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REVIEW

Is physical performance affected by non-steroidal anti-inflammatory drugs use? A systematic review and meta-analysis

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ABSTRACT

Objective: This systematic review and meta-analysis aim to analyze the effects of ingesting non-steroidal anti-inflammatory drugs (NSAIDs) on physical performance, muscle strength, and muscle damage in three different moments: immediately, 24 and 48 h after resistance exercise practice.

Methods: Relevant studies were researched in three databases (PubMed, Web of Science and SPORTDiscus) in April 2023. After excluding duplicates, the decision to include or exclude studies was made by two independent investigators in the following steps: (I) the study title; (II) the study abstract; and (III) the complete study manuscript. The following characteristics were recorded: (I) first author, (II) year of publication, (III) sample size, (IV) method of NSAIDs administration, (V) exercise protocol, and (VI) analyzed variable results. The studies selected were divided into trials that evaluated the effects of NSAIDs ingestion on performance indices of resistance exercise, endurance exercise and resistance training.

Results: The meta-analysis, based only on resistance exercises, revealed that both performance and muscle strength were similar between placebo or NSAID treatment immediately and 24 h after resistance exercise practice. An ergolytic effect was found 48 hours after resistance exercise (mean effect size (ES) = −0.42; 95% CI: −0.71, −0.12; $p = 0.132$), as well as reduced muscle strength (ES = −0.50; 95% CI: −0.83, −0.16; $p = 0.072$). Additionally, NSAID use did not prevent muscle waste as seen by the unchanged CK plasma concentration at all timetables.

Conclusion: The data of the present meta-analysis indicate that NSAID use is ineffective in improving resistance performance and muscle strength, as well as exercise recovery. When considering the practical application of using NSAIDs to improve exercise capacity and strength gains, the present data supports that consumption of analgesic drugs as an endurance performance enhancer or as a muscle anabolic must not be recommended.

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KEYWORDS
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1. Introduction

Sports activities frequently cause musculoskeletal injuries, which are accompanied by inflammatory responses, including pain. To conquer inflammatory responses, NSAIDS are often used. In fact, because the use of NSAIDs is currently not classified as doping, their consumption is not only commonplace in elite sports, but also among physically active individuals [1]. Such drugs have been considered as an important ally in the musculoskeletal recovery strategy, preventing pain and accelerating physical healing, and potentially affecting physical performance [2]. These analgesic drugs are also being taken to avoid the inherent pain associated with training and competition, as well as to eventually develop a competitive edge in sports.

NSAIDs are among the most used drugs in the world. The non-medical prescribing policy and the low cost, which ease access to these medications, helps explain their popularity [3–5]. These drugs comprise a class of medications capable of exerting antipyretic, anti-inflammatory, and analgesic therapeutic effects by inhibiting cyclooxygenases (COX), which are required for the synthesis of prostaglandins, thromboxanes, and prostacyclins [6].

Studies have been conducted associating the effects of specific classes of NSAIDs on physical performance. However, the results are conflicting due to the different protocols and measurement techniques. Although it is commonly accepted that NSAIDs could improve physical performance through decreased pain perception and increased pain tolerance [7,8], there is evidence that these drugs may also reduce the thermal challenge of exercise [9] and even attenuate central fatigue development [10,11]. On the other hand, it seems that

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these medications can also negatively influence exercise capacity by altering muscle metabolism in response to resistance training, leading to reduced protein synthesis and increased creatine kinase (CK) level [12–14]. Even though not being specific, CK is widely used as an injury marker as it provides a reliable assessment of muscle functional capacity [14].

All together, these disagreeing findings indicate that NSAIDs can interfere in key mechanisms related to physical performance, supporting that further analysis should be relevant to expand the perspective of the use of these drugs and provide useful guidance for the sporting community on safe prescription of NSAIDs, including their clinical use. Thus, this systematic review and meta-analysis was carried out in order to verify the interference of the use of NSAIDs by heathy individuals in physical performance and muscle strength and damage. The study tests the hypothesis that the use of NSAIDs increase physical performance and muscle strength, while decreasing muscle damage.

2. Methods

2.1. Search strategy

The protocol for this systematic review and meta-analysis was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42021240727). The systematic review and meta-analysis was conducted and reported according to the guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [15]. The systematic search was performed without language and date restriction in April 2023. The following electronic databases were used as sources: PubMed, Web of Science and SPORTDiscus. The search strategy used combinations of the following keywords: non-steroidal anti-inflammatory drugs OR paracetamol OR ibuprofen AND hypertrophy OR strength OR performance OR exercise OR satellite cells OR protein synthesis.

