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BASIC STUDY

The effects of exercise-induced muscle damage on varying intensities of endurance running performance: A systematic review and meta-analysis

Les effets des lésions musculaires induites par l'exercice sur les intensités variables de la performance de course d'endurance : une revue systématique et une méta-analyse

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KEYWORDS
Exercise-induced muscle damage ;
Delayed onset muscle damage ;
Running economy ;
Endurance running

Summary
Objectives. — This systematic review and meta-analysis investigated the effects of exercise-induced muscle damage (EIMD) on sub-maximal and maximal effort running performance.
News. — Physiological responses during sub-maximal running across two exercise stages (low intensity < 75% $\dot{V}O_{2\,max}$ and high intensity > 75% $\dot{V}O_{2\,max}$) were meta-analytically examined 24- and 48-hours after EIMD. Delayed onset muscle soreness (DOMS), intramuscular enzymes (creatine kinase [CK] and myoglobin [Mb]) and muscle function at the same time points were examined to confirm EIMD. Alterations to maximal-effort running performance 24- and 48-hours after EIMD were qualitatively analysed.
Prospects and projects. — Significant increases in DOMS, intramuscular enzymes, and decreases in muscle function were found 24 and 48 h after EIMD ($P < 0.05$). During low intensity running (< 75% $\dot{V}O_{2\,max}$), running economy (RE) and ventilation ($\dot{V}_E$) were unchanged 24 h after EIMD ($P > 0.05$), however, were significantly increased at 48 h ($P < 0.05$). Physiological responses during high intensity running (> 75% $\dot{V}O_{2\,max}$) were all significantly increased 24 and 48 h after EIMD

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($P < 0.05$). There was insufficient number of studies for maximal-effort running performance (time-to-exhaustion and time-trial performance) to be meta-analysed, however, 3 studies reported that outcome measures were impaired for up to 48 h post-EIMD.
Conclusion. — Endurance runners contemplating eccentric exercise to improve performance should consider the effects that EIMD has on running performance and periodise training accordingly.

MOTS CLÉS
Lésions musculaires induites par l'exercice ;
Douleurs musculaires à apparition retardée ;
Économie de course ;
Course d'endurance

Résumé
Objectifs. — Cette revue systématique et cette méta-analyse ont étudié les effets des lésions musculaires induites par l'exercice (LMIE) sur les performances de course à l'effort maximal et sous-maximal.
Méthodologie et résultats. — Les réponses physiologiques lors de la course sous-maximale à travers deux étapes d'exercice (faible intensité < 75 % $\dot{V}O_{2\,max}$ et haute intensité > 75 % $\dot{V}O_{2\,max}$) ont été examinées méta-analytiquement 24 et 48 heures après des LMIE. Les douleurs musculaires à apparition retardée (DMR), les enzymes intramusculaires (créatine kinase [CK] et myoglobine [Mb]) et la fonction musculaire ont été examinées aux mêmes moments pour confirmer les LMIE. Les modifications de la performance de course à effort maximal 24 et 48 heures après les LMIE ont été analysées qualitativement.
Perspectives et projets. — Des augmentations significatives des DMR, des enzymes intramusculaires et des diminutions de la fonction musculaire ont été trouvées 24 et 48 h après les LMIE ($p < 0,05$). Pendant la course à faible intensité (< 75 % $\dot{V}O_{2\,max}$), l'économie de course (RE) et la ventilation ($\dot{V}_E$) étaient inchangées 24 h après les LMIE ($p > 0,05$), mais elles étaient significativement augmentées à 48 h ($p < 0,05$). Les réponses physiologiques pendant la course à haute intensité (> 75 % $\dot{V}O_{2\,max}$) étaient toutes significativement augmentées 24 et 48 h après les LMIE ($p < 0,05$). Il n'y avait pas suffisamment d'études sur la performance de course à effort maximal (délai jusqu'à l'épuisement et performance contre la montre) pour être méta-analysées ; cependant, 3 études ont rapporté que les mesures des résultats étaient altérées jusqu'à 48 h après les LMIE.
Conclusion. — Les coureurs d'endurance qui envisagent des exercices excentriques pour améliorer leurs performances doivent tenir compte des effets des LMIE sur les performances de course et périodiser l'entraînement en conséquence.

1. Introduction

The prescription of exercise is fundamental to promote adaptation and improvements in athletic performance [1]. Nevertheless, exercise that involve strenuous, unaccustomed, and/or eccentric-biased activity exhibits substantial stress on the skeletal muscle, resulting in exercise-induced muscle damage (EIMD). The initial manifestations of EIMD include disruption to the sarcomeres and excitation-contraction (E-C) coupling system, followed by an inflammatory response, promoting the breakdown, removal, and resynthesis of damaged muscle fibres [2]. This disturbance to muscle fibre integrity often elicits EIMD-related symptoms, including delayed onset muscle soreness (DOMS), leakage of intramuscular enzymes (such as creatine kinase [CK]) into the circulation, and impaired muscle function [3], which can last for several days depending on the intensity and duration of the exercise completed [4]. Moreover, at their peak, typically 24—48 h after damage-inducing exercise, symptoms of EIMD impair several measures relating to athletic performance, such as peak power output [5], sprint and agility [6], jumping capability [7], and isometric and isokinetic strength [8].

Exercise-induced muscle damage also impairs determinants of running performance. Indeed, several studies have reported that running economy (RE), defined as the oxygen cost for a given sub-maximal running intensity, is elevated in the days after EIMD [9—21] with perturbations attributed to alterations in running stride pattern [9]. Likewise, minute ventilation [$\dot{V}_E$ during sub-maximal running is increased 24—48 h after EIMD [9—25], with the activation of nociceptive muscle afferents [15] being the suggested cause. Furthermore, running time-trial and time-to-exhaustion performance are also compromised in the days after EIMD [18,23,25], with an altered sense of effort [18], a reduction in neural drive, and increased inflammatory production [25] being the posited mechanisms.

Nevertheless, the negative consequences of EIMD on the physiological cost of sub-maximal running are not universally reported across the literature. There are studies that have shown no deleterious effects of EIMD on physiological responses during sub-maximal running [25—30]. However, these equivocal findings may be due to discrepancies in the methodological approaches used by previous studies (such as the type of EIMD protocol and the intensity of the endurance running protocol). The divergent EIMD and endurance running protocols make it difficult to provide a comprehensive interpretation of the effects of EIMD on running endurance performance. It is, therefore, important to systematically review the research, address the methodological distinctions, and ascertain the effects of EIMD on running performance based on a collection of findings from several studies.

Recent narrative reviews [31—33] provide some insight into the consequences of EIMD on endurance performance, however, the findings were solely based on the oxygen cost of running, with no reference to other physiological measures (such as $\dot{V}_E$) during sub-maximal running protocols. Given the importance of the pulmonary system during endurance performance [34], it is useful for $\dot{V}_E$ response to EIMD during sub-maximal running to be systematically and meta-analytically reviewed. Furthermore, simulated running time-trials, whereby participants complete a fixed amount of work or cover a set distance in the shortest time possible, enables the effects of EIMD to be examined in a setting indicative of how endurance athletes compete. However, this has yet to be considered in any reviews published thus far. Finally, runners commonly undertake strenuous exercises comprising eccentric contractions, such as resistance training, plyometrics, downhill and long-distance running to improve running performance [32,33,35]. Such training practices are known to elicit EIMD-related symptoms [9—25], therefore, a systematic review and meta-analysis of this topic would improve practical recommendations for runners engaging in various modes of training practices. The aims of the systematic review and meta-analysis were: (1) to investigate the effects of EIMD on physiological responses during sub-maximal running; and (2) examine the effects of EIMD on running time-trial and time-to-exhaustion performance.

2. Methods

To ensure transparency and complete reporting, the methodology of this systematic review and meta-analysis was conducted in accordance with the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [36].

2.1. Inclusion/exclusion criteria

To be included in this systematic review and meta-analysis, studies had to meet the following PICO criteria:

- participants: healthy human male and female adults;
- intervention studies examined the acute effects of lower limb muscle-damaging exercise (downhill running, plyometrics, resistance exercise, isokinetic dynamometry, distance running) on RE and $\dot{V}_E$ responses during fixed, sub-maximal running (minimum of 5 mins) and maximal-effort running performance, including time-trial (time taken to run a fixed distance or distance covered in a fixed time) and time-to-exhaustion performance (time duration at fixed-intensity running) running protocols;
- comparison: studies compared sub-maximal and maximal-effort running performance from pre-EIMD to 24 and 48 h after the muscle-damaging exercise;
- outcome: studies confirmed presence of EIMD via changes in one of the following indirect markers: elevations in blood levels of intramuscular enzymes (such as CK and Mb), increases in DOMS, and decreases in muscle function (MF) (such as isometric torque, isokinetic torque, and vertical jump height).

