Novel factors associated with Analgesic and Anti-Inflammatory Medication (AAIM) use in distance runners: pre-race screening among 76654 race entrants - SAFER study VI

Adrian Rotunno [1], Martin Schwellnus [1,2,3], Sonja Swanevelder [4], Esme Jordaan [4,5], Dina C Janse Van Rensburg [1], Wayne Derman [2,6]

[1] Sport, Exercise Medicine and Lifestyle Institute (SEMLI) and Section Sports Medicine, Faculty of Health Sciences, University of Pretoria, South Africa
[2] International Olympic Committee (IOC) Research Centre, South Africa
[3] Emeritus Professor, Faculty of Health Sciences, University of Cape Town, South Africa
[4] Biostatistics Unit, South African Medical Research Council
[5] Statistics and Population Studies Department, University of the Western Cape
[6] Institute for Sport and Exercise Medicine, Faculty of Medicine & Health Sciences, University of Stellenbosch

Address for correspondence:
Martin P. Schwellnus, Director: Sport, Exercise Medicine and Lifestyle Institute (SEMLI) and Section Sports Medicine, Faculty of Health Sciences, University of Pretoria, South Africa, Sports Campus, Burnett Street, Hatfield, Pretoria 0020, South Africa
Telephone: -27-12-420 6057 Fax number: -27-12-362 3369
Email: mschwell@iafrica.com

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Adrian Rotunno (ARS): data collection, data interpretation, manuscript (first draft), manuscript editing
Martin Schwellnus (MS): principle investigator, responsible for the overall content as guarantor, study concept, study planning, data collection, data interpretation, manuscript (first draft), manuscript editing, facilitating funding
Sonja Swanevelder (SS): study planning, data analysis including statistical analysis, data interpretation, manuscript editing
Esme Jordaan (EJ): study planning, data analysis including statistical analysis, data interpretation, manuscript editing
Dina Janse Van Rensburg (DJvR): data interpretation, manuscript (first draft), manuscript editing

Wayne Derman (WD): study concept, study planning, data collection, data interpretation, manuscript editing

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Abstract:

Objective: Analgesic / anti-inflammatory medication (AAIM) increases the risk of medical complications during endurance races. We determined how many runners use AAIM before or during races, AAIM types, and factors associated with AAIM use.

Design: Cross-sectional study

Setting: 21.1km and 56km races

Participants: 76654 race entrants

Methods: Participants completed pre-race medical screening questions on AAIM use, running injury or exercise-associated muscle cramping (EAMC) history, and general medical history.

Main outcome measures: AAIM use, types of AAIM (% runners; 95% CI), and factors associated with AAIM use (gender, age, race distance, history of running injury or EAMC, history of chronic diseases) (Prevalence Ratio: PR).

Results: Overall 12.2% (12.0-12.5) runners used AAIM 1 week before and/or during races (56km =18.6%; 18.0-19.1, 21.1km=8.3%; 8.1-8.6)($p<0.0001$). During races, NSAIDs (5.3%; 5.1-5.5) and paracetamol (2.6%; 2.4-2.7) were used mostly. Independent factors (adjusted PR for gender, age, race distance; $p<0.0001$) associated with AAIM use were running injury (2.7; 2.6-2.9), EAMC (2.0; 1.9-2.1), CVD symptoms (2.1; 1.8-2.4), known CVD (1.7; 1.5-1.9), CVD risk factors (1.6; 1.5-1.6), allergies (1.6; 1.5-1.7), cancer (1.3; 1.1-1.5) and respiratory (1.7; 1.6-1.8), gastrointestinal (2.0; 1.9-2.2), nervous system (1.9; 1.7-2.1), kidney/bladder (1.8; 1.6-2.0), endocrine (1.5; 1.4-1.7), hematological/immune (1.5; 1.2-1.8) diseases.

Conclusions: 12.2% runners use AAIM before and/or during races, mostly NSAIDs. Factors (independent of gender, age and race distance) associated with AAIM use history of injuries, EAMC and numerous chronic diseases. We suggest a pre-race screening and educational program to reduce AAIM use in endurance athletes to promote safer races.

Introduction

Health benefits of regular exercise are well established, and > 150 min per week of moderate- to high-intensity exercise [1-3] is universally recommended as an important component of a healthy lifestyle to prevent and treat non-communicable disease.[1,4-7] Not surprisingly, in the last 2-3 decades, participation in mass community-based endurance sports events (running, cycling, swimming and triathlons) has seen a steady growth worldwide [8] with notable increases in older participants.[9] Recreational distance running remains one of the most popular forms of endurance exercise, and since 1976 there is a reported increase of >12 fold in overall participation numbers in distance races such as the marathon (http://www.runningusa.org/annual-reports - accessed on 1 February 2018).

