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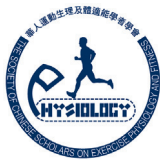
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# Non-steroidal anti-inflammatory drugs on core body temperature during exercise: A systematic review

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## ABSTRACT

**Background/Objective:** Because of their anti-pyretic effects, some individuals prophylactically use non-steroidal anti-inflammatory drugs (NSAIDs) to blunt core temperature (T<sub>c</sub>) increases during exercise, thus, potentially improving performance by preventing hyperthermia and/or exertional heat illness. However, NSAIDs induce gastrointestinal damage, alter renal function, and decrease cardiovascular function, which could compromise thermoregulation and increase T<sub>c</sub>. The aim of this systematic review was to evaluate the effects of NSAIDs on T<sub>c</sub> in exercising, adult humans.

**Methods:** We conducted searches in MEDLINE, PubMed, Cochrane Reviews, and Google Scholar for literature published up to November 2020. We conducted a quality assessment review using the Physiotherapy Evidence Database scale. Nine articles achieved a score  $\geq$  seven to be included in the review. **Results:** Seven studies found aspirin, ibuprofen, and naproxen had no effect ( $p > .05$ ) on T<sub>c</sub> during walking, running, or cycling for  $\leq$  90 min in moderate to hot environments. Two studies found significant T<sub>c</sub> changes. In one investigation, 81 mg of aspirin for 7–10 days prior to exercise significantly increased T<sub>c</sub> during cycling ( $p < .001$ ); final T<sub>c</sub> at the end of exercise =  $38.3 \pm 0.1$  °C vs. control =  $38.1 \pm 0.1$  °C. In contrast, participants administered 50 mg rofecoxib for 6 days experienced significantly lower T<sub>c</sub> during 45 min of cycling compared to placebo (NSAID T<sub>c</sub> range  $\approx$  36.7–37.2 °C vs control  $\approx$  37.3–37.8 °C,  $p < 0.05$ ).

**Conclusions:** There are limited quality studies examining NSAID effects on T<sub>c</sub> during exercise in humans. The majority suggest taking non-selective NSAIDs (e.g., aspirin) 1–14 days before exercise does not significantly affect T<sub>c</sub> during exercise. However, it remains unclear whether T<sub>c</sub> increases, decreases, or does not change during exercise with other NSAID drug types (e.g., naproxen), higher dosages, chronic use, greater exercise intensity, and/or greater environmental temperatures.

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## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain and inflammation by inhibiting prostaglandins integral in signaling vasodilation, increased vascular permeability, and fever.<sup>1–3</sup> Specifically, NSAIDs target two cyclooxygenase isoforms (COX-1 and COX-

2) that catalyze prostaglandin production from arachidonic acid. COX-1, inherently present in tissues, yields prostaglandins that regulate gastric mucosa, platelet aggregation, and renal blood flow. COX-2, present in small amounts and upregulated by inflammatory mediators, produces prostaglandins that promote pain, inflammation, and fever during an injury/illness.<sup>1,4</sup> Non-selective NSAIDs

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(e.g., aspirin, naproxen, ibuprofen) indiscriminately inhibit both COX isoforms.<sup>3</sup> However, due to varying chemical make-ups, non-selective NSAIDs have a greater affinity toward one COX isoform over the other. For instance, aspirin has a greater affinity for COX-1 whereas naproxen has greater affinity for COX-2.<sup>3</sup> A selective NSAID (e.g., celecoxib) targets COX-2, inhibiting the inflammatory responses while maintaining the important regulatory and protective COX-1 functions.<sup>5</sup>