2.2. Study selection

After excluding duplicates, the decision to include or exclude studies was made by two independent investigators in the following steps: (I) the study title; (II) the study abstract; and (III) the complete study manuscript. Discrepant decisions were blindly resolved by a third investigator.

Eligible studies that met all the following criteria were included in this systematic review: (I) prospective design related to physical exercise performance, (II) use of NSAIDs regardless of its administration time during exercise practice, (III) human subjects, healthy and over 18 years old, (IV) only studies written in English. Animal studies, studies approaching minors or disease states reviews, abstracts and case studies were excluded from the analysis. The studies were divided according to the type of exercise or training into the following groups: 1 – resistance exercise, 2 – endurance exercise, and 3 – resistance training.

The outcome of interest for the current meta-analysis, based only on resistance exercises (group 1), was the possible interaction between resistance performance parameters and NSAID use. Thus, the variables analyzed after NSAID supplementation and exercise practice were: physical performance, strength and muscle damage. The three parameters were considered at times 0, 24 and 48 h after exercise.

Muscle damage is characterized by the presence of strength loss, soreness, and/or increase in blood CK level. CK was chosen as a marker of injury because of its common use and, in the case of strength, because of its ability to provide a reliable assessment of muscle functional capacity [14].

2.3. Data extraction

All data were extracted from the eligible studies by two independent investigators. Discrepant extractions were blindly resolved by a third investigator. The following characteristics were recorded: (I) first author, (II) year of publication, (III) sample size, (IV) method of NSAIDs administration, (V) exercise protocol, and (VI) analyzed variable results. The characteristics included on the tables of analysis were: characteristics of the subjects (sex, age), drugs used and their respective protocol, exercise protocol and variables included.

The extracted data were grouped according to the different time of drug use, and the type of exercise or training (resistance exercise, endurance exercise, and resistance training), and subsequently arranged based on the analyzed variables. Corresponding numerical values were extracted using the WebPlotDigitizer (version 4.3, Ankit Rohatgi) program for those studies whose results were not mathematical.

2.4. Risk of bias assessment

Two independent investigators assessed the risk of bias using an adapted Grading of Recommendations Assessment, Development and Evaluation (GRADE) instrument [16,17]. Discrepant reviews were blindly resolved by a third investigator. Using this approach, it was possible to evaluate the risk of bias in each study included in the present systematic review. Domains reflecting sequence generation, use of placebo, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other sources of bias were evaluated.

After the risk of bias evaluation, the quality of the articles was classified according to the number of negative responses as: high, moderate, low, and very low. Only moderate and high-quality articles were selected in the present study, aiming at the inclusion of robust and methodologically reliable studies.

2.5. Statistical analysis

The mean and standard deviation values of the performance indexes in both NSAID use and placebo trials were obtained from the data provided in the selected studies. Heterogeneity was evaluated using the χ^2 test for homogeneity and the I^2 statistic. The effect size (Cohen's d or Hedges' g) was calculated for the performance indexes in each study. Then, a weighted-mean estimate of the effect size was calculated to account for differences in the sample sizes. The mean unweighted effect size and associated 95% CI were also calculated. We used Cohen's