However, there is also equally strong evidence that moderate- to high-intensity exercise can acutely, and transiently, increases the risk of a range of acute medical complications during races.[10,11] These complications include serious cardiac incidents [12-16] and non-cardiac complications typically related to severe fluid and electrolyte abnormalities (mainly hyponatraemia)[17-19], acute kidney injury and renal failure [20-23], exertional heat stroke [24-28] and gastrointestinal bleeding.[29] Risk factors associated with acute medical complications (cardiac and non-cardiac) were recently reviewed [9], and one of the risk factors is the use of medication, immediately before or during races .[9]

The most common type of medication used by athletes is prescription and over-the-counter (OTC) analgesic and / or anti-inflammatory medication (AAIM).[30] AAIM use during training, competition and recovery is common practice in many athletes including Olympic athletes [31] [32], Paralympic athletes [33], elite track and field athletes [34], football (soccer) players [35-38], athletes participating in multi-coded sports events [39], college athletes [40] and athletes

participating in triathlon [41,42] and endurance cycling.[43] [44] Furthermore, the types of AAIM typically used in athlete populations are non-steroidal anti-inflammatory drugs [(NSAIDs) oral, topical and injectable forms], analgesics (paracetamol, opioids, other non-opioids), anesthetics (injectable, transdermal), and other over the counter (OTC) medication.[30]

In distance runners, the prevalence of AAIM use immediately before or during races has only been reported in a few studies notably in ultra-marathon (> 42.2km race distances) runners [45-47], marathon (42.2km) runners [29,45,46], half-marathon (21.1km) runners [45], and amateur female runners.[48] These studies consistently show a high prevalence of AAIM use immediately before or during a race that is highest in ultra-marathon runners (60-70%) [45-47] compared with marathon and half-marathon runners (26-49%) [29,45,46] or female amateur runners (35%).[48]

This high prevalence of AAIM use in distance runners is of concern because there are well-documented serious adverse events (AE's) that are associated with AAIM use during endurance events. The AE's during exercise include increased risk of gastro-intestinal injury [29,45,49,50], renal injury [29,51-55], cardiovascular side effects [29,50,53], and possible detrimental effects on the healing processes to damaged muscle, tendons and bone.[41,56] In one study among 3913 marathon runners, the overall incidence of self-reported AEs was 5 times higher (overall risk difference of 13%) in AAIM users, and this incidence increased significantly with increasing medication dose.[29]

The main limitations of studies that reported the prevalence of AAIM use in runners are selection bias (samples selected for the studies are not necessarily representative of the target populations), response rates that are either not reported [45] or are very low (11.3%) [46] to moderate (56%) [29] and, with the exception in the one study among 3913 marathon runners [29], relatively small sample sizes. [45,46,48] Furthermore, as far as we are aware, the factors associated with AAIM use in runners, immediately before or during races, are not well documented. In only a few studies, the reasons for AAIM use by athletes are reported and

include pain relief from injury and related painful conditions such as Exercise Associated Muscle Cramping (EAMC), injury prophylaxis, peer pressure, faster recovery and the belief that AAIM use will result in earlier return to play or improve athletic performance.[40-42 48]

The purpose of this study is to determine the prevalence of AAIM use in half marathon and ultra-marathon runners, the types of medication used, and to identify independent factors (runner demographics, race distance, running injury, EAMC history, and a history of underlying chronic medical conditions) that may be associated with AAIM use in these runners.

Methods

This study formed part of a series of on-going SAFER (Strategies to reduce Adverse medical events For the ExerciseR) studies.[57] We previously documented a high rate of acute medical complications in runners participating in the 2008 to 2011 Old Mutual Two Oceans Marathon races, including sudden death [11,58], and this precipitated the design and implementation of an online pre-race medical screening program for all race entrants from 2012 to 2015. In this post-intervention period, all race entrants (n = 106743) completed a pre-race medical screening questionnaire as part of the online registration process. Of these, 76654 (71.8% 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 for this study [male = 44042 (57.5%); female = 32612 (42.5%)] (Table 1).