Physically active individuals are known to prophylactically take NSAIDs in an attempt to blunt pain and inflammation during exercise, and controversy exists as to whether individuals may also use NSAIDs to try to mitigate core temperature (T<sub>c</sub>) increases during exercise.<sup>6</sup> Theoretically, NSAIDs may prevent exertional hyperthermia, including exertional heat stroke (EHS), via their antipyretic effect.<sup>6</sup> It is important to briefly mention EHS pathophysiology to understand how NSAIDs may positively or negatively alter T<sub>c</sub> and exertional heat illness risk. The gastrointestinal (GI) and immune systems largely influence EHS development.<sup>7–10</sup> During exercise, increased metabolic heat production, hypoxia, and mechanical pressures damage the GI epithelial barrier.<sup>11–14</sup> As GI permeability increases, endotoxin leaks from the GI tract into the blood stream.<sup>10</sup> The immune system and liver remove endotoxin from the blood, allowing the person to continue activity. When the body becomes overloaded, pro-inflammatory mediators (e.g., cytokines) are released to counteract endotoxin. Unfortunately, cytokines also promote necrosis, vasodilation, further induce GI damage, and promote fever.<sup>7,8,15</sup> If unmitigated, the end result is a systemic inflammatory response that propagates EHS and, in severe cases, will lead to multi-system organ failure.<sup>10</sup> Theoretically, NSAIDs could improve a person's heat tolerance during exercise by mitigating fever and the overall inflammatory response. On the other hand, NSAIDs induce GI damage and decrease cardiovascular function,<sup>16–20</sup> which would compromise thermoregulation and increase T<sub>c</sub>.<sup>10,21–23</sup>

Animal studies evaluating NSAIDs' effect on T<sub>c</sub> while under heat and/or exercise stress are conflicting. In monkeys exposed to passive heat, controls experienced a  $1.6 \pm 0.14$  °C increase in T<sub>c</sub> whereas acetylsalicylate resulted in as little as a  $0.2 \pm 0.05$  °C increase.<sup>24</sup> Rats running in a temperate environment administered indomethacin experienced a 0.4 °C T<sub>c</sub> increase compared to controls who experienced a 0.8–1.0 °C increase.<sup>25</sup> In contrast, high oral indomethacin doses decreased mice survival rate by 45% during passive heat stress<sup>26</sup> and resulted in a 67% mortality rate when mice exercised for 90 min.<sup>27</sup> The latter investigation did not examine T<sub>c</sub> or GI damage markers that may explain why the combination of strenuous exercise and indomethacin decreased survival; however, the former investigation attributed decreased survival to hemorrhaging in the GI tract caused by combining indomethacin with heat stress.<sup>26</sup>

NSAID use is prevalent among physically active adolescents and adults and from recreational to elite athletes.<sup>28–32</sup> NSAIDs are perceived as performance enhancing, but using NSAIDs to prevent hyperthermia or EHS remains controversial and the risks (i.e., GI, increased cardiovascular strain) may outweigh any potential benefits towards improved heat-tolerance.<sup>6</sup> The purpose of this systematic review was to examine existing literature on the effects that selective and non-selective NSAIDs have on T<sub>c</sub> in exercising adult humans.

## Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist were used to guide this review.<sup>33</sup>

## Inclusion and exclusion criteria

We utilized the participants, interventions, comparisons, and study design (PICOS) framework. The population of interest was exercising humans  $\geq 18$  years old. The intervention was any selective or non-selective NSAID compared to a placebo or control group. The outcome was T<sub>c</sub> measured through a valid assessment (i.e., rectal thermistor, ingestible thermistor, or esophageal thermistor).<sup>34</sup> All studies had to be in the English language, original, and utilize a randomized control trial design. Excluded studies consisted of case report studies and review articles; studies using passive hyperthermia only, animals, steroidal anti-inflammatories, and/or acetaminophen; and studies using other tools to measure body temperature (e.g., oral, aural, temporal) were not included, because they can produce invalid results in exercising individuals.<sup>34</sup>

## Search strategy and study selection

In November 2020, the following databases were searched: MEDLINE, PubMed, Google Scholar, and the Cochrane Reviews. Key words for searches included: NSAIDs, non-steroidal anti-inflammatory drugs, ibuprofen, naproxen, salicylate, aspirin, acetylsalicylic acid, indomethacin, core temperature, temperature, heat, heat illness, hyperthermia, cold, thermoregulation, exercise, and physical activity. The flow-chart for inclusion of relevant studies is provided in Fig. 1. A total of 16 articles were included for a quality assessment review.

