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Clifford, Tom, Jeffries, Owen, Stevenson, Emma J and Davies, Kelly A Bowden (2019) The effects of vitamin C and E on exercise-induced physiological adaptations: a systematic review and Meta-analysis of randomized controlled trials. *Critical Reviews in Food Science and Nutrition*, 60 (21). pp. 3669-3679. ISSN 0007-9006

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**Version:** Accepted Version

**Publisher:** Taylor & Francis

**DOI:** <https://doi.org/10.1080/10408398.2019.1703642>

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1 **TITLE: THE EFFECTS OF VITAMIN C AND E ON EXERCISE-INDUCED**  
2 **PHYSIOLOGICAL ADAPTATIONS: A SYSTEMATIC REVIEW AND META-**  
3 **ANALYSIS OF RANDOMISED CONTROLLED TRIALS**

4 Authors: Tom Clifford<sup>1,2\*</sup>; Owen Jeffries; Emma J. Stevenson<sup>1</sup>; Kelly A. Bowden Davies<sup>1</sup>

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6 <sup>1</sup>Institute of Cellular Medicine, Newcastle University, William Leech Building, Newcastle on  
7 Tyne, NE2 4HH, UK;<sup>2</sup> School of Sport, Exercise and Health Sciences, Loughborough  
8 University, Loughborough, UK, LE11 3TU.

9

10 **Running title:** Vitamin C and E and exercise adaptations: A meta-analysis

11 **Keywords:** Antioxidant; vitamin; skeletal muscle; endurance performance; resistance training.

12 \*Corresponding author: Tom Clifford, School of Sport, Exercise and Health Sciences,  
13 Loughborough University, Loughborough, UK, LE11 3TU. Email: t.clifford@lboro.ac.uk.

14 The material presented in this manuscript is original and it has not been submitted for  
15 publication elsewhere while under consideration by Critical Reviews in Food Science and  
16 Nutrition.

17

18 Abstract word count: 199

19 Main text word count: 4950

20 References: 46

21 Tables: 2

22 Figures: 7

23 Online Supplementary Material: 1

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31 **Abstract**

32 We conducted a systematic review and meta-analysis of randomized controlled trials  
33 examining the effect of vitamin C and/or E on exercise-induced training adaptations. Medline,  
34 Embase and SPORTDiscus databases were searched for articles from inception until June 2019.  
35 Inclusion criteria was studies in adult humans where vitamin C and/or E had to be consumed  
36 alongside a supervised exercise training program of  $\geq 4$  weeks. Nine trials were included in the  
37 analysis of aerobic exercise adaptations and nine for resistance training (RT) adaptations.  
38 Vitamin C and/or E did not attenuate aerobic exercise induced improvements in maximal  
39 aerobic capacity ( $\dot{V}O_{2\max}$ ) (SMD -0.14, 95% CI: -0.43 to 0.15,  $P = 0.35$ ) or endurance  
40 performance (SMD -0.01, 95% CI: -0.38 to 0.36,  $P = 0.97$ ). There were also no effects of these  
41 supplements on lean mass and muscle strength following RT (SMD -0.07, 95% CI: -0.36 to  
42 0.23,  $P = 0.67$ ) and (SMD -0.15, 95% CI: -0.16 to 0.46,  $P = 0.35$ ), respectively. There was also  
43 no influence of age on any of these outcomes ( $P > 0.05$ ). These findings suggest that vitamin  
44 C and/or E does not inhibit exercise-induced changes in physiological function. Studies with  
45 larger sample sizes and adequate power are still required.

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## 54 **Introduction**

55 Vitamin C and E are commonly used dietary supplements by athletes (Knapik et al., 2016). In  
56 the absence of deficiency, the motivation to consume them is related to athlete beliefs in their  
57 ability to enhance performance or maintain health, owing to their antioxidant properties  
58 (Parnell, Wiens, & Erdman, 2015). Indeed, both vitamin C and E are key dietary sources of  
59 antioxidants which function to neutralize reactive species (RS) produced as part of normal daily  
60 living (Sies & Stahl, 1995). However, intense exercise generates large amounts of RS, either  
61 from increased oxidative metabolism or increased cellular damage, and the resulting change in  
62 redox metabolism — in favor of a pro-oxidant environment, has been linked to fatigue, illness  
63 and muscle-damage during exercise (Cooper, Vollaard, Choueiri, & Wilson, 2002; Powers,  
64 Nelson, & Hudson, 2011). Accordingly, both vitamins C and E, taken alone or in combination,  
65 have been examined extensively for their ability to enhance performance or recovery after  
66 exercise.