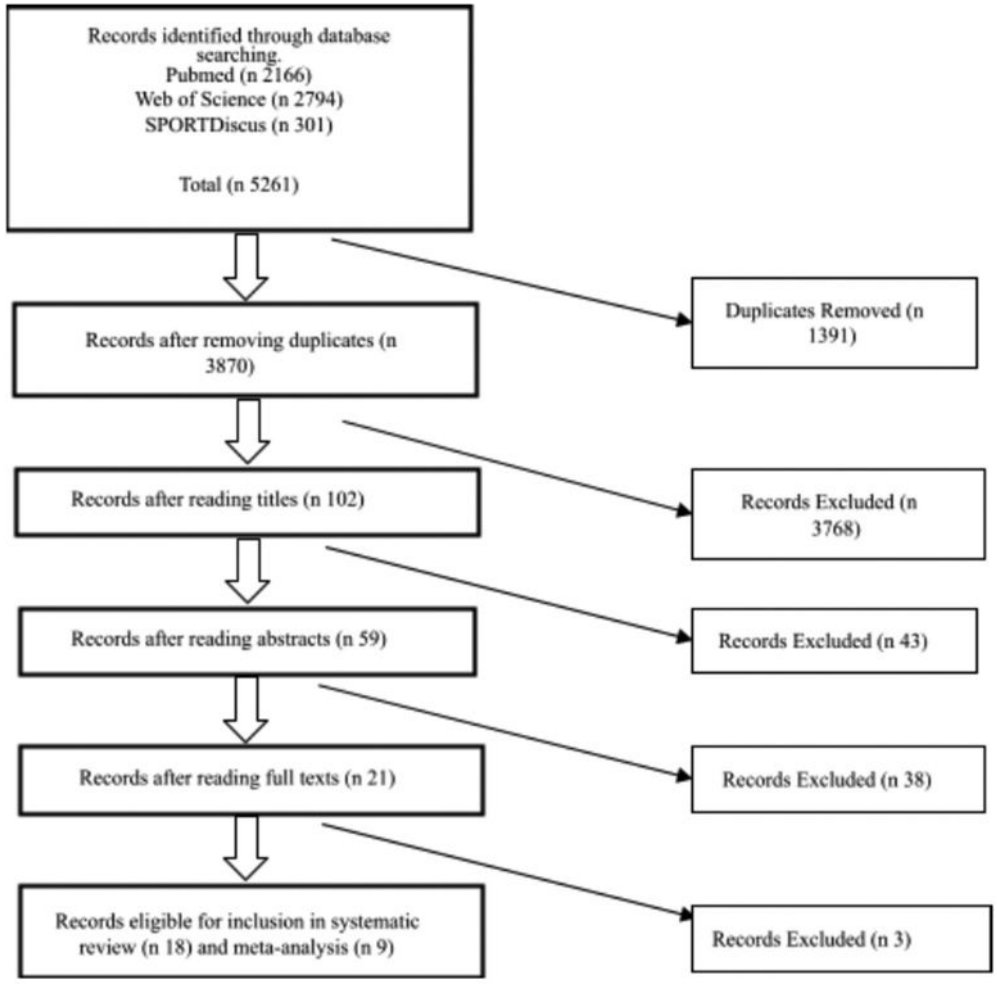

Figure 1. Summary of the study selection process, including the systematic review and meta-analysis.

classification of the effect size magnitude, where d < 0·20 for negligible effect; d = 0·20–0·49 for small effect; d = 0·50–0·79 for moderate effect; and d > 0·8 for large effect [18].

3. Results

3.1. Systematic review

A total of 5,261 studies were identified through the database and reference searches. After removing the duplicates and excluding papers that did not meet the eligibility criteria following a review of their titles, abstracts and full texts, 18 studies (188 trials, n = 238 individuals) were selected for inclusion in the systematic review (Figure 1). The characteristics of the subjects, the exercise/physical training protocols, the NSAID administration protocol, the number of individuals in each trial and study and the variables in each trial evaluated in each study are summarized in supplementary tables : 1 – resistance exercise, 2 – endurance exercise, and 3 – resistance training.

3.2. Meta-analysis

The meta-analysis was based only on resistance exercises. Nine studies (66 trials, n = 87 individuals) were included.

3.2.1. Post-exercise performance

After pooling the data from 17 trials (n = 59), the mean effect size was 0.01 (95% CI: −0.20 to 0.22), which indicates that NSAIDs have a non-significant effect on post-exercise performance ($p > 0.05$; Figure 2). According to a random effects analysis, no heterogeneity was observed among these studies ($I^2 = 17.7\%$; Q = 19.43, df = 16, $p = 0.25$).

3.2.2. 24 h post-exercise performance

After pooling the data from 6 trials (n = 27), the mean effect size was −0.08 (95% CI: −0,46 to 0.30), which indicates that NSAIDs have a non-significant effect on performance 24 h post-exercise ($p > 0.05$; Figure 2). According to a random effects analysis, no heterogeneity was observed among these studies ($I^2 = 0.0\%$; Q = 3.06, df = 5, $p = 0.69$).

3.2.3. 48 h post-exercise performance

After pooling the data from 8 trials (n = 37), the mean effect size was −0.42 (95% CI: −0.71 to −0.12), which indicates that NSAIDs induce a small and significant decrease on performance 48 h post-exercise ($p < 0.05$; Figure 2). According to a random effects analysis, no heterogeneity was observed among these studies ($I^2 = 37.3\%$; Q = 11.16, df = 7, $p = 0.13$).

