THE VITAMIN E CONSUMPTION EFFECT ON MUSCLE DAMAGE AND OXIDATIVE STRESS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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EFEITO DA INGESTÃO DE VITAMINA E SOBRE OS DANOS MUSCULARES E O ESTRESSE OXIDATIVO: UMA REVISÃO SISTEMÁTICA COM META-ANÁLISE DE ENSAIOS CONTROLADOS RANDOMIZADOS

EFECTO DEL CONSUMO DE VITAMINA E SOBRE EL DAÑO MUSCULAR Y EL ESTRÉS OXIDATIVO: UNA REVISIÓN SISTEMÁTICA CON METAANÁLISIS DE ENSAYOS CONTROLADOS ALEATORIOS

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ABSTRACT

Introduction: Vitamin E supplementation may protect against exercise-induced muscle damage (EIMD) through possible inhibition of free radical formation and cell membrane stabilization. However, there is no systematic review of this topic. This fact maintains academic stalemates that may have a resolution. Objective: This systematic review with meta-analysis aims to provide a comprehensive literature review on the hypothesis of the benefit of vitamin E supplementation on oxidative stress and muscle damage induced by aerobic exercise. Methods: A random-effects model was used, weighted mean difference (WMD) and 95% confidence interval (CI) were applied to estimate the overall effect. Results: The results revealed a significant effect of vitamin E supplementation on reducing creatine kinase (CK) and lactate dehydrogenase (LDH). In addition, a subgroup analysis resulted in a significant decrease in CK concentrations in trials with immediate and <24 hours post-exercise CK measurement; <1000 at daily vitamin E intake; ≤1 at weekly intake; 1 at six weeks and >6 weeks experimental duration, studies on aerobic exercise and training were part of the crossover study. Conclusion: Vitamin E can be seen as a priority agent for recovery from muscle damage. ***Evidence Level II; Therapeutic Studies – Investigating the results.***

Keywords: Vitamin E; Creatine Kinase; Lactate Dehydrogenase; Malondialdehyde; Meta-Analysis.

RESUMO

Introdução: A suplementação de vitamina E pode ter um efeito protetor contra danos musculares induzidos pelo exercício (EIMD) através da possível inibição da formação radical livre e estabilização da membrana celular. Todavia, não há uma revisão sistemática sobre esse tema. Tal fato mantém empasses acadêmicos que podem ter uma resolução. Objetivo: Esta revisão sistemática com meta-análise objetiva fornecer uma análise bibliográfica abrangente na hipótese do benefício na suplementação de vitaminas E sobre o estresse oxidativo e os danos musculares induzidos pelo pelo exercício aeróbico. Métodos: Foi utilizado um modelo com efeitos aleatórios, diferença média ponderada (ADM) e intervalo de confiança de 95% (IC) foram aplicados para estimar o efeito geral. Resultados: Os resultados revelaram um efeito significativo da suplementação de vitamina E na redução da creatina-quinase (CK) e lactato-desidrogenase (LDH). Além disso, uma análise do subgrupo resultou em uma diminuição significativa das concentrações de CK em ensaios com medição imediata e <24 horas de CK após o exercício; <1000 no consumo diário de vitamina E; ≤1 no consumo semanal; 1 em 6 semanas e >6 semanas de duração experimental, estudos sobre exercício aeróbico e treinamento fizeram parte do estudo cruzado. Conclusão: A vitamina E pode ser vista como um agente prioritário de recuperação de danos musculares. ***Nível de evidência II; Estudos Terapêuticos - Investigação de Resultados.***

Descritores: *Vitamina E; Creatina Quinase; Lactato Desidrogenase; Malondialdeído; Metanálise.*

RESUMEN

Introducción: La suplementación con vitamina E puede tener un efecto protector contra el daño muscular inducido por el ejercicio (EIMD) a través de la posible inhibición de la formación de radicales libres y la estabilización de la membrana celular. Sin embargo, no existe ninguna revisión sistemática sobre este tema. Este hecho mantiene un impasse académico que puede tener resolución. Objetivo: Esta revisión sistemática con meta-análisis tiene como objetivo proporcionar una amplia revisión de la literatura sobre la hipótesis del beneficio de la suplementación con vitamina E sobre el estrés oxidativo y el daño muscular inducido por el ejercicio aeróbico. Métodos: Se utilizó un modelo de efectos aleatorios, se aplicó la diferencia de medias ponderada (DMP) y el intervalo de confianza (IC) del 95% para estimar el efecto global. Resultados: Los resultados revelaron un efecto significativo de la suplementación con vitamina E en la reducción de la creatina quinasa (CK) y la lactato deshidrogenasa (LDH). Además, un análisis de subgrupos dio como resultado una disminución significativa de las concentraciones de CK en los ensayos con

medición de CK inmediata y <24 horas después del ejercicio; <1000 en la ingesta diaria de vitamina E; ≤1 en la ingesta semanal; 1 en 6 semanas y >6 semanas de duración experimental, los estudios sobre el ejercicio aeróbico y el entrenamiento formaron parte del estudio cruzado. Conclusión: La vitamina E puede resultar un agente prioritario para la recuperación del daño muscular. ***Nivel de evidencia II; Estudios terapéuticos - Investigación de resultados.***