Studies were excluded if: (1) they were conducted in animals; (2) they investigated the effects of EIMD on endurance modalities other than running, such as cycling and upper arm ergometry; (3) the outcome measures were collected to examine the chronic adaptations to training, rather than the acute responses (such as the effects of a 6-week plyometric training program on RE); (4) any interventions, supplements and recovery strategies were used to attenuate any changes in running performance post-EIMD, however, data from any non-treatment groups, if EIMD evoked significant changes in the key indirect markers listed above were included, for example, placebo group data for a study that examined the impact of a supplement to ameliorate EIMD was included, however, the supplement group data was excluded; (5) the paper was not written in English; and (6) findings were reported as a conference abstract, review, or case study.

2.2. Outcome measures

Studies were examined for the effects of EIMD on running endurance performance across three outcome measures: (1) sub-maximal running (minimum of 5 mins); (2) running time-trial performance; and (3) running time-to-exhaustion performance. The outcome measures for sub-maximal running included RE and $\dot{V}_E$ responses. The outcome measures for running time-trial performance comprised distance covered in a fixed time (such as 30 mins) or time-to-completion of a fixed distance (such as 5 km). The outcome measures for running time-to-exhaustion included time-to-reach volitional exhaustion during fixed-intensity running (such as 80% $\dot{V}O_{2\,max}$).

2.3. Search strategy

All literature that investigated the effects of EIMD on running endurance performance was searched and collated in May 2020 using the following online databases; PubMed, Cinhal, Scopus, SPORTDiscus, and Web of Science. MeSH headings were used for the literature search in PubMed, whilst, free text terms, with a date restriction of the past two years, were used for the other databases (please see Table 1 for a list of all search terms used during the literature search). There were no limits used on the status or language of the publication in the search strategy. A summary of the literature search and selection process, in accordance with the PRISMA guidelines is shown in Fig. 1. A screening of the reference lists of all included studies was also conducted to locate any additional studies missed from the database literature search.

Table 1 Search terms and databases used in the literature search.

Initial search: assessment retrieval	Database and search terms	Limitations
MeSH headings	PubMed: ''Humans''[Mesh] and ''Muscle, Skeletal''[Mesh] or ''Muscular Diseases''[Mesh] or ''Pain/etiology''[Mesh] or ''Pain/physiopathology''[Mesh] or ''Myalgia''[Mesh] OR ''Creatine Kinase''[Mesh] or ''Cumulative Trauma Disorders''[Mesh] or ''Muscle Strength''[Mesh] or ''L-Lactate Dehydrogenase''[Mesh] or ''Myoglobin''[Mesh] or ''Muscle Fatigue''[Mesh] and ''Running''[Mesh]	
Free text terms	Cinhal, Scopus, SPORTDiscus, Web of Science: ''Muscle damage'' or ''Creatine Kinase'' or Myoglobin or ''Lactate dehydrogenase'' or Sore or Soreness and running	Publication date from 09/05/2018—09/05/2020

2.4. Selection process

Abstract screening was completed by two reviewers (DB and JC) with post-graduate qualifications in Sport and Exercise Science. Using the inclusion criteria, shown above, abstracts were highlighted as either ''yes'' (meeting the criteria), ''maybe'' (possibly meeting the criteria) or ''no'' (not meeting the criteria). Inter-reviewer reliability of the inclusion criteria was performed on a randomly selected 40% sample of abstracts. Using the weighted kappa statistic, the inter-rater reliability of the inclusion criteria was 0.887 (0.777—0.997), which is considered excellent [37]. Full text articles were then extracted and further screened in accordance with the inclusion/exclusion criteria.

2.5. Data extraction, assessment of quality, and risk of bias

Data was extracted into a custom-built excel spread sheet for the following: (1) participant characteristics (sex, sample size, training status, age, stature, body mass, $\dot{V}O_{2\,max}$); (2) lower limb muscle-damaging protocol; (3) indirect markers of EIMD and the time points they were collected (i.e., 24 and 48 h post-EIMD); (4) type of running protocols (i.e., exercise intensity and duration, time-to-exhaustion and time trial distance); and (5) type of outcome measures collected during the running protocols. The pre-and post-EIMD outcome measures were extracted as mean ± standard deviation. To assess the methodological quality of each study, the Kmet scoring tool [38] was used. The checklist for assessing the quality of quantitative studies, originally comprising 14 items, was modified to accommodate confounding factors pertinent to studies investigating the effects of EIMD on sub-maximal and maximal effort running performance. Upon reviewing the checklist instructions, items 5, 6, 7, and 12 were deemed not appropriate and were replaced with items assessing whether: (1) participants avoided lower limb muscle-damaging exercise for at least 6 months prior to data collection [39]; (2) outcome measures were collected for 48 h over consecutive days; (3) studies confirmed presence of EIMD via measuring changes in indirect markers of muscle damage; and (4) participants avoided any unaccustomed or strenuous exercise and any analgesic, anti-oxidant, and nutritional supplements during the study. Each item was scored a 'two', 'one', or 'zero' based on whether the item was met, partially met, or not met, respectively. For the modified items, a description was provided to determine the scoring, for example, 'two' was awarded if outcome measures were collected for 48 h over consecutive days (e.g., outcome measures were collected at 24 and 48 h); 'one' if studies collected outcome measures for 48 h, but not over consecutive days (e.g., outcome measures were collected at 48 h, but not at 24 h); and 'zero' if outcome measures were only collected at 24 h post-EIMD. A summary score was calculated for each study by summing the total of 'met' and 'partially met' items with a maximum score of 28. The score was rated against the following classification of quality: excellent (24—28); good (19—23); fair (14—18); and poor (< 13). The participant selection bias was minimised by incorporating studies with all healthy adult participants, irrespective of gender and training status.

2.6. Statistical methods

The RevMan software was used to conduct the meta-analysis to determine the effects of EIMD on running performance (RevMan, Version 5.4, Copenhagen: The Nordic Cochrane Centre, 2014). All outcome measures of interest (such as, the physiological, metabolic, and perceptual responses during fixed, sub-maximal running, time-to-complete a time trial, and time-to-exhaustion during fixed intensity running) from each study were reported as mean ± standard deviation at baseline (i.e., before the muscle damage protocol) and 24 and 48 h post-EIMD. The heterogeneity of data between each study was determined using the I^2 statistic, with values of 25%, 50%, and 75% classified as low, moderate, and high, respectively. Forest plots were generated as random effects models to control for inter-study heterogeneity, with the overall summary effect reported as standardised mean differences (SMD). The SMD values of 0.2, 0.5, and 0.8 were classified as small, moderate, and large, respectively [40]. The level of significance for each SMD was determined based on Z-scores and the associated *P*-value, with the alpha level set at 0.05.