## Quality assessment

Two researchers independently assessed the methodologic quality of studies using the Physiotherapy Evidence Database (PEDro) scale.<sup>35</sup> An inclusion score of 7/10 was selected for an article to be included in data synthesis. If discrepancy existed between reviewers, a discussion occurred to determine whether a reviewer missed or misunderstood a study aspect. A third independent review was conducted if an agreement was not reached; this reviewer was blinded to the previous reviews. Cohen's  $\kappa$  determined agreement between the two reviewers and revealed very good agreement ( $\kappa = 0.886$ ,  $p < 0.001$ ). After a consensus meeting, agreement improved ( $\kappa = 0.952$ ,  $p < 0.001$ ). The third independent reviewer was required to review 1 article to resolve disagreement. Although some studies included other outcome variables, the focus of this review is on T<sub>c</sub>; therefore, only T<sub>c</sub> data is discussed.

## Results

Table 1 contains final PEDro scores for the 16 articles. Mean PEDro score for the 16 articles =  $7.3 \pm 2.5$ , indicating moderate quality research in this area. Specific results are presented in Table 2 for the nine studies meeting inclusion criteria and achieving a PEDro score of 7/10. Seven studies showed no significant T<sub>c</sub> difference between non-selective NSAIDs and controls.<sup>36–42</sup> Across these seven studies, drug dosage varied from low to high doses administered between 1 and 14 days; exercise mode included running, walking, or cycling and ranged from 45 to 90 min; and environment ranged from thermoneutral (18 °C) to hot (38.9 °C).

Two of the nine studies identified significant differences between NSAID and control groups. One study found significantly greater T<sub>c</sub> with aspirin use during passive heating ( $p < .005$ ) that remained higher during exercise ( $p < .001$ ).<sup>18</sup> In the one study that used a selective COX-2 inhibitor,<sup>43</sup> no T<sub>c</sub> difference occurred when participants ran in a warm environment. However, T<sub>c</sub> was 0.33 °C lower during the subsequent 45 min cycling bout in the NSAID

