UNIVERSITYOF BIRMINGHAM

University of Birmingham Research at Birmingham

Effects of resistance training to muscle failure on acute fatigue

Vieira, João Guilherme ; Veiga Sardeli, Amanda; Dias, Marcelo Ricardo ; Filho, José Elias ; Campos, Yuri ; Sant'Ana, Leandro ; Leitão, Luis ; Reis, Victor ; Wilk, Michal ; Novaes, Jeferson ; Vianna, Jeferson

DOI: 10.1007/s40279-021-01602-x

License: Other (please specify with Rights Statement)

Document Version Peer reviewed version

Citation for published version (Harvard):

Vieira, JG, Veiga Sardeli, A, Dias, MR, Filho, JE, Campos, Y, Sant'Ana, L, Leitão, L, Reis, V, Wilk, M, Novaes, J & Vianna, J 2021, 'Effects of resistance training to muscle failure on acute fatigue: a systematic review and meta-analysis', Sports Medicine. https://doi.org/10.1007/s40279-021-01602-x

Link to publication on Research at Birmingham portal

Publisher Rights Statement:

This AAM is subject to Springer Nature re-use terms: https://www.springernature.com/gp/open-research/policies/accepted-manuscript-terms

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.

•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?) Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Sports Medicine

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

Manuscript Number:	SPOA-D-21-00005					
Full Title:	Effects of Resistance Training until Muscle and Meta-Analysis	Failure on Fatigue: A Systematic Review				
Article Type:	Review Article					
Funding Information:	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (001)	BSc João Guilherme Vieira				
	Fundação para a Ciência e a Tecnologia (UID04045/2020)	PhD Victor Reis				
	Fundação para a Ciência e a Tecnologia PhD Luis Leitão (UIDP/04748/2020)					
Abstract:	Background					
	The proper manipulation of resistance train maximum potential of neuromuscular adapt to perform RT to failure (TF) or not to failure biomechanical properties, metabolic stress, perceived exertion (RPE). The sum of these process and, consequently in long-term ada term adaptations, it is important to determin TNF.	ing (RT) variables is a key factor to reach tations. Among those variables, the option e (TNF) directly affect the magnitude of muscle damage and the rating of e results could interfere on the adaptative aptations. Therefore, as this affects long- te the exact difference between the TF and				
	Objective					
	The aim of the present study was to identify fatigue (biomechanical properties, metaboli	the summarized acute effect of TF on cresponse, muscle damage, and RPE).				
	Methods					
	A systematic search was performed in July with crossover designs that investigated the variables - vertical jump height and velocity output, and isometric force), metabolic resp muscle damage (blood creatine kinase [CK were analyzed in the following time points: 6h, 24h, and 48h post (biomechanical prop- of muscle damage, we did not include 6h. F performed.	2020, in seven databases. Only studies e acute biomechanical properties (kinematic of movement; and kinetic variables - power ionse (blood lactate and blood ammonia),]), and RPE were selected. The outcomes immediately post-exercise (all outcomes), erties and muscle damage). In the analysis Fixed or Random-effects meta-analysis were				
	Results					
	Nineteen studies were included in the system analysis. The results showed greater loss of to TNF (SMD = -1.08 [-1.58; -0.57]; $p < 0.0$ increase in metabolic response (RMD = 5.5 muscle damage (RMD = 190.16 IU·L -1 [1 = 2.47 [1.25; 3.68]; $p < 0.001$) for TF comp that training status ($p = 0.668$), time point affect biomechanical properties. However, of velocity of movement test (SMD = -2.47 [-3) concentration was higher in TF than TNF (F 0.001) and only after 48h the blood CK leve 208.51 IU·L -1 [42.88; 374.15]; $p = 0.014$	ematic review and twelve in the meta- of biomechanical properties for TF compared D01). Furthermore, there was larger 44 mmol·L -1 [4.16; 6.92]; $p < 0.001$), D0.65; 279.66]; $p < 0.001$) and RPE (SMD bared to TNF. Subgroup analyses showed ($p = 0.984$) and load ($p = 0.131$) did not greater loss occurred on upper limbs .35; -2.13]; $p < 0.001$). Blood ammonia RMD = 42.17 µmol·L -1 [34.67; 49.67]; $p <$ els were higher in TF than TNF (RMD =).				
	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).
João Guilherme Vieira, BSc Federal University of Juiz de Fora Juiz de Fora - Minas Gerais, MG BRAZIL
Federal University of Juiz de Fora
João Guilherme Vieira, BSc
João Guilherme Vieira, BSc
Amanda Veiga Sardeli, PhD
Marcelo Ricardo Dias, PhD
José Elias Filho, MSc
Yuri Campos, MSc
Leandro Sant'Ana, MSc
Luis Leitão, PhD
Victor Reis, PhD
Michal Wilk, PhD
Jefferson Novaes, PhD
Jeferson Vianna, PhD
Thank you for your consideration of this manuscript.
Brad Schoenfeld, PhD City University of New York City - Lehman College brad.schoenfeld@lehman.cuny.edu An expert in the field of resistance training
Jozo Grgic Victoria University Melbourne jozo.grgic@live.vu.edu.au An expert in the field of resistance training
Alex Ribeiro, PhD University of Northern Parana alex.sribeiro@kroton.com.br An expert in the field of resistance training
Fernando Pareja-Blanco, PhD Universidad Pablo de Olavide fparbla@upo.es An expert in the field of resistance training

Timothy Suchomel, PhD Carroll University tsuchome@carrollu.edu An expert in the field of resistance training
Jonato Prestes, PhD Universidade Católica de Brasília jonato@ucb.br An expert in the field of resistance training

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.