67 Notwithstanding, evidence for beneficial effects of vitamin C and E on any aspect of exercise  
68 performance is equivocal. In fact, some recent studies report negative effects with these  
69 vitamins, suggesting that the typical dose found in supplements (often  $\geq 10$  x the recommended  
70 daily allowance) can actually impair recovery or blunt exercise-induced training adaptations  
71 (Bjørnsen et al., 2015; Close et al., 2006; Gomez-Cabrera et al., 2008). Indeed, the last decade  
72 has seen a growing concern that dampening exercise-induced RS could actually mitigate or at  
73 least lessen some of the physiological adaptations evoked by exercise training (Gomez-Cabrera  
74 et al., 2008; Paulsen et al., 2014a). A key function of the RS produced during exercise is to  
75 stimulate molecular pathways via proteins such as peroxisome proliferator-activated receptor-  
76  $\gamma$  coactivator (PGC1- $\alpha$ ) and mitogen-activated protein kinases (MAPK), that lead to  
77 improvements in aerobic capacity and muscle hypertrophy, respectively (Gomez-Cabrera et  
78 al., 2008; Morrison et al., 2015; Paulsen et al., 2014b).

79 The possibility that vitamin C and E supplementation blunts adaptations to aerobic exercise  
80 (AE), such as improvements in maximal aerobic capacity ( $\dot{V}O_{2\max}$ ), has been the subject of  
81 several recent investigations; however, results so far have been mixed. For example, in one  
82 study (Gomez-Cabrera et al., 2008), supplementing rats with vitamin C suppressed the  
83 exercise-induced increase in  $\dot{V}O_{2\max}$  and PGC-1 $\alpha$  — a key marker of mitochondrial biogenesis.  
84 Furthermore, in the human participants,  $\dot{V}O_{2\max}$  improved after 8 weeks of exercise training,  
85 but the improvements were ~11% lower (albeit not statistically significant) in those taking  
86 vitamin C compared to those who were not. In contrast, 12 weeks of cycling training  
87 supplemented with vitamin C (500 mg·day<sup>-1</sup>) and E (400 IU·day<sup>-1</sup>) improved  $\dot{V}O_{2\max}$  and  
88 maximal power output relative to a placebo (PLA) supplement (Yfanti et al., 2011).

89 Similarly mixed findings have been reported when examining the influence of vitamin C and  
90 E on adaptations associated with resistance training (RT), such as muscle hypertrophy and  
91 muscle strength. Improvements in isometric muscle torque were similar between a PLA and  
92 vitamin C and E supplemented group following 4 weeks of RT (Theodorou et al., 2011).  
93 However, vitamin C (1000 mg·day<sup>-1</sup>) and E (400 IU·day<sup>-1</sup>) supplementation in conjunction  
94 with a 10 week RT program had no effect on hypertrophy or lower body muscle strength,  
95 whereas in contrast upper body strength, as measured by 1 repetition maximum (RM), was  
96 lower in the vitamin vs. PLA group (Paulsen et al., 2014b). Another study from the same group  
97 (Bjørnsen et al., 2015) examined vitamin C and E supplementation in older adults ( $\geq 60$  years  
98 of age) during 12 weeks of RT and reported that lean mass gains were ~2.5% lower in the  
99 supplemented versus PLA group, providing further evidence that these vitamins might negate  
100 exercise-induced benefits.

101 The lack of consensus regarding vitamin C and E supplementation and exercise-induced  
102 adaptations has led to intense debate in the literature (Gomez-Cabrera, Ristow, & Vina, 2012;  
103 Higashida, Kim, Higuchi, Holloszy, & Han, 2011) and remains a contentious issue in sports

104 and exercise nutrition (Ismaeel, Holmes, Papoutsis, Panton, & Koutakis, 2019). It is important  
105 to note the findings from these studies not only have important implications for athletes but for  
106 the general population as well, who also frequently report a high consumption of vitamin C  
107 and E supplements for their purported health benefits (Bailey, Gahche, Miller, Thomas, &  
108 Dwyer, 2013). Moreover, from a clinical perspective, exercise is one of the most effective  
109 prescriptive tools for improving health and reducing disease burden (Gleeson et al., 2011). It  
110 is therefore important to understand whether these commonly consumed over the counter  
111 dietary supplements can mitigate some of the beneficial adaptations to exercise in athletes and  
112 the general population.