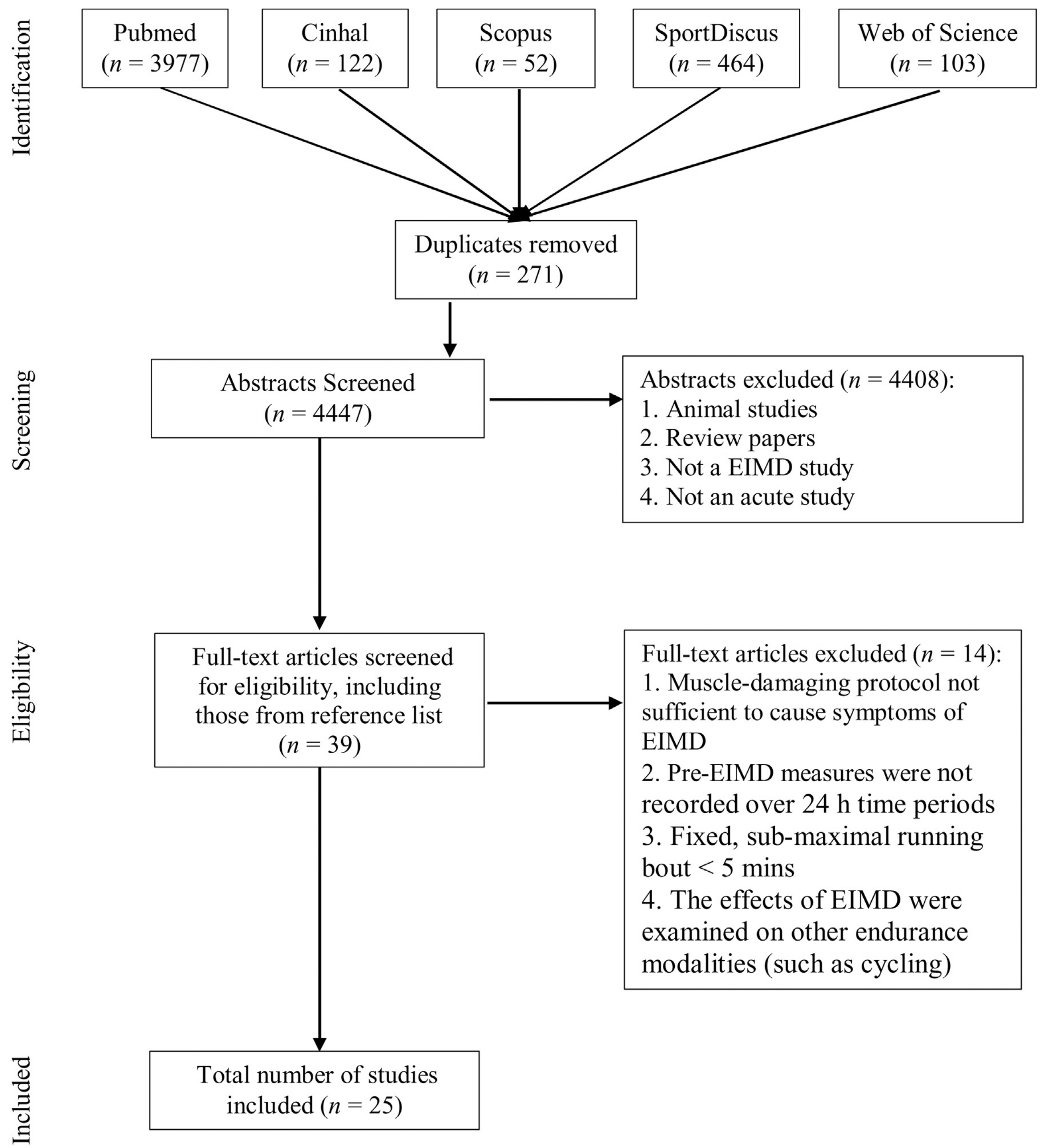

Figure 1 Flow chart of the search strategy in accordance with the PRISMA guidelines.

3. Results

3.1. Systematic literature search

The literature search found 4718 items, which, after duplicates were removed, yielded a total of 4,447 abstracts to be screened in the selection process. Following abstract screening, 39 full-text articles were screened for eligibility. Searches of reference lists revealed no additional studies. After further screening against the inclusion/exclusion criteria, 14 studies were removed, leaving 25 studies for inclusion in the final meta-analysis (see Fig. 1).

3.2. Participants

Across the identified studies examining the effects of EIMD on sub-maximal and maximal effort running, a total sample size of 336 participants (306 males and 30 females) were recruited. The mean age, stature, body mass, and $\dot{V}O_{2\,max}$ of all participants were 24.9 (20.5—35.2 years), 175.8 (167—183 cm), 73.5 (63.1—83.8 kg), and 52.2 (41.8—65 ml·kg^{-1}·min^{-1}), respectively. Regarding training background, 11 studies recruited recreational runners who engaged in 2—3 endurance sessions per week, 3 studies recruited experienced and well-trained distance runners and triathletes with an average training volume ranging from 40—60 km·week, 3 studies recruited participants who regularly engaged in physical activity, however, provided no detail on the number of training sessions per week, 3 studies recruited physical education and sport science students, 1 study recruited soccer players training 5 days (14 hours) per week, 2 studies recruited untrained participants, and 2 studies did not report participants training background.

3.3. Methodological descriptions

All 25 studies adopted a repeated measures design, whereby baseline measures were repeated in the 24 and 48 h after lower limb muscle-damaging exercise. A range of exercise protocols were used to elicit EIMD, with the most common being downhill running (12 studies), followed by lower limb resistance exercise (7 studies), eccentric maximal voluntary contractions (MVC) (2 studies), marathon running (2 studies), plyometrics (1 study), and duathlon (1 study). For indirect muscle damage markers, 22 studies measured changes in CK, Mb, and DOMS ranging from 24 to 48 h after EIMD. Muscle function was measured in 19 studies across the 24 to 48 h period post-EIMD. Only 1 study failed to measure any indirect markers of EIMD. The effects of EIMD on sub-maximal running were assessed across a range of exercise intensities (~58—90% $\dot{V}O_{2\,max}$). Given the board exercise range, extracted data were split into lower (< 75% $\dot{V}O_{2\,max}$) and higher (> 75% $\dot{V}O_{2\,max}$) stages. Ten studies examined the impact of EIMD on sub-maximal running over more than one exercise intensity (4 studies examined 2 different exercise intensities, 5 studies examined 3 exercise intensities, and 1 study examined 4 exercise intensities). During low-intensity sub-maximal running, RE was examined in 13 studies, with 11 and 25 data sets extracted at 24 and 48 h post-EIMD, respectively. Minute ventilation was recorded in 9 studies, with 6 and 20 data sets extracted at 24 h and 48 h post-EIMD, respectively. During high-intensity sub-maximal running, RE was investigated in 17 studies, with 13 and 19 data sets extracted at 24 and 48 h after EIMD, respectively. Minute ventilation was recorded in 14 studies, with 11 and 16 data sets extracted at 24 h and 48 h post-EIMD, respectively. Due to insufficient data, a forest plot for the effects of EIMD on running time-trial and time-to-exhaustion performance was not generated, however, study details are provided in Table 2 below.

3.4. Methodological quality

The assessment of methodological quality using the Kmet et al. [38] checklist ranged from fair to excellent (refer to Table 3). Items relating to subject characteristics (item 4), analytic methods (item 10), estimate of variance (item 11), results reported in sufficient detail (item 13), and conclusions supported by the results (item 14) were scored very highly with most studies meeting the criteria. Items relating to method of subject/comparison group selection or source of information/input variables (item 3), outcome measures being collected for 48 h over consecutive days (item 6), confirming the presence of EIMD via indirect markers of muscle damage (item 7), and outcome and exposure measures well defined and robust to measurement/misclassification bias and means of assessment reported (item 8) were scored highly with the majority of studies meeting, or partially meeting, the criteria. Items relating to question/objective sufficiently described (item 1), study design evident and appropriate (item 2), sample size appropriate (item 9), and participants avoided any unaccustomed or strenuous exercise and analgesic agents, and antioxidant and nutritional supplements during the study (item 12) were scored moderately with most studies partially meeting the criteria. Item on whether participants avoided lower limb muscle-damaging exercise for at least 6 months prior to data collection (item 5) was rated the lowest with half the studies meeting the criteria.

3.5. Quantitative analysis

3.5.1. Indirect markers of muscle damage

The lower limb muscle-damaging protocols used in the identified studies were effective at evoking symptoms of EIMD (Fig. 2). Blood levels of intramuscular enzymes (CK and Mb) were significantly elevated at 24 h ($Z = 10.47$, $P < 0.00001$) and 48 h ($Z = 10.18$, $P < 0.00001$) post-EIMD, with a large magnitude of difference shown (SMD = 1.42 and 1.37 at 24 and 48 h, respectively). Furthermore, inter-study heterogeneity for intramuscular enzymes was low at 24 h ($I^2 = 0\%$) and 48 h ($I^2 = 46\%$) after muscle-damaging exercise. Delayed onset muscle soreness was also significantly increased at 24 h ($Z = 10.32$, $P < 0.00001$) and 48 h ($Z = 12.15$, $P < 0.00001$) after EIMD, with a large magnitude of difference (24 h: SMD = 3.00; 48 h: SMD = 3.06) and moderate inter-study heterogeneity shown (24 h: $I^2 = 61\%$; 48 h: $I^2 = 57\%$). Muscle function was significantly reduced at 24 h ($Z = 5.84$, $P < 0.00001$) and 48 h ($Z = 6.92$, $P < 0.00001$) post muscle-damaging exercise, with a large magnitude of difference (24 h: SMD = −1.08; 48 h: SMD = −0.90) and moderate inter-study heterogeneity (24 h: $I^2 = 73\%$; 48 h: $I^2 = 62\%$).

3.5.2. Sub-maximal running: stage 1

Stage 1 comprised those studies that examined RE and $\dot{V}_E$ responses during sub-maximal running at an exercise intensity equivalent to below 75% $\dot{V}O_{2\,max}$ (Fig. 3). The meta-analysis revealed that, whilst there was no significant change in RE at 24 h ($Z = 1.15$, $P = 0.25$), RE was significantly increased 48 h post-EIMD ($Z = 1.94$, $P = 0.05$). Low inter-study heterogeneity was identified for RE at 24 h ($I^2 = 0\%$) and 48 h ($I^2 = 18\%$) after muscle-damaging exercise. However, the magnitude of differences in RE were small at both 24 h (SMD = 0.11) and 48 h (SMD = 0.12) after EIMD. Similarly, $\dot{V}_E$ was unchanged at 24 h ($Z = 1.68$, $P = 0.09$) and significantly increased at 48 h after muscle-damaging exercise ($Z = 2.39$, $P = 0.02$), with low inter-study heterogeneity (24 h: $I^2 = 0\%$; 48 h: $I^2 = 0\%$) and a small magnitude of difference (24 h: SMD = 0.20; 48 h: SMD = 0.16).