Please address all correspondence concerning this manuscript to me at joaoguilhermevds@gmail.com Thank you for your consideration of this manuscript.

Best regards BSc João Guilherme Vieira

1	Title: Effects of Resistance Training until Muscle Failure on Fatigue: A Systematic Review and Meta-Analysis
1 2	
2 3 3 4 5 4	Running heading: Resistance Training to Muscle Failure and Fatigue
6 7 5	João Guilherme Vieira ¹ , Amanda Veiga Sardeli ² , Marcelo Ricardo Dias ^{1,3} , José Elias Filho ¹ , Yuri Campos ^{1,4} , Leandro
8 96 10 11 7	Sant'Ana ¹ , Luis Leitão ^{5,6} , Victor Reis ⁷ , Michal Wilk ⁸ , Jefferson Novaes ⁹ , Jeferson Vianna ¹
12 13 8	1- Postgraduate Program in Physical Education, Federal University of Juiz de Fora (UFJF), Juiz de Fora, Brazil.
14 15 9	2- Laboratory of Exercise Physiology – FISEX, Federal University of Campinas (UNICAMP), Campinas, Brazil.
16 17 10	3- Laboratory of Exercise Physiology and Morphofunctional Evaluation – LABFEX, Granbery Methodist College, Juiz
18 19 11	de Fora, Brazil.
20 21 <u>12</u>	4- Study Group and Research in Neuromuscular Responses, Federal University of Lavras (UFLA), Lavras, Brazil
22 23 13	5- Superior School of Education of Polytechnic Institute of Setubal, Setubal, Portugal.
24 25 14	6- Life Quality Research Centre, 2040-413, Rio Maior, Portugal
27 <u>15</u>	7- Research Center in Sports Sciences, Health Sciences & Human Development – CIDESD, Vila Real, Portugal.
² 916	8- Institute of Sport Sciences, Jerzy Kukuczka Academy of Physical Education in Katowice, Katowice, Poland.
³¹ 17 32 ³³ 18	9- Postgraduate Program in Physical Education, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil.
³⁵ 19	Corresponding author contact details:
³⁷ 20	João Guilherme Vieira, BSc. Postgraduate Program of the Faculty of Physical Education and Sports of the Federal
³⁹ 21 40 ⁴¹ 22	University of Juiz de Fora, Brazil. Phone: +55 32 98444-8415. E-mail: joaoguilhermevds@gmail.com.
$\frac{43}{43}$	ORCID:
⁴⁵ ₄ 24	João Guilherme Vieira – 0000-0002-3860-4630; Amanda Veiga Sardeli – 0000-0003-0575-7996; Marcelo Ricardo Dias
⁴⁷ ₄₈ 25	- 0000-0001-8912-340X; José Elias Filho - 0000-0002-4251-0290; Yuri Campos - 0000-0001-8344-1087; Leandro
⁴⁹ ₅₀ 26	Sant'Ana - 0000-0002-0156-4030; Luis Leitão - 0000-0002-1981-6638; Victor Reis - 0000-0002-4996-1414; Michal
⁵¹ 27 52 7 ⁵³ 28	Wilk - 0000-0001-5799-6337; Jefferson Novaes – 0000-0001-9304-6574; Jeferson Vianna – 0000-0003-1594-4429.
55 56 29	Declarations:
57 58 30	(i) Funding - João Guilherme Veira was financed in part with the BSc scholarship by the Coordenação de
59 60 31 61 62 63	Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001. Victor Reis received funding by

Portuguese Foundation for Science and Technology, I.P., Grant/Award Number UID04045/2020. Luis Leitão received
 funding by Portuguese Foundation for Science and Technology, I.P., Grant/Award Number UIDP/04748/2020.

(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.

52 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 = 0.014).

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:

• 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-

114 26]. The muscle fatigue is a complex multifactorial phenomenon that depend on task, and its etiology is controversial and 115 the cause of intense debates [27, 28]. However, fatigue limits the strength capacity and the sarcomere shortening velocity 2 [22, 29-33], leading to higher impairment of neuromuscular functions. In this way, numerous studies have reported 4 reduction in power output [7, 11, 25], vertical jump height, velocity of movement [22, 32] and isometric force [10, 34], 6 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

1₄6

2 1**;47**

4 1548

6 1⁄49

8 1950

10 1**1151**

12 1**152**

14

22 2**1357**

24 2**1558**

26 2**1/59** 28

2**160** 30

63 64 65

1**1553** 16 1**1754** 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 1₃79

4 1580

6 **1⁄81**

8 19**82**

10 1**183**

12 1**184**

18 1**1987**

20 2**1288**

22 2**1389**

24 2**1590**

26 2**1⁄91** 28

2**192** 30

 3^{+}_{32} 3^{+}_{34} 3^{+}_{36} 3^{+}_{36} 3^{+}_{36} 3^{+}_{36} 3^{+}_{36} 3^{+}_{36} 3^{+}_{44} 4^{+}_{44} 4^{+}_{46} 4^{+}_{45} 3^{+}_{55} 5^{+}_{55} 5^{+}_{55} 5^{+}_{55} 5^{+}_{55} 5^{+}_{55} 5^{+}_{55} 5^{+}_{56} $5^{$

178 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 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.

