Effects of resistance training to muscle failure on acute fatigue

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Effects of Resistance Training until Muscle Failure on Fatigue: A Systematic Review and Meta-Analysis

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Abstract:

Background

The proper manipulation of resistance training (RT) variables is a key factor to reach maximum potential of neuromuscular adaptations. Among those variables, the option to perform RT to failure (TF) or not to failure (TNF) directly affect the magnitude of biomechanical properties, metabolic stress, muscle damage and the rating of perceived exertion (RPE). The sum of these results could interfere on the adaptative process and, consequently in long-term adaptations. Therefore, as this affects long-term adaptations, it is important to determine the exact difference between the TF and TNF.

Objective

The aim of the present study was to identify the summarized acute effect of TF on fatigue (biomechanical properties, metabolic response, muscle damage, and RPE).

Methods

A systematic search was performed in July 2020, in seven databases. Only studies with crossover designs that investigated the acute biomechanical properties (kinematic variables - vertical jump height and velocity of movement; and kinetic variables - power output, and isometric force), metabolic response (blood lactate and blood ammonia), muscle damage (blood creatine kinase [CK]), and RPE were selected. The outcomes were analyzed in the following time points: immediately post-exercise (all outcomes), 6h, 24h, and 48h post (biomechanical properties and muscle damage). In the analysis of muscle damage, we did not include 6h. Fixed or Random-effects meta-analysis were performed.

Results

Nineteen studies were included in the systematic review and twelve in the meta-analysis. The results showed greater loss of biomechanical properties for TF compared to TNF (SMD = -1.08 [-1.58; -0.57]; $p < 0.001$). Furthermore, there was larger increase in metabolic response (RMD = 5.54 mmol·L^{-1} [4.16; 6.92]; $p < 0.001$), muscle damage (RMD = 190.16 IU·L^{-1} [100.65; 279.66]; $p < 0.001$) and RPE (SMD = 2.47 [1.25; 3.68]; $p < 0.001$) for TF compared to TNF. Subgroup analyses showed that training status ($p = 0.668$), time point ($p = 0.984$) and load ($p = 0.131$) did not affect biomechanical properties. However, greater loss occurred on upper limbs velocity of movement test (SMD = -2.47 [-3.35; -2.13]; $p < 0.001$). Blood ammonia concentration was higher in TF than TNF (RMD = 42.17 µmol·L^{-1} [34.67; 49.67]; $p < 0.001$) and only after 48h the blood CK levels were higher in TF than TNF (RMD = 208.51 IU·L^{-1} [42.88; 374.15]; $p = 0.014$).

Conclusions

TF caused a higher fatigue considering the decline on biomechanical properties, and an increase in metabolic response, muscle damage and RPE. Furthermore, we observed slower neuromuscular recovery on TF compared to TNF. Those differences highlight the importance of an adequate RT prescription specially when TF is applied.

Protocol Registration

The original protocol was prospectively registered (CRD42020192336) in the International Prospective Register of Systematic Review (PROSPERO).

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Dear Steve McMillan, Ph.D. / Roger Olney, Ph.D.

We are submitting a study entitled: "Effects of Resistance Training until Muscle Failure on Fatigue: A Systematic Review and Meta-Analysis" for consideration by Sports Medicine.

In this systematic review and meta-analysis, we show that resistance training performed to failure causes substantially higher fatigue compared to resistance training not performed to failure. We observed that upper limbs exercises lead to higher declines on velocity of movement after resistance training performed to failure than not performed to failure. These results are more interesting because we explored different subgroup analyses such as, training status, time point, and load. This study is in accordance with the scope of Sports Medicine. All authors approved the submission of the study to the Sports Medicine and declare no conflict of interest. We also declare that the study has not been published or submitted for publication elsewhere.

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Thank you for your consideration of this manuscript.

Best regards BSc João Guilherme Vieira

Title: Effects of Resistance Training until Muscle Failure on Fatigue: A Systematic Review and Meta-Analysis

Running heading: Resistance Training to Muscle Failure and Fatigue

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(ii) Conflict of interest – João Guilherme Vieira, Amanda Veiga Sardeli, Marcelo Ricardo Dias, José Elias Filho, Yuri de Almeida Campos, Leandro de Oliveira Sant'Ana, Luis Leitão, Victor Machado Reis, Jefferson da Silva Novaes, Jeferson Macedo Vianna declare that they have no conflicts of interest relevant to the content of this systematic review and meta-analysis.

(iii) Availability of data and material – the database that supports the conclusions of this systematic review is available from the corresponding author on request.

(iv) Ethics approval – not applicable.

(v) Consent – not applicable.

(vi) Author contributions – João Guilherme Vieira, Amanda Veiga Sardeli, Marcelo Ricardo Dias, Jefferson Novaes, and Jeferson Vianna designed the manuscript. João Guilherme Vieira wrote the draft of the manuscript. João Guilherme Vieira and Marcelo Ricardo Dias conducted the literature search. João Guilherme Vieira and Marcelo Ricardo Dias wrote the methods, results, and tables/figures of the manuscript. Amanda Veiga Sardeli conducted the meta-analysis of the manuscript. João Guilherme Vieira and José Elias Filho reviewed the methods and helped in choosing the tool to assess the quality of the articles used in this systematic review. Amanda Veiga Sardeli, José Elias Filho, Jefferson Novaes, and Jeferson Vianna systematically guided João Guilherme Vieira during the article writing process. Yuri Campos, Leandro Sant'Ana, Luis Leitão, Victor Reis, and Michal Wilk, reviewed the manuscript and the English language and contributed technically to the quality of the manuscript. All authors read and approved the final manuscript.

Abstract

Background: The proper manipulation of resistance training (RT) variables is a key factor to reach maximum potential of neuromuscular adaptations. Among those variables, the option to perform RT to failure (TF) or not to failure (TNF) directly affect the magnitude of biomechanical properties, metabolic stress, muscle damage and the rating of perceived exertion (RPE). The sum of these results could interfere on the adaptative process and, consequently in long-term adaptations. Therefore, as this affects long-term adaptations, it is important to determine the exact difference between the TF and TNF.

Objective: The aim of the present study was to identify the summarized acute effect of TF on fatigue (biomechanical properties, metabolic response, muscle damage, and RPE).

Methods: A systematic search was performed in July 2020, in seven databases. Only studies with crossover designs that investigated the acute biomechanical properties (kinematic variables - vertical jump height and velocity of movement; and kinetic variables - power output, and isometric force), metabolic response (blood lactate and blood ammonia), muscle damage (blood creatine kinase [CK]), and RPE were selected. The outcomes were analyzed in the following time points: immediately post-exercise (all outcomes), 6h, 24h, and 48h post (biomechanical properties and muscle damage). In the analysis of muscle damage, we did not include 6h. Fixed or Random-effects meta-analysis were performed.

Results: Nineteen studies were included in the systematic review and twelve in the meta-analysis. The results showed greater loss of biomechanical properties for TF compared to TNF (SMD = -1.08 [-1.58; -0.57]; $p < 0.001$). Furthermore, there was larger increase in metabolic response (RMD = 5.54 mmol·L^{-1} [4.16; 6.92]; $p < 0.001$), muscle damage (RMD = 190.16 IU·L^{-1} [100.65; 279.66]; $p < 0.001$) and RPE (SMD = 2.47 [1.25; 3.68]; $p < 0.001$) for TF compared to TNF. Subgroup analyses showed that training status ($p = 0.668$), time point ($p = 0.984$) and load ($p = 0.131$) did not affect biomechanical properties. However, greater loss occurred on upper limbs velocity of movement test (SMD = -2.47 [-3.35; -2.13]; $p < 0.001$). Blood ammonia concentration was higher in TF than TNF (RMD = 42.17 µmol·L^{-1} [34.67; 49.67]; $p < 0.001$) and only after 48h the blood CK levels were higher in TF than TNF (RMD = 208.51 IU·L^{-1} [42.88; 374.15]; $p = 0.014$).

Conclusions: TF caused a higher fatigue considering the decline on biomechanical properties, and an increase in metabolic response, muscle damage and RPE. Furthermore, we observed slower neuromuscular recovery on TF compared to TNF. Those differences highlight the importance of an adequate RT prescription specially when TF is applied.

Protocol Registration: The original protocol was prospectively registered (CRD42020192336) in the International Prospective Register of Systematic Review (PROSPERO).

Key points:

- Resistance training performed to failure leads to a greater decline on kinematic and kinetic variables, as well as a higher metabolic response and higher rating of perceived exertion compared to resistance training not performed to failure.
- Upper limbs exercises lead to higher declines on velocity of movement after resistance training performed to failure than not performed to failure.
- The muscle damage is more pronounced on resistance training performed to failure compared to not performed to failure, mainly 48h after the end of the training session.

1 Introduction

Resistance training (RT) is traditionally used by athletes and non-athletes to increase force, power output, velocity of movement, strength-endurance, balance, coordination, muscle hypertrophy which can increase sports and the daily life activities performance [1]. The RT prescription can be systematically altered by manipulation of training variables, such as, muscle action, external load used, number of performed repetitions, sets, rest interval, velocity of movement, type and sequence of exercises, and frequency of training [2]. The proper manipulation of those variables can induce neuromuscular adaptations [3]. Although the majority of variables have been explored in scientific literature, there are some doubts and controverse considering the optimal number of repetitions to be performed in each set in relation to the maximal number that could be performed [4]. The resistance exercise performed to momentary failure can be defined as the moment in which the individual tries to perform the repetition but is not capable to complete the concentric phase of the movement maintain a correct technic [5].

It is reasonable to hypothesize that exertion with RT performed to failure (TF) is substantially higher compared with RT not performed to failure (TNF), considering the number of repetitions performed in TF is the maximum that the individual is capable to accomplish [6-12]. The higher effort during TF may require the recruitment of motor units with higher excitability threshold [13, 14], leading to higher increases in strength and muscle cross-sectional area [15, 16]. The known increase of muscle strength and mass lead TF to be widely used; however, is suggested that TF should be used for four weeks in a periodization [17], because TF increases training strain (product of the mean weekly rating of perceived exertion (RPE) and the training monotony score for the week) [18], which may potentially contribute to poor fatigue management and overtraining [19]. Thus, the assessment of fatigue caused by this type of protocol become extremely relevant.

The high level of exertion required during TF, limits the movement execution through different factors, such as muscle fatigue, general fatigue, pain, breath/pulse, and negative affect [20]. Physiologically, TF breaks cellular homeostasis by depleting phosphocreatine storages, significantly reduced adenosine triphosphate and the total muscle adenine nucleotides *pool* [21], which contributes to tissue damage [22] and increase the acute markers of fatigue [21, 23-

26]. The muscle fatigue is a complex multifactorial phenomenon that depend on task, and its etiology is controversial and the cause of intense debates [27, 28]. However, fatigue limits the strength capacity and the sarcomere shortening velocity [22, 29-33], leading to higher impairment of neuromuscular functions. In this way, numerous studies have reported reduction in power output [7, 11, 25], vertical jump height, velocity of movement [22, 32] and isometric force [10, 34], after TF compared to TNF.

Reductions in performance and increased metabolic response (i.e., increase in blood lactate and ammonia concentrations) are both strongly dependent of different factors. Linnamo et al. [34, 35] noticed that women during TF had lower blood lactate concentration and different levels of force in the maximum voluntary isometric contraction test compared to men. McLester, Bishop [36] reported that younger men undergoing TF had improved recovery capacity compared to older men. Thus, based on previous studies [35, 36], we noticed that there is interindividual variability among different fatigue markers, considering factors such as age and sex. Consequently, understand the differences between protocols TF and TNF, would improve the training load control, since the increase in training stress may impair neuromuscular adaptations [18].

Thus, considering all these controversial results, the aim of the present study was to identify the summarized acute effect of TF on fatigue (biomechanical properties, metabolic response, muscle damage, and RPE) by analyzing previous literature. Furthermore, we aim to investigate how the characteristics of individuals, protocols, and methods of assessments of the different outcomes are mediating the different results. We hypothesized that TF would cause a higher decline on biomechanical properties, while TNF would cause lower increase in metabolic response, muscle damage, and RPE. The results of the present meta-analysis will allow coaches and physical trainers to understand TF and improve training prescription regarding its safety and efficiency.

