Chronic prescription medication use in endurance runners: a cross-sectional study in 76,654 race entrants – SAFER XV

Running Title: **Chronic prescription medication use in endurance runners**

Marcel Jooste, MBChB [1], Martin Schwellnus, MBBCh, MSc (Med) MD [2,3,4], Nicola Sewry, PhD [2], Dina C (Christa) Janse Van Rensburg, MBChB, MSc, MMed, MD [1], Dimakatso A. Ramagole, MBChB, MSc [1], Sonja Swanevelder, MSc [5], Esme Jordaan, MSc [5,6]

[1] *Section Sports Medicine & Sport, Exercise Medicine and Lifestyle Institute (SEMLI), Faculty of Health Sciences, University of Pretoria, South Africa*

[2] *Sport, Exercise Medicine and Lifestyle Institute (SEMLI), Faculty of Health Sciences, University of Pretoria, South Africa*

[3] *International Olympic Committee (IOC) Research Centre, South Africa*

[4] *Emeritus Professor of Sport and Exercise Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*

[5] *Biostatistics Unit, South African Medical Research Council*[6] *Statistics and Population Studies Department, University of the Western Cape*

Address for correspondence:

Martin P. Schwellnus, Director: Sport, Exercise Medicine and Lifestyle Institute (SEMLI), 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

Author Current Position Titles:

Marcel Jooste (MJ): Medical practitioner, Section Sports Medicine & SEMLI, University of Pretoria

Martin Schwellnus (MS): Director, SEMLI, University of Pretoria

Nicola Sewry (NS): Senior Post Doctoral fellow, SEMLI, University of Pretoria

Christa Janse Van Rensburg (CJVR): Head of Department, Section Sports Medicine, University of Pretoria

Dimakatso A. Ramagole (DR): Lecturer, Section Sports Medicine, University of Pretoria

Sonja Swanevelder (SS): Senior Scientist, Biostatistics Unit, South African Medical Research Council

Esme Jordaan (EJ): Specialist Scientist, Biostatistics Unit, South African Medical Research Council

Abstract

Objective: To determine the prevalence of chronic prescription medication (CPM) use in distance runners (by age and sex) and to compare CPM use in 21.1km vs. 56km race entrants.
Methods: A cross-sectional study of 76654 race entrants who completed a pre-race medical screening questionnaire during race registration, which included questions on the use of CPM and CPM use in eight main categories of CPM. Prevalence (%, 95%CIs) and prevalence ratios (PR) are reported.
Results: The prevalence of any CPM use was 12.5% (12.2-12.8). CPM use was higher in older age categories vs. the youngest age category (31-40yrs vs. ≤30yrs: PR=1.4; 41-50yrs vs. ≤30yrs: PR=2.1; >50yrs vs. ≤30yrs: PR=3.4) ($p<0.0001$) and females vs. males (PR=1.1; $p<0.0001$). The use of any CPM was significantly higher in 21.1km vs. 56km race entrants (PR=1.2; $p<0.0001$). Prevalence of CPM use in main categories were: blood pressure lowering medication (3.7%), cholesterol lowering medication (3.6%), asthma medication (3.1%), and medication to treat anxiety/depression (2.6%). The pattern of CPM in the main categories differed between 21.1km and 56km race entrants.
Conclusions: 1 in 8 race entrants use CPM, with a higher prevalence of use among older race entrants, female vs. males, and 21.1km vs. 56km race entrants. Frequent CPM used are blood pressure lowering medication, cholesterol lowering medication, asthma medication, and medication to treat anxiety/depression. Use of CPM medications may increase the risk of medical complications during exercise and these data help identify subgroups of entrants that may be at higher risk for race medical encounters.

Key words:
Runners, athletes, endurance, medication use, prescription medication

Introduction:

There is a growing awareness of the irrefutable and considerable health benefits associated with regular exercise. Moreover, there is an increase in the participation in mass community-based endurance sporting events, in particular marathon running [1,2], where increased participation is especially popular among older runners and female runners [1,3]. However, prolonged moderate- to high-intensity exercise such as distance running also transiently increases the risk for moderate and serious medical encounters in a variety of organ systems [4-8]. Older participants [9], those less accustomed to exercise [9], and those with known chronic diseases [9,10], are at higher risk.

The incidence of, and risk factors associated with these medical encounters at distance running events has been reported [11-14]. The use of chronic prescription medication (CPM) is part of several international pre-participation screening questionnaires to identify individuals at higher risk of medical complications during exercise [15-17] and has been identified as a potential risk factor for developing medical encounters during long-distance running races [1,18]. CPM use during exercise may increase the risk of cardiovascular complications, severe fluid and electrolyte abnormalities, acute renal failure, rhabdomyolysis, exertional heat stroke, gastrointestinal bleeding, and tendon injuries [18]. Several categories of CPM are specifically associated with an increased risk of cardiovascular side effects during exercise, including beta-blockers, anti-arrhythmic drugs, anti-coagulants and antiplatelet drugs, beta2-agonists, psychoactive drugs, narcotics and stimulants [19]. The use of certain categories of CPM has also been associated with overuse injuries [20] and a history of exercise associated muscle cramps (EAMC) [21] among participants in mass community-based endurance events.

The prevalence of use of categories of CPM in elite athletes has been described among Olympic athletes [22-33], Paralympic athletes [22,34], and elite track and field athletes [35], usually as part of a doping control declaration. The prevalence of asthma medication use has been reported in elite endurance athletes [36], recreational endurance athletes [37,38], cross-country skiers [39,40], and road runners [41]. However, the use of CPM in endurance athletes, particularly in those participating in mass community-based endurance sporting events, has not been well-studied. In one study among 591 masters (mean age of 50 years) endurance athletes the prevalence of CPM use in 11 categories was reported [42]. In this study, the most common CPM used was lipid lowering medication followed by anti-depressant medication. The pattern of medication use was different in male and female athletes [42].