3.5.3. Sub-maximal running: stage 2

Stage 2 comprised those identified studies that examined the physiological and perceptual responses during fixed, sub-maximal running at an exercise intensity equivalent to above 75% $\dot{V}O_{2\,max}$ (Fig. 3). The meta-analysis revealed that RE was significantly increased at 24 h ($Z = 4.25$, $P < 0.0001$) and 48 h ($Z = 5.37$, $P < 0.00001$) after muscle-damaging exercise, with

Table 2 Methodological description and qualitative results of EIMD, sub-maximal and maximal effort running performance outcome measures.

Study	Participant characteristics	EIMD protocol	Running performance protocol	EIMD outcome	Sub-maximal running outcome	Maximal effort outcome
Baumann et al. [56]	Recreationally active for at least 3 × per week (45 mins per session), n = 11 males, age = 27.5 ± 1.7 y, stature = 179 ± 1 cm, BM = 83.8 ± 3.1, $\dot{V}O_{2\,max}$ = 50.05 ± 1.67 mL·kg^{-1}·min^{-1}	6 × 5 mins downhill running at 12.9 km·h^{-1} with −12% gradient	10 mins at 65% $\dot{V}O_{2\,max}$ 10 mins at 75% $\dot{V}O_{2\,max}$	↑ CK 48 h ↑ DOMS 48 h ↓ MF 48 h	↑ RE 48 h at 65% $\dot{V}O_{2\,max}$ ↔ RE 48 h at 75% $\dot{V}O_{2\,max}$ ↔ V_E 48 h at 65% & 75% $\dot{V}O_{2\,max}$	None
Braun & Dutto [9]	Well trained triathletes & distance runners (training volume = 60.4 km.week^{-1}), n = 9 males, age = 31.4 ± 5.4 y, stature = 178.6 ± 5.3 cm, BM = 75.7 ± 9.6 kg, $\dot{V}O_{2\,max}$ = 58.4 ± 7.7 mL·kg^{-1}·min^{-1}	30 mins downhill running at 70% $\dot{V}O_{2\,max}$ with −10% gradient	5 mins at 65% $\dot{V}O_{2\,max}$ 5 mins at 75% $\dot{V}O_{2\,max}$ 5 mins at 85% $\dot{V}O_{2\,max}$	↑ DOMS 48 h	↑ Mean RE 48 h ↑ Mean V_E 48 h	None
Burnett et al. [26]	Recreational distance runners (training volume = 3—7 h per week), n = 6 females, age = 24.5 ± 3.5 y, stature = 170 ± 6.6 cm, BM = 63.6 ± 9.2 kg, $\dot{V}O_{2\,max}$ = 2.78 ± 0.25 L·min^{-1}	30 mins downhill running at 70% $\dot{V}O_{2\,max}$ with −15% gradient	5 mins at 65% $\dot{V}O_{2\,max}$ 5 mins at 75% $\dot{V}O_{2\,max}$ 5 mins at 85% $\dot{V}O_{2\,max}$	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h	↔ RE at 24 & 48 h at 65%, 75%, & 85% $\dot{V}O_{2\,max}$	None
Burt et al. [15]	Regularly engaged in PA, n = 10 males, age = 22.8 ± 2.5 y, stature 177 ± 6 cm, BM = 75.9 ± 8.8 kg, $\dot{V}O_{2\,max}$ = 52 ± 6.1 mL·kg^{-1}·min^{-1}	10 sets of 10 Smith machine squats at 80% BM	10 mins at LT (80% $\dot{V}O_{2\,max}$)	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h ↑ V_E 24 & 48 h	None
Burt et al. [16]	2—3 × ET per week, n = 9 males, age = 25.8 ± 4.1 y, stature = 180 ± 9 cm, BM = 79.6 ± 9.9 kg, $\dot{V}O_{2\,max}$ = 54.2 ± 3.2 mL·kg^{-1}·min^{-1}	10 sets of 10 Smith machine squats at 80% BM	10 mins at LTP (87% $\dot{V}O_{2\,max}$)	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h ↑ V_E 24 & 48 h	None
Burt et al. [17]	2—3 × ET per week, n = 8 males, age = 24.3 ± 1.7 y, stature = 181 ± 8 cm, BM = 77.4 ± 10.8 kg, $\dot{V}O_{2\,max}$ = 54.2 ± 5.5 mL·kg^{-1}·min^{-1}	10 sets of 10 Smith machine squats at 80% BM	10 mins at LTP (85% $\dot{V}O_{2\,max}$)	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h ↑ V_E 24 & 48 h	None
Burt et al. [18][a]	2—3 × ET per week, n = 8 males, age = 26 ± 5 y, stature = 179 ± 5 cm, BM = 79.5 ± 7.8 kg, $\dot{V}O_{2\,max}$ = 54.8 ± 3.5 mL·kg^{-1}·min^{-1}	5 sets of 10 Smith machine squats at 80% BM	5 mins at LTP (86% $\dot{V}O_{2\,max}$) 3 km time-trial	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h ↑ V_E 24 & 48 h	↑ Time to complete time-trial at 48 h

Table 2 (*Continued*)

Study	Participant characteristics	EIMD protocol	Running performance protocol	EIMD outcome	Sub-maximal running outcome	Maximal effort outcome
Burt et al. [18][b]	2–3 × ET per week, *n* = 8 males, age = 27 ± 4 y, stature = 177 ± 10 cm, BM = 76.7 ± 9.8 kg, $\dot{V}O_{2max}$ = 54.2 ± 4.1 mL·kg^{-1}·min^{-1}	10 sets of 10 Smith machine squats at 80% BM	5 mins at LTP (86% $\dot{V}O_{2max}$) 3 km time-trial	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h ↑ $\dot{V}_E$ 24 & 48 h	↑ Time to complete time-trial at 48 h
Calbet et al. [57]	Physical education students, *n* = 9 males & 6 females, age = 24 ± 1.1 y, 175.6 ± 0.8 cm, BM = 66.6 ± 2.9 kg, $\dot{V}O_{2max}$ = 56.1 ± 4.6 mL·kg^{-1}·min^{-1}	Duathlon (5 km running, 16 km cycling, 2 km running)	6 mins at 58% $\dot{V}O_{2max}$ 6 mins at 63% $\dot{V}O_{2max}$ 6 mins at 67% $\dot{V}O_{2max}$ 6 mins at 71% $\dot{V}O_{2max}$		↑ RE 48 h at 58%, 63%, 67%, & 71% $\dot{V}O_{2max}$ ↔ $\dot{V}_E$ 48 h at 58%, 63%, 67%, & 71% $\dot{V}O_{2max}$	None
Chen et al. [10]	Soccer training 5 × per week, *n* = 10 males, age = 20.5 ± 1.5 y, stature = 173 ± 7 cm, BM = 66 ± 7.6 kg, $\dot{V}O_{2max}$ = 54.6 ± 4.6 mL·kg^{-1}·min^{-1}	30 mins downhill running at 70% $\dot{V}O_{2max}$ with −15% gradient	5 mins at 65% $\dot{V}O_{2max}$ 5 mins at 75% $\dot{V}O_{2max}$ 5 mins at 85% $\dot{V}O_{2max}$	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h at 65%, 75%, & 85% $\dot{V}O_{2max}$ ↑ $\dot{V}_E$ 24 & 48 h at 85% $\dot{V}O_{2max}$	None
Chen et al. [11]	Healthy & PA, *n* = 12 males, age = 22.4 ± 0.9 y, stature = 173.3 ± 6.4 cm, BM = 66.2 ± 10.2 kg	30 mins downhill running at 70% $\dot{V}O_{2max}$ with −26% gradient	5 mins at 85% $\dot{V}O_{2max}$	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 48 h ↑ $\dot{V}_E$ 48 h	None
Chen et al. [12]	*n* = 12 males, age = 20.2 ± 1.3 y, stature = 173.5 ± 6.5 cm, BM = 65.7 ± 7.3 kg, $\dot{V}O_{2max}$ = 55.7 ± 4.8 ml·kg^{-1}·min^{-1}	30 mins downhill running at 70% $\dot{V}O_{2max}$ with −15% gradient	5 mins at 85% $\dot{V}O_{2max}$	↑ Mb 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h ↑ $\dot{V}_E$ 24 & 48 h	None
Chen et al. [13]	n = 10 males, age = 21.1 ± 2.3 y, stature = 174.5 ± 5.8 cm, BM = 67.8 ± 6.9 kg, $\dot{V}O_{2max}$ = 55.3 ± 6.3 mL·kg^{-1}·min^{-1}	30 mins downhill running at 70% $\dot{V}O_{2max}$ with −15% gradient	5 mins at 85% $\dot{V}O_{2max}$	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 48 h ↑ $\dot{V}_E$ 48 h	None
Chen et al. [14]	*n* = 15 males, age = 21.5 ± 1.6 y, stature = 172 ± 6 cm, BM = 64.8 ± 8.4 kg, $\dot{V}O_{2max}$ = 49.8 ± 5.4 mL·kg^{-1}·min^{-1}	30 mins downhill running at 70% $\dot{V}O_{2max}$ with −16% gradient	5 mins at 70% $\dot{V}O_{2max}$ 5 mins at 80% $\dot{V}O_{2max}$ 5 mins at 90% $\dot{V}O_{2max}$	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↔ RE & $\dot{V}_E$, at 70% $\dot{V}O_{2max}$ ↑ RE & $\dot{V}_E$ at 80% & 90% $\dot{V}O_{2max}$	None