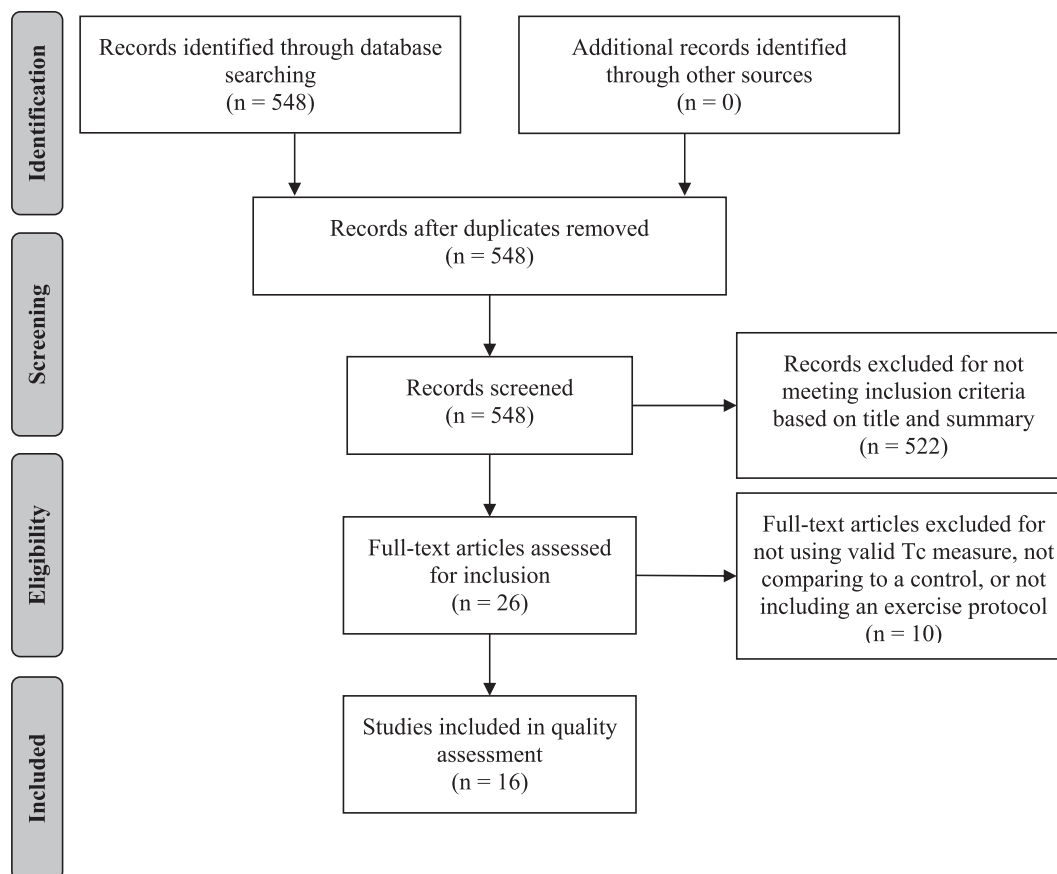


Fig. 1. PRISMA flow chart illustrating the different phases of the literature search and study selection.

group versus control ( $p = .03$ ), and Tc remained significantly lower throughout the 1-h recovery ( $p < .001$ ).<sup>43</sup>

## Discussion

It is difficult to make a definitive statement on whether NSAIDs significantly affect Tc during exercise. In general, prophylactic non-selective NSAID use for 14 days or less does not significantly increase or decrease Tc during exercise compared to controls. However, it is important to consider the context of this supposition, because there are limited high quality studies examining this topic and the methodology varies considerably among the existing investigations.

As some of the oldest, most inexpensive, and widely used NSAIDs, aspirin and ibuprofen are often researched. Aspirin has a greater affinity for COX-1.<sup>44,45</sup> Daily low-doses (~81 mg/day) will completely inhibit all platelets in ~10 days.<sup>44</sup> As a result, daily low-dose aspirin is recommended for individuals with cardiovascular disease risk to prevent strokes and myocardial infarctions.<sup>45</sup> Using a methodological approach where participants take aspirin daily for 7–14 days and complete some type of physical activity, whether planned exercise or as part of their job (e.g., firefighters),<sup>36,37</sup> is applicable to a large population. Interestingly, the three studies with similar aspirin doses over 7–14 days yielded different Tc results.<sup>18,36,37</sup> Participant characteristics and exercise may explain the discrepancy. Bruning et al.<sup>18</sup> used passive heat exposure then long duration, continuous, moderate-intense cycling in a warm environment. Participants were older and euhydrated with fair to average  $\text{VO}_{2\text{peak}}$ . This was the only study to show Tc was higher during exercise. NSAIDs may increase Tc by impairing sweat

responses.<sup>46,47</sup> However, based on a lack of significant sweat rate or skin temperature responses during exercise between control and NSAIDs,<sup>18,37,43</sup> Tc differences likely occurred through other mechanisms. Bruning et al.<sup>18</sup> attributed higher Tc to decreased skin blood flow, which prevented the body from dissipating heat as it would if it had a normal vascular response. Appropriate cardiovascular function is essential to thermoregulation, as the body redistributes blood flow to dissipate heat while also supplying working muscles and maintaining cardiac output.<sup>48</sup> Poor cardiovascular fitness is highly associated with increased thermoregulatory strain.<sup>49,50</sup> Therefore, it is possible the Tc results in Bruning et al.<sup>18</sup> were confounded by the participants' being older and exercising for longer with poor cardiovascular conditioning compared to the younger, more aerobically fit participants in Hostler et al.<sup>37</sup> and McEntire et al.<sup>36</sup>

Before we discuss potential reasons why many of the reviewed studies did not find NSAIDs altered Tc during exercise, it is important to understand that the fever mechanism is different than the mechanism for exertional hyperthermia. A fever occurs when the body initiates a cascade of events that promote heat gain, and this is predominately mediated by prostaglandins.<sup>51</sup> These events trigger the set-point temperature in the hypothalamus to increase from ~37 °C to, for example, 40 °C in order to fight off an infection. In contrast, during exercise, the hypothalamic set-point temperature is not changed. Instead, the body is producing metabolic heat, and when temperatures exceed ~37 °C, physiological responses are initiated to promote heat loss. The most important heat loss mechanism is sweat evaporation.<sup>48</sup> When evaporation is sufficient to maintain Tc (heat loss  $\approx$  heat gain) this is referred to as compensable heat strain.<sup>48,52</sup> When evaporative heat loss is