Apart from the data reported in this one study, the prevalence of any CPM use, and the use of specific categories of CPM, have not been reported among athletes participating in mass community-based endurance sporting events. Data on the prevalence of CPM use by participants in these events are

important for race medical directors and will assist to identify subgroups of participants who may be at higher risk for medical encounters on race day. This information could also improve the approach to the prevention and management of medical encounters at mass community-based endurance races.

The main aim of this study is to determine the prevalence of any CPM use, and specific main categories of CPM use, in distance runners (by age and sex category). A secondary aim is to determine if any CPM use, or specific main categories of CPM use, differ in 21.1km vs. 56km race entrants.

Materials and Methods:

This study is part of the ongoing SAFER (Strategies to reduce Adverse medical events For the ExerciseR) study series [14].

Study design, participants and data collection

Data for this cross-sectional study were collected from participants at the Two Oceans Marathon races (21.1km and 56km races) in Cape Town, South Africa, from 2012-2015. During these four years, all race entrants (n = 106743) completed a compulsory online pre-race medical screening questionnaire at the time of race registration. Participants of this study comprised 76654 of these entrants (71.8% of all race entrants) that gave consent for their personalised medical data to be used for ongoing research purposes. Before the onset of the study, permission was obtained from the research ethics committees of the University of Cape Town (REC 009/2011) (REC 030/2013) to collect the data. Further permission was obtained from the research ethics committee of the University of Pretoria (REC 612/2019) to continue with the study and to perform subsequent analysis of the results.

Online pre-race medical screening questionnaire

The online pre-race medical screening questionnaire was designed and implemented as part of a pre-race medical screening and educational intervention system to reduce the risk of medical encounters in endurance athletes [14]. The main elements of the online medical screening questionnaire have previously been described [2]. In summary, the questionnaire consisted of demographic questions (including age, sex, and race distance), training related questions and questions related to factors that are associated with a possible increased risk of adverse medical events in moderate- to high-intensity exercise such as distance running [1]. This included: symptoms of cardiovascular disease (CVD); risk factors for CVD; history of diagnosed specific chronic disease; history of prescribed medication used to treat chronic medical conditions or injuries; medication use during racing; history of running injuries; and history of EAMC.

Chronic Prescription Medication (CPM) Use

In the questionnaire, entrants were specifically asked to answer the following question related to CPM use: "*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*?" In response to a "yes" answer to this question, entrants were asked to indicate the type of medication(s) that they are taking from the following list of main categories of CPM: blood pressure lowering medication, cholesterol lowering medication, asthma medication, anti-depressant medication, anxiolytic medication, allergy medication, oral medication for diabetes mellitus, injectable medication for diabetes mellitus, heart failure medication, medication to control heart rhythm, medication to treat other heart disease, other prescription medication (not specified). After our initial analysis, and the observation of a low prevalence of use of certain types of medication categories, we grouped CPM that may be used for similar conditions as follows: anxiolytic medication and anti-depressant medication were grouped as "anxiety / depression medication"; oral medication for diabetes mellitus and injectable medication for diabetes mellitus were grouped as "any diabetes medication"; heart failure medication and medication to control heart rhythm and medication to treat other heart disease were grouped as "any heart medication".

Outcome variables

The main outcome variable is CPM use. We report the prevalence of any CPM use (expressed as a % of all race entrants) and the prevalence of use of main categories of CPM (expressed as a % of all race entrants) by age categories and sex. We also compare CPM use in 21.1km vs. 56km race entrants.

Statistical analysis of data

All data from the 2012 to 2015 medical questionnaire database were entered into an Excel spreadsheet (Microsoft 2010) and then analyzed using both the SAS 9.4 statistical program (SAS Institute Inc, Cary, North Carolina) and the STATA/SE (v15.1) statistical program (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

For the binary outcome of *any CPM use*, Modified Poisson regression models (using SAS) were used, applying a robust error estimator (log link function) to estimate the prevalence (%) and 95% confidence intervals (CIs), which was calculated as the measure of association. The correlated structure of the data, due to the same runners taking part in several years over the 4-year study period, was accounted for by using an exchangeable correlation matrix. A regression model with race distance, sex and age category prevalence (% and 95% CIs) and prevalence ratios (and 95% CIs) are reported for any CPM use, as well as a model with 2 interaction terms race distance*sex and race distance*age category.

The outcome [*categories of CPM* with 8 main categories] was previously described. Because of the multiple outcomes, we used a multinomial logistic regression (STATA) to estimate the prevalence for 8 categories of CPM compared to the control group (no CPM use). This model comparing race distances was adjusted for sex and age category. An interaction model comparing race distances with sex categories and age category is also reported. In STATA the correlated structure of the data was accounted for by specifying that the standard errors allow for intragroup correlation and thus specifying that runners with the same ID belongs to the same cluster. Prevalence (%) and prevalence ratios (95% CIs), were reported for all results. For all binomial regression models statistical significance was 5%, however for the multinomial logistic regression models statistical significance was 1%.

Results:

Race entrant demographics

The study population was 76654 consenting race entrants. A comparison of race entrant demographics (by age category, sex, and race distance) of all race entrants to the study population of consenting race entrants is shown in Table 1.

Table 1: Comparison of race entrant demographics of all race entrants and consenting race entrants (by age category, sex, and race distance)

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

All entrants: all individual entrants with duplicate runners adjusted for in all analysis

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

There were no differences between all race entrants and our study population with regards to age category and sex. However, compared to all race entrants, our study population was slightly over-

represented in the 21.1km race distance (61.4% vs. 60.7%) (p=0.0011). From here on, the "consenting race entrants" are referred to as "all race entrants".