Table 2 (*Continued*)

Study	Participant characteristics	EIMD protocol	Running performance protocol	EIMD outcome	Sub-maximal running outcome	Maximal effort outcome
Doma et al. [22]	2—3 (30—60 mins) moderate intensity running sessions per week, n = 14 males, age = 24 ± 3.9 y, stature = 183 ± 11 cm, BM = 77.4 ± 14 kg, $\dot{V}O_{2\,max}$ = 48.1 ± 6.1 mL·kg^{-1}·min^{-1}	3 sets of 6 squats, single-leg leg press, leg extension, & leg curls at 95% 6RM	10 mins at 90% VT2 (86% $\dot{V}O_{2\,max}$)	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↔ RE 24 & 48 h ↑ $\dot{V}_E$ 24 & 48 h	None
Doma et al. [23]	2—3 (30—60 mins) moderate intensity running sessions per week, n = 12 males, age = 24 ± 4 y, stature = 181 ± 10 cm, BM = 79.3 ± 10.9 kg, $\dot{V}O_{2\,max}$ = 48.2 ± 6.5 mL·kg^{-1}·min^{-1}	3 sets of 6 squats, single-leg leg press, leg extension, & leg curls at 95% 6RM	10 mins at 90% VT2 (85% $\dot{V}O_{2\,max}$) TTE at 110% VT2	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↔ RE 24 & 48 h ↔ $\dot{V}_E$ 24 & 48 h	↓ TTE at 24 and 48 h
Hamill et al. [58]	Recreational runners (< 20 miles per week), n = 10 females, age = 23.4 ± 2.8 y, stature = 167 ± 7 cm, BM = 63.1 ± 7.9 kg, $\dot{V}O_{2\,max}$ = 47.6 ± 4.3 mL·kg^{-1}·min^{-1}	30 mins downhill running at 73.5% HRmax with −15% gradient	15 mins at 80% $\dot{V}O_{2\,max}$	↑ CK 48 h ↑ DOMS 48 h	↔ RE 48 h	None
Kyrolainen et al. [27]	Triathletes (training volume = 160 km per month), n = 6 males & 1 female, age = 29 ± 5 y, stature = 182 ± 7 cm, BM = 82 ± 11.2 kg, $\dot{V}O_{2\,max}$ = 65 ± 7.6 mL·kg^{-1}·min^{-1}	Marathon (26.2 km run)	5 mins at 3.82 m·s^{-1} (64% $\dot{V}O_{2\,max}$)	↑ CK 48 h	↔ RE 48 h	None
Lima et al. [19]	Healthy, n = 15 males, age = 22.8 ± 2.3 y, stature = 177 ± 4 cm, BM = 78.6 ± 8.9 kg, $\dot{V}O_{2\,max}$ = 42.5 ± 4.1 mL·kg^{-1}·min^{-1}	30 mins downhill running at 70% $\dot{V}O_{2\,max}$ with −15% gradient	5 mins at 80% $\dot{V}O_{2\,max}$	↑ CK 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h ↑ $\dot{V}_E$ 24 & 48 h	None
Lima et al. [20]	Physical education students, n = 15 males, age = 22.8 ± 2.8 y, stature = 174 ± 7 cm, BM = 79.5 ± 11.8 kg, $\dot{V}O_{2\,max}$ = 41.8 ± 5.7 mL·kg^{-1}·min^{-1}	30 mins downhill running at 70% $\dot{V}O_{2\,max}$ with −15% gradient	5 mins at 80% $\dot{V}O_{2\,max}$	↑ CK 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h	None
Lima et al. [21]	Physical education students, n = 45 males, age = 22.8 2.5 y, stature = 176 ± 5 cm, BM = 78.9 ± 9.8 kg, $\dot{V}O_{2\,max}$ = 42.7 ± 4.4 mL·kg^{-1}·min^{-1}	30 mins downhill running at 70% $\dot{V}O_{2\,max}$ with −15% gradient	5 mins at 80% $\dot{V}O_{2\,max}$	↑ CK 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↑ RE 24 & 48 h ↑ $\dot{V}_E$ 24 & 48 h	None
Marcora & Bosio [25]	Sport science students, recreational runners & triathletes 2 (30 mins) × ET per week, n = 12 males & 3 = females, age = 31 ± 9 y, stature = 175 ± 9 cm, BM = 72.7 ± 9.6 kg, $\dot{V}O_{2\,max}$ = 53.3 ± 6.1 mL·kg^{-1}·min^{-1}	10 sets of 10 drop jumps from 35 cm bench	10 mins at 70% $\dot{V}O_{2\,max}$ 30 mins time-trial (run as far as possible in allotted time)	↑ CK 48 h ↑ DOMS 48 h ↓ MF 48 h	↔ RE 48 h ↔ $\dot{V}_E$ 48 h	↓ distance covered during the time-trial at 48 h

Table 2 (*Continued*)

Study	Participant characteristics	EIMD protocol	Running performance protocol	EIMD outcome	Sub-maximal running outcome	Maximal effort outcome
Paschalis et al. [28]	Healthy, n = 10 males, age = 23 ± 1 y, stature = 175 ± 0.5 cm, BM = 74 ± 0.5 kg, $\dot{V}O_{2\,max}$ = 52.5 ± 2.4 mL kg^{-1}·min^{-1}	12 sets of 10 eccentric MVCs	6 mins at 133 m·min^{-1} (55% $\dot{V}O_{2\,max}$) 6 mins at 200 m·min^{-1} (75% $\dot{V}O_{2\,max}$)	↑ CK 24 & 48 h ↑ DOMS 24 & 48 h ↓ MF 24 & 48 h	↔ RE 24 & 48 h at 55% & 75% $\dot{V}O_{2\,max}$ ↔ $\dot{V}_E$ 24 & 48 h at 55% & 75% $\dot{V}O_{2\,max}$	None
Paschalis et al. [29][a]	Healthy, n = 24 males (n = 12 exercise group[1], n = 12 rest group[2]), age = 22 ± 3 y, stature = 176 ± 5 cm, BM = 74 ± 6 kg, $\dot{V}O_{2\,max}$ = 49.9 ± 6.5 mL kg^{-1}·min^{-1}	12 sets of 10 eccentric MVCs	6 mins at 2.2 m·sec^{-1} (55% $\dot{V}O_{2\,max}$) 6 mins at 3.3 m·sec^{-1} (75% $\dot{V}O_{2\,max}$)	↑ CK 48 h ↑ DOMS 48 h ↓ MF 48 h	↔ RE 48 h at 55% & 75% $\dot{V}O_{2\,max}$ ↔ $\dot{V}_E$ 48 h at 55% & 75% $\dot{V}O_{2\,max}$	None
Paschalis et al. [29][b]				↑ CK 48 h ↑ DOMS 48 h ↓ MF 48 h	↔ RE 48 h at 55% & 75% $\dot{V}O_{2\,max}$ ↔ $\dot{V}_E$ 48 h at 55% & 75% $\dot{V}O_{2\,max}$	
Quinn & Manley [30]	Endurance runners & triathletes (training volume = 56 km over 4—5 days a week), age = 35.2 ± 11.1 y, stature = 171.2 ± 14.5 cm, BM = 73.6 ± 11.9 kg, $\dot{V}O_{2\,max}$ = 63.6 ± 12.7 mL·kg^{-1}·min^{-1}	26 km run	5 mins at 3.1 m·sec^{-1} (55% $\dot{V}O_{2\,max}$) 5 mins at 3.6 m·sec^{-1} (64% $\dot{V}O_{2\,max}$) 5 mins at 4 m·sec^{-1} (71% $\dot{V}O_{2\,max}$)	↑ CK 24 & 48 h ↔ MF 24 & 48 h	↔ RE 24 & 48 h at 55%, 64%, & 71% $\dot{V}O_{2\,max}$ ↔ $\dot{V}_E$ 24 & 48 h at 55%, 64%, & 71% $\dot{V}O_{2\,max}$	None
Scott et al. [24]	PA who ran 3 × per week, n = 7 males & 4 females, age = 27.7 ± 5.95 y, stature = 170.5 ± 5.5 cm, BM = 67.85 ± 7.1 kg, $\dot{V}O_{2\,max}$ = 57.5 ± 4.7 mL·kg^{-1}·min^{-1}	4 sets of 10 barbell squats at 50—150% BM; 3 sets of 10 lunges at 20—50% BM; 3 sets of 10 step-ups & downs at 20—50% BM; 3 sets of 10 stiff leg deadlifts at 22.5—105 kg	30 mins at 2.5 mmol·l^{-1} (74% $\dot{V}O_{2\,max}$)	↑ DOMS 24 h	↔ RE 24 h	None