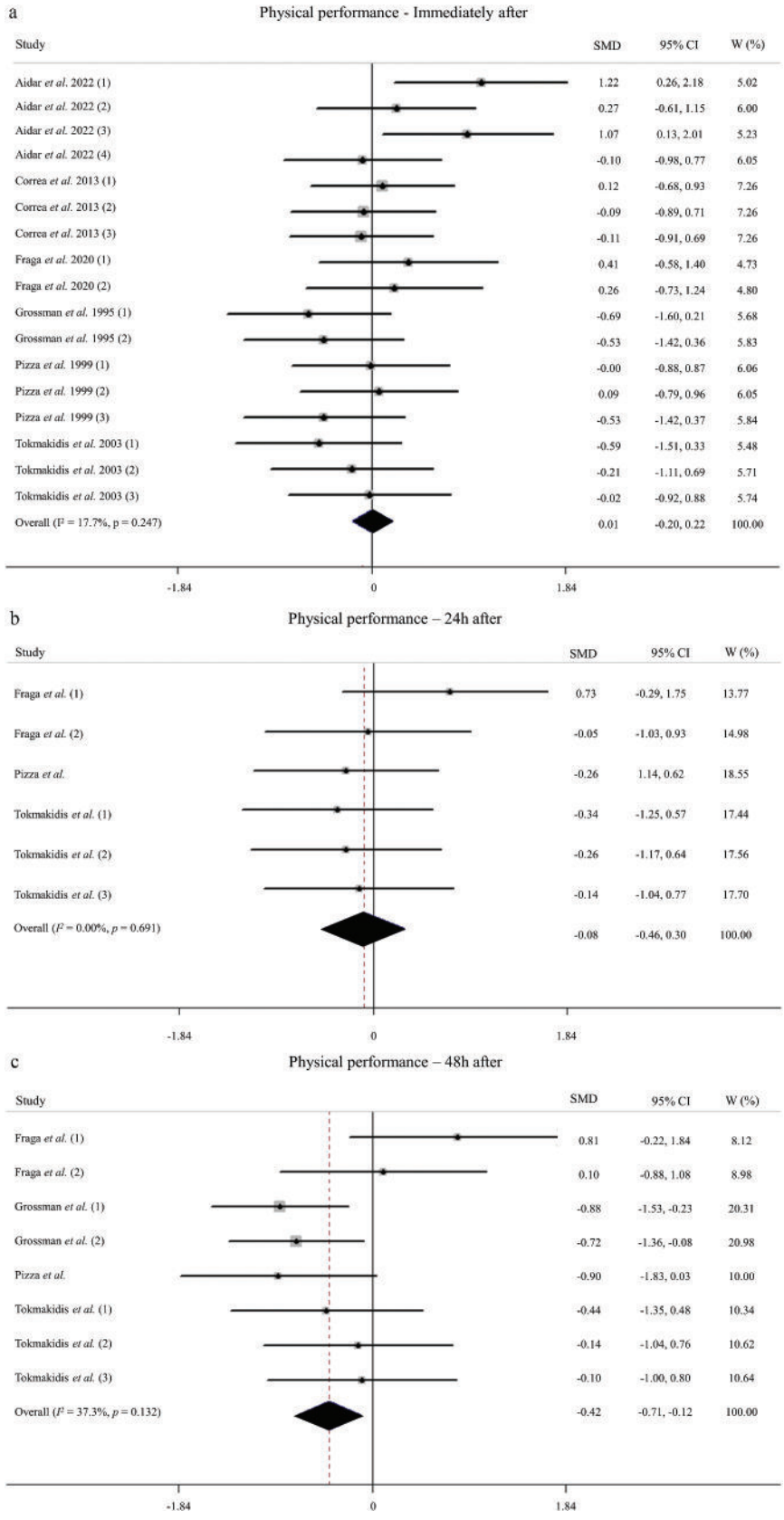

Figure 2. Post exercise performance meta-analysis' forest plot following NSAIDs ingestion. a- Post exercise performance forest plot. b-24hrs post exercise performance forest plot. c- 48hrs post exercise performance forest plot. SMD, standardized mean difference.

