BMJ Open Sport & Exercise Medicine

What is known about the health effects of non-steroidal anti-inflammatory drug (NSAID) use in marathon and ultraendurance running: a scoping review

Eve Pannone,[1] Rebecca Abbott [1,2]

To cite: Pannone E, Abbott R. What is known about the health effects of non-steroidal anti-inflammatory drug (NSAID) use in marathon and ultraendurance running: a scoping review. *BMJ Open Sport & Exercise Medicine* 2024;**10**:e001846. doi:10.1136/bmjsem-2023-001846

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjsem-2023-001846).

Accepted 22 January 2024

[1]Medical School, University of Exeter, Exeter, UK
[2]Evidence Synthesis Team, NIHR Applied Research Collaboration South West (PenARC), University of Exeter, Exeter, UK

Correspondence to
Dr Rebecca Abbott;
r.a.abbott@exeter.ac.uk

ABSTRACT

This systematic scoping review aimed to understand the extent and scope of evidence on the health risks of non-steroidal anti-inflammatory drug (NSAID) use in marathon and ultraendurance running. NSAIDs are commonly consumed by runners to combat pain and inflammation; however, the health risks of consuming these drugs during marathon and ultrarunning events are currently not fully understood. Four databases (Cochrane Library, PubMed, MEDLINE and SPORTDiscus) were searched to identify articles focusing on running events of 26.2 miles or further, and they must have reported on the health risks of NSAID use. There was no restriction on the study design or the date of publication. Thirty studies were ultimately included: 4 randomised controlled trials, 1 cross-sectional study, 11 retrospective reviews, 4 case reports, 1 non-randomised control trial, and 9 prospective observational studies. The literature showed that potential health concerns of NSAID use could be split into five categories: electrolyte balance and hyponatraemia; acute kidney injury (AKI); gastrointestinal disturbances; oxidative stress, inflammation and muscle damage; other medical concerns. None of these sections had clear statistically significant links with NSAID use in ultraendurance running. However, potential links were shown, especially in AKI and electrolyte balance. This review suggests there is very limited evidence to show that NSAIDs have a negative impact on the health of ultrarunning athletes. Indications from a few non-randomised studies of a possible effect on kidney function need exploring with more high-quality research.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The use of non-steroidal anti-inflammatory drug (NSAIDs) is common in marathon and ultraendurance running, but the health consequences are not fully understood.

WHAT THIS STUDY ADDS

⇒ This study shows that there are potential links between NSAID use and several different negative health effects during long-distance running. However, there is not enough robust research to prove cause and effect.

⇒ In particular, indications from a few non-randomised studies of a possible effect on kidney function need exploring with more high-quality research.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More research is needed to understand the full health risks associated with NSAID use in marathon and ultraendurance running.

⇒ The role of external contributory factors such as heat, hydration status and race profile must be fully accounted for in future research.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a type of medication used for their antipyretic, anti-inflammatory and analgesic properties, and examples include aspirin, ibuprofen, diclofenac and naproxen. They are commonly taken by recreational athletes and elite professionals to combat pain and inflammation, even though it has been shown that they may not improve performance.[1] A recent review of the prevalence of non-medical NSAID use found a common and systematic use of NSAIDs above recommended doses by elite and non-elite athletes.[2] Prevalence rates have been reported as high as 84% in triathletes and 88% of recreational runners consuming some form of the drug in 12 months.[3 4]

There are concerns that NSAID use across sports is harmful to health.[5] Evidence of harm in cycling and triathlon with NSAID use before or during sport has been reported[6 7]: effects ranging from acute kidney injury (AKI) to gastrointestinal issues. The evidence for ultradistance events, particularly running, is less clear. Ultradistance running has been associated with adverse effects on kidney health, with the authors of this review proposing NSAID use as a possible factor in

this.[5] More recently, there has been controversy within the world of ultraendurance running as the Ultra Tour de Mont Blanc, one of the world's leading events, which banned the use of ibuprofen due to 'negative health risks'[8] despite limited research available as to what these health risks are.

Therefore, the aim of this scoping review was to identify and bring together the currently available research, looking specifically at ultraendurance running and exploring how NSAIDs affect the health of individuals participating in these long-distance races.

METHODS

A scoping review was undertaken to identify the extent of currently available evidence and any gaps for further research.[9] This review is being reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses scoping review reporting guidelines.[10] This review followed the five-step methodological framework from Arksey and O'Malley,[11] which includes (1) identification of the research question; (2) identification of relevant studies, (3) selection of eligible studies; (4) charting data and (5) collation and summary of results. Since it is a scoping review, this study did not look to quality appraise the evidence but presents a narrative on the patterns that appear from the literature identified based on the main research question of 'What are the health effects of NSAID use in ultraendurance running?'. Before the initial search, a protocol was produced to outline the process for this study. The protocol is available on request from the authors.

In February 2023, searches were conducted for published literature in the following databases: Cochrane Library, PubMed, MEDLINE Ovid and SPORTDiscus (via EBSCO host). Searching advice was obtained from an information specialist, and the full search strategy is shown in online supplemental file 1. Using the 'population, intervention, comparison, outcome' (PICO) framework,[12] studies were searched for using a combination of population and intervention in both the title and abstract. Both title and abstract screening and full-text screening were undertaken by one reviewer (EP), with a second reviewer (RA) screening 25% of the records.