Descriptores: *Vitamina E; Creatina Quinasa; Lactato Deshidrogenasa; Malondialdehído; Metaanálisis.*

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INTRODUCTION:

Different types of exercise results in muscular dysfunction [1], increased muscle soreness lasting several days [2], and increased concentrations of myofiber proteins (creatine kinase (CK) and lactate dehydrogenase (LDH)) in the blood) [3]. Loss of muscle force in combination with increased muscle damage may have a detrimental effect on muscle function [4]. The effect of exercise training might require using antioxidant supplements to prevent muscle damage and oxidative stress. Some antioxidants have been introduced to protect the cells from free radicals such as vitamins C and E, carotenoids, and flavonoids [5-7]. Recent systematic review and meta-analysis have focused on nutritional interventions during recovery of exercise in an attempt to reduce muscle damage and impairments in muscle function [8-10]. A previous meta-analysis with 6 studies carried out by Stepanyan et al. [10], had assessed the effects of vitamins E supplementation on CK and MDA levels, which some studies did not investigate[11-16], while others were conducted after this study [13,17,18]. Furthermore, LDH measurements were not examined in this paper.

In this field, all relevant studies have been included, as far as the quality of available data permits, and the effects of vitamins E on recovery following exercise-induced muscle damage (EIMD) have been assessed in more detail than in the previous meta-analysis in 2013 [10]. The current meta-analysis assessed indirect markers of muscle damage, including CK and LDH serum concentration, and oxidative stress marker (MDA serum concentration) among trained and untrained healthy adult participants of both sexes, looking at reported clinical trials (crossover and parallel randomized clinical trials). This systematic review and meta-analysis provides a comprehensive literature analysis regarding the hypothesis that vitamins E supplementation can help EIMD and oxidative stress.

METHODS

Search Strategy

The systematic review and meta-analysis was reported based on the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19]. A computerized literature search was performed from inception to November 2021 using Medline, Embase, Cochrane Library, Scopus and a supplementary Google Scholar search. The search was restricted to studies published in English language. The following phrases and their combinations of MeSH and non-MeSH terms were used, including: "vitamin E", "tocopherol", "alpha tocopherol", " beta tocopherol", "tocotrienol", "antioxidant vitamins", "antioxidants", "exercise", "physical exercise", "eccentric exercise", "aerobic exercise", "athlete", "oxidative stress", "malondialdehyde", "muliascle damage" "creatine kinase", "lactate dehydrogenase", "controlled trial", "randomized", "randomised", "random", "randomly", "randomized clinical trial", "RCT", "blinded", "double blind", "double blinded", "trial", "controlled clinical trial", "crossover procedure", "cross-over trial", "double blind procedure "and "equivalence trial". Reference lists of all articles were examined for further eligible studies identification.

Eligibility Criteria

Studies were selected by applying the following Population-Intervention-Comparator-Outcomes-Study design (PICOS) criteria[19]: 1) subjects received oral vitamin E supplementation, as a nutritional strategy; 2) original randomized-controlled trial researches; 3) reporting at least one outcome measure of muscle damage indices (creatine kinase (CK) and lactate dehydrogenase (LDH)) and 4) outcome measure of oxidative stress index (malondialdehyde (MDA)) 5) presented data of interest as mean and standard deviation (SD) of CK, LDH and MDA in both intervention and placebo groups. Exclusion criteria were: 1) using a mixture of vitamin E only in intervention group (vitamin C, Coenzyme Q10 and etc), not including a placebo group; 2) semi experimental, nonrandomized trials and trials without control groups; 3) experimental and animal studies; 4) reviews, letters to editor, editorial articles, or case reports; 5) duplicate studies with the same population (several papers reported the same data); and 6) enrolled pregnant or lactating women.

Study quality

Since it has been adopted that trial inclusion with a high risk of bias may distort the results of a meta-analysis [19,20], the Cochrane Collaboration tool was used for evaluating the risk of bias. The quality of all included studies were evaluated by the following factors: randomization sequence generation; allocation concealment; blinding of participants, personnel, investigator, and assessor; attrition rates; and financial interest by companies. These were given a rating of high, unclear, or low risk of bias. A randomized controlled trial (RCT) was ranked as having high, medium, or low-risk overall based on the key areas of allocation concealment, reporting of attrition rates, and participants and assessor (low = all key areas rated low, high = all 4 factors rated high, and medium = 2 or 3 factors rated high or unclear).

