Recent acute prerace systemic illness in runners increases the risk of not finishing the race: SAFER study V

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ABSTRACT

Aim There are limited data on the negative effects of exercise in athletes with acute infective illness. The aim of this study was to determine whether a recently diagnosed prerace acute illness in runners affects the ability to finish a race.

Methods Runners were prospectively evaluated in the 3 days before the race for acute infective illness and then received participation advice using clinical criteria based on systemic or localised symptoms/signs. We compared the did-not-start and the did-not-finish frequencies of ill runners (Ill=172: localised=58.7%; systemic=41.3%) with that of a control group of runners (Con=53 734).

Results Runners with a systemic illness were 10.4% more likely not to start compared with controls (29.6% vs 19.2%) ($p=0.0073$). The risk difference of not starting the race in runners who were advised not to run the race compared with controls was 37.3% (56.5% vs 19.2%, $p<0.0001$). Compared with controls, runners with illness had a significantly ($p<0.05$) greater risk (any illness (5.2% vs 1.6%), systemic illness (8.0% vs 1.6%), illness <24 hours before the race (11.1% vs 1.6%)) and relative risk (prevalence risk ratio) (any illness=3.4, systemic illness=4.9, systemic illness <24 hours before the race=7.0) of not finishing the race.

Conclusions Runners with prerace acute systemic illness, and particularly those diagnosed <24 hours before race day, are less likely to finish the race, indicating a reduction in race performance.

INTRODUCTION

Is it safe for an athlete with recent or current symptoms of an acute illness to train or compete? This remains a challenging clinical decision for any Sport and Exercise Medicine (SEM) physician. There are only a small number of studies with evidence-based return-to-play (RTP) guidelines to assist SEM physicians in providing safe participation advice to an athlete with an acute illness.^{1,2} This is surprising, given that there are many studies showing that acute illness, particularly respiratory tract (RT) illness, is the most common reason for medical consultations in SEM clinics,³ as well as in tournament settings.^{4–14} RT symptoms may not always be due to an infection and it is important to consider other factors such as allergy.^{15–19} Risk factors for acute illness, particularly RT illness in athletes, include training load,^{19–23} environment,⁵ travel to a distant country^{23 24} and allergy.^{15 25 26}

The current RTP guidelines for athletes with acute RT illness are an adaptation of a clinical

tool known as the ‘neck check,’ which was first proposed in 1993²⁷ and subsequently adapted by others.^{28–31} This tool is based on localised (above the neck) versus systemic (below the neck) symptoms and signs, but limited research data support its use.^{1 2} In particular, we are not aware of any data where localised or systemic symptoms of acute illness affect exercise performance. We showed in a recent study that runners with self-reported symptoms of prerace acute illness, who started a race, had a higher did-not-finish (DNS) frequency (2.1%) compared with controls (1.3%) ($p=0.0346$), particularly runners with systemic symptoms (2.4%; risk ratio=1.90).³² However, in this, and other previous studies,^{15 20 32 33} the diagnosis of pre-event acute illness was based on self-reported symptoms only.

The aims of this study were to (1) document the type of acute illness in runners presenting to a Pre-Race acute Illness Medical Assessment (PRIMA) facility in the 3 days before a race; (2) determine if runners with acute illness advised to not start the race, did start; and (3) determine if runners with acute illness, who decided to start the race, finished the race.

METHODS

Type of study

This was a prospective cohort study.

Study participants

All the runners who registered for the 56 km or the 21.1 km races in the 2013 and/or the 2014 Old Mutual Two Oceans Marathon in Cape Town, South Africa ($n=53\,976$) were considered as possible study participants. Runners who were concerned about symptoms of acute illness in the 3 days before the race had the opportunity of a free medical assessment at a PRIMA facility—part of the ‘Medical Village’ at the compulsory prerace registration venue. We advertised the PRIMA facility in educational health emails sent out to all registered runners in the 3 months before the race, as well as on the event website and magazine. In 2013, a prerace email invited runners concerned about acute illness to the medical facility before the race, and in 2014 runners also received text messages 6 and 4 days before the race. The main sponsor’s stall, providing complimentary wellness checks (including blood pressure, cholesterol and glucose), referred several runners with symptoms of acute illness to the PRIMA medical facility. The PRIMA

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facility was open for the duration of the Registration Expo in the 3 days prior to the race.

