience  Independent risk factor	<ul style="list-style-type: none"> <li>• As above</li> </ul>	<ul style="list-style-type: none"> <li>• As above</li> </ul>	4

**Table 4.5.: Risk factors associated with GIT medical encounters in distance running events (by risk factor, study design and study reference, main finding/s and level of evidence) (continued)**

Finish time	Cross-sectional [296]	Increased risk with a faster finishing time	<ul style="list-style-type: none"> <li>As above</li> </ul>	<ul style="list-style-type: none"> <li>As above</li> </ul>	4
Not completing race	Cross-sectional [295]	Increased risk if not completing the race  Independent risk factor	<ul style="list-style-type: none"> <li>As above</li> </ul>	<ul style="list-style-type: none"> <li>As above</li> </ul>	4
Composition of fluid intake	RCT [299]	Increased risk with intake of carbohydrate containing drinks  Independent risk factor	<ul style="list-style-type: none"> <li>RCT</li> </ul>	<ul style="list-style-type: none"> <li>Study relative smaller size (n=98)</li> </ul>	1b
	Cross-sectional [294]	Increased risk with intake of carbohydrate containing drinks  Independent risk factor	<ul style="list-style-type: none"> <li>See before</li> </ul>	<ul style="list-style-type: none"> <li>See before</li> </ul>	4
Fluid intake	Cross-sectional [300]	Increased risk with lower fluid intake	<ul style="list-style-type: none"> <li>Detailed data collection</li> </ul>	<ul style="list-style-type: none"> <li>Small study size</li> <li>Possible recall bias</li> </ul>	4
Temperature of fluid intake	RCT [301]	No effect	<ul style="list-style-type: none"> <li>RCT</li> <li>Both intestinal and cytokine profiles tested</li> </ul>	<ul style="list-style-type: none"> <li>Small test (n=12)</li> </ul>	1b
Dietary intake (pre-race)	Cross-sectional [302]	No effect	<ul style="list-style-type: none"> <li>High response rate (93%)</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> <li>Included training data</li> </ul>	4
	Cross-sectional [294]	No effect	<ul style="list-style-type: none"> <li>Multilinear regression analysis</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> <li>Training data included</li> </ul>	4
Dietary intake (during race)	Prospective cohort [293]	No effect	<ul style="list-style-type: none"> <li>Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>Race at 1,900 m altitude</li> </ul>	1b
	Cross-sectional [295]	Increased risk if not accustomed to the dietary intake	<ul style="list-style-type: none"> <li>Multilinear regression analysis</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> </ul>	4
	Cross-sectional [300]	Decreased risk with dietary fat intake	<ul style="list-style-type: none"> <li>Novel finding</li> </ul>	<ul style="list-style-type: none"> <li>Small sample size</li> <li>Other factors possibly involved</li> </ul>	4
Dehydration	RCT [303]	Increased risk with dehydration	<ul style="list-style-type: none"> <li>RCT</li> </ul>	<ul style="list-style-type: none"> <li>Only 16 subjects</li> <li>Laboratory study</li> </ul>	1b
	Cross-sectional [304]	Increased risk with dehydration	<ul style="list-style-type: none"> <li>One of first studies</li> </ul>	<ul style="list-style-type: none"> <li>Cross-sectional design</li> </ul>	4

**Table 4.5.: Risk factors associated with GIT medical encounters in distance running events (by risk factor, study design and study reference, main finding/s and level of evidence) (continued) (continued)**

Experiencing GIT symptoms out of the race	Cross-sectional [294]	Increased risk if experiencing GIT symptoms out of the race  Independent risk factor	• Multilinear regression analysis	• Cross-sectional design • Included training data	4
	Cross-sectional [302]	Increased risk if experiencing GIT symptoms out of the race  Independent risk factor	• High response rate (93%)	• Cross-sectional design • Included training data	4
Bacterial overgrowth	Case-series [305]	No effect	• Novel study in runners	• Study design	4
<b>Extrinsic</b>					
Environmental conditions	Non RCT [306]	Increased risk in warmer conditions	• Study design	• Laboratory based • 10 subjects	1c
	Non RCT [307]	Increased risk in warmer conditions	• Study design • Follow-up on previous study	• Laboratory based	1c
Race distance	Cross-sectional [304]	Increased risk with increasing distance	•	• Cross-sectional design • 39% response rate	4

In summary, the following are independent risk factors associated with GIT encounters in distance runners: female sex, younger age, higher BMI, not completing the race, less running experience, use of analgesics / NSAID medication, experiencing GIT encounters in general (outside of running), composition of fluid intake, dehydration, dietary intake during the race and warmer environmental temperature.

Of specific interest are the modifiable risk factors: use of analgesics, composition of fluid intake, dietary intake during the race and dehydration. Future larger, race specific high-level studies are required to further evaluate GIT medical encounters in distance running events.

#### **4.7.6. Genitourinary system**

One of the most serious complications of the genitourinary system that can occur in distance running is acute kidney injury (AKI), previously described as acute renal failure (ARF).

#### **4.7.6.1. *Acute kidney injury***

Until recently, definition and quantification of renal damage lacked definition. This has recently been addressed with the concept of AKI, where renal injury is classified based on changes in serum creatine (s-Cr) or changes in urinary output with increasing damage. Furthermore, this is important as episodes of increased s-Cr has been associated with an increased mortality rate [308-310]. Risk factors associated with AKI in distance running events will now be reviewed.

#### **Risk factors associated with AKI in distance running events**

Risk factors associated with AKI in distance running events have been investigated in several studies including case control/cross-sectional studies, [311-314] retrospective cohort studies [315], prospective cohort studies [316, 317], and a single RCT [318]. In a recently published systematic review, risk factors associated with AKI during endurance exercise were identified [319]. By analysing data from 11 case reports that included 27 individual cases requiring hospitalization, the risk factors associated with AKI were identified as rhabdomyolysis (in 85% cases), nephrotoxic medication use (66% cases) and recent or current systemic illness.

The results of all these studies, including the systematic review, are summarised in Table 4.6. From this review, a number of intrinsic and extrinsic risk factors associated with AKI in distance runners could be identified, including the following: exertional rhabdomyolysis, use of medication (especially NSAIDs), EAH, EHS, latent myopathy, dehydration, recent or current viral or bacterial infection and, more rarely, mitochondrial myopathies and enzyme deficiencies. These risk factors will now be briefly reviewed. For the purposes of this dissertation, only the most common risk factors will be discussed in detail and a summary of all the risk factors is depicted in Table 4.6.

**Table 4.6.: Risk factors associated with AKI 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 finding/s	Strengths	Limitations	Level of Evidence [15]
<b>Intrinsic</b>					
Exertional Rhabdomyolysis	Systematic review [320]	Increased risk with ER	<ul style="list-style-type: none"> <li>• Systematic review</li> <li>• Included 43 publications</li> </ul>	<ul style="list-style-type: none"> <li>• Included other endurance sports</li> </ul>	2a
	Systematic review [319]	Increased risk with ER	<ul style="list-style-type: none"> <li>• Systematic review</li> <li>• Included 11 studies</li> </ul>	<ul style="list-style-type: none"> <li>• Lacking long-term outcomes</li> </ul>	2a
	Retrospective cohort [321]	Increased risk with ER	<ul style="list-style-type: none"> <li>• Long study period (2003-2015)</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> </ul>	2b
	Review [322]	Increased risk with ER		<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
NSAIDs	RCT [318]	Increased risk and severity with NSAID use	<ul style="list-style-type: none"> <li>• RCT</li> <li>• Multi-site</li> </ul>	<ul style="list-style-type: none"> <li>• Results not reaching significance</li> <li>• Study did not fully explore causative relationship</li> </ul>	1b
	Systematic review [319]	Increased risk with NSAID use	<ul style="list-style-type: none"> <li>• See above (ER)</li> </ul>	<ul style="list-style-type: none"> <li>• See above (ER)</li> </ul>	2a
	Prospective cohort [317]	Increased risk with NSAID use	<ul style="list-style-type: none"> <li>• Prospective cohort</li> <li>• Multi-site</li> </ul>	<ul style="list-style-type: none"> <li>• Multi-stage ultramarathon events in desert</li> </ul>	1b
	Case series [171]	Increased risk with NSAID use	<ul style="list-style-type: none"> <li>• Good follow-up</li> </ul>	<ul style="list-style-type: none"> <li>• Case series</li> </ul>	4
	Case series [323]	Increased risk with NSAID use	<ul style="list-style-type: none"> <li>• 19 cases in 18 years from 1 race in 1 renal unit</li> </ul>	<ul style="list-style-type: none"> <li>• Case series</li> </ul>	4
	Case study [324]	Increased risk with NSAID use	<ul style="list-style-type: none"> <li>• One of first reported post-race</li> </ul>	<ul style="list-style-type: none"> <li>• Case study</li> </ul>	4
	Editorial review [325]	Increased risk with NSAID use		<ul style="list-style-type: none"> <li>• Editorial</li> </ul>	5
Exercise-associated hyponatraemia	Case series [171]	Higher risk with EAH	<ul style="list-style-type: none"> <li>• Good follow-up of outcomes</li> </ul>	<ul style="list-style-type: none"> <li>• Case series</li> </ul>	4
	Case series [312]	Higher risk with EAH	<ul style="list-style-type: none"> <li>• Good follow-up of outcomes</li> </ul>	<ul style="list-style-type: none"> <li>• Case-series</li> </ul>	4
	Case series [168]	Higher risk with EAH	<ul style="list-style-type: none"> <li>• Good follow-up of outcomes</li> </ul>	<ul style="list-style-type: none"> <li>• Case series</li> </ul>	4

**Table 4.6.: Risk factors associated with AKI in distance running events (by risk factor, study design and study reference, main finding/s, strengths, limitations and level of evidence) (continued)**

Exertional Heatstroke	Retrospective cohort [315]	Higher risk with EHS	<ul style="list-style-type: none"> <li>• Long study period (1980-2002)</li> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective design</li> <li>• Military study in recruits</li> </ul>	2b
	Case study [308]	Higher risk with EHS	<ul style="list-style-type: none"> <li>• Detailed documentation</li> </ul>	<ul style="list-style-type: none"> <li>• Case study</li> </ul>	4
	Case study [326]	Higher risk with EHS		<ul style="list-style-type: none"> <li>• Case study</li> </ul>	4
	Case study [147]	Higher risk with EHS	<ul style="list-style-type: none"> <li>• Long-term follow-up</li> </ul>	<ul style="list-style-type: none"> <li>• Case study</li> </ul>	4
	Review [138]	Higher risk with EHS	<ul style="list-style-type: none"> <li>• New concepts</li> </ul>	<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
Recent/current illness	Systematic review [319]	Increased risk with recent/current illness <sup>↑</sup>	<ul style="list-style-type: none"> <li>• See above (ER)</li> </ul>	<ul style="list-style-type: none"> <li>• See above (ER)</li> </ul>	2a
Dehydration	Prospective cohort [327]	Higher risk with dehydration	<ul style="list-style-type: none"> <li>• Prospective design</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of measured baseline bloods</li> </ul>	1b
	Prospective cohort [328]	Higher risk with dehydration	<ul style="list-style-type: none"> <li>• Prospective design</li> <li>• Baseline bloods and urine</li> </ul>	<ul style="list-style-type: none"> <li>• Small cohort</li> </ul>	1b
Sex	Prospective cohort [317]	Females at higher risk Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective cohort</li> <li>• Multisite</li> </ul>	<ul style="list-style-type: none"> <li>• Multistage ultramarathon event in desert</li> </ul>	1b
Weight loss during race	RCT [318]	Higher risk with weight loss during race Independent risk factor	<ul style="list-style-type: none"> <li>• See above (NSAID)</li> </ul>	<ul style="list-style-type: none"> <li>• See above (NSAID)</li> </ul>	1b
	Prospective cohort [317]	Higher risk with weight loss during race Independent risk factor	<ul style="list-style-type: none"> <li>• See above (sex)</li> </ul>	<ul style="list-style-type: none"> <li>• See above (sex)</li> </ul>	1b
Finishing performance/speed variability	RCT [318]	Faster runners at higher risk Independent risk factor	<ul style="list-style-type: none"> <li>• See above (NSAID)</li> </ul>	<ul style="list-style-type: none"> <li>• See above</li> <li>• (NSAID)</li> </ul>	1b
	Prospective cohort [317]	Faster runners at higher risk	<ul style="list-style-type: none"> <li>• See above (sex)</li> </ul>	<ul style="list-style-type: none"> <li>• See above (sex)</li> </ul>	1b
	Prospective cohort [329]	Higher risk with increased speed variability Independent risk factor	<ul style="list-style-type: none"> <li>• Prospective cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Smaller cohort</li> <li>• Only certain time splits independent risk factor, rest univariate</li> </ul>	1b

## **a. Intrinsic risk factors associated with AKI in distance running events**

The three most common risk factors associated with AKI are exertional rhabdomyolysis (ER), non-steroidal anti-inflammatory drug (NSAID) use and exercise-associated hyponatraemia (EAH).

### *i. Exertional rhabdomyolysis*

Exertional rhabdomyolysis (ER) is a risk factor for AKI in exercise. Between 4% and 33% of ER cases may lead to AKI [330]. It is interesting to note that some studies have reported CK concentrations up to 80 000 IU without AKI [331, 332], while other studies report cases that developed AKI where the CK concentrations were not always elevated above 5000 IU [323].

In a recent systematic review, the relationship between ER and AKI in endurance sports was described [320]. The review included a total of 43 studies where biomarkers of ER and AKI were reported in endurance events. In these 43 studies a total of 345 (43.5%) participants were diagnosed with ER (defined as serum CK activity >5000) and 130 (16.39%) participants were diagnosed with ER and AKI. Of these 130 cases, 96.92% were in endurance runners, compared to participants of other sports, such as endurance cycling or swimming. The increased concentrations of muscle and kidney injury markers usually returned to baseline after 5.86 days. In summary, studies show evidence of a relationship between ER and AKI. However, further well conducted prospective cohort studies with longer follow-up periods are required.

A detailed discussion of intrinsic and extrinsic risk factors specifically associated with ER is beyond the scope of this chapter. However, the main results of studies that identified intrinsic and extrinsic risk factors associated with ER in runners are summarised in Table 4.7.

The main risk factors associated with ER in distance runners are:

1. Male sex
2. Age -older than 35 years
3. BMI over 30
4. African-American ethnicity
5. Smoking
6. Unaccustomed exercise

7. Use of certain medications (statins and anti-psychotic medication)

8. Sickle Cell Trait

**Table 4.7. Risk factors associated with exertional rhabdomyolysis 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 finding/s	Strengths	Limitations	Level of Evidence [15]
<b>Intrinsic</b>					
Sex	Retrospective cohort [333]	Males at higher risk Independent risk factor	<ul style="list-style-type: none"> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> <li>• Military study</li> </ul>	2b
	Review [334]	Males at higher risk		<ul style="list-style-type: none"> <li>• Review</li> </ul>	5
	Retrospective cohort [321]	Males at higher risk	<ul style="list-style-type: none"> <li>• Long study period (2003-2015)</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> </ul>	2b
Ethnicity	Retrospective cohort [335]	Non-Hispanic blacks at increased risk	<ul style="list-style-type: none"> <li>• Very large cohort of U.S. army recruits, 10 installations</li> <li>• 5-year period</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> <li>• Military study</li> </ul>	2b
	Retrospective cohort [333]	African- Americans at increased risk	<ul style="list-style-type: none"> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> <li>• Military study</li> </ul>	2b
Age	Retrospective cohort [333]	>35 years group at higher risk	<ul style="list-style-type: none"> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> <li>• Military study</li> </ul>	2b
BMI	Retrospective cohort [333]	BMI >30 at higher risk Independent risk factor	<ul style="list-style-type: none"> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> <li>• Military study</li> </ul>	2b
Smoking	Retrospective cohort [333]	Smokers at higher risk Independent risk factor	<ul style="list-style-type: none"> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> <li>• Military study</li> </ul>	2b
Unaccustomed exercise	Retrospective cohort [335]	Increased risk with unaccustomed exercise	<ul style="list-style-type: none"> <li>• Very large cohort of U.S. army recruits, 10 installations</li> <li>• 5-year period</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> <li>• Military study</li> </ul>	2b
Use of medication	Retrospective cohort [333]	Higher risk with statin and anti-psychotic medication use Independent risk factor	<ul style="list-style-type: none"> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> <li>• Military study</li> </ul>	2b
Sickle cell trait	Retrospective cohort [333]	Higher risk with SCT Independent risk factor	<ul style="list-style-type: none"> <li>• Large cohort</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective cohort</li> <li>• Military study</li> </ul>	2b
Mitochondrial myopathies	Case report [336]	Increased risk with mitochondrial myopathies		<ul style="list-style-type: none"> <li>• Case report</li> <li>• Rare</li> </ul>	4
CAT 2 enzyme deficiency	Case report [336]	Higher risk with CAT 2 enzyme deficiency		<ul style="list-style-type: none"> <li>• Case report</li> <li>• Rare</li> </ul>	4

### *ii. Non-steroidal anti-inflammatory drugs (NSAIDs)*

It is well known that up to 75% of runners ingest medication, including NSAIDs during endurance events, such as distance running [206, 207, 302, 318]. NSAIDs may negatively affect renal function by potentiating the action of arginine vasopressin (AVP) at the collecting duct of the kidney [337], reducing renal blood and increase renal vascular resistance after exercise [337]. These data therefore suggest that NSAIDs can compromise renal function and potentiate the risk of developing AKI.