2 Methods

A systematic review of the literature was performed according to the Cochrane Handbook for Systematic Reviews of Interventions (version 6.1.0) [37] and following the checklist for the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [38].

2.1 Protocol and registration

The original protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) on July 18, 2020 (Registration number: CRD42019138954).

2.2 Eligibility criteria

The five PICOS criteria [39] were: (1) a population of healthy men between 18 and 40 years old, trained or untrained in RT, without history of bone, muscle or articular injury; (2) RT sessions intervention performed until failure; (3) compared to RT sessions performed without maximum effort with sub maximum load; (4) assessing as outcomes biomechanical properties (kinematic variables - vertical jump height, velocity of movement; and kinetic variables - power output (mean and peak) and isometric force), metabolic response (blood lactate and blood ammonia), muscle damage (blood creatine kinase [CK]) and RPE variables; (5) with randomized controlled designs, counterbalanced crossover or repeated measure designs for TF and TNF.

We included as TF studies naming their RT protocols as concentric muscle failure, maximum repetitions, maximum number of repetitions, and maximum effort with no repetition in reserve. For TNF, the absence of these terms indicated the absence of TF.

2.3 Selection criteria

The inclusion criteria adopted to study selection were: (1) original studies; (2) RT-based intervention; (3) studies assessing at least one of the outcomes of interest. Exclusion criteria were: (1) duplicated studies; (2) studies not written in English language; (3) non-RT-based training protocols; (4) studies combining RT to other types of training (aerobic, flexibility, etc..); and (5) studies involving special populations (hypertensive, diabetics, obese, elderly, children, people with low back pain, coronary patients, osteoarthritic patients, and pregnant).

2.4 Information sources

The studies were retrieved from electronic database search and from a comprehensive sweeping in the reference list of the included studies. A highly sensitive search was conducted in July 2020 in the following databases: Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Library, Embase®, PubMed®, Scopus, SPORTDiscus, and Web of Science.

2.5 Search strategy

A pilot search and a previous study [40] supported the selection of the adequate descriptors for the search strategy. The search strategy combined the descriptors using the Booleans operators (AND/OR/NOT) in the following way: (“resistance training” OR “resistance exercise” OR “strength training” OR “strength exercise” OR “weight training” OR “weight exercise” OR “weightlifting” OR “weight-lifting” OR “weight lifting”) AND (“repetition failure” OR “repetition to failure” OR “repetitions to failure” OR “muscle failure” OR “muscular failure” OR “momentary failure” OR “failure” OR “failure training” OR “nonfailure” OR “non-failure” OR “not to failure” OR “volitional interruption”) NOT (“review” OR “blood flow restriction” OR “heart failure” OR “supplement” OR “obesity”).

2.6 Study selection

The studies retrieved in each database was clustered using the EndNote X9 software (Clarivate Analytics, Philadelphia, USA), and the duplicate studies were automatically and manually removed. The titles and abstracts were assessed according to the eligibility criteria by two independent researchers (JGV e MRD). The conflicts were decided by a third reviewer (JEF). The researchers were not blinded for authors, institutions, or journals. The abstract not offering enough information to be evaluated were send to the next phase, in which the full-text were read. When some information was absent or incomplete the authors were contacted by e-mail.

2.7 Data collection process

Two independent reviewers (JGV e MRD) extracted the data from the full-text, using a standardized and previously structured protocol. The data collected covered the characteristics of participants (age, height, body mass and training experience) and training protocols (study design, exercises, prescription, velocity of movement, volume, and outcomes). When the values of required data were not presented numerically, the software WebPlotDigitizer, version 4.2 (San Francisco, California, USA) was used to extract data from graphs (JGV). After the extraction, the data extracted by both reviewers were compared and the divergences were decided by both and a third reviewer (JV).

2.8 Risk of bias in the primary studies

After the literature search and selection, risk of bias assessment was performed independently by two authors (JGV and JEF) using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials [41]. Selection bias (random sequence generation and allocation concealment), Performance bias (blinding of participants and researchers), Detection bias (blinding of outcome assessment), Attrition bias (incomplete outcome data), Reporting bias (selective reporting), and Other bias (anything else, ideally prespecified) were evaluated. Some other biases, such as Equipment bias, Effort bias, and Familiarization bias, were considered in the analysis of Other bias [42]. Equipment bias was the absence of appropriateness and reliability of the equipment used in the assessment of a determined outcome. Effort bias was the absence of a declaration of authors that all participants were encouraged to execute the concentric phase of movement in the most explosive way possible, when velocity of movement was not a controlled. Finally, the familiarization bias was when participants did not have an adequate familiarization with the protocols in a determined study. These factors may in some way affect biomechanical properties, metabolic response, muscle damage, and RPE.

2.9 Statistical analysis

The meta-analysis were performed at the Comprehensive Meta-Analysis (CMA) software, version 3.3.070 (Biostat Inc., Englewood, New Jersey, USA) [43], with the level of significance set at $p < 0.05$. We performed four main meta-analysis, one for each outcome (biomechanical properties, metabolic response, muscle damage, and RPE). The effect size (ES) was calculated based on the difference of variations (pre-post) between the TF and the TNF (A), or difference of post exercise assessments between TF and the TNF (B), when the studies did not show pre values. Biomechanical properties and metabolic response were analyzed based on A and B design, while muscle damage was analyzed based on only A designs and RPE was analyzed only based on B design. When the variables were presented in the same unit in all studies, we calculated the raw/absolute effect (metabolic response and muscle damage). However, when the variables were not presented in the same unit in all studies, we calculated the standardized effect by the standard deviation (biomechanical properties and RPE). When there was significant heterogeneity ($p < 0.05$), we calculated the randomized effect (metabolic response and RPE) and when there was no significant heterogeneity ($p < 0.05$) we used fixed effects (biomechanical properties and muscle damage) [44]. The magnitude of the ES was classified as: small (0.20–0.49), moderate (0.50–0.79) and large (> 0.80) based on Cohen guidelines [45]. The heterogeneity between the studies was quantified through the I^2 statistic. The result of this test indicates the percentage of heterogeneity found. Results with up to 25% are considered to be of low heterogeneity, about 50% moderate and above 75% high heterogeneity [46]. Publication bias was analyzed by the Egger test and a *p*-value 5% ($p < 0.05$) was considered significant [47]. To avoid sample overlapping in the analysis we selected just one sample of each study. For studies that had more than one biomechanical variables of interest, we selected for the main analysis the countermovement jump [48]. In addition, we selected the load of 75% 1RM or 10RM, a decision that incorporated only studies that had more than one intervention with different loads, since studies with only one intervention used this load [10, 22, 31, 35]. The time point selected for each main analysis involved some aspects, such as being present in all studies (biomechanical properties) [4, 10, 11, 22, 31, 32, 35], the main time point of interest for the study (metabolic response and muscle damage) [4, 10, 12, 22, 23, 25, 31, 32, 35]. Nevertheless, due to methodological differences between studies and to identify the effects of these differences on the overall fatigue markers, following main analyses we also performed subgroup analyses. For subgroup analyses, we tested the effect of time point (immediately post-exercise, 6h, 24h and 48h post). Regarding the analysis of muscle damage we did not include 6h, reported in one study [22], due to the fact that CK increases ~100% within 8h after RT, with peak levels observed between 24 and 96h after the initial exercise [49]. In addition to the time point, we tested the effect of more subgroups for biomechanical properties, such as training status (trained and untrained), test performed (countermovement jump [CMJ], maximal voluntary isometric contraction [MVIC], Velocity of movement against V_1-load for bench press [velocity BP], and Velocity of movement against V_1-load for squat [velocity SQ]), and load (70, 75, 80, 85, 90% 1RM). Finally, for the metabolic response we tested the effect of ammonia. The Q-test was used to identify differences between categories of subgroups, considered significant when the p was < 0.05.

2.10 Quality of the evidence

The quality of the evidence was assessed trough the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [50]. GRADE approach suggests the classification of randomized controlled trials initially as high-quality studies (score 4), that goes through specific risk of bias assessments to identify whether their scores need to be reduced to moderate, low or very low. The following topics were assessed: 1) quality of the original studies; 2) inconsistency of the results (heterogeneity); 3) indirect evidence; 4) imprecision; and 5) publication bias. One point was removed from the quality of the original studies when 50% of the studies in a determined meta-analysis had > 1 item assessed as high risk [42]. For inconsistency we remove a point if statistical heterogeneity was found [42]. The risk of indirect evidence was assessed considering three factors: 1) when the participants differed from the population of interest; 2) when the interventions differed from the specific desired intervention; and 3) when substitute outcomes were used instead of the relevant ones. The imprecision was assessed based on total sample size < 100 participants [42].

3 Results

3.1 Study selection

The flow diagram of the literature search is presented in Figure 1. The database search generated a total of 4144 studies, in which 19 were included in the systematic review and 12 in the meta-analysis.

###Insert Figure 1###

3.2 Study characteristics

Among the 203 participants included in the analysis, 39 (18.93%) were overlapped in different studies [21, 24, 29, 30, 34]. Thus, to avoid sample overlapping the data of only 167 participants was analyzed, in which 112 (67.06%) were trained and 55 (32.93%) untrained. One study (0.59%) did not clearly report the training status of its participants and was excluded from this specific subgroup analysis [23]. Three studies included participants within 2 to 4 years of RT experience [29, 30, 32] and in other three studies, participants with at least one year of experience were recruited [8, 11, 12]. Two studies included participants with more than 3 years of RT experience [4, 22]. Furthermore, one study recruited participants with more than six months of experience [10] and other study recruited participants with more than 3 weeks of experience [6]. It is noteworthy that one study included participants with two years of experience in squat exercise only [7]. In studies with untrained individuals, three of them recruited participants physically active [34, 35, 51] and other three recruited recreational endurance athletes [21, 24, 25]. Finally, one of them recruited participants with untrained status and applied experimental sessions before and after a period of 10 weeks systemized RT intervention [31]. The characteristics of participants are detailed in the Table 1.

###Insert Table 1###

All the studies included followed a cross-over design with a washout period (range: 2-60 days) between the interventional sessions. While 10 studies compared one TF protocol with one TNF protocol [6, 10, 11, 21, 23-25, 29, 30, 35] other nine studies compared one or more TF protocol with one or more TNF protocol [4, 7, 8, 12, 22, 31, 32, 34, 51]. The multiarticular exercises were more common among exercise protocols, especially when the sessions included only one or two exercises: nevertheless, monoarticular exercises were also applied in other protocols. The studies applied the smith machine or other equipment. The load applied in the protocols was ≥ 70% 1RM (range: 70-90%); however, a few studies prescribed the training based on maximum number of repetitions [4, 11, 21, 23-25, 34, 35, 51]. The training volume was not equalized in 14 studies [4, 6-8, 12, 23, 24, 29-32, 34, 35, 51]. A more detailed description of the included studies can be found in Table 2.

###Insert Table 2###

3.3 Risk of bias in the primary studies

Only one study reported the use of random sequence generation [11]. All studies were classified as unclear risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and selective reporting, since there was not enough information for this judgment. All studies had low risk of bias for incomplete outcome data. Six studies had high risk of bias for other bias, such as the equipment bias for two studies [7, 51], effort bias in four studies [6, 11, 23, 51] and familiarization bias in two studies [10, 23]. The Figure 2 shows the individual results of each study and the percentage distribution of risk of bias.

###Insert Figure 2###

3.4 Main outcomes

The main results showed that the decline in biomechanical properties was higher for TF compared to TNF (SMD = -1.08 [-1.58, -0.57]; $p < 0.001$) (Figure 3A). Subgroup analysis showed the training status ($p = 0.668$), time point ($p = 0.984$), and load ($p = 0.131$) did not affect different biomechanical properties between TF and TNF. The higher loss with TF compared to TNF occurred within the Velocity BP test (SMD = -2.47 [-3.35, -2.13]; $p < 0.001$). Regarding the time-course of the results, TF led to significant reduction in biomechanical properties immediately, 6h, 24h and 48h after the training session compared to TNF.