Analyses and measures of treatment effect

For every study, mean differences and SD were computed for continuous variables. Standardized mean differences were used for variables pooled on the different scales. Between-study heterogeneity was assessed using the chi-squared ($\chi 2$) test and quantified using the I^2 statistic, which represents the percentage of the total variation across studies that is attributable to heterogeneity rather than to chance. Significant heterogeneity was defined with a P-value of <0.05.

The random effects model was applied to calculate the weighted mean differences (WMDs) with 95% confidence intervals (CIs) for estimating the overall effect. Publication bias was assessed by Egger's regression asymmetry and test Begg's rank correlation test. Funnel plots depicted the effect sizes (differences in means) against their corresponding standard errors. Also, statistical analyses were performed using STATA 11.2 software (StataCorp, College Station, Texas, USA).

RESULTS

Search results and overview of included studies

Our search led to 588 relevant studies. After duplicates removing, a wide screening range of the titles and abstracts and careful assessment was performed on 572 related articles. Of these, 32 articles remained after considering the inclusion and exclusion criteria for the eligibility. Finally, 13 articles, including, 29 effect sizes for CK, 5 effect sizes for LDH and 19 effect

sizes for MDA, which studied a total of 246, 99 and 126 participants respectively and aged 20.3 – 55 years, were identified in the current systematic review and meta-analysis. This listed number is inclusive of people who were dropouts in some studies. Participants tended to be young, but two studies evaluated vitamin E effects on CK, LDH and MDA concentration for elderly men in addition to youth[11,21]. In addition, all participants were men, except in one study which women participated (n = 20) [22], and in one study both men and women participated (n = 19)[16].

One study was not randomized[17] and data from one article was not directly accessible from the published papers, and we did not receive raw data for trial from the authors[12]. Figure 1 represents the selection process and reasons for excluding the studies and the data in Table 1 illustrates the main characteristics of the articles in our systematic review and meta-analysis.

In brief, the studies were published between 1990 and 2018. The total number of participants who completed the studies in inclusion criteria was 118 participants in the intervention and 128 in the placebo groups for CK, 49 participants in the intervention and 50 in the placebo groups for LDH and 62 participants in the intervention and 64 in the placebo groups for MDA. The dose of vitamin E supplementation was 130 to 1200 IU/day among these studies and the duration of these trials ranged between 1 to 84 days. Three studies used a randomized crossover design[14,18,23], and all of them had the design of double-blind. Among 16 studies 5 studies were conducted in n the United States[11,16,21,24,25]. The effect of vitamin E on CK, LDH and MDA concentration together was examined in one study[22]; 12 studies only reported CK[11,13-16,18,21-26], 4 studies only reported LDH[18,22,26,27] and 6 studies only reported MDA[11,14,21,22,24,25].

Results from quality assessments

Table 2 presented the quality details of bias assessment**.** Briefly, participants random allocation was mentioned in all included trials. However, three studies described the method of random sequence generation [11,22,27]. Seven studies reported allocation concealment [13,14,18,21-24]. Most studies represented low risk of bias based on selective reporting; nevertheless, 3 studies had high risk of bias [13,23,24]. All studies had a low risk of bias for incomplete outcome data. Nine studies had a low risk of bias for blinding of participants and personnel [14-16,18,21-23,25,27] and just one studies had low risk of bias regarding blinding outcome assessors [15]. All of studies had unclear or low risk of bias regarding other potential threats to validity.

Findings from the meta-analysis

Effects of vitamin E supplementation on serum CK concentration

According to our analysis on 29 trials, in overall, vitamin E consumption had significant effect on CK concentration: (WMD = -26.92; 95% CI: -47.295, -6.553; P = 0.010). There was significant heterogeneity among the studies (Cochran's Q test = 148.67, P = 0.000, I^2 = 81.2 %) (Figure 2). Subgroup analysis was conducted to investigate if the effect of vitamin E supplementation on serum CK is different according to follow-ups after exercise, dose of vitamin E, duration of studies, exercise type, train status and study design. Some of subgroup analysis revealed that vitamin E supplementation resulted in a significant decrease in CK concentrations in trials with immediately and <24 hours measurement of CK after exercise, <1000 IU/day

