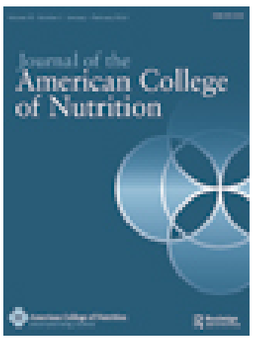

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The Effect of L-Carnitine Supplementation on Exercise-Induced Muscle Damage: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Habib Yarizadh[a,b], Sakineh Shab-Bidar[b], Behzad Zamani[b], Ali Nazary Vanani[b], Hussein Baharlooi[d], and Kurosh Djafarian[c]

[a]Students' Scientific Center, Tehran University of Medical Sciences, Tehran, Iran; [b]Community Nutrition Department, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [c]Clinical Nutrition Department, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [d]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Accumulating evidence of previous experimental studies indicated that L-Carnitine positively ameliorates muscle damage. However, findings from trials vary substantially across studies. Therefore, current meta-analysis aimed to examine the effects of L-Carnitine supplementation on exercise-induced muscle damage. An electronic search of the online literature databases (Medline (PubMed), Scopus and Google Scholar) was performed up to November 2018. Either a fixed-effects model or a random-effects model (Diasorin-Liard) was used in order to estimate the effects size. Cochran's Q test and I2 tests were used to assess the heterogeneity among the studies. Funnel plot and Egger's regression test were also employed in order to assess the publication bias. Of 604 studies, seven eligible randomized controlled trials (RCTs) were included in this meta-analysis. Pooled data from seven studies showed that L-Carnitine resulted in significant improvements in muscle soreness (MS) at the five follow-up time points (0, 24, 48, 72 and 96 hours (h)) compared to placebo. Also, pooled data indicated that L-Carnitine significantly reduced creatine kinase (CK), myoglobin (Mb), and lactate dehydrogenase (LDH) levels at one follow-up period (24 h). However, no effects have been observed beyond this period. Our outcomes indicate that L-Carnitine supplementation improves delayed-onset muscle soreness (DOMS) and markers of muscle damage. Further research is needed to clarify impacts of L-Carnitine on DOMS after different types of mechanical or chemical damages.

KEY TEACHING POINTS

- The effect of L-Carnitine supplementation on exercise-induced muscle damage has come under scrutiny over many years.
- This systematic review and meta-analyses study investigated the effects of L-Carnitine supplementation on exercise-induced muscle damage.
- Overall, summary results indicate that L-Carnitine supplementation improves muscle soreness and markers of muscle damage (CK, LDH, and Mb).
- Overall, L-carnitine supplementation ameliorated muscle damage only in resistance training groups and untrained population.

ARTICLE HISTORY
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KEYWORDS
Muscle soreness; supplementation; L-carnitine; muscle damage; meta-analysis

Background

It is now widely recognized that regular exercise has beneficial effects for individuals with obesity, diabetes, or cardiovascular diseases. On the other hand, exercise sometimes leads to an ambiguous pain in the muscle tissues of inexperienced trainees, which is known as delayed-onset muscle soreness (DOMS) (1). DOMS is a common phenomenon during recovery after exercise which reduces the quality of life in athletes. It may also cause a significant reduction in the body performance and produces a less than optimal training intensity. Note that it can also affect non-exercisers and interfere with their daily activities (2). DOMS usually occurs 24 hours after unaccustomed or strenuous exercise and following exercise involving eccentric contractions which are mainly experienced at myotendinous junctions (3–5). The peak of discomfort and ambiguous pain caused in DOMS is 24 to 48 hours after training and usually alleviates within 72 to 96 hours (6). The grade of DOMS depends on various factors such as exercise duration, type of training, training status, and intensity of the exercise (2,7). Researchers are always looking for ways to mitigate its negative effects (8). Several recommendations have been suggested to reduce the effects of DOMS and to speed up recovery including cold water immersion, massage, oxygen therapy, compression garments, taking nonsteroidal anti-inflammatory drugs, electromyostimulation, stretching,

CONTACT Kurosh Djafarian kdjafarian@tums.ac.ir Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran No 44, Hojjat-dost Alley, Naderi St., Keshavarz Blvd, Tehran, Iran.
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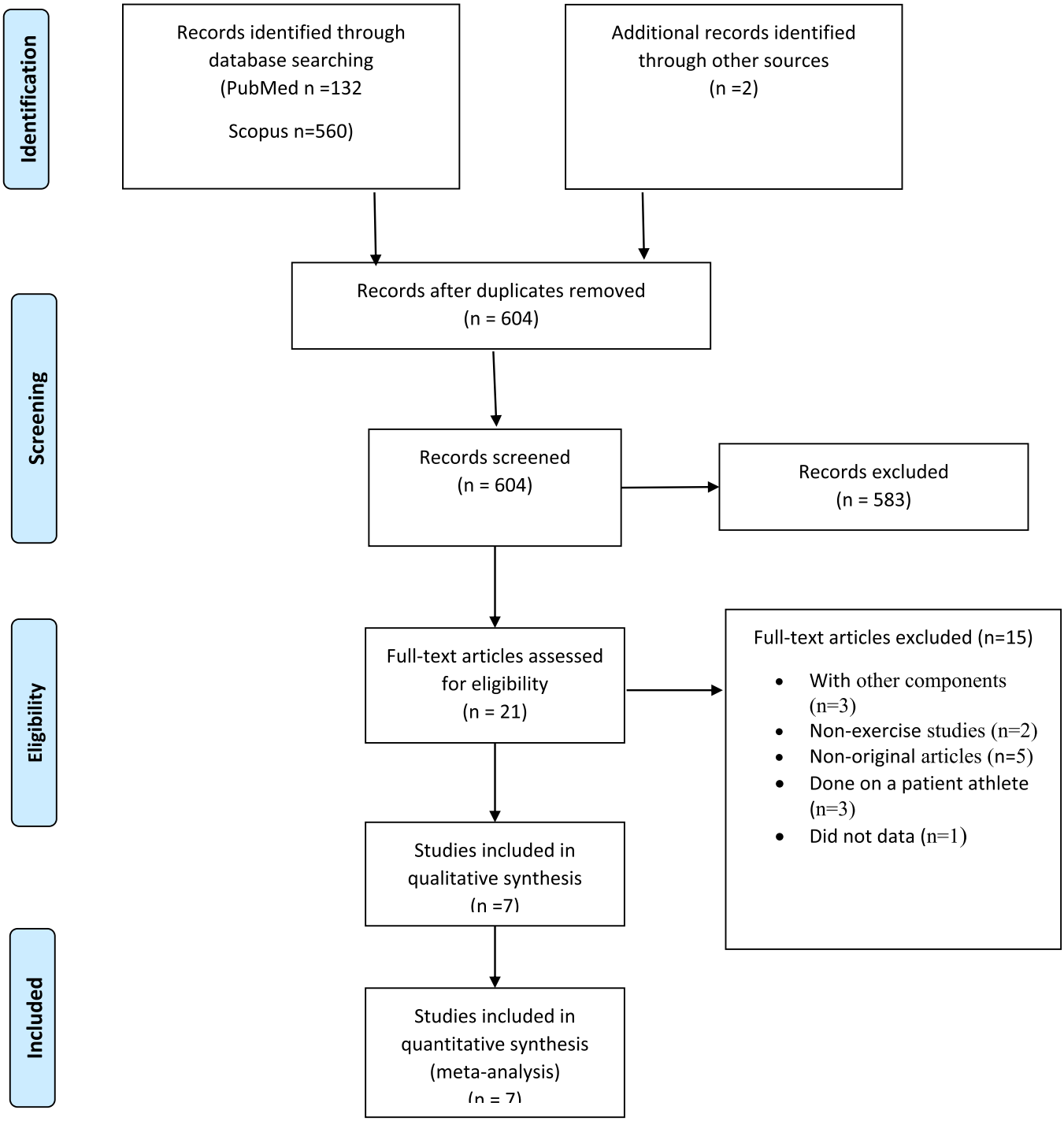