Table 1: The profile by race type, gender and age groups of all race entrants and study participants (race entrants who gave consent)

		All race entrants (n=106743)		Study participants (Consenting race entrants) (n=76654)		p value
		N	%	N	%	p
Race type	21.1km	64740	60.7	47069	61.4	*p= 0.0011
	56km	42003	39.4	29585	38.6	
Gender	Males	61815	57.9	44042	57.5	p=0.0520
	Females	44928	42.1	32612	42.5	
Age groups	≤ 30 years	27710	26.0	20168	26.3	p= 0.3643
	31–40 years	35049	32.8	25045	32.7	
	41–50 years	26964	25.3	19340	25.2	
	≥ 50 years	17020	15.9	12101	15.8	

p: p value
*: Study participants significantly different from "All race entrants" ($p<0.05$)

In the study group, compared to all entrants, there were equal proportions of runners by gender and age groups (Table 1). However, the proportion of study participants in the 21.1km race category was significantly higher compared to all the race entrants (Study participants = 61.4%; All race entrants = 60.7%) (0.7% higher; p=0.0011). (Table 1)

Prior to the onset of the study we obtained permission from the Research Ethics Committees of the University of Cape Town (REC 009/2011)(REC 030/2013), and permission to complete the data collection and the subsequent analysis of the results was obtained from 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, based on the European Society of Cardiology (ESC) and the European Association of Cardiovascular Prevention and Rehabilitation (EACPR) guidelines.[59,60] The questionnaire was administered to race entrants from 2012 to 2015 and included the following categories of medical history: symptoms of cardiovascular disease (CVD), risk factors for CVD, and history of diagnosed chronic disease (CVD, respiratory, metabolic or hormonal,

gastrointestinal, nervous system, renal or bladder, hematological or immune system, cancer, allergies), general prescription medication use, medication use during racing, and a past history of collapse during racing. These factors are all associated with a possible increased risk of acute medical complications in moderate-to high-intensity exercise such as distance running.[9]

In the medical screening tool, runners were specifically asked to answer the following question related to analgesic / anti-inflammatory (AAIM) medication use for injuries: "*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?*" In response to a "yes" answer to this question, runners were grouped as non-users or users of AAIM (AAIM users = 10140, 21.1km = 4048, 56km = 6092). Runners that responded with a "yes" answer were then asked to complete two additional questions related to a) use of AAIM in the week before a race, or use of AAIM during races, and b) the type of AAIM used (Appendix A). In the overall user group we included runners that reported AAIM use 1) only in the week before races, 2) only during races, or 3) both in the week before, and during races.

Main outcome variables

Prevalence of AAIM use in race entrants: overall use, different types of AAIM use, and use one week before races, or during races

We describe the overall prevalence of AAIM use in race entrants (as a % of all race entrants in the study), and the prevalence of use of different types of AAIM (anti-inflammatory medication such as NSAIDs and cortisone, and analgesic medication) by runners in two periods - the week before a race, and during a race.

Factors associated with AAIM use in runners

In this study, we specifically wanted to investigate the factors associated with AAIM use in race entrants in the following three main categories of factors: 1) runner demographics (age, gender and race distance), 2) a history of running injuries or EAMC, and 3) a history of risk factors for cardiovascular disease (CVD), symptoms of CVD, and existing chronic disease (CVD, respiratory disease, endocrine disease, gastrointestinal [GIT] disease, nervous system or psychiatric disease, kidney or bladder disease, hematological system disease, immune system disease, cancer, and allergies).

Statistical analysis

All data from the 2012-2015 runner and medical screening database were entered into an Excel spread sheet (Microsoft 2010) and then analyzed using the SAS 9.4 statistical program (SAS Institute Inc., Cary, North Carolina, USA). The binary-scaled response variable was the response to the questions on medication use to treat injuries before or during a race (including anti-inflammatory drugs, cortisone or pain killers). Due to the cross-sectional nature of the study, we used log-binomial regression to directly estimate risk ratios (RR) for the main category risk factors. However, convergence problems may arise with binomial regression models; in this case, they may fail to provide an estimate of the RR. To avoid this, we approximated the relative risk by using the Poisson regression model with a robust error variance. The correlated structure of the data (a runner could run multiple years and have more than one injury in a year) was accounted for by using an unstructured correlation matrix. Risk ratios (95% CIs), also indicated as prevalence ratios (PRs), were reported for all the results. The statistical significance level was 5%, unless specified otherwise.