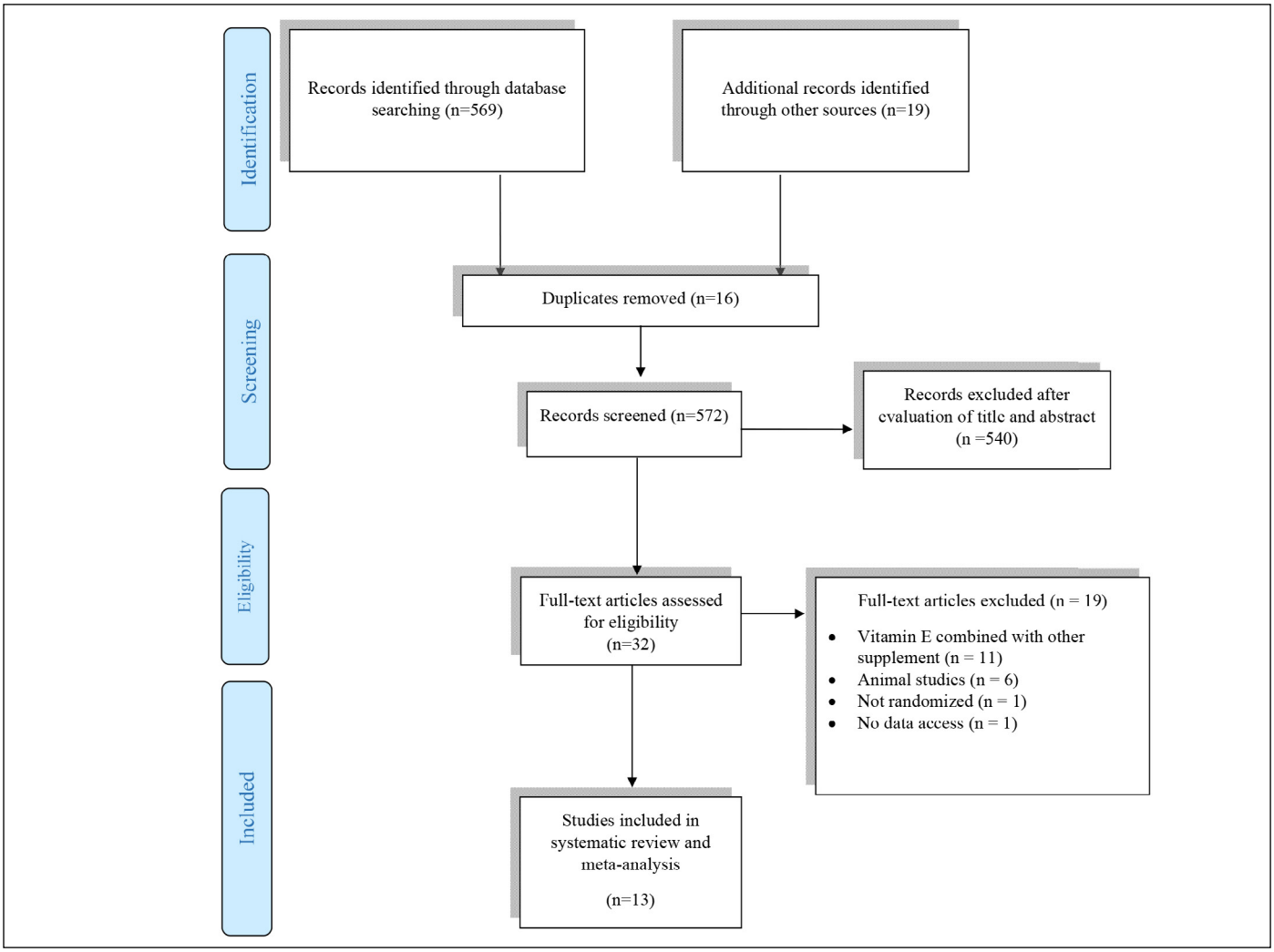

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection process.

Table 1. Summary of relevant sources of data.

Author (year)	Study Design Characteristics						Average age (y)	Sample Size		Exercise type	Muscle damage indices	Oxidative stress indices
	design	country	training status	vitamin E dose (IU/d)	duration (D)	gender		vitamin E	control			
Kashef et al. (2018) * # [17]	RP	Iran	U	400	30	M	22.8	10	10	resistance	CK	MDA
Bataineh et al. (2017) [13]	RP	Jordan	T	400	5	M	31	7	7	aerobic	CK	
Santos et al. (2016) [18]	CP	Brazil	^†	550	1	M	24.2	9	9	aerobic	CK, LDH	
Taghiyar et al. (2013) [22]	RP	Iran	T	400	28	F	22.5	10	10	aerobic	CK, LDH	MDA
Silva et al. (2010) [27]	RP	Brazil	U	800	21	M	22.5	11	10	resistance	LDH	
Keong et al. (2006) [14]	CP	Malaysia	T	130	42	M	24.9	18	18	aerobic	CK	MDA
Gaeini et al. (2006) ¥ # [12]	RP	Iran	T	1000	56	M	20.3	^	^	aerobic	CK	MDA
Sacheck et al. (2003) [21]	RP	USA	U	1000	84	M	26.4	8	8	aerobic	CK	MDA
Sacheck et al. (2003) [21]	RP	USA	U	1000	84	M	71.4	8	8	aerobic	CK	MDA
Avery et al. (2003) [25]	RP	USA	T	1200	21	M	22.5	9	9	resistance	CK	MDA
Beaton et al. (2002) [15]	RP	Canada	U	1200	30	M	20.3	9	7	resistance	CK	
Niess et al. (2001) [23]	CP	Germany	T	500	8	M	25.3	9	9	aerobic	CK	
Buchman et al. (1999) [16]	RP	USA	U	1000	14	M & F	18–55	5	14	aerobic	CK	
Itoh et al. (1999) [26]	RP	Japan	U	1200	28	M	21.4	7	7	aerobic	CK, LDH	
Cannon et al. (1990) [11]	RP	USA	U	800	48	M	<30	4	5	aerobic	CK	MDA
Cannon et al. (1990) [11]	RP	USA	U	800	48	M	>55	6	6	aerobic	CK	MDA
McBride et al. (1990) [24]	RP	USA	T	1200	14	M	21	6	6	resistance	CK	MDA