Figure 1. Summary of search strategy and selection process based on included and excluded studies.

combination modalities, ultrasound, homeopathy, electrical current, and antioxidant supplementations (8–12). L-carnitine is a naturally occurring antioxidant synthesized from methionine and lysine (13). However, it can also be obtained through diet (14). The effects of L-carnitine supplementation on DOMS and muscle damage have been investigated in several studies (15–18). Most studies have shown that L-carnitine supplementation has a positive effect on DOMS and muscle damage (19–21), while other studies have reported reverse effects (17). To clarify this inconsistency, we conducted a comprehensive meta-analysis of all published clinical trials entitled the effects of L-carnitine supplementation on DOMS and biochemical markers of muscle damage.

Methods

This study was carried out based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Search strategy

An electronic search of the online literature databases (MEDLINE [PubMed], Scopus, and Google Scholar) was

conducted up to November 2018. The following keywords used in combination to find the relevant articles: "carnitine," "L-carnitine," "levocarnitine," "muscle damage," "muscle soreness," "exercise-induced muscle damage," "skeletal muscle damage," "muscle weakness," and "muscular atrophy." The reference list of all available papers was reviewed to achieve additional relevant studies (Figure 1).

Inclusion and exclusion criteria for studies

Studies that involved human participants treated with an L-carnitine intervention either "after exercise" or "before and after exercise" were included if they met the following criteria: (1) the study design was a randomized controlled trial; (2) outcomes were muscle soreness and/or biochemical markers related to the risk of developing muscle damage (CK, LDH, and myoglobin); (3) authors measured at least one variable at baseline and again at immediately and/or 24 and/or 48 and/or 72 hours after the exercise; (4) participants of the study did not have any metabolic, cardiovascular, or musculoskeletal disorders; and (5) the study population can be either female or male participants with any background of education or training.

The followings were considered as exclusion criteria: 1) papers utilized extra interventions like drugs, diet, and other supplements 2) studies without control group.

Data extraction and management

Two authors (HY and BZ) independently selected studies for inclusion and extracted the data. All trials categorized from the database and manual searches were reviewed by two authors to determine eligibility using a screening form. The arguing studies were discussed and were passed to the third researcher (SS-B). The following data were extracted from the included studies: the first author's name, study location (country), year of publication, study population, characteristics of participants (gender, age, body weight, and body mass index), supplement dosage, study design, training status, type of exercise, classification of the exercise, and duration of trial.

Quality assessment

We used the Jadad scale to assess methodological quality for seven studies. The Jadad score is a 5-point scale, including the following: randomization, method of randomization, double-blinding, method of double-blinding, and reports of dropouts and withdrawals (22). Out of the 5 points, low-quality studies are scored <3 and high-quality ≥ 3 (23).

Data synthesis and statistical analysis

In this study, Stata software version 14 (Stata Corp Lp, College Station, Texas, USA) was used for all statistical analyses. Random and fixed effects models were utilized in order to obtain pooled estimates of L-carnitine supplementation impacts on muscle damage (CK, LDH, myoglobin, and muscle soreness (MS)), using weighted mean difference (WMD). When there was evidence of statistical between-studies heterogeneity, we examined our results using the random-effects model. Otherwise, a fixed-effect model was used. Heterogeneity was evaluated using a Cochran's Q test and I^2 statistic. To detect potential sources of heterogeneity, we performed subgroup analysis. The predefined criteria for subgroup analysis was based on training status (trained/untrained), sex (male/female), different types of L-carnitine (L-carnitine and L-carnitine L-tartrate), and exercise (aerobic and resistance). In parallel studies that reported *SE*, *SD* was calculated by the following equation: $SD = SE \times \sqrt{n}$ (where n is the number of cases in each group). In case of crossover studies, we have calculated sample size, *SD*, and also *SE* according to the studies conducted by Diana R. Elbourne and Lech Madeyski (24,25). In addition, there were some studies that data were extracted from graphs using GetData Graph Digitizer 2.24 (16,18–21). To assess the influence of each study on the overall mean difference, we used a sensitivity analysis by the one-study remove approach. Publication bias was assessed by visual evaluation of the funnel plot and Egger's test. A p value < 0.05 was considered statistically significant.

Results

Included studies

To exclude irrelevant papers and those without primary data, we screened the manuscripts based on the titles, abstracts, and full texts sequentially. After removing 90 irrelevant papers from the primary articles, 604 publications remained. After screening title and abstracts, 21 potentially relevant papers were selected for full-text review. Fifteen papers were removed for the following reasons: combination therapy of L-carnitine and other ingredients (n = 3), non-exercise studies (n = 2), non-original articles (5), insufficiency of data on muscle damage at the end of the intervention (n = 1), and investigating populations with chronic disease(s) (n = 3). Finally, seven studies were included in this systematic review and meta-analysis (15–21). In addition, if a study was conducted on the results of various doses of L-carnitine (19) or on different sexes (20), each dose or gender was included as a separate study in the analysis. In some studies, data were not accessible due to the presentation of outcomes in the graphic form(s) (16,18–21). The flow diagram of study selection is shown in Figure 1.