PRIMA: history and examination

We recorded all the data, including demographic information (name, gender and unique race number) and the race for which they were registered, on electronic tablets (Galaxy Tab 2 V.10.1; Samsung, Korea). PRIMA staff (SEM physicians in 2013 and either nurses or SEM physicians in 2014) obtained a medical history, referring runners with any one (or more) of the following symptoms of an acute illness for a physical examination:

- ▶ any systemic symptoms of infection: fever, myalgia, general body aches, excessive fatigue, malaise, arthralgia or headaches;
- ▶ any lower RT symptoms of infection: productive or non-productive cough, wheezing, 'tight' chest, chest pain or shortness of breath;
- ▶ gastrointestinal symptoms: abdominal pain, cramps, nausea, vomiting or diarrhoea;
- ▶ any symptoms suggestive of cardiac disease: chest pain, shortness of breath or palpitations;
- ▶ a sore throat;
- ▶ any runners requesting a physical examination.

A SEM physician conducted the general and specific physical examination in a private cubicle after informed consent by the runner. A nurse (in 2014) recorded vital sign investigations: tympanic thermometry (Braun Thermoscan, IRT 4520), resting blood pressure and resting heart rate. The SEM physician conducted a general and specific systemic examination of the following systems: ear, nose and throat; respiratory, cardiac, abdominal, neurological or musculoskeletal systems. We recorded and securely stored all clinical data, including the final working diagnosis and secondary diagnoses.

Diagnostic groups

Two clinicians assessed the clinical data of all runners with any upper or lower RT symptoms, gastrointestinal symptoms or systemic symptoms of illness (fever, fatigue, malaise, myalgia, arthralgia, general body aches, headaches) to identify possible acute infection. Tympanic temperature and heart rate were considered in cases where the diagnosis of an infection was unclear. We considered a tympanic temperature $\geq 37.5^{\circ}\text{C}$ in men, and $\geq 37.1^{\circ}\text{C}$ in women to be above normal,³⁴ and we used a resting HR of >75 beats/min as an indicator of possible infection, in the context of appropriate symptoms and clinical signs. A sinus bradycardia (<60 beats/min) is seen in up to 80% of trained endurance athletes³⁵ and the resting HR can increase by 10–15 beats/min with infection.³⁶

We assigned diagnostic codes to categorise illness in runners as localised or systemic as follows. We defined a localised illness as either a localised upper respiratory tract illness (URTI) that included rhinitis (infected or not infected), pharyngitis, laryngitis, sinusitis (congestion) or any other localised illness. In the absence of an exudate or any systemic features, we classified cervical lymphadenopathy with localised throat erythema as a localised pharyngitis. In cases where clinicians recorded two diagnoses of localised illness in a runner, we categorised the illness as a localised illness.

We defined systemic infective illness as an URTI with systemic features, other systemic infective illness (mostly 'influenza'-like illnesses), suspected myopericarditis, lower respiratory tract illness (LRTI) and gastroenteritis. In the case where a runner

presented with symptoms and signs of both a 'localised' illness and a systemic illness, we categorised the illness as systemic.

Advice given to runners reporting to the PRIMA facility

On completion of the medical assessment at the PRIMA facility, medical staff gave runners advice regarding participation on race day. In the illness group, we based advice on the current RTP clinical guidelines using the differentiation between a localised illness and a systemic illness (see online supplementary table 1).

Race day data: race starting and finishing

We tracked all runners during race day with an electronic 'Champion-chip' attached to one of the runner's shoes. The runners crossed mats at the starting line, along the route and at the finish line, allowing the chip data to be identified and recorded. We categorised runners as 'non-starters' (DNS; did-not-start) if any of the course mats (at the start, on the course or at the finish) captured no data, and 'non-finishers' if the mat at the finish line captured no data.

Main measures of outcome

- ▶ the prevalence (%) of runners with symptoms, a clinical diagnosis and the diagnostic category (localised vs systemic) of runners in the illness group;
- ▶ the frequency (%) of runners who were given advice not to run;
- ▶ the absolute and relative risk of runners with illness not starting the race (DNS);
- ▶ the absolute and relative risk of runners with illness not finishing the race (DNF).

Research ethics and informed consent

Research ethics approval for this study was obtained from the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town prior to starting the study (REC: 441/2012). The Research Ethics Committee of the Faculty of Health Science at the University of Pretoria (433/2015) also approved the study.