To be eligible, the study must have focused on marathon or ultraendurance running, which for this study was defined as over 26.2 miles[13] and must have reported on the health risks or associated health outcomes of NSAID use. There was no restriction on the study design or the date of publication. Studies had to have been accessible in English to be included.

The data were charted using Microsoft Excel software, and relevant data were extracted (author, year, journal, title, location, method, size, measurements taken, health concern, age, gender, distance, use of NSAIDs, key outcomes). The results were collated and presented according to the health concerns identified.

Ethics approval was granted by the University of Exeter College of Medicine and Health Research Ethics Committee under the 'overarching ethics approval for Postgraduate Taught Masters independent research projects of low-risk typology'.

RESULTS

The initial search identified 194 articles. Endnote referencing software was used to remove duplicate studies (n=37). Following initial screening, looking at the title and abstract, 36 articles were removed for not focussing on NSAIDs, 30 were removed for not focussing on running of marathon length or longer and 4 were removed since they were not in English. Nine were removed due to not focussing on health effects. This left 78 studies further screened at full text to ensure they met the inclusion and exclusion criteria. On further screening, 23 were removed due to the inability to obtain free article access and 25 were irrelevant, leaving 30 articles included in this scoping review (see figure 1).

The studies were predominantly from the USA (N=15) and England (N=7), with other locations including South Africa, New Zealand, Denmark, Italy and the Czech Republic. More men were included, with seven studies having zero female participants. Seven studies did not mention the distribution of female to male participants, and only one study had more women than men.[14] The most common distance studied was equally marathon and 160 km (both n=8) and also studied were 110 km, 80 km, 89 km, 60 km, ironman triathlon, 24-hour races and multisport adventure racing. The most common NSAID reported was ibuprofen, reported in eight studies, followed by naproxen, but many did not report NSAID type. There were only four randomised control trials, the rest being case reports, observational studies, case reviews and cross-sectional studies. Table 1 summarises the main characteristics of the included studies.

Most of the studies (n=27) focused on four health outcome areas. The findings of these studies are presented under headings related to the health concerns[1]: electrolyte balance and hyponatraemia[2]; AKI[3]; gastrointestinal (GI) disturbances[4]; oxidative stress and muscle damage[5]; other medical concerns. Within each area of health concern, a summary of the extent of the evidence is presented, followed by a synthesis showcasing experimental data first (if available), followed by observational data. Figure 2 shows the five main areas of health concern with the proportion of statistically significant results.

Electrolyte balance and hyponatraemia

Fourteen of the studies focused on disturbances in electrolyte balance, with the focus being on exercise-associated hyponatraemia (EAH), which is defined by an acute drop in sodium (Na) concentration to 135 mmol/L or below during or 24 hours after physical activity.[15] The studies showed mixed results with regards to whether NSAIDs influenced the electrolyte balance of runners, with six of the studies showing no statistically significant results,[16–21] six of the studies showing a correlation between NSAID use and disturbed electrolytes,[22–27] and two of the studies