CK = Creatine kinase; LDH = Lactate dehydrogenase; MDA = Malondialdehyde; RP = randomized controlled trial; CP = cross-over studies; M = male; F = Female; D=Days; Y=years; T=trained; U= untrained. †Coded in the meta-analysis as untrained. * Not randomized; # Excluded from meta-analysis; ^ Unknown; ¥ No data access.

Table 2. Cochrane Risk of Bias Assessment.

Study	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall Risk of Bias
Bataineh et al. (2017)[13]	U	L	H	H	L	H	U	High
Santos et al. (2016)[18]	U	L	L	U	L	L	L	Medium
Taghiyar et al. (2013)[22]	L	L	L	U	L	L	L	Medium
Silva et al. (2010)[27]	L	U	L	U	L	L	L	Medium
Keong et al. (2006)[14]	U	L	L	U	L	L	L	Medium
Sacheck et al. (2003)[21]	U	L	L	U	L	L	L	Medium
Avery et al. (2003)[25]	U	U	L	U	L	L	U	Medium
Beaton et al. (2002)[15]	U	U	L	L	L	L	L	Medium
Niess et al. (2001)[23]	U	L	L	U	L	H	L	Medium
Buchman et al. (1999)[16]	U	U	L	U	L	L	U	Medium
Itoh et al. (1999)[26]	U	U	U	H	L	L	L	Medium
Cannon et al. (1990)[11]	L	U	U	U	L	L	L	Medium
McBride et al. (1990)[24]	U	L	H	H	L	H	U	High

L, low risk of bias; H, high risk of bias; M, medium risk of bias; U, unclear risk of bias.

vitamin E consumption, all ≤1 week, 1 – 6 weeks and >6 weeks trial duration, studies on aerobic exercise and trained participant and cross over study design.

Effects of vitamin E supplementation on LDH concentration

As outlined in Figure 3, our preliminary analysis indicated that vitamin E supplementation have significant effect in serum LDH concentration compared to placebo (WMD = -45.24; 95% CI: -86.44, -4.03; P= 0.031). Also, significant heterogeneity was observed among studies (Cochran's Q test = 109.59, P= 0.000, I^2 = 93.0 %).

Effects of vitamin E supplementation on MDA concentration

The effect of the vitamin E supplementation on MDA concentration was evaluated in 19 arms of clinical trials and pooled mean difference from inverse variance method showed no significant reduction in MDA concentration (WMD = 0.07; 95% CI: -0.03, 0.16; p = 0.020) with considerable between-study heterogeneity (P= 0.000, I^2 = 78.0) (Figure 4). Subgroup analysis of follow-ups after exercise, dose of vitamin E, duration of studies and exercise type, train status and study design had no significant effect on MDA concentration in any subgroups.

Sensitivity analysis and publication bias

Sensitivity analysis indicated that the removal of any of the studies from the meta-analysis, create no change in the results of the meta--analysis on CK and LDH concentration whereas, the results on MDA concentration were sensitive to omitting 1 study [14]. The results of Begg's test did not determine any evidence of publication bias in studies that examine the effect of vitamin E consumption on CK (Begg's test, P = 0.894) and on MDA (Begg's test, P = 0.512). Also, the results of Egger's test did not determine any evidence of publication bias in studies that examine the effect of vitamin E consumption on LDH (Egger's test, P = 0.346)

DISCUSSION

The results of the current meta-analysis, performed on 23 randomized controlled trials, revealed beneficial effects of vitamin E supplementation in decreasing CK and LDH concentration during training protocols of different periods.