Univariate regression models on all main category of factors associated with AAIM use obtained the crude unadjusted risk ratio (PRs and 95% CIs) of AAIM use for each factor

separately. The multiple regression models, by main categories of injuries, symptoms, and chronic disease adjusted the univariate PRs for gender, age category and race type. Final multiple regression models included all significant main category risk factors, adjusted for gender, age category and race distance. Crude numbers, prevalence and 95% confidence intervals are reported throughout.

Results

Overall prevalence of AAIM use (in the week before and/or during races)

The overall prevalence of use of AAIM, in the week before and/or during races, in this population was 12.2% (95%CI: 12.0-12.5), and this was significantly higher in 56km (18.6%, 95%CI: 18.0-19.1) compared to 21.1km (8.3%, 95%CI: 8.1-8.6) race entrants ($p<0.0001$).

Prevalence of different types of AAIM used in the week before a race, or during a race

The prevalence of use of different types of AAIM used in the week before a race or during a race for all race entrants, 21.1km race entrants, and 56km race entrants is depicted in Table 2.

The main observation from these tables is that NSAID's are the most frequent AAIM used (%, 95% CIs) by all race entrants, 21.1km and 56km race entrants, both in the week before a race (all = 8.6%, 8.4-8.9; 21.1km = 6.3%, 6.0-6.5; 56km = 12.8%, 12.4-13.3), and during races (all = 5.3%, 5.1-5.5; 21.1km = 3.1%, 2.9-3.2; 56km = 9.2, 8.8-9.5). This is followed by analgesic use (mainly paracetamol) and less commonly, corticosteroid use (Tables 2). The 56km race entrants also consistently reported higher prevalence of use of all specific AAIM, compared with 21.1km race entrants (Table 2).

Table 2: The prevalence of different types of analgesic / anti-inflammatory (AAIM) use in the week before a race, or during a race in all race entrants, 21.1km race entrants and 56km race entrants (% race entrants; 95% CI) (n= 76654)

		All race entrants		21.1km race entrants		56km race entrants	
Medication group	**Specific medication**	**n**	**% race entrants (95%CIs)**	**n**	**% race entrants (95%CIs)**	**n**	**% race entrants (95%CIs)**
One week before and/or during a race	**Any AAIM**	**9352**	**12.2 (12.0-12.5)**				
One week before a race	**Any AAIM**	**8288**	**10.0 (9.8-10.3)**	**3547**	**7.1 (6.9-7.4)**	**4741**	**15.1 (14.6-15.6)**
Analgesics	Paracetamol	2206	2.8 (2.6-2.9)	999	2.0 (1.9-2.2)	1207	4.0 (3.7-4.2)
	Codeine	210	0.3 (0.2-0.3)	95	0.8 (0.1-4.7)	115	0.4 (0.3-0.4)
	Other analgesics	476	0.6 (0.5-0.7)	171	0.4 (0.3-0.4)	305	1.0 (0.9-1.1)
Anti -inflammatory medication	All NSAIDs	7148	8.6 (8.4-8.9)	3120	6.3 (6.0-6.50	4028	12.8 (12.4-13.3)
	Oral NSAIDs	5102	6.1 (6.0-6.3)	2227	4.5 (4.3-4.7)	2875	9.1 (8.8-9.5)
	Topical NSAIDs	4602	5.6 (5.5-5.8)	2020	4.1 (3.9-4.3)	2582	8.3 (7.9-8.6)
	All cortisone	919	1.1 (1.0-1.2)	305	0.6 (0.6-0.7)	614	1.8 (1.6-2.0)
	Cortisone (oral)	193	0.2 (0.2-0.3)	76	0.2 (0.1-0.2)	117	0.4 (0.3-0.5)
	Cortisone (injection)	776	0.9 (0.8-1.0)	247	0.5 (0.4-0.6)	529	1.6 (1.3-1.8)
During a race	**Any AAIM**	**5945**	**7.1 (6.9-7.3)**	**1934**	**3.9 (3.7-4.1)**	**4011**	**12.5 (12.1-12.90**
Analgesics	Paracetamol	2080	2.6 (2.4-2.7)			1491	4.8 (4.5-5.1)
	Codeine	181	0.2 (0.2-0.2)	47	0.1 (0.1-0.1)	134	0.4 (0.3-0.50
	Other analgesics	816	1.0 (0.9-1.1)	182	0.4 (0.3-0.4)	634	2.0 (1.8-2.2)
Anti- inflammatory medication	All NSAIDs	4409	5.3 (5.1-5.5)	1505	3.1 (2.9-3.2)	2904	9.2 (8.8-9.5)
	Oral NSAIDs	3015	3.6 (3.5-3.8)	965	2.0 (1.8-2.1)	2050	6.4 (6.1-6.8)
	Topical NSAIDs	2337	2.9 (2.8-3.0)	907	1.9 (1.7-2.0)	1430	4.6 (4.4-4.9)
	All cortisone	110	0.1 (0.1-0.2)	40	0.1 (0.1-0.1)	70	0.2 (0.2-0.3)
	Cortisone (oral)	42	0.0 (0.0-0.1)	17	0.0 (0.0-0.1)	25	0.1 (0.1-0.1)
	Cortisone (injection)	71	0.1 (0.1-0.1)	26	0.1 (0.0-0.1)	45	0.2 (0.1-0.2)