BM: body mass; CK: creatine kinase; DOMS: delayed onset muscle soreness; EIMD: exercise-induced muscle damage; ET: endurance training; HRmax: maximum heart rate; LT: lactate threshold; LTP: lactate turnpoint; Mb: myoglobin; MF: muscle function; MVC: maximal voluntary contraction; n: sample size; PA: physically active; RE: running economy; RM: repetition maximum; $\dot{V}_E$: minute ventilation; $\dot{V}O_{2\,max}$: maximum oxygen uptake; VT2: ventilatory threshold; ↑ : increase; ↓ : decrease; ↔ : no change

[a] Low volume group.

[b] High volume group.

Table 3 The Kmet et al. [40] assessment of methodological quality for all included studies.

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total	Rating
Baumann et al. [58]	1	2	2	2	0	1	2	1	1	2	2	2	2	2	22	Good
Braun & Dutto [9]	1	1	2	2	0	1	0	2	1	2	2	2	2	2	20	Good
Burnett et al. [26]	2	1	2	2	0	2	1	1	0	2	2	2	2	2	21	Good
Burt et al. [15]	1	1	1	2	2	2	2	1	1	2	2	1	2	2	22	Good
Burt et al. [16]	1	1	2	2	2	2	2	1	2	2	2	1	2	2	24	Excellent
Burt et al. [17]	1	2	2	2	2	2	2	2	1	2	2	2	2	2	26	Excellent
Burt et al. [18]	1	1	2	2	2	1	2	1	1	2	2	1	2	2	22	Good
Calbet et al. [59]	1	1	1	2	0	1	0	1	1	2	2	0	0	2	14	Fair
Chen et al. [10]	1	1	2	2	1	2	2	1	1	2	2	1	1	2	21	Good
Chen et al. [11]	1	1	1	1	0	1	2	2	1	2	2	2	2	2	20	Good
Chen et al. [12]	1	1	0	2	0	2	2	2	1	2	2	2	2	2	21	Good
Chen et al. [13]	1	1	0	2	0	1	2	1	1	2	2	2	2	2	19	Good
Chen et al. [14]	1	1	1	2	2	2	2	2	1	2	2	1	2	2	23	Good
Doma et al. [22]	1	1	2	2	2	2	2	2	2	2	2	1	2	2	25	Excellent
Doma et al. [23]	1	1	2	2	2	2	2	2	2	2	2	1	2	2	25	Excellent
Hamill et al. [60]	1	1	1	2	0	1	1	2	1	2	2	0	2	2	18	Fair
Kyrolainen et al. [27]	1	1	2	2	0	1	1	2	1	2	2	0	2	2	19	Good
Lima et al. [19]	1	1	2	2	2	1	2	1	2	2	2	1	2	2	23	Good
Lima et al. [20]	1	2	1	2	2	1	2	2	1	2	2	1	2	2	23	Good
Lima et al. [21]	1	1	1	2	2	1	2	2	1	2	2	1	2	2	22	Good
Marcora & Bosio [25]	1	2	2	2	0	0	2	2	2	1	2	2	2	1	21	Good
Paschalis et al. [28]	1	1	1	2	2	2	2	2	1	2	2	1	2	2	23	Good
Paschalis et al. [29]	1	1	1	2	2	1	2	1	1	2	2	1	2	2	21	Good
Quinn & Manley [30]	1	1	2	2	0	2	1	1	1	2	2	1	1	1	18	Fair
Scott et al. [24]	1	1	2	2	0	0	0	2	1	2	2	1	2	2	18	Fair

moderate inter-study heterogeneity (24 h: $I^2 = 70\%$; 48 h: $I^2 = 62\%$) and a moderate magnitude of difference (24 h: SMD = 0.74; 48 h: SMD = 0.62). Similarly, $\dot{V}_E$ was significantly increased at 24 h ($Z = 4.18$, $P < 0.0001$) and 48 h ($Z = 6.18$, $P < 0.00001$) post-EIMD, with moderate to high inter-study heterogeneity (24 h: $I^2 = 77\%$; 48 h: $I^2 = 60\%$) and a large magnitude of difference (24 h: SMD = 0.99; 48 h: SMD = 0.89).

3.6. Qualitative analysis

Given only three studies were found to investigate the effects of EIMD on running time-trial and running time-to-exhaustion performance, the results were not included in the meta-analysis [41], and alternatively, will be reported qualitatively. With regards to running time-trial performance, Marcora and Bosio [25] reported distance covered during a 30-minute time-trial was significantly reduced by 4% 48 h after EIMD. Similarly, Burt et al. [18] demonstrated 3 km running time-trial performance was significantly slower by 7 and 9% 48 h after low and high-volume muscle-damaging exercise, respectively. Finally, Doma et al. [23] found time-to-exhaustion at a running speed corresponding to 110% ventilatory threshold (VT) 2 was reduced 24 and 48 h after EIMD.

4. Discussion

This is the first systematic review and meta-analysis to investigate the effects of EIMD on the physiological responses during sub-maximal running and maximal effort running performance. As anticipated, indirect markers of muscle damage were significantly increased for up to 48 hours after muscle-damaging exercise, confirming that determinants of running performance were meta-analytically examined during periods of EIMD. Results from the meta-analysis provide quantitative evidence that EIMD augments RE and $\dot{V}_E$ during subsequent sub-maximal running for up to 48 h post-EIMD. Furthermore, studies included in the systematic review report that EIMD compromises maximal-effort running performance during time-to-exhaustion and time-trial protocols for up to 48 h after EIMD. It therefore appears that muscle-damaging exercises impairs varying intensities of running performance for several days post-EIMD.

Several studies have associated increases in RE during sub-maximal running after EIMD to alterations in gait kinematics [9,10,14—18]. Burt et al. [15] demonstrated that changes in oxygen uptake during sub-maximal running were inversely correlated with changes in stride length after EIMD (individual correlations ranging from −0.71 to −0.92). Deviation from optimal stride pattern incurs increases in RE [9,42], and it is posited that individuals alter their running pattern to limit discomfort associated with concurrent increases in DOMS after EIMD [18].

Other researchers [10,14—16] have attributed the disturbance to RE after EIMD to an impaired ability to utilise the stretch-shortening cycle (SSC). Muscle-damaging exercise reduces stretch reflex sensitivity and muscle stiffness regulation, causing a decline in the force potential of the SSC [43]. It is possible that reductions in musculotendinous