Actual evidence that ingestion of NSAIDs during exercise is associated with subsequent AKI comes from a number of case studies [324, 325] and one RCT. In one of the first case series, four cases of AKI were reported after an ultra-marathon where runners reported the ingestion of NSAIDs during the race [323]. To our knowledge, only one double blind randomised controlled trial (RCT) has been conducted, which studied NSAIDs and subsequent AKI in endurance running [318]. In this study, 89 ultramarathon runners participated in the study and 47% took ibuprofen, while 53% took a placebo. The overall incidence of AKI was 44% and this was higher in those taking ibuprofen versus placebo (52% vs. 34%). The severity of AKI was also greater in the ibuprofen group. In contrast, in a prospective cohort study in a 161 km endurance race the use of NSAIDS and development of AKI showed no evidence of an association [327].

In summary, there is conflicting evidence that NSAIDs taken during endurance exercise is associated with and increased risk of AKI. Future larger RCT's require to be conducted to confirm the causal association between AKI and NSAIDs.

### *iii. Exercise-associated hyponatraemia (EAH)*

There is some evidence from case studies to suggest that EAH is associated with AKI in distance running [168, 171]. This association was described in a case series conducted on four runners that developed AKI after an 89 km ultra-marathon in 2010 [312]. The objective of the study was to evaluate common factors associated with AKI in these 4 runners. Common factors found were hyponatraemia (3 runners) and the fact that all 4 runners ingested an analgesic during the race (3 runners ingested a NSAID). It is of further interest that all runners ingested the same anti-cramp electrolyte solution and that 3 of the 4 runners were novices. All the runners had a delayed presentation of 1-4 days after the race and were hospitalised for management of the AKI at the same hospital. Limitations to this study were a small sample of

individual cases, no control group, no data on other possible risk factors and that it only documented the runners that presented to one specific hospital and thus may underrepresent the true extent of the condition. It is important to note that the risk factors associated with AKI in this study are only suggested risk factors and not proven independent risk factors.

In another more recent case series, a cluster of five cases of ER and EAH was documented at the 161 km 2009 Western States Endurance Run [171]. Three of the 5 cases developed AKI and these runners tended to be faster, younger, more likely to have had an injury that interfered with training and more likely to have used NSAIDs during the race. In seven similar previously documented cases of ER and EAH, 57% suffered renal impairment secondary to the ER and 86% had symptomatic hyponatraemia [168, 313, 338, 339].

It is of interest to note that in some cases there is an association between AKI, rhabdomyolysis and EAH. These data may suggest a relationship between this triad of conditions (EAH, rhabdomyolysis and AKI). Whether the combination of EAH, in addition to rhabdomyolysis, is causal or independently associated with AKI is currently the subject of debate [340] [171] and requires further investigation.

## **Summary**

AKI is one of the serious and potentially life-threatening medical encounters that occur in distance running events. AKI is a diagnosis that is often overlooked in the endurance runner, which may be in part due to the delayed presentation and absence of symptoms immediately post-race. There are several intrinsic and extrinsic risk factors that have been associated with acute renal encounters, in particular AKI, in distance runners (summarised in Table 4.6.).

These risk factors have largely been identified through case studies and case series (level 4 evidence). As a result, a direct cause-effect relationship between these risk factors and AKI has not been established. Yet, the data from these case series suggest that combinations of factors may increase the risk of AKI in distance runners. More recently, data from prospective cohort studies and one RCT (NSAIDs and AKI) identified independent risk factors associated with AKI in endurance runners. These include the following: female sex, weight loss during the race, faster finishing times and increased speed variability [317, 318, 329]. However, the relationship between individual and combinations of risk factors associated with AKI need to

be established by conducting further large prospective cohort studies and larger RCT on the relationship between NSAIDs and AKI. These studies are required to determine the cause-effect relationship between the risk factors and medical encounters.

Finally, the long-term sequelae of repeated episodes of AKI in the endurance runner needs to be determined. In the general population there is an increased morbidity and mortality rate associated with repeated episodes of AKI [309]. Furthermore, there is a need for more accurate markers for both subclinical and functional AKI diagnosis following endurance running events.

#### **4.7.7 Dermatological system**

A comprehensive review of the literature shows that there are limited data regarding risk factors associated with dermatological medical encounters during endurance running. More specifically, there are only data regarding the risk factors associated with blisters, which is the most common dermatological medical encounter in runners. Data related to risk factors associated with blisters in distance runners will now be reviewed.

#### **Risk factors associated with foot blisters in distance running events**

There are a few studies evaluating the risk factors associated with blisters in distance running events, including one retrospective cohort study [93], two prospective cohort studies [95, 341] and two RCT's [342, 343]. Some data from the military is included as these study populations are comparable [344, 345]. These data are depicted in Table 4.8. and the results will be summarised.

**Table 4.8.: Risk factors associated with blisters in distance running events (by risk factor, study design and study reference, main findings, strength, limitation and level of evidence)**

Risk factor	Study design and study reference	Main finding/s	Strengths	Limitations	Level of Evidence [15]
<b>Intrinsic risk factors</b>					
Age	Retrospective cohort [93]	Higher age at increased risk	<ul style="list-style-type: none"> <li>6-year study period</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective design</li> <li>Specific older age category not documented</li> </ul>	2b
	Prospective cohort [95]	Age (>18 years) at increased risk Independent risk factor	<ul style="list-style-type: none"> <li>Prospective study design</li> </ul>	<ul style="list-style-type: none"> <li>Multiday desert event</li> </ul>	1b
Ethnicity	Prospective cohort [346]	African-Americans at lower risk Independent risk factor	<ul style="list-style-type: none"> <li>Prospective study design</li> </ul>	<ul style="list-style-type: none"> <li>Military march study (21 km)</li> </ul>	1b
Recent illness	Prospective cohort [346]	Higher risk with illness in past 12 months Independent risk factor	<ul style="list-style-type: none"> <li>Prospective study design</li> </ul>	<ul style="list-style-type: none"> <li>Military march study (21 km)</li> <li>Mechanism unclear</li> </ul>	1b
Foot type	Prospective cohort [346]	Pes planus (flat feet) group at higher risk Independent risk factor	<ul style="list-style-type: none"> <li>Prospective study design</li> </ul>	<ul style="list-style-type: none"> <li>Military march study (21 km)</li> <li>Mechanism unclear</li> </ul>	1b
Use of smokeless tobacco products	Prospective cohort [344]	Increased risk with the use of smokeless tobacco products Independent risk factor	<ul style="list-style-type: none"> <li>Prospective study design</li> </ul>	<ul style="list-style-type: none"> <li>Cross-country march (121 km)</li> <li>Mechanism unclear</li> </ul>	1b
	Prospective cohort [346]	Increased risk with the use of smokeless tobacco products Independent risk factor	<ul style="list-style-type: none"> <li>Prospective study design</li> </ul>	<ul style="list-style-type: none"> <li>Military march study (21 km)</li> <li>Mechanism unclear</li> </ul>	1b
Running experience	Prospective cohort [341]	Lower risk in more experienced males Independent risk factor	<ul style="list-style-type: none"> <li>Prospective study design</li> </ul>	<ul style="list-style-type: none"> <li>Multistage endurance race (219 km)</li> </ul>	1b

**Table 4.8.: Risk factors associated with blisters in distance running events (by risk factor, study design and study reference, main findings, strength, limitation and level of evidence) (continued)**

Extrinsic risk factors					
Race distance	Retrospective cohort [68]	Shorter race distance at lower risk (0.2 / 1000)	• Consistent low incidence	• Retrospective design	2b
	Prospective cohort [347]	Longer race distance at higher risk (9 / 1000)	• Prospective design	• No direct comparison in same race	1b
	Prospective cohort [348]	Longer race distance at higher risk (3.3 / 1000)	• Prospective design	• No direct comparison in same race	1b
	Prospective cohort {Roberts, 2000 #19}	Longer race distance at higher risk (4.1 / 1000)	• Prospective design	• No direct comparison in same race	1b
Type of sock	RCT [342]	Use of acrylic fibres socks at lower risk	• RCT design	• Small study	1c
Antiperspirants	RCT [345].	Use of antiperspirants at lower risk	• RCT design	• Military hike (21 km)	1c
Taping	RCT [343].	Lower risk with taping	• RCT design	• Multi-stage desert race (250 km) not always comparable to single day marathon	1c

There are some data that identified independent risk factors associated with blister formation during military marching. These factors are ethnicity, recent illness, foot type and the use of tobacco products. In studies conducted during multi-stage endurance running older age and increasing race distance were identified as independent risk factors associated with foot blisters. It must be noted that all the above risk factors have been identified in groups participating in multi-stage races, over varying terrain. Therefore, these data may not be applicable to single day running events. Further studies during shorter, single day events are needed. In addition, there is a paucity of data regarding risk factors associated with dermatological conditions other than blisters in distance running and this also requires further study.

## Summary

- It is important to identify the risk factors associated with medical encounters and to identify the individuals who are at risk of developing medical encounters.
- In general, there are limited data regarding the risk factors associated with medical encounters during mass participation endurance running events.
- The risk for SCA / SCD and SD in distance runners is very low, however this risk cannot be disregarded. The most common causes for SCA / SCD have been well described in both the younger (<35 years) and older (>35 years) athletes and the risk factors associated with SCA / SCD in both these population groups are known.
- There are other non-cardiac causes that may result in SD such as EHS, EAH and other electrolyte abnormalities, AKI and intra-cranial bleeds. There are few data regarding the risk factors associated with these causes, and this requires further research.
- The risk for serious/potentially life-threatening medical encounters is higher than that for SCA / SCD and SD, but despite this higher risk, there are very limited data available on the risk factors associated with these conditions. Risk factors associated with serious/life-threatening medical encounters should be identified and modified where applicable.
- More common moderate medical encounters represent the majority of medical encounters during distance running events (as discussed in Chapter 2), but there are also limited data on the risk factors of these moderate medical encounters.
- There are numerous intrinsic and extrinsic risk factors associated with moderate medical encounters during distance running events. These need to be identified in the various categories of severity and by organ system. Some of these risk factors are modifiable and / or transient, including: acute medical illness, use of certain medication, environmental conditions, runner education, training status, hydration status, use of supplements and medication (especially analgesics and NSAIDs), race distance, participant number and course technicality.

- Knowledge of the risk factors associated with medical encounters in distance running events is important to firstly plan optimal medical care for an event and secondly design and implement prevention programs to reduce the risk.
- Research to identify risk factors associated with medical encounters in a mass participation community-based running events such as the Two Oceans Marathon races (56 km and 21.1 km) are important. It is desirable to determine independent risk factors associated with these medical encounters using multivariate models.

The focus of the following two Chapters (Chapter 5 and 6), will be placed on identifying possible risk factors associated with medical complications in both a 21.1 km and 56 km race. Following this, the aim is to develop a pre-race medical screening tool, based on the literature review (Chapter 4), risk factors identified in the next two Chapters (Chapter 5 and 6) and the international pre-exercise medical screening guidelines.

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## CHAPTER 5

### STUDY 2: LESS EXPERIENCE AND RUNNING PACE ARE POTENTIAL RISK FACTORS FOR MEDICAL COMPLICATIONS DURING A 56 KM ROAD RUNNING RACE: A PROSPECTIVE STUDY IN 26 354 RACE STARTERS - SAFER STUDY II

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#### 5.1. ABSTRACT

**Background:** It is important to identify risk factors associated with medical complications during ultra-marathons so that prevention programmes can be developed.

**Objective:** To determine risk factors for medical complications during ultra-marathons.

**Design:** Prospective study

**Setting:** Two Oceans ultra-marathon (56 km) races

**Participants:** 26 354 race starters

**Methods:** Medical complications (defined as any runner requiring assessment by a doctor at the race medical facility or a local hospital on race day) were recorded over 4 years. Complications were sub-divided according to the system that was affected and by final diagnosis. A Poisson regression model was used to determine risk factors for any medical complication, and more common specific complications.

**Results:** Risk factors for medical complications during 56 km road races were less running experience ( $\leq 1$  medal vs. 2-4 medals,  $p=0.0097$ ), and both fastest ( $< 6$  vs. 6-7 min/km,  $p=0.0051$ ) and slowest ( $> 7$  vs. 6-7 min/km,  $p<0.0001$ ) running pace category. Year of observation was also associated with risk of complications (2009 vs. 2008,  $p=0.0176$ ; 2009 vs. 2010,  $p=0.0007$ ; 2010 vs. 2011,  $p=0.0112$ ). Risk factors for specific common medical complications were: postural hypotension (slowest pace), serious exercise-associated muscle cramping (older age, fastest pace), gastrointestinal complaints (slowest pace), and dermatological complaints (fastest pace).

**Conclusion:** Less experience and running at either a slow or a fast pace were risk factors for complications during 56 km road running. Annual variation may also affect risk. Risk factors for specific medical complications were also identified. These data can now form the basis for the future implementation of a pre-race medical screening, risk stratification and educational intervention program to reduce the risk of medical complications in distance running and other endurance events.

## 5.2. INTRODUCTION

It has been documented that distance running [1, 2], including ultra-marathon running [1, 3, 4] can be associated with medical complications in a variety of organ systems. In keeping with the recent interest in protecting the health of the athlete, it is important to identify risk factors for medical complications during ultra-marathon running so that medical care facilities can be planned for race day, and that effective prevention programmes can be developed and tested.

Although the incidence of medical complications during marathon running [5] and multi-staged ultra-marathon running [1] has been reported, the incidence and types of medical complications in single-day 56 km ultra-marathon running events has only recently been reported [4]. In this study, we showed an overall incidence of 12.98 medical complications per 1000 runners starting a 56 km ultra-marathon race (1 in 77 runners starting the race), with an incidence of serious/life-threatening medical complications of 0.65 (1 in 1538 runners starting the race). Furthermore, we showed that the most common medical complication in 56 km runners (per 1000 starters) was postural hypotension (2.77/1000), followed by serious exercise-associated muscle cramping (sEAMC) (1.9/1000), gastrointestinal complaints (1.86/1000), musculoskeletal complaints (1.82/1000) and dermatological complaints (1.48/1000) [4].

There are very few published prospective cohort studies that report risk factors for medical complications in ultra-marathon runners, or similar endurance events. There are some studies that identified age [1], gender [1, 6], running intensity (running pace) [7, 8], running experience [9], and environmental conditions [10] as possible risk factors for some specific medical complications that can occur during endurance events. However, we are not aware of any systematic investigation to determine independent risk factors associated with medical complications during single-day ultra-marathon running events. This information is vital to 1) design prevention programmes and thereby reduce the risk of medical complications (serious and less serious) during ultra-marathon running, and 2) to plan optimal medical care during community-based endurance events.

One such event is the Two Oceans ultra-marathon (56 km), which takes place annually during late summer in Cape Town, South Africa. This popular and growing race draws over 6000 national and international entrants per year. The aim of this study was to identify independent

risk factors that are associated with the development of medical complications during a single-day ultra-marathon running event. In addition, we wanted to determine independent risk factors associated with specific more common medical conditions in different organ systems in ultra-marathon runners.

### **5.3. METHODS**

#### **Type of study**

This is a prospective study that consists of a 4-year cohort (2008–2011) of runner data collected through the race registry as well as medical admissions data.

#### **Participants and demographics**

This study forms part of a series of studies that were initiated to determine the incidence and risk factors for adverse medical events in endurance runners, and to then develop strategies to reduce this risk – the **SAFER** (Strategies to reduce Adverse medical events For the Exercise**R**) studies [11]. It was part of a large prospective cohort study that was conducted in all the participants of the Two Oceans Marathon races (including a 21 km half-marathon and a 56 km ultra-marathon) over a 4-year period (2008 to 2011) [4]. Details of the study methodology have been described [4]. In summary, during the 4-year study period, a total of 26 354 runners started the 56 km races (85.4% of all registrations for the 56 km race) and only runners who started the race were included as participants in this study. This database of runners is registered with the Research Ethics Committee of the University of Cape Town (REC ref: R 030/2013) and permission to investigate the incidence, nature and factors associated with medical complications during endurance running in the Two Oceans races was obtained from the Research Ethics Committee of the University of Cape Town (REC ref: 009/2011; REC ref: 441/2012).

This cohort of 26 354 runners consisted of 19 998 males and 6 356 females. Race entrants are required to be 20 years or older and there is no upper limit to the age. The demographics by year of participation, age groups (< 30 years, 31-40 years, 41-50 years and > 50 years) and gender of all the race starters in the 4-year study period is depicted in Table 5.1.

**Table 5.1.: Demographics of all 56 km race starters (gender, age groups and year of participation)**

Gender	Age groups (years)	2008	2009	2010	2011	All runners
<b>Males</b>	≤ 30	511	513	722	582	2328
	31 - 40	1589	1616	1985	1700	6890
	41 - 50	1633	1675	1995	1623	6926
	> 50	852	922	1140	940	3854
	<b>All</b>	<b>4585</b>	<b>4726</b>	<b>5842</b>	<b>4845</b>	<b>19998</b>
<b>Females</b>	≤ 30	176	149	261	188	774
	31 - 40	545	545	738	581	2409
	41 - 50	557	564	727	560	2408
	> 50	156	164	240	205	765
	<b>All</b>	<b>1434</b>	<b>1422</b>	<b>1966</b>	<b>1534</b>	<b>6356</b>

### **Medical data collection and incidence of medical complications**

Full details of the medical data collection procedure have been reported [4]. In summary, accurate and comprehensive medical data concerning all medical complications were recorded during the 4-year study period. A “medical complication” was defined as a medical condition that required medical care on race day that was of sufficient severity to warrant a medical assessment by a doctor, either in the medical facility at the end of the race, or at one of the referral hospitals (for runners that were assessed by medical staff on the route). Medical complication data entered into the database was recorded in a standardized format and included the organ system affected (cardiovascular, respiratory, fluid and electrolyte imbalance, central nervous system, thermoregulatory, musculoskeletal, gastrointestinal, dermatological, metabolic, renal, and other) and the specific final diagnosis.

### **Incidence of medical complications**

The crude incidence of any medical complications was calculated as medical admissions per 1000 runners who started the races, and this has been reported by year of observation and race type [4]. These incidences were also reported in sub-groups of runners by race type, system affected and final diagnosis [4]. In this study, the incidence of medical complications will additionally be reported by previous running experience in the Two Oceans 56 km races (< 1

previous medal, 2-4 previous medals, > 5 previous medals), and running pace (< 6 min/km, 6-7 min/km, > 7 min/km).