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 V₁load for bench press [velocity BP], and Velocity of movement against V₁-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∉43

2⁄44

246

2347

2548

2749

250

2151

241 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 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]. Thecharacteristics 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 \geq 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-

###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.

335 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 metaanalysis 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 cm³) and the gluteus maximus (764.1 ± 138.0 cm³), the more active muscles in the Velocity SQ [4, 22, 31, 32] are considerable bigger than deltoid (380.5 ± 157.5 cm³), triceps brachii (371.1 ± 177.3 cm³) and pectoralis major (290.0 ± 169.0 cm³) 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,

366 32], lower heart rate variability [29, 30] or even the higher time needed to the restoration of the muscle adenine nucleotides367 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 μ mol·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 μ mol·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 $IU \cdot L^{-1}$ [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

429

4₃₀

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.

Conclusions

4563 In conclusion the results of the present systematic review and meta-analysis show that TF caused higher increase 4;64 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].

References

Suchomel TJ, Nimphius S, Bellon CR, Stone MH. The Importance of Muscular Strength: Training 1. Considerations. Sports Med. 2018;48(4):765-85. doi:10.1007/s40279-018-0862-z.

2. ACSM. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2009;41(3):687-708. doi:10.1249/MSS.0b013e3181915670.

3. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res. 2010;24(10):2857-72. doi:10.1519/JSC.0b013e3181e840f3.

4. Sánchez-Medina L, González-Badillo JJ. Velocity loss as an indicator of neuromuscular fatigue during resistance training. Med Sci Sports Exerc. 2011;43(9):1725-34. doi:10.1249/MSS.0b013e318213f880.

5. Steele J, Fisher J, Giessing J, Gentil P. Clarity in reporting terminology and definitions of set endpoints in resistance training. Muscle Nerve. 2017;56(3):368-74. doi:10.1002/mus.25557.

6. McGuigan MR, Egan AD, Foster C. Salivary Cortisol Responses and Perceived Exertion during High Intensity and Low Intensity Bouts of Resistance Exercise. J Sports Sci Med. 2004;3(1):8-15.

 Vasquez LM, McBride JM, Paul JA, Alley JR, Carson LT, Goodman CL. Effect of resistance exercise performed to volitional failure on ratings of perceived exertion. Percept Mot Skills. 2013;117(3):881-91. doi:10.2466/27.29.PMS.117x30z8.

8. Hiscock DJ, Dawson B, Peeling P. Perceived exertion responses to changing resistance training programming variables. J Strength Cond Res. 2015;29(6):1564-9. doi:10.1519/jsc.00000000000775.

 Santos WDN, Vieira CA, Bottaro M, Nunes VA, Ramirez-Campillo R, Steele J, et al. Resistance Training Performed to Failure or Not to Failure Results in Similar Total Volume, but With Different Fatigue and Discomfort Levels. J Strength Cond Res. 2019. doi:10.1519/jsc.000000000002915.

10. Shibata K, Takizawa K, Tomabechi N, Nosaka K, Mizuno M. Comparison Between Two Volume-Matched Squat Exercises With and Without Momentary Failure for Changes in Hormones, Maximal Voluntary Isometric Contraction Strength, and Perceived Muscle Soreness. J Strength Cond Res. 2019. doi:10.1519/jsc.00000000003279.

11. Fonseca FS, Costa BDV, Ferreira MEC, Paes S, Lima-Junior D, Kassiano W, et al. Acute effects of equated volume-load resistance training leading to muscular failure versus non-failure on neuromuscular performance. J Exerc Sci Fit. 2020. doi:10.1016/j.jesf.2020.01.004.

12. Martorelli AS, de Lima FD, Vieira A, Tufano JJ, Ernesto C, Boullosa D, et al. The interplay between internal and external load parameters during different strength training sessions in resistance-trained men. Eur J Sport Sci. 2020:1-10. doi:10.1080/17461391.2020.1725646.

 Willardson JM. The application of training to failure in periodized multiple-set resistance exercise programs. J Strength Cond Res. 2007;21(2):628-31. doi:10.1519/r-20426.1.

Willardson JM, Norton L, Wilson G. Training to failure and beyond in mainstream resistance exercise programs.
 Strength Condit J. 2010;32(3):21-9.

506 15. Drinkwater EJ, Lawton TW, Lindsell RP, Pyne DB, Hunt PH, McKenna MJ. Training leading to repetition
 507 failure enhances bench press strength gains in elite junior athletes. J Strength Cond Res. 2005;19(2):382-8. doi:10.1519/r 508 15224.1.

 Karsten B, Fu YL, Larumbe-Zabala E, Seijo M, Naclerio F. Impact of Two High-Volume Set Configuration Workouts on Resistance Training Outcomes in Recreationally Trained Men. J Strength Cond Res. 2019. doi:10.1519/jsc.000000000003163.

17. Schoenfeld BJ, Grgic J. Does training to failure maximize muscle hypertrophy? Strength Condit J. 2019;41(5):108-13.

Carroll KM, Bernards JR, Bazyler CD, Taber CB, Stuart CA, DeWeese BH, et al. Divergent Performance
 Outcomes Following Resistance Training Using Repetition Maximums or Relative Intensity. Int J Sports Physiol Perform.
 2018:1-28. doi:10.1123/ijspp.2018-0045.