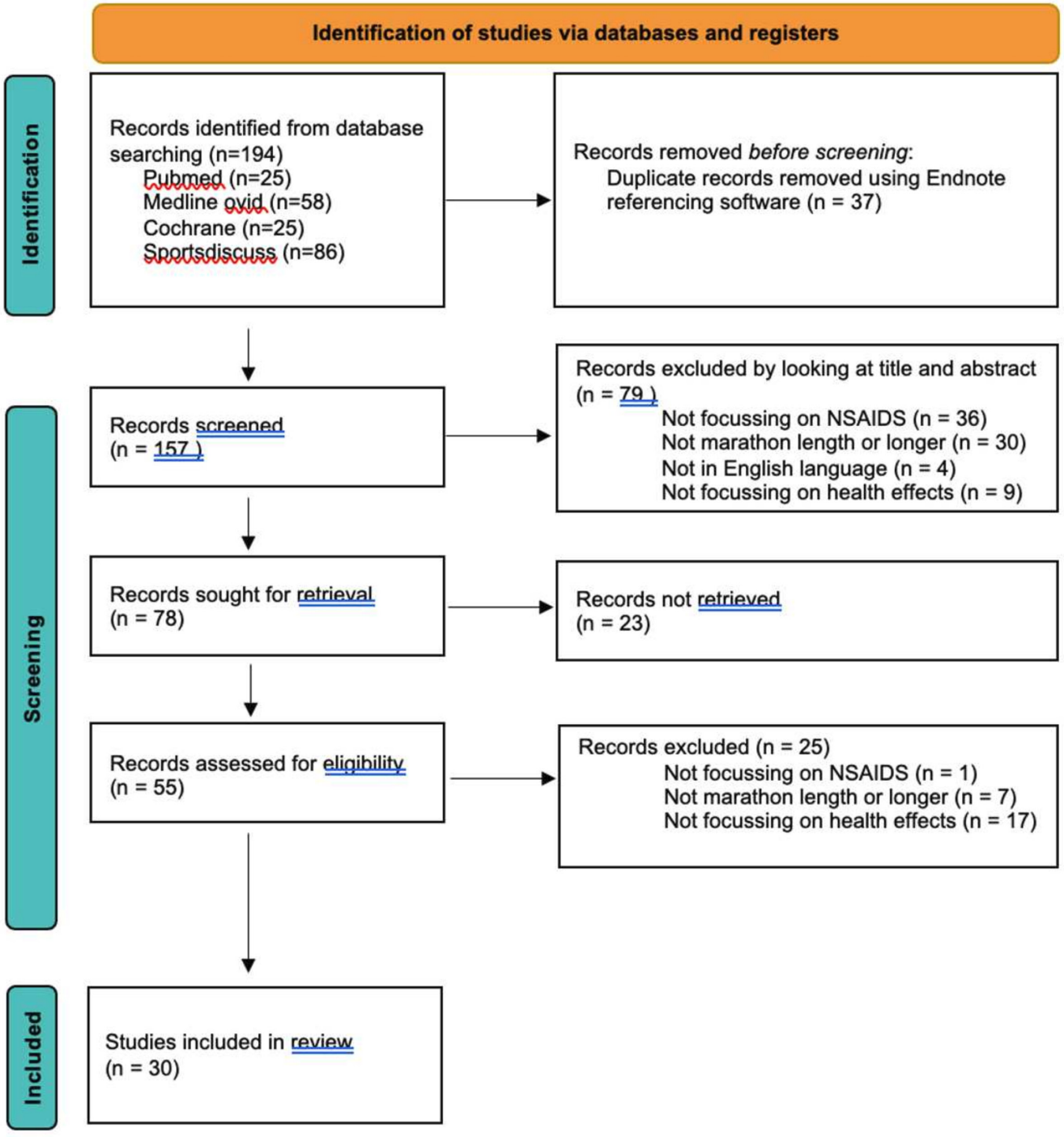

Figure 1 PRISMA flow diagram showing process of record exclusion. NSAID, non-steroidal anti-inflammatory drug; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses.

had insufficient data to conclude.[28] The length of the running event did not seem to influence the results, with studies looking at athletes participating in running events ranging from marathons up to 160 km showing and not showing statistically significant results.

There was only one randomised control trial among this group.[16] This study examined 54 participants competing in the 160 km Western States Endurance run. The study found there was no significant alteration in serum electrolytes in those who had taken ibuprofen before and during the ultrarace (n=29), compared with placebo (n=25).[16]

Six prospective observational studies found mixed results regarding the effect of NSAIDs on electrolyte balance, with 50% (n=3) finding statistically significant results. A UK-based study found that among marathon runners taking ibuprofen, the average serum Na decreased by 2.1 mmol/L compared with a control

Table 1 An overview of the included studies, organised by health risk

First author	Year	Country	Study design	Run distance	**Health event**	Outcome	NSAID consumed (if known)
Bruso, JR	2010	USA	retrospective case series	161 km	Hyponatremia	correlation between NSAID use and hyponatraemia	
Urso, C	2014	Italy	review		Hyponatremia	conflicting data, more research required	
Dumke, CL	2007	USA	randomised control trial	160 km	Hyponatremia	no significant correlation between NSAIDs and hyponatraemia	ibuprofen
Chlíbková, D	2014	Czech Republic	cross sectional	24 hours	Hyponatremia	no significant correlation between NSAIDs and hyponatraemia	
Davies, DP	2001	USA	retrospective review	marathon	Hyponatremia	correlation between NSAID use and hyponatraemia	
Hew, TD	2003	England	retrospective review	marathon	Hyponatremia	no significant correlation between NSAIDs and hyponatraemia	
Hoffman, MD	2013	USA	retrospective review	161 km	Hyponatremia	no significant correlation between NSAIDs and hyponatraemia	
Hoffman, M	2014	USA	review	100 mile	Hyponatremia	NSAIDs may increase risk of EAH'	
Hsieh, M	2002	USA	observational study	marathon	Hyponatremia	insufficient data to draw conclusions	
Khodaee, M	2021	USA	prospective observational study	161 km	Hyponatremia	no significant correlation between NSAIDs and hyponatraemia	
Reid, SA	2004	New Zealand	prospective observational study	marathon	Hyponatremia	correlation between NSAID use and potassium disturbances	
Wharam, PC	2006	USA	prospective observational study	ironman	Hyponatremia	correlation between NSAID use and hyponatraemia	
Whatmough, S	2018	UK	prospective observational study	marathon	Hyponatremia	correlation between NSAID use and hyponatraemia	ibuprofen

Continued

Table 1 Continued

First author	Year	Country	Study design	Run distance	**Health event**	Outcome	NSAID consumed (if known)
Page, AJ	2007	New Zealand	prospective observational study	60 k	Hyponatremia	no significant correlation between NSAIDs and hyponatraemia	17 taking diclofenac, 7 ibuprofen
Lipman, GS	2017	USA	randomised control trial	80 km	AKI	no significant correlation between NSAIDs and AKI	ibuprofen
Scheer, V	2020	USA	case report	110K	AKI	NSAIDs may increase risk of AKI	naproxen
Tidmas, V	2022	England	narrative review		AKI	more research is needed	
Wetschler, M	2017	USA	prospective observational study	40 mile multidiscipline adventure race	AKI	no significant correlation between NSAIDs and AKI	
Boulter, J	2011	South Africa	retrospective case series	89 km	AKI	trend between NSAID use and AKI but not enough data to be statistically significant	Cataflam, Myprodol and Voltaren
Clarkson, MP	2007	New Zealand	review	marathon	AKI	NSAIDs may increase risk of AKI	
Pasternak, A	2019	England	case report	100 mile	GI disturbance	no evidence that NSAIDs caused the injury	
Robertson, JD	1987	England	prospective observational study	marathon	GI disturbance	study did not focus on NSAIDs so conclusions cannot be drawn	naproxen
Guy, JH	2018	England	review		GI disturbance	further research is required	
Grames, C	2012	USA	case review	marathon	GI disturbance	no evidence that NSAIDs caused the injury	ibuprofen
McAnulty, S	2007	USA	control trial	161 km	Oxidative stress	significant increase in oxidative stress in NSAID users	ibuprofen
De Souza, RF	2022	England	randomised control trial	42 km	Oxidative stress and muscle damage	significant decrease in oxidative stress in NSAID users	ibuprofen
Nieman, DC	2009	USA	prospective observational study	160 km	Oxidative stress and URTI	significant increase in oxidative stress in NSAID users	ibuprofen
Christensen, B	2012	Denmark	randomised control trial	36 km	cartilage damage	significant impact on collagen synthesis in NSAID users	indomethacin