###Insert Figure 3###

The results showed that lactate (RMD = 5.54 mmol·L^{-1} [4.16, 6.92]; p < 0.001) (Figure 3B) and ammonia concentration (RMD = 42.17 mmol·L^{-1} [34.67; 49.67]; p < 0.001) were significantly higher in TF compared to TNF. The CK, a muscle damage marker, increased significantly more in TF compared to TNF (RMD = 190.16 IU·L^{-1} [100.65, 279.66]; p < 0.001) (Figure 3C). However, subgroup analysis showed that only after 48h the CK levels were higher in TF (RMD = 208.51 IU·L^{-1} [42.88, 374.15]; p = 0.014). Finally, RPE was significantly higher in TF than TNF (SMD = 2.47 [1.25, 3.68]; p < 0.001) (Figure 3D). The results of all subgroup analysis, including time points for each variable, are presented in Table 3. Figure 4 graphically shows the result according to time for all outcomes.

###Insert Table 3###

###Insert Figure 4###

3.5 Publication bias and quality of the evidence

Egger tests showed no significant risk of publication bias in the main meta-analysis of metabolic response (p = 0.104) and muscle damage (p = 0.269). However, significant risk publication bias were found for the of biomechanical properties (p = 0.003) and RPE (p = 0.001). Table 4 shows the quality of evidence (GRADE) details, in which there was low quality of the evidence for biomechanical properties and metabolic response, moderate quality of evidence for muscle damage and very low for RPE (Table 4).

###Insert Table 4###

4 Discussion

The present study aimed to find the summarized difference between TF and TNF regarding biomechanical properties, metabolic response, muscle damage and RPE. Among the main findings there was significant loss of kinematic and kinetic variables and higher increase in blood lactate, muscle damage and RPE following TF than TNF. Furthermore, the higher reduction was seen when velocity BP test were applied and a higher increase in the ammonia with TF compared to TNF. There was no other significant difference among the other subgroup's categories tested.

4.1 Biomechanical properties

There was large reduction of biomechanical properties with TF (SMD = -1.08 [-1.58, -0.57]), in a low quality analysis (GRADE score = 2). Perhaps, the different time under tension would explain the higher neuromuscular impairment with TF. The time under tension is an indicator of effort and amounts to the total sum of the concentric, eccentric, and isometric components of a repetition and refers to the period in which the muscle undergo an external load action during the sets, by dynamic or isometric contractions [52]. Although, none of the studies included in this meta-analysis equalized the time under tension or at least reported that they did it [4, 10, 11, 22, 31, 32, 35], the higher number of repetitions performed, mainly the higher number of concentric movements in TF have been determinant factors to increase the muscle fatigue [53-56].

A prolonged time under tension associated with the resistance exercise performed for muscle failure causes a significant increase in the blood lactate and ammonia, which is associated with peripheral mechanisms of fatigue [21, 24, 25]. In general, the increase in concentration of metabolic markers lead to a reduction in performance, because it indicates a considerable use of lactic glycolysis as a source of energy, that is likely associated to reduced intramuscular ATP and compromises strength, velocity of movement, and power output of sarcomeres contraction [21, 24-26, 57]. A complex interaction between central (e.g., reduced motor drive) and peripheral (e.g., accumulation of H^+ ions in the muscle) mechanisms of the fatigue with TF influence the muscle system potential to perform work [58-60].

It is noteworthy that no difference between the subgroup categories were found among biomechanical properties, except for the different tests performed (CMJ, MVIC, velocity BP, and velocity SQ), because a considerable decline in performance (SMD: -2.74; [-3.35, -2.13] $p < 0.001$) was found in the Velocity BP test [4, 22, 31, 32]. Other interesting aspect was that only Velocity BP tests were performed in upper limbs. The differences in the muscle size of upper and lower limbs likely explain the higher decline in velocity of movement in the upper limbs [61]. The quadriceps femoris (1,417.4 ± 440.8 cm^3) and the gluteus maximus (764.1 ± 138.0 cm^3), the more active muscles in the Velocity SQ [4, 22, 31, 32] are considerable bigger than deltoid (380.5 ± 157.5 cm^3), triceps brachii (371.1 ± 177.3 cm^3) and pectoralis major (290.0 ± 169.0 cm^3) which are the muscles activated in Velocity BP [4, 22, 31, 32].

Despite no significant differences have been found among the different time points analyzed ($p = 0.984$), the TF showed higher decline in biomechanical properties within the time points until 48h after training session (SMD: -1.00) compared to TNF. The velocity of movement and the vertical jump height was recovered within 6h following TNF, however, the kinematic variables were not totally restored 48h after TF [29]. It seems that at 48h post-exercise, the high volume protocols until muscle failure (12, 10, and 8 repetitions) are notably the ones which are more affected regarding muscle performance [32], since, the lower the number of repetitions in reserve, the higher the decline in biomechanical properties [4]. The lower rate of recovery can be explained by the higher muscle tissue damage caused by TF [12, 22, 31, 32], lower heart rate variability [29, 30] or even the higher time needed to the restoration of the muscle adenine nucleotides pool [62].

4.2 Metabolic response

There was a large increase in the metabolic response to TF compared with TNF (RMD: 5.54 mmol·L^{-1} [4.16, 6.92]), specifically on lactate concentration, with a low quality of evidence (GRADE score 2). The increased levels of blood lactate is a physiological response to acidification of the internal environment, a process arising from the increase in H^+ ions and concomitantly reduction on blood pH [63, 64] that reduce the muscular functions by the following mechanisms : (1) reduction in the transition from the cross bridge from the low to the high strength state; (2) inhibition of the sarcomere shortening velocity; (3) tinhibition of myofibrillar ATPase; (4) inhibition of the glycolytic rate; (5) reduction in the cross bridge activation by competitively inhibiting Ca^{2+} binding to troponin C; and (6) reduction in the Ca2 + uptake by inhibiting sarcoplasmic ATPase (leading to subsequent reduction in Ca^{2+} release) [63, 64]. Gorostiaga et al. [25] observed that peak power output changes during leg press begin to decline after the power generated during the 2 first repetitions (100%) when the blood lactate concentration exceed near ~5-6 mmol·L^{-1}. Considering that TNF reached a peak lactate of 4.4 mmol·L^{-1} compared to 10.3 mmol·L^{-1} in TF, it seems evident that neuromuscular performance had declined more in TF.

A higher blood lactate concentration can trigger the release of important hormones. Pareja-Blanco et al. [30] compared two RT protocols, differing in the number of repetitions per set related to the maximum repetition number (3 sets 12 repetitions [TF] versus 3 sets 6 repetitions [TNF]) and reported that TF led to higher growth hormone (GH) and prolactin concentration when compared with TNF. It seems that higher concentration of H^+ ions and blood lactate mediate the GH release in the hypophysis [65], besides increase the prolactin concentration due to the cellular homeostasis break [66, 67].

Subgroup analysis also showed significantly increase in the ammonia concentration in TF compared to TNF (RMD: 42.17 µmol·L^{-1}). Indeed, it has been reported that TF leads to high muscular energetic and a unbalance important depletion of muscle purines, while TNF allows the cellular maintenance of homeostasis [4, 21, 25]. During high-intensity exercise and during TF, there is a decrease in ADP rephosphorylation capacity coupled with a high ATP turnover rate, that seems to be an important feature of conditions that result in reduced concentration of muscular ATP, increase approximately stoichiometric in AMP deamination to IMP and ammonia [25, 68]. Curiously, as in the case of blood lactate, there is also an association between the decline in peak power output and the elevation of blood ammonia concentration from ~40 µmol·L^{-1} (r = -0.87) [25], which explains the kinetic variable decline. The curvy association between metabolic and kinematic variable was recently related with upper and lower limb exercises, showing that blood ammonia begin to increase constantly above the resting values only when there is considerable loss in the velocity of movement (over ~30% for squat and ~35% for bench press) [4].

4.3 Muscle damage

Muscle damage was higher with TF when compared with TNF (RMD: 190.15 IU·L^{-1} [100.65, 279.66]), in a moderate quality of evidence analysis (GRADE score = 3). Regarding the time-course of muscle damage, despite both TF and TNF seems to increase muscle damage immediately and 24h after the end of the training session, no difference was found between groups. However, there was significantly higher muscle damage at 48h post-TF compared with TNF, that seems to be caused by an additional increase in TF-induced muscle damage, while TNF-induced damage already begins to decrease.

In theory, the higher number of repetitions performed in TF compared to TNF increase the number of eccentric and concentric actions, which is known to augment muscle damage [69]. In fact, higher muscle damage occurs with higher number of repetitions independently of being performed to failure [22, 32]. Even though when the volume was equalized for TF and TNF the higher muscle damage was seen for TF [22], reinforcing that the repetitions closer to failure may be critical for muscle damage. Despite there was not enough data to continuous meta-analysis the muscle damage after 48h, Morán-Navarro, Pérez [22] already showed no muscle damage was found following 72h in highly trained young men.

Some confounding factors such as interindividual variability on CK levels [49, 70] and the repeated bout effect [71] could mask a pronounced tissue damage which in turns can cause severe health consequences [72-74]. In this way, other muscle damage markers, such as muscle pain, transient loss of muscle strength and local inflammation should be considered in a comprehensive muscle damage assessment. Unfortunately, the present study did not explore other muscle damage markers; however, CK is indirect markers of muscle damage relatively low cost and simple to be assessed [49].

It is noteworthy that not always the elevated blood CK levels indicate performance impairment. Çakir-Atabek, Dokumaci [75] showed that after 60 maximal voluntary eccentric contractions of the elbow flexors, the strength decline was associated to a higher oxidative stress environment. Specifically, this oxidative environment was characterized by an increase in oxidation of carbonylated protein, increased total oxidative state and higher oxidative stress index (percent ratio of the oxidant status to the antioxidant status), and it was not related to blood CK levels. Meanwhile, considering our results and the lack of studies following CK levels for longer periods after TF, it seems prudent to give a minimum 48h recovery before the performance of the next training sessions.

4.4 Rating of perceived exertion

Higher RPE scores were found after TF when compared with TNF (SMD: 2.47 [1.25, 3.68]), in a very low evidence quality analysis (GRADE score = 1). The higher RPE scores for TF could be caused by general fatigue, muscle fatigue, cardiovascular stress and pain [20]. Specifically, the other outcomes assessed in the present study have been associated to RPE in previous studies, such as the higher lactate concentration [76], and the lower power output [77]. Nevertheless, there is an important association between mental fatigue and exercise tolerance [78], which would suggest the higher anxiety, tiredness and tension observed in TF session could be cause of higher RPE compared to TNF [51].

RPE is a convenient, validated, low-cost method, comprising perceptive scores that are linearly associated with physiological variables used in training load control in different modalities [79-82]. On the other hand, the acute factors regulating RPE scores post RT are not clear. For instance, Sweet, Foster [83] suggested external load is the main regulator of RPE, while Hiscock, Dawson [8] showed volumetric load is the main regulator of RPE response (number of repetitions x lifted weight [kg]). This controversy could be partially explained by the presence or absence of failure.

In summary, it seems higher RPE scores are given post TF when compared with TNF, presumably due to higher fatigue and mental stress. An interesting factor is that different TF protocols intensities led to similar RPE scores as previously reported [7].

4.5 Future research

Future research should compare TF to lower number of reserve repetitions in the TNF protocols and also equalize the time under tension between protocols, to better isolate the effects coming from the failure stimuli itself. Since only one study explored different time points of recovery [22] and none of them assessed at outcomes at 72h or longer periods, there is a need for more clarifications regarding the duration of TF effects on human body.

4.6 Limitations

The present study combined data from different studies, aiming to summarize the true difference between TF and TNF fatigue response. These studies did not define muscle failure through the same criteria and compared protocols with different numbers of repetitions which could affect our summarized effects.

The moderate to high inconsistency between studies (biomechanical properties - I^2 =51,88%; metabolic response- I^2 = 77.92%; e RPE - I^2 = 87.11%) suggest some considerable difference among studies; however, subgroup analysis were performed to isolate those differences and clarify the cause of different effects.