Study features

Characteristics of the studies are summarized in Table 1, which has 12 items for nine studies. A total of 79 individuals enrolled in the review, which included 70 men (88%) and 9 women (12%). Regarding their training status, 34 and 45 individuals were trained and untrained, respectively. These articles were published from 1993 to 2014. The mean sample size was 11 participants. The participants were from 22 to 51.9 years old. All eligible articles

Table 1. Demographic characteristics of the included studies.

Study first author (year)	Study population	Study design	Train status	Type of exercise	Mean age and gender	Mean weight (kg)	Mean BMI	L-Carnitine Daily Dose (g)	Sample size	Duration (week)	Jaded score	Outcome variables and time of measurement post exercise
Decombaz J. (1993)	Healthy men	Crossover	Trained	Aerobic	24.9 (Male)	70.6	22.2	3 g L-carnitine	9	1	1	CK (0 h)
Giamberardino M. (1996)	Healthy men	Crossover	Untrained	Resistance	26 (Male)	68.3	22.8	3 g L-carnitine	6	3	1	CK (0, 24, 48, 72, 96 h)
Colombani P. (1996)	Endurance-trained male athletes	Crossover	Trained	Aerobic	36 (Male)	69	21.8	2 g L-carnitine	7	4	3	DOMS (24, 48, 96 h)
Volek J. S. (2002)	Recreationally weight-trained men	Crossover	Trained	Resistance	23.7 (Male)	78.7	24.51	2 g L-carnitine L-tartrate	10	3	3	CK (0, 24 h) LDH (0, 24 h)
Spiering B. A. (2007)	Healthy men	Crossover	Trained	Resistance	22 (Male)	83	27.41	1 g L-carnitine L-tartrate	8	3	2	CK (0, 24, 48, 96 h) Myoglobin (0, <24, 24, 48, 72, 96 h) DOMS (24, 48, 72, 96 h)
Spiering B. A. (2007)	Healthy men	Crossover	Trained	Resistance	22 (Male)	83	27.41	2 g L-carnitine L-tartrate	8	3	2	myoglobin (<24 and 0 h) DOMS (24, 48, 72 h)
Ho J. Y. (2010)	Healthy men	Crossover	Untrained	Resistance	51.9 (Male)	82.2	26.6	2 g L-carnitine L-tartrate	9	3	3	myoglobin (<24 and 0 h) DOMS (24, 48, 72 h)
Ho J. Y. (2010)	Healthy women	Crossover	Untrained	Resistance	45.4 (Female)	65.4	24.2	2 g L-carnitine L-tartrate	9	3	3	CK (0, 24, 48, 96 h) Myoglobin (0, <24, 24, 48, 96 h) DOMS (0, 24, 48, 96 h)
Parandak K. (2014)	Healthy young men	Parallel	Untrained	Aerobic	22 (Male)	73.5	22.71	2 g L-carnitine	21	2	3	CK (0, 24, 48, 96 h)

were randomized controlled trials, six of the trials were crossover studies, and the one remaining was a parallel study. In crossover studies, the washout periods between each of the conditions were 1 to 4 weeks. One study was carried out in Italy (16), two in Sweden (15,17), three in the United States (18–20), and one in Iran (21). These articles prescribed different doses of L-carnitine ranging from 1 to 3 grams. Intervention durations were between 1 and 4 weeks. Quality assessment of the included studies determined by Jadad score. The quality of these studies ranged from 1 to 3 points; three trials were categorized as low-quality publications (Jadad score <3) and four trials were categorized as high-quality (Jadad score ≥3).

Details of outcome

Muscle soreness was reported in six studies (four publications). All studies assessed muscle soreness via visual analog scale (26). Three biochemical markers of muscle damage were reported in the studies as follows: CK was reported in seven studies (six publications), myoglobin in five studies (three publications), and LDH in two studies (two publications).

Follow-up

Based on the observations for each outcome, all selected articles went through several periods of time. The majority of the included studies reported multiple periods of time, e.g., immediately post-exercise (0 hours); fewer than 24 hours after exercise (< 24 hours); and 24, 48, 72, and 96 hours after exercise. We focused on reported outcomes immediately post-exercise (0 hours) and subsequent days (24, 48, 72, and 96 hours).

Meta-analysis of muscle soreness

In this comparison, six studies have provided data on muscle soreness. Based on the follow-up period, a pooled result was calculated in five subcategories. Two studies reported only one follow-up period (immediately after exercise [0 hours]). Four studies sampled 24 and 48 hours post-exercise, four studies 72 and 96 hours after exercise. Pooled analysis demonstrated that the L-carnitine supplementation significantly ameliorated muscle soreness in the all of follow-up periods (0 hours: WMD = −1.05 mm, 95% confidence interval [CI]: −1.56 to −0.57, $p < 0.001$, n = 2; 24 hours: WMD = −1.73 mm, 95% CI: −2.17 to −1.28, $p < 0.001$; n = 6; 48 hours: WMD = −1.66 mm, 95% CI: −2.10 to −1.22, $p < 0.001$, n = 6; 72 hours: WMD = −1.05 mm, 95% CI: −1.58 to −0.52, $p < 0.001$, n = 4; 96 hours: WMD = −0.21 mm, 95% CI: −0.31 to −0.12, $p < 0.001$, n = 4). In the same vein, there was significant heterogeneity in findings of three follow-up periods (48 hours: I^2 = 56.2%, $p = 0.04$, 72 hours: I^2 = 83%, $p < 0.001$, and 96 hours: I^2 = 85.8%, $p < 0.001$; Figure 2).