Statistical analysis of data

We used a Poisson regression model using a robust error estimator (log link function) to analyse each individual symptom group and subgroups. This cohort consists of correlated data, which we accounted for by using an unstructured correlation matrix. We estimated the prevalence risk ratio (PRR), risk difference (RD) and 95% CI by a modified Poisson regression using robust error variances and considered p values of <0.05 as statistically significant. In addition, we report both absolute risk (%) and RD (% difference) between groups.

RESULTS

Demographics of the study population

We assessed a total of 242 runners in the 2 years of the study and excluded 70 runners diagnosed with a non-infective illness. Therefore, a total of 172 runners had symptoms and signs suggestive of acute infective illness and this comprised the illness study cohort (0.3% of all race registrants). The remaining runners who did respond to the PRIMA facility at registration ($n=53\,734$) were the control group of runners for this study. We compared outcome variables for the illness group (main cohort) and that of the control group.

The sex distribution in the illness group was similar to that of the control group in both the 56 km and the 21.1 km races.

Table 1 The final clinical diagnosis in the illness group (n=172)

Clinical diagnosis			n	% of illness group
Localised illness (n=101)	Localised URTI	All localised URTI	99	57.6
		Sinusitis	36	20.9
		Pharyngitis	30	17.4
		Rhinitis (non-infective)	28	16.3
		Laryngitis	3	1.7
		Rhinitis (infective)	2	1.2
	Other localised infective illness		2	1.2
Systemic illness (n=71)	URTIs with systemic symptoms		39	22.7
	LRTI		18	10.5
	Infective gastroenteritis		9	5.2
	Other systemic infective illness		4	2.3
	Suspected myopericarditis		1	0.6

LRTI, lower respiratory tract illness; URTI, upper respiratory tract illness.

Of the 66 runners in the 56 km illness cohort, 52 (78.8%) were male and 14 were female (21.2%). Of the 21 343 runners in the control group that registered for the 56 km race, 15 508 (72.7%) were male and 5835 (27.3%) were female. Among the 106 runners in the 21.1 km illness cohort, 48 (45.3%) were male and 58 (54.7%) were female. Of the 32 391 runners in the control group that registered for the 21.1 km race, 15 932 (49.2%) were male and 16 459 (50.8%) were female.

Prevalence of symptoms, clinical diagnosis and diagnostic category (localised vs systemic) of runners in the illness group

Some of the 172 runners in the illness group reported up to eight symptoms. Sinus congestion (40.1%) followed by cough (38.4%, and divided evenly between productive and non-productive types), sore throat (37.8%), runny nose (25.6%), fever (13.4%) and fatigue (12.8%) were the most common symptoms (suffered by >10% of runners in the illness group).

We based the final diagnosis on clinical assessment, and 11 runners were assessed by medical history only, while 161 were assessed by medical history and physical examination. Of the 172 runners in the illness group, 101 (58.7%) had a localised illness and 71 (41.3%) a systemic illness (table 1).

The proportions of runners in the illness subgroups varied on the different days that runners were evaluated before the race. Almost half (49.4%) of runners with illness (85 of the 172

runners with illness) were evaluated in the 24 hours before the race started, during which the largest proportion of runners with systemic illness was seen (46.5%) (33 of the 71 runners with systemic illness).

Advice given to runners with acute illness

We provided educational information to 143 of the 172 runners (83.1%) of the illness group, and 11 runners that we assessed after a medical history only were in this group. We advised 23 runners (13.4%) with a suspected systemic illness not to run, based on a clinical diagnosis (medical history and physical examination). Of these runners, 12 had a LRTI, 6 a generalised URTI, 4 a systemic illness and in 1, we suspected a myopericarditis.

Absolute and relative risk of not starting the race

Absolute and relative risk of not starting the race in all runners

Of all the 53 976 runners who registered for the race in 2013 and 2014, a total of 10 358 (19.2 %) did not start the race. In the control group of 53 734 runners, 10 309 were non-starters (19.2%). Within the illness group of 172 runners, 38 did not start (22.1%). Runners in the illness group did not have a significantly higher absolute risk (RD=−3.5%, 95% CI −9.7 to 2.7) (p=0.2630) or relative risk (PRR=1.16, 95% CI 0.89 to 1.52) (p=0.2693) of not starting the race (adjusted for the demographic variables of year of race, gender and race type (21.1 km vs 56 km)).