Another limitation was the absence of other populations such as women and elderly, and thus our results may be limited to young healthy men.

It is important to emphasize a common mistake in many meta-analyses: the sample overlapping. In the present systematic review, there were multiple publications based on the same data and different analysis of the same participants [21, 24, 29, 30, 34]. Thus, we did not repeat the results from the same individuals in the main analysis, leading to a very robust information, even though they were analyzed properly in secondary subgroup analyses.

5 Conclusions

In conclusion the results of the present systematic review and meta-analysis show that TF caused higher increase in fatigue **in** healthy young men when compared with TNF, as given by the decline on biomechanical properties, increase in metabolic response, in muscle damage and in RPE in. Regarding some practical aspects of RT prescription, the need to perform TF is still inconclusive, since a couple of studies show that it does not lead to higher muscle hypertrophy, strength, pennation angle, fascicle length or muscle activation, when compared with TNF [40, 84-89]. The maintenance of neuromuscular performance during RT session and the accelerated rate of recovery post TNF [11, 22, 25, 29-32] enables a higher training frequency concomitantly to higher total training volume, and these two factors are essential to increase muscle hypertrophy and strength [40, 90-93].

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Table 1. Characteristics of the participants.

Study	Participants (*n* = 206)	Age (years)	Height (cm)	Weight (kg)	Training status
Arent et al. (2005) [51]	15	22.0 ± 0.7	180.8 ± 1.9	77.8 ± 2.9	Untrained
Fonseca et al. (2020) [11]	22	21.4 ± 2.3	Not reported	78.1 ± 6.7	Trained
González-Badillo et al. (2016) [29]	9	23.3 ± 3.9	175.0 ± 0.03	75.3 ± 9.2	Trained
Gorostiaga et al. (2010) [24]	6	34.0 ± 6.0	179.0 ± 5.0	74.5 ± 7.2	Untrained
Gorostiaga et al. (2012) [21]	6	34.0 ± 6.0	179.0 ± 5.0	74.5 ± 7.2	Untrained
Gorostiaga et al. (2014) [25]	13	34.4 ± 5.4	177.4 ± 6.0	74.1 ± 6.3	Untrained
Hiscock et al. (2015) [8]	10	26.3 ± 8.4	181.3 ± 5.6	78.1 ± 9.1	Trained
Linnamo et al. (1998) [35]	8	27.1 ± 1.9	181.3 ± 3.1	74.4 ± 9.0	Untrained
Linnamo et al. (2005) [34]	8	27.1 ± 1.9	181.3 ± 3.1	74.4 ± 9.0	Untrained
Martorelli et al. (2020) [12]	12	24.1 ± 4.4	177.0 ± 3.3	82.0 ± 6.4	Trained
McGuigan et al. (2004) [6]	8	21.6 ± 1.2	180.0 ± 0.1	86.6 ± 11.0	Trained
Morán-Navarro et al. (2017) [22]	10	21.5 ± 4.0	175.2 ± 7.2	72.4 ± 8.4	Trained
Pareja-Blanco et al. (2016) [30]	10	23.6 ± 3.7	175.0 ± 0.03	75.0 ± 8.7	Trained
Pareja-Blanco et al. (2019) [31]	10	20.6 ± 2.7	175.0 ± 0.10	71.7 ± 12.5	Untrained
Pareja-Blanco et al. (2020) [32]	10	22.1 ± 3.5	175.0 ± 0.07	73.5 ± 10.7	Trained
Raastad et al. (2000) [23]	9	26.9 ± 4.2	Not reported	81.4 ± 9.6	Not reported
Sánchez-Medina & González-Badillo et al. (2011) [4]	18	25.6 ± 3.4	176.6 ± 7.5	75.9 ± 9.1	Trained
Shibata et al. (2019) [10]	10	20.5 ± 1.1	174.0 ± 3.8	65.7 ± 4.8	Trained
Vasquez et al. (2013) [7]	12	21.9 ± 1.3	177.9 ± 6.4	77.8 ± 8.0	Trained
Mean ± SD	10.8 ± 4.0	25.2 ± 4.6	177.7 ± 2.6	76.0 ± 4.4	-
Range (minimum - maximum)	22.0 – 6.0	34.4 – 20.5	181.3 – 174.0	86.6 – 65.7	-

n: sample size; SD: standard deviation.

Table 2. Summary and characteristics of the studies included in the review.

Study	Study design	Resistance exercise (s)	Prescription	Velocity of Movement	Volume	Outcome measure (s)
Arent et al. (2005) [51]	Counterbalanced order and cross-over design	Bench press Lat pulldown Shoulder press Seated rows Triceps extensions Biceps curls	**TF:** 3x10 @100% 10RM **TNF 1:** 3x10 @70% 10RM **TNF 2:** 3x10 @40% 10RM 90 s interval between sets	Not reported	Not equalized	Rating of perceived exertion (au) (Borg scale 15-point)
Fonseca et al. (2020) [11]	Controlled, randomized, and cross-over design	Back squat	**TF:** 4x12 @12RM **TNF:** 8x6 @12RM 3 min interval between sets	Not controlled	Equalized	Vertical jump height - CMJ (cm) Power output for back squat (w) Rating of perceived exertion (au) (Foster scale 10-point)
González-Badillo et al. (2016) [29]	Cross-over design	Bench press Back squat	**TF:** 3x8 @80% 1RM **TNF:** 3x4 @80% 1RM 5 min interval between sets	Concentric phase in maximal intended velocity and eccentric phase not reported	Not equalized	Vertical jump height - CMJ (%) Muscle damage - CK ($IU{\cdot}L^{-1}$) Velocity of movement against V_1-load for bench press (%) Velocity of movement against V_1-load for back squat (%)
Gorostiaga et al. (2010) [24]	Randomized order and cross-over design	Leg press	**TF:** 1x10 @10RM **TNF:** 1x5 reps @10RM	Concentric and eccentric phase performed as fast as possible	Not equalized	Metabolic response - Ammonia ($\mu mol{\cdot}L^{-1}$) Metabolic response - Lactate ($mmol{\cdot}L^{-1}$) Power output for leg press (w)
Gorostiaga et al. (2012) [21]	Randomized order and cross-over design	Leg press	**TF:** 5x10 @10RM **TNF:** 10x5 reps @10RM 2 min interval between sets	Concentric and eccentric phase performed as fast as possible	Equalized	Power output for leg press (w)
Gorostiaga et al. (2014) [25]	Randomized order and cross-over design	Leg press	**TF:** 5x10 @10RM **TNF:** 10x5 reps @10RM 2 min interval between sets	Concentric and eccentric phase performed as fast as possible	Equalized	Metabolic response - Ammonia ($\mu mol{\cdot}L^{-1}$) Metabolic response - Lactate ($mmol{\cdot}L^{-1}$) Power output for leg press (w)

Table 2. Summary and characteristics of the studies included in the review (continued).

Study	Study design	Resistance exercise (s)	Prescription	Velocity of Movement	Volume	Outcome measure (s)
Hiscock et al. (2015) [8]	Randomized and cross-over design	Bench press Leg press Lat pulldown Leg curl Triceps pushdown	**TF 1:** 3xmaximum number of repetitions @70% 1RM, 1 min interval between sets **TF 2:** 3xmaximum number of repetitions @70% 1RM, 3 min interval between sets **TF 3:** 3xmaximum number of repetitions @40% 1RM, 1 min interval **TF 4:** 3xmaximum number of repetitions @40% 1RM, 3 min interval between sets. **TNF 1:** 3x8 @70% 1RM, 3 min interval between sets. **TNF 2:** 3x14 @40% 1RM, 3 min interval between sets.	2 s concentric phase and 2 s eccentric phase	Not equalized	Rating of perceived exertion (au) (Borg CR-10 scale 10-point)
Linnamo et al. (1998) [35]	Non-randomized order and cross-over design	Sit-up Bench press Leg extension (leg press)	**TF:** 5x10 @10RM **TNF:** 5x10 @40% 10RM 2 min interval between sets	TF: Concentric phase with self-selected velocity and resisting the load during the eccentric phase TNF: Concentric and eccentric phase performed as fast as possible	Not equalized	Metabolic response - Lactate ($mmol \cdot L^{-1}$) Isometric force - Maximum voluntary isometric contraction for leg extension (leg press) (%)

Table 2. Summary and characteristics of the studies included in the review (continued).

Study	Study design	Resistance exercise (s)	Prescription	Velocity of Movement	Volume	Outcome measure (s)
Linnamo et al. (2005) [34]	Non-randomized order and cross-over design	Sit-up Bench press Leg extension (leg press)	**TF:** 5x10 @10RM **TNF 1:** 5x10 @40% 10RM **TNF 2:** 5x10 @70% 10RM 2 min interval between sets	TF e TNF 2: Concentric phase with self-selected velocity and resisting the load during the eccentric phase TNF 1: Concentric and eccentric phase performed as fast as possible	Not equalized	Metabolic response - Lactate ($mmol \cdot L^{-1}$) Isometric force - Maximum voluntary isometric contraction for leg extension (leg press) (%)
Martorelli et al. (2020) [12]	Counterbalanced order and cross-over design	Back squat Bench press	**TF 1: 5**xmaximum number of repetitions @75% 1RM, 2 min interval between sets **TF 2:** 5xmaximum number of repetitions @90% 1RM, 3 min interval between sets **TNF:** 5x6 @50% 1RM, 2 min interval between sets	2 s concentric phase and 2 s eccentric phase. TNF concentric phase was performed as fast as possible	Not equalized	Metabolic response - Lactate ($mmol \cdot L^{-1}$) Muscle damage - CK ($IU \cdot L^{-1}$) Rating of perceived exertion (au) (Foster scale 10-point)
McGuigan et al. (2004) [6]	Randomized and cross-over design	Back squat Bench press	**TF:** 6x10 @75% 1RM **TNF:** 3x10 @30% 1RM 2 min interval between sets.	Not reported	Not equalized	Rating of perceived exertion (au) (Foster scale 10-point)
Morán‑ Navarro et al. (2017) [22]	Controlled, randomized, and cross-over design	Bench press Back squat	**TF:** 3x10 @75% 1RM. **TNF 1:** 3x5 @75% 1RM. **TNF 2:** 6x5 @75% 1RM. 5 min interval between sets	Concentric phase in maximal intended velocity and eccentric phase not reported	Equalized in one of the conditions	Metabolic response - Ammonia ($\mu mol \cdot L^{-1}$) Vertical jump height - CMJ (%) Muscle damage - CK ($IU \cdot L^{-1}$) Velocity of movement against V_1-load for bench press (%) Velocity of movement against V_1-load for back squat (%)

Table 2. Summary and characteristics of the studies included in the review (continued).

Study	Study design	Resistance exercise (s)	Prescription	Velocity of Movement	Volume	Outcome measure (s)
Pareja-Blanco et al. (2016) [30]	Randomized order and cross-over design	Bench press Back squat	**TF:** 3x12 @70% 1RM **TNF:** 3x6 @70% 1RM 5 min interval between sets	Concentric phase in maximal intended velocity and eccentric phase not reported	Not equalized	Vertical jump height - CMJ (%) Muscle damage - CK ($IU \cdot L^{-1}$) Velocity of movement against V_1-load for bench press (%) Velocity of movement against V_1-load for back squat (%)
Pareja-Blanco et al. (2019) [31]	Randomized order and cross-over design	Bench press Back squat	**TF:** 3x10 @75% 1RM **TNF 1 (trained):** 3x5 @75% 1RM **TNF 2 (untrained):** 3x5 @75% 1RM 5 min interval between sets.	Concentric phase in maximal intended velocity and eccentric phase in velocity ~0.50 $m \cdot s^{-1}$	Not equalized	Vertical jump height - CMJ (%) Muscle damage - CK ($IU \cdot L^{-1}$) Velocity of movement against V_1-load for bench press (%) Velocity of movement against V_1-load for back squat (%)
Pareja-Blanco et al. (2020) [32]	Randomized order and cross-over design	Bench press Back squat	**TF 1:** 3x12 @70% 1RM **TNF 1:** 3x6 @70% 1RM **TF 2:** 3x10 @75% 1RM **TNF 2:** 3x5 @75% 1RM **TF 3:** 3x8 @80% 1RM **TNF 3:** 3x4 @80% 1RM **TF 4:** 3x6 @85% 1RM **TNF 4:** 3x3 @85% 1RM **TF 5:** 3x4 @90% 1RM **TNF 5:** 3x2 @90% 1RM 5 min interval between sets	Concentric phase in maximal intended velocity and eccentric phase in velocity 0.40-0.70 $m \cdot s^{-1}$	Not equalized	Vertical jump height - CMJ (%) Muscle damage - CK ($IU \cdot L^{-1}$) Velocity of movement against V_1-load for bench press (%) Velocity of movement against V_1-load for back squat (%)

Table 2. Summary and characteristics of the studies included in the review (continued).