Prevalence of any chronic prescription medication (CPM) use in all race entrants

The number and prevalence (%; 95% CI) of CPM use in all race entrants is shown in Table 2.

Table 2: The number and prevalence (%; 95% CI) of chronic prescription medication (CPM) use in all race entrants (n=76654), by race distance, age category and sex

		n	Prevalence (%; 95% CI)	PR (95% CI)	p-value
All		10143	12.5 (12.2-12.8)		
Race Distance	21.1km	6619	13.8 (13.5-14.2)	1.2 (1.2-1.3)	<0.0001
	56km	3524	11.1 (10.7-11.6)	-	
Age category (years)	≤ 30	1505	7.0 (6.6-7.4)	-	
	31-40	2521	9.9 (9.4-10.3)	1.4 (1.3-1.5)	<0.0001
	41-50	2865	14.6 (14.1-15.2)	2.1 (2.0-2.2)	<0.0001
	> 50	3252	23.7 (22.8-24.6)	3.4 (3.2-3.6)	<0.0001
Sex	Females	4514	13.3 (12.8-13.8)	1.1 (1.1-1.2)	<0.0001
	Males	5629	11.6 (11.3-12.0)	-	

CPM: Chronic prescription medication
n: number of entrants using CPM
%: modelled prevalence of CPM use

Of the 76654 race entrants, 10143 reported chronic prescription medication use. The overall prevalence of any CPM use was 12.5% (Table 2). There was a higher prevalence ratio (PR) of any CPM use in older age categories compared to the youngest age (p<0.0001). CPM use was significantly higher in female (13.3%) vs. male (11.6%) race entrants (PR=1.1; p<0.0001).

Prevalence of main categories of CPM use in all race entrants

The number and prevalence (%; 95% CI) of main categories of CPM use in all race entrants is shown in Table 3.

Table 3: The number and prevalence (%; 95% CI) of chronic prescription medication (CPM) use in all entrants, by main categories of CPM

Main category of CPM	n	Prevalence (%; 95% CI)
Blood pressure lowering medication	2495	3.7 (3.5-4.0)
Cholesterol lowering medication	2400	3.6 (3.4–3.8)
Asthma medication	2062	3.1 (2.9–3.3)
Anxiety / depression medication	1760	2.6 (2.5–2.8)
Allergy medication	691	1.0 (0.9–1.1)
Any diabetes medication	538	0.8 (0.7–0.9)
Any heart medication	229	0.3 (0.3–0.4)
Other medication	2807	4.2 (4.0–4.4)

CPM: Chronic prescription medication
n: number of entrants using CPM, entrants could report more than one category of medication.
%: modelled prevalence of use of each category of CPM

The most frequent main category of CPM used in all race entrants (% of all race entrants) was blood pressure lowering medication (3.7%), followed by cholesterol lowering medication (3.6%), asthma medication (3.1%), medication to treat anxiety / depression (2.6%) and allergy medication (1.0%). The prevalence of "other medication" was 4.2%, and this comprised of a variety of medication categories, e.g. medication to treat thyroid conditions, hormone replacement therapy, uric acid lowering medication, epilepsy medication, and anti-gastroesophageal reflux medication.

Prevalence of any CPM use in 21.1km vs. 56km race entrants

The number, modelled prevalence (%; 95% CI) and prevalence ratio (PR; 95% CI) of any CPM use in 21.1km vs. 56km race entrants (by age category and sex) is shown in Table 4.

Table 4: The number, modelled prevalence (%; 95% CI) and prevalence ratio (PR; 95% CI) of any chronic prescription medication (CPM) use in 21.1km vs. 56km entrants (by age category and sex)

		21.1km entrants				56km entrants				21.1km vs. 56km	
		n	Prevalence (%; 95% CI)	PR (95% CI)	p-value	n	Prevalence (%; 95% CI)	PR (95% CI)	p-value	PR (95% CI)	p-value
All*		6619	13.8 (13.5-14.2)			3524	11.1 (10.7-11.6)			1.2 (1.2-1.3)	<0.0001
Age category (years)	≤ 30	1258	7.6 (7.1–8.0)	-		247	7.5 (6.6–8.4)	-		1.0 (0.9 – 1.2)	0.8642
	31-40	1595	10.9 (10.4–11.5)	1.4 (1.3-1.6)	<0.0001	926	9.2 (8.6–9.8)	1.2 (1.1-1.4)	0.0023	1.2 (1.1 – 1.3)	<0.0001
	41-50	1630	16.6 (15.7–17.4)	2.2 (2.0-2.4)	<0.0001	1235	13.2 (12.4–14.0)	1.8 (1.5-2.0)	<0.0001	1.3 (1.2 – 1.4)	<0.0001
	> 50	2136	26.9 (25.7–28.2)	3.6 (3.3-3.8)	<0.0001	1116	21.1 (19.7–22.5)	2.8 (2.5-3.2)	<0.0001	1.3 (1.2 – 1.4)	<0.0001
Sex	Females	3332	14.4 (13.8–14.9)	1.1 (1.0-1.1)	0.0090	1182	13.5 (12.6–14.4)	1.3 (1.2-1.4)	<0.0001	1.1 (1.0 – 1.1)	0.0946
	Males	3287	13.4 (12.9–13.9)	-		2342	10.3 (9.7–10.8)	-		1.3 (1.2 – 1.4)	<0.0001

n: number of entrants
%: modelled prevalence of entrants using CPM within each category
PR: Prevalence ratio
For the PRs, ≤30yrs is the reference age category, and males is the reference category for sex when comparing within race distance
*These values are adjusted for age category and sex

The prevalence of any CPM use was significantly higher in 21.1km (13.8%) vs. 56km (11.1%) race entrants (PR=1.2; p<0.0001). In both the 21.1km and 56km race entrants, CPM use was higher in female entrants, and all older age categories compared to the youngest category (≤30 years). When comparing CPM use in 21.1km vs. 56km race entrants, the prevalence of use was significantly higher among the 21.1k race entrants in all age categories except in the youngest age category and was higher in males (PR=1.3; p<0.0001) but not females (PR=1.1; p=0.0946).