Absolute and relative risk of not starting the race in the control and illness groups and the illness subgroups based on advice given

The DNS frequencies, PRR and RD (adjusted for the demographic variables of year of race, gender and race type (21.1 km vs 56 km)) in the control group and the illness group, based on advice given, are depicted in table 2.

Within the illness group, 13 of the 23 runners (56.5%) who were advised not to run did not start the race. The absolute and relative risk of not starting the race was not different in the subgroup of runners who received information only or other advice, compared with the control group. However, the absolute risk (PRR=3.1, 95% CI 2.2 to 4.3; p<0.0001) and relative risk (RD=40.0%, 95% CI 19.7 to 60.3; p=0.0001) of not starting the race were significantly higher in the subgroup of runners who were advised not to run, compared with the control group. With respect to athlete compliance, these data indicate that 43.5% of runners in this group were non-adherent to advice.

Table 2 The DNS frequencies, RD and PRR in the control and illness groups, based on advice given

	Starters		DNS		RD (%) versus control*	p Value†	PRR versus control‡ (95% CI)	p Value§
	N	%	N	%				
Control group (n=53,734)	43 425	80.8	10 309	19.2	—			
Illness group (n=172)	134	77.9	38	22.1	−3.5 (−9.5 to 2.7)	0.2630	1.16 (0.89 to 1.52)	0.2693
Information (n=143)	119	83.2	24	16.8	−1.9 (−8.1 to 4.3)	0.5493	0.88 (0.62 to 1.25)	0.4679
Advised not to run (n=23)	10	43.5	13	56.5	40.0 (19.7–60.3)	0.0001	3.07 (2.18 to 4.32)	<0.0001
Other advice (n=6)	5	83.3	1	16.7	—	—	0.94 (0.19 to 4.54)	0.9387

*RD—adjusted for demographic variables: year of race, race type (21.1 km and 56 km), gender.

†p value: pairwise versus control group for RD.

‡PRR—adjusted for demographic variables: year of race, race type (21.1 km and 56 km), gender.

§p Value: pairwise versus control group for PRR.

DNS, did-not-start; PRR, prevalence risk ratio; RD, risk difference.

Table 3 The DNS frequencies, RD and PRR in the control and illness groups (and subgroups of localised vs systemic illness) diagnosed in two time periods before the race

	Starters		DNS		RD (%) versus control*	p Value†	PRR versus control‡ (95% CI)	p Value§
	N	%	%	%				
Control group (n=53,734)	43 425	80.8	10 309	19.2				
Illness group (n=172)	134	77.9	38	22.1	−3.5 (−9.5 to 2.7)	0.2630	1.16 (0.89 to 1.52)	0.2693
Localised illness (n=101)	84	83.2	17	16.8	−2.0 (−9.4 to 5.4)	0.6046	0.87 (0.57 to 1.33)	0.5265
Systemic illness (n=71)	50	70.4	21	29.6	11.6 (1.1–22.2)	0.0309	1.59 (1.13 to 2.23)	0.0073
>24 hours before race (n=38)	32	84.2	6	15.8	−1.6 (−13.6 to 10.5)	0.8005	0.89 (0.46 to 1.74)	0.7403
<24 hours before race (n=33)	18	54.5	15	45.5	27.1 (10.4–43.8)	0.0015	2.38 (1.67 to 3.41)	<0.0001

*RD—adjusted for demographic variables: year of race, race type (21.1 km and 56 km), gender.

†p Value: pairwise versus control group for RD.

‡PRR—adjusted for demographic variables: year of race, race type (21.1 km and 56 km), gender.

§p Value: pairwise versus control group for PRR.

DNS, did-not-start; PRR, prevalence risk ratio; RD, risk difference.

Absolute and relative risk of not starting the race in the control and illness subgroups with either localised or systemic illness

Of the 172 runners in the illness group, 101 (58.7%) had a localised illness and 71 (41.3%) had a systemic illness. The absolute risk (RD) and relative risk (PRR) (adjusted for year of race, race type and gender) of not starting the race in the subgroup of runners with localised illness and systemic illness reported >24 hours before the race were not different from that in the control group (table 3).