113 While a number of scholarly reviews on this topic have been published in the last decade  
114 (Ismaeel et al., 2019; Mankowski, Anton, Buford, & Leeuwenburgh, 2015; Merry & Ristow,  
115 2016; Nikolaidis, Kerksick, Lamprecht, & McAnulty, 2012), no study to date has attempted to  
116 systematically review and meta-analyse the effects of vitamin C and E on key physiological  
117 markers of exercise adaptations such as  $\dot{V}O_{2\max}$  and lean mass. Thus, we undertook a systematic  
118 review and meta-analysis of randomized controlled trials to examine whether vitamin C and/or  
119 E supplementation in combination with an AE or RT exercise program blunts adaptations to  
120 key physiological markers of performance in humans.

## 121 **Methods**

122 The study protocol for this systematic review was pre-registered on the PROSPERO database  
123 (registration number: CRD42019138726). This systematic review was reported according to  
124 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines  
125 (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

126 **Search strategy:** Medline, Embase and SPORTDiscus were searched for articles from  
127 inception until June 11<sup>th</sup> 2019. Our search strategy was based on a PICOS methodology and

128 full details are available in the Online Supplementary Material. Briefly, using Boolean logic  
129 and truncations, the following terms and keywords were searched: antioxidant, anti-oxidant,  
130 vitamin c, ascorbic acid, vitamin e, beta-tocopherol, gamma-tocopherol, alpha-tocopherol,  
131 tocopherol, exercise, resistance training, eccentric, endurance, strength, aerobic, muscle  
132 hypertrophy, training, adaptation, exercise performance, randomized controlled trial,  
133 controlled clinical trial, randomized, placebo, randomly, trial, humans. Two investigators (TC  
134 and KBD) independently screened the abstracts and titles from the searches and then retrieved  
135 the relevant full-texts to assess eligibility based on the below outlined inclusion criteria. The  
136 full-text articles included were also searched manually for any additional studies but none were  
137 identified from these searches. A flow diagram of our search strategy is depicted in Figure 1.

138 **Study selection:** Inclusion criteria were: 1) Adult participants ( $\geq 18$  years); 2) vitamin C or  
139 vitamin E supplementation (alone or together) combined with a supervised exercise training  
140 program lasting  $\geq 4$  weeks; 3) a comparator group that received an inert control supplement or  
141 no supplement but completed the same training program as the intervention group; 4) reporting  
142 of pre to post changes in either lean mass, muscle strength,  $\dot{V}O_{2\max}$  or endurance performance;  
143 5) randomized controlled controls performed in humans. Crossover and parallel designs were  
144 eligible. We excluded studies in which other nutrients were taken alongside vitamin C and/or  
145 E and if the exercise programs were not supervised and recorded by the researchers. The full  
146 text of articles deemed to meet these criteria were retrieved and screened for their eligibility by  
147 two investigators (KBD and TC) (see Online Supplementary Material for list of studies  
148 excluded). Both investigators agreed on the articles to be included in the systematic review  
149 and meta-analysis. In the event of any disagreements, these were resolved by a 3<sup>rd</sup> author (OJ).

150 **Data extraction:** Two investigators (TC and KBD) extracted data from the studies and  
151 tabulated them into a Microsoft Excel Spreadsheet. If data were not available in the full-text  
152 articles then data was extrapolated from figures using online software (WebPlotDigitizer,

153 Version 3.12) ( $n = 2$  studies) or the mean delta changes presented in the articles were used for  
154 analysis ( $n = 2$ ). One author was contacted to retrieve muscle strength data that was not  
155 available in the full-text; however, we did not receive a reply and therefore this data was not  
156 included in the meta-analysis (see Table 2). Data for studies in which the main outcomes were  
157  $\dot{V}O_{2\max}$  or endurance performance are presented in Table 1 and for those in which lean mass  
158 and muscle strength were the main outcomes are presented in Table 2. Some studies reported  
159 fat free mass and others lean mass (Table 2); for consistency and clarity, we refer to both as  
160 lean mass in the text.

### 161 **Heterogeneity, risk of bias, and sensitivity analyses**

162 Heterogeneity was assessed with the  $\chi^2$  (see Figures 4 - 7) and  $I^2$  statistic;  $P > 0.10$  indicates  
163 significant heterogeneity, and interpreted as follows:  $<25\%$  indicates low risk,  $25-75\%$   
164 indicates moderate risk, and  $>75\%$  indicates a high risk (Higgins, Thompson, Deeks, &  
165 Altman, 2003). The Cochrane risk of bias tool was used to assess study quality (Higgins et al.,  
166 2011). This was performed by two authors (TC and KBD) and disagreements were resolved  
167 through discussion. Risk was assessed based on the study's primary outcome and using the  
168 intention to treat risk of bias tool. Sensitivity analyses were performed whereby trials at unclear  
169 or high risk of bias were removed from the analyses to check for any meaningful changes in  
170 the mean effect sizes.