### **Statistical analysis of data**

All data were entered into an Excel spread sheet (Microsoft 2010) and then analysed using the SAS (v9.3) statistical programme (SAS Institute Inc., Cary NC, USA). The medical complications data were analysed with a Poisson regression model, using a robust error estimator (log link function). This cohort consists of correlated data as 43% of runners ran this race more than once during the 4-year period. The correlated structure was accounted for by using an unstructured correlation matrix. This was to estimate the Incidence Rates (IR's) and confidence intervals (CI). Group comparisons and 95% confidence intervals for these IR's and differences were also obtained. Regression analyses were conducted to determine risk factors associated with the development of any medical complication during 56 km running and then separately for the five most common medical complications that occurred. Risk factors investigated included year of race, gender, age group, running experience category and running pace category. The year of race was included in the analyses as a proxy for environmental conditions on race day to determine if it was a risk for medical complications. The mean (SD) temperature, humidity, rainfall, wind speed and calculated Wet Bulb Globe Temperature (WBGT) index during the race period (06h00 to 12h00 on race day) for each year of race have previously been reported [4].

The five most common complications were postural hypotension, serious exercise-associated muscle cramping (sEAMC), gastrointestinal complaints, musculoskeletal complications and dermatological complications [4]. Risk factors for these common medical complications were analyzed. Risk factors were chosen on the basis that 1) there are reports that these factors are related to risk of medical complications [1, 6-10, 12], and that these data were accurately recorded in the study period [4]. Risk factors therefore included the following: year of observation (as a proxy for environmental conditions), gender, age, running experience, and running pace. The adjusted model for any medical complication was reported with all risk factors present irrespective if they were significant, but for the five most common specific complications, the adjusted models only included the significant risk factors due to the small numbers present.

## 5.4. RESULTS

### **Incidence and risk factors associated with the development of any medical complication during 56 km running**

The incidence (12.98/1000 runners starting the race; 95%CI; 11.67-14.43) of any medical complication during a 56 km race by year of observation (environmental conditions), gender, age group, running experience and running pace is depicted in Table 5.2.

**Table 5.2.: The incidence (per 1000 runners starting the race: 95%CI) of any medical complication during a 56 km race by year of observation (environmental conditions), gender, age group, running experience group and running pace group**

Variable	Category	Incidence	95% CI	
Year of observation	2008	10.97	8.64	13.94
	2009	16.31	13.44	19.79
	2010	10.65	8.61	13.19
	2011	14.78	12.12	18.02
Gender	Female	13.48	10.91	16.66
	Male	12.85	11.32	14.58
Age groups (years)	20-30	14.45	10.82	19.30
	31-40	12.39	10.29	14.91
	41-50	12.77	10.60	15.38
	> 50	13.73	10.65	17.70
Running experience (medals)	≤ 1	16.44	13.82	19.56
	2-4	10.62	8.59	13.12
	≥ 5	12.14	10.12	14.57
Running pace (min/km)	< 6	13.38	11.22	15.95
	6-7	9.30	7.65	11.31
	> 7	16.73	13.73	20.40

### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of any medical complication during a 56 km race by gender ( $p=0.7046$ ), or age category ( $p=0.8130$ ). However, there was a significant difference in the incidence by year of observation (environmental conditions) ( $p=0.0080$ ), with a higher incidence in a) 2009 (ambient temperature (mean  $\pm$  SD) of  $17.1 \pm 1.4$  °C compared with both 2008 (ambient temperature of  $18.2 \pm 1.9$  °C) ( $p=0.0101$ ) and 2010 (ambient temperature of  $16.3 \pm 0.8$  °C) ( $p=0.0034$ ), and b) 2011 (ambient temperature of  $11.5 \pm 2.1$  °C compared with 2010 (ambient temperature of  $16.3 \pm 0.8$  °C) ( $p=0.0270$ ) (Table 5.3.).

**Table 5.3.: Environmental conditions on race day for each year. Values are mean (SD).**

	Temperature (°C)	Humidity (%)	Rainfall (mm)	Wind speed (knots)	WBGT index*
<b>2008</b>	18.2 (1.9)	77 (8)	0	9.6 (2.4)	16.5 (2.4)
<b>2009</b>	17.1 (1.4)	83 (7)	0	7.8 (1.0)	15.4 (1.6)
<b>2010</b>	16.3 (0.8)	93 (3)	0	3.5 (0.6)	15.2 (1.4)
<b>2011</b>	11.5 (2.1)	87 (2)	0	1.5 (1.3)	13.5 (2.9)

\*: Wet Bulb Globe Temperature (WBGT) Index – calculated using temperature (°C), humidity, time of day and cloud cover data

There was also a significant difference in the incidence by running experience category ( $p=0.0061$ ), with a higher incidence in runners with the least running experience category ( $\leq 1$  medals) compared with runners in the intermediate category (2-4 medals) ( $p=0.0018$ ) and runners in the most experienced category ( $\geq 5$  medals) ( $p=0.0183$ ). Finally, there was a significant difference in the incidence by running pace category ( $p=0.0001$ ). Both runners in the fastest pace category ( $< 6$  min/km) ( $p=0.0063$ ) and runners in the slowest category ( $> 7$  min/km) ( $p<0.0001$ ) had a higher incidence of any medical complication compared with runners in the intermediate pace category (6-7 min/km).

### *Multiple regression analysis*

In the adjusted model, factors associated with an increased risk of developing any medical complication in a 56 km race were: year of observation (environmental conditions) (2009 vs.

2008,  $p=0.0176$ ; 2009 vs. 2010,  $p=0.0007$ ; 2010 vs. 2011,  $p=0.0112$ ), less running experience ( $\leq 1$  medals vs. 2-4 medals,  $p=0.0097$ ), and both fastest ( $< 6$  vs. 6-7 min/km,  $p=0.0051$ ) and slowest ( $> 7$  vs. 6-7 min/km,  $p<0.0001$ ) running pace category.

### **Incidence and risk factors associated with the development of postural hypotension during 56 km running**

In our study, the incidence of postural hypotension was 2.77/1000 runners starting the race (95%CI; 2.20-3.48) (1 in every 361 race starters). The incidence (per 1000 runners starting the race) of postural hypotension during a 56 km race by year of observation (environmental conditions), gender, age group, running experience and running pace is depicted in Table 5.4.

**Table 5.4.: The incidence (per 1000 runners starting the race: 95%CI) of postural hypotension during a 56 km race by year of observation (environmental conditions), gender, age group, running experience group and running pace group**

Variable	Category	Incidence	95% CI	
Year of observation	2008	3.14	2.00	4.93
	2009	2.68	1.66	4.32
	2010	2.23	1.40	3.56
	2011	3.36	2.21	5.11
Gender	Female	3.36	2.19	5.16
	Male	2.65	1.99	3.52
Age groups (years)	20-30	1.98	0.90	4.37
	31-40	2.28	1.46	3.58
	41-50	3.37	2.35	4.84
	> 50	3.33	1.96	5.65
Running experience (medals)	$\leq 1$	2.56	1.62	4.04
	2-4	2.59	1.70	3.96
	$\geq 5$	3.22	2.25	4.61
Running pace (min/km)	< 6	1.95	1.20	3.17
	6-7	2.48	1.67	3.69
	> 7	4.83	3.31	7.04

### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of postural hypotension during a 56 km race by gender ( $p=0.3852$ ), year of observation (environmental conditions) ( $p=0.5628$ ), age category ( $p=0.3786$ ), and category of running experience ( $p=0.6681$ ). However, there was a significant difference in the incidence by running pace category ( $p=0.0260$ ). Runners in the slowest category ( $> 7$  min/km) had a higher incidence of postural hypotension compared with runners in the intermediate pace category (6-7 min/km) ( $p=0.0163$ ) and runners in the fastest pace category ( $< 6$  min/km) ( $p=0.0039$ ).

### *Multiple regression analysis*

In the adjusted model, the only factor associated with an increased risk of developing postural hypotension in a 56 km race was slow running pace ( $> 7$  vs. 6-7 min/km,  $p=0.0163$ ;  $> 7$  vs.  $< 6$  min/km,  $p=0.0039$ ).

### **Incidence and risk factors associated with the development of serious Exercise-Associated Muscle Cramping (sEAMC) during 56 km running**

In this study, the incidence of sEAMC was 1.90/1000 runners starting the race (95% CI; 1.44-2.50) (1 in every 526 race starters). The incidence (per 1000 runners starting the race) of sEAMC during a 56 km race by year of observation (environmental conditions), gender, age group, running experience and running pace is depicted in Table 5.5.

**Table 5.5.: The incidence (per 1000 runners starting the race: 95%CI) of serious Exercise-Associated Muscle Cramping (sEAMC) during a 56 km race by year of observation (environmental conditions), gender, age group, running experience group and running pace group**

Variable	Category	Incidence	95% CI	
Year of observation	2008	1.01	0.45	2.24
	2009	2.15	1.25	3.69
	2010	2.20	1.37	3.53
	2011	2.22	1.32	3.75
Gender	Female	1.11	0.53	2.34
	Male	2.17	1.61	2.93
Age groups (years)	20-30	1.96	0.88	4.36
	31-40	2.07	1.32	3.23
	41-50	0.87	0.43	1.73
	> 50	3.72	2.31	5.97
Running experience (medals)	≤ 1	2.32	1.46	3.68
	2-4	1.46	0.83	2.57
	≥ 5	1.98	1.28	3.07
Running pace (min/km)	< 6	2.89	1.98	4.20
	6-7	1.12	0.64	1.98
	> 7	1.51	0.79	2.90

#### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of sEAMC during a 56 km race by year of observation (environmental conditions) ( $p=0.1686$ ), and category of running experience ( $p=0.4325$ ). However, there was a significant difference in the incidence by gender ( $p=0.0482$ ), age category ( $p=0.0072$ ) and running pace category ( $p=0.0231$ ). Male runners had a higher incidence of sEAMC compared with female runners ( $p=0.0482$ ). Runners in the 31-40 year category had a higher incidence of sEAMC

compared with runners in the 41-50 year category ( $p=0.0393$ ). Runners in the oldest age category ( $> 50$  years) also had a higher incidence of sEAMC compared with runners in the 41-50 year category ( $p=0.0007$ ). Runners in the fastest pace category ( $< 6$  min/km) had a higher incidence of sEAMC compared with runners in the intermediate pace category (6-7 min/km) ( $p=0.0066$ ) but not compared to the runners in the slowest category ( $> 7$  min/km) ( $p=0.0921$ ).

### *Multiple regression analysis*

In the adjusted model, the factors associated with an increased risk of developing sEAMC in a 56 km race were older age ( $> 50$  years vs. 20-30 years,  $p=0.0775$ ;  $> 50$  years vs. 31-40 years,  $p=0.0219$ ;  $> 50$  years vs. 41-50 years,  $p=0.0004$ ) and faster running pace ( $< 6$  vs. 6-7 min/km,  $p=0.0027$ ;  $< 6$  vs.  $>7$  min/km,  $p=0.0339$ ). When comparing the older age ( $> 50$  years) with the younger age (20-30 years), there was only a marginal significant difference ( $p=0.0775$ ). It should be noted that there were only 6 runners with sEAMC in the young age group, and this limits this power of the analysis.

### **Incidence and risk factors associated with the development of gastrointestinal complaints during 56 km running**

In this study, the incidence of gastrointestinal complaints was 1.86/1000 runners starting the race (95%CI; 1.41-2.46) (1 in every 538 race starters). The incidence (per 1000 runners starting the race) of gastrointestinal complaints during a 56 km race by year of observation (environmental conditions), gender, age group, running experience and running pace is depicted in Table 5.6.

**Table 5.6.: The incidence (per 1000 runners starting the race: 95%CI) of gastrointestinal complaints during a 56 km race by year of observation (environmental conditions), gender, age group, running experience group and running pace group**

Variable	Category	Incidence	95% CI	
Year of observation	2008	1.18	0.56	2.46
	2009	1.99	1.10	3.61
	2010	2.33	1.47	3.69
	2011	1.68	0.89	3.15
Gender	Female	1.87	1.06	3.30
	Male	1.82	1.31	2.52
Age groups (years)	20-30	1.89	0.85	4.21
	31-40	1.85	1.13	3.01
	41-50	1.43	0.83	2.49
	> 50	2.59	1.47	4.56
Running experience (medals)	≤ 1	2.26	1.40	3.65
	2-4	1.28	0.70	2.33
	≥ 5	1.97	1.28	3.05
Running pace (min/km)	< 6	0.84	0.41	1.73
	6-7	1.65	1.04	2.60
	> 7	3.24	2.07	5.08

#### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of gastrointestinal complaints during a 56 km race by gender ( $p=0.9282$ ), year of observation (environmental conditions) ( $p=0.3962$ ), age category ( $p=0.5871$ ) and category of running experience ( $p=0.2654$ ). However, there was a significant difference in the incidence by running pace category ( $p=0.0082$ ). Runners in the slowest pace category ( $> 7$  min/km) had

a higher incidence of gastrointestinal complaints compared with runners in the intermediate pace category (6-7 min/km)( $p=0.0369$ ) and runners in the fastest pace category ( $< 6$  min/km) ( $p=0.0020$ ).

#### *Multiple regression analysis*

In the adjusted model, the factors associated with a decreased risk of developing gastrointestinal complaints in a 56 km race were slower running pace ( $> 7$  vs. 6-7 min/km;  $p=0.0408$ ;  $> 7$  vs.  $< 6$  min/km;  $p=0.0019$ ). Although there was an overall age group and gender interaction ( $p=0.0392$ ), indicating that the risk of gastrointestinal complaints in males and females was not necessarily the same within each age group, no individual differences in the incidences were significant.

#### **Incidence and risk factors associated with the development of musculoskeletal complaints during 56 km running**

In this study, the incidence of musculoskeletal complications was 1.82/1000 runners starting the race (95%CI; 1.37-2.42) (1 in every 549 race starters). The incidence (per 1000 runners starting the race) of musculoskeletal complaints during a 56 km race by year of observation (environmental conditions), gender, age group, running experience and running pace is depicted in Table 5.7.

**Table 5.7.: The incidence (per 1000 runners starting the race: 95%CI) of musculoskeletal complaints during a 56 km race by year of observation (environmental conditions), gender, age group, running experience group and running pace group**

Variable	Category	Incidence	95% CI	
Year of observation	2008	1.34	0.67	2.68
	2009	2.64	1.62	4.30
	2010	1.42	0.79	2.57
	2011	2.06	1.20	3.55
Gender	Female	1.43	0.75	2.75
	Male	1.97	1.44	2.70
Age groups (years)	20-30	3.26	1.76	6.05
	31-40	2.39	1.57	3.63
	41-50	1.08	0.58	2.01
	> 50	1.31	0.59	2.92
Running experience (medals)	≤ 1	3.09	2.07	4.61
	2-4	1.46	0.83	2.57
	≥ 5	1.19	0.68	2.10
Running pace (min/km)	< 6	1.61	0.97	2.66
	6-7	1.13	0.64	1.98
	> 7	2.85	1.77	4.58

#### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of musculoskeletal complaints during a 56 km race by gender ( $p=0.3463$ ) and year of observation (environmental conditions) ( $p=0.3315$ ). The incidence of musculoskeletal complaints was only marginally different by age category ( $p=0.0567$ ) and running pace category ( $p=0.0736$ ).

There was a significant difference in the incidence of musculoskeletal complaints by category of running experience ( $p=0.0287$ ). There was a higher incidence of musculoskeletal complaints in runners with the least experience ( $\leq 1$  medals) compared with runners in the intermediate category (2-4 medals) ( $p=0.0341$ ) and runners in the most experienced category ( $\geq 5$  medals) ( $p=0.0069$ ).

#### *Multiple regression analysis*

In the adjusted model, none of the explored factors were associated with an increased risk of developing musculoskeletal complaints in a 56 km race ( $p>0.05$ ).

#### **Incidence and risk factors associated with the development of dermatological complaints during 56 km running**

In this study, the incidence of dermatological complications was 1.48/1000 runners starting the race (95%CI; 1.08-2.03) (1 in every 676 race starters). The incidence (per 1000 runners starting the race) of dermatological complaints during a 56 km race by year of observation (environmental conditions), gender, age group, running experience and running pace is depicted in Table 5.8.

**Table 5.8.: The incidence (per 1000 runners starting the race: 95%CI) of dermatological complaints during a 56 km race by year of observation (environmental conditions), gender, age group, running experience group and running pace group**

Variable	Category	Incidence	95% CI	
Year of observation	2008	1.34	0.67	2.68
	2009	1.65	0.89	3.07
	2010	0.91	0.43	1.90
	2011	2.22	1.32	3.75
Gender	Female	1.75	0.97	3.16
	Male	1.42	0.98	2.05
Age groups (years)	20-30	1.31	0.49	3.48
	31-40	1.52	0.90	2.57
	41-50	1.95	1.23	3.09
	> 50	0.66	0.21	2.04
Running experience (medals)	≤ 1	2.45	1.56	3.84
	2-4	0.97	0.49	1.95
	≥ 5	1.19	0.68	2.10
Running pace (min/km)	< 6	2.46	1.63	3.70
	6-7	1.03	0.57	1.86
	> 7	0.67	0.25	1.79

*Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of dermatological complaints during a 56 km race by gender ( $p=0.5700$ ), year of observation (environmental conditions) ( $p=0.2426$ ), and age category ( $p=0.1613$ ). In the incidence of dermatological complaints there was only a marginal difference between the categories of running experience ( $p=0.0750$ ).