Prevalence of main categories of CPM use in 21.1km vs. 56km race entrants

The number and prevalence (%; 95% CI) of main categories of CPM use in 21.1km vs. 56km entrants is shown in Table 5 (adjusted for age category and sex).

Table 5: The number and prevalence (%; 95% CI) of main categories of chronic prescription medication (CPM) use in 21.1km vs. 56km entrants (adjusted for age category and sex)

	21.1km entrants		56km entrants		21.1km vs. 56km entrants	
Main category of CPM	**n**	**Prevalence (%; 95% CI)**	**n**	**Prevalence (%; 95% CI)**	**PR (%; 95% CI)**	**p-value**
Blood pressure lowering medication	1608	3.9 (3.6–4.1)	887	2.3 (2.1–2.5)	1.9 (1.7–2.1)	<0.0001
Cholesterol lowering medication	1523	3.7 (3.5–3.9)	877	2.3 (2.1–2.5)	1.8 (1.6–2.1)	<0.0001
Asthma medication	1299	2.6 (2.4–2.7)	763	2.6 (2.4–2.8)	1.1 (0.9–1.2)	0.3060
Anxiety / depression medication	1175	2.3 (2.1–2.4)	585	2.1 (1.9–2.3)	1.1 (1.0–1.3)	0.0530
Allergy medication	503	1.0 (0.9–1.1)	188	0.6 (0.5–0.7)	1.8 (1.5–2.2)	<0.0001
Any diabetes medication	375	0.9 (0.7–1.0)	163	0.5 (0.4–0.6)	2.1 (1.6–2.6)	<0.0001
Any heart medication	157	0.4 (0.3–0.5)	72	0.2 (0.1–0.2)	2.3 (1.7–3.2)	<0.0001
Other medication	1927	3.8 (3.6–4.0)	880	3.0 (2.7–3.2)	1.4 (1.3–1.5)	<0.0001

CPM: Chronic prescription medication
n: number of entrants using CPM, entrants could report more than one category of medication.
%: modelled prevalence of use of each category of CPM
PR: Prevalence ratio

Among the 21.1km entrants, the most commonly used main categories of CPM were blood pressure lowering medication (3.9%), “other medication” (3,8%), and cholesterol lowering medication (3.7%). Among the 56km entrants, “other medication” (3.0%) and asthma medication (2,6%) were the most commonly used main categories of CPM. Apart from asthma medication and medication to treat anxiety / depression, the prevalence of CPM use for all the main categories was significantly higher in 21.1km vs. 56km race entrants (p<0.0001).

Prevalence of main categories of CPM use by age category, sex and race distance (21.1km vs. 56km)

The prevalence (%; 95% CI) of main categories of CPM use by age category, sex and race distance (21.1km vs. 56km) is shown in Table 6.

Table 6: The prevalence (%; 95% CI) of main categories of chronic prescription medication (CPM) use by age category, sex and race distance (21.1km vs. 56km)