19. Foster C. Monitoring training in athletes with reference to overtraining syndrome. Med Sci Sports Exerc. 1998;30(7):1164-8. doi:10.1097/00005768-199807000-00023.

20. Emanuel A, Smukas I, Halperin I. An analysis of the perceived causes leading to task-failure in resistanceexercises. PeerJ. 2020;8:e9611. doi:10.7717/peerj.9611.

21. Gorostiaga EM, Navarro-Amézqueta I, Calbet JA, Hellsten Y, Cusso R, Guerrero M, et al. Energy metabolism during repeated sets of leg press exercise leading to failure or not. PLoS One. 2012;7(7):e40621. doi:10.1371/journal.pone.0040621.

Morán-Navarro R, Pérez CE, Mora-Rodríguez R, Cruz-Sánchez E, González-Badillo JJ, Sánchez-Medina L, et al. Time course of recovery following resistance training leading or not to failure. Eur J Appl Physiol. 2017;117(12):2387-99. doi:10.1007/s00421-017-3725-7.

 Raastad T, Bjøro T, Hallén J. Hormonal responses to high- and moderate-intensity strength exercise. Eur J Appl Physiol. 2000;82(1-2):121-8. doi:10.1007/s004210050661.

4.

24. Gorostiaga EM, Navarro-Amézqueta I, Cusso R, Hellsten Y, Calbet JA, Guerrero M, et al. Anaerobic energy expenditure and mechanical efficiency during exhaustive leg press exercise. PLoS One. 2010;5(10):e13486. doi:10.1371/journal.pone.0013486.

Gorostiaga EM, Navarro-Amézqueta I, Calbet JA, Sánchez-Medina L, Cusso R, Guerrero M, et al. Blood ammonia and lactate as markers of muscle metabolites during leg press exercise. J Strength Cond Res. 2014;28(10):2775-85. doi:10.1519/jsc.00000000000496.

26. Párraga-Montilla JA, García-Ramos A, Castaño-Zambudio A, Capelo-Ramírez F, González-Hernández JM,
Cordero-Rodríguez Y, et al. Acute and Delayed Effects of a Resistance Training Session Leading to Muscular Failure on
Mechanical, Metabolic, and Perceptual Responses. J Strength Cond Res. 2020;34(8):2220-6.
doi:10.1519/jsc.000000000002712.

27. Enoka RM, Duchateau J. Muscle fatigue: what, why and how it influences muscle function. J Physiol. 2008;586(1):11-23. doi:10.1113/jphysiol.2007.139477.

Place N, Yamada T, Bruton JD, Westerblad H. Muscle fatigue: from observations in humans to underlying mechanisms studied in intact single muscle fibres. Eur J Appl Physiol. 2010;110(1):1-15. doi:10.1007/s00421-010-1480-0.

29. González-Badillo JJ, Rodríguez-Rosell D, Sánchez-Medina L, Ribas J, López-López C, Mora-Custodio R, et al. Short-term Recovery Following Resistance Exercise Leading or not to Failure. Int J Sports Med. 2016;37(4):295-304. doi:10.1055/s-0035-1564254.

Pareja-Blanco F, Rodríguez-Rosell D, Sánchez-Medina L, Ribas-Serna J, López-López C, Mora-Custodio R, et al. Acute and delayed response to resistance exercise leading or not leading to muscle failure. Clin Physiol Funct Imaging. 2016;37(6):630-9. doi:10.1111/cpf.12348.

31. Pareja-Blanco F, Rodríguez-Rosell D, González-Badillo JJ. Time course of recovery from resistance exercise before and after a training program. J Sports Med Phys Fitness. 2019;59(9):1458-65. doi:10.23736/s0022-4707.19.09334-

3 32. Pareja-Blanco F, Rodríguez-Rosell D, Aagaard P, Sánchez-Medina L, Ribas-Serna J, Mora-Custodio R, et al.
4 Time Course of Recovery From Resistance Exercise With Different Set Configurations. J Strength Cond Res.
5 2020;34(10):2867-76. doi:10.1519/jsc.00000000002756.

33. Vøllestad NK. Measurement of human muscle fatigue. J Neurosci Methods. 1997;74(2):219-27. doi:10.1016/s0165-0270(97)02251-6.

34. Linnamo V, Pakarinen A, Komi PV, Kraemer WJ, Häkkinen K. Acute hormonal responses to submaximal and maximal heavy resistance and explosive exercises in men and women. J Strength Cond Res. 2005;19(3):566-71. doi:10.1519/r-15404.1.

35. Linnamo V, Häkkinen K, Komi PV. Neuromuscular fatigue and recovery in maximal compared to explosive strength loading. Eur J Appl Physiol Occup Physiol. 1998;77(1-2):176-81. doi:10.1007/s004210050317.

36. McLester JR, Bishop PA, Smith J, Wyers L, Dale B, Kozusko J, et al. A series of studies--a practical protocol for testing muscular endurance recovery. J Strength Cond Res. 2003;17(2):259-73. doi:10.1519/1533-4287(2003)017<0259:asospp>2.0.co;2.

37. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions. version 6.1 (updated September 2020) ed: Cochrane Collaboration; 2020.

38. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100. doi:10.1371/journal.pmed.1000100.

39. Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al. How to formulate research recommendations. Bmj. 2006;333(7572):804-6. doi:10.1136/bmj.38987.492014.94.