There was a significant difference in the incidence of dermatological complaints by running pace category ( $p=0.0130$ ). Runners in the fastest pace category ( $< 6$  min/km) had a higher incidence of dermatological complaints compared with runners in the intermediate pace category (6-7 min/km) ( $p=0.0179$ ) and runners in the slowest pace category ( $> 7$  min/km) ( $p=0.0166$ ).

#### *Multiple regression analysis*

In the adjusted model, the only factor associated with an increased risk of dermatological complaints in a 56 km race was a faster running pace ( $< 6$  vs. 6-7 min/km,  $p=0.0179$ ;  $< 6$  vs.  $> 7$  min/km,  $p=0.0166$ ).

#### **Summary of risk factors associated with the development of medical complications during 56 km running**

Independent risk factors associated with any medical complication, and the most common specific medical complications (postural hypotension, serious EAMC, gastrointestinal, musculoskeletal and dermatological) in a 56 km race are depicted in Table 5.9.

**Table 5.9.: A summary of risk factors for any medical complications and more common medical complications in the multiple model during a 56 km race**

	<b>Year</b>	<b>Gender</b>	<b>Age</b>	<b>Running experience</b>	<b>Running pace</b>
<b>Any medical complication</b>	2009 (2 <sup>nd</sup> highest temp)			Least experience	Faster pace Slower pace
<b>Postural hypotension</b>					Slower pace
<b>Serious EAMC</b>			Older age		Faster pace
<b>Gastrointestinal complication</b>					Slower pace
<b>Musculoskeletal complication</b>					
<b>Dermatological complication</b>					Faster pace

## 5.5. DISCUSSION

In this study, the incidence and risk factors for any medical complication, and specific common medical complications during a 56 km race are reported. A regression model was used to determine independent risk factors that may be associated with the development of 1) any medical complications, and 2) more specific common medical complications during 56 km running. Risk factors that were entered into the model were: year of observation (a proxy for environmental conditions), gender, age, running experience, and running pace.

The main findings of this study were firstly, that running pace (both slowest and fastest pace categories), less running experience, and the years of observation (environmental conditions) were risk factors for the development of any medical complication during a 56 km race.

Secondly, risk factors associated with specific common medical complications were identified as follows: postural hypotension (slow running pace), serious EAMC (older age; fast running

pace), gastrointestinal complaints (slow running pace), and dermatological complaints (fast running pace).

Running pace, specifically running in the slowest running pace category was the most important risk factor, as this category had the highest risk of developing any medical complication, and more specifically, postural hypotension or gastrointestinal complaints. We are aware of only one study where running pace was investigated as a possible risk factor for medical complications in runners participating in a 7-day multi-staged ultra-marathon race [1], and in this study, slower running pace was not related to an increased risk for medical complications. However, this is a different race type, and running pace as a risk factor for medical complications during a single-day ultra-marathon has not been reported. An obvious possible explanation for our observation is that medical complications that developed during the race resulted in a slower running pace. However, as we do not have accurate data on the running pace variation during the race, the time of onset of the medical complication during the race, and pre-race medical complications or disease, we cannot exclude other possible reasons for our observation. Although our model did consider age and gender, we did not have any data on other variables that may also determine slow running pace, particularly training history. Therefore, although a slower running pace was associated with the risk for medical complications, including postural hypotension and gastrointestinal complaints, the cause-effect relationship of this factor would have to be explored in future studies.

In our study, a faster running pace was predictive of any medical complications, and indeed specific complications such as serious exercise-associated muscle cramping (sEAMC), and dermatological complaints. The association between running at a faster running pace and EAMC has previously been postulated [13], and documented in some studies in runners [7] and tri-athletes [14]. The possible mechanisms for this have also been explored and may be related to the development of premature fatigue resulting in abnormal neuromuscular control [15]. The results of this study therefore support the hypothesis that running at a faster pace is a risk factor for the development of sEAMC.

We are aware of only one study where risk factors for dermatological complaints in ultra-marathon runners competing in a 7-day staged event have been reported [1]. In that study, no specific risk factors for dermatological complaints were identified. In our study, most of the dermatological complaints were skin abrasions, friction injuries and cuts from minor falls

(data not reported) and this is similar for that reported in marathon runners [5] and ultra-marathon runners [1]. Although speculative, a faster running pace may be associated with an increased risk of friction injuries and minor falls. The Two Oceans races attract large fields and there is overcrowding, particularly at the start of the race. Runners can be advised to use anti-chafing creams and exercise caution to reduce the risk of falling when running at a faster pace. Finally, we did not have any data on pre-race dermatological conditions in these runners, and this may have to be explored in future studies.

In our study, age was not a risk factor for medical complications in general, and other common specific medical complications. The exception was that older age was associated with an increased risk of sEAMC. Our data are in support of results reported in one of the earliest cross sectional studies [16]. However, older age was not shown to be a risk factor associated with EAMC in another prospective study in runners with EAMC [7] or in case-control studies in endurance athletes with a history of EAMC [14, 17]. Therefore, the association between older age and EAMC requires further study.

A novel finding in our study was that less running experience was a risk factor for any medical complications. As mentioned previously, most of the dermatological complaints were skin abrasions, friction injuries and cuts from minor falls. These skin conditions are preventable, and less running experience could well be associated with an increased risk of these complications. Runner education, targeted at the less experienced runner could reduce the risk of these complications.

Finally, the year of observation was predictive of any medical complication, but not any of the more common specific medical complications. We included this variable into the model because of the potential variation in environmental conditions that may occur from year to year. However, our data show that, in general, environmental conditions on race day (ambient temperature, humidity, rainfall, wind speed, and WBGT index) were quite similar in the four-year study period (Table 5.1.). The highest incidence of medical complications was recorded in 2009 and 2011. Environmental conditions in 2009 did not differ substantially from those in 2008 and 2010 (Table 5.3.), but the ambient temperature was lower in 2011. Therefore, aside from colder conditions in 2011, there is no obvious pattern to explain the effect of the year of observation through variation in environmental conditions. Factors other than environmental conditions, such as the risk profile (other than age, gender, race pace, race experience) of the

race starters may have played a role in the higher incidences recorded in 2009 and 2011. These would have to be explored in future studies.

The strengths of this study are that it is, to our knowledge, the largest prospective study to date to determine possible risk factors for any medical complication and specific common medical complications during a 56 km ultra-marathon race. Furthermore, we collected comprehensive and accurate data on all runners who registered and started the races, and the medical records for all medical complications. A recognized limitation of our study was that we could not include all the possible intrinsic and extrinsic risk factors for medical complications into our model as these data were not available. In future studies, additional pre-race medical and training history, as well as history of previous medical complications would have to be included into models that assess risk factors for medical complications in ultra-marathon runners.

## **5.6. SUMMARY AND CONCLUSION**

In summary, our study identified, for the first time, risk factors for all medical complications and specific common medical complications in runners participating in a 56 km race. These data can have important practical clinical implications in that ultra-marathon runners who are at higher risk of developing any medical complication and indeed some more common specific medical complications can now be identified. For example, older runners can now be advised that running at a faster pace may increase their risk of sEAMC. Similarly, race directors can identify the inexperienced runners as a group with a higher risk of medical complications and plan medical care appropriately. Furthermore, these data form the basis of further studies to identify risk factors for medical complications in endurance runners and then develop prevention strategies to reduce complications.

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## CHAPTER 6

### STUDY 3: OLDER FEMALES ARE AT HIGHER RISK FOR MEDICAL COMPLICATIONS DURING 21 KM ROAD RACE RUNNING: A PROSPECTIVE STUDY IN 39 511 RACE STARTERS - SAFER STUDY III

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#### 6.1. ABSTRACT

**Background:** The half-marathon (21 km) race is a very popular mass, community-based distance running event. It is important to determine risk factors for medical complications during these events, so that prevention programmes can be developed.

**Objective:** To determine risk factors associated with medical complications during 21 km road running events.

**Design:** Prospective study

**Setting:** Two Oceans half-marathon (21 km) races

**Participants:** 39 511 starters in the 21 km race

**Methods:** Medical complications (defined as any runner requiring assessment by a doctor at the race medical facility or a local hospital on race day) were recorded over a 4-year study period. Medical complications were sub-divided according to the system affected and by final diagnosis. A Poisson regression model was used to determine risk factors for any medical complication and more common specific complications.

**Results:** Independent risk factors for medical complication during 21 km running were older female runners (females  $>50$  vs.  $\leq 50$  years;  $p < 0.0001$ ) and year of observation (2008 vs. 2011;  $p = 0.0201$ ; 2009 vs. 2011:  $p = 0.0019$ ; 2010 vs. 2011:  $p = 0.0096$ ). Independent risk factors for specific common medical complications were: postural hypotension (females, slow running pace), musculoskeletal complaints (less running experience, slower running pace), and dermatological complaints (females).

**Conclusion:** Older female runners are at higher risk of developing medical complications during 21 km road running races. Environmental conditions, in particular cold climate, may also play a role. Less running experience and slower running pace are associated with specific medical complications. Medical staff can now plan appropriate care on race days, and interventions can be developed to reduce the risk of medical complications in 21 km races.

## 6.2. INTRODUCTION

The Two Oceans 21 km race takes place annually during late summer in Cape Town, South Africa. This is a relatively new category of race in the Two Oceans race series, and the number of entrants has increased dramatically over the past decade. Currently, the entries are limited to about 15 000 runners per year, and entries are over-subscribed. Importantly, entries to the 21 km race are open to both experienced and novice runners of all ages > 16 years, and require no qualifying time. These races can therefore attract entrants that are not regular exercisers (“weekend-warriors”).

It is well established that vigorous physical activity, such as distance running, may also be associated with a number of medical complications, including life-threatening medical complications in a variety of systems [1]. In a large prospective study over a 4-year period, we documented the incidence and nature of medical complications during the 21 km race [2]. These data showed an incidence of 5.14 medical complications per 1000 runners starting the 21 km race (1 in 195 runners starting the race) and an incidence of serious/life-threatening medical complications of 0.51 (1 in 1961 runners starting the race) [2]. In this study, we also showed that the most common medical complications in 21 km runners (per 1000 starters) were dermatological complaints (1.29/1000), followed by postural hypotension (1.06/1000), musculoskeletal complaints (0.96/1000), serious exercise-associated muscle cramping (sEAMC) (0.25/1000) and gastrointestinal complaints (0.23/1000) [2].

However, we are not aware of any systematic analysis to determine the independent risk factors associated with medical complications in 21 km running events. There are some data indicating that age [3, 4], gender [4, 5], running intensity (running pace) [6, 7], running experience [8], and environmental conditions [9] are possible risk factors for some specific medical complications during endurance exercise. However, these and other potential risk factors for medical complications have not been studied in 21 km runners. This information is vital to 1) plan medical care during these popular community-based events and 2) to design prevention programmes and thereby reduce the risk of medical complications (serious and less serious) during recreational running.

Therefore, the aim of this study was to identify independent risk factors that are associated with medical complications during 21 km running. In addition, we wanted to determine which risk factors are associated with specific more common medical conditions in different organ systems in 21 km runners

### **6.3. METHODS**

#### **Type of study**

This is a prospective study in a 4-year cohort (2008–2011) of runner data that was collected from the race registry and medical admissions data.

#### **Participants and demographics**

This study forms part of a series of studies that were initiated to determine the incidence and risk factors for adverse medical events in exercising individuals, and to then develop strategies to reduce this risk – the **SAFER** (Strategies to reduce Adverse medical events For the Exercise**R**) studies [10]. More specifically, this study is a component of a large prospective study that was conducted in all the participants of the Two Oceans Marathon races (consisting of a 21 km and a 56 km ultra-marathon) over a 4-year period (2008 to 2011) and the details of the study methodology has been fully described [2]. In summary, during the 4-year study period, a total of 39 511 21 km runners started the races (78.3% of all registrations for the 21 km) and only runners who started the race were included as participants in this study. Starters consisted of 21 028 males and 18 483 females, and all race entrants are required to be 16 years or older and there is no upper limit to the age. The demographics of all the 21 km race starters by gender, age groups (< 30 years, 31-40 years, 41-50 years and > 50 years) and by year of participation in the 4-year study period is depicted in Table 6.1.

**Table 6.1.: Demographics of all the 21 km race starters (gender, age groups and year of participation)**

<b>Gender</b>	<b>Age groups (years)</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>2011</b>	<b>All runners</b>
<b>Males</b>	≤ 30	2089	2337	1838	1815	8079
	31 - 40	1470	1508	1290	1306	5574
	41 - 50	1121	1052	901	832	3906
	> 50	877	973	837	782	3469
	<b>All</b>	<b>5557</b>	<b>5870</b>	<b>4866</b>	<b>4735</b>	<b>21028</b>
<b>Females</b>	≤ 30	1515	1956	1931	1978	7380
	31 - 40	1258	1364	1325	1411	5358
	41 - 50	896	1010	930	928	3764
	> 50	497	496	498	490	1981
	<b>All</b>	<b>4166</b>	<b>4826</b>	<b>4684</b>	<b>4807</b>	<b>18483</b>

For purposes of conducting research on these runners, this database of runners is registered with the Research Ethics Committee of the University of Cape Town (REC ref: 030/2013) and permission to investigate the incidence, nature and factors associated with medical complications during endurance running in the Two Oceans races was obtained from the Research Ethics Committee of the University of Cape Town (REC ref: 009/2011; REC ref: 441/2012).

### **Medical data collection**

Details of the medical data collection procedure has been reported [2]. In summary, accurate and comprehensive medical data on all medical complications were recorded during the 4-year study period. A “medical complication” was defined as a medical condition that required medical care on race day that was of sufficient severity to warrant a medical assessment by a doctor, either in the medical facility at the end of the race, or at one of the referral hospitals (for runners that were assessed by medical staff on the route). Medical complication data entered into the database was recorded in a standardized format and included the system affected (cardiovascular, respiratory, fluid, electrolyte and acid base imbalance, central nervous system, thermoregulatory, musculoskeletal, gastrointestinal, dermatological, metabolic, renal, and other) and the specific final diagnosis.

## **Incidence of medical complications**

The crude incidence of any medical complications was calculated as medical admissions per 1000 runners who started the races, and this has already been reported by year of observation and race type [2]. These incidences were also reported in sub-groups of runners by race type, system affected, and final diagnosis (for the 5 most common medical conditions) [2]. In this paper, the incidence of medical complications will additionally be reported by age groups (< 30 years, 31-40 years, 41-50 years and > 50 years), previous running experience in the Two Oceans 21 km races ( $\leq 1$  previous medal,  $\geq 2$  previous medals), and running pace (< 6 min/km, 6-7 min/km, > 7 min/km).

## **Statistical analysis of data**

All data were entered into an Excel spread sheet (Microsoft 2010) and then analysed using the SAS (v9.3) statistical programme (SAS Institute Inc., Cary NC, USA). The medical complications data were analysed with a Poisson regression model, using a robust error estimator (log link function). This cohort consists of correlated data as 29% of runners ran this race more than once during the 4-year period. The correlated structure was accounted for by using an unstructured correlation matrix. This was to estimate the Incidence Rates (IR's) and confidence intervals (CI). Group comparisons and 95% confidence intervals for these IR's and differences were also obtained. Regression analyses were conducted to determine risk factors associated with the development of any medical complication during 21 km running and then also for the 5 most common medical complications that occurred. Risk factors investigated included year of race, gender, age group, running experience category and running pace category. The year of race was included in the analyses as a proxy for environmental conditions on race day to determine if it was a risk for medical complications. The mean (SD) temperature, humidity, rainfall, cloud cover, wind speed during the race period (06h00 to 12h00 on race day) and calculated WBGT index for each year of race has already been reported [2]. The five most common complications were postural hypotension, serious exercise-associated muscle cramping (sEAMC), gastrointestinal complaints, musculoskeletal complications and dermatological complications. The adjusted model for any medical complication was reported as adjusting for all 5 risk factors (being present in the model), irrespective if they were significant. Due to the small number of reported specific complications, the adjusted models for these only included the significant risk factors.

## 6.4. RESULTS

### Incidence and risk factors associated with the development of any medical complication during 21 km running

The incidence (5.14 per 1000 runners starting the race) (95% CI: 4.48-5.90) of any medical complication during a 21 km race by year of observation (as a proxy for environmental conditions), gender, age group, running experience and running pace is depicted in Table 6.2a.

**Table 6.2a.: The incidence (per 1000 runners starting the race: 95%CI) of any medical complication during a 21 km race by year of observation (environmental conditions), gender, age group, running experience group and running pace group**

Variable	Category	Incidence	95% CI	
Year of observation	2008	4.74	3.55	6.32
	2009	3.93	2.91	5.31
	2010	4.92	3.69	6.56
	2011	7.04	5.55	8.94
Gender	Female	6.70	5.62	7.99
	Male	3.68	2.95	4.59
Age groups (years)	16-30	5.08	4.08	6.33
	31-40	4.43	3.34	5.88
	41-50	4.43	3.17	6.19
	> 50	7.47	5.51	10.13
Running experience (medals)	≤1	5.89	4.93	7.05
	2+	4.26	3.43	5.28
Running pace (min/km)	< 6	3.79	2.87	4.99
	6-7	3.54	2.65	4.73
	> 7	5.53	4.39	6.96

### *Univariate regression analysis*

The crude unadjusted analysis showed that there was a significant difference in the incidence of any medical complication during 21 km running by gender (females > males) ( $p < 0.0001$ ). Although there was overall no significant difference in the incidences between the age categories ( $p = 0.1173$ ), the following individual comparisons were significant: the > 50 age group had a higher incidence vs. a) 16-30 ( $p = 0.0444$ ), b) 31-40 ( $p = 0.0139$ ), and c) 41-50 ( $p = 0.0234$ ). There was also a significant difference in the incidence by year of observation (environmental conditions) ( $p = 0.0308$ ), with a higher incidence in 2011 (colder ambient temperature of 11.5 (2.1) °C) compared with both 2008 (ambient temperature of 18.2 (1.9) °C) ( $p = 0.0376$ ) and 2009 (ambient temperature of 17.1 (1.4) °C) ( $p = 0.0030$ ). There was also a significant difference in the incidence by running experience category ( $p = 0.0231$ ), with a higher incidence in runners with the least experience ( $\leq 1$  medals) compared with runners in the more experienced category (2+ medals) ( $p = 0.0228$ ). Finally, there was a significant difference in the incidence by running pace category ( $p = 0.0421$ ). Runners in the slowest pace category ( $> 7$  min/km) had a higher incidence of any medical complication compared with runners in the intermediate pace category (6-7 min/km) ( $p = 0.0189$ ) and runners in the fast pace category ( $< 6$  min/km) ( $p = 0.0384$ ).