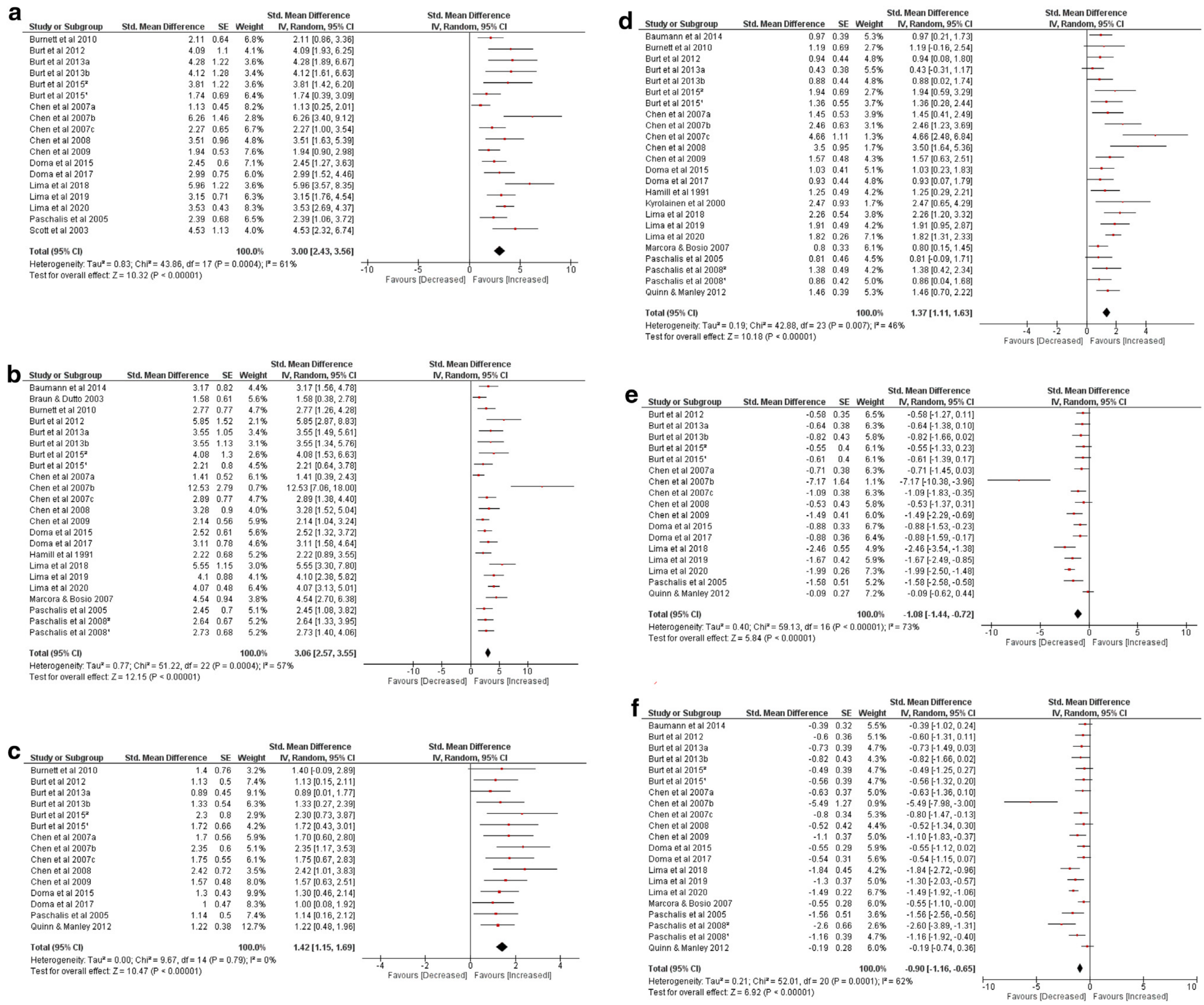

Figure 2 Forest plots for delayed onset muscle soreness (DOMS), creatine kinase, and muscle function at 24 and 48 h after EIMD; a) and b) represent DOMS at 24 and 48 h after EIMD, respectively; c) and d) represent CK at 24 and 48 h after EIMD, respectively; and e) and f) show changes in muscle function at 24 and 48 h post-EIMD, respectively.

stiffness after EIMD lead to an inability to absorb and utilise elastic energy during running and the subsequent increase in energy cost.

The effects of EIMD on RE have also been attributed to alterations in neuromuscular function. It is suggested that impaired neuromuscular control after muscle-damaging exercise requires additional motor unit activation to produce the same resultant force during sub-maximal running [27]. Reductions in MVC force after EIMD have coincided with increases in EMG activity during sub-maximal running [18]. Furthermore, given the linear relationship between EMG activity and oxygen consumption [44], it is plausible that alterations in oxygen metabolism during sub-maximal running after EIMD are reflective of an increase in motor unit activity to ensure the same pre-EIMD running speed is completed.

Whilst recent narrative reviews [31—33] provide a qualitative assessment of the consequences of EIMD on RE, they do not evaluate the effects of EIMD on other physiological responses during running endurance performance. For the first time, this systematic review provides meta-analytical evidence that $\dot{V}_E$ responses during sub-maximal running are increased in the days after EIMD. Several mechanisms have been suggested to explain the elevations in sub-maximal $\dot{V}_E$ response after EIMD, including reduced RE [10], increased acidosis [9], and increased muscle afferent discharge [15].

Ventilatory responses during sub-maximal running post-EIMD are concomitant with changes in RE and blood lactate, speculating that increases in $\dot{V}_E$ occur to facilitate an elevation in RE [10] or to excrete additional carbon dioxide produced from the increased bicarbonate buffering of lactic acidosis [45]. However, studies [45—47] have demonstrated increases in $\dot{V}_E$ during endurance exercise after EIMD without contemporaneous rises in oxygen uptake, blood lactate, or carbon dioxide, implying that other mechanisms might be involved.

Indeed, $\dot{V}_E$ responses during exercise are controlled through a combination of central command and afferent

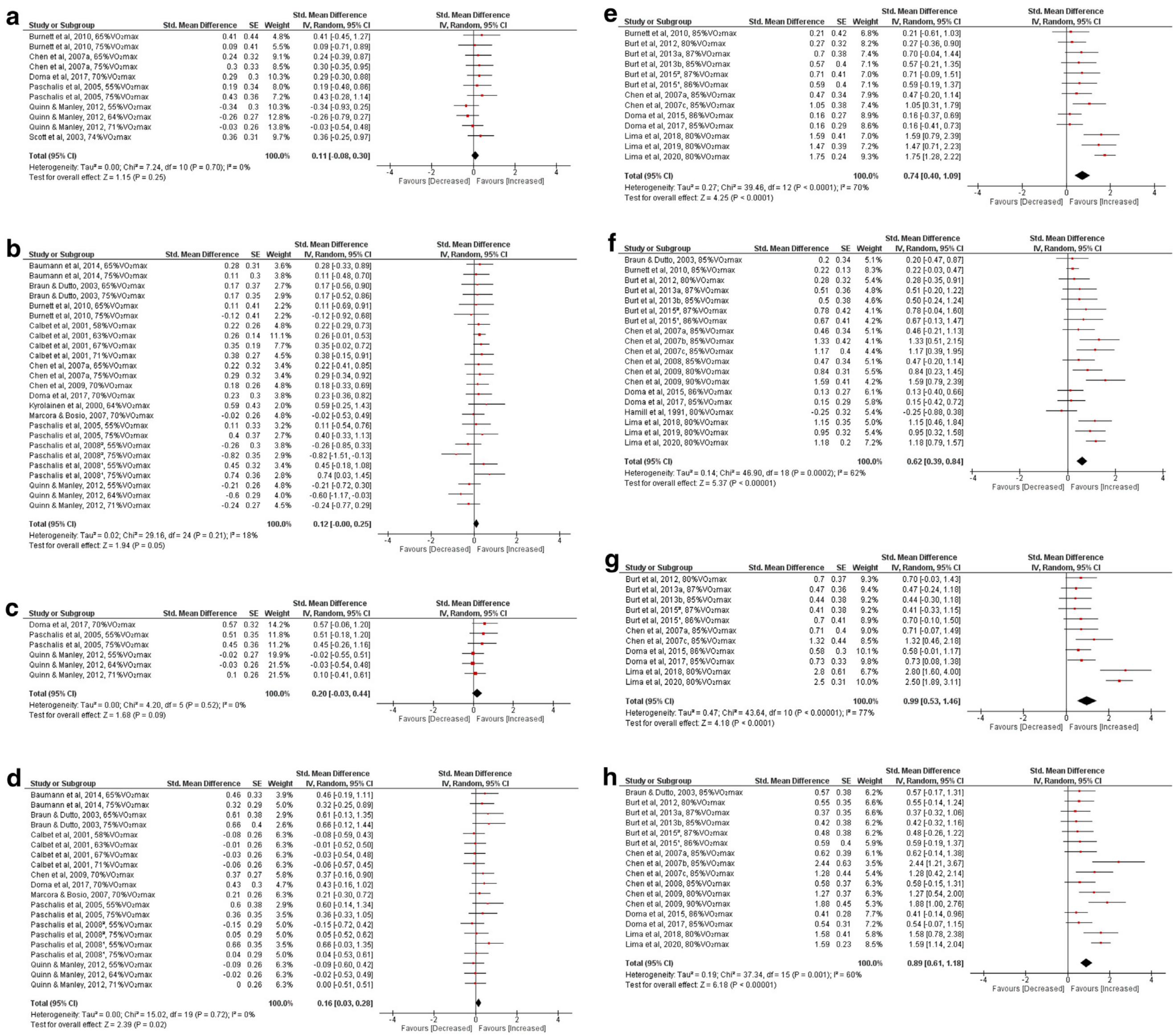

Figure 3 Forest plots for physiological responses during low intensity (< 75% $\dot{V}O_{2\,max}$) and high intensity (> 75% $\dot{V}O_{2\,max}$) sub-maximal running at 24 and 48 h after EIMD; a) and b) represent RE during low intensity (< 75% $\dot{V}O_{2\,max}$) sub-maximal running at 24 and 48 h after EIMD, respectively; c) and d) represent $\dot{V}_E$ during low intensity (< 75% $\dot{V}O_{2\,max}$) sub-maximal running at 24 and 48 h after EIMD, respectively; e) and f) represent RE during high intensity (> 75% $\dot{V}O_{2\,max}$) sub-maximal running at 24 and 48 h after EIMD, respectively; g) and h) represent $\dot{V}_E$ during high intensity (> 75% $\dot{V}O_{2\,max}$) sub-maximal running at 24 and 48 h after EIMD, respectively.