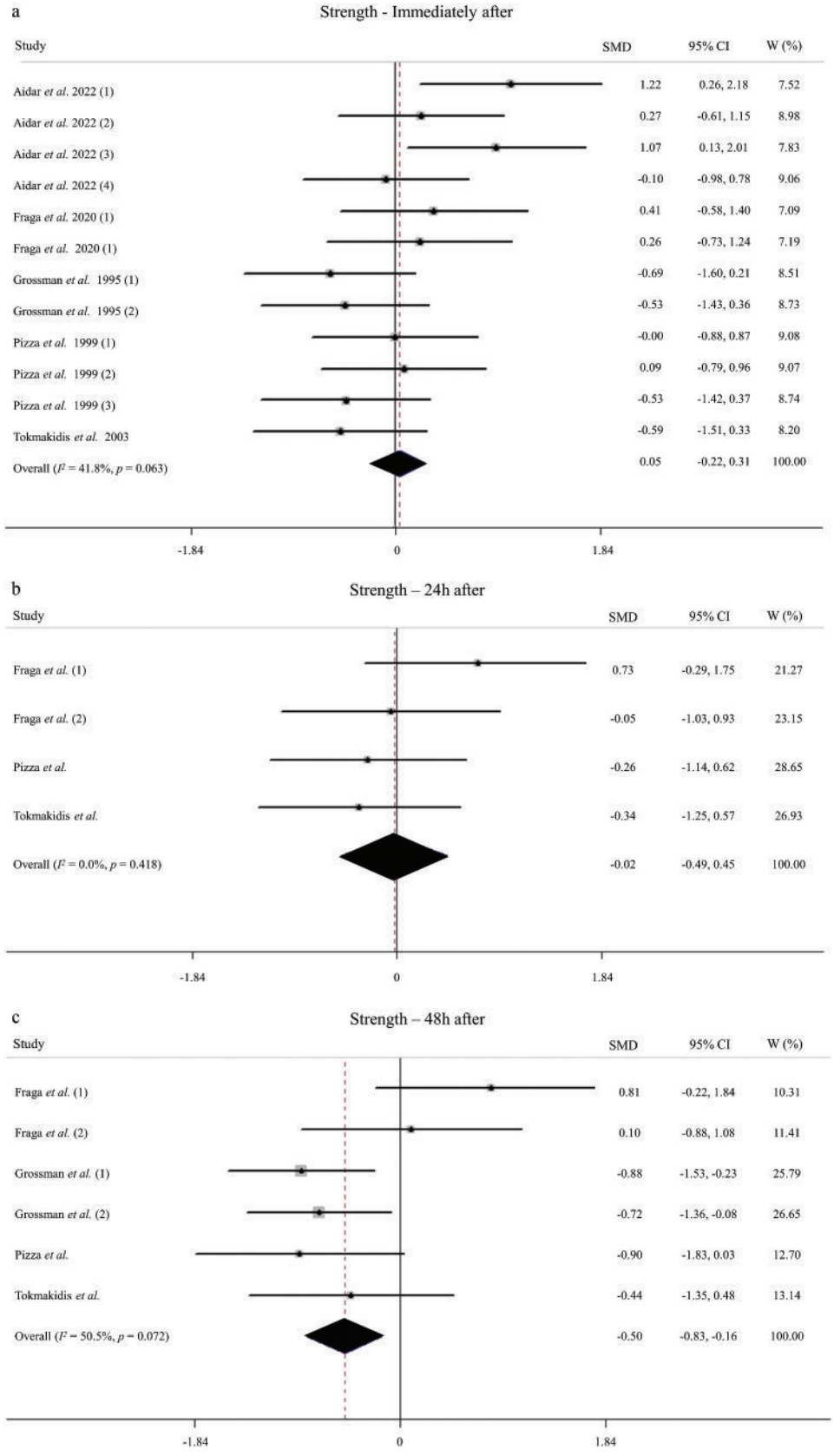

Figure 3. Post exercise strength meta-analysis' forest plot following NSAIDs ingestion. a- Post exercise strength forest plot. b-24hrs post exercise strength fofest plot. c- 48hrs post exercise strength forest plot. SMD, standardized mean difference.

3.2.4. Post exercise strength

After pooling the data from 12 trials ($n = 47$), the mean effect size was 0.05 (95% CI: −0.22 to 0.31), which indicates that NSAIDs have a non-significant effect on strength levels post-exercise ($p > 0.05$; Figure 3). According to a random effects analysis, heterogeneity was observed among these studies ($I^2 = 41.8\%$; Q = 19.43, df = 11, $p = 0.063$).

3.2.5. 24 h post-exercise strength

After pooling the data from 4 trials ($n = 27$), the mean effect size was −0.02 (95% CI: −0.49 to 0.45), which indicates that NSAIDs have a non-significant effect on strength 24 h post-exercise ($p > 0.05$; Figure 3). According to a random effects analysis, no heterogeneity was observed among these studies ($I^2 = 0.0\%$; Q = 2.84 df = 3, $p = 0.42$).

3.2.6. 48 h post-exercise strength

After pooling the data from 6 trials ($n = 37$), the mean effect size was −0.50 (95% CI: −0.83 to −0.17), which indicates that NSAIDs have a medium and significant effect on strength levels 48 h post-exercise ($p < 0.05$; Figure 3). According to a random effects analysis, no heterogeneity was observed among these studies ($I^2 = 50.5\%$; Q = 10.10, df = 5, $p = 0.07$).

3.2.7. Post-exercise CK

After pooling the data from 5 trials ($n = 36$), the mean effect size was 0.31 (95% CI: −0.12 to 0.75), which indicates that NSAIDs have a non-significant effect on CK levels post-exercise ($p > 0.05$; Figure 4). According to a random effects analysis, no heterogeneity was observed among these studies ($I^2 = 30.6\%$; Q = 5.76, df = 4, $p = 0.22$).