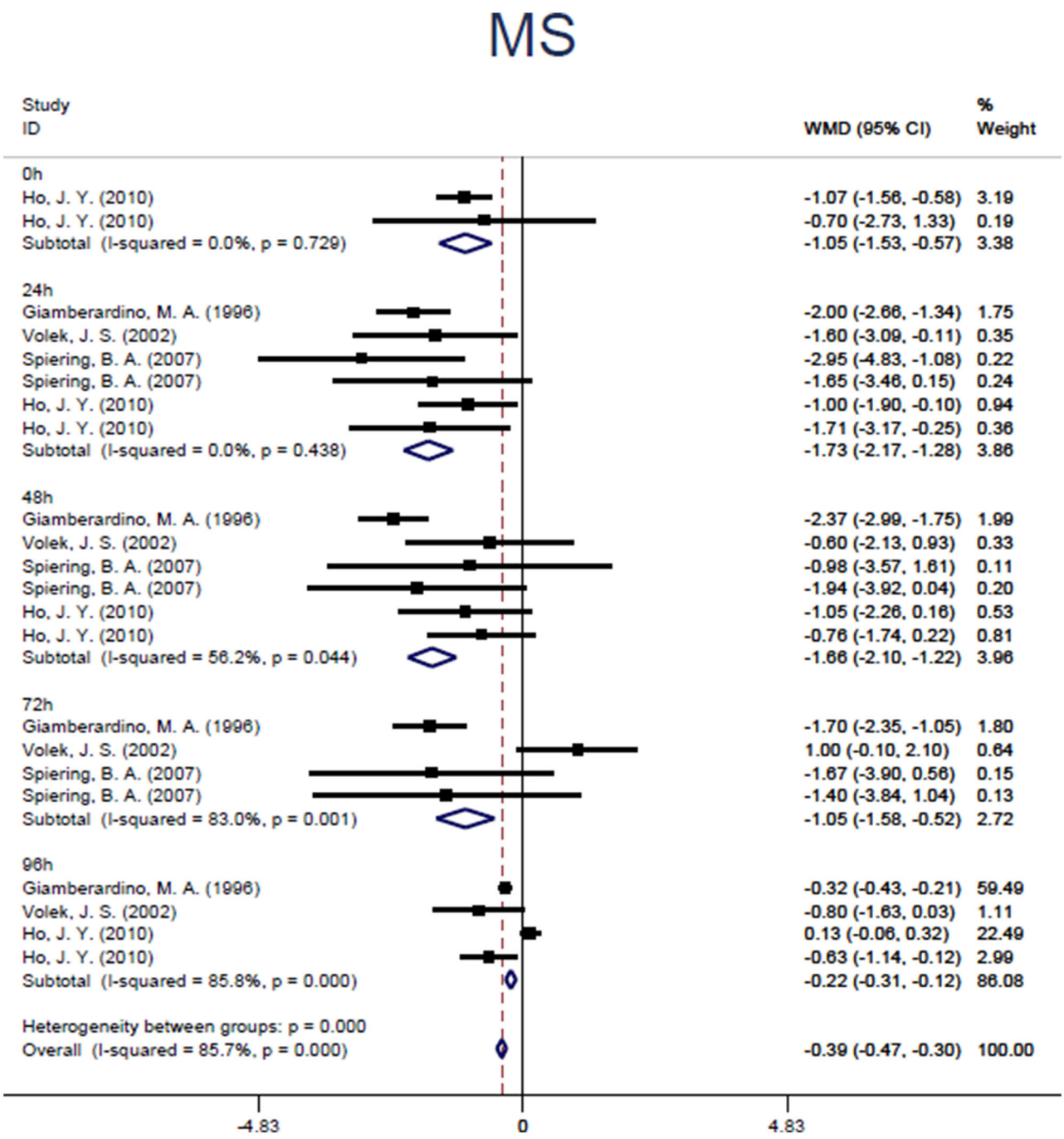

Figure 2. Forest plot presenting weighted mean difference (WMD) and 95% confidence intervals for muscle soreness.

A meta-analysis of muscle damage

CK

In this regard, six studies presented data for CK. The pooled result is according to four subcategories based on follow-up periods (immediately and 24, 48, and 96 hours after exercise). Six studies reported CK immediately (0 hours) and four studies described at 48 and 96 hours after exercise. There were no significant differences between groups at 0 hours (WMD = −9.53 U/L, 95% CI: −19.67 to 0.61, $p = 0.06$), 48 hours (WMD = −32.31 U/L, 95% CI: −69.75 to 5.13, $p = 0.09$), and 96 hours (WMD = −4.28 U/L, 95% CI: −20.59 to 12.08, $p = 0.60$). In the 24-hour follow-up, our results indicate that CK levels are significantly decreased following the L-carnitine supplementation (WMD= −37.70 U/L, 95% CI: −57.02 to −18.38, $p < 0.001$; Figure 3). There was significant heterogeneity between the studies at 48 hours' follow-up ($I^2 = 68.1\%$, $p = 0.02$).

LDH

Two studies recorded LDH levels immediately and 24 hours after exercise. Pooled results showed that the level of LDH was significantly lower than control group in 24-hour follow-up (WMD = −84.08 U/L, 95% CI: −140.9 to −27.27, $p = 0.00$), while no significant effect was observed immediately after exercise (WMD= −46.08 U/L, 95% CI: −109.14 to 16.98, $p = 0.15$; Figure 4). There was significant