AAIM: Analgesic and anti-inflammatory medication
NSAIDs: Non-steroidal anti-inflammatory drugs

Factors associated with AAIM use in race entrants

Factors associated with AAIM use in race entrants were explored for three main categories of factors: 1) runner demographics, 2) a history of running injuries or EAMC, and 3) a history of chronic disease (risk factors for CVD, symptoms of CVD, and previously diagnosed chronic disease). Univariate regression models on all main category of factors associated with AAIM use obtained the crude unadjusted prevalence risk ratio (PR) for AAIM use in these three categories, and these data are provided in Supplementary tables (Table S1, Table S2 and Table S3). The unadjusted PR of AAIM use was significantly higher in female vs. male runners ($p=0.0365$), 56km vs. 21.1km runners ($p<0.0001$), and older age groups (41-50 years and > 50 years) vs. younger age groups (31-40 years and $\leq$ 30 years) ($p<0.0001$) (Table S1) (unadjusted data).

Subsequently, factors independent of gender, race type and age group were explored in a multiple regression model. The adjusted (by gender, age and race type) prevalence ratios (PR; with 95% confidence intervals - CI) and % of race entrants using AAIM by factors in our second (history of injuries and EAMC) and third category (CVD symptoms, CVD risk factors and chronic disease) of risk factors in the multiple regression model are depicted in Table 3.

A history of a running injury was associated with the highest risk (PR = 2.7; 95%CI 2.6-2.9) ($p<0.0001$) of AAIM use in race entrants. For more specific groups of running injuries, the prevalence risk of AAIM use varied between 2.0-2.4 ($p<0.0001$) for race entrants reporting a history of muscle injuries, tendon injuries and EAMC. There was also a significantly higher PR of AAIM use in race entrants that reported CVD symptoms, CVD risk factors and chronic disease. A PR > 2.0 was associated with a history of CVD symptoms and GIT disease ($p<0.0001$), and a PR that varied between 1.5 and 1.9 was associated with a history of nervous system / psychiatric disease, kidney / bladder disease, CVD, respiratory disease, risk factors for CVD, allergies, endocrine disease and hematological / immune disease

(p<0.0001). The PR of AAIM use was also significantly higher in entrants with a history of cancer (PR = 1.3) (p = 0.0003).

Table 3: Multiple regression model - the adjusted (by gender, age group and race type) prevalence ratio (PR; with 95% confidence intervals - CI) of race entrants using AAIM, by category two (history of injuries and EAMC) and category three factors (CVD symptoms, CVD risk factors and chronic disease)

			% AAIM use	n	PR	p
History of injuries and EAMC	Any running injury	no	10.6	68323		
		yes	29.0	8331	2.7 (2.6-2.9)	<0.0001
	Any tendon injury	no	12.3	74660		
		yes	29.0	1994	2.4 (2.2- 2.5)	<0.0001
	Any muscle injury	no	12.1	73448		
		yes	26.9	3206	2.2 (2.1-2.4)	<0.0001
	History of EAMC	no	11.2	66040		
		yes	22.6	10614	2.0 (1.9-2.1)	<0.0001
CVD symptoms, CVD risk factors and chronic disease	Any CVD symptoms	no	12.6	75801		
		yes	26.6	853	2.1 (1.8-2.4)	<0.0001
	Any GIT disease	no	12.4	74597		
		yes	25.4	2057	2.0 (1.9-2.2)	<0.0001
	Any nervous system / psychiatric	no	12.5	74794		
		yes	23.4	1860	1.9 (1.7-2.1)	<0.0001
	Any kidney / bladder disease	no	12.7	75533		
		yes	23.1	1121	1.8 (1.6-2.0)	<0.0001
	Any history of CVD	no	12.6	75244		
		yes	21.5	1410	1.7 (1.5-1.9)	<0.0001
	Any respiratory disease	no	12.1	69573		
		yes	20.5	7081	1.7 (1.6-1.8)	<0.0001
	Any risk factor for CVD	no	12.0	67333		
		yes	18.7	9321	1.6 (1.5-1.6)	<0.0001
	Any allergies	no	12.1	68887		
		yes	19.7	7767	1.6 (1.5-1.7)	<0.0001
	Any endocrine disease	no	12.6	74543		
		yes	19.2	2111	1.5 (1.4-1.7)	<0.0001
	Hematological / immune disease	no	12.8	76061		
		yes	18.9	593	1.5 (1.2-1.8)	<0.0001
	Any cancer	no	12.8	75446		
		yes	16.5	1208	1.3 (1.1-1.5)	0.0003