3.2.8. 24 h post-exercise CK

After pooling the data from 4 trials ($n = 37$), the mean effect size was −1.48 (95% CI: −3.02 to 0.07), which indicates that NSAIDs have a non-significant effect on CK levels 24 h post exercise ($p > 0.05$; Figure 4). According to a random effects analysis, heterogeneity was observed among these studies ($I^2 = 86.0\%$; Q = 21.49, df = 3, $p = 0.00$).

3.2.9. 48 h post-exercise CK

After pooling the data from 4 trials ($n = 39$), the mean effect size was −0.83 (95% CI: −1.68 to 0.019), which indicates that NSAIDs have a non-significant effect on CK levels 48 h post exercise ($p > 0.05$; Figure 4). According to a random effects analysis, heterogeneity was observed among these studies ($I^2 = 67.9\%$; Q = 9.34, df = 3, $p = 0.03$).

3.3. Risk of bias

The risk of bias was assessed in 18 studies in the systematic review. The studies selected in the present systematic review consistently controlled the risk of bias, and were therefore deemed moderate to high quality (Table 1).

4. Discussion

The present study was based on randomized controlled trials that evaluated the effects of NSAIDs on exercise performance in healthy individuals. Performance indices of resistance exercises were analyzed immediately, 24 and 48 h after resistance exercise practice. Despite the promising effects of NSAIDs on physical performance, the current evidences point to the direction that the use of NSAIDs is followed by a non-significant effect up to 24 h, in addition to decreased resistance performance after 48 h of exercise practice. Similarly, strength levels are unaffected by NSAIDs consumption up to 24 h, being this response reduced after 48 h of exercise practice. Simultaneously, CK levels are unchanged at all timetables. Thus, taking as whole, these results bring evidence that NSAIDs intake are ineffective in increasing resistance capacity and strength gain. Therefore, the potential benefits of using these medications in order to maximize performance and brawniness should be carefully considered by strength-training enthusiasts.

Agreeing with our work, a recent systematic review was also unable to conclude on the existence of an ergogenic effect of NSAIDs on sport performance indices since the evidence level of the included studies was low, and the doses tested and the exercises performed were very heterogeneous and far from those observed in real-life practices [36]. Based on such outcome, the current meta-analysis included only moderated and high-quality studies ranked in accordance with the GRADE instrument [37]. Moreover, different protocols and measurement techniques, such as type of exercise, use of placebo as control and half-life of the drug, were distinguished to eventually delineate consistent and applicable conclusions to the reality of sports practice. As such, the most widely prescribed and over-the-counter doses of NSAIDs were listed in the study. Moreover, their administration should have taken place during the course of the regular routine of resistance exercise practice. Trials were also gathered according to the moment at which a resistance assessment was conducted after regular strength exercise practice; i.e. 0, 24, and 48 h after exercise. This comparison approach was done with the view to focus on the effects of NSAIDs during a routine of resistance training, in addition to providing information about the duration of the drug's action.

The present analysis revealed no significant effect of NSAIDs on resistance-exercise performance immediately and 24 h after exercise practice. In turn, resistance-exercise performance was decreased 48 h after exercise practice. The effects of NSAIDs on exercise physiology are still conflicting, and there is no consensus that NSAIDs enhances athletic performance [36,38]. Nonetheless, it is well accepted that successful athletic performance relies also on the ability to tolerate pain, both induced by exercise and training or by musculoskeletal injuries [39]. Indeed, pain seems very much involved in limiting exercise performance and strength gain by reducing task engagement or work rate, which manifests themselves as an adjustment in the athlete's pacing strategy as a protective mechanism [40]. Thus, if pain restricts the maintenance of exercise, then any mechanism that may either reduce its levels or raise its tolerance may positively influence exercise performance by enabling an athlete to go above the normal