40. Davies T, Orr R, Halaki M, Hackett D. Effect of Training Leading to Repetition Failure on Muscular Strength:
 A Systematic Review and Meta-Analysis. Sports Med. 2016;46(4):487-502. doi:10.1007/s40279-015-0451-3.

41. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool
for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928. doi:10.1136/bmj.d5928.

42. Jukic I, Ramos AG, Helms ER, McGuigan MR, Tufano JJ. Acute Effects of Cluster and Rest Redistribution Set Structures on Mechanical, Metabolic, and Perceptual Fatigue During and After Resistance Training: A Systematic Review and Meta-analysis. Sports Med. 2020. doi:10.1007/s40279-020-01344-2.

43. Bax L, Yu LM, Ikeda N, Moons KG. A systematic comparison of software dedicated to meta-analysis of causal studies. BMC Med Res Methodol. 2007;7:40. doi:10.1186/1471-2288-7-40.

44. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97-111. doi:10.1002/jrsm.12.

45. Cohen J. The concepts of power analysis. Statistical power analysis for the behavioral sciences: Hillsdale, New Jersey: Academic Press, Inc; 1988.

46. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60. doi:10.1136/bmj.327.7414.557.

47. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test.
Bmj. 1997;315(7109):629-34. doi:10.1136/bmj.315.7109.629.

48. Claudino JG, Cronin J, Mezêncio B, McMaster DT, McGuigan M, Tricoli V, et al. The countermovement jump to monitor neuromuscular status: A meta-analysis. J Sci Med Sport. 2017;20(4):397-402. doi:10.1016/j.jsams.2016.08.011.

49. Koch AJ, Pereira R, Machado M. The creatine kinase response to resistance exercise. J Musculoskelet Neuronal Interact. 2014;14(1):68-77.

50. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. Bmj. 2004;328(7454):1490. doi:10.1136/bmj.328.7454.1490.

Arent S, Landers D, Matt K, Etnier J. Dose-Response and Mechanistic Issues in the Resistance Training and
Affect Relationship. J Sport Exerc Psychol. 2005;27:92-110. doi:10.1123/jsep.27.1.92.

52. Wilk M, Tufano JJ, Zajac A. The Influence of Movement Tempo on Acute Neuromuscular, Hormonal, and Mechanical Responses to Resistance Exercise-A Mini Review. J Strength Cond Res. 2020;34(8):2369-83. doi:10.1519/jsc.000000000003636.

53. Tran QT, Docherty D. Dynamic training volume: a construct of both time under tension and volume load. J Sports Sci Med. 2006;5(4):707-13.

54. Tran QT, Docherty D, Behm D. The effects of varying time under tension and volume load on acute neuromuscular responses. Eur J Appl Physiol. 2006;98(4):402-10. doi:10.1007/s00421-006-0297-3.

55. Lacerda LT, Martins-Costa HC, Diniz RC, Lima FV, Andrade AG, Tourino FD, et al. Variations in Repetition Duration and Repetition Numbers Influence Muscular Activation and Blood Lactate Response in Protocols Equalized by Time Under Tension. J Strength Cond Res. 2016;30(1):251-8. doi:10.1519/jsc.000000000001044.

56. Lacerda LT, Costa CG, Lima FV, Martins-Costa HC, Diniz RCR, Andrade AGP, et al. Longer Concentric Action Increases Muscle Activation and Neuromuscular Fatigue Responses in Protocols Equalized by Repetition Duration. J Strength Cond Res. 2019;33(6):1629-39. doi:10.1519/jsc.00000000002148.

57. Iglesias-Soler E, Carballeira E, Sánchez-Otero T, Mayo X, Jiménez A, Chapman ML. Acute effects of distribution of rest between repetitions. Int J Sports Med. 2012;33(5):351-8. doi:10.1055/s-0031-1299699.

58. Kent-Braun JA, Le Blanc R. Quantitation of central activation failure during maximal voluntary contractions in
 humans. Muscle Nerve. 1996;19(7):861-9. doi:10.1002/(sici)1097-4598(199607)19:7<861::Aid-mus8>3.0.Co;2-7.

59. Gandevia SC. Neural control in human muscle fatigue: changes in muscle afferents, motoneurones and motor
 cortical drive [corrected]. Acta Physiol Scand. 1998;162(3):275-83. doi:10.1046/j.1365-201X.1998.0299f.x.

618 60. Izquierdo M, Ibañez J, Calbet JA, González-Izal M, Navarro-Amézqueta I, Granados C, et al. Neuromuscular
619 fatigue after resistance training. Int J Sports Med. 2009;30(8):614-23. doi:10.1055/s-0029-1214379.

61. Ribeiro AS, Schoenfeld BJ, Nunes JP. Large and small muscles in resistance training: Is it time for a better definition? Strength Condit J. 2017;39(5):33-5. doi:10.1519/SSC.0000000000333.

62. Stathis CG, Zhao S, Carey MF, Snow RJ. Purine loss after repeated sprint bouts in humans. J Appl Physiol (1985). 1999;87(6):2037-42. doi:10.1152/jappl.1999.87.6.2037.

63. Gladden LB. Lactate metabolism: a new paradigm for the third millennium. J Physiol. 2004;558(Pt 1):5-30. doi:10.1113/jphysiol.2003.058701.