AAIM: Analgesic and anti-inflammatory medication
CVD: Cardiovascular disease
GIT: Gastrointestinal
EAMC: Exercise Associated Muscle Cramping
% AAIM use: frequency (%) of runners with history of AAIM use in each category
n: number of race entrants
PR: Prevalence ratio
CI: confidence interval
p: p-value

Discussion

The main findings of this study were: 1) in runners the prevalence of AAIM use, either in the week before a race or during a race, was 12.2% (about 1 in 8 runners) and this was significantly higher in 56km (18.6%; about 1 in 5 runners) compared to 21.1km (8.3%; about 1 in 12 runners), 2) the most frequent type of medication used, both in the week before a race and during a race, was NSAIDs, followed by analgesics (mainly paracetamol), 3) independent factors (adjusted for gender, age group and race distance) with the highest prevalence risk (PR) of AAIM use in race entrants were a history running injuries (2.2 to 2.7 higher risk) or EAMC (2.0 times higher risk), and 4) novel independent factors associated with AAIM use in runners were symptoms of CVD, CVD risk factors and a number of underlying chronic diseases (PR varied between 1.3 - 2.0 times higher risk).

The overall prevalence of AAIM use in our 56km and 21km running population is considerably lower than previously reported use in ultra-marathon runners (60-70%) [45-47] and marathon or half-marathon runners (26-49%).[29,45,46] The precise reasons for this are not apparent but may be related to a number of factors including timing of the questionnaire administration, details of the questionnaire methodology used, selection bias in most previous studies, low response rates in some previous studies and considerable differences in the populations that were studied (ranging from multistage ultra-marathon runners to amateur female recreational runners). Therefore, we cannot, with confidence, compare our reported prevalence of AAIM use data to those reported in previous studies. However we, do acknowledge that our reported prevalence of AAIM use in 56km runners is considerably lower compared with prevalence of AAIM use (%) in runners participating in multi-staged ultra-marathon races over a number of days (70% [45] and 60.5% [47]), and also in races that are considerably longer in duration than our 56km race (67km = 49.2% and 112km = 60.3%.[46] Longer race duration is a consistent factor associated with increasing AAIM use [45,46] and this also confirmed by data from our study showing a significantly higher prevalence of use in

56km vs. 21.1km runners. However, AAIM use in our 56km and 21.2km running populations are still lower than the 49% reported for 42.2km runners [29] and 26% for 21.1km runners [45] respectively. The precise reasons for higher prevalence of AAIM use in different populations of runners participating in races of the same duration require further study, and that includes the development of a consensus tool to measure and determine AAIM use in athletic populations. Although we report a lower prevalence of AAIM use in our population of runners, the dangers of AAIM use, which have been documented in a prospective study in runners [29] still warrant the same concern and attention to protect athlete health.

We found that NSAIDs were the most commonly used type of AAIM used before (8.6%) and during (5.3%) events, followed by paracetamol (before = 2.8%; during = 2.6%). A similar trend was observed in the 56km vs. 21.1km races. This finding is consistent with all previously published data on the types of AAIM used by runners immediately before and during races [29,45-48], or by athletes participating in different sports.[31-42]