### *Multiple regression analysis*

In the adjusted model (Table 6.2b.), there was a significant interaction effect between age category and gender ( $p = 0.0257$ ), which indicates that the trend for the incidences in the age categories were different for males and females. More specifically, females older than 50 years had a higher risk of a medical complication compared to females younger than 50 years of age ( $p = 0.0001$ ). This was not true for males older than 50 years of age, who did not have a higher risk of medical complications compared with younger males. An additional independent factor associated with an increased risk of developing any medical complication in 21 km running was year of observation (2008 vs. 2011,  $p = 0.0201$ ; 2009 vs. 2011,  $p = 0.0019$ ; 2010 vs. 2011,  $p = 0.0096$ ).

**Table 6.2b.: The incidence (per 1000 runners starting the race: 95%CI) of any medical complication during a 21 km race for the adjusted model**

Variable	Category	Incidence	95% CI	
Year of observation	2008	3.81	2.75	5.27
	2009	3.21	2.28	4.53
	2010	3.56	2.52	5.03
	2011	6.21	4.75	8.12
Gender	Age groups (years)			
Females	16-30	5.60	4.14	7.58
	31-40	3.07	1.91	4.96
	41-50	5.28	3.42	8.15
	> 50	11.70	7.60	17.96
Males	16-30	2.72	1.77	4.19
	31-40	3.75	2.44	5.76
	41-50	2.00	1.00	4.00
	> 50	3.37	1.90	5.97

It is noted that the higher incidence was in 2011, and this was a race that took place in colder environmental conditions) (Table 6.3.) [2].

**Table 6.3.: Environmental conditions on race day for each year. Values are mean (SD).**

	Temperature (°C)	Humidity (%)	Rainfall (mm)	Wind speed (knots)	WBGT index*
<b>2008</b>	18.2 (1.9)	77 (8)	0	9.6 (2.4)	16.5 (2.4)
<b>2009</b>	17.1 (1.4)	83 (7)	0	7.8 (1.0)	15.4 (1.6)
<b>2010</b>	16.3 (0.8)	93 (3)	0	3.5 (0.6)	15.2 (1.4)
<b>2011</b>	11.5 (2.1)	87 (2)	0	1.5 (1.3)	13.5 (2.9)

\*: Wet Bulb Globe Temperature (WBGT) Index – calculated using temperature (°C), humidity, time of day and cloud cover data

## **Incidence and risk factors associated with the development of postural hypotension during 21 km running**

In our study, the incidence (per 1000 race starters) of postural hypotension was 1.06 (95% CI: 0.79-1.44) (1 in every 943 race starters). The incidence (per 1000 runners starting the race) of postural hypotension during a 21 km race by year of observation (environmental conditions), gender, age group, running experience and running pace is depicted in Table 6.4.

**Table 6.4.: The incidence (per 1000 runners starting the race: 95%CI) of postural hypotension during a 21 km race by year of observation, gender, age group, running experience group and running pace group**

<b>Variable</b>	<b>Category</b>	<b>Incidence</b>	<b>95% CI</b>	
Year of observation	2008	0.72	0.35	1.52
	2009	0.75	0.38	1.50
	2010	1.26	0.72	2.22
	2011	1.58	0.95	2.62
Gender	Female	1.52	1.05	2.21
	Male	0.67	0.40	1.13
Age groups (years)	16-30	1.04	0.64	1.70
	31-40	0.73	0.37	1.47
	41-50	1.18	0.61	2.26
	> 50	1.66	0.87	3.19
Running experience (medals)	≤1	1.04	0.68	1.60
	2+	1.09	0.71	1.68
Running pace (min/km)	< 6	0.77	0.42	1.43
	6-7	0.38	0.16	0.92
	> 7	1.46	0.94	2.29

### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of postural hypotension during 21 km running by year of observation (environmental conditions) ( $p=0.2232$ ), age category ( $p=0.4387$ ), and category of running experience ( $p=0.8817$ ). However, there was a significant difference in the incidence by gender ( $p=0.0118$ ), where females had a higher incidence of postural hypotension. Further, there was also a significant difference in the running pace category ( $p=0.0141$ ). Runners in the slowest category ( $> 7$  min/km) had a higher incidence of postural hypotension compared with runners in the intermediate pace category (6-7 min/km) ( $p=0.0077$ ). There was no significant difference between the runners in the fastest pace category ( $< 6$  min/km) compared to the intermediate pace category (6-7min) ( $p=0.2027$ ) and the slowest category ( $> 7$ min/km) ( $p=0.1006$ ).

### *Multiple regression analysis*

In the adjusted model, the only independent factors associated with an increased risk of developing postural hypotension in 21 km running were female gender ( $p=0.0394$ ) and slow versus intermediate running pace ( $> 7$  vs. 6-7 min/km;  $p=0.0139$ ).

### **Incidence and risk factors associated with the development of serious Exercise-Associated Muscle Cramping (sEAMC) during 21 km running**

In our study, the incidence (per 1000 race starters) of sEAMC was 0.25 (95% CI: 0.14-0.47) (1 in 4000 runners). The incidence (per 1000 runners starting the race) of sEAMC during a 21 km race by year of observation, gender, age group, running experience and running pace is depicted in Table 6.5.

**Table 6.5.: The incidence (per 1000 runners starting the race: 95%CI) of serious Exercise-Associated Muscle Cramping (sEAMC) during a 21 km race by year of observation (environmental conditions), gender, running experience group and running pace group. (Age model not analysed, because of small numbers.)**

Variable	Category	Incidence	95% CI	
Year of observation	2008	0.10	0.02	0.73
	2009	0.19	0.05	0.75
	2010	0.63	0.28	1.40
	2011	0.11	0.02	0.75
Gender	Female	0.33	0.15	0.73
	Male	0.19	0.07	0.51
Age groups (years) *				
Running experience (medals)	≤1	0.30	0.13	0.66
	2+	0.21	0.08	0.56
Running pace (min/km)	< 6	0.23	0.08	0.72
	6-7	0.38	0.16	0.92
	> 7	0.15	0.04	0.62

\*: Too few sEAMC's reported per age category to analyse

#### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of sEAMC during 21 km running by gender (p=0.4078), year of observation (p=0.2675), category of running experience (p=0.5732) or running pace category (p=0.5273).

#### *Multiple regression analysis*

In the adjusted model, there were no risk factors associated with an increased risk of developing sEAMC in 21 km running, as the numbers were too small.

## **Incidence and risk factors associated with the development of gastrointestinal complaints during 21 km running**

In our study, the incidence (per 1000 race starters) of gastrointestinal complaints was 0.23 (95% CI: 0.12-0.44) (1 in 4348 race starters). The incidence (per 1000 runners starting the race) of gastrointestinal complaints during a 21 km race by year of observation, gender, age group, running experience and running pace is depicted in Table 6.6.

**Table 6.6: The incidence (per 1000 runners starting the race: 95%CI) of gastrointestinal complaints during a 21 km race by year of observation (environmental conditions), gender, age group, running experience group and running pace group**

<b>Variable</b>	<b>Category</b>	<b>Incidence</b>	<b>95% CI</b>	
Year of observation	2008	0.31	0.10	0.96
	2009	0.19	0.05	0.75
	2010	0.11	0.02	0.75
	2011	0.32	0.10	0.98
Gender	Female	0.22	0.08	0.58
	Male	0.24	0.10	0.57
Age groups (years)	16-30	0.20	0.06	0.61
	31-40	0.37	0.14	0.98
	41-50	0.13	0.02	0.93
	> 50	0.19	0.03	1.31
Running experience (medals)	≤ 1	0.20	0.08	0.53
	2+	0.26	0.11	0.63
Running pace (min/km)	< 6	0.23	0.08	0.72
	6-7	0.15	0.04	0.61
	> 7	0.15	0.04	0.62

### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of gastrointestinal complaints during 21 km running by gender ( $p=0.8925$ ), year of observation ( $p=0.6646$ ), age category ( $p=0.7741$ ), category of running experience ( $p=0.6891$ ) and running pace category ( $p=0.8818$ ).

### *Multiple regression analysis*

In the adjusted model, there were no factors associated with an increased risk of developing gastrointestinal complaints in 21 km running, as the numbers were too small.

### **Incidence and risk factors associated with the development of musculoskeletal complaints during 21 km running**

In our study, the incidence (per 1000 race starters) of musculoskeletal complaints was 0.96 (95% CI: 0.70-1.32) (1 in every 1042 race starters). The incidence (per 1000 runners starting the race) of musculoskeletal complaints during a 21 km race by year of observation (environmental conditions), gender, age group, running experience and running pace is depicted in Table 6.7.

**Table 6.7.: The incidence (per 1000 runners starting the race: 95%CI) of musculoskeletal complaints during a 21 km race by year of observation (environmental conditions), gender, age group, running experience group and running pace group**

Variable	Category	Incidence	95% CI	
Year of observation	2008	1.03	0.56	1.92
	2009	0.75	0.38	1.50
	2010	0.63	0.28	1.41
	2011	1.48	0.87	2.49
Gender	Female	1.03	0.66	1.62
	Male	0.91	0.58	1.42
Age groups (years)	16-30	0.98	0.59	1.62
	31-40	0.92	0.49	1.71
	41-50	1.05	0.52	2.09
	> 50	0.93	0.39	2.23
Running experience (medals)	≤ 1	1.29	0.88	1.90
	2+	0.63	0.36	1.10
Running pace (min/km)	< 6	0.62	0.31	1.23
	6-7	0.38	0.16	0.92
	> 7	1.39	0.88	2.20

### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of musculoskeletal complaints during 21 km running by gender ( $p=0.6901$ ), year of observation (environmental conditions) ( $p=0.3011$ ) and age category ( $p=0.9940$ ). There was a significant difference in the incidence of musculoskeletal complaints by pace category ( $p=0.0248$ ). Runners in the slowest pace category ( $> 7$  min/km) had a higher incidence of musculoskeletal complaints compared with runners in the intermediate pace category (6-7 min/km) ( $p=0.0110$ ).

There was a significant difference in the incidence of musculoskeletal complaints by category of running experience ( $p=0.0324$ ). There was a higher incidence of musculoskeletal complaints in runners with the least experience ( $\leq 1$  medals) compared with runners in the more experienced category (2+ medals) ( $p=0.0379$ ).

### *Multiple regression analysis*

In the adjusted model, the independent factors associated with an increased risk of developing musculoskeletal complaints in 21 km running were least race experience ( $\leq 1$  vs. 2+;  $p=0.0315$ ) and slower running pace ( $> 7$  vs. 6-7min/km;  $p=0.0259$ ).

### **Incidence and risk factors associated with the development of dermatological complaints during 21 km running**

In our study, the incidence (per 1000 race starters) of dermatological complications was 1.29 (95% CI: 0.98-1.70) (1 in every 775 race starters). The incidence (per 1000 runners starting the race) of dermatological complaints during a 21 km race by year of observation (environmental conditions), gender, age group, running experience and running pace is depicted in Table 6.8.

**Table 6.8.: The incidence (per 1000 runners starting the race: 95%CI) of dermatological complaints during a 21 km race by year of observation, gender, age group, running experience group and running pace group**

Variable	Category	Incidence	95% CI	
Year of observation	2008	1.34	0.78	2.31
	2009	1.03	0.57	1.86
	2010	0.95	0.49	1.82
	2011	1.90	1.20	3.01
Gender	Female	1.69	1.19	2.40
	Male	0.95	0.62	1.48
Age groups (years)	16-30	1.23	0.79	1.93
	31-40	1.10	0.63	1.94
	41-50	0.92	0.44	1.92
	> 50	2.40	1.39	4.13
Running experience (medals)	≤1	1.44	1.00	2.07
	2+	1.14	0.75	1.74
Running pace (min/km)	< 6	1.08	0.64	1.82
	6-7	1.46	0.93	2.28
	> 7	1.23	0.76	2.00

#### *Univariate regression analysis*

The crude unadjusted analysis showed that there was no significant difference in the incidence of dermatological complaints during 21 km running by year of observation (environmental conditions) ( $p=0.3191$ ), running experience category ( $p=0.4104$ ) and running pace category ( $p=0.6923$ ). There was overall no significant difference between the age categories ( $p=0.2581$ ), except a significant difference in the > 50 age group compared with the 41-50 age group ( $p=0.0400$ ). There was a significant difference in the incidence of dermatological complaints by gender ( $p=0.0481$ ). Female runners had a higher incidence of dermatological complaints compared with male runners ( $p=0.0481$ ).

*Multiple regression analysis*

In the adjusted model, the only independent factor associated with an increased risk of dermatological complaints in 21 km running was female gender ( $p=0.0481$ ).

**Summary of risk factors associated with the development of medical complications during 21 km running**

Independent risk factors associated with any medical complication, and more common specific medical complications (postural hypotension, serious EAMC, gastrointestinal, musculoskeletal and dermatological) in 21 km runners are depicted in Table 6.9.

**Table 6.9.: A summary of risk factors for any medical complications and more common medical complications during 21 km running**

	<b>Year</b>	<b>Gender</b>	<b>Age</b>	<b>Running experience</b>	<b>Running pace</b>
<b>Any medical complication</b>	2011 (Colder temperature)	Older females			
<b>Postural hypotension</b>		Female			Slower pace
<b>Serious EAMC</b>					
<b>Gastrointestinal complication</b>					
<b>Musculoskeletal complication</b>				Least experience	Slower pace
<b>Dermatological complication</b>		Female			

## 6.5. DISCUSSION

In this study, the incidence and risk factors for any medical complication, and specific common medical complications during 21 km running are reported. In addition, a Poisson regression model was used to determine risk factors that may be associated with the development of any medical complications, and more specific common medical complications during 21 km running. Risk factors that were entered into the model were: year of observation (environmental conditions), gender, age, running experience, and running pace.

The first main findings of this study were that older females and the year of observation (colder environmental conditions) were risk factors for the development of any medical complication during 21 km running. Secondly, we identified risk factors associated with specific common medical complications in 21 km runners as follows: postural hypotension (female gender and slow running pace), musculoskeletal complaints (less running experience and slower pace) and for dermatological complaints (female gender). We could not identify specific risk factors associated with the development of sEAMC and gastrointestinal complaints in 21 km runners, because of the small numbers.

In this study, runners in the slowest running pace category had a higher risk of developing postural hypotension and musculoskeletal complaints. The most likely explanation for this observation is that the slower running pace is related to the development of symptoms during the race. In our study we could not study a cause-effect relationship between these parameters, as we did not have data on the onset of the complication during the race or changes in running pace during the race. Our model did consider year of observation age, gender, running pace and running experience, but we did not have any data on other variables that may influence running pace, particularly training history. A slow running pace may also be indicative of inadequate training, and this variable together with other determinants of running pace as risk factors for medical complications such as postural hypotension would have to be explored in future studies.

In this study, older females were at increased risk of developing any medical complication. More specifically, females were at increased risk of developing postural hypotension and dermatological complaints. In only two previous studies in runners, were the risks of medical

complications assessed by gender. In marathon runners, no differences in the incidence of any medical complications were observed in female compared with male runners [11], but during a multi-staged 240 km ultra-marathon, female runners were at slightly higher risk of developing medical complications [4]. In only one study in ultra-marathon runners, risk factors for dermatological complaints have been reported and in that study female runners were not at higher risk of dermatological complaints [4]. As in other studies [4, 11], most of the dermatological complaints in our study were skin abrasions, friction injuries and cuts from minor falls (data not reported).

In our study, older age in females was a risk factor for developing any medical complications, but was not associated with any common specific medical complications. Older age may therefore be a risk factor for other less common medical complications in 21 km runners. We did not have sufficient sample sizes in the other less common categories of medical complications, and this aspect would have to be explored in future analyses using larger cohorts.

A further finding in our study was that less running experience was a risk factor for the development of musculoskeletal complaints. This is perhaps not surprising, as runners with less experience (frequently novice runners) may not have prepared adequately for the race and suffered from minor musculoskeletal injury. A pre-race running injury in these runners may also have been a factor, and this would have to be explored in future studies.

Finally, the year of observation (the year in which the ambient temperature was colder than in other years) was predictive of any medical complication, but not of any of the more common specific medical complications. We included this variable into the model because of the potential variation in environmental conditions that may occur from year to year. Our data show that, in general, environmental conditions on race day (ambient temperature, humidity, rainfall and wind speed) were quite similar in the four-year study period, with the exception that in 2011, the ambient temperature was about 5°C cooler than in other years (Table 6.3.). The highest incidence of medical complications was recorded in this year. As reported in one previous study, we also show that colder environmental conditions can increase the risk of medical complications [11], and this information can assist race organizers in the planning of medical care. We do recognize that factors, other than environmental conditions, may also

have played a role in the higher incidence of medical complication that we reported in 2011. These would have to be explored in future studies.

The strengths of this study are firstly, to our knowledge, this is the largest prospective study to date to determine possible risk factors for any medical complication and specific common medical complications during 21 km running. Secondly, we had data on all the runners who registered and started the races in the 4-year study period. Thirdly, the medical data we recorded on all medical complications was both comprehensive and accurate. One of the limitations of our study was that we could not include all the possible intrinsic and extrinsic risk factors for medical complications into our model as these data were not available. In future studies, additional pre-race medical and training history, as well as history of previous medical complications would have to be included to determine other possible risk factors for medical complications in 21 km runners. Furthermore, in the older age categories, the number of participants was smaller, and this may limit the precision of the findings. More specifically, the precision of the incidence of medical complications for the subgroup females older than 50 years was lower than that of the other subgroups due to relatively smaller samples in this subgroup.