**Table 1**  
Physiotherapy evidence database (PEDro) scale scores of critically reviewed articles.

	Bass & Jacobson <sup>66</sup>	Bradford et al. <sup>43</sup>	Bruning et al. <sup>18</sup>	de Meersman <sup>40</sup>	Downey & Darling <sup>67</sup>	Emerson et al. <sup>42</sup>	Farquhar & Kenney <sup>38</sup>	Farquhar et al. <sup>39</sup>
Eligibility criteria specified (no points)								
1. Subjects were allocated randomly to groups (in a crossover study, subjects were allocated randomly in the order in which treatments were received).	X	✓	✓	✓	X	✓	✓	✓
2. Allocation was concealed	X		✓	✓	X	✓	✓	X
3. The groups were similar at baseline regarding the most important prognostic indicators	✓	✓	✓	✓	✓	✓	✓	✓
4. There was blinding of all subjects	X	✓	✓	✓	X	✓	✓	✓
5. There was blinding of all therapists who administered the therapy	X	✓	✓	✓	X	✓	✓	X
6. There was blinding of all assessors who measured at least 1 key outcome	X	✓	✓	✓	X	✓	✓	X
7. Measures of at least 1 key outcome were obtained from more than 85% of the subjects initially allocated to groups	✓	✓	✓	✓	✓	X	✓	✓
8. All subjects for whom outcome measures were available received the treatment or control condition as allocated, or, where this was not the case, data for at least 1 key outcome were analyzed by “intention to treat”	✓	✓	✓	✓	✓	✓	✓	✓
9. The results of between-groups statistical comparisons are reported for at least 1 key outcome	✓	✓	✓	✓	✓	✓	✓	✓
10. The study provides both point measures and measures of variability for at least 1 key outcome	X	✓	✓	✓	✓	✓	✓	✓
Total PEDro scale score	4	10	10	10	5	9	10	7
	Fujii et al. <sup>68</sup>	Fujii et al. <sup>69</sup>	Hostler et al. <sup>37</sup>	Jacobson & Bass <sup>70</sup>	Lambert et al. <sup>41</sup>	McEntire et al. <sup>36</sup>	Ryan et al. <sup>71</sup>	Veltmeijer et al. <sup>72</sup>
Eligibility criteria specified (no points)								
1. Subjects were allocated randomly to groups (in a crossover study, subjects were allocated randomly in the order in which treatments were received).	X	X	✓	X	✓	✓	X	✓
2. Allocation was concealed	X	X	✓	X	X	✓	X	X
3. The groups were similar at baseline regarding the most important prognostic indicators	✓	✓	✓	✓	✓	✓	✓	✓
4. There was blinding of all subjects	X	X	✓	X	✓	✓	✓	X
5. There was blinding of all therapists who administered the therapy	X	X	✓	X	✓	✓	X	X
6. There was blinding of all assessors who measured at least 1 key outcome	X	X	✓	X	✓	✓	X	X
7. Measures of at least 1 key outcome were obtained from more than 85% of the subjects initially allocated to groups	X	✓	X	X	✓	X	✓	✓
8. All subjects for whom outcome measures were available received the treatment or control condition as allocated, or, where this was not the case, data for at least 1 key outcome were analyzed by “intention to treat”	✓	✓	✓	✓	✓	✓	✓	✓
9. The results of between-groups statistical comparisons are reported for at least 1 key outcome	✓	✓	✓	✓	✓	✓	✓	✓
10. The study provides both point measures and measures of variability for at least 1 key outcome	✓	✓	✓	X	✓	✓	✓	✓
Total PEDro scale score	4	5	9	3	9	9	6	6

X = article did not meet criteria, ✓ = article met criteria.

impaired, for instance due to high relative humidity or wearing protective clothing, an uncompensable heat situation occurs (heat gain > heat loss).<sup>48,53,54</sup> Beyond simply being in a hot, humid environment, many factors, including the person’s heat acclimatization status, hydration status, aerobic fitness, pre-existing medical conditions, or, as it relates to this review, medication use can impair thermoregulation and increase hyperthermia risk.<sup>52,53,55</sup>