Continued

Table 1 Continued

First author	Year	Country	Study design	Run distance	**Health event**	Outcome	NSAID consumed (if known)
Pearce, PZ	2007	USA	case report	ironman (marathon)	Pericarditis	NSAIDs may have masked the symptoms of pericarditis, delaying treatment	ibuprofen
Gorski, T	2011	England	survey study	3.8 km swim, 180 km cycle, 42.2 km run	All		

group where the serum Na increased by an average of 2.3 mmol/L, which indicates an increased risk of hyponatremia (p=0.0039).[23] Results from a study focussing on athletes competing in an ironman (3.8 km swim, 180 km cycle and 42.2 km run) supported these results by finding a correlation between NSAID use and the incidence of hyponatraemia. In this study, 100% of athletes developing hyponatraemia had taken NSAIDs.[22] A 2004 New Zealand study focused specifically on potassium (K) levels rather than Na levels, and it found an 8.3% magnitude increase in mean K levels in those who consumed NSAIDs (p=0.0007).[24] These three studies are contrasted with research by Khodaee *et al*, which found that there was no statistically significant relationship between the use of NSAIDs and the 20% of 84 participating runners who were biochemically diagnosed with hyponatremia.[17] Similarly, in a study by Page *et al*, there was no significant relationship between NSAID use and electrolyte levels following a 60 km mountain run. However, interestingly, the participants of this study mainly took diclofenac, whereas most other studies focused on ibuprofen.[18] A 2002 USA-based study examined 51 runners requiring intravenous rehydration following a standard marathon.

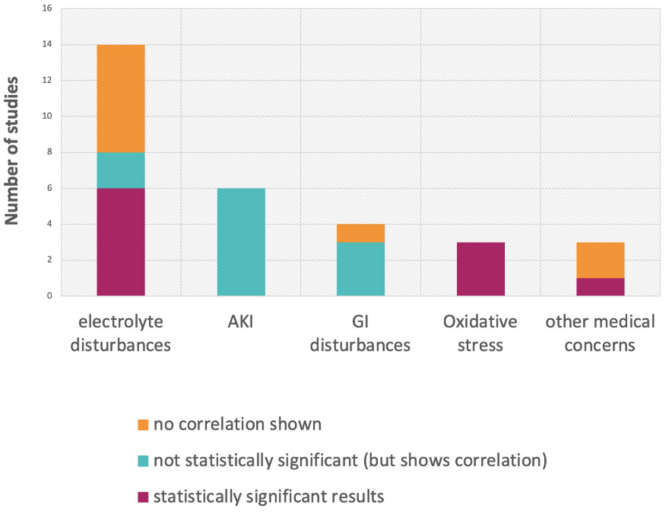

Figure 2 Bar chart depicting strength of the included studies findings by health outcome. AKI, acute kidney injury; GI, gastrointestinal.

Of these, three (5.6%) had hyponatraemia, of which one of the three had taken an NSAID, and data was not available on the other two. Due to the small number, analysis of the relationship with NSAID use was not possible.[28]

Four of the studies focussing on electrolytes and hyponatraemia were retrospective observational trials, and two out of the four did not find any correlation between NSAID use and electrolyte disturbances. Out of the studies which did not find any significant correlation between NSAID use and electrolyte disturbance, one was a study focused on marathon distance,[19] and the other looked at 100 mile ultradistance,[20] which suggests that the results are not dependent on race distance. These results contrast with a study by Davis *et al*, which found that 28% of runners presenting to hospitals with severe hyponatraemia following a marathon had taken NSAIDs, compared with just 4.6% of those without hyponatraemia. This study also found that hyponatraemia was related to slower finishing times and the female gender.[25] Similar results were found by Bruso et al. in their 2010 USA-based study of ultra runners.[26]

A 2014 cross-sectional study looked at 12 ultra-runners and found that 8.3% developed EAH (n=1), and 25% of the participants consumed NSAIDs (n=3). The participants who developed hyponatraemia did not consume NSAIDs; however, such a small sample size makes it impossible to conclude.[21]

Acute kidney injury

AKI is generally measured using creatinine (Cr) levels. 'Risk' of injury is defined as 1.5× baseline Cr, and 'injury' can be defined as 2× baseline Cr.[29]

Six of the included studies focused specifically on the link between NSAID consumption and an increased risk of AKI. The results from the studies mirror those looking at electrolyte imbalances, with a mix of significant and insignificant results. All studies reported a potential link, but there was insufficient evidence to show statistically significant results. The studies varied in study design and the distance of the event that the runners competed in.