The practical clinical implications of these data are that, for the first time, 21 km runners who are at higher risk of developing any medical complication and some common specific medical complications can now be identified. Apart from assisting medical staff to plan appropriate care on race days, interventions, including runner education programmes can now be developed to reduce the risk of medical complications in 21 km runners.

## **6.6. SUMMARY AND CONCLUSION**

- To our knowledge, the SAFER III study is the first study to systematically document risk factors for all medical complications and specific common medical complications during running in a population of 21 km runners
- Older females and the year of observation (colder environmental conditions) were risk factors for the development of any medical complication during 21 km running.
- Independent risk factors associated with specific common medical complications in 21 km runners as follows: postural hypotension (female gender and slow running pace),

musculoskeletal complaints (less running experience and slower pace) and for dermatological complaints (female gender).

- Clinicians taking care of distance runners can now start to identify sub-groups of 21 km runners that are at higher risk of developing any medical complication, and specific common medical complications during races
- Data from this study will form the basis for further clinical studies to first develop and then test the effects of intervention strategies to reduce the risk of adverse medical events during 21 km running

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## CHAPTER 7

### STUDY 4: LEISURE ATHLETES AT RISK OF MEDICAL COMPLICATIONS: OUTCOMES OF PRE-PARTICIPATION SCREENING AMONG 15778 ENDURANCE RUNNERS - SAFER VII

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#### 7.1. ABSTRACT

**Objective:** International guidelines for pre-participation screening of masters/leisure athletes to identify those that require medical assessment exist, but have not been implemented in mass-community based sports events. We determined the prevalence of runners who, according to these guidelines, would require a medical assessment before participating in a distance running event.

**Methods:** Participants of the 2012 Two Oceans races (21.1 and 56 km) in South Africa (n=15778) completed an online pre-race medical screening questionnaire using European pre-participation screening guidelines. We determined the prevalence of runners that would require a pre-race medical assessment, based on risk factors, symptoms and disease.

**Results:** The pre-participation “self-assessment of risk” screening identified 4941 runners (31.3%; 95% CI 30.6-32.0) that would need to undergo a full pre-participation medical assessment prior to running, if the current pre-participation screening guidelines are applied. Although musculoskeletal complaints and prescription medication use were the main triggers for a medical assessment, 16.8 % (n=2657) runners should undergo medical evaluation for suspected cardiac disease based on the questionnaire results: 3.4% (n=538) reporting existing CVD (very high risk) and 13.4% (n=2119) reporting multiple CVD risk factors (high risk). Other possible risk factors were reported as follows: history of chronic diseases (respiratory = 13.1%, gastro-intestinal = 4.3%, nervous system = 3.8%, metabolic/endocrine = 3.5%, allergies = 13.9%); chronic prescription medication = 14.8%, used medication before or during races = 15.6%; past history of collapse during a race = 1.4%.

**Conclusions:** Current guidelines identified that >30% runners would require a full medical assessment before race participation - mainly linked to runners reporting musculoskeletal conditions. We suggest a revision of guidelines and propose that pre-race screening should be considered to identify runners with a “very high”, “high” and “intermediate risk” for medical complications during exercise. Pre-race screening and educational intervention could be implemented to reduce medical complications during exercise.

## 7.2. INTRODUCTION

Regular participation in physical activity (> 150min per week at moderate- to high-intensity) has numerous health benefits, including the prevention and management of chronic non-communicable disease [1] [2]. Recreational running has become an increasingly popular form of regular physical activity and participation in community based recreational distance running events such as the 21.1km (half-marathon), marathon (42.2km), and ultra-marathon races has concomitantly increased [3]. Annual reports from Running USA (<http://www.runningusa.org/annual-reports> - accessed on 1 March 2017) show an increase of >12 fold in overall participation in marathon runners since 1976, specifically increases in participation in the older age groups (> 40 years).

Whilst the health benefits of exercise are numerous, medical complications during moderate- to high-intensity vigorous physical activity, such as distance running, in a variety of organ systems have been described [4] [5] [6]. Acute cardiac events, including myocardial infarction and sudden death, are described in both younger and older runners [7] [8] [9] [10].

Determining the risk of sudden death during exercise, in particular during distance running events such as the half-marathon (21.1 km) and marathon (42.2 km) [11] [12] using pre-screening tests and detailed diagnostics (ECG) has been proposed [5-8, 13-16].

Pre-participation screening for CVD is routinely recommended and performed for younger competitive elite athletes across the world [17] [18] [19] but not in leisure athletes older than 35 years, despite an exponentially higher risk of acute cardiac episodes in these older athletes due to increased incidences of atherosclerotic coronary artery disease [20]. Pre-participation screening guidelines for masters ( $\geq 50$  years) and leisure athletes have been proposed by the American Heart Association (AHA) [21], American College of Sports Medicine (ACSM) [22], Canadian Physical Activity Readiness Questionnaire (PAR-Q+) and the Physical Activity Readiness Medical Examination (ePARMed-X+) [23], and the European Society of Cardiology (ESC) together with the European Association of Cardiovascular Prevention and Rehabilitation (EACPR) [24].

These guidelines “provide a pragmatic and practical approach to identifying higher-risk individuals to minimize the risk of sudden cardiac death (SCD)” [25]. The screening process begins with a “self-assessment of risk” which is followed up by medical intervention for

identified high-risk athletes. The “self-assessment of risk”, as recommended by the ESC and EACPR, can be conducted by the individual athlete or by non-physician health professionals [25] and is based on the recommended AHA/American College of Sports Medicine (ACSM) pre-participation screening questionnaire for individuals at Health/Fitness facilities[26]. The initial “self-assessment of risk”. In section 1, health information related to known cardiovascular disease, cardiovascular symptoms, medication use, and other health issues is collected and in section 2, known risk factors for cardiovascular disease are identified. If the respondents provide one positive response to any question related to section 1 (health information), or if 2 or more risk factors are identified in section 2, they are advised to undergo a thorough medical assessment by a qualified physician before participating in moderate- to high-intensity exercise, such as distance running [25]. More recently, a task force from the ACSM published revised screening guidelines, and in these new guidelines, risk factors for CVD (section 2) were omitted [22].

We are only aware of one study where the ESC/EACPR screening guidelines were applied to adult participants > 40 years of age [27]. In this study, based on “self-assessment of risk”, approximately 95% of women and 93.5% of men were advised to consult a physician before embarking on exercise [27]. We are not aware of any studies describing the outcome of the ESC/EACPR screening guidelines when applied to participants in mass community based endurance events. `

In the first of our **SAFER** (**S**trategies to reduce **A**dverse medical events **F**or the **E**xercise**R**) studies [5, 28] we report a high risk of serious of cardiac and non-cardiac medical complications at endurance events [5].

In this study, as part of the ongoing SAFER initiative, we wanted to determine the prevalence of runners who, according to the current European guidelines for “risk self-assessment”, would be at higher risk of acute cardiac medical complications and be required to undergo a medical assessment before participating in the Two Oceans 21.1 km or 56 km races. Furthermore, we wanted to determine the factors in the current guidelines that trigger this recommendation. As a secondary aim, we also explore the prevalence of other potential “risk factors” associated with serious non-cardiac medical complications such as other chronic systemic diseases, use of medication and previous collapse during exercise [6] that are not currently routinely included in international pre-exercise screening guidelines.

### 7.3. METHODS

#### *Setting*

The Old Mutual Two Oceans Marathon races are mass community-based running events that take place annually during late summer in Cape Town, South Africa. Approximately 25 000 runners are attracted to the two main events, the 21.1 km (half-marathon) and the 56 km (ultra- marathon) races every year. Males and females of all ages older than 16 years can enter, and entries to the 21.1 km race are open to novice runners and require no qualifying time. Entries for the 56 km race requires completion of any one of the following qualifying times: a standard 42.2 km marathon in < 5 hours, 50 km in < 6 ½ hours, 56 km in < 7 hours, 90km in < 12 hours, or a 100km race in < 13 ½ hours. A high rate of acute medical complications, including sudden death, in the runners competing in the Old Mutual Two Oceans Marathon races [5, 29] precipitated the design and implementation of an online pre-race medical screening programme for all race entrants in 2012.

#### *Participants*

In 2012, all race entrants (n=25455) completed a pre-race medical screening questionnaire as part of the online registration process. Of these, 15778 (62.0% of all race entrants) gave informed consent that their personalized medical data could be used for research purposes and these runners were designated as participants in this study. The study participants were representative (for gender, age and race type) of all race entrants (Table 7.1.).

**Table 7.1.: The profile by race type, sex, and age groups of all race entrants and runners who participated in this study**

		All race entrants (n=25 455)		Runners participating in this study (n=15 778)	
		N	%	N	%
Race type	21.1 km	16 284	64.0	10 786	68.4
	56 km	9 171	36.0	4 992	31.6
Gender	Males	14 775	58.0	8 916	56.5
	Females	10 680	42.0	6 862	43.5
Age groups	≤ 30 years	7 471	29.4	4 951	31.4 *
	31–39 years	8 074	31.7	4 499	28.5
	≥ 40 years	9 910	38.9	6 328	40.1 *
Males x Age	Males < 45 years	21150	83.1	13304	84.3
	Males > 45 years	4305	16.9	2474	15.7*
Females x Age	Females < 55 years	25013	98.3	15509	98.3
	Females > 55 years	442	1.7	269	1.7

\*: Significantly different from all race entrants (p<0.05)

The 15778 study participants consisted of 8916 (56.5%) male and 6862 (43.5%) female entrants. In the study group, compared to all entrants, there were equal proportions of athletes in the 21.1 km and 56 km races and in males vs. females. In the age categories there were equal proportions of runners in the age group 31 to 39 years old (All=31.7%, Study group=28.5%), but there was a large proportion of runners in the younger (<30 years) (All=29.4%, Study group=31.4%) and older (>40 years) (All=38.9%, Study group=40.1%) age groups (Table 7.1.).

For purposes of conducting research on this population, permission to investigate the prevalence of risk factors for cardiovascular disease, existing medical diseases, allergies, medication use and injury history during endurance running in the Two Oceans races was

obtained from the Research Ethics Committee of the University of Cape Town (REC 009/2011) (REC 030/2013) and the Research Ethics Committee of the University of Pretoria (REC 433/2015).

### ***Online pre-race medical screening questionnaire***

An online pre-race medical screening questionnaire (OPRMSQ) or “self-assessment of risk” was developed to identify runners that are at possible increased risk of acute medical complications during moderate-to high intensity exercise such as a distance running race [6]. The questions were based on the ESC and the EACPR guidelines for pre-exercise screening [25] with additional questions on general prescription medication use, including medication use during racing and a past history of collapse during racing.

The main elements of the questionnaire (Table 7.2.) consisted of 2 injury related questions (muscle cramping and running injuries) and 13 questions that included the following categories of medical history: cardiovascular disease (CVD), symptoms of CVD, risk factors for CVD, other chronic disease (respiratory disease, metabolic or hormonal disease, gastrointestinal disease, nervous system disease, renal or bladder disease, haematological or immune system disease, cancer, allergies), With the exception of a question regarding pregnancy, the OPRMSQ included all the questions in the AHA/ACSM pre-participation screening questionnaire for individuals at Health/Fitness facilities [26], as recommended by the ESC and the EACPR for the pre-participation screening of leisure athletes engaging in moderate- to high-intensity exercise [24].

**Table 7.2.: Summary: Main elements of the medical screening questionnaire**

<b>Medical screening questionnaire – self-assessment of risk *</b>	
1.	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, cardiomyopathy, myocarditis, use of a pacemaker, or inherited heart defect?
2.	Do you currently suffer from any symptoms of heart or blood vessel disease, including any of the following: shortness of breath when sitting or lying down, shortness of breath with mild exercise, waking up with shortness of breath at night, palpitations that make you dizzy, chest pain when sitting or performing exercise or when you are emotionally stressed, pain (or discomfort) in the neck jaw arms at rest or during exercise, dizziness during exercise or fainting spells)?
3.	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)?
4.	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?
5.	Do you suffer from any respiratory (lung) disease including asthma, emphysema (COPD), wheezing, cough, postnasal drip, hay fever, or repeated flu like illness?
6.	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?
7.	Do you suffer from any diseases of the nervous system including past history of stroke or transient ischemic attack (TIA), frequent headaches, epilepsy, depression, anxiety attacks, muscle weakness, nerve tingling, loss of sensation, or chronic fatigue?
8.	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?
9.	Do you suffer from any disease of the blood or immune system including anemia, recurrent infections, HIV/AIDS, leukemia, or are you using any immunosuppressive medication?
10.	Do you suffer from any growths or cancer, including a past history of cancer?
11.	Do you suffer from any allergies including a past history of allergies, to medication, plant material, or animal material?
12.	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?
13.	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?
14.	Do you, or did you suffer from any symptoms of a running injury (muscles tendons bones ligaments or joints) in the last 12 months?
15.	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)?

\*: Once a participant answered “yes” to any of the main screening questions, further details were obtained using “dropdown” boxes with additional questions

## Statistical analysis

All data from the runner and medical questionnaire database were analysed using the SAS Enterprise Guide (V6.1) statistical package (SAS Institute Inc., Cary, North Carolina, USA). Crude numbers, prevalence and 95% confidence intervals are reported throughout.

## 7.4. RESULTS

### *Prevalence of risk factors for cardiovascular disease (CVD), symptoms of CVD, and existing CVD in runners*

**Table 7.3.:** The prevalence of existing cardiovascular disease (CVD), history of any symptoms of CVD, or any risk factor for CVD in all runners (n=15 778) (% runners; 95% CI)

		All runners (n=15 778)			
		n	%	95% CI	
<b>Any existing CVD</b>		360	2.3	2.1	2.5
	Myocardial infarction (MI)	31	0.2	0.1	0.3
	Angina	22	0.1	0.1	0.2
	Coronary artery bypass graft (CABG)	19	0.1	0.1	0.2
	Angioplasty – no stent	10	0.1	0.0	0.1
	Angioplasty – with stent	31	0.2	0.1	0.3
	Coronary artery disease (CAD)	80	0.5	0.4	0.6
	Heart failure	1	0.01	0.0	0.0
	Heart transplant	0	0.0	-	-
	Angioplasty with/without stent	40	0.3	0.2	0.3
	Heart failure/transplant	1	0.01	0.0	0.0
	Arrhythmia	70	0.4	0.3	0.6
	Rheumatic fever	33	0.2	0.1	0.3
	Heart murmur	98	0.6	0.5	0.7
	Pacemaker	6	0.04	0.0	0.1
	Inherited cardiac condition	11	0.1	0.0	0.1
	Other	64	0.4	0.3	0.5

**Table 7.3.: The prevalence of existing cardiovascular disease (CVD), history of any symptoms of CVD, or any risk factor for CVD in all runners (n=15 778) (% runners; 95% CI) (continued)**

<b>Any history of symptoms of CVD</b>	284	1.8	1.6	2.0
Swollen ankles	40	0.3	0.2	0.3
Water retention	25	0.2	0.1	0.2
Shortness of breath sit/lying	8	0.1	0.0	0.1
Short breath mild exercise	39	0.3	0.2	0.3
Waking up short breath	4	0.03	0.0	0.1
Palpitations/no dizziness	22	0.1	0.1	0.2
Palpitations/dizziness	4	0.03	0.0	0.1
Chest pain sitting	4	0.03	0.0	0.1
Chest pain/exercise	8	0.1	0.0	0.1
Chest pain normal	20	0.1	0.1	0.2
Pain in the neck, jaw or arms at rest	52	0.3	0.2	0.4
Chest pain	32	0.2	0.1	0.3
Dizziness during exercise	46	0.3	0.2	0.4
Fainting	23	0.2	0.1	0.2
Dizziness/fainting	61	0.4	0.3	0.5
Chronic cough	21	0.1	0.1	0.2
Painful calves during walking	72	0.5	0.4	0.6
<b>Any risk factors for CVD</b>	2544	16.1	15.5	16.7
High blood pressure	696	4.4	4.1	4.7
High Blood cholesterol concentration	921	5.8	5.5	6.2
Cigarette smoking	335	2.1	1.9	2.4
Overweight	186	1.2	1.0	1.4
Diabetes mellitus	150	1.0	0.8	1.1
Family history of heart disease	688	4.4	4.0	4.7
Males >45 years	2474	15.7	15.1	16.3
Females >55 years	269	1.7	1.5	1.9

\*: Prevalence (%) in all runners

The prevalence of existing CVD, symptoms of CVD, and risk factors for cardiovascular disease (CVD) in runners is depicted in Table 7.3. In this group of distance runners (n=15778), 360 (2.3%; 95% CI 2.1-2.5) reported suffering from existing CVD. The most common reported cardiovascular condition in runners with existing CVD (n=360) was a heart

murmur (0.6%; 95% CI 0.5-0.7), followed by known coronary artery disease (0.5%; 95% CI 0.4-0.6), and arrhythmia (0.4%; 95% CI 0.3-0.6) (Table 7.2.). Other reported specific CVD's were a history of rheumatic fever (0.2%; 95% CI 0.1-0.3), and myocardial infarction (0.2%; 95% CI 0.1-0.3). In this category of "other", less than 0.4% of runners reported existing CVD.