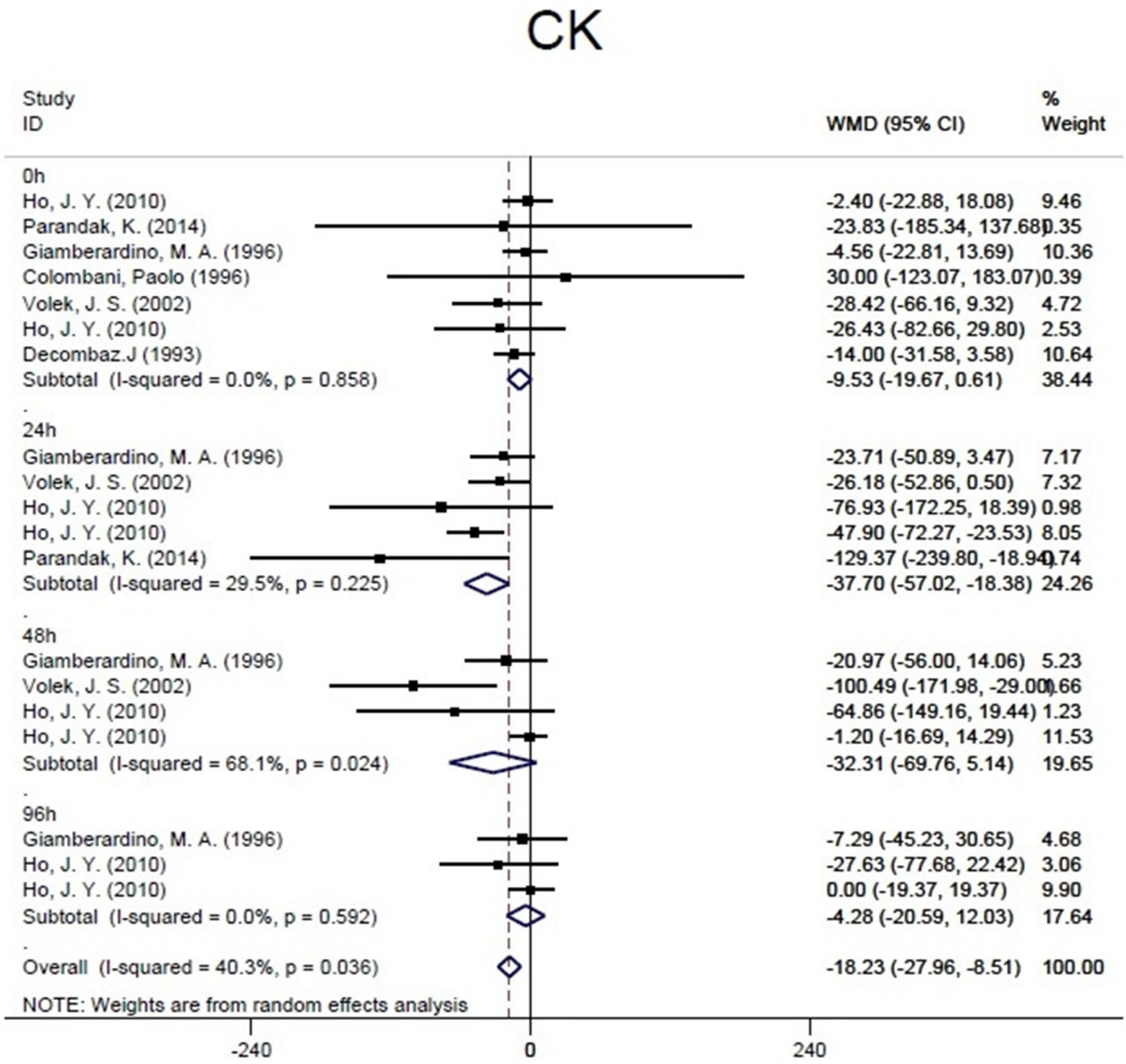

Figure 3. Forest plot presenting weighted mean difference (WMD) and 95% confidence intervals for creatine kinase.

heterogeneity between the studies at 24 hours' follow-up (I^2 = 85%, $p = 0.01$).

Myoglobin

Five studies in this comparison presented data on myoglobin. Based on follow-up periods, pooled results were categorized in five groups. Five studies (three publications) provided data on myoglobin concentration at immediately (0 hours). Eleven studies had enough data for < 24 hours and three studies had data for 24 hours, 48 hours, and 96 hours after exercise. Pooled analysis demonstrated that the L-carnitine supplementation significantly decreased myoglobin concentration in the one of follow-up periods (< 24 hours: WMD = −23.64 µg/L, 95% CI: −34.82 to −12.46, $p < 0.001$), while no significant effect was observed other follow-up periods (0 hours: WMD = −10.88 µg/L, 95% CI: −25.09 to 3.33, $p = 0.13$; < 24 hours: WMD= −2.47 µg/L, 95% CI: −11.67 to 6.73, $p = 0.59$; 48 hours: WMD = 1.02 µg/L, 95% CI: −9.22 to 11.26, $p = 0.84$; and 96 hours: WMD = −2.62 µg/L, 95% CI: −13.60 to 8.35, $p = 0.94$). There was significant heterogeneity immediately (0 hours) and < 24 hours, 48 hours, and 96 hours after exercise (0 hours: I^2 = 89.7%, $p < 0.001$; < 24 hours: I^2 = 82.9%, $p < 0.001$; 48 hours: I^2 = 52.8%, $p < 0.12$; and 96 hours: I^2 = 77.8%, $p = 0.01$; Figure 5).

Subgroup analysis

To identify the potential sources of heterogeneity, overall subgroup analysis was conducted according to training status (trained/untrained), types of L-carnitine (L-carnitine/L-carnitine L-tartrate), and types of exercise (aerobic/resistance). The followings are the significant sources of heterogeneity in our meta-analysis: training status for muscle soreness (untrained individuals: WMD = −1.098, 95% CI = −1.856 to −0.341, $p = 0.001$), training status for CK

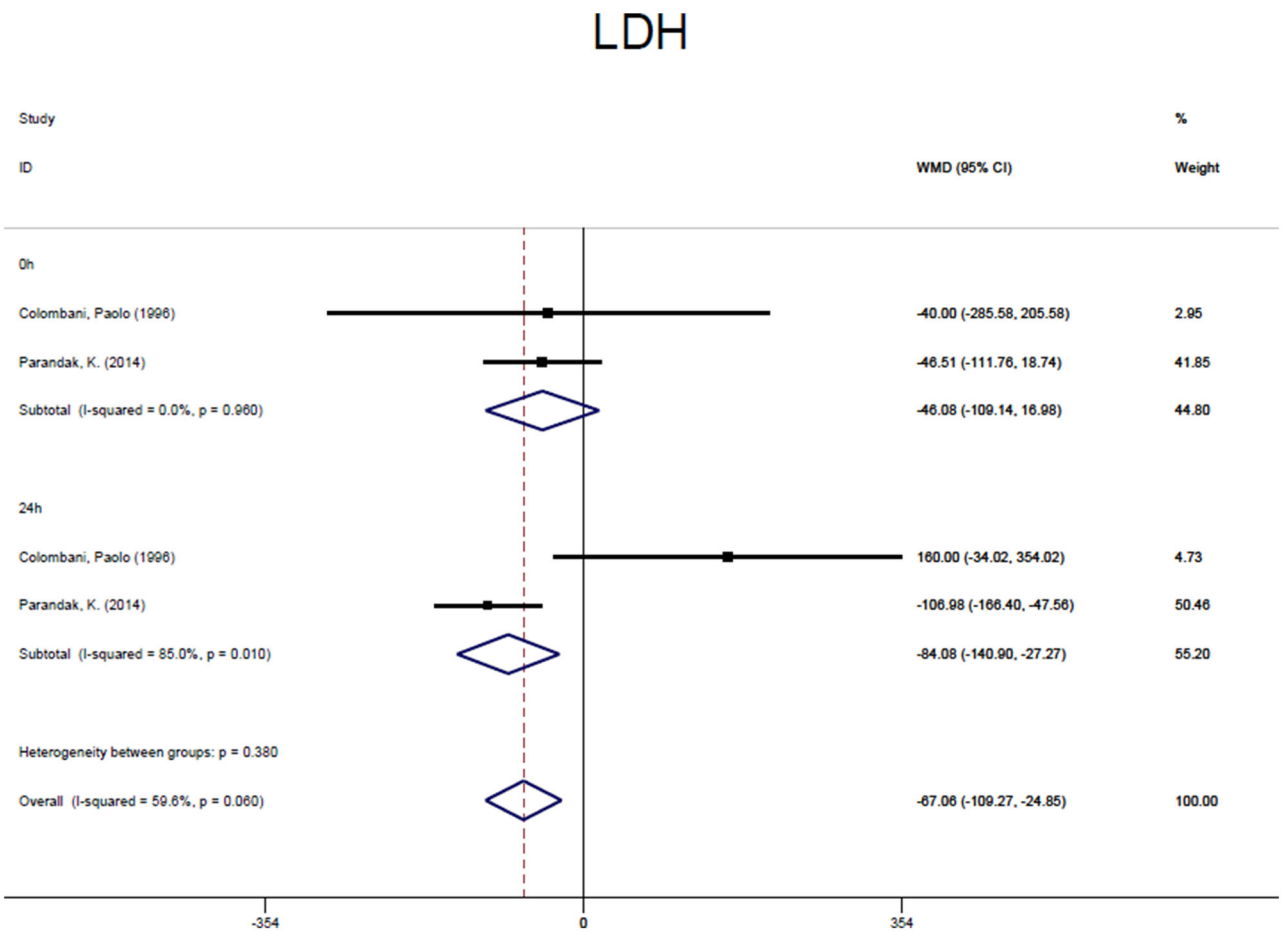

Figure 4. Forest plot presenting weighted mean difference (WMD) and 95% confidence intervals for lactate dehydrogenase.