		21.1 km			56 km			21.1km vs. 56km (across age categories and sex)	
		Prevalence (%; 95% CI)	PR (95% CI)	p-value	Prevalence (%; 95% CI)	PR (95% CI)	p-value	PR (95% CI)	p-value
Blood pressure lowering medication									
Age category (years)	≤ 30	0.2 (0.2–0.3)	-		0.3 (0.1–0.5)	-		0.9 (0.6-1.4)	0.7423
	31-40	1.6 (1.3–1.8)	6.9 (4.7–10.0)	<0.0001	1.3 (1.0–1.5)	4.6 (2.3 –9.4)	<0.0001	1.2 (1.0-1.5)	0.0531
	41-50	4.7 (4.1–5.2)	22.7 (15.6–33.0)	<0.0001	3.1 (2.6–3.5)	11.7 (5.8–23.5)	<0.0001	1.5 (1.2-1.8)	<0.0001
	> 50	10.4 (9.6–11.3)	65.8 (45.6–95.2)	<0.0001	7.1 (6.3–8.0)	32.0 (16.0–64.1)	<0.0001	1.5 (1.3-1.8)	<0.0001
Sex	Females	2.1 (1.8–2.4)	-		1.6 (1.3–2.0)	-		1.2 (1.0-1.5)	0.0622
	Males	4.3 (4.0–4.6)	2.2 (1.9–2.5)	<0.0001	3.3 (3.0–3.6)	2.0 (1.5–2.6)	<0.0001	1.3 (1.1-1.5)	0.0005
Cholesterol lowering medication									
Age category (years)	≤ 30	0.5 (0.4–0.7)	-		0.3 (0.2–0.5)	-		1.1 (0.8-1.6)	0.5014
	31-40	1.4 (1.1–1.6)	2.6 (1.9–3.6)	<0.0001	1.3 (1.0–1.6)	3.9 (2.1–6.9)	<0.0001	1.2 (0.9-1.5)	0.2004
	41-50	4.2 (3.7–4.7)	9.1 (6.7–12.5)	<0.0001	3.1 (2.7–3.6)	9.9 (5.5–17.8)	<0.0001	1.5 (1.3-1.8)	<0.0001
	> 50	9.5 (8.8–10.3)	27.1 (20.0–36.5)	<0.0001	6.7 (5.9–7.6)	24.9 (13.9–44.7)	<0.0001	1.6 (1.3-2.0)	<0.0001
Sex	Females	1.5 (1.3–1.7)	-		1.3 (1.0–1.6)	-		1.3 (1.0-1.7)	0.0465
	Males	4.5 (4.1–4.8)	3.2 (2.7–3.7)	<0.0001	3.4 (3.1–3.7)	2.6 (2.0–3.4)	<0.0001	1.4 (1.2-1.6)	<0.0001
Asthma medication									
Age category (years)	≤ 30	2.2 (2.0–2.5)	-		2.2 (1.7–2.7)	-		0.9 (0.7-1.1)	0.3587
	31-40	2.5 (2.2–2.7)	1.2 (1.0–1.4)	0.0810	2.3 (2.0–2.6)	1.1 (0.8–1.4)	0.6240	1.0 (0.8-1.1)	0.6808
	41-50	3.0 (2.6–3.3)	1.6 (1.3–1.9)	<0.0001	2.4 (2.1–2.7)	1.2 (0.9–1.6)	0.2280	1.1 (1.0-1.3)	0.1746
	> 50	3.6 (3.2–4.1)	2.4 (2.0–2.9)	<0.0001	3.5 (2.9–4.0)	2.0 (1.5–2.7)	<0.0001	1.1 (0.9-1.3)	0.4953
Sex	Females	3.1 (2.9–3.4)	-		4.2 (3.7–4.6)	-		0.8 (0.7-0.9)	0.0017
	Males	2.2 (2.0–2.4)	0.7 (0.6–0.8)	<0.0001	1.8 (1.6–2.1)	0.4 (0.4–0.5)	<0.0001	1.3 (1.1-1.4)	0.0013
Anxiety / Depression medication									
Age category (years)	≤ 30	2.0 (1.8–2.3)	-		2.3 (1.7–2.8)	-		0.8 (0.6-1.0)	0.0675
	31-40	2.7 (2.4–3.0)	1.4 (1.2–1.6)	<0.0001	1.7 (1.5–2.0)	0.8 (0.6–1.0)	0.0910	1.3 (1.1-1.5)	0.0068
	41-50	2.5 (2.2–2.9)	1.4 (1.2–1.7)	<0.0001	1.9 (1.6–2.2)	0.9 (0.7–1.2)	0.4130	1.2 (1.0-1.5)	0.0565
	> 50	2.6 (2.2–3.0)	1.9 (1.5–2.3)	<0.0001	2.2 (1.7–2.7)	1.2 (0.8–1.7)	0.3020	1.2 (0.9-1.6)	0.1325
Sex	Females	3.2 (3.0–3.5)	-		3.6 (3.2–4.1)	-		0.9 (0.8-1.0)	0.1214
	Males	1.6 (1.4–1.7)	0.5 (0.4–0.6)	<0.0001	1.2 (1.1–1.4)	0.3 (0.3–0.4)	<0.0001	1.4 (1.2-1.6)	0.0002
Allergy medication									
Age category (years)	≤ 30	0.9 (0.7–1.0)	-		0.5 (0.2–0.7)	-		1.7 (1.1-2.7)	0.0255
	31-40	1.0 (0.9–1.2)	1.2 (1.0–1.6)	0.0820	0.7 (0.5–0.8)	1.5 (0.8–2.5)	0.1940	1.5 (1.1-2.1)	0.0040
	41-50	1.2 (1.0–1.4)	1.6 (1.2–2.1)	0.0010	0.6 (0.4–0.7)	1.3 (0.7–2.4)	0.3510	1.9 (1.4-2.7)	<0.0001
	> 50	1.2 (0.9–1.5)	2.0 (1.5–2.8)	<0.0001	0.7 (0.5–1.0)	2.0 (1.1–3.9)	0.0290	1.6 (1.0-2.4)	0.0390
Sex	Females	1.1 (1.0–1.2)	-		0.8 (0.6–1.0)	-		1.4 (1.1-1.9)	0.0118
	Males	1.0 (0.8–1.1)	0.9 (0.7–1.1)	0.2420	0.5 (0.4–0.7)	0.7 (0.5–0.9)	0.0190	1.9 (1.5-2.5)	<0.0001
Any diabetes medication									
Age category (years)	≤ 30	0.4 (0.3–0.5)	-		0.3 (0.1–0.6)	-		1.2 (0.7-2.1)	0.4778
	31-40	0.5 (0.4–0.7)	1.6 (1.1–2.3)	0.0240	0.3 (0.2–0.4)	0.9 (0.4–1.8)	0.7070	1.9 (1.3-2.8)	0.0023
	41-50	1.0 (0.8–1.3)	3.3 (2.2–4.9)	<0.0001	0.7 (0.5–0.8)	2.1 (1.0–4.2)	0.0490	1.7 (1.2-2.4)	0.0014
	> 50	1.7 (1.4–2.1)	7.3 (5.1–10.5)	<0.0001	0.9 (0.6–1.2)	3.4 (1.6–7.2)	0.0020	2.5 (1.7-3.6)	<0.0001
Sex	Females	0.6 (0.5–0.7)	-		0.3 (0.2–0.5)	-		1.8 (1.2-2.7)	0.0035
	Males	0.9 (0.8–1.1)	1.7 (1.3–2.2)	<0.0001	0.6 (0.5–0.8)	1.8 (1.1–2.9)	0.0180	1.7 (1.3-2.2)	<0.0001
Any heart medication									
Age category (years)	≤ 30	0.0 (0.0–0.1)	-		0.0 (-0.0–0.1)	-		1.7 (0.2-13.9)	0.6364
	31-40	0.1 (0.0–0.1)	1.9 (0.7–4.9)	0.1850	0.1 (0.0–0.1)	2.3 (0.3–19.0)	0.4290	1.3 (0.5-3.7)	0.6132
	41-50	0.3 (0.2–0.4)	8.6 (3.7–20.1)	<0.0001	0.2 (0.1–0.3)	7.0 (0.9–52.4)	0.0590	1.9 (1.0-3.8)	0.0539
	> 50	1.2 (1.0–1.5)	44.2 (20.4–95.8)	<0.0001	0.8 (0.5–1.0)	33.6 (4.6–246.7)	0.0010	2.1 (1.3-3.3)	0.0030
Sex	Females	0.1 (0.1–0.2)	-		0.1 (0.0–0.2)	-		1.4 (0.5-3.6)	0.5188
	Males	0.5 (0.4–0.6)	3.8 (2.5–6.0)	<0.0001	0.3 (0.2–0.4)	2.4 (1.2–5.1)	0.0180	2.1 (1.2-4.0)	0.0154
Other medication									
Age category (years)	≤ 30	2.4 (2.1–2.6)	-		1.8 (1.3–2.3)	-		1.1 (0.8-1.4)	0.5009
	31-40	3.1 (2.8–3.5)	1.4 (1.2–1.6)	<0.0001	2.2 (1.9–2.5)	1.2 (0.9–1.7)	0.2050	1.3 (1.1-1.5)	0.0023
	41-50	4.7 (4.2–5.2)	2.3 (2.0–2.7)	<0.0001	2.9 (2.5–3.3)	1.7 (1.3–2.3)	<0.0001	1.5 (1.3-1.7)	<0.0001
	> 50	8.3 (7.6–9.0)	5.1 (4.4–5.9)	<0.0001	5.2 (4.5–5.9)	3.6 (2.7–4.9)	<0.0001	1.4 (1.2-1.7)	<0.0001
Sex	Females	5.4 (5.1–5.7)	-		5.1 (4.5–5.6)	-		1.2 (1.0-1.3)	0.0236
	Males	2.6 (2.4–2.8)	0.5 (0.4–0.6)	<0.0001	2.1 (1.8–2.3)	0.4 (0.3–0.5)	<0.0001	1.5 (1.3-1.7)	<0.0001