Study	Study design	Resistance exercise (s)	Prescription	Velocity of Movement	Volume	Outcome measure (s)
Raastad et al. (2000) [23]	Counterbalanced order and cross-over design	Back squat Front squat Leg extension	**TF:** 3x3 @3RM for squats, 6 min interval between sets 3x6 @6RM for leg extension, 4 min interval between sets **TNF:** 3x3 @70% 3RM for squats, 6 min interval between sets 3x6 @76% 6RM for leg extension, 4 min interval between sets	Not reported	Not equalized	Metabolic response - Lactate (mmol·L^{-1})
Sánchez-Medina & González-Badillo et al. (2011) [4]	Parallel design for the exercises and cross-over for the conditions design	Bench press or Back squat	**TF 1:** 3x12 @12RM **TNF 1:** 3x6 @12RM **TNF 2:** 3x8 @12RM **TNF 3:** 3x10 @12 RM **TF 2:** 3x10 @10RM **TNF 4:** 3x6 @10RM **TNF 5:** 3x8 @10RM **TF 3:** 3x8 @8RM **TNF 6:** 3x4 @8RM **TNF 7:** 3x6 @8RM **TF 4:** 3x6 @6RM **TNF 8:** 3x3 @6RM **TNF 9:** 3x4 @6RM **TF 5:** 3x4 @4RM **TNF 10:** 3x2 @4RM 5 min interval between sets	Concentric phase in maximal intended velocity and eccentric phase in velocity controlled	Not equalized	Metabolic response - Ammonia (μmol·L^{-1}) Metabolic response - Lactate (mmol·L^{-1}) Vertical jump height - CMJ (%) Velocity of movement against V_1-load for bench press (%) Velocity of movement against V_1-load for back squat (%)

Table 2. Summary and characteristics of the studies included in the review (continued).

Study	Study design	Resistance exercise (s)	Prescription	Velocity of Movement	Volume	Outcome measure (s)
Shibata et al. (2019) [10]	Non-randomized order and cross-over design	Back squat	**TF:** 3xmaximum number of repetitions @75% 1RM **TNF:** 6xtotal number of reps performed TF @75% 1RM 3 min interval between sets	2 s concentric phase and 2 s eccentric phase	Equalized	Metabolic response - Lactate ($mmol·L^{-1}$) Isometric force - Maximum voluntary isometric contraction for leg extension (n) Rating of perceived exertion (au) (Borg CR-10 scale 10-point)
Vasquez et al. (2013) [7]	Randomized order and cross-over design	Back squat	**TF 1:** 1xmaximum number of repetitions @50% 1RM **TNF 1:** 1x3 @50% 1RM **TF 2:** 1xmaximum number of repetitions @70% 1RM **TNF 2:** 1x3 @70% 1RM **TF 3:** 1xmaximum number of repetitions @90% 1RM **TNF 3:** 1x3 @90% 1RM 3 min interval between conditions	Concentric phase in maximal intended velocity and eccentric phase in velocity controlled	Not equalized	Power output for back squat (W/kg) Rating of perceived exertion (au) (Borg scale 15-point)

au: arbitrary units; CK: creatine kinase; CMJ: countermovement jump; min: minutes; RM: repetition maximum; s: seconds; TF: resistance training performed to failure; TNF: resistance training not performed to failure.

Table 3. Results for the subgroup analyses.

Independent or dependent variables	SMD or RMD	95% CI	*p*-value	I^2 % (*p*-value)	*K*	*p*-value (difference)
Biomechanical properties (SMD)						
Training status						
Trained	-1.10	-1.79; -0.40	0.002	66.04 (0.019)	5.0	0.668
Untrained	-0.88	-1.57; -0.20	0.012	0.00 (0.832)	2.0	
Test performed						
CMJ (cm or %)	-1.14	-1.86; -0.43	0.001	67.5 (0.015)	5.0	< 0.001
MVIC (N or %)	-1.04	-1.73; -0.34	0.003	0.00 (0.855)	2.0	
Velocity BP ($m \cdot s^{-1}$ or %)	-2.74	-3.35; -2.13	< 0.001	0.00 (0.970)	4.0	
Velocity SQ ($m \cdot s^{-1}$ or %)	-1.64	-2.16; -1.11	< 0.001	20.39 (0.288)	4.0	
Time point						
Immediately post-exercise (until 60 s)	-1.08	-1.58; -0.57	< 0.001	51.89 (0.052)	7.0	0.984
6h post	-1.17	-1.73; -0.61	< 0.001	51.06 (0.130)	3.0	
24h post	-1.05	-1.72; -0.38	0.002	57.27 (0.053)	5.0	
48h post	-1.00	-1.48; -0.51	0.001	36.68 (0.192)	4.0	
Load						
70%	-1.36	-2.76; 0.03	0.054	84.50 (0.001)	3.0	0.131
75%	-1.25	-1.66; -0.84	< 0.001	5.20 (0.383)	6.0	
80%	-2.57	-3.46; -1.68	< 0.001	0.00 (0.368)	2.0	
85%	-1.79	-3.67; 0.08	0.061	80.40 (0.023)	2.0	
90%	-1.33	-2.06; -0.60	< 0.001	31.01 (0.228)	2.0	
Metabolic response (RMD)						
Secondary analysis						
Ammonia ($\mu mol \cdot L^{-1}$)	42.17	34.67; 49.67	< 0.001	56.41 (0.101)	3.0	< 0.001
Muscle damage (RMD)						
Time point						
Immediately post-exercise (until 5min) ($IU \cdot L^{-1}$)	58.58	-3.01; 120.16	0.062	0.00 (0.869)	3.0	0.099
24h post ($IU \cdot L^{-1}$)	96.07	-26.72; 218.85	0.125	0.00 (0.837)	2.0	
48h post ($IU \cdot L^{-1}$)	208.51	42.88; 374.15	0.014	67.01 (0.048)	3.0	

CI: confidence interval; CMJ: countermovement jump; I^2: heterogeneity between studies; *K*: number of studies; MVIC: maximal voluntary isometric contraction; RMD: raw mean difference; SMD: standardized mean difference; Velocity BP: Velocity of movement against V_1-load for bench press; Velocity SQ: Velocity of movement against V_1-load for squat.

Table 4. Summary of meta-analysis findings and quality of evidence synthesis.

Outcome	Summary of findings				Quality of evidence synthesis (GRADE)					
	k	*n*	Effect [95% CI]	Direction effect compared to TNF	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall quality
Biomechanical properties	7	78	-1.08 [-1.58; -0.57]	↓	No serious limitations	No important inconsistency	No serious indirect evidence	-1	-1	Low
Metabolic response	6	60	5.54 [4.16; 6.92]	↑	No serious limitations	-1	No serious indirect evidence	-1	No important publication bias	Low
Muscle damage response	4	42	190.16 [100.65; 279.66]	↑	No serious limitations	No important inconsistency	No serious indirect evidence	-1	No important publication bias	Moderate
RPE	6	74	2.47 [1.25; 3.68]	↑	No serious limitations	-1	No serious indirect evidence	-1	-1	Very low

CI: confidence interval; *K*: number of studies; *n*:sample size; RPE: rating of perceived exertion.

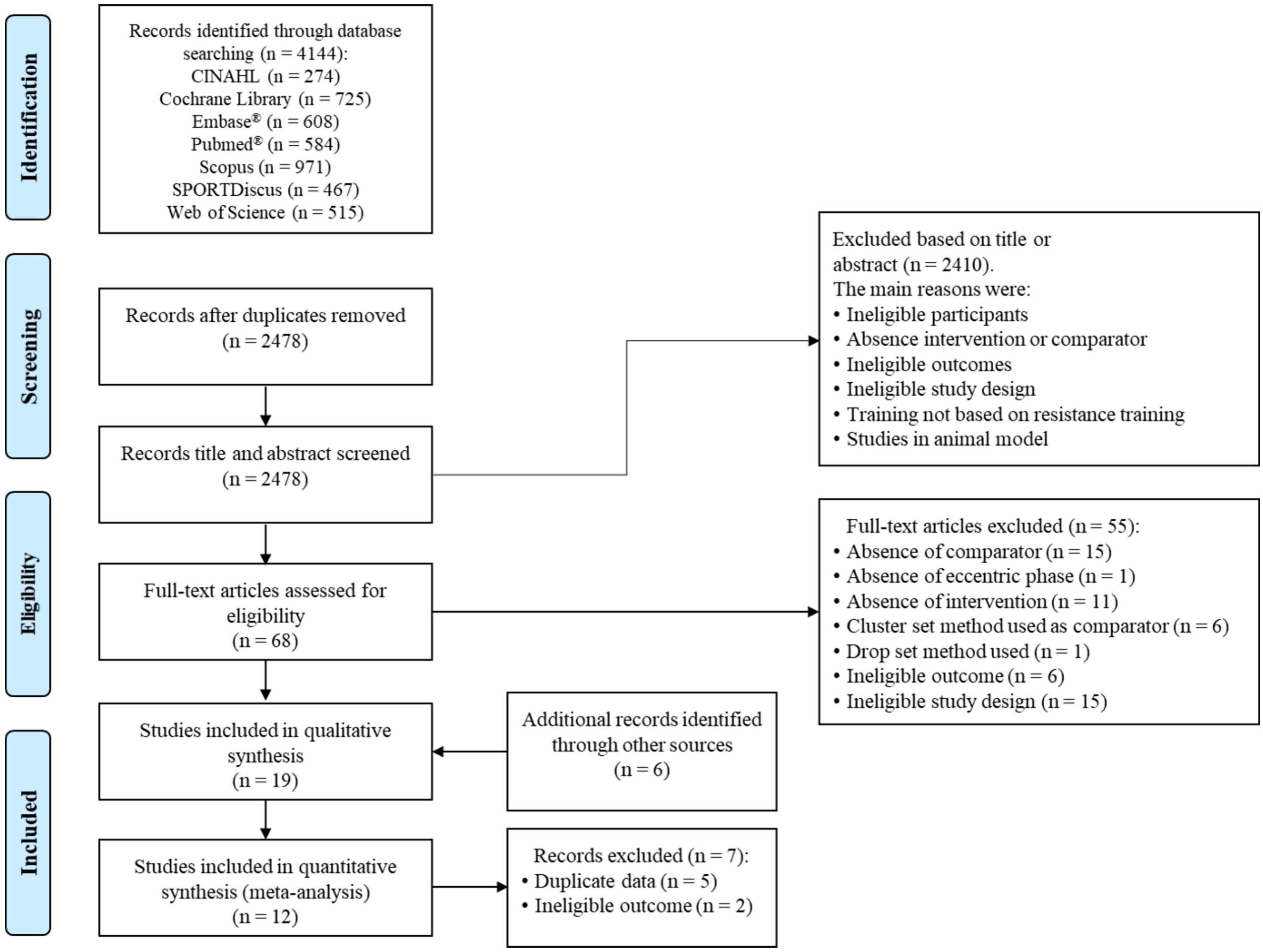


Fig 1. Flow diagram of study selection.