concentration (untrained individuals: WMD = −16.02, 95% CI = −27.40 to −4.63, $p = 0.006$), training status for myoglobin concentration (untrained individuals: WMD = −15.28, 95% CI = −23.27 to −7.28, $p = 0.006$), and type of exercise for CK concentration (resistance training: WMD = −21.93, 95% CI = −34.96 to −8.90, $p = 0.001$). Types of L-carnitine did not yield to a significant effect for muscle soreness and CK levels. Additionally, we need to declare that there were insufficient data to assess heterogeneity for LDH level.

Publication bias and sensitivity analysis

The results of the influence analysis did not change the significance level of our finding after the removal of each individuals study for muscle soreness, CK, LDH, and myoglobin. Visual assessment of the funnel plot and Egger's test demonstrated significant publication bias only for muscle soreness, CK, and myoglobin (all $p < 0.001$; Figures 6, 7, and 9). No publication bias was observed for LDH ($p = 0.31$; Figure 8).

Discussion

The present systematic review and meta-analyses study investigated the effects of L-carnitine supplementation on exercise-induced muscle damage. Our results illustrated that L-carnitine supplementation improves the MS in each follow-up time point compared to control groups. Also, it decreased the levels of CK, LDH, and myoglobin in a 24-hour follow-up period but did not affect parameters in any other follow-up time period. Training status accounted for some of the heterogeneity among studies. In addition, our findings reveal that L-carnitine supplementation improves the MS and concentration of myoglobin in an untrained population, but not in trained individuals. Moreover, L-carnitine supplementation ameliorated CK concentration only in resistance training groups.

Delayed-onset muscle soreness (DOMS) is a pathological condition with variety of symptoms such as tenderness, pain on movement, a sensation of stiffness and swelling of the muscles. These symptoms usually occur 8 to 10 hours after the training, reaches the peak of symptoms after 24 to 48 hours and decreases toward extinction mostly after 72 to 96 hours. Note that DOMS can affect both psychological and physical aspects of the body and typically leads to a decline in exercise performance and quality of life (27,28). In search of a solution, many studies have claimed that L-carnitine supplementation diminishes the muscle damage parameters (18–21), but it is still less clear whether it leads to an improvement in muscle damage in athletes and untrained individuals. To the best of our knowledge, this is the first systematic review and

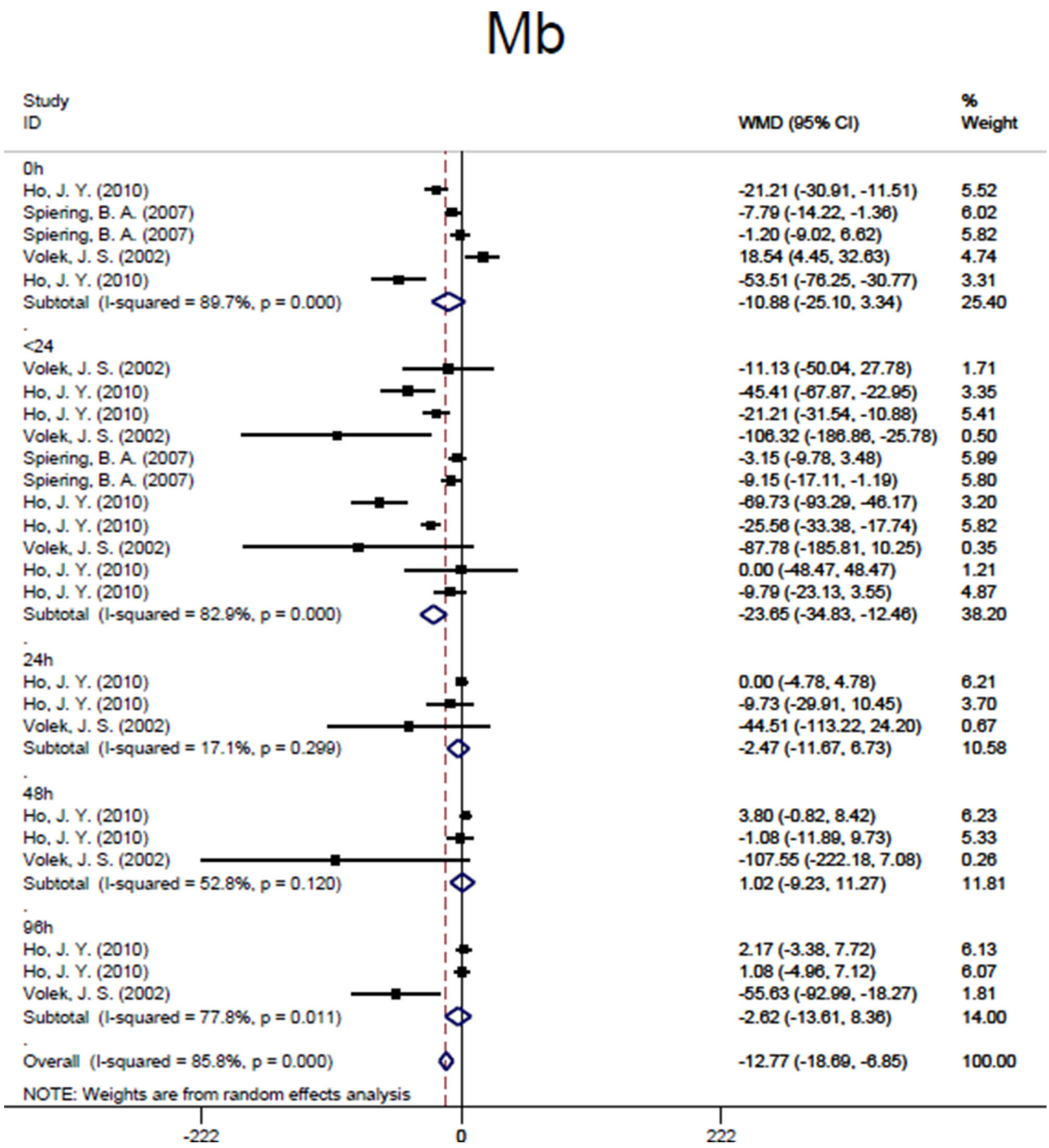

Figure 5. Forest plot presenting weighted mean difference (WMD) and 95% confidence intervals for myoglobin.

meta-analyses to investigate the effects of L-carnitine supplementation on exercise-induced muscle damage.