%: modelled prevalence of use of each category of CPM
PR: Prevalence ratio

Main categories of CPM use by age category in 21.1km race entrants:

The use of all main categories of CPM in 21.1km race entrants was highest in the oldest age category, except for medication to treat anxiety / depression. The most common main category of CPM used

among the oldest age category was blood pressure lowering medication (10.4%) followed by cholesterol lowering medication (9.5%). In the youngest age category, use of "other medication" (2.4%) and asthma medication (2.2%) was highest.

Main categories of CPM use by age category in 56km race entrants:
Apart from medication to treat anxiety / depression, all main categories of CPM use in 56km race entrants was highest in the oldest age category. The most common main categories of CPM used among the oldest age category were blood pressure lowering medication (7.1%) followed by cholesterol lowering medication (6.7%). In the youngest age category, the most frequent use of CPM was medication to treat anxiety / depression (2.3%) and asthma medication (2.2%).

Main categories of CPM use by sex in 21.1km race entrants:
In 21.1km race entrants, the prevalence of main categories of CPM use was significantly higher in males vs. females for heart medication (PR=3.8), cholesterol lowering medication (PR=3.2), blood pressure lowering medication (PR=2.2) and any diabetes medication (PR=1.7). The use of allergy medication was similar in male and female 21.1km entrants. The prevalence of CPM use was significantly lower in male vs. female 21km race entrants for medication to treat anxiety / depression (PR=0.5), other medication (PR=0.5), and asthma medication (PR=0.7).

Main categories of CPM use by sex in 56km race entrants:
In 56km race entrants, the prevalence of main categories of CPM use was significantly higher in males vs. females for cholesterol lowering medication (PR=2.6) and blood pressure lowering medication (PR=2.0), and significantly lower in male vs. female 56km race entrants for medication to treat anxiety / depression (PR=0.3), asthma medication (PR=0.4) and other medication (PR=0.4).

Discussion:

The first main finding of this study was that the prevalence of any CPM use in all race entrants was 12.5% (1 in 8 entrants) and that the prevalence of use was significantly higher in: a) older race entrants (>50; PR=33.4), b) female compared to male race entrants (PR=1.1), and c) 21.1km compared to 56km race entrants (PR=1.2). Secondly, the most frequent main category of CPM used was blood pressure lowering medication (3.7%), followed by cholesterol lowering medication (3.6%), asthma medication (3.1%), and medications to treat anxiety / depression (2.6%). Finally, the frequency of main categories of CPM use differed between the age categories, sexes, and race distances. This information has specific relevance to race medical directors by identifying subgroups of race entrants that are at higher risk of CPM use. CPM use is considered a risk factor for medical

complications during exercise [1,18] and is part of most international recommendations for pre-participation screening [15-17].