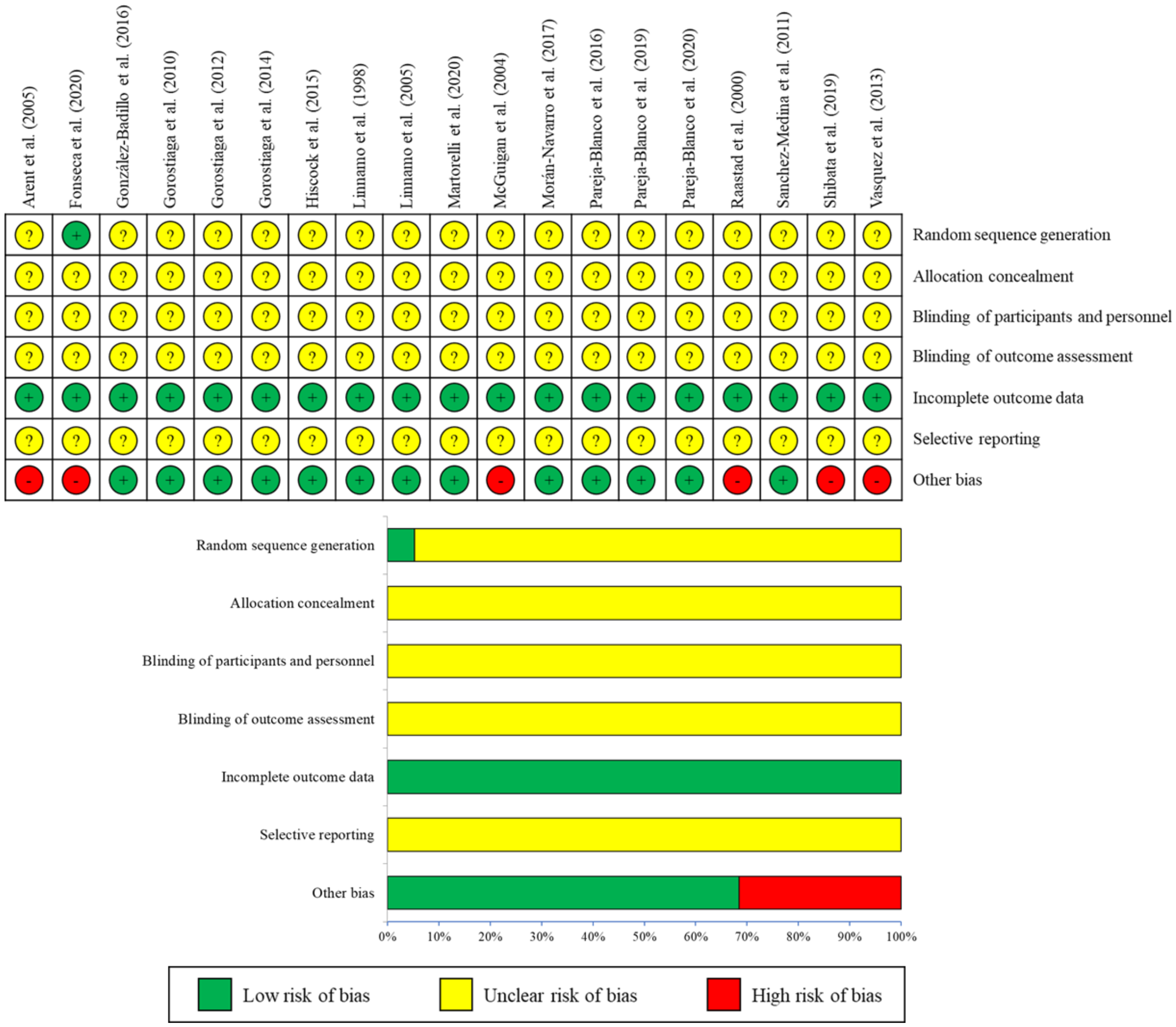


Fig 2. Risk of bias in the primary studies.

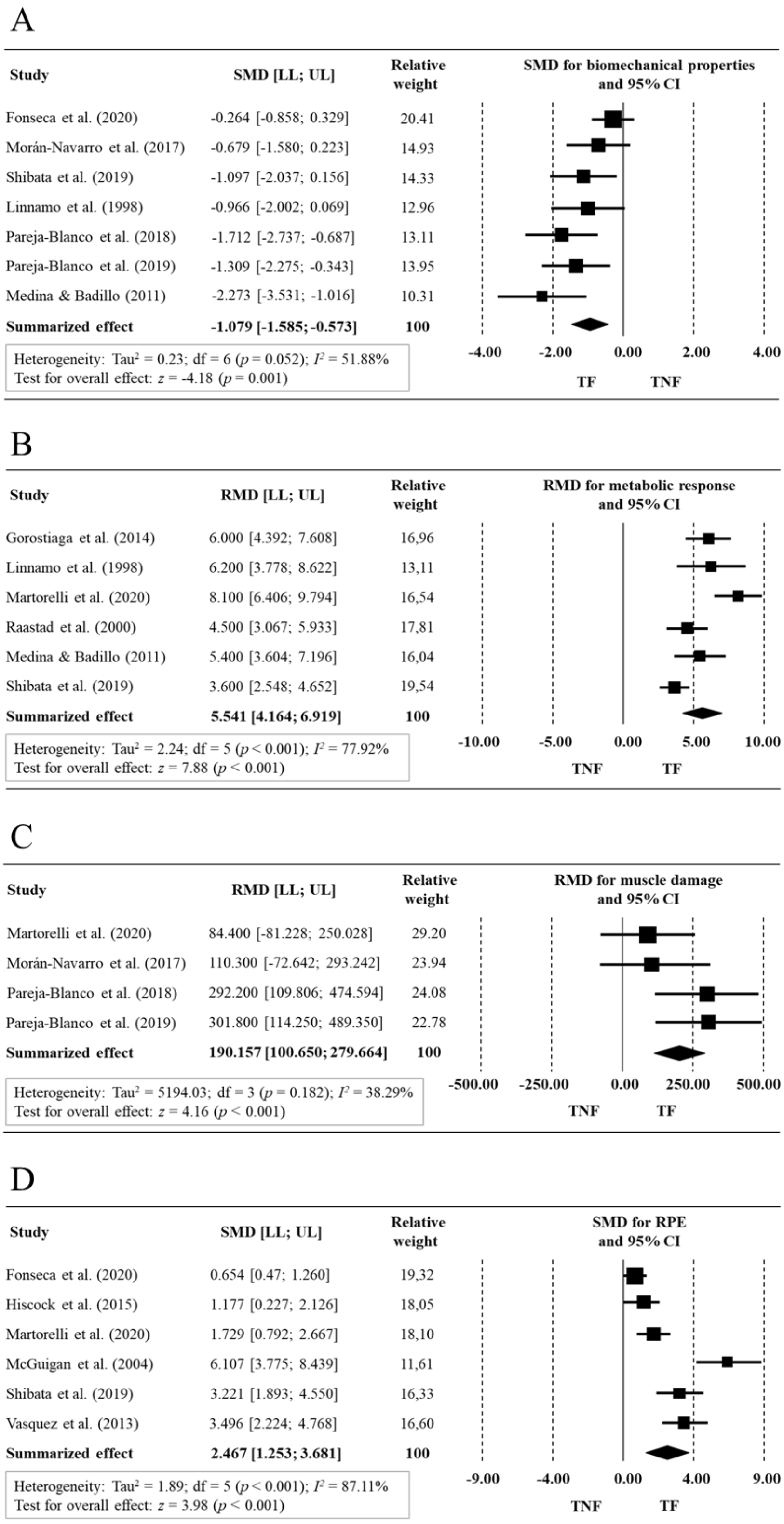


Fig 3. Forest plot of standardized mean difference (biomechanical properties and RPE) and raw mean difference (metabolic response and muscle damage) of the acute effects of TF compared to TNF.

Legend: CI: confidence interval; df: degrees of freedom; I^2: heterogeneity between studies; LL: low limit; RMD: raw mean difference; RPE: rating of perceived exertion; SMD: standardized mean difference; TF: resistance training performed to failure; TNF: resistance training not performed to failure; UL: upper limit.