A few reviews have examined the positive effects of different treatment modalities on recovery after training. Rahimi et al. (29) have recently reported the benefits of using branched-chain amino acid supplementation to prevent and treat muscle soreness after exercise. They demonstrated that branched-chain amino acid supplementation reduced the level of CK at two follow-up time points (24 hours and after 24 hours), while it did not have any effect on muscle soreness and level of LDH at all follow-up time points. Karlic et al. (30) have reviewed the supplementation of L-carnitine in athletes. They concluded that L-carnitine supplementation has beneficial effects on training and recovery after strenuous exercise. A similar study was undertaken by Brass et al. regarding the effects of propionyl-L-carnitine on exercise performance in patients with claudication. This review illustrated that propionyl-L-carnitine was associated with improvement in peak walking distance as compared to placebo (31). Also, in a review by Fielding et al. (28), the authors concluded that L-carnitine alleviated muscle soreness and muscle damage markers (CK, LDH, and Mb).

Some studies inconsistently explained the underlying mechanism of muscle damage. Generally, either mechanical or chemical damages are typically reported in muscle

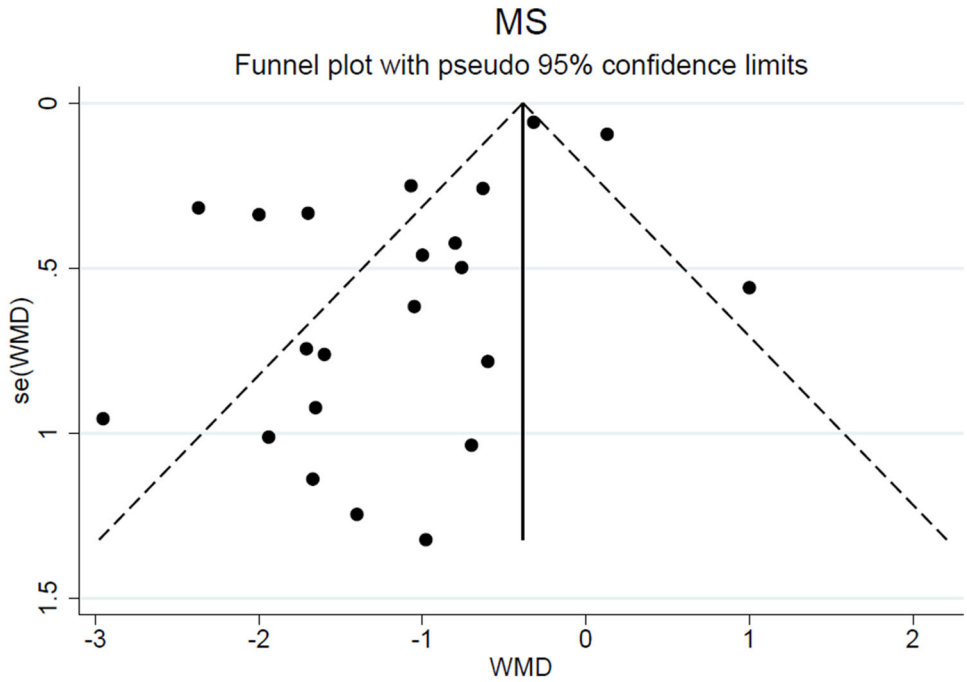

Figure 6. Funnel plot for evaluating publication bias in muscle soreness.

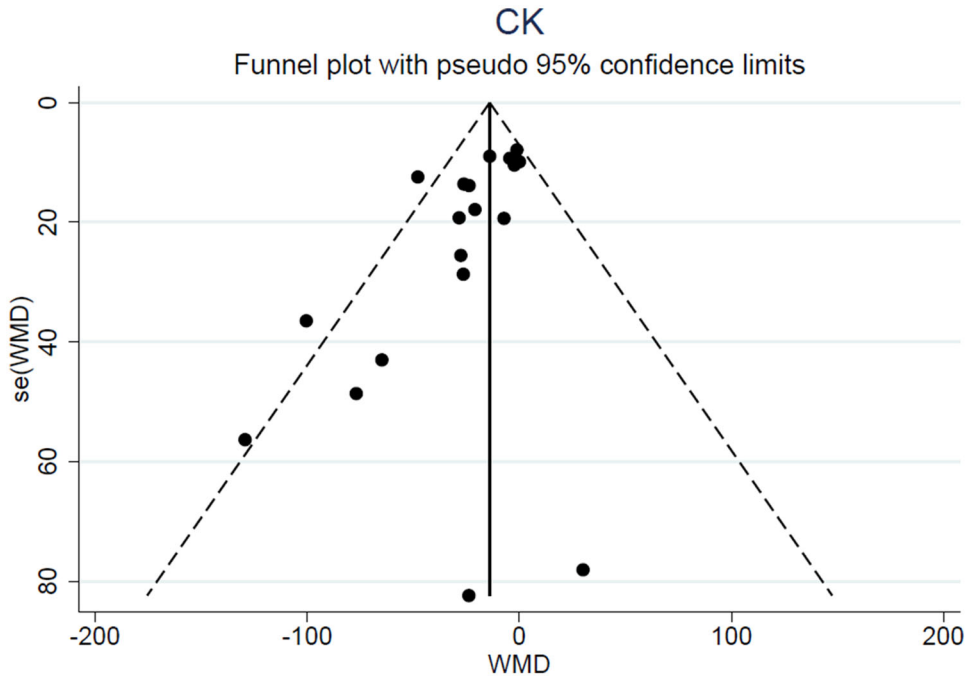

Figure 7. Funnel plot for evaluating publication bias in creatine kinase.