64. Cairns SP. Lactic acid and exercise performance : culprit or friend? Sports Med. 2006;36(4):279-91. doi:10.2165/00007256-200636040-00001.

65. Gordon SE, Kraemer WJ, Vos NH, Lynch JM, Knuttgen HG. Effect of acid-base balance on the growth hormone response to acute high-intensity cycle exercise. J Appl Physiol (1985). 1994;76(2):821-9. doi:10.1152/jappl.1994.76.2.821.

66. MacLean DA, Graham TE, Saltin B. Branched-chain amino acids augment ammonia metabolism while attenuating protein breakdown during exercise. Am J Physiol. 1994;267(6 Pt 1):E1010-22. doi:10.1152/ajpendo.1994.267.6.E1010.

67. Rojas Vega S, Hollmann W, Strüder HK. Influences of exercise and training on the circulating concentration of prolactin in humans. J Neuroendocrinol. 2012;24(3):395-402. doi:10.1111/j.1365-2826.2011.02266.x.

68. Jansson E, Dudley GA, Norman B, Tesch PA. ATP and IMP in single human muscle fibres after high intensity exercise. Clin Physiol. 1987;7(4):337-45. doi:10.1111/j.1475-097x.1987.tb00177.x.

69. Kang MS, Kim J, Lee J. Effect of different muscle contraction interventions using an isokinetic dynamometer on muscle recovery following muscle injury. J Exerc Rehabil. 2018;14(6):1080-4. doi:10.12965/jer.1836440.220.

70. Clarkson PM, Hubal MJ. Exercise-induced muscle damage in humans. Am J Phys Med Rehabil. 2002;81(11Suppl):S52-69. doi:10.1097/00002060-200211001-00007.

Chen TC, Yang TJ, Huang MJ, Wang HS, Tseng KW, Chen HL, et al. Damage and the repeated bout effect of
arm, leg, and trunk muscles induced by eccentric resistance exercises. Scand J Med Sci Sports. 2019;29(5):725-35.
doi:10.1111/sms.13388.

72. O'Connor FG, Brennan FH, Jr., Campbell W, Heled Y, Deuster P. Return to physical activity after exertional
rhabdomyolysis. Curr Sports Med Rep. 2008;7(6):328-31. doi:10.1249/JSR.0b013e31818f0317.

73. Hubal MJ, Devaney JM, Hoffman EP, Zambraski EJ, Gordish-Dressman H, Kearns AK, et al. CCL2 and CCR2 polymorphisms are associated with markers of exercise-induced skeletal muscle damage. J Appl Physiol (1985). 2010;108(6):1651-8. doi:10.1152/japplphysiol.00361.2009.

74. Rawson ES, Clarkson PM, Tarnopolsky MA. Perspectives on Exertional Rhabdomyolysis. Sports Med. 2017;47(Suppl 1):33-49. doi:10.1007/s40279-017-0689-z.

75. Çakir-Atabek H, Dokumaci B, Aygün C. Strength Loss After Eccentric Exercise Is Related to Oxidative Stress but Not Muscle Damage Biomarkers. Res Q Exerc Sport. 2019;90(3):385-94. doi:10.1080/02701367.2019.1603990.

76. Kraemer WJ, Noble BJ, Clark MJ, Culver BW. Physiologic responses to heavy-resistance exercise with very short rest periods. Int J Sports Med. 1987;8(4):247-52. doi:10.1055/s-2008-1025663.

77. Hardee JP, Lawrence MM, Utter AC, Triplett NT, Zwetsloot KA, McBride JM. Effect of inter-repetition rest on ratings of perceived exertion during multiple sets of the power clean. Eur J Appl Physiol. 2012;112(8):3141-7. doi:10.1007/s00421-011-2300-x.

Marcora SM, Staiano W, Manning V. Mental fatigue impairs physical performance in humans. J Appl Physiol (1985). 2009;106(3):857-64. doi:10.1152/japplphysiol.91324.2008.

Foster C, Florhaug JA, Franklin J, Gottschall L, Hrovatin LA, Parker S, et al. A new approach to monitoring
 exercise training. J Strength Cond Res. 2001;15(1):109-15.

80. Robertson RJ, Goss FL, Rutkowski J, Lenz B, Dixon C, Timmer J, et al. Concurrent validation of the OMNI perceived exertion scale for resistance exercise. Med Sci Sports Exerc. 2003;35(2):333-41. doi:10.1249/01.Mss.0000048831.15016.2a.

81. Borg G, Ljunggren G, Ceci R. The increase of perceived exertion, aches and pain in the legs, heart rate and blood lactate during exercise on a bicycle ergometer. Eur J Appl Physiol Occup Physiol. 1985;54(4):343-9. doi:10.1007/bf02337176.

82. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. Eur J Appl Physiol Occup Physiol. 1987;56(6):679-85. doi:10.1007/bf00424810.

83. Sweet TW, Foster C, McGuigan MR, Brice G. Quantitation of resistance training using the session rating of perceived exertion method. J Strength Cond Res. 2004;18(4):796-802. doi:10.1519/14153.1.

84. Sundstrup E, Jakobsen MD, Andersen CH, Zebis MK, Mortensen OS, Andersen LL. Muscle activation strategies during strength training with heavy loading vs. repetitions to failure. J Strength Cond Res. 2012;26(7):1897-903. doi:10.1519/JSC.0b013e318239c38e.