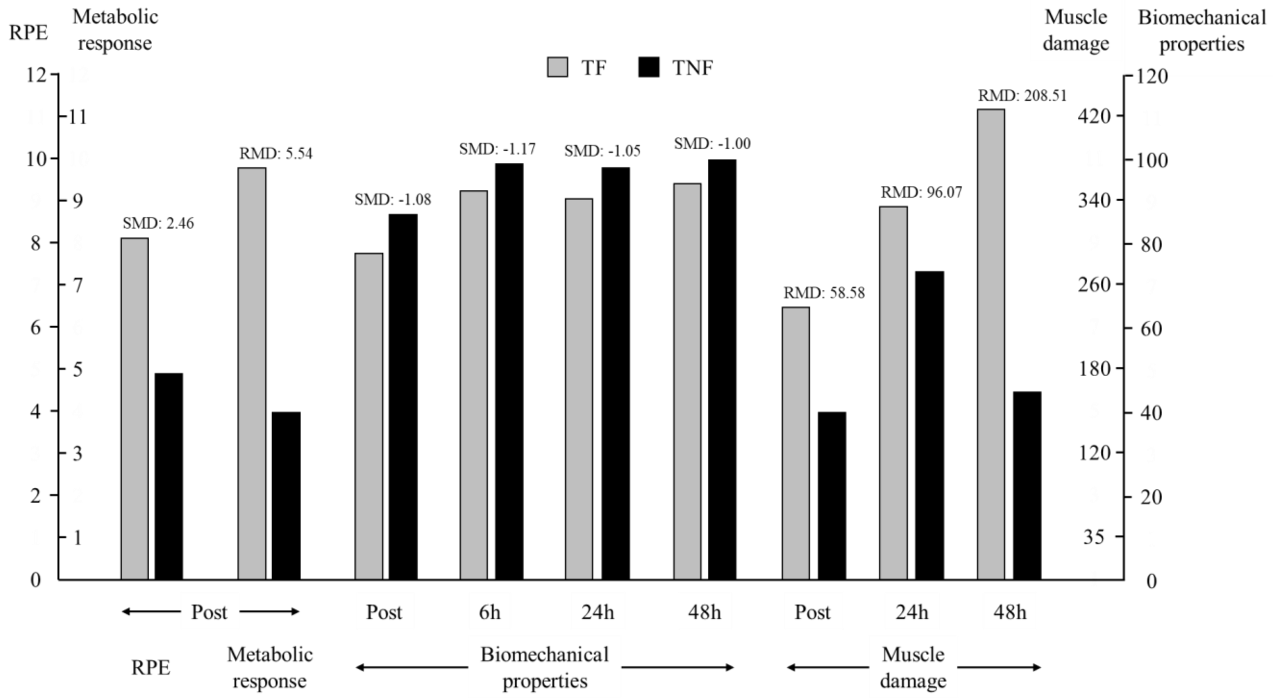
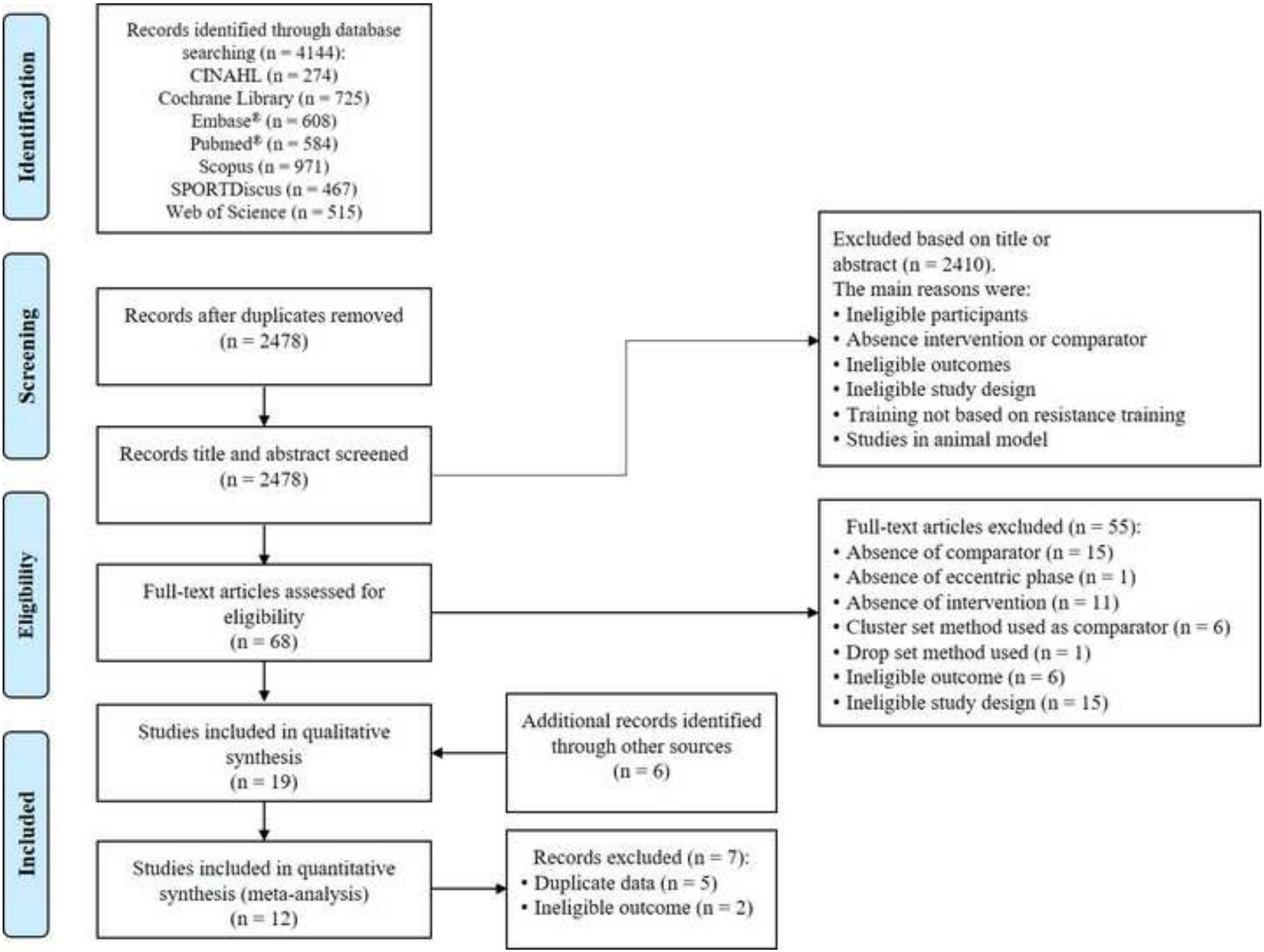
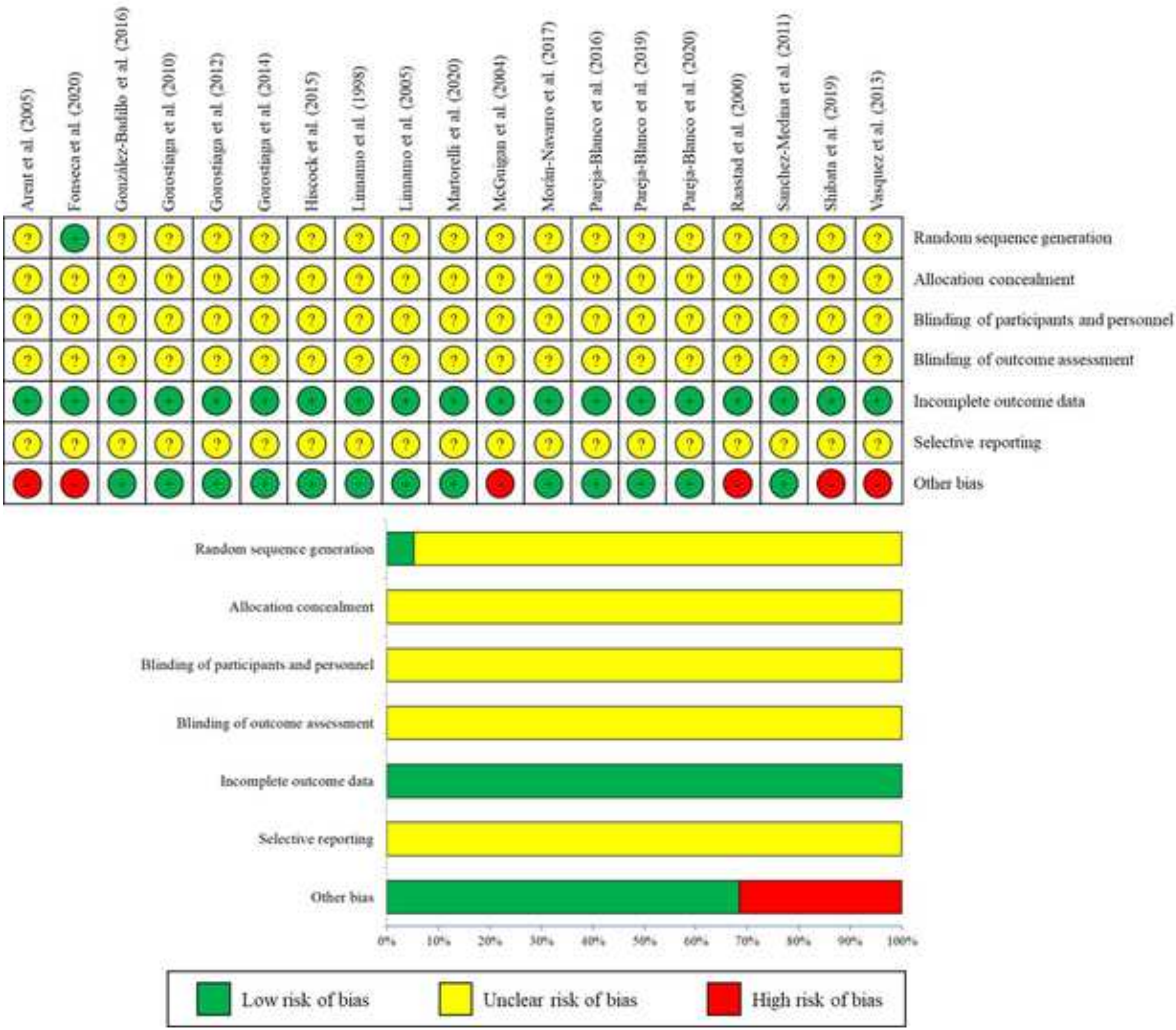
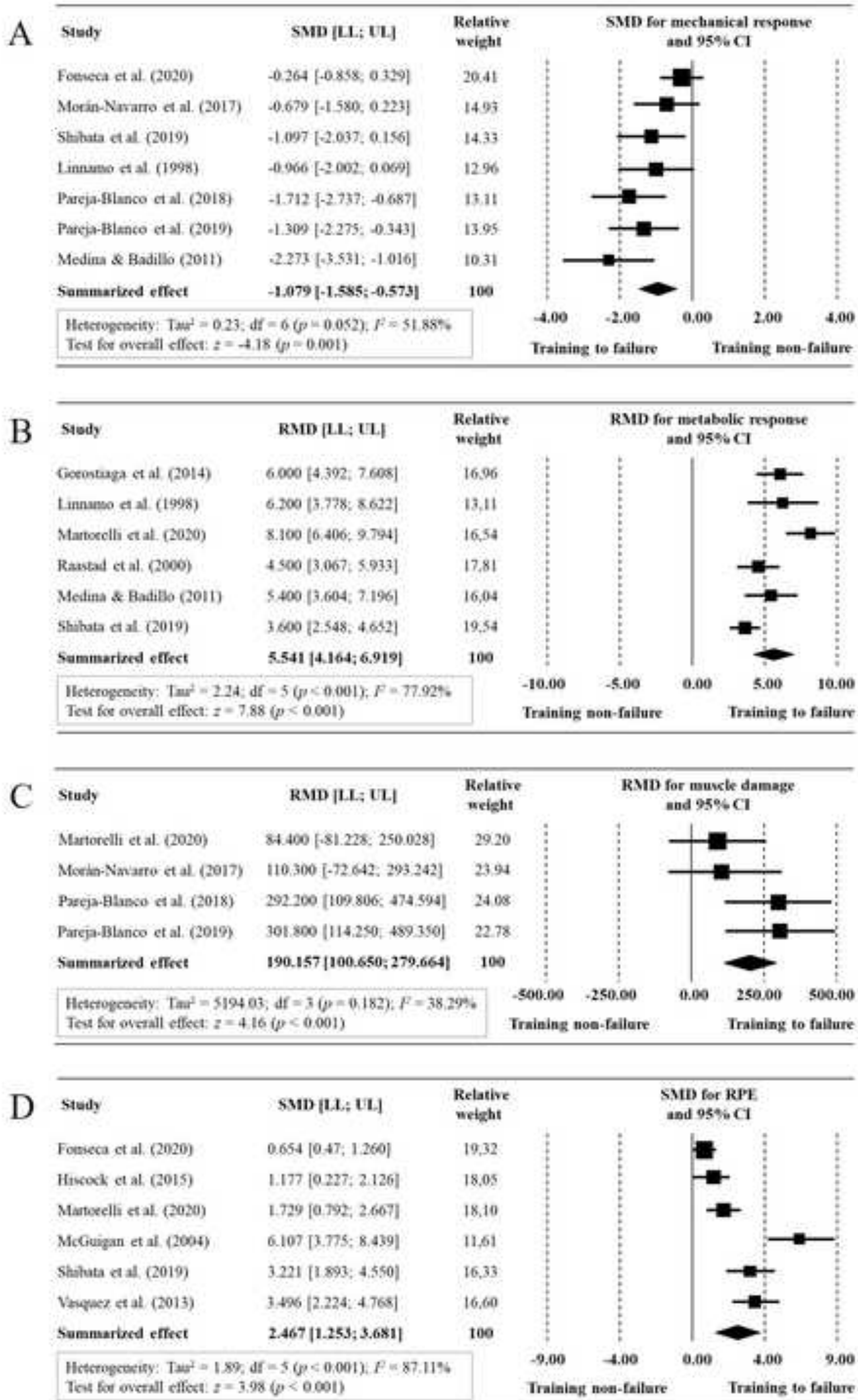


Fig 4. Changes in biomechanical properties, metabolic response, muscle damage and RPE with TF compared with TNF. Legend: RMD: raw mean difference; RPE: rating of perceived exertion; SMD: standardized mean difference; TF: resistance training performed to failure; TNF: resistance training not performed to failure.