The main novel findings in our study are related to factors associated with AAIM use. The unadjusted prevalence ratio of AAIM use in our population showed that female runners, older runners, 56km vs. 21.1km runners, runners with a history of musculoskeletal injuries or EAMC and runners with symptoms of CVD, risk factors for CVD and those with a variety of underlying chronic diseases have a significantly higher risk of AAIM use. In the adjusted (for gender, age and race distance) analysis independent factors associated with AAIMs use were a history of musculoskeletal injuries or EAMC, and runners with symptoms of CVD, risk factors for CVD and those with a variety of previously diagnosed chronic diseases. Notably, from our study, the highest PR for AAIM use was a history of running injuries. Previous studies have reported the possible reasons for AAIM use in athletes with injury and these include: pain relief, injury prophylaxis, peer pressure to participate, completing the race, faster recovery and the belief that AAIM use will result in earlier return to play or improve athletic performance.[40-42,48]

Our finding that there is an increased risk of AAIM use in runners with a history of EAMC is novel. Although the etiology of EAMC is still under investigation, numerous factors are associated with EAMC and include increased exercise intensity (running speed) resulting in premature muscle fatigue [61,62], a history of a running injury [61], a history of pre-race muscle damage [62] or injury [63], a history of muscle cramping [61,62], and possible genetic factors.[64] The final common pathway of these factors is that they are all associated with increased motor neuron hyper-excitability.[65] EAMC presents as a painful involuntary muscle contraction and it is therefore not surprising that AAIM use will be higher in these runners in order to prevent or treat EAMC during races. However, the precise relationship between AAIM use and EAMC requires further study.

Finally, we also identified that runners with a history of CVD symptoms, CVD risk factors and a number of underlying chronic diseases have a significantly higher risk of AAIM use immediately before or during races. We are not aware of any previous data reporting this finding. A possible explanation is that the underlying chronic diseases may be associated with more musculoskeletal complaints, either from the underlying condition, or from chronic medication that is prescribed in the treatment of chronic disease. For example, in patients with cardiovascular disease and hypercholesterolemia, well-documented side effects of commonly prescribed medications such as statins are generalized muscle aches, tenderness, and weakness (broadly myalgia). This pain itself may encourage runners to take AAIM and predispose them to an increased likelihood of AAIM use during running. Another possible explanation is habitual pill taking behavior. Chronic diseases frequently require daily doses of multiple tablets, and if a runner is in the habit of regularly taking tablets, there may be a lower threshold for AAIM consumption when pain is experienced. However, the precise reasons for the association between increased risk of AAIM use and CVD symptoms, CVD risk factors and underlying chronic disease require further study.

We believe that our data are particularly important for race organizers and medical teams that are responsible for mass community based running events. They need to be aware of the prevalence of AAIM use, types of medication consumed and the profile of runners that use AAIM immediately before and during races because this will influence the likelihood of serious cardiovascular events [29,50,53], renal injury [29,51-55], or serious gastro-intestinal injury [29,45,49,50] during an event. Race organizers and medical teams could consider targeted educational interventions to reduce AAIM use and the subsequent risk of medical complications. Furthermore, as the profile of recreational endurance athletes participating in mass-community based events reflects an increasing older population, there may be an additional higher risk of adverse events in those athletes that use AAIM and have underlying chronic disease.

The main strength of this study is that it is the largest study to examine the prevalence of use of analgesics and anti-inflammatory medication use in recreational endurance runners. Furthermore, in contrast to previous studies in runners, selection bias is minimal as we showed that the dataset is representative of the athlete population studied and reflects the age and gender of all the race entrants in our population. The notable exception is a small but significant over-representation of 21.1km runners in our population. A further strength of the study is that we used a multiple regression analysis to identify independent factors associated with AAIM use in an athlete's running career. As with all previous studies the main limitation of this study is that the data are self-reported, and that the survey wording can affect the interpretation of the data, as in previous studies. We also acknowledge that not all potential variables associated with AAIM use could be included in our model, and that we cannot infer any causal relationships between AAIM use and the risk factors we identified because of the cross-sectional study design. Finally, in this study we do not report on the relationship between AAIM use and adverse medical events over the 4-year study period, but this will be explored in future SAFER studies.

Summary and conclusion

In summary, the data from this study highlight the importance that race medical directors and their teams must be aware of the prevalence of AAIM use of runners during races, the types of AAIM used, associated factors, and the potential risk of adverse events in runners participating in their events. We support initiatives to introduce a pre-race medical screening and educational program to create awareness of the dangers of AAIM use during endurance sports in order to reduce the prevalence of use, and subsequent risk of adverse events to ensure a safer race for the participants and responsible medical teams alike. An area for future research is to measure the effectiveness of such an intervention. Finally, it is the role of every health care professional to counsel athletes on the potential dangers and side effects of AAIM use, in particular NSAIDs, when competing in endurance sports events.