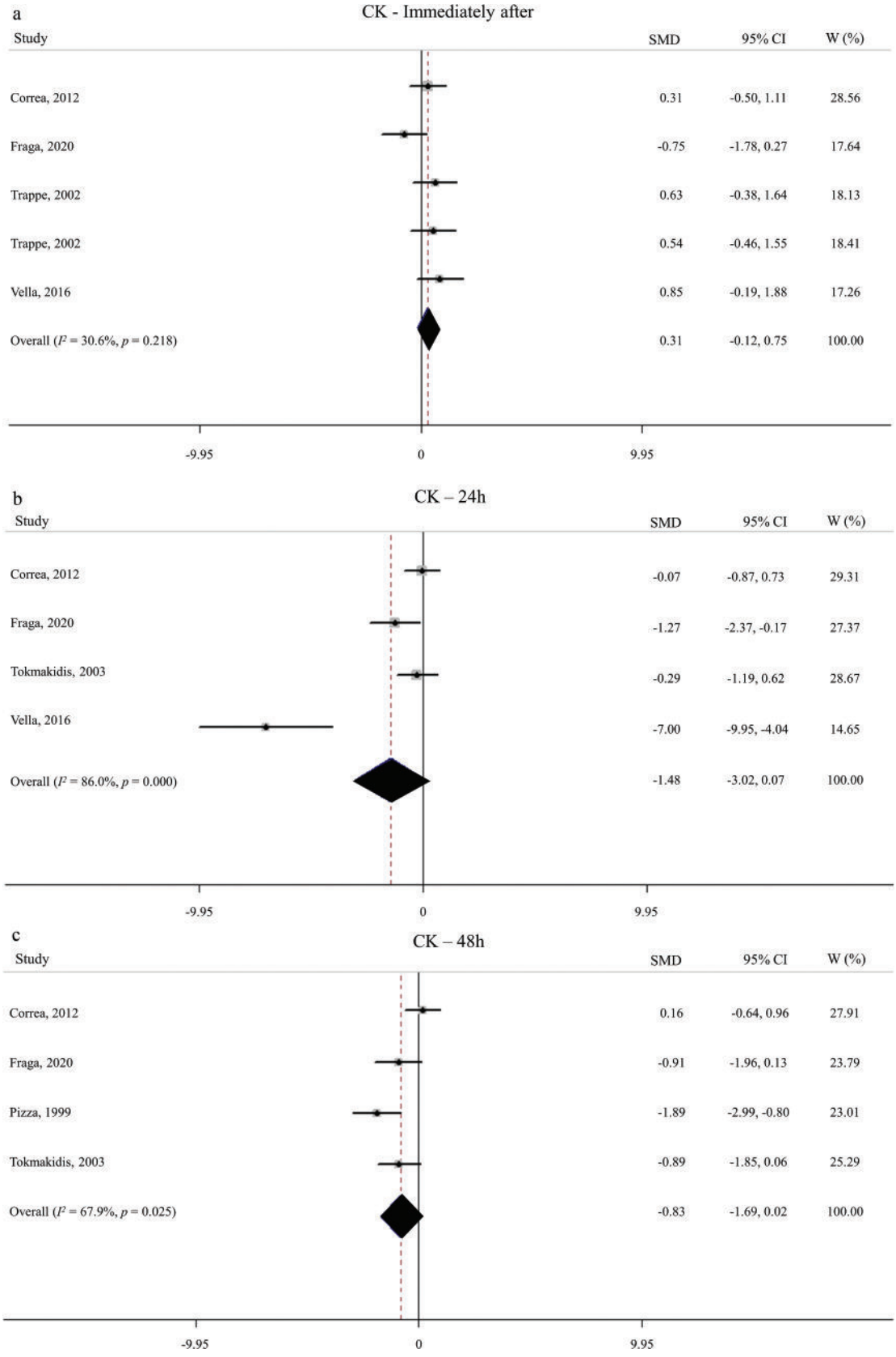

Figure 4. Post exercise CK meta-analysis' forest plot following NSAIDs ingestion. a- Post exercise CK forest plot. b-24hrs post exercise CK forest plot. c- 48hrs post exercise CK forest plot. SMD, standardized mean difference.

Table 1. Risk of bias assessment.

Reference	Absence of allocation secrecy	Absence of masking (blinding)	Incomplete follow-up	Selective reporting of outcomes	Other limitations	Quality
Aidar, 2022 [19]	No	No	No	No	No	High
Baldwin, 2001 [20]	No	Yes	No	No	No	Moderate
Candow, 2013 [21]	No	No	Yes	No	No	Moderate
Correa, 2012 [22]	No	No	No	No	No	Moderate
Correa, 2013 [23]	No	No	No	No	No	Moderate
Da Silva, 2015 [24]	No	No	No	No	No	High
De Souza, 2020 [25]	No	No	Yes	No	No	High
De Souza, 2022 [26]	No	Yes	No	No	No	Moderate
Donnely, 1990 [27]	No	No	Yes	No	No	High
Fraga, 2020 [28]	No	No	No	No	No	Moderate
Grossman, 1995 [29]	No	No	No	No	No	High
Holden, 1992 [30]	No	No	No	No	No	High
Pizza, 1999 [31]	Yes	No	No	No	No	High
Sayers, 2000 [32]	No	No	No	No	No	Moderate
Tokmakidis, 2003 [33]	No	No	Yes	No	No	Moderate
Trappe, *2002* [13];	No	No	No	No	No	High
Trappe, 2011 [34]	No	No	No	No	No	High
Vella, *2016* [35];	No	No	No	No	No	High

protective threshold [40,41]. Thereby, over-the-counter analgesics, such as NSAIDs, have been widely consumed by athletes and physically active individuals as a way to avoid pain and inflammation, which could limit the continuation and the upgrade of their regular athletic activities [2,7]. In opposition to such premise, the results demonstrated herein support that NSAIDs do not act as ergogenic aids in the case of resistance exercises. In the best-case scenario, due to their powerful analgesic and anti-inflammatory effects, these medications may avoid possible deleterious changes on resistance capacity up to 24 h after exercise practice.