85. Nóbrega SR, Ugrinowitsch C, Pintanel L, Barcelos C, Libardi CA. Effect of Resistance Training to Muscle
Failure vs. Volitional Interruption at High- and Low-Intensities on Muscle Mass and Strength. J Strength Cond Res.
2018;32(1):162-9. doi:10.1519/jsc.00000000001787.

86. Lasevicius T, Schoenfeld BJ, Silva-Batista C, Barros TS, Aihara AY, Brendon H, et al. Muscle Failure Promotes
Greater Muscle Hypertrophy in Low-Load but Not in High-Load Resistance Training. J Strength Cond Res. 2019.
doi:10.1519/jsc.000000000003454.

682 87. Lacerda LT, Marra-Lopes RO, Diniz RCR, Lima FV, Rodrigues SA, Martins-Costa HC, et al. Is Performing
683 Repetitions to Failure Less Important Than Volume for Muscle Hypertrophy and Strength? J Strength Cond Res.
2
684 2020;34(5):1237-48. doi:10.1519/jsc.00000000003438.

88. Santanielo N, Nóbrega SR, Scarpelli MC, Alvarez IF, Otoboni GB, Pintanel L, et al. Effect of resistance training to muscle failure vs non-failure on strength, hypertrophy and muscle architecture in trained individuals. Biol Sport. 2020;37:9. doi:10.5114/biolsport.2020.96317.

89. Vieira JG, Dias MRC, Lacio M, Schimitz G, Nascimento G, Panza P, et al. Resistance Training with Repetition to Failure or not on Muscle Strength and Perceptual Responses. J Exerc Physiol Online. 2019;16(3).

90. Schoenfeld BJ, Ogborn D, Krieger JW. Effects of Resistance Training Frequency on Measures of Muscle
Hypertrophy: A Systematic Review and Meta-Analysis. Sports Med. 2016;46(11):1689-97. doi:10.1007/s40279-016-0543-8.

91. Schoenfeld BJ, Ogborn D, Krieger JW. Dose-response relationship between weekly resistance training volume and increases in muscle mass: A systematic review and meta-analysis. J Sports Sci. 2017;35(11):1073-82. doi:10.1080/02640414.2016.1210197.

92. Figueiredo VC, de Salles BF, Trajano GS. Volume for Muscle Hypertrophy and Health Outcomes: The Most Effective Variable in Resistance Training. Sports Med. 2018;48(3):499-505. doi:10.1007/s40279-017-0793-0.

93. Schoenfeld BJ, Contreras B, Krieger J, Grgic J, Delcastillo K, Belliard R, et al. Resistance Training Volume
Enhances Muscle Hypertrophy but Not Strength in Trained Men. Med Sci Sports Exerc. 2019;51(1):94-103.
doi:10.1249/mss.00000000001764.

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.

- 62

64

Study	Study design	Resistance exercise (s)	Prescription	Velocity of Movement	Volume	Outcome measure (s)
Arent et al. (2005)	Counterbalan	Bench press	TF: 3x10 @100% 10RM	Not reported	Not equalized	Rating of perceived exertion (au)
[51]	ced order and	Lat pulldown	TNF 1: 3x10 @70% 10RM	-	-	(Borg scale 15-point)
	cross-over	Shoulder press	TNF 2: 3x10 @40% 10RM			
	design	Seated rows	90 s interval between sets			
		Triceps				
		extensions				
		Biceps curls				
Fonseca et al.	Controlled,	Back squat	TF: 4x12 @12RM	Not controlled	Equalized	Vertical jump height - CMJ (cm)
(2020) [11]	randomized,		TNF: 8x6 @12RM			Power output for back squat (w)
	and cross-		3 min interval between sets			Rating of perceived exertion (au)
	over design					(Foster scale 10-point)
González-Badillo	Cross-over	Bench press	TF: 3x8 @80% 1RM	Concentric phase in	Not equalized	Vertical jump height - CMJ (%)
et al. (2016) [29]	design	Back squat	TNF: 3x4 @80% 1RM	maximal intended		Muscle damage - CK (IU·L ^{-1})
			5 min interval between sets	velocity and eccentric		Velocity of movement against V1-
				phase not reported		for bench press (%)
						Velocity of movement against V ₁ -
						for back squat (%)
Gorostiaga et al.	Randomized	Leg press	TF: 1x10 @10RM	Concentric and	Not equalized	Metabolic response - Ammonia
(2010) [24]	order and		TNF: 1x5 reps @10RM	eccentric phase		$(\mu mol \cdot L^{-1})$
	cross-over			performed as fast as		Metabolic response - Lactate (mm
	design			possible		¹)
						Power output for leg press (w)
Gorostiaga et al.	Randomized	Leg press	TF: 5x10 @10RM	Concentric and	Equalized	Power output for leg press (w)
(2012) [21]	order and		TNF: 10x5 reps @10RM	eccentric phase		
	cross-over		2 min interval between sets	performed as fast as		
	design			possible		
Gorostiaga et al.	Randomized	Leg press	TF: 5x10 @10RM	Concentric and	Equalized	Metabolic response - Ammonia
(2014) [25]	order and		TNF: 10x5 reps @10RM	eccentric phase		$(\mu mol \cdot L^{-1})$
	cross-over		2 min interval between sets	performed as fast as		Metabolic response - Lactate (mm
	design			possible		¹)
						Power output for leg press (w)