Damage of skeletal muscle is a phenomenon that can happen because of several factors, such as cell necrosis or rupture, representing about 10-55% of total muscular injuries [28]. The muscle tissue damage

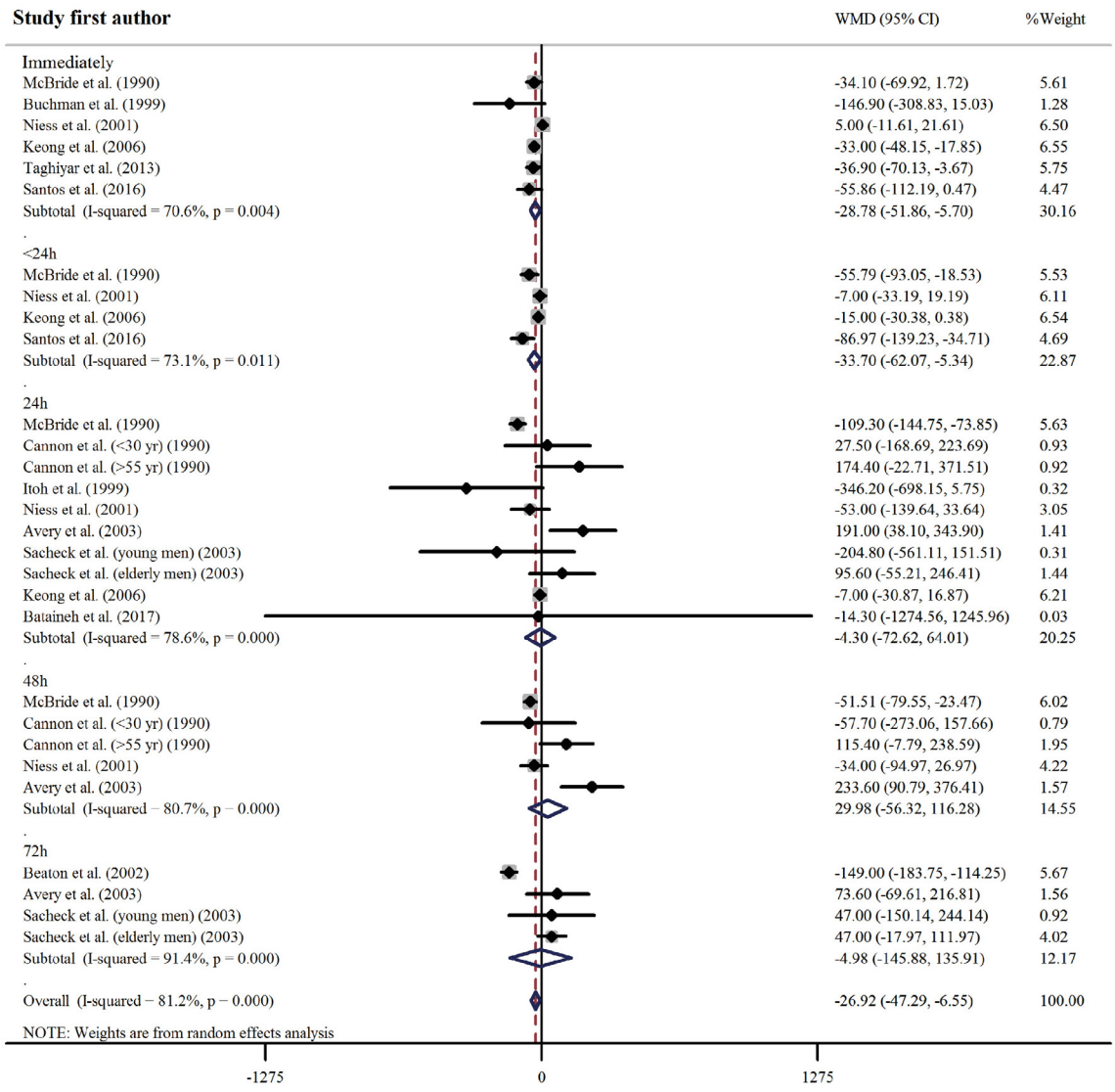

Figure 2. Forest plot of the effect of vitamin E supplementation on creatine kinase subgrouped by follow up times after exercise. WMD = weighted mean difference; CI = confidence interval.