There was only one double-blind randomised control trial. This trial found that participants taking 400 mg ibuprofen during a multi-stage ultra-endurance race

were more likely to develop AKI (22 of 42 participants) compared with placebo (16 out of 47), which was a difference of 18% (p=0.14). While this difference was not big enough to be statistically significant, the authors concluded that consideration should be taken before using NSAIDs during endurance running.[14] In a prospective observational study of 88 participants in a 40 mile adventure race, the average NSAID intake of those with AKI was 374 mg compared with 250 mg of those without. However, as with the double-blind randomised control trial, these results were insignificant.[30]

A retrospective case series of four runners who developed AKI following the Comrade's marathon (89 km) in South Africa found that three runners had ingested NSAIDs during the race, and the other runner consumed an NSAID 1 week before the race, which could indicate a link between NSAID use and AKI. The study also found that all four runners had taken the same anti-cramp electrolyte supplement, which may have been a confounding variable. In addition, the sample size is so small that conclusions cannot accurately be drawn.[31] A 2020 case report from the USA found that a runner developed AKI following a 110 km ultramarathon, having consumed 500 mg of naproxen immediately before the race, which the authors conclude may have been a risk factor.[32]

Two review articles focus on the possible mechanism and confounding factors that influence AKI in ultrarunning but are inconclusive, noting that too many of the studies are too small.[33 34]

GI disturbances

Four of the 30 studies focus on GI issues among the ultrarunners, including one prospective observational study, one review and two case reports. Out of the four studies, none of them found a clear correlation between NSAID use and GI issues.

A prospective observational study by Robertson *et al* focused on gastrointestinal blood loss and found that overall, there was a significant increase in faecal blood loss when participating in marathon running, and this blood loss was exacerbated by analgesic consumption. However, despite the significant blood loss, it was not clinically important. This study did not focus solely on NSAIDs, and the drugs taken were a combination of aspirin, paracetamol and naproxen. Therefore, it is not possible to distinguish if NSAIDs were the cause.[35]

Case reports by Pasternak *et al* and Grames *et al* both document cases of runners taking NSAIDs and then developing GI issues during an endurance race. However, neither study puts NSAID use down as the cause of the GI disturbances. The report by Pasternak *et al* focuses on a 37-year-old male runner competing in the Western States 100 mile ultra-marathon, where he consumed an NSAID and immediately vomited and experienced severe chest and abdominal pain. He was treated for Boerhaave's syndrome (spontaneous rupture of the oesophagus), and even though the pain seemed to start as soon as an NSAID was consumed, the fact that the patient immediately vomited the drug shows it is unlikely that this was a cause.[36] The case report by Grames *et al* describes a case of a 20-year-old female runner developing ischaemic colitis at mile 12 of a marathon. The runner took 800 mg of ibuprofen thrice daily for 3 weeks before the marathon; however, the study highlights that it is unclear if the ibuprofen could have contributed to the colitis, so future research is needed in this area.[37]

A potential cause for a relation between NSAID use and GI disturbance is described in a review by Guy *et al*, which found that prolonged exercise in the heat can cause GI injury, and the consumption of NSAIDs may also compromise GI integrity, which can cause leakage of endotoxins. When the two are combined, there can be an even greater risk of endotoxemia (leakage of endotoxins due to increased GI permeability). However, they acknowledge that further research is required in this area to determine the full impact.[38]

Oxidative stress and muscle damage

During long-distance running events, athletes experience physiological stresses such as oxidative stress and systemic inflammation. Three of the included studies focused on oxidative stress in relation to NSAIDs, including one randomised control trial,[39] one non-randomised control trial,[40] and one observational study.[41] All three studies found statistically significant results; however, interestingly, two of the studies found an increase in oxidative stress, and one found a decrease in oxidative stress.

The randomised control trial found lower levels of creatine kinase (CK) in the group of six marathon runners who consumed 800 mg ibuprofen compared with the six placebo runners, which suggests lower levels of oxidative stress. Despite changes in the CK levels, there was no change in athletic performance between groups.[39]

A non-randomised control trial by McAnulty *et al* measured oxidative stress using F2 iso-prostanes, plasma nitrate, and plasma urate in 160 km ultrarunners. The ibuprofen users consumed 1800 mg ibuprofen in total. The results showed a significant increase in F2 iso-prostanes in the ibuprofen group, which signified a significant increase in oxidative stress. The plasma nitrate and urate levels did not differ between groups. This race was much longer than the marathon studied in the randomised control trial, and the amount of ibuprofen consumed was higher, which may account for the different results.[40]

An observational study also looked at the 160 km Western States Endurance Run, where 70% of runners used ibuprofen before or during the race. The study looked at levels of inflammatory parameters such as cytokines, creatinine, creatine phosphate (CRP), and neutrophils. The study found that compared with the control group, there were 25–88% higher plasma levels of cytokines in the ibuprofen group and significant elevations in neutrophils and serum CRP. Similarly to the randomised control trial, the different biochemical

findings did not translate to any differences in side effects or running performance.[41]

Other medical concerns

Collagen synthesis

A 2012 randomised control trial investigated the effects of NSAIDs on tendon tissue adaptation by looking at NH2-terminal propeptide of type 1 (PINP) and prostaglandin E2 (PGE2) concentrations. Results showed that the PGE2 levels were significantly decreased after the race in the NSAID group, whereas they were unchanged in the placebo group. This signifies that the NSAIDs reduced the collagen synthesis increase normally associated with prolonged exercise. There was a significant increase in PINP in the placebo group post-race, but the levels were unchanged in the NSAID group. These two results suggest that NSAID consumption blunts the exercise-induced increase in collagen synthesis in the patellar tendon.[42]