damage (32). Chemical damage is particularly caused by overproduction of reactive oxygen specious (ROS) during eccentric overload (33). For example, Volek et al. suggested that transient hypoxia and hyperactivity of adenylate kinase could be caused by eccentric exercise (18). This event increases ROS levels, leading to peroxidation of membranous unsaturated fatty acids (34,35). Thereafter, intracellular proteins like CK, LDH, and Mb leak into the blood circulation and their levels depend on various factors including where the primary site of muscle damage occurred, kind of exercise (aerobic and resistance), and training status of the participants (trained and untrained). On the other hand, numerous biological components prevent from muscle injury (18). This meta-analysis shows that L-carnitine significantly reduces these symptoms, possibly through inhibition of lipid peroxidation and an increase of membrane integrity which reduces the leakage of constituents such as CK and LDH. In addition, L-carnitine increases blood flow and cellular metabolism (at rest and during exercise), creating a balance between oxygen demand and oxygen supply that ameliorates DOMS (36–38). Nevertheless, the study by Giamberardino et al. provided no data regarding potential

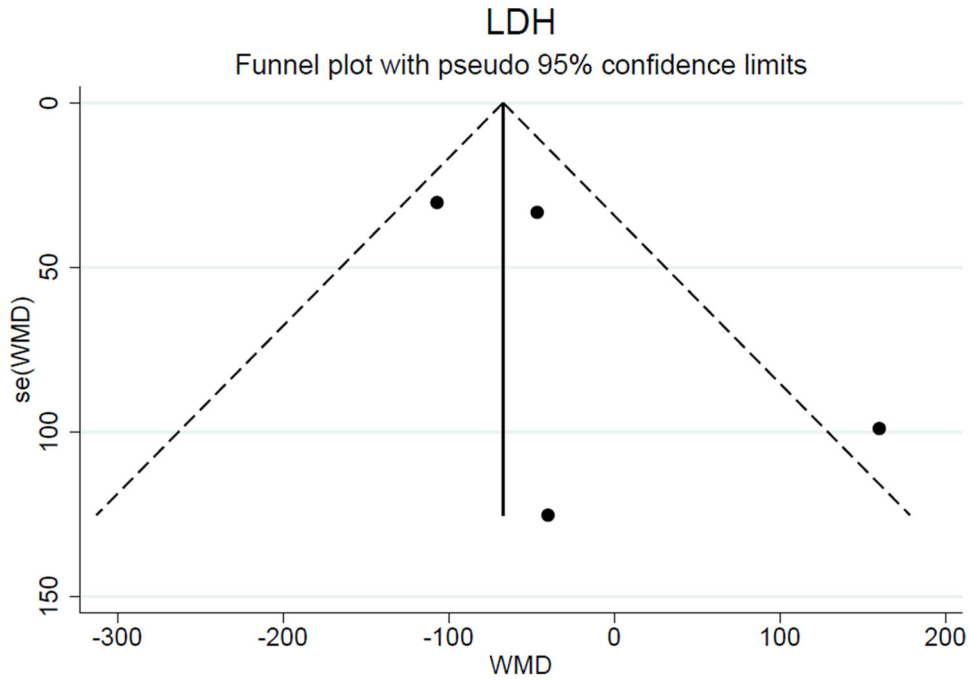

Figure 8. Funnel plot for evaluating publication bias in lactate dehydrogenase.

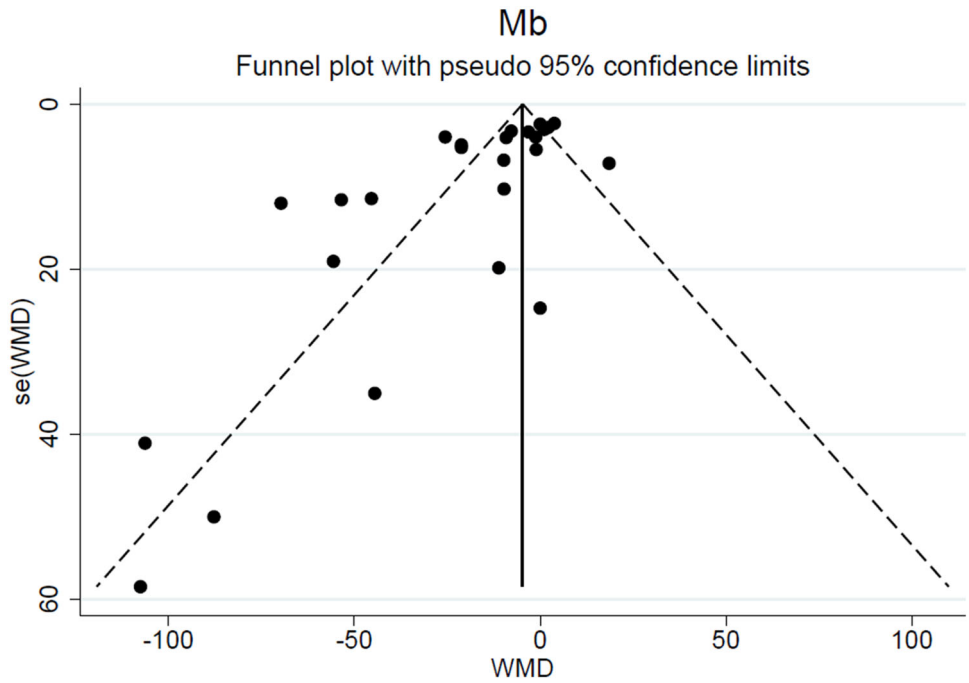

Figure 9. Funnel plot for evaluating publication bias in myoglobin.

mechanisms to explain the beneficial effects of L-carnitine supplementation (16). However, further trials may provide a better understanding about the exact mechanism of this condition.

Next, we found that L-carnitine has higher effects on untrained individuals compared with trained participants. It could be due to the fact that trained individuals are at a higher level of this antioxidant before the study and are, therefore, less susceptible to facilitated adaptation by L-carnitine (29).

In this meta-analysis, an exhaustive search was performed on three electronic databases and complementary sources. However, we acknowledged that some research associated with our study (such as conference proceedings) may have been overlooked. Some of the studies included in this meta-analysis are low-quality, which might affect the results. In addition, there were five studies in which data were extracted from graphs. The results are derived from healthy adult males and more investigations are required to evaluate the hypothesis on other populations, more research is required to confirm whether these findings are generalizable to children, women, and older adults. Also, some athletes can show different individual responses to exercise that may be related to differences in membrane permeability and differences in biomarker clearance rates. Eventually given that normal exercises are not necessarily lead to muscle damages.

But investigations have been performed on people with an extreme muscle injury to show the beneficial effects of L-carnitine.

Conclusions

This meta-analysis and systematic review indicates that L-carnitine supplementation improves DOMS and markers of muscle damage, especially in untrained individuals. Nevertheless, additional research is necessary to investigate the effect of L-carnitine on these markers in the athlete with reference to different training status and different types of exercise (aerobic and resistance) on different muscles (upper and lower body) after various types of mechanical or chemical damages.

Conflict of interest

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