Of the runners surveyed, 284 (1.8%; 95% CI 1.6-2.0) reported at least one symptom of CVD. The more common specific symptoms of CVD in runners were painful calves during walking (0.5%; 95% CI 0.4-0.6), a history of dizziness or fainting during exercise (0.4 %; 95% CI 0.3-0.5), pain in the neck, jaw or arms (0.3%; 95% CI 0.2-0.4), swollen ankles (0.3%; 95% CI 0.2-0.3), shortness of breath with mild exercise (0.3%; 95% CI 0.2-0.3), and chest pain (0.20%; 95% CI 0.1-0.2) (Table 7.2.). Other possible symptoms of CVD (water retention, palpitations, chronic cough) were reported by  $\leq$  0.2% of runners. The total number of runners who reported either known CVD or symptoms suggestive of CVD was 538, which is 3.4% of all the runners.

In this group of runners, 2544 (16.1%; 95% CI 15.5-16.7) reported at least one risk factor for CVD. The most common risk factor for CVD in runners was a combination of male and age > 45 years (15.7%; 95% CI 15.1-16.3). Other common specific risk factors for CVD included high blood cholesterol concentration (5.8%; 95% CI 5.5-6.2), high blood pressure (4.4%; 95% CI 4.1-4.7), and a family history of heart disease (4.4%; 95% CI 4.0-4.7). Less than 4% of runners reporting other CVD risk factors such as smoking, being overweight or suffering from diabetes mellitus (Table 7.2.). The total number of runners who reported more than one risk factor for CVD was 2119, which is 13.4% of all the runners.

*Prevalence of chronic diseases in other organ systems in runners*

**Table 7.4.: The prevalence of runners (% runners; 95% CI) with disease in other organ systems, medication use and history of collapse (n=15 778)**

Chronic disease / medication use	All runners (n=15 778)			
	n	% *	95% CI	
History of respiratory disease	2061	13.1	12.5	13.6
Asthma	928	5.9	5.5	6.3
Allergies/hay fever	1359	8.6	8.2	9.1
Recurrent respiratory tract infections	76	0.5	0.4	0.6
Previous lung complaints	31	0.2	0.1	0.3
COPD	3	-	-	-
Interstitial lung disease	1	-	-	-
Cystic fibrosis	2	-	-	-
Other respiratory complaints	20	-	-	-
History of metabolic or endocrine disease	552	3.5	3.2	3.8
History of gastrointestinal (GIT) disease	683	4.3	4.0	4.7
History of nervous system disease	593	3.8	3.5	4.1
History of kidney or bladder disease	358	2.3	2.0	2.5
History of blood or immune system disease	138	0.9	0.7	1.0
History of growths/cancers	298	1.9	1.7	2.1
History of any allergy	2189	13.9	13.3	14.4
History of chronic prescription medication use	2333	14.8	14.2	15.3

\*: Prevalence (%) in runners

In this study, 2061 runners (13.1%; 95% CI 12.5-13.6) reported a history of respiratory disease. The more common specific respiratory diseases were reported as follows: allergies/hay fever (8.6%; 95% CI 8.2-9.1) and asthma (5.9%; 95% CI 5.5-6.3) (Table 7.4.). Runners also reported a history of other chronic disease, including GIT disease (4.3%; 95% CI 4.0-4.7, n=683), metabolic and endocrine disease (3.5%; 95% CI 3.2-3.8, n=552), and kidney or bladder disease (2.3%; 95% CI 2.0-2.5, n=358). Furthermore, 13.9% (95% CI 13.3-14.4, n=2189) runners reported a history of any allergy, while 14.8% (95% CI 14.2-15.3, n=2333) runners reported the use of chronic prescription medication.

*Prevalence of medication use by runners one week before, or during racing*

**Table 7.5.: The prevalence of more specific medication use during a race in all the runners (% runners; 95% CI) (n= 15 778)**

Medication group	Specific medication	All runners (n=15 778)			
		n	% of all runners	95% CI's	
<b>One week before a race</b>					
Analgesics	Paracetamol	621	3,9	3.6	4.2
	Codeine	67	0,4	0.3	0.5
	Other analgesics	212	1,3	1.2	1.5
Anti -inflammatory medication		2022	12,8	12.3	13.3
	NSAIDs	1442	9,1	8.7	9.6
	Cortisone (any)	255	1,6	1.4	1.8
	Cortisone pills	43	0,3	0.2	0.4
	Cortisone injection	228	1,5	1.3	1.6
<b>During a race</b>					
Analgesics	Paracetamol	484	3,1	2.8	3.3
	Codeine	46	0,3	0.2	0.4
	Other pain killers	278	1.8	1.6	2.0
Any anti- inflammatory medication		1227	7,8	7.4	8.2
	NSAIDs	776	4,9	4.6	5.3
	Cortisone (any)	41	0,3	0.2	0.3
	Cortisone pills	14	0,1	0.0	0.1
	Cortisone injection	29	0,2	0.1	0.3

NSAIDs: Non-steroidal anti-inflammatory drugs

In this group of runners, 2459 runners (15.6%; 95% CI 15.0-16.2) reported using medication to treat injuries either before or during races. In the week before a race, runners commonly used anti-inflammatory medication (12.8%; 95% CI 12.3-13.3), specifically non-steroidal anti-inflammatory medications (NSAIDs) (9.1%; 95% CI 8.7-9.6), while 3.9% (95% CI 3.6-4.2) of runners reported using paracetamol, and 1.6% (95% CI 1.4-1.8) used cortisone in the week prior to a race (Table 7.5.).

During the race, the most common reported specific medication used was also anti-inflammatory medication (7.8%, 95% CI 7.4-8.2), more specifically, the NSAIDs (4.9%; 95% CI 4.6-5.3). In addition, 3.1% (95% CI 2.8-3.3) of the runners used paracetamol during a race, followed by the use of other analgesics (1.8%; 95% CI 1.6-2.0) (Table 7.5.).

### ***Prevalence of past history of collapse during training or racing in runners***

In this group of runners, 196 (89.1%, 95% CI: 84.9 – 93.2) reported a history of collapse either during training or during a race.

The total number of runners who reported any known underlying chronic diseases, and/or medication use, and/or a past history of collapse was 7738, which is 49.1% of all runners.

### ***In how many runners did the pre-participation “self-assessment of risk” medical screening (using the ESC/EACPR guidelines) identify the need to undergo a full pre-participation medical assessment prior to running?***

The pre-participation “self-assessment of risk” screening identified 4941 runners (31.3%; 95% CI 30.6-32.0) that would need to undergo a full pre-participation medical assessment prior to running, if the current ESC/EACPR pre-participation screening guidelines are applied [24] [25]. Of these runners, 16.8 % (n=2657) runners should undergo medical evaluation for suspected cardiac disease based on the questionnaire results: 3.4% (n=538) reporting existing CVD (very high risk) and 13.4% (n=2119) reporting multiple CVD risk factors (high risk). The specific criteria (by Section 1 and 2 of the AHA/ACSM screening recommendations in the ESC/EACPR guidelines), that were responsible for the recommendation to undergo a full medical assessment (expressed as a % of the 4941 runners that were identified), are depicted in Table 7.6.

**Table 7.6.: Runners with specific criteria, expressed as a % (95% CI) of all runners (n=4941) that were identified by the current ESC/EACPR guidelines (Sections 1 and 2) to undergo a pre-exercise medical assessment**

Sections / main categories per section	Specific criteria	All identified runners (n=4941)			
		N	%	95%CI	
<b>Section 1 – Medical conditions</b>					
<b>History</b>	Heart attack	50	1.0	0.7	1.3
	Heart surgery	19	0.4	0.2	0.6
	Coronary angioplasty	40	0.8	0.6	1.1
	Heart rhythm disturbance <sup>1</sup>	74	1.5	1.2	1.8
	Heart valve disease	64	1.3	1.0	1.6
	Heart failure	1	0.0	0.0	0.1
	Cardiac transplantation	-	-	-	-
	Congenital heart disease	11	0.2	0.1	0.4
<b>Symptoms / medication use</b>	Chest pain with exertion	31	0.6	0.4	0.9
	Unreasonable breathlessness	48	1.0	0.7	1.3
	Dizziness or fainting	61	1.2	0.9	1.5
	Heart medication <sup>2</sup>	-	-	-	-
<b>Other health issues</b>	Musculoskeletal conditions	2710	54.9	53.5	56.2
	Concerns about exercise	-	-	-	-
	Prescription medications	2333	47.2	45.8	48.6
	Pregnant <sup>3</sup>	-	-	-	-
<b>Section 2 – Risk factors</b>					
<b>CVD Risk factors</b>	Male > 45 years (n=1152)	1152	23.3	22.1	24.5
	Female > 55 years <sup>4</sup> (n=142)	142	2.9	2.4	3.3
	Smoking	218	4.4	3.8	5.0
	High blood pressure <sup>5</sup>	641	13.0	12.0	13.9
	High cholesterol <sup>6</sup>	760	15.4	14.4	16.4
	Diabetic / medication for diabetes	140	2.8	2.4	3.3
	Family history of CVD	514	10.4	9.6	11.3
	Physical inactivity <sup>7</sup>	-	-	-	-
	Overweight <sup>8</sup>	156	3.2	2.7	3.6

<sup>1</sup>: Includes pacemaker / implantable defibrillator / rhythm disturbance; <sup>2</sup>: No specific question on heart medication; <sup>3</sup>: No question on pregnancy; <sup>4</sup>: No specific question about hysterectomy or being post-menopausal; <sup>5</sup>: No specific question on unknown blood pressure and blood pressure medication; <sup>6</sup>: No specific question about unknown cholesterol; <sup>7</sup>: No question on physical inactivity – all participants entered a distance running event; <sup>8</sup>: Question was on “obesity” and not specific to > 20 pounds overweight

\*: significantly different between 56 km and 21.1 km runners

The main criteria that would lead to the recommendation for referral to undergo a full medical assessment before competing was a self-reported musculoskeletal condition (54.9% of the runners that were identified). The use of prescription medication and the gender/age criterion (male gender: over 45 years) followed as criteria for referral. Risk factors associated with

CVD, including a high serum cholesterol concentration, high blood pressure and diabetes mellitus were also common criteria for referral.

Of the 4941 runners that were identified through the screening process, 22% were identified because of CVD risk factors, 23% were identified because of other medical conditions plus one other risk factor for CVD, and another 55% were identified because of other medical conditions, with no CVD risk factors. Almost half of the athletes with any one CVD risk factor were not identified to undergo a pre-participation medical assessment prior to participation (1996/4244).

We also noted that 2% more 56 km runners (n=1630, 32.7%) were identified to undergo screening by the guidelines, compared to 21 km runners (n=3311, 30.7%), and 1.4% more male runners (n=2847, 31.9%) were identified compared to female runners (n=2094, 30.5%).

## **7.5. DISCUSSION**

The main finding of this study was that an online pre-participation “self-assessment of risk”, as currently recommended by European guidelines could be implemented successfully during pre-race registration in a community-based mass sports participation (distance running) event. In >15 000 recreational distance runners, the pre-race screening tool identified that over 30% of entrants for this event would, according to current European guidelines, require referral for a full medical assessment prior to participation in the distance races (moderate-to-high intensity exercise). Additional findings of this study were as follows: a) 2.3% runners reported suffering from existing CVD, 1.8% reported current symptoms suggestive of existing CVD, and 16.1% reported at least one risk factor for CVD, b) the prevalence of other existing chronic diseases, by organ systems was as follows: respiratory (13.1%), gastro-intestinal (4.3%), nervous system (3.8%), metabolic or endocrine system (3.5%), c) 13.9% runners reported suffering from allergic disease, d) 14.8% runners reported using chronic medication, e) 15.6% of runners reported using medication to treat injuries 7 days before or during races, and f) 1.4% of all runners reported a past history of collapse during a race.

International pre-exercise screening recommendations in leisure athletes [24] [25] [22] are currently not applied at community-based mass participation events and there are few data

that these guidelines are indeed appropriate for pre-event medical screening of leisure athletes. To our knowledge, this is the first study to report pre-participation screening data to determine the risk profile of participants in such a community-based mass participation distance running event and we cannot compare our main finding to any other similar population of recreational athletes. We do note that distance running events (21.1 km and ultra-marathon), such as the ones described in our study, are hosted all over the world, are becoming increasingly popular, and that participation in these events is encouraged as part of promoting a healthy active lifestyle. As far as we are aware, in most cases, these events are also open-entry and attract runners from all age groups. This can result in an increased proportion of runners that require no pre-entry qualifying times and enter races that require no pre-event medical screening criteria.

Data reported on medical complications of participants during such events are largely limited to retrospective analysis of the incidence of sudden cardiac arrest and death. However, cardiac arrest and sudden death only represent the most severe medical complications during such events. There are few published data regarding other medical complications that do not necessarily lead to cardiac arrest, but are still regarded as potentially serious or life-threatening [5, 30].

We show that the presence of musculoskeletal complaints (54.9% of runners) was the main criteria identified by the current European guidelines [24, 25], for recommending consulting a physician before exercise, and that 32.34% of the runners that would be referred for a medical assessment, reported musculoskeletal complaints as their only criteria for referral. Distance running is associated with a high prevalence of musculoskeletal complaints; therefore, we question the value of including the history of a musculoskeletal problem as part of a screening tool for this population as this would require referral of a large number of runners for pre-participation medical examinations.

The use of prescription medication (47.2% of runners) was the next most common criteria identified by the current European guidelines [24, 25], for recommending consulting a physician before exercise. The potential risk of a medical complication during exercise, as a result of prescription medication, can vary greatly and is related to the underlying medical condition for which the medication is prescribed, as well as the side effect profile of the medication. Some pharmacological agents may be associated with an increased risk of

developing cardiac arrhythmias [31] [32-34], renal complications including acute renal failure [35], rhabdomyolysis [36, 37], gastrointestinal bleeding [38-40], and risk of tendon injuries including acute tendon rupture [41, 42]. We recommend that a screening tool could be modified to include more specific information about classes of medication that may be associated with increased risk of medical complications during exercise.

In our study, we did explore the prevalence of underlying chronic medical conditions in this population of runners. We identified that 2.3% of all runners reported known existing cardiovascular disease (CVD) and the most common CVD's were coronary artery disease (0.5%), and arrhythmia (0.4%). A history of a heart murmur was reported by 0.6% runners, but this may not necessarily indicate CVD. Furthermore, 1.8% runners reported symptoms that may be suggestive of CVD, but we acknowledge that some of the symptoms, such as painful calves when walking and chronic cough, are not specific and may not indicate underlying CVD. As is recommended by international guidelines [22, 25], we would strongly recommend that runners with existing CVD and those with symptoms suggestive of CVD undergo a full medical assessment before participating in moderate- to high-intensity exercise such as distance running events, because they represent a "very high risk" group for developing potentially serious acute cardiovascular complications during a distance-running event.

Our data showed that 16.1% of runners reported at least one risk factor for CVD, with 13.4% reporting more than one risk factor. The most common specific risk factors for CVD were high blood cholesterol concentration (5.8%), high blood pressure (4.4%) and a family history of heart disease (4.4%). In addition, over 15% of the runners were males > 45 years. According to the European guidelines [24, 25], older runners (males  $\geq$  45 years; females  $\geq$  55 years) with one or more risk factors for CVD, and runners of younger age with two or more risk factors for CVD require medical assessment before engaging in moderate- to high-intensity exercise such as distance running. The recently revised recommendations by the ACSM excluded risk factors for CVD as criteria for a pre-exercise medical assessment [22]. However, in our experience at the Two Oceans races, runners who died or suffered from serious/life-threatening medical complications were mostly in this "high risk" group. Therefore, we would recommend that runners with  $\geq$ 1 risk factor for CVD undergo a full medical assessment before participating in these moderate- to high-intensity exercise events,

until there is stronger evidence that the risk of an acute medical complication in runners falling into this category is not increased.

In our population of runners, the prevalence of existing disease in other organ systems varied between 1.9% (cancer) to 13.1% (respiratory disease). We recognise that there is a variable risk of a medical complication in this group of runners and the risk is likely based on many factors such as: a) the stage of the disease including the presence or absence of multi-organ complications of a disease, b) the level of control of the disease, c) side effects of any treatment (e.g. medication, radiation therapy, previous surgery), and d) the effect of significant environmental conditions or physiological stress such as moderate-to-high intensity exercise in “unmasking” disease exacerbation or any of the above (a to c). We recognise the complexity and individual variability of determining the specific risk of a medical complication during exercise in the presence of an underlying chronic disease. We suggest that underlying chronic disease constitutes at least an “intermediate risk” for medical complications during exercise and should be included in any pre-race screening programme for leisure athletes, and that these runners undergo a full medical assessment before participating in these events.

The finding that 15.6% of runners reported ingestion of pharmacological agents, mainly anti-inflammatory medication (7.8%) and more specifically NSAIDs (4.9%), in the 7 days before or during races is of concern. The association between NSAID use and medical complications is known, specifically the risk of acute renal [35] and gastro-intestinal complications [38-40]. We therefore suggest that the use of these medications during racing also constitutes an “intermediate risk” for medical complications during exercise and should be included in any pre-race screening programme for recreational athletes.

Finally, in our study, 1.4% runners reported a past history of collapse during exercise. It is well-established that a history of collapse during exercise can be indicative of a more serious medical complication [43] [44, 45], therefore we suggest that this constitutes an “intermediate risk” and this information should be included in any pre-race screening programme for recreational athletes.

The main strengths of this study are that it is, as far as we are aware, the first study to report on the feasibility and outcomes of an online pre-race medical screening tool for a large

population of recreational runners participating in a mass community-based distance running event. Furthermore, we report the data on a large sample size that is a representative sample (age, gender and race type) of race entrants with a response rate of 62.8%.

Limitations of this study are firstly that we note that older males were under-represented in the consent sample and this is a limitation since the proportion of athletes identified for screening could then be under-reported in this study. A further limitation is that data are self-reported and that not all runners may have fully understood the questions asked or may have under-appreciated the importance of the request for accuracy in the answers. Therefore, again the data discussed in this paper may indeed be under-reported. If this is in fact the case, the risk profile of runners in this the sample may under-represent the actual risk profile. Finally, although runners in the higher risk categories (existing CVD and those with risk factors for CVD) were advised (by email communication) to undergo medical evaluation, we do not report data on how many actually took up this advice and how many developed any medical complications. In future studies, we will address this limitation.