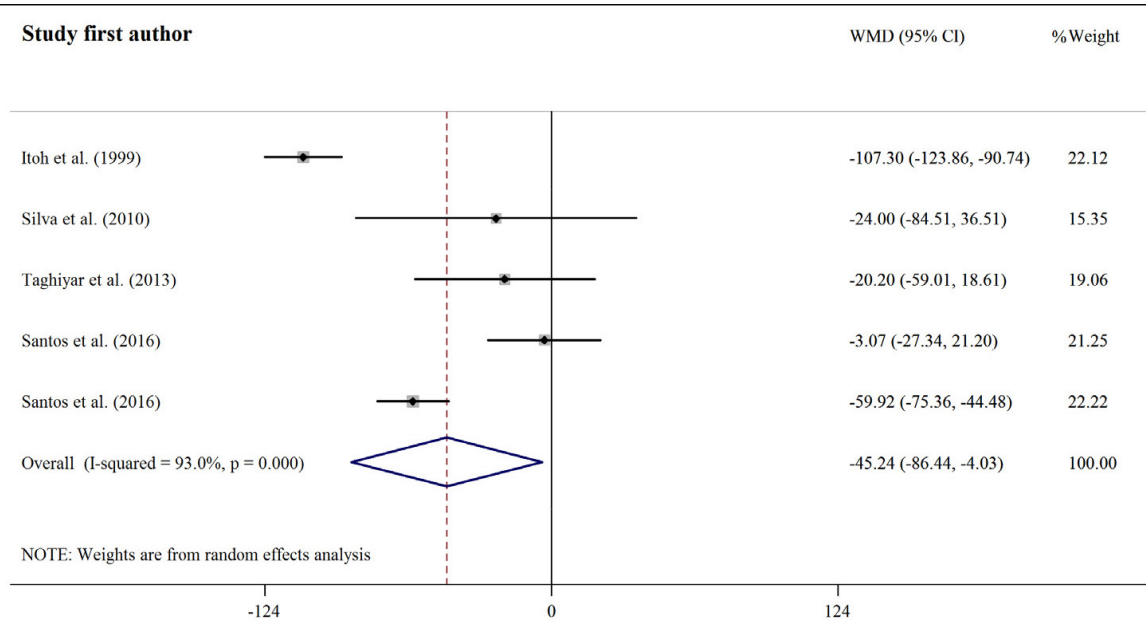

Figure 3. Forest plot of the effect of vitamin E supplementation on lactate dehydrogenase subgrouped by follow up times after exercise. WMD = weighted mean difference; CI = confidence interval.