Cardiac injury

A case report by Pearce *et al* looked at a case of a 44-year-old male athlete competing in an ironman triathlon in 2004. The athlete had been 'anti-inflammatory loading' with 400 mg ibuprofen three times per day. Anti-inflammatory loading is a technique where NSAIDs are taken the week before the event to establish a therapeutic blood level to prevent inflammation, but not taken on race day in the hope of preventing side effects. He was admitted to the hospital, where it was discovered he had suffered from a cardiac injury, which the author of the article believes was viral acute pericarditis. The author believes that the use of NSAIDs did not cause the pericarditis but could have masked symptoms.[43]

Combination of all medical conditions

A survey study by Gorski *et al* looked at ibuprofen use among triathletes and the commonly reported side effects. No clinical data were recorded in this study; the figures are based on athlete reports, so it is impossible to know cause and effect. However, the survey showed that out of 327 athletes, 196 reported NSAID use. Two athletes suffered from hyponatremia, both of whom had consumed an NSAID. Twenty-seven per cent of athletes were aware of kidney problems being a potential side effect of NSAID use in endurance sports. Still, over half the participants recognised GI disturbances as a possible side effect. The study found the number of athletes who reported GI disturbances as a side effect was slightly higher among the NSAID users. It is important to note that this study looked at triathlons, not just running. Therefore, the results may differ when running independently.[44]

DISCUSSION

Summary

This is the first review to have brought together the evidence on health risks associated with NSAID use in ultraendurance running. Studies are looking at other endurance sports, such as cycling.[6] However, the different physiological strains on the body during running mean that the effects of NSAIDs may be different in running compared with cycling. This scoping review identified 30 primary studies relating to the health effects of NSAID use in marathon and ultraendurance running published between 1987 and 2022. The studies focused on running events of various distances, from marathons to 160 km. A range of adverse health effects were described, these being electrolyte disturbances, AKI, GI issues, oxidative stress and muscle damage, cartilage damage and cardiac complications. The evidence accumulated across the studies suggests there is limited evidence to show that NSAIDs have a negative impact on the health of ultrarunning athletes. Indications from a few non-randomised studies of a possible effect on kidney function need exploring with more high-quality research.

How this compares to whats already known

Studies have found that regular or prolonged use of NSAIDs can increase the risk of GI issues in the general public.[45] Therefore, it is surprising that research did not suggest a statistically significant correlation between NSAID use in ultrarunning and GI distress. Interestingly, only one study focused on cardiovascular implications,[43] given that this is an area of risk, which is often considered in the clinical setting, with evidence showing that there is an increased risk of cardiovascular events from taking NSAIDs.[46] Studies have shown that kidney injury is frequent in ultramarathon runners,[47] and it has been shown that kidney injury has been associated with NSAID use[48] and so it is unsurprising that a potential link was found between NSAID use in ultraendurance running and AKI.[31]

Limitations and strengths

Many of the included studies had small sample sizes. For example, the randomised control trial by Christensen *et al* had only 15 participants.[42] Only seven of the 30 studies had over 100 participants, making it difficult to achieve statistically significant results. Another limitation is the study designs which have been used to investigate this area: only four randomised control trials were identified,[14 16 39 42] and some of these had relatively few participants. To fully investigate whether NSAIDs are the cause of health issues, the research needs larger randomised control studies. There was no consistency in the type or dose of NSAID throughout the studies. Many of the studies did not state which NSAIDs the participants took, and most of those that did focused on ibuprofen. Two of the studies had participants consume naproxen,[32 35] and the remaining studies looked at a combination of indomethacin,[42] cataflam,[31] and diclofenac.[18]

In terms of methods, the strengths of this study were that the search was conducted across four separate databases using systemic, comprehensive terms guided by an information specialist. The review followed best practices

in methods and reporting. A potential limitation was that two independent reviewers did not undertake title and abstract screening. However, inter-rater reliability of the 25% of double-reviewed records showed highly consistent decision-making.

Future research opportunities

Studies have shown that outside of an exercise setting, some types of NSAID are more likely to cause harmful side effects,[49] so more research looking at whether different types or dosages influence health effects in ultraendurance running may be beneficial. In particular, there is a need to recognise that fixed doses of NSAIDs will have a disproportionate effect on those with smaller body weights and perhaps adjusting doses to body weight would be more appropriate. A review article by Urso *et al* agrees that more research is required to determine the extent of the role of NSAIDs and what classifications and dosages pose an issue.[50] Many of the studies mentioned how external factors such as heat, hydration status and race profile may have confounded the health effects displayed.[18 41] More research on how these factors influence whether NSAIDs have any effect on the athlete would hopefully shed more clarity on the overall picture. There also is a need to recognise the likely individual variability in NSAID metabolism and to understand how clinical conditions and other medications may hinder or exacerbate the potential effects of NSAID use.[51] Finally, while there appeared to be no differences in the results depending on how far the athletes were running, it would be interesting to research whether there is variation in health effects depending on the distance.