The absolute and relative risk of not starting the race was significantly higher in the subgroup of runners with systemic illness, compared with the control group. Similarly, compared with the control group, the absolute risk and relative risk of not starting the race were significantly higher in the subgroup of runners who reported systemic illness <24 hours before the race. However, these data should be interpreted with some caution as the numbers of non-starters in these subgroups were small.

Absolute and relative risk of not finishing the race

The DNF frequencies and PRR (adjusted for year of race, race type and gender) in the control group, illness group and subgroups of the illness group (localised or systemic illness) are depicted in table 4. The absolute risk could not be calculated due to small numbers of non-finishers and non-convergence.

In the 84 starters who had localised illness, 3 did not finish (3.6%), 2 of whom were evaluated the day before the race. In the 50 runners who started the race despite having a systemic illness, 4 did not finish (8.0%). Two of these non-finishers were among the 32 runners who were evaluated >24 hours before the

race (6.3%) and the remaining 2 non-finishers were among the 18 runners evaluated within 24 hours of the race start (11.1%).

The absolute risk (unadjusted DNF) (% runners) of not finishing the race was 1.6% in the control group and 5.2% in the illness group. In the systemic illness group, 8.0% of runners did not finish the race, and this was 6.3% and 11.1%, respectively, for runners with systemic symptoms >24 hours, and <24 hours before the race. As a result of the small sample size in the illness subgroups, the adjusted absolute risk (RD) for the DNF groups could not be obtained.

The relative risk (PRR) of not finishing the race in the subgroup of runners with localised illness was not different from that in the control group, but was significantly higher in the illness group and subgroup of runners with systemic illness compared with the control group. Similarly, compared with the control group, the relative risk of not finishing the race was significantly higher in the subgroup of runners who reported systemic illness >24 hours and <24 hours before the race. These data should be interpreted with some caution as the numbers of runners in these subgroups were small.

DISCUSSION

This study investigated the race outcomes (DNS, DNF) based on diagnosis and adherence to advice given by healthcare practitioners of runners presenting with acute illness in the 3 days before an endurance race (21.1 km and 56 km). Our main findings were: (1) 43.5% of the runners in the illness group were non-adherent to advice given and started the race—including 29.6% of runners with systemic illness; (2) runners with

Table 4 The DNF frequencies and PRR in the control and illness groups (and subgroups of localised vs systemic illness) diagnosed in two time periods before the race

Starters	Finishers		DNF		PRR versus control* (95% CI)	p Value†
	N	%	N	%		
Control group (n=43,425)	42,750	98.4	675	1.6		
Illness group (n=134)	127	94.8	7	5.2	3.40 (1.76 to 6.58)	0.0003
Localised illness (n=84)	81	96.4	3	3.6	2.45 (0.85 to 7.07)	0.0986
Systemic illness (n=50)	46	92.0	4	8.0	4.87 (2.20 to 10.75)	<0.0001
>24 hours before race (n=32)	30	93.7	2	6.3	3.73 (1.20 to 11.65)	0.0233
<24 hours before race (n=18)	16	88.9	2	11.1	7.03 (2.37 to 20.83)	0.0004

*PRR—adjusted for demographic variables: year of race, race type (21.1 km and 56 km), gender.

†p Value: pairwise versus control group for PRR.

DNF, did-not-finish; PRR, prevalence risk ratio.

localised illness started and finished the race in a similar proportion to control runners; and (3) runners in the illness group had a significantly higher risk of not finishing the race, and this was highest in runners with systemic illness in the 24 hours preceding the race start. This last finding needs to be interpreted with some caution because of the small numbers.

In our study, the DNS frequency for the total race population (19.2%) is lower than that previously reported in the literature,^{37,38} but higher than our more recently reported DNS frequency of 6.6%.³² We educated runners on the importance of monitoring symptoms as these could change over time (particularly those that we saw >24 hours before the race). We emphasised that runners can make an informed decision about their fitness to compete on race day, based on their symptoms. In our illness group, we used the frequency of not starting the race as a measure of 'adherence to advice' given to the runners. We do acknowledge that acute illness may not have been the only reason for not starting the race and that a number of other factors could affect the decision to start the race.