Our first consideration for the lack of Tc affect among studies is related to environmental temperatures and humidity. Wet-bulb globe temperature (WBGT) provides the most accurate indication of the environmental heat strain, accounting for dry bulb, wet bulb, and black bulb temperatures.<sup>56</sup> Moderate risk for heat illness begins around 29 °C WBGT with extreme risk above 32 °C WBGT.<sup>56</sup> Impaired sweat evaporation begins around 50% relative humidity,<sup>57</sup> and, as we mentioned, the ability to effectively evaporate sweat (lose heat) is what makes a condition either compensable or uncompensable. The majority of investigations used hot to extremely hot environments (>30 °C dry, wet, or WBGT).<sup>18,36–39,42</sup>

However, only two studies reported >50% humidity.<sup>42,43</sup> The environmental strain among many of the investigations was likely not enough to lead to an uncompensable condition.

Even in the absence of a febrile state, NSAIDs lower Tc by inhibiting prostaglandin production.<sup>58,59</sup> All non-selective NSAID doses in the reviewed studies should have been enough to reduce fever and theoretically alter Tc. No studies reported differences in baseline or pre-exercise temperature between NSAIDs and control, suggesting NSAIDs did not elicit an anti-pyretic effect or mask a response by “cooling” individuals prior to exercise. During exercise, it is possible inflammation is driving Tc responses. Therefore, NSAID doses would need to be sufficient enough to elicit an anti-inflammatory affect. Ibuprofen study dosages (1.3 and 3.0 g/day)<sup>38,39</sup> were less than recommended (3.6 g/day)<sup>60</sup> to inhibit inflammation. Similarly, only one study<sup>40</sup> administered an aspirin dose within the recommended 2.4–5.4 g/day range for anti-inflammatory affects.<sup>60</sup> While the dosage administered by Emerson et al. (220 mg)<sup>42</sup> should have provided an anti-inflammatory