Future policy implications

Several studies reported statistically significant differences between NSAID and control groups in biochemical markers such as oxidative stress; however, this did not influence performance or overall health.[39] It is then important to question whether practice guidelines must be changed based on these findings, given that the athletes do not suffer from them. The clinical findings caused by NSAID use may not have any practical impacts on their own. However, it may be that when combined with the other factors, there is a clinical significance.[18 41] A 2007 review by Clarkson *et al* agrees with this. It suggests that AKI in marathon runners may occur due to a 'perfect storm' where many factors come into play, NSAID use possibly being one of them, others including heat stress and dehydration.[34] Despite the lack of clear evidence proving that NSAIDs have a negative effect on an ultrarunner's health, an article in the magazine Ultrarunning advises to 'Avoid the use of NSAIDs during exercise'.[27] Other studies agree that such frequent use of NSAIDs in endurance sports is concerning and that policies need to be put in place to raise awareness of the potential risks among ultraendurance runners.[33] Overall, it seems that caution should be taken when taking NSAIDs prophylactically for endurance sports, especially given studies have shown that NSAIDs may not have any performance-enhancing benefits.[1]

Contributors EP and RA designed the project. EP carried out the main screening with RA supporting a percentage. EP carried out the main analysis and drafted the manuscript. RA contributed and commented to both the analysis and overall manuscript.

Funding This research was undertaken as an independent research project within the MSc Extreme Medicine, University of Exeter. RA is employed within the National Institute for Health and Care Research (NIHR) Applied Research Collaboration (ARC) South West Peninsula. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethics approval was granted by the University of Exeter College of Medicine and Health Research Ethics Committee under the 'overarching ethics approval for Postgraduate Taught (PGT) Masters independent research projects of low-risk typology'.

Provenance and peer review Not commissioned; externally peer-reviewed.

ORCID iD

Rebecca Abbott http://orcid.org/0000-0003-4165-4484

REFERENCES

1 Da Silva E, Pinto RS, Cadore EL, *et al*. Nonsteroidal anti-inflammatory drug use and endurance during running in male long-distance runners. *J Athl Train* 2015;50:295–302.
2 Brennan R, Wazaify M, Shawabkeh H, *et al*. A scoping review of non-medical and extra-medical use of non-steroidal anti-inflammatory drugs (NSAIDs). *Drug Saf* 2021;44:917–28.
3 Rudgard WE, Hirsch CA, Rosenbloom C, *et al*. Amateur endurance athletes' use of non-steroidal anti-inflammatory drugs: a cross-sectional survey. *Int J Pharm Pract* 2019;27:105–7.
4 Rosenbloom CJ, Morley FL, Ahmed I, *et al*. Oral non-steroidal anti-inflammatory drug use in recreational runners participating in Parkrun UK: prevalence of use and awareness of risk. *Int J Pharm Pract* 2020;28:561–8.
5 Hodgson LE, Walter E, Venn RM, *et al*. Acute kidney injury associated with endurance events-is it a cause for concern? A systematic review. *BMJ Open Sport Exerc Med* 2017;3:e000093.
6 Chlíbková D, Ronzhina M, Nikolaidis PT, *et al*. Non-steroidal anti-inflammatory drug consumption in a multi-stage and a 24-h mountain bike competition. *Front Physiol* 2018;9:1272.
7 Vingren JL, Boyett JC, Lee EC, *et al*. A single dose of Ibuprofen impacts IL-10 response to 164-km road cycling in the heat. *Res Q Exerc Sport* 2023;94:344–50.
8 UTMB bans Painkillers at all events - Canadian running magazine. Available: https://runningmagazine.ca/trail-running/utmb-bans-painkillers-at-all-events/ [Accessed 30 May 2023].
9 Munn Z, Peters MDJ, Stern C, *et al*. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol* 2018;18:143.
10 Tricco AC, Lillie E, Zarin W, *et al*. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med* 2018;169:467–73.