Overall prevalence of CPM use in race entrants

The overall prevalence of any CPM use in all race entrants (12.5%), is considerably lower than the prevalence of CPM use within the general population where most of the entrants reside (18%)[43]. The only previous study to have described overall CPM use in endurance athletes reported a much higher prevalence (34%), but this was among a sample of 591 masters athletes with a mean age of 50 years [42]. It is also difficult to compare our data on the prevalence of CPM use to that reported in the existing literature because of the inconsistencies in the timing of use and the definition of the medications studied. Studies reported CPM use at the time of the competition or race [25-31,38,40,41], in the 3 days before competition [32], the past 7 days [22,24,35], and within the past 12 months [22,24,36,37]. The definition of what constitutes CPM also varied and included; physician prescribed medication [22,24,36], daily prescription medication [33,40,42,44], medication used for >180 days [45], current medication [25-31], and self-reported use of medication on doping control forms [34,46]. In several other studies, CPM was not defined [35,37-39,41]. Because there was no formal definition of CPM in the literature, we used the following definition of CPM use: "*medication used on a daily, weekly, or monthly basis in order to treat a chronic medical condition*". We suggest that future studies use a standardised definition of CPM and that may require the development of such a definition by consensus.

CPM use by age category

Apart from medication to treat anxiety / depression, the prevalence of use of all main categories of CPM was consistently higher in the older age categories compared to the youngest age category with a similar trend in both race distances. This finding is expected, as older populations generally have a higher prevalence of chronic diseases and therefore use prescription medication [43]. The finding that the use of medication to treat anxiety / depression was not affected by age may be explained by the complexity of grouping two medication categories together. Generally, the prevalence of anxiety disorders decreases with age [47], while the prevalence of depressive disorders increases with age. For this reason, the use of the main category of medication to treat anxiety / depression was likely not affected by age. We are not aware of any previous studies comparing CPM use within different age categories among endurance athletes and could not compare our data to other athlete populations. In the last 2-3 decades, the average age of race entrants in distance events has increased, with significantly higher numbers of race entrants > 40 years of age[1]. Our data are relevant to race

medical directors, who should be aware that in our study population, over 43% of 21.1km race entrants and over 34% of 56km race entrants > 40 years of age reported CPM use.

CPM use by sex

We show that CPM use was higher in female (13.3%) compared to male (11.6%) race entrants, with a similar trend in both race distances. This finding is consistent with the observation in other studies where the use of some single main categories of CPM (e.g. asthma medication) was higher in female vs. male athletes [24,29,35,37,42,46]. We are not aware of any previous studies where the overall CPM use among female vs. male endurance athletes was compared. This finding is also in keeping with the 2016 South African demographics and health survey, which showed that females are more likely to use prescribed medications for a chronic condition, compared to males (21% vs. 14%)[43]. As with increasing age, the tendency over the past 2-3 decades is that endurance running events attract greater numbers of female entrants and race medical directors should be aware that about 14% of all female race entrants use CPM.

CPM use by race distance

We report a significantly higher prevalence of CPM use in 21.1km vs. 56 km race entrants for both males and females. We are not aware of any previous studies reporting CPM use among entrants for different race distances and therefore cannot compare our findings to previous reports. We do note that entries to 21.1km races do not require qualifying times and therefore attract entrants who are not necessarily regular exercisers and who may lead sedentary lifestyles. These participants are more likely to have underlying medical conditions and thus use CPM. The relevance of this information to race medical directors is that the prevalence of CPM use is likely to be higher among entrants for shorter race distances, rather than longer (ultra-marathon) events.

Main categories of CPM use by age categories, sex and race distance

A novel finding from our study is that we also report the prevalence of use of main categories of CPM use by sex and age groups for each of the two race distances (Table 6). We cannot compare these results to any previous published reports. The most frequent main category of CPM used was blood pressure lowering medication (3.7%), followed by cholesterol lowering medication (3.6%), asthma medication (3.1%), and medications to treat anxiety / depression (2.6%). The prevalence of blood pressure lowering medication use among our study participants is significantly lower than that of the 12.5% reported in the general population[43]. The prevalence of blood pressure medication,

cholesterol lowering medication and mediation to treat anxiety / depression in our study was lower than reported in one study among master athletes (6.1-9.8%, 6.9% and 6.6% for blood pressure medication, cholesterol lowering medication and medication to treat anxiety / depression respectively). These findings are likely to be related to the older mean age (50 years) of the master athletes [42,45].

Clinical relevance of the findings

We believe that the results of this study are of particular relevance for health professionals, specifically for race medical directors to: 1) identify subgroups of race entrants with a low (<2% of entrants; < 1 in 50 entrants), moderate (2-5% of entrants; 1 in 20 to 1 in 50 entrants) or higher (>5% of entrants; > 1 in 20 entrants) prevalence of CPM use by main categories of CPM, and 2) to then consider potential side effects of CPM that may increase the risk of specific medical complications during an endurance running event (Table 7).

Table 7: Summary and clinical relevance: Prevalence of chronic prescription medication (CPM) use (low, moderate, high) in runner subgroups with potential medical complications during a race, by main categories of CPM