Declaration of Helsinki: Permission to analyze the medical histories of the study participants 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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Appendix A: Questions related to AAIM use

1. **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

2. **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

3. **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

Supplementary Material

Table S1: Univariate regression model - the unadjusted prevalence ratio (PR; with 95% confidence intervals - CI) and % race entrants reporting analgesic / anti-inflammatory (AAIM) use by gender, a race type (21.1km and 56km), age group

		% AAIM users	n	PR (95% CI)	p
Gender	Female	12.5	32612		
	Male	12.0	44042	1.05 (1.0-1.1)	0.0365
Race type	21.1km	8.3	47069		
	56km	18.6	29585	2.2 (2.1-2.3)	<0.0001
Age group	≤ 30 years	8.1	20168	1.5 (1.4-1.6)[a]; 1.8 (1.7-2.0)[b]; 1.9 (1.8-2.1)[c]	<0.0001[a,b,c]
	31–40 years	12.4	25045	1.2 (1.1-1.3)[b]; 1.3 (1.2-1.3)[c]	<0.0001[b,c]
	41–50 years	14.8	19340	1.1 (1.0-1.1)[c]	0.0959
	≥ 50 years	15.6	12101		

AAIM: Analgesic and anti-inflammatory medication
% AAIM use: frequency (%) of runners with history of AAIM use in each category
n: number of race entrants
PR: Prevalence ratio
CI: confidence interval
p: p-value
[a]: vs 31-40 years
[b]: vs 41-50 years
[c]: vs > 50 years

Table S2: Univariate regression model - the unadjusted prevalence ratio (PR; with 95% confidence intervals - CI) and % race entrants reporting analgesic / anti-inflammatory (AAIM) use by musculoskeletal injuries and EAMC

		n	PR (95% CI)	p
Any running injury	no	68323		
	yes	8331	2.8 (2.6-2.9)	<0.0001
Any muscle injury	no	73448		
	yes	3206	2.2 (2.1-2.4)	<0.0001
Any tendon injury	no	74660		
	yes	1994	2.4 (2.2-2.6)	<0.0001
History of EAMC	no	66040		
	yes	10614	2.2 (2.1-2.3)	<0.0001

AAIM: Analgesic and anti-inflammatory medication
EAMC: Exercise Associated Muscle Cramping
% AAIM use: frequency (%) of runners with history of AAIM use in each category
n: number of race entrants
PR: Prevalence ratio
CI: confidence interval
p: p-value

Table S3: Univariate regression model - the unadjusted prevalence ratio (PR; with 95% confidence intervals - CI) and % race entrants reporting analgesic / anti-inflammatory (AAIM) use by main category of chronic disease history

		% AAIM users	n	PR (95% CI)	p
Any history of CVD	no	12.1	75244		
	yes	21.1	1410	1.7 (1.5-2.0)	<0.0001
Any risk factor for CVD	no	11.5	67333		
	yes	17.8	9321	1.6 (1.5-1.6)	<0.0001
Any symptoms of CVD	no	12.1	75801		
	yes	23.9	853	2.0 (1.7-2.3)	<0.0001
Any respiratory disease	no	11.6	69573		
	yes	18.4	7081	1.6 (1.5-1.7)	<0.0001
Any endocrine disease	no	12.0	74543		
	yes	19.0	2111	1.6 (1.4-1.8)	<0.0001
Any GIT disease	no	11.9	74597		
	yes	23.4	2057	2.0 (1.8-2.2)	<0.0001
Any nervous system / psychiatric disease	no	12.0	74794		
	yes	21.5	1860	1.8 (1.6-2.0)	<0.0001
Any kidney or bladder disease	no	12.1	75533		
	yes	22.3	1121	1.8 (1.6-2.1)	<0.0001
Any hematological or immune disease	no	12.2	76061		
	yes	17.8	593	1.5 (1.2-1.8)	0.0006
Any cancer	no	12.1	75446		
	yes	17.1	1208	1.4 (1.2-1.6)	<0.0001
Any allergies	no	11.6	68887		
	yes	18.1	7767	1.6 (1.5-1.7)	<0.0001

AAIM: Analgesic and anti-inflammatory medication
CVD: Cardiovascular disease
GIT: Gastrointestinal
% AAIM users: frequency (%) of runners with a history of AAIM use in each category
n: number of race entrants
PR: Prevalence ratio
CI: confidence interval
p: p-value