feedback [46,48]. It is posited that increases in central command, to ensure the same force during sub-maximal running is maintained because of decrements in muscle function after EIMD, activate regions of the brain that control ventilatory response. Alternatively, it is postulated that EIMD stimulates a discharge from Group III and IV muscle afferents that is projected via the spinal cord to the ventilation control regions of the brain; resulting in an increase in $\dot{V}_E$ during endurance exercise [46—48]. Amann et al. [49] found pharmacologically blocking Group III and IV afferents significantly reduced $\dot{V}_E$ during sub-maximal cycling to imply a cause-and-effect relationship, however, it remains to be seen if afferent activation via EIMD causes the increase in $\dot{V}_E$ during sub-maximal running.

Despite the current meta-analysis informing that EIMD alters physiological responses during sub-maximal running, these changes are not comprehensively found across the literature, with some studies reporting no effect of EIMD on sub-maximal running [25—30]. The discrepancy is suggested to be due to the exercise intensity adopted, with EIMD having a greater effect on physiological and perceptual responses during higher exercise intensities [14,31]. To investigate this claim, the current meta-analysis analysed physiological responses changes across two different exercise intensities: stage 1 = lower exercise intensity < 75% $\dot{V}O_{2\,max}$ and stage 2 = higher exercise intensity > 75% $\dot{V}O_{2\,max}$. Results provided partial support for this assertion, with RE and $\dot{V}_E$ responses during lower exercise intensities remaining unaltered 24 h after EIMD. Running economy and $\dot{V}_E$ were significantly increased at 48 h post-EIMD, however the SMD were small for RE (0.12) and $\dot{V}_E$ (0.16). In contrast, RE and $\dot{V}_E$ during higher intensity running were all significantly increased 24 and 48 h after EIMD.

Alongside exercise intensity, the mode of muscle-damaging exercise also appears to influence the physiological responses during sub-maximal running. In our systematic review, most studies demonstrating increases in RE and $\dot{V}_E$ during sub-maximal running used downhill running or heavy, high-volume squats to induce EIMD. It is posited that increased muscle mass or greater magnitude and specificity of EIMD during these modes of muscle-damaging exercise may explain the differences [31], however, it remains to be elucidated whether different modes of EIMD evoke contrasting physiological responses during sub-maximal running.

Whilst studies investigating the effects of EIMD on sub-maximal running performance enable physiological responses to be examined during steady-state exercise, they do lack action fidelity. Alternatively, simulated time-trials enables the effects of EIMD to be examined in a setting indicative of how endurance athletes compete. Unfortunately, only three studies to date have investigated the effects of EIMD on running time-trial and time-to-exhaustion performance and, thus, there was insufficient data to perform the meta-analysis. From the three studies, it was clear that EIMD impairs running time-trial performance [18,23,25]. Interestingly, despite the decrease in time-trial performance, perceptual responses appear to be unchanged after EIMD [18,25], implying that in a muscle damaged state, RPE is greater for a lower exercise intensity. It is suggested that muscular pain incurred after EIMD alters the sense of effort during the time-trial, resulting in individuals adopting a slower speed [18,25]. Alternatively, during time-to-exhaustion running [23], whereby individuals maintain speed for as long as possible, it is posited that an increase in central motor command, to ensure the same running speed can be maintained after EIMD, increased sense of perception [50], and led to the premature termination of time-to-exhaustion performance [23,51].

Alternatively, the CNS might reduce neural drive to the peripheral muscles during time-trial running after EIMD in attempts to protect against further injury. Despite the conscious effort to cover as much distance or run as fast as possible, muscle fibres may have been ''spared'' during time-trial performance after EIMD as a protective mechanism by the subconscious brain to prevent further injury [52].

The inflammatory response associated with EIMD has also been hypothesised to reduce running time-trial performance [25]. Interleukin (IL)-1, a primary mediator of the muscle's inflammatory response to EIMD [53], is speculated to have a direct effect on the brain [54]. Carmichael et al. [54] attributed decrements in endurance performance after EIMD to elevated concentrations of IL-1 in the cortex and cerebellum regions of the brain in mice, however, this has yet to be confirmed in human participants.

Although the effects of EIMD have been shown to impair endurance performance that is indicative of athletic competition, studies are limited to short-term (10—30 mins) and short distance (3 km) time-trial performance, recruitment of recreational active participants, and adoption of laboratory-based protocols. Future research is warranted investigating the impact of EIMD on running performance during event-specific distances in a field-based environment among well-trained athletes.

Aligning with other reviews, the current meta-analysis is not without limitations. Firstly, the I^2 value was moderate to large (> 50%) for several outcomes, although the majority presented with low to moderate inter-study heterogeneity (0—69%). Secondly, a wide range of exercise intensities (58—90% $\dot{V}O_{2\,max}$) were used to examine the effects of EIMD on sub-maximal running performance, and whilst attempts were made to examine responses across low and high stages, the intensities delineating the boundaries between high and low were arbitrary and did not account for inter-individual differences. For example, running at 70% $\dot{V}O_{2\,max}$ may be low intensity for an individual in one study, but high intensity for another [46]. Thirdly, there was variability in the exercise modality used to induce EIMD, and whilst EIMD was confirmed via changes in the indirect markers (CK, DOMS, and muscle function), the distinct modes of muscle-damaging exercise may have influenced the severity and specificity of EIMD. Finally, whilst the assessment of methodological quality [38] for the included studies was rated from fair to excellent, the systematic review did identify studies that did not account for potential confounding factors, such as: 1) a sample size calculation was not performed, making it unclear if studies had sufficient statistical power; 2) ensuring participants avoided unaccustomed and strenuous exercise, analgesic agents, antioxidants, and nutritional supplements during the study, which may have impacted findings; 3) ensuring participants had avoided lower limb EIMD in the 6 months prior to data collection and, thus, reducing risk of the repeated bout effect influencing the results. Future studies examine the effects of EIMD on endurance performance should consider the highlighted methodological limitations to minimise potential biases.

Based on the findings of the current systematic review and meta-analysis, several recommendations can be suggested for future studies. Firstly, given the contrasting modes of EIMD used in the studies contributing to the meta-analysis, future studies should examine the effects of EIMD modality (such as plyometrics versus downhill running) on endurance performance. Secondly, only 3 studies have investigated the impact of EIMD on time-trial performance. Future studies could enable the effects of muscle-damaging exercise to be examined in an environment indicative of an athletic competition. Although most studies investigated the effects of EIMD on endurance performance in recreational runners, future studies should examine if perceived responses are concomitant in well-trained and elite level endurance athletes. Furthermore, out of the 25 studies used in the current meta-analysis, only 30 female participants were recruited compared to 306 males. Given the influence that menstrual cycle has on the level of EIMD response [55], future studies investigating the effects of EIMD on endurance performance should consider including more female runners. Finally, our meta-analysis only examined the effects of EIMD on sub-maximal and maximal-effort running performance, despite studies previously reporting on the negative impacts of EIMD on sub-maximal and maximal-effort cycling performance [46,47,52], there is a need to examine the effects of EIMD on other endurance modalities, such as rowing and swimming.

5. Conclusion

In conclusion, the systematic review and meta-analysis identified that physiological responses during sub-maximal running are altered in the days after EIMD. Coaches and athletes should periodise their training when implementing eccentric exercise (downhill running, lower limb resistance exercise and/or plyometrics) to improve future endurance performance by considering the acute effects of unaccustomed/strenuous bouts of these training modalities. More research is needed to ascertain the effects of EIMD on endurance performance in well-trained and elite level runners, female runners, in measure reflective of athletic competition (time-trial running), and the role EIMD modality has on endurance performance responses.

Disclosure of interest

The authors declare that they have no competing interest.

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