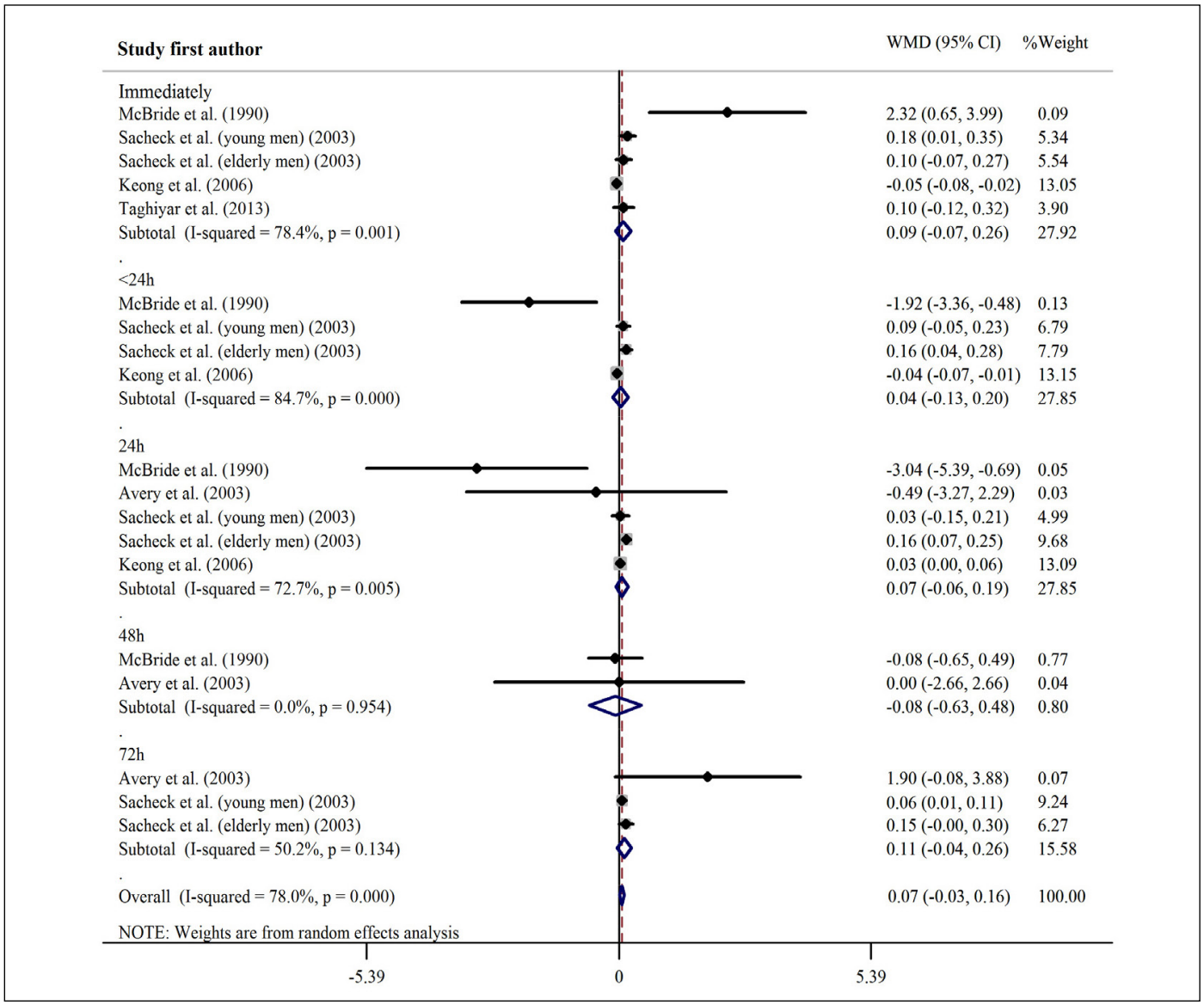

Figure 4. Forest plot of the effect of vitamin E supplementation on malondialdehyde subgrouped by follow up times after exercise. WMD = weighted mean difference; CI = confidence interval.

can be defined as the plasma membrane disruption, accompanied by the muscle proteins loss (i.e. CK, LDH, myoglobin), proteins of serum influx, increased crowd of inflammatory infiltrates in the muscle fibers (i.e. neutrophils and macrophages), delayed onset muscle soreness (DOMS), functional impairment (loss of strength), and some possible structural disorders like sarcomere Z lines disarrangement [29,30]. The ingestion of antioxidant vitamins has been proposed to attenuate muscle damage through prevention of muscle fiber lipids peroxidation that leads to cellular disruption. Vitamin E is the major lipid soluble, chain-breaking antioxidant [31]. Vitamin E accumulates in the cell membranes phospholipid bilayer and limits lipid peroxidation within the membrane [32]. Vitamin E supplementation has been shown to significantly decrease the amount of membrane damage and lipid peroxidation associated with different types of exercise [24]. We suggest this mechanistic explanation for the lower CK and LDH response with vitamin E supplementation, which vitamin E may have enhanced membrane stability and thereby lowered enzyme release.

Subgroup analysis showed the effect of vitamin E supplementation on lowering serum CK is significant in immediately and <24 hours follow-ups after exercise. The responses of CK might depend on where the early site of muscle damage occurred, the training situation of the participants [33], the type and familiarity with the exercise used and therefore the limit of myocellular specific proteins release. In this regard, trials with trained participants had a significant decrease in CK concentrations with vitamin E supplementation. The high intra- and inter individual variation in CK responses question their accuracy at scaling the value of muscle damage because this parameters, rather than providing evidence for its progression, mostly serve as indirect indicators of recovery and as global markers for damage [8,9,34].

Also, subgroup analysis revealed that vitamin E supplementation resulted in a significant decrease in CK concentrations in studies that conducted on aerobic exercise and not resistance exercise. The major feature of skeletal muscle damage without cell necrosis is the muscle fibers disruption, specifically the basal lamina sheath. Regarding mechanical stimuli, specifically resistance exercise, it is known that it can promote micro damage in muscle fibers imposed by contractions or overload and, according to the length, intensity and volume the degree and severity of damage and discomfort may be compounded over time and persist chronically [17,25]. For these reasons, vitamin E cannot be effective enough for resistance exercise.

Contrary to expectations, dose of <1000 IU/day vitamin E had significant effect on lowering CK. It can be speculated that participant in all

studies that used <1000 IU/day vitamin E, conducted aerobic exercise except one study [27]. Above-mentioned subgroup analysis indicated that vitamin E supplementation decreased CK in t with aerobic exercise.

The present meta-analysis had several limitations. No included studies in this meta-analysis blinded the providers/ assessors except one study. Due to the nature of physical activity interventions, blinding in such studies may be challenging. Moreover, evidence was downgraded due to the lack of homogeneity among included articles and subgroup hypothesis were not sufficient for founding the source of heterogeneity. However, follow-ups after exercise explained potential between-study heterogeneity. Lack of information about data on intensity and frequency of exercise, genetic background, lifestyle factors and lack of complete baseline CK and LDH data for subgroup analysis make overall interpretation of the results difficult.

CONCLUSION

In summary, the findings within the present meta-analysis indicate that supplementation with vitamin E appears to be effective at attenuating the immediate muscle damage that occurs after aerobic exercise muscle injury. But, due to high heterogeneity and the medium risk of bias for articles, we suggest that these facts be taken into account and the data be interpreted with caution by the readers.

AUTHORS' CONTRIBUTION: Each author made a significant contribution to the manuscript. Yanling Zhou: concept and design of the work. Li liang: analysis and critical review.

All authors declare no potential conflict of interest related to this article

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