Main category of CPM	Prevalence of use of CPM			Potential medical complications during a race as a result of side effects (with subclasses where applicable)
	Low CPM use (<2% of entrants)	Moderate CPM use (2-5% of entrants)	High CPM use (≥5% of entrants)	
Blood pressure lowering medication	• 21.1km entrants (<40yrs) • 56km entrants (<40yrs, females)	• 21.1km entrants (41-50yrs, males and females) • 56km entrants (41-50yrs, males)	• 21.1km entrants (>50yrs) • 56km entrants (>50yrs)	• Electrolyte abnormalities[48-50] (Diuretics, ACE-I) • Dehydration[50] (Diuretics, ACE-I) • Rhabdomyolysis[51] (Diuretics) • Acute kidney injury • EHS[48,52] (Diuretics, β-blockers) • Skeletal muscle cramps / EAMC[53,54] (Diuretics, CCB, ACE-I, β-blockers) • EAPH[55] (Diuretics)
Cholesterol lowering medication	• 21.1km entrants (<40yrs, females) • 56km entrants (<40yrs, females)	• 21.1km entrants (41-50yrs, males) • 56km entrants (41-50yrs, males)	• 21.1km entrants (>50yrs) • 56km entrants (>50yrs)	• Myopathy (Statins) • Rhabdomyolysis[51] (Statins) • EAMC[21] (Statins, Fibrate) • EHS[18,50] (statins)
Asthma medication	• 56km entrants (males)	• 21.1km entrants (All age groups, males and females) • 56km entrants (All age groups, females)	-	• Hypokalaemia[19,49] (β-2 agonist) • Arrhythmias[49] (β-2 agonist) • Skeletal muscle cramps / EAMC[53,54] (β-2 agonist)
Anxiety / depression medication	• 21.1km entrants (males) • 56km entrants (31 to 50 years, males)	• 21.1km entrants (All age groups, females) • 56km entrants (≤30yrs, >50yrs, females)	-	• QT-prolongation[19,56] (TCA, SSRI) • EHS[18,52] (SSRI)
Allergy medication	• 21.1km entrants (All age groups, males and females)	-	-	• EHS[52,57] (Antihistamine) • Rhabdomyolysis[51] (Antihistamine)

	• 56km entrants (All age groups, males and females)			
Any diabetes medication	• 21.1km entrants (All age groups, males and females) • 56km entrants (All age groups, males and females)	-	-	• Hypoglycaemia (Insulin) • Skeletal muscle cramps / EAMC[54]
Any heart medication	• 21.1km entrants (All age groups, males and females) • 56km entrants (All age groups, males and females)	-	-	• Electrolyte abnormalities[48-50] (Diuretics, ACE-I) • Dehydration[50] (Diuretics, ACE-I) • Rhabdomyolysis[51] (Diuretics) • EHS[48,52] (Diuretics, β-blockers) • Skeletal muscle cramps / EAMC[53,54] (Diuretics, ACE-I, β-blockers) • QT-prolongation[58] (Anti-arrhythmic drugs)
Other medication	• 56km entrants (≤30yrs)	• 21.1km entrants (≤30 to 50yrs, males) • 56km entrants (31-50yrs, males)	• 21.1km entrants (>50yrs, females) • 56km entrants (>50yrs, females)	• Various (dependent on side effect profile of the medication)

ACE-I: Angiotensin converting enzyme inhibitor
ARB: Angiotensin receptor blocker
CCB: Calcium channel blocker
CPM: Chronic prescription medication
EAMC: Exercise associated muscle cramping
EAPH: Exercise Associated Postural Hypotension
EHS: Exertional heat stroke
SSRI: Selective serotonin reuptake inhibitor
TCA: Tricyclic antidepressant

From these data, race medical directors can now identify subgroups of race entrants that are likely to use main categories of CPM by age category, sex and race distance. The potential risk of a medical complication during exercise as a result of CPM use can be related to the underlying medical condition for which the medication is prescribed, and the side effect profile of the medication. For researchers, this information is also valuable because the association between specific main categories of CPM use and medical encounters during races still needs further investigation.

This is the largest study that documented the use of CPM among endurance athletes and is the first study to determine the prevalence of categories of CPM use in 21.1km and 56km runners. We show that apart from age categories and sex, CPM use differs in 21.1km vs. 56km race entrants. We had a high response rate (71.8% of all race entrants) and a representative study population, thereby reducing the risk of selection bias. We recognise that there are limitations to this study. Our data are self-reported and because of the cross-sectional study design, we cannot determine cause-effect. The questionnaire was only available in the English language, though the official language of communication to all race entrants is English, and this is also an official language in the country. We also acknowledge that the main categories of CPM may contain several different classes of medication (for example, asthma medication may include B-2 agonists, corticosteroids, ipratropium

bromide, and theophylline), and this should be further investigated, as individual classes of medication could have different effects on endurance athletes. We list only some medical complications of main categories of CPM use, subsequently, the association, as well as the cause-effect relationship between these CPM categories and actual medical complications, requires further study.

Conclusion/Summary:

In summary, this is the largest study documenting the prevalence of CPM use in endurance athletes. 1 in 8 race entrants used CPM, with the prevalence of use higher among older race entrants, females compared to males, and 21.1km compared to 56km race entrants. We identified the most commonly used main categories of CPM and that the pattern of use of these categories of CPM differed between the age categories, sexes, and race distances. CPM use by endurance athletes has been associated with gradual onset injuries [20], a history of exercise associated muscle cramps (EAMC) [21] and an increased risk of medical encounters during races, including cardiovascular complications, severe fluid and electrolyte abnormalities, acute renal failure, rhabdomyolysis, exertional heat stroke, and gastrointestinal bleeding [18]. Our data can assist race medical directors to appropriately identify subgroups of participants with a higher frequency of CPM use, who may be at potentially higher risk of medical encounters. This information can contribute toward making mass community-based endurance events safer. In future studies, we will explore the associations between CPM use (in general, and by main categories) and risk of medical encounters at these events.

Author contributions:

Marcel Jooste (MJ): study concept, study planning, data collection, data interpretation, manuscript (first draft), manuscript editing

Martin Schwellnus (MS): principal investigator, responsible for the overall content as guarantor, study concept, study planning, data collection, data interpretation, manuscript (first draft), manuscript editing, facilitating funding

Nicola Sewry (NS): data interpretation, manuscript (first draft), manuscript editing

Christa Janse Van Rensburg (CJVR): study planning, data interpretation, manuscript editing

Dimakatso A. Ramagole (DR): study planning, data interpretation, manuscript editing

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

Conflicts of Interest Statement:

The authors declare no conflicts of interest.

Data sharing statement:

No additional data are available

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