## **7.6. SUMMARY AND CONCLUSION**

We describe the development and implementation of a relatively low-cost pre-race screening tool to determine the “self-assessment of risk” of a medical complication during exercise in a community-based mass participation distance running event. We show that by using current screening guidelines, > 30% of all runners entering for these events would require a full medical assessment, where a history of a musculoskeletal complaint and the use of prescription medication were the main criteria in the existing guidelines that triggered a referral to undergo a full medical assessment. We suggest a revision of the screening guidelines triggering a full medical assessment and propose risk stratification and educational intervention (Table 7) as follows: 1) excluding the question on musculoskeletal complaints from triggering a full medical assessment, 2) including a question on prescription medication but refining it for specific classes of drugs that could potentially increase the risk of medical complications during exercise, and 3) including questions on other chronic diseases with organ system and disease specific recommendations on full medical assessment. Finally, future studies, should determine the feasibility and implementation of such a screening and educational intervention programme on reducing medical complications during these events.

This pre-race screening programme is on-going and has already been implemented in other large endurance events. In future, we will continue to report on the relationship of the risk profile of endurance athletes (“very high risk”, “high risk” and “intermediate risk” groups) and the actual risk of medical complications during endurance events. These data will assist in decision-making regarding pre-participation screening guidelines for these leisure distance-running athletes.

Declaration of Helsinki: Permission to analyse the medical histories of the study subjects was obtained from the Research Ethics Committee of the University of Cape Town (REC 009/2011) (REC 030/2013) and the Research Ethics Committee of the University of Pretoria (REC 433/2015). This study complied with the Declaration of Helsinki’s ethical principles for conducting medical research involving human participants.

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## CHAPTER 8

### SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

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#### 8.1. SUMMARY AND CONCLUSIONS

The health benefits of regular exercise at moderate- to high-intensity in a weekly dose of 150 min are undisputed [1] and universally accepted in health policy documents [2-4] . Distance running is a particularly popular form of exercise and in the last two to three decades there is well documented increase in participation in community-based mass participation recreational distance running events [5, 6] . However, and somewhat paradoxically, moderate- to high-intensity exercise, such as distance running, can be associated with the development of medical complications, affecting different organ systems. Vigorous exercise can precipitate sudden cardiac arrest (SCA) leading to sudden cardiac death (SCD) and this has been documented in distance running events [7-14]. In contrast to SCA and SCD, there is a limited body of evidence describing the incidence and nature of other medical complications during exercise [15], including non-cardiac serious/life-threatening complications[16, 17] . Health professional are mandated to prescribe exercise at the appropriate dose, but have an equally important responsibility to ensure that the prescription of exercise is safe and not leading to unwanted complications (negative side effects). The main focus of this dissertation is to enhance the body of knowledge that can lead to the prescription of “safer” exercise. This was based on the four Step van Mechelen Model [18].

The first aim of this dissertation was to accurately document the incidence and nature of medical complications during prolonged moderate- to high-intensity exercise, specifically distance running (step one of the van Mechelen Model: quantifying the problem). The focus of this study was to not only investigate cardiac complications, but also serious/life-threatening and less serious non-cardiac medical complications. The setting was a large annual community-based mass participation distance running event comprising a 21.1 km and a 56 km running race, and the study was conducted over a 4-year period. The second aim was to identify potential risk factors associated with the development of medical complications in a 21.1 km and 56 km (step 2 of the van Mechelen Model: establishing the aetiology and mechanisms of injury / illness). Identifying these risk factors is important so that future interventions can be planned, implemented and tested with the aim to reduce these adverse

medical events. A final aim of the dissertation was to develop a pre-race screening tool to risk stratify race entrants for the development of medical complications, and to document the prevalence of entrants in higher risk categories (step 3 of the van Mechelen Model: introducing a preventative measure). These data could then be used to implement an educational intervention to reduce the risk of medical complications and make these events safer for participants (step 4 of the van Mechelen Model: assessing effectiveness).

The main findings of the first study were that 1) the overall (serious/life-threatening and non-serious) medical complication was 8.27/1000 race starters, 2) the incidence of any medical complication was significantly higher in the 56 km runners compared to the 21.1 km runners, 3) the incidence of serious/life-threatening medical complications was similar in the 21.1 km and 56 km race and 4) the incidence of medical complications by organ system were accurately documented. During the four-year study period, fatalities only occurred in the 21.1 km race.

The second and third studies explored the risk factors associated with all medical complications, severe life-threatening medical complications and medical complications by organ system involvement in the two races (21.1 km and 56 km) using a multivariate analysis to identify independent risk factors. The main risk factors associated with medical complications in the 56 km race were less experience and slower running pace while the main risk factor in the 21.1 km was being an older female. A unique novel strength of these studies was that risk factors associated with the development of specific medical complications by organ system were identified. However, in these studies there were no data available on the pre-race medical history of entrants and we concluded that in future studies, pre-race medical and training history, as well as history of previous medical complications would have to be included to determine the “risk profile” of entrants and develop a risk stratification model.

In the final study described in this dissertation, data from the 3 studies, together with existing international guidelines for the pre-screening of leisure/master’s athletes were used to develop (Appendix C) and test a pre-race medical screening questionnaire. The number of entrants that would be flagged to undergo a pre-race medical assessment, based on the current guidelines was determined and a risk stratification system was developed. In this study four novel risk categories for medical complications (very high risk, high risk, intermediate risk and low risk) were developed and the prevalence (%) of entrants in each category was

documented. The results of this study laid the foundation for a future study to determine the feasibility and implementation of such a pre-screening and educational intervention programme to reduce medical complications during these events. This pre-race screening and educational intervention research is ongoing and has already been implemented in large endurance events.

## **8.2 RECOMMENDATIONS**

Ongoing well-designed epidemiological studies are required to accurately document the overall incidence of medical complications in distance running events. These need to include a comparison of medical complication rates in various running distances, other endurance sports and in different climatic conditions. There are limited data on the perspective of medical care provided at races as a variable that predicts the risk for medical complications. Furthermore, there are also limited data on the distribution of clinical presentations on the race course. Both these aspects require further studies.

The methods used in this series of studies contributed significantly to the recently published international consensus statement [19] on definitions and methods of data recording and reporting at mass community-based endurance sports events. Future studies in this field will now utilize these definitions and methods of recording data specifically in other community-based mass participation endurance sports events such as cycling, triathlon and others.

More studies are required to identify independent risk factors associated with medical complications in other distance running events (5 km, 10 km, 42 km and ultra-marathon) as well as in cycling and triathlon events. The focus of these studies should be not only on SCA and SCD but also on serious/life-threatening non-cardiac medical complications. Finally, in future studies, the survey instrument needs further validation. In the future, step 4 of the van Mechelen model should be evaluated if interventions that emanate from the survey result in a change in medical complications. Future studies should evaluate the feasibility and implementation of a pre-race screening and educational intervention programme in other settings focusing on different race distances, endurance events, and populations. This work will be a logical extension of the results of studies discussed in this dissertation and contribute to the promotion of safer physical activity.

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**APPENDIX A**

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**METHODOLOGY OF SEARCH STRATEGY**

**METHODOLOGY OF SEARCH STRATEGY**

**Chapter 2: A review of the incidence of medical encounters during mass participation community-based distance running events**

A search was conducted on the PubMed and Google Scholar databases, using the following three levels with keywords in different combinations as follows:

**Section 2.4.1. A review of the incidence of sudden death, sudden cardiac death and sudden cardiac arrest in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]

AND

- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]

AND

- Level 3 terms: defining medical encounters: [death OR sudden death OR sudden cardiac death OR sudden cardiac arrest OR mortality]

**Section 2.4.2. A review of the incidence of serious/ life-threatening medical encounters in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR, distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]

AND

- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]

AND

- Level 3 terms: defining medical encounters: [serious OR life-threatening OR serious life-threatening OR transfer OR hospital transfer]

**Section 2.4.3. A review of the incidence of moderate medical encounters in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]
- AND
- Level 3 terms: defining medical encounters: [medical encounters OR medical complications OR presentations OR evaluations]

**Section 2.5.1.1. Incidence of exertional heatstroke in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]
- AND
- Level 3 terms: defining medical encounter: [heatstroke OR exertional heatstroke OR classic heatstroke OR hyperthermia OR heat exhaustion OR heat fatigue OR heat syncope]

**Section 2.5.1.2. Incidence of rhabdomyolysis in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]
- AND
- Level 3 terms: defining medical encounter: [rhabdomyolysis OR exertional rhabdomyolysis OR creatine kinase]

### **Section 2.5.1.3. Incidence of fluid and electrolyte disorders in distance running**

- Level 1 terms: defining the population of distance runners: [distance running OR, distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]
- AND
- Level 3 terms: defining medical encounter: [dehydration OR weight loss OR sodium OR hyponatraemia OR hypernatraemia OR electrolyte disorders OR magnesium OR hypomagnesaemia OR hypermagnesemia OR calcium OR hypercalcemia OR hypocalcemia OR potassium OR hypokalaemia OR hyperkalaemia OR phosphate OR hypophosphataemia]

### **Section 2.5.2.1. Incidence of Exercise-Associated Collapse in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR, ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]
- AND
- Level 3 terms: defining medical encounter: [exercise-associated collapse OR exercise-associated postural hypotension OR collapse OR orthostatic intolerance OR syncope]

### **Section 2.5.3. Incidence of respiratory encounters in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]
- AND
- Level 3 terms: defining medical encounter: [respiratory OR asthma OR infections OR upper respiratory tract infection OR respiratory tract infection OR exercise induced bronchospasm OR allergy OR non-cardiac pulmonary oedema OR exercise-induced anaphylaxis]

#### **Section 2.5.4.1. Incidence of EAMC in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR, distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR, epidemiology OR, rate OR, frequency]
- AND
- Level 3 terms: defining medical encounter: [muscle cramps OR exercise induced muscle cramps OR heat cramps]

#### **Section 2.5.5. Incidence of medical encounters in the gastrointestinal system**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]
- AND
- Level 3 terms: defining medical encounter: [gastro-intestinal OR gastro-intestinal system OR nausea OR vomiting OR abdominal pain OR rectal bleeding OR gastro-intestinal ischaemia OR ischaemic colitis]

#### **Section 2.5.6. . Incidence of medical encounters in the genitourinary system**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR, marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]
- AND
- Level 3 terms: defining medical encounter: [athletic pseudonephritis OR haematuria OR proteinuria OR renal artery dissection OR acute renal failure OR acute kidney injury]

### **Section 2.5.7. Incidence of dermatological encounters in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR, distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (incidence of medical encounters): [incidence OR epidemiology OR rate OR frequency]
- AND
- Level 3 terms: defining medical encounter: [dermatology OR dermatological OR blisters OR chafing OR cuts OR bruising]

## **Chapter 4: A review of the risk factors associated with medical encounters in community-based distance running events**

### **Section 4.4.: Risk factors associated with sudden cardiac arrest and sudden cardiac death (SCA / SCD) in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounters: [death OR sudden death OR sudden cardiac death OR sudden cardiac arrest OR mortality]

### **Section 4.6.: Risk factors associated with any medical encounter in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounters: [medical encounters OR medical complications OR presentations OR evaluations]

**Section 4.7.1.1.: Risk factors associated with exertional heatstroke in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounter: [heatstroke OR exertional heatstroke OR classic heatstroke OR hyperthermia OR heat exhaustion OR heat fatigue OR heat syncope]

**Section 4.7.1.2.: Risk factors associated with exercise-associated hyponatraemia in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounter: [sodium OR hyponatraemia OR hypernatraemia OR electrolyte disorders]

**Section 4.7.2.1.: Risk factors associated with EAC in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounter: [exercise-associated collapse OR exercise-associated postural hypotension OR collapse OR orthostatic intolerance OR syncope]

**Section 4.7.3.: Risk factors associated with respiratory tract infections during distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounter: [respiratory OR infections OR upper respiratory tract infection OR respiratory tract infection OR allergy]

**Section 4.7.4.1.: Risk factors associated with EAMC in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounter: [muscle cramps OR exercise induced muscle cramps OR heat cramps]

**Section 4.7.5.: Risk factors associated with gastrointestinal tract encounters in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- Level 3 terms: defining medical encounter: [gastro-intestinal OR gastro-intestinal system OR nausea OR vomiting OR abdominal pain OR rectal bleeding OR gastro-intestinal ischaemia OR ischaemic colitis]

#### **Section 4.7.6.1.: Risk factors associated with AKI in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounter: [acute renal failure OR renal failure OR acute kidney injury]

#### **Table 4.7.: Risk factors associated with exertional rhabdomyolysis in distance running events**

- - Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounter: [rhabdomyolysis OR exertional rhabdomyolysis OR creatine kinase]

#### **Section 4.7.7.: Risk factors associated with foot blisters in distance running events**

- Level 1 terms: defining the population of distance runners: [distance running OR distance runners OR marathon OR ultra-marathon OR half-marathon OR endurance OR mass-participation]
- AND
- Level 2 terms: defining the outcome (risk factors for medical encounters): [risk OR risk factors OR predictors OR intrinsic risk OR extrinsic risk OR internal risk OR external risk]
- AND
- Level 3 terms: defining medical encounter: [dermatology OR dermatological OR blisters]

**APPENDIX B**

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**MEDICAL CONSEQUENCES IN ENDURANCE SPORTS  
TWO OCEANS MARATHON LONGITUDINAL STUDY: 2013-2015  
PRE-RACE MEDICAL QUESTIONNAIRES**

## Part 1: Medical questionnaire at the time of entry

Dear Runner,

### **Medical information required during race entry process**

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.

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.

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.

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.

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?*	<input type="text"/>	years
For how many years have you participated in distance races?*	<input type="text"/>	years
In the last 12 months, on average, how many times a week do you run (train and race)?*	<input type="text"/>	per week
In the last 12 months, what is your average weekly training distance?*	<input type="text"/>	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)*	<input type="text"/>	min/km
In the past 12 months, please indicate the average percentage time that you run/train on a <u>treadmill</u> ?	<input type="text"/>	% time on treadmill
In the past 12 months, please indicate the average percentage time that you run/train on tar roads?	<input type="text"/>	% 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?	<input type="text"/>	% 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)?	<input type="text"/>	% time on gravel roads
In the past 12 months, please indicate the average percentage time that you run/train on footpaths/single tracks?	<input type="text"/>	% time on footpaths / single tracks
What is your current body weight?*	<input type="text"/>	kg
What is your height?*	<input type="text"/>	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

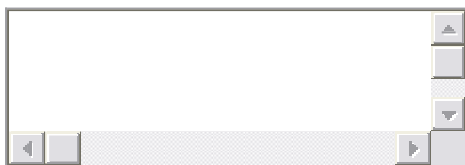
- Past history of allergies to medication
- Past history of allergies to plant material
- Past history of allergies to animal material
- History of any other allergies

**\* 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**

**Please 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 C**

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**METHODS TO DEVELOP AN ONLINE MEDICAL  
PRE-RACE SCREENING TOOL**

## DEVELOPMENT OF AN ONLINE PRE-RACE MEDICAL SCREENING QUESTIONNAIRE (OPRMSQ)

### **Aim:**

An online pre-race medical screening questionnaire (OPRMSQ) or “self-assessment of risk” was developed with the aim to identify runners that are at potential increased risk of acute medical complications during moderate-to high intensity exercise as a distance running race.

### **Methods:**

An online pre-race medical screening questionnaire (OPRMSQ) or “self-assessment of risk” was developed and based on the following principles:

1. International guidelines for pre-exercise screening

Questions, as recommended by the European Society of Cardiology and the European Association on Cardiovascular Prevention and Rehabilitation for the pre-participation screening of leisure athletes engaging in moderate- to high-intensity exercise [1] [2], were used as the basis for the OPRMSQ. In addition, questions from the American Heart Association/ American College of Sports Medicine pre-participation screening questionnaire for individuals at Health/Fitness facilities [3], with the exception of a question regarding pregnancy, were also included.

2. Data from epidemiological studies (described in chapter 3 of this thesis):

The study reported in Chapter 3 identified several common reasons for medical encounters in endurance distance runners [4]. These medical conditions included the following: Exercise Associated Collapse (EAC), Exercise Associated Muscle Cramping (EAMC), medication use during training / racing and musculoskeletal injuries. Therefore, screening questions to identify these runners at risk were also included in the OPRMSQ.

### **Outcome:**

The main components of the OPRMSQ questionnaire therefore included 2 injury-related questions (running injuries and muscle cramping) and 13 questions that included the following categories of medical history: cardiovascular disease (CVD), symptoms of CVD, risk factors for CVD, other chronic disease (respiratory disease, metabolic or hormonal

disease, gastrointestinal disease, nervous system disease, renal or bladder disease, hematological or immune system disease, cancer, allergies), and medication use.

### References:

1. Corrado, D., et al., *Risk of sports: do we need a pre-participation screening for competitive and leisure athletes?* Eur Heart J, 2011. **32**(8): p. 934-44.
2. Borjesson, M., et al., *Cardiovascular evaluation of middle-aged/ senior individuals engaged in leisure-time sport activities: position stand from the sections of exercise physiology and sports cardiology of the European Association of Cardiovascular Prevention and Rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(3): p. 446-58.
3. Whitfield, G.P., et al., *Application of the American Heart Association/American College of Sports Medicine Adult Preparticipation Screening Checklist to a nationally representative sample of US adults aged  $\geq 40$  years from the National Health and Nutrition Examination Survey 2001 to 2004.* Circulation, 2014. **129**(10): p. 1113-20.
4. Schwabe, K., et al., *Medical complications and deaths in 21 and 56 km road race runners: a 4-year prospective study in 65 865 runners--SAFER study I.* Br J Sports Med, 2014. **48**(11): p. 912-8.