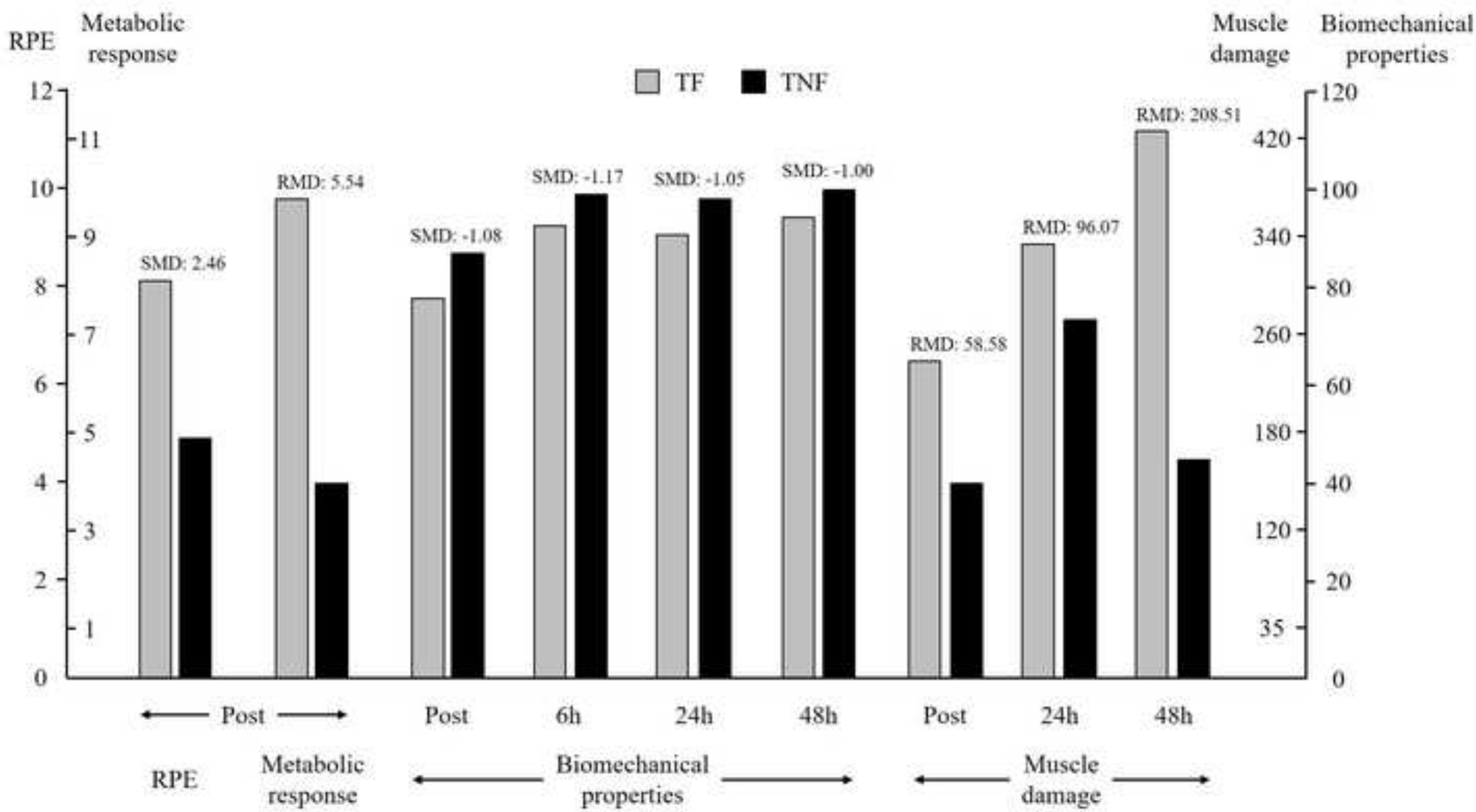

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 4144):
CINAHL (n = 274)
Cochrane Library (n = 725)
Embase® (n = 608)
Pubmed® (n = 584)
Scopus (n = 971)
SPORTDiscus (n = 467)
Web of Science (n = 515)
Records after duplicates removed (n = 2478)
Records title and abstract screened (n = 2478)
Excluded based on title or abstract (n = 2410).
The main reasons were:
• Ineligible participants
• Absence intervention or comparator
• Ineligible outcomes
• Ineligible study design
• Training not based on resistance training
• Studies in animal model
Full-text articles assessed for eligibility (n = 68)
Full-text articles excluded (n = 55):
• Absence of comparator (n = 15)
• Absence of eccentric phase (n = 1)
• Absence of intervention (n = 11)
• Cluster set method used as comparator (n = 6)
• Drop set method used (n = 1)
• Ineligible outcome (n = 6)
• Ineligible study design (n = 15)
Studies included in qualitative synthesis (n = 19)
Additional records identified through other sources (n = 6)
Studies included in quantitative synthesis (meta-analysis) (n = 12)
Records excluded (n = 7):
• Duplicate data (n = 5)
• Ineligible outcome (n = 2)


Arent et al. (2005)
Fonseca et al. (2020)
González-Badillo et al. (2016)
Gorostiaga et al. (2010)
Gorostiaga et al. (2012)
Gorostiaga et al. (2014)
Hiscock et al. (2015)
Linnamo et al. (1998)
Linnamo et al. (2005)
Martorelli et al. (2020)
McGuigan et al. (2004)
Morán-Navarro et al. (2017)
Pareja-Blanco et al. (2016)
Pareja-Blanco et al. (2019)
Pareja-Blanco et al. (2020)
Raastad et al. (2000)
Sanchez-Medina et al. (2011)
Shibata et al. (2019)
Vasquez et al. (2013)
Random sequence generation
Allocation concealment
Blinding of participants and personnel
Blinding of outcome assessment
Incomplete outcome data
Selective reporting
Other bias
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

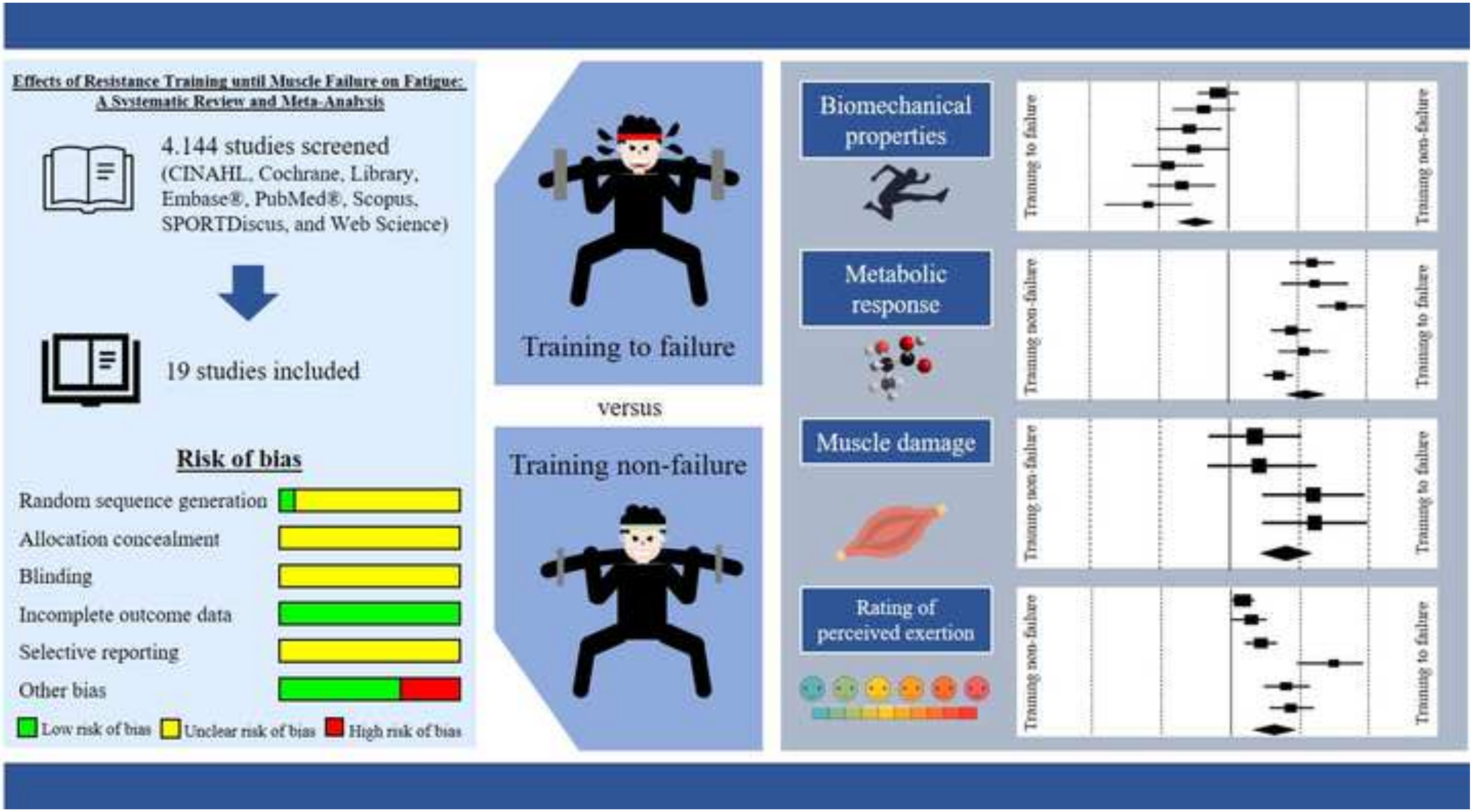

A
Study
SMD [LL; UL]
Relative weight
SMD for mechanical response and 95% CI
Fonseca et al. (2020) -0.264 [-0.858; 0.329] 20.41
Morán-Navarro et al. (2017) -0.679 [-1.580; 0.223] 14.93
Shibata et al. (2019) -1.097 [-2.037; 0.156] 14.33
Linnamo et al. (1998) -0.966 [-2.002; 0.069] 12.96
Pareja-Blanco et al. (2018) -1.712 [-2.737; -0.687] 13.11
Pareja-Blanco et al. (2019) -1.309 [-2.275; -0.343] 13.95
Medina & Badillo (2011) -2.273 [-3.531; -1.016] 10.31
Summarized effect -1.079 [-1.585; -0.573] 100
Heterogeneity: Tau² = 0.23; df = 6 (p = 0.052); I² = 51.88%
Test for overall effect: z = -4.18 (p = 0.001)
-4.00 -2.00 0.00 2.00 4.00
Training to failure
Training non-failure
B
Study
RMD [LL; UL]
Relative weight
RMD for metabolic response and 95% CI
Gorostiaga et al. (2014) 6.000 [4.392; 7.608] 16.96
Linnamo et al. (1998) 6.200 [3.778; 8.622] 13.11
Martorelli et al. (2020) 8.100 [6.406; 9.794] 16.54
Raastad et al. (2000) 4.500 [3.067; 5.933] 17.81
Medina & Badillo (2011) 5.400 [3.604; 7.196] 16.04
Shibata et al. (2019) 3.600 [2.548; 4.652] 19.54
Summarized effect 5.541 [4.164; 6.919] 100
Heterogeneity: Tau² = 2.24; df = 5 (p < 0.001); I² = 77.92%
Test for overall effect: z = 7.88 (p < 0.001)
-10.00 -5.00 0.00 5.00 10.00
Training non-failure
Training to failure
C
Study
RMD [LL; UL]
Relative weight
RMD for muscle damage and 95% CI
Martorelli et al. (2020) 84.400 [-81.228; 250.028] 29.20
Morán-Navarro et al. (2017) 110.300 [-72.642; 293.242] 23.94
Pareja-Blanco et al. (2018) 292.200 [109.806; 474.594] 24.08
Pareja-Blanco et al. (2019) 301.800 [114.250; 489.350] 22.78
Summarized effect 190.157 [100.650; 279.664] 100
Heterogeneity: Tau² = 5194.03; df = 3 (p = 0.182); I² = 38.29%
Test for overall effect: z = 4.16 (p < 0.001)
-500.00 -250.00 0.00 250.00 500.00
Training non-failure
Training to failure
D
Study
SMD [LL; UL]
Relative weight
SMD for RPE and 95% CI
Fonseca et al. (2020) 0.654 [0.47; 1.260] 19.32
Hiscock et al. (2015) 1.177 [0.227; 2.126] 18.05
Martorelli et al. (2020) 1.729 [0.792; 2.667] 18.10
McGuigan et al. (2004) 6.107 [3.775; 8.439] 11.61
Shibata et al. (2019) 3.221 [1.893; 4.550] 16.33
Vasquez et al. (2013) 3.496 [2.224; 4.768] 16.60
Summarized effect 2.467 [1.253; 3.681] 100
Heterogeneity: Tau² = 1.89; df = 5 (p < 0.001); I² = 87.11%
Test for overall effect: z = 3.98 (p < 0.001)
-9.00 -4.00 0.00 4.00 9.00
Training non-failure
Training to failure

Figure

Click here to access/download;Figure;Figure 4 - Changes in study outcomes.jpg



Figure



Effects of Resistance Training until Muscle Failure on Fatigue: A Systematic Review and Meta-Analysis
4.144 studies screened
(CINAHL, Cochrane, Library, Embase®, PubMed®, Scopus, SPORTDiscus, and Web Science)
19 studies included
Risk of bias
Random sequence generation
Allocation concealment
Blinding
Incomplete outcome data
Selective reporting
Other bias
Low risk of bias
Unclear risk of bias
High risk of bias
Training to failure
versus
Training non-failure
Biomechanical properties
Metabolic response
Muscle damage
Rating of perceived exertion
Training to failure
Training non-failure