In our study, 43.5% of runners with acute illness were non-adherent to our advice and started the race. Runners with systemic illness were significantly less likely to start than runners in the control group, or runners with localised illness. This difference was even larger in runners we evaluated <24 hours before the race, and we attribute this to the minimal time for improvement of their clinical condition. Of interest was that some of the 56 km runners we advised against running expressed a wish to participate in the 21.1 km race instead, perceiving it as less 'risky.' This is in keeping with the observations reported during the Aberdeen marathon, where a third of the 'drop-out' respondents indicated they would have entered a half marathon if given the option.³⁸ Finally, we are not aware of any data exploring the concept of adherence to advice by athletes who have evidence of acute illness, and we suggest that further research be conducted to explore this area.

In this study, not finishing the race is used as a proxy for the impact of an acute illness on race performance. Our results show that 3.6% of runners with localised illness did not finish the race compared with 1.6% in the control group, and these data are similar to the 1.9% runners with self-reported prerace localised symptoms that we reported from our recently published data.³² These two studies are, to the best of our knowledge, the first clinical data from prospective studies to indicate that the RTP criteria, if only localised symptoms and signs present, are a useful and valid clinical tool to advise athletes with acute illness on RTP. However, we encourage further research in this area, particularly with more specific diagnoses and larger sample sizes, and more accurate measures of performance (eg, split and finishing times compared with previous or personal best running times).

However, we also show that, compared with runners in the control group, 5.2% of runners in the illness group, and 8% of runners in the systemic illness group, did not finish the race (relative risks of 3.4 and 4.9, respectively). These findings are also similar to the DNF frequencies we recently reported for runners with any self-reported illness (2.1%) and self-reported systemic symptoms (2.4%).³² However, a novel finding in this study was that 11.1% of runners with clinically diagnosed systemic illness in the 24 hours period just before the race did not finish the race (relative risk of 7.03 higher than control; $p=0.0004$). This finding has important clinical implications and suggests that recent clinically diagnosed systemic illness (<24 hours before exercise) significantly affects exercise performance. However, it is important to note that these findings should be interpreted

with some caution due to the small numbers of participants in these subgroups, and further studies with larger sample sizes are needed.

Our study also has several limitations including: (1) runners who presented to the PRIMA facility were self-selected; (2) the prevalence of acute illness in the entire race population is not known; (3) reasons for not starting or finishing are not known; and (4) the sample sizes in subgroups of runners are too small to conduct a detailed analysis. We suggest further investigations to determine whether there is a link between acute illness and medical complications during exercise.

CONCLUSION

Among runners with a clinically diagnosed prerace acute infective illness, symptoms are mostly localised to the upper RT, but a significant number of runners have an URTI with generalised symptoms. Of the runners with acute illness who were advised not to run, 43.5% ran anyway. In runners with illness, and subgroups of runners with systemic illness or systemic illness less than 24 hours before the race, who ran anyway, the risk of not finishing the race was 3.6%, 8.0% and 11.1%, respectively, compared with controls (1.6%). Therefore, runners with systemic illness, and particularly those diagnosed <24 hours before race day, were less likely to finish the race, indicating a reduction in race performance. These data are important to improve the medical care of runners (and other athletes) presenting with acute illness before training and competition.

What are the findings?

- ▶ 43.5% of runners with an acute infective illness, clinically diagnosed in the 3 days before a race, were non-adherent to advice not to run the race.
- ▶ Runners with systemic illness who elected to start the race despite being advised not to had an 8% chance of not finishing the race, compared with runners in the control group of 1.6% (relative risk of 4.9).
- ▶ If diagnosed with an acute systemic illness within 24 hours of the race, 11.1% of runners do not finish the race compared with 1.6% of runners in the control group (relative risk of 7.0).

How might it impact on clinical practice in the future?

- ▶ Sport and Exercise Medicine physicians can expect that only about 50% of recently diagnosed acutely ill runners will adhere to advice about not participating in a race.
- ▶ Runners with systemic symptoms and signs of acute prerace illness have an increased risk of not completing the race—more so if systemic symptoms and signs are present in the 24 hours before a race.

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Contributors LG: study planning, data collection, data interpretation, manuscript drafting and editing. MS: responsible for the overall content as guarantor, study concept, study planning, data collection, data interpretation, manuscript (first draft), manuscript editing, facilitating funding. WD: study planning, data collection, data interpretation, manuscript editing. SS: study planning, data analysis including statistical analysis, data interpretation, manuscript editing. EJ: study planning, data analysis including statistical analysis, data interpretation, manuscript editing.

Competing interests None declared.

Patient consent Obtained.

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