**Table 2**  
Results from included articles on NSAIDs and Tc during exercise.

	Bruning et al. <sup>18</sup>	de Meersman <sup>40</sup>	Hostler et al. <sup>37</sup>	Lambert et al. <sup>41</sup>	McEntire et al. <sup>40</sup>
Participants	N = 14 Males and females Age = 55 ± 1 years VO <sub>2peak</sub> = 29.5 ± 1.7 mL/kg/min	N = 8 Males Age 21–34 years Baseline VO <sub>2max</sub> not reported	N = 102 Male and female firefighters Age = 31.9 ± 9.1 years VO <sub>2max</sub> = 44.6 ± 7.2 mL/kg/ min	N = 17 Males and females Age = 27 ± 1 years VO <sub>2max</sub> = 62.2 ± 2.1 mL/kg/min	N = 15 Male firefighters Age = 30.5 ± 9.3 years VO <sub>2max</sub> = 46.6 ± 7.0 mL/kg/min
NSAID	Aspirin	Aspirin	Aspirin	Aspirin	Aspirin
Dose	81 mg 1 x day for 7–10 days	500 mg 6 x day for 1 day	81 mg/day for 14 days	325 mg 4 x day for 1 day	81 mg/day for 14 days
Timing <sup>a</sup>	Morning of trial	Last dose not reported; mean drug concentration = 17 ± 8 mg/100 mL	Morning of trial	Morning of trial	Last dose not reported
Exercise	120 min recumbent cycle at 60% VO <sub>2peak</sub>	60 min run at 50% VO <sub>2max</sub>	50 min intermittent walking at 4.5 km/h with 2.5% incline and 2.5 km/h with 0% incline	60 min run at 70% VO <sub>2max</sub>	45 min walk at 6.4 km/h
Environment	30 °C dry/22 °C wet bulb, 40% RH	18 ± 0.5 °C, 43 ± 2% RH	38.9 ± 1.1 °C, 19.8 ± 3.8% RH	22.4 °C, 48% RH	38.8 ± 2.1 °C, 24.9 ± 9.1% RH
Tc Measure	Esophageal	Rectal	Ingestible thermistor	Rectal	Ingestible thermistor
Tc Results	NSAID range ≈ 37.1–38.2 °C, significantly higher than control range ≈ 36.6–37.9 °C, p < .001	At 60 min NSAID = 38.2 ± 0.52 °C and control = 37.9 ± 0.56 °C No significant difference, p > .05	Range ≈ 36.7–39.4 °C No significant difference, p > .05	Mean = 38.4 ± 0.1 °C No significant difference, p > .05	At 45 min NSAID = 39.0 ± 0.7 °C and control = 39.1 ± 0.6 °C No significant difference, p = .69
	Emerson et al. <sup>42</sup>	Farquhar & Kenney <sup>38</sup>	Farquhar et al. <sup>39</sup>	Bradford et al. <sup>43</sup>	
Participants	N = 11 Males and females Age = 27.8 ± 6.5 years VO <sub>2max</sub> = 41.4 ± 5.7 mL/kg/min	N = 16 Females Younger age = 24 ± 2 years Older age = 64 ± 2 years Younger VO <sub>2max</sub> = 41.2 ± 2.2 mL/kg/min Older VO <sub>2max</sub> = 29.1 ± 1.7 mL/kg/min	N = 12 Males and females Age = 25 ± 1 years VO <sub>2max</sub> = 54 ± 1 mL/kg/min	N = 10 Males Age = 23 ± 5 years VO <sub>2max</sub> = 53.1 ± 5.3 mL/kg/min	
NSAID	Naproxen	Ibuprofen	Ibuprofen	Rofecoxib	
Dose	220 mg 3 x day for 1 day	400 mg 3 x day for 3 days	400 mg 3 x day for 4 days	25 mg 2 x day for 6 days	
Timing <sup>a</sup>	~1 h before	~30 min before	Morning of trial	~1½ hours before	
Exercise	80 min cycling at 70% VO <sub>2max</sub> then 10 min at max effort	60 min walk at 60% VO <sub>2max</sub>	45 min run at 65% VO <sub>2max</sub>	45 min run at ~75% VO <sub>2max</sub> then 45 min cycle at matched perceived intensity	
Environment	35.7 ± 1.3 °C, 53.2 ± 3.2% RH 22.7 ± 1.8 °C, 52.4 ± 5.5% RH	36 °C dry/24 °C wet bulb	36 °C dry/24 °C wet bulb	28 °C, 50% RH	
Tc Measure	Rectal	Rectal	Rectal	Rectal	
Tc Results	At 90 min mean = 38.2 ± 0.3 °C No significant difference, p > .05	At 60 min, younger NSAID = 38.74 ± 0.08 °C and control = 38.81 ± 0.10 °C; older NSAID = 38.50 ± 0.16 °C and control = 38.45 ± 0.13 °C No significant difference, p > .05	At 45 min NSAID = 39.2 ± 0.1 °C and control = 38.9 ± 0.1 °C No significant difference, p > .05	Run range ≈ 37.2–38.0 °C No significant difference, p > .05 Cycling NSAID range ≈ 36.7–37.2 °C significantly lower than control range ≈ 37.3–37.8 °C, p < .05	

Abbreviations: RH = relative humidity; Tc = core temperature; VO<sub>2max</sub> = maximal oxygen consumption; VO<sub>2peak</sub> = peak oxygen consumption.<sup>a</sup> Timing refers to when the last NSAID dose was taken prior to exercise.

effect, higher doses (550 mg) may be necessary.<sup>60,61</sup>

Our next consideration is regarding drug plasma concentrations. Drug effects on Tc would most likely come at peak plasma concentrations, which is influenced by the drug formulation (e.g., tablet, enteric coated, rapid-release) and when the last dose was administered prior to exercise. Ibuprofen peak plasma concentrations occur about 2 h after administration.<sup>62</sup> In Farquhar & Kenney,<sup>38</sup> the peak plasma concentration likely occurred after exercise ended. This may have occurred in Farquhar et al.<sup>39</sup> as well, but we are unable to determine exactly when the last dose was administered. Peak naproxen plasma concentrations occur 1–3 h after administration.<sup>61</sup> A lack of Tc difference in Emerson et al.<sup>42</sup> may be because peak concentration occurred at the end of exercise. Oral, uncoated aspirin's effects are rapid, with peak plasma concentration occurring ~30 min after administration.<sup>63</sup> Discrepancy between investigations that administered aspirin for 7–10 days<sup>18,36,37</sup> could be related to peak concentration, where aspirin taken the morning of a trial would peak before exercise began. When further considering dose and timing, if aspirin's effect on Tc during exercise is attributed to inhibited platelet function and skin blood flow,<sup>18</sup> a one-day, acute aspirin dose may not alter platelet aggregation and skin blood flow to the extent that Tc would be negatively affected.