The effect of NSAIDs was also pronounced in relation to muscle strength. Although such parameter was not affected by the use of the drugs immediately and after 24 h, it remained lower after 48 h of exercise practice. This response goes in agreement with recent reports that ibuprofen compromises resistance-exercise-induced muscle hypertrophy [12,38]. It is noteworthy that NSAIDs are drugs, which act on the inflammation cascade, mainly acting by inhibiting cyclooxygenases and, consequently, decreasing the production of inflammatory mediators, such as prostaglandins, prostacyclin, and thromboxanes [6]. Precisely by blocking cyclooxygenase, NSAIDs can alter the acute and chronic response to resistance training through impaired protein synthesis. Moreover, decreased prostaglandins have been associated with diminished protein synthesis and reduced type I and type II fiber size [13,42].

In front of the fact that past 48 h of exercise practice, both resistance-exercise performance and muscle strength were decreased under the influence of NSAIDs, and since there is no strong evidence to support claims that NSAIDs influence exercise recovery [36], other aspects that could limit exercise performance, such as recovery itself, should be taken into consideration. Adequate rest and recovery after exercise, so that the muscles can repair, rebuild, and strengthen, have proved crucial for better athletic performance [43,44]. Therefore, it is probable that the muscle overload induced by repetitive resistance exercise assessments, not followed by proper recovery, may have contributed to the reduced resistance performance and muscle strength seen after 48 hours of exercise practice.

The data demonstrated here support evidences that NSAIDs are ineffective in avoiding exercise-induced muscle wasting [13,42] since creatine kinase (CK) serum was unaffected by these analgesic drugs at all timetables. This response may be attributable to their inability to blunt muscle inflammatory cell concentrations after injurious exercise [42].

Since information about the applicability of NSAIDs on sports practice is constantly evolving, their administration should respond to precise criteria. Thus, diverging from previous reviews, the results reported here evidence that AINEs consumption does not affect resistance exercise performance, neither muscle gain in healthy individuals, and even induces a deleterious effect over these parameters. In other words, despite the benefits of analgesia and anti-inflammation, the use of NSAIDs as an ergogenic agent, prophylactically to prevent the pain inherent in the practice of physical activity, or to block the limiting discomfort of musculoskeletal injuries, is in practical terms pointless and should be reconsidered by resistance-trained athletes.

Some limitations of this study need to be clarified. Due to the heterogeneity of the studies, the current meta-analysis uses the standardized mean difference [37], which is a similar method of current NSAIDs literature review [36]. Nonetheless, the present study represents a different and stricter perspective of analysis. In addition, this review demonstrates that regardless of group, exercise or drug administration heterogeneity, the findings are fundamental to support NSAID studies, and therefore, their real effect among exercise practitioners. The results on resistance exercises and its relationship with NSAIDs are still scarce. Furthermore, there is a lack of standardization of the dosage of the drugs administered and the resistance exercise conducted. More studies should also be conducted to better assess the relationship between NSAID use and post-exercise serum CK levels due to the low number of participants in each study, as well as the small number of studies about the theme.

5. Conclusion

In conclusion, additionally to not improving resistance-exercise performance and muscle strength, NSAIDs negatively influence these parameters after 48 h of exercise practice. Therefore, this meta-analysis brings valuable information about the ineffectiveness of NSAIDs in improving resistance performance and muscle strength, and even the existence of a possible ergolytic effect of NSAIDs, which goes in the opposite direction to the benefit strength-training enthusiasts aim to receive by takings the analgesic drugs. From athletes, spreading to physically active or in rehabilitation individuals, NSAIDs have been taken indiscriminately to avoid pain and inflammation associated with training, competition, or musculoskeletal injuries, but also to gain a competitive advantage. However, when considering the practical application of using NSAIDs to improve exercise capacity and strength gains, the present data supports that consumption of analgesic drugs as an endurance performance enhancer or as a muscle anabolic must not be recommended. Thus, beyond the concerns about the potential adverse effects and the ethical issues, the current data call for awareness among athletes and others involved in sports performance and rehabilitation about the practical effectiveness of using NSAIDs as an ergogenic aid.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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