11 Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol* 2005;8:19–32.
12 Schardt C, Adams MB, Owens T, *et al*. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:1–6.
13 Scheer V, Tiller NB, Doutreleau S, *et al*. Potential Long-Term Health Problems Associated with Ultra-Endurance Running: A Narrative Review. *Sports Med* 2022;52:725–40.
14 Lipman GS, Shea K, Christensen M, *et al*. Ibuprofen versus placebo effect on acute kidney injury in ultramarathons: a randomised controlled trial. *Emerg Med J* 2017;34:637–42.
15 Rosner MH. Exercise-associated hyponatremia. *Trans Am Clin Climatol Assoc* 2019;130:76–87.
16 Dumke CL, Nieman DC, Oley K, *et al*. Ibuprofen does not affect serum electrolyte concentrations after an ultradistance run. *Br J Sports Med* 2007;41:492–6;
17 Khodaee M, Saeedi A, Harris-Spinks C, *et al*. Incidence of exercise-associated hyponatremia during a high-altitude 161-km ultramarathon. *Phys Act Nutr* 2021;25:16–22.
18 Page AJ, Reid SA, Speedy DB, *et al*. Exercise-associated hyponatremia, renal function, and nonsteroidal antiinflammatory drug use in an ultraendurance mountain run. *Clin J Sport Med* 2007;17:43–8.
19 Hew TD, Chorley JN, Cianca JC, *et al*. The incidence, risk factors, and clinical manifestations of hyponatremia in marathon runners. *Clin J Sport Med* 2003;13:41–7.
20 Hoffman MD, Fogard K, Winger J, *et al*. Characteristics of 161-km ultramarathon finishers developing exercise-associated hyponatremia. *Res Sports Med* 2013;21:164–75.
21 Chlíbková D, Knechtle B, Rosemann T, *et al*. The prevalence of exercise-associated hyponatremia in 24-hour ultra-mountain bikers, 24-hour ultra-runners and multi-stage ultra-mountain bikers in the Czech Republic. *J Int Soc Sports Nutr* 2014;11:3.
22 Wharam PC, Speedy DB, Noakes TD, *et al*. NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. *Med Sci Sports Exerc* 2006;38:618–22.
23 Whatmough S, Mears S, Kipps C. Serum sodium changes in marathon participants who use NSAIDs. *BMJ Open Sport Exerc Med* 2018;4:e000364.
24 Reid SA, Speedy DB, Thompson JMD, *et al*. Study of hematological and biochemical parameters in runners completing a standard marathon. *Clin J Sport Med* 2004;14:344–53.
25 Davis DP, Videen JS, Marino A, *et al*. Exercise-associated hyponatremia in marathon runners: a two-year experience. *J Emerg Med* 2001;21:47–57.
26 Bruso JR, Hoffman MD, Hew-Butler T, *et al*. Case series: rhabdomyolysis and hyponatremia at the 161-km 2009 Western States endurance run. *Med Sci Sports Exerc* 2010;42:426–7.
27 The basics on Hyponatremia - ultra running magazine. Available: https://ultrarunning.com/featured/the-basics-on-hyponatremia/ [Accessed 13 Jun 2023].
28 Hsieh M, Roth R, Davis DL, *et al*. Hyponatremia in runners requiring on-site medical treatment at a single marathon. *Med Sci Sports Exerc* 2002;34:185–9.
29 Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. *Clin Biochem Rev* 2016;37:85–98.
30 Wetschler M, Radler D, Christensen M, *et al*. Biochemistry in endeavor adventure racers study (BEARS). *Cureus* 2017;9:e1024.
31 Boulter J, Noakes TD, Hew-Butler T. Acute renal failure in four Comrades Marathon runners ingesting the same electrolyte supplement: coincidence or causation? *S Afr Med J* 2011;101:876–8.
32 Scheer V. Severe kidney injury after a 110-km trail race. *Cureus* 2020;12:e7814.
33 Tidmas V, Brazier J, Bottoms L, *et al*. Ultra-endurance participation and acute kidney injury: a narrative review. *IJERPH* 2022;19:16887.
34 Clarkson PM. Exertional rhabdomyolysis and acute renal failure in marathon runners. *Sports Med* 2007;37:361–3.
35 Robertson JD, Maughan RJ, Davidson RJ. Faecal blood loss in response to exercise. *Br Med J (Clin Res Ed)* 1987;295:303–5.
36 Pasternak A, Ellero JA, Maxwell S, *et al*. Boerhaave's syndrome in an ultra-distance runner. *BMJ Case Rep* 2019;12:e230343.
37 Grames C, Berry-Cabán CS. Ischemic colitis in an endurance runner. *Case Rep Gastrointest Med* 2012;2012:356895.
38 Guy JH, Vincent GE. Nutrition and supplementation considerations to limit endotoxemia when exercising in the heat. *Sports (Basel)* 2018;6:12.
39 de Souza RF, de Matos DG, Lopes Dos Santos J, *et al*. Effects of ibuprofen during 42-km trail running on oxidative stress, muscle fatigue, muscle damage and performance: a randomized controlled trial. *Res Sports Med* 2022;25:1–11.
40 McAnulty SR, Owens JT, McAnulty LS, *et al*. Ibuprofen use during extreme exercise: effects on oxidative stress and PGE2. *Med Sci Sports Exerc* 2007;39:1075–9.
41 Nieman DC. Immune function responses to ultramarathon race competition. *Medicina Sportiva* 2009;13:189–96.
42 Christensen B, Dandanell S, Kjaer M, *et al*. Effect of anti-inflammatory medication on the running-induced rise in patella tendon collagen synthesis in humans. *J Appl Physiol (1985)* 2011;110:137–41.
43 Pearce PZ. Novel presentation of acute pericarditis in an Ironman triathlete. *Curr Sports Med Rep* 2007;6:179–82.
44 Gorski T, Cadore EL, Pinto SS, *et al*. Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med* 2011;45:85–90.
45 Laine L. GI risk and risk factors of NSAIDs. *J Cardiovasc Pharmacol* 2006;47 Suppl 1(Supplement 1):S60–6.
46 Reddy KS, Roy A. Cardiovascular risk of NSAIDs: time to translate knowledge into practice. *PLoS Med* 2013;10:e1001389.
47 Hoffman MD, Weiss RH. Does acute kidney injury from an ultramarathon increase the risk for greater subsequent injury? *Clin J Sport Med* 2016;26:417–22.
48 NSAIDS: acute kidney injury. 2023. Available: https://www.uptodate.com/contents/nsaids-acute-kidney-injury [Accessed 23 May 2023].
49 Barcella CA, Lamberts M, McGettigan P, *et al*. Differences in cardiovascular safety with non-steroidal anti-inflammatory drug therapy-a nationwide study in patients with osteoarthritis. *Basic Clin Pharmacol Toxicol* 2019;124:629–41.
50 Urso C, Brucculeri S, Caimi G. Physiopathological, epidemiological, clinical and therapeutic aspects of exercise-associated hyponatremia. *J Clin Med* 2014;3:1258–75.
51 Bruno A, Tacconelli S, Patrignani P. Variability in the response to non-steroidal anti-inflammatory drugs: mechanisms and perspectives. *Basic Clin Pharmacol Toxicol* 2014;114:56–63.