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	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)	The 2: 3x14 @40% TRM, 3 min interval between sets. 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	Not equalized	Metabolic response - Lactate (mmol ¹) Isometric force - Maximum voluntation isometric contraction for leg extensition (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·L ¹) Isometric force - Maximum voluntary isometric contraction for leg extension (leg press) (%)
Martorelli et al. (2020) [12]	Counterbalan ced order and cross-over design	Back squat Bench press	TF 1: 5xmaximum 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·I ¹) Muscle damage - CK (IU·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 $(\mu \text{mol} \cdot \text{L}^{-1})$ Vertical jump height - CMJ (%) Muscle damage - CK (IU·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 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 -loa for bench press (%) Velocity of movement against V ₁ -loa 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·s ⁻¹	Not equalized	Vertical jump height - CMJ (%) Muscle damage - CK ($IU \cdot L^{-1}$) Velocity of movement against V ₁ -loa for bench press (%) Velocity of movement against V ₁ -loa 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 TNF 4: 3x6 @85% 1RM TNF 4: 3x3 @85% 1RM TNF 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·s ⁻¹	Not equalized	Vertical jump height - CMJ (%) Muscle damage - CK (IU·L ⁻¹) Velocity of movement against V ₁ -loa for bench press (%) Velocity of movement against V ₁ -loa 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.	Counterbalan	Back squat	TF: 3x3 @3RM for squats,	Not reported	Not equalized	Metabolic response - Lactate (mmol·L
(2000) [23]	ced order and	Front squat	6 min interval between sets			¹)
	cross-over	Leg extension	3x6 @6RM for leg			
desi	design		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			
Sánchez-Medina &	Parallel	Bench press or	TF 1: 3x12 @12RM	Concentric phase in	Not equalized	Metabolic response - Ammonia
González-Badillo	design for the	Back squat	TNF 1: 3x6 @12RM	maximal intended	1.00 equalitee	$(\text{umol}\cdot\text{L}^{-1})$
et al. (2011) [4]	exercises and	Duck squu	TNF 2: 3x8 @12RM	velocity and eccentric		Metabolic response - Lactate (mmol·L
et ul. (2011) [1]	cross-over for		TNF 3: 3x10 @12 RM	nhase in velocity		
	the conditions		TE 2. 3v10 @10PM	controlled) Vertical jump height CMI (%)
	design		TNE 4 : $3x6 @ 100M$	controlled		Velocity of movement against V. load
	ucsign		TNE 5. 3_{x} 8 @ 10 M			for banch pross (%)
			TE 2. $2_{\pi^0} \otimes \text{PDM}$			Valacity of movement against V load
			TNE (: 2=4 @9DM			velocity of movement against v_1 -road
			INF 0: 3X4 @8RM			for back squat (%)
			INF 7: 3X0 @8RM			
			IF 4: 3X0 @0KM			
			TNF 9: 3x4 @6RM			
			TF 5: 3x4 @4RM			
			TNF 10: 3x2 @4RM			
			5 min interval between sets			

Study	Study design	Resistance exercise (s)	Prescription	Velocity of Movement	Volume	Outcome measure (s)
Shibata et al. (2019) [10]	I et al. Non- Back squat TF: 3xmaximum number of 2 s concentric phase Equalized [10] randomized repetitions @75% 1RM and 2 s eccentric order and TNF: 6xtotal number of phase cross-over reps performed TF @75% design 1RM	Equalized	Metabolic response - Lactate (mmol·L ¹) Isometric force - Maximum voluntary isometric contraction for leg extension (n)			
	-		3 min interval between sets			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)
resistance training	not performed to fa	ilure.			. ,	

Independent or dependent variables	SMD or RMD	95% CI	<i>p</i> -value	I^2 % (<i>p</i> -value)	Κ	<i>p</i> -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 (μ mol·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·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	
$48h \text{ post (IU} \cdot L^{-1})$	208.51	42.88; 374.15	0.014	67.01 (0.048)	3.0	

CI: confidence interval; CMJ: countermovement jump; I²: 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 V₁-load for bench press; Velocity SQ: Velocity of movement against V₁-load for squat.

Outcome	Summary of findings			Quality of evidence synthesis (GRADE)						
	k	п	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]	Ļ	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

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





Fig 2. Risk of bias in the primary studies.

Study	SMD [LL; UL]	Relative weight	SMD for biomechanical propert 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: Tau ² = 0.23; d	df = 6 (p = 0.052); I^2 = 51.88%	6	-4.00	-2.00	0.00	2.00	4.00	
Test for overall effect: $z = -4.18$ ($p = 0.001$)				TI	T T	NF		

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				÷=-	- 1	
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: Tau ² = 2.24; df = 5 ($p < 0.001$); $I^2 = 77.9$ Test for overall effect: $z = 7.88$ ($p < 0.001$)		92%	-10.00	-5.00 TN	0.00 F	5.00 TF	10.0	

С

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: $Tau^2 = 5194.0$ Test for overall effect: $z = 4$	03; df = 3 (p = 0.182); I^2 = 38.2	9% -50	00.00 -250.00 0.00 250.00 500.0 TNE TE				

D

Study	SMD [LL; UL]	Relative weight	e 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: Tau ² = 1.89; df = 5 ($p < 0.001$); I^2 = 87.11% Test for overall effect: $z = 3.98$ ($p < 0.001$)		11%	-9.00	-4.00 TN	0.00 F	4.00 TF	9.00

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.

