Rofecoxib was the only COX-2 selective NSAID among the articles reviewed.<sup>43</sup> COX-2 selective NSAIDs are extremely effective at reducing pain and inflammation.<sup>3</sup> The anti-inflammatory affect could explain the decreased Tc during cycling and 1-h recovery after exercise.<sup>43</sup> COX-2 inhibitors cause less GI damage because they do not inhibit the GI protective prostaglandins produced by COX-1.<sup>3</sup> Less GI damage could also explain the lower Tc among those administered rofecoxib; however, GI damage and plasma endotoxin were not measured in the study. The investigators attributed the Tc difference to lower cardiovascular strain,<sup>43</sup> but this was not seen when participants ran. We suggest another explanation for the Tc results could be the timing of the last dose. Rofecoxib plasma concentration peaks within 2–3 h.<sup>64</sup> Participants in Bradford et al.<sup>43</sup> would experience peak plasma concentrations toward the end of the running/beginning of the cycling and throughout recovery, which aligns with when Tc was significantly lower. It should be noted rofecoxib was withdrawn from the market in 2004 due to an increased risk of cardiovascular events.<sup>65</sup>

#### Limitations and future research

Several limitations exist in the available research on NSAIDs and Tc during exercise. No studies were included in the critical appraisal that used indomethacin or other commonly used NSAIDs or prescription strength dosages. Indomethacin is extremely potent<sup>66</sup> and generally more effective at reducing pain and inflammation than aspirin or ibuprofen.<sup>3</sup> To date, celecoxib remains one of the only available selective COX-2 inhibitors on the market and is only available through prescription. Therefore, celecoxib use is not as predominant in physically active populations. In general, the amount of drug available to elicit effects at a given time (e.g., during exercise) is highly dependent on timing, dosage, administration route, formulation, and individual factors that affect how the person will respond to the drug (e.g., body composition, nutritional status, history of medication use). For research to determine to what extent NSAIDs affect Tc, investigators need to administer drug doses based on body weight and/or measure drug plasma concentrations.

Although hyperthermia or EHS can occur in cooler environments, few of the reviewed studies used environments that were hot with high humidity to investigate the compounding effects of exercise and uncompensable heat stress with NSAID use. Due to restrictions in human subjects' research, participants are rarely

allowed to exceed Tc > 39.5 °C and EHS cannot be induced. Five studies averaged a Tc < 39 °C<sup>18,38,40,42,67</sup> and only one had participants who exceeded 39.5 °C.<sup>36</sup> By limiting the Tc, participants in controlled laboratory studies may inherently have less thermoregulatory strain than participants in field or case studies. Responses to exercise and NSAIDs will differ between individuals who are well-conditioned vs recreationally active, heat acclimatized or non-acclimatized, or have previously used NSAIDs or have never used NSAIDs. Hydration status, nutrition, pre-existing or current illness, sleep, and numerous other factors can also influence thermoregulation by compromising the cardiovascular, GI, and/or immune systems. Not only do these factors need to be controlled for, more research needs to examine the physiological mechanisms responsible for potential interactions between NSAIDs, heat stress, and exercise.

#### Conclusion

The overall results of this review do not support the belief that NSAIDs decrease Tc and therefore provide some performance benefit to exercising individuals by mitigating hyperthermia. It is possible non-selective NSAIDs may increase Tc by altering thermoregulatory function. However, more research is needed, and results may vary between different populations. We recommend individuals participating in intense exercise in a thermal environment taking NSAIDs use caution. Additionally, sports medicine professionals working with individuals known to be using NSAIDs, who may also have other intrinsic or extrinsic exertional heat illness risks, should be aware of the potential consequences associated with combining NSAIDs, exercise, and heat.

#### Declaration of competing interest

The authors have no other conflict of interests to disclose.

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