### 171 **Statistical Analysis**

172 The meta-analysis was conducted using Review Manager 5.1 (Cochrane Collaboration, UK).  
173 Standardized mean differences (SMDs) and 95% confidence intervals with forest plots were  
174 calculated for our outcome measures ( $\dot{V}O_{2\max}$ , endurance performance, lean mass and muscle  
175 strength). To account for the potential heterogeneity in study designs we employed a random  
176 effects model. As in previous studies (Clifford et al., 2018; Lara et al., 2016), in instances



177 where studies have used several methods to assess an outcome (e.g., muscle strength), we  
178 calculated a pooled average of the SMDs for inclusion in the meta-analysis. This was to reduce  
179 bias arising from results in individual tests (Clifford et al., 2018; Lara et al., 2016). However,  
180 the findings were not different whether we modelled these tests as a pooled average or  
181 separately (data not shown). The relevant studies have been labeled in the captions in Figures  
182 5 and 7. Funnel plots to evaluate bias were performed and are included in the Online  
183 Supplementary Material; however, we stress these should be interpreted cautiously, as tests for  
184 funnel plot asymmetry is not recommended when a meta-analysis contains fewer than 10  
185 studies, due to the low power for detecting true effects not ascribed to chance (Higgins, 2011).

## 186 **Results**

### 187 **Search results**

188 Results from our search strategy are presented in Figure 1. We identified 1660 articles from  
189 three databases, which was reduced to 1361 after removing duplicates. After the initial  
190 screening, we retrieved thirty full-texts; twelve were excluded and eighteen were deemed  
191 eligible and included in the review and meta-analysis. Of those, nine articles were included in  
192 the meta-analysis to measure the effects of vitamin C and/or E combined with AE, and nine  
193 were included to evaluate the effects when combined with RT. No additional studies were  
194 found from searches of the retrieved full-texts.

### 195 **Aerobic capacity**

#### 196 *Studies characteristics*

197 Table 1 summarizes the studies examining the effects of vitamin C and/or E on  $\dot{V}O_{2\max}$  or  
198 endurance performance. Of the nine studies, only one did not measure  $\dot{V}O_{2\max}$  (Nalbant et al.,  
199 2009). The eight trials that measured  $\dot{V}O_{2\max}$  had a total of 189 participants (n = 94 in the

200 intervention (INT) condition and  $n = 95$  in the control (CON) trials) and all reported pre- and  
201 post-training measures of  $\dot{V}O_{2\max}$ . None of the participants were elite athletes, with most  
202 reported as being healthy and sedentary or recreationally and physically active. Two trials were  
203 performed in older adults ( $\geq 65$  years of age) (Collins et al., 2003; Jessup, Horne, Yarandi, &  
204 Quindry, 2003), one of which was in patients presenting with claudication pain, a symptom of  
205 peripheral arterial disease (Collins et al., 2003). All trials were randomized, parallel groups  
206 designs, and all but one study (Gomez-Cabrera et al., 2008) contained a PLA plus exercise  
207 group. The aforementioned study made comparisons between a supplemented group and a non-  
208 supplemented group that performed the same exercise program. Four studies provided both  
209 vitamin C and vitamin E as the INT (Morrison et al., 2015; Paulsen et al., 2014b; Yfanti et al.,  
210 2012; C. Yfanti et al., 2011), while two provided only vitamin C (Gomez-Cabrera et al., 2008;  
211 Roberts, Beattie, Close, & Morton, 2011) and two only vitamin E (Collins et al., 2003; Jessup  
212 et al., 2003). The most common dose was  $1000 \text{ mg}\cdot\text{day}^{-1}$  of vitamin C (4/8 studies) and  $\geq 400$   
213  $\text{IU}\cdot\text{day}^{-1}$  of vitamin E (6/8 studies). The length of the training programs for muscle strength  
214 and supplementation periods varied, ranging from 4 weeks to 24 weeks; however, only two  
215 were longer than 12 weeks. Two studies provided participants with the supplements for 4 weeks  
216 prior to the exercise training (Yfanti et al., 2012; Yfanti et al., 2011).

217 Three studies included tests of endurance performance alongside pre to post changes in  $\dot{V}O_{2\max}$   
218 (Collins et al., 2003; Paulsen et al., 2014b; Roberts et al., 2011) while one study measured  
219 endurance performance only (Nalbant et al., 2009); a separate meta-analysis was performed for  
220 these four trials and outcomes. In this analysis, there were 114 participants in total ( $n = 57$  in  
221 the INT group and  $n = 57$  in the CON group).

222 Table 2 summarizes the studies examining the effects of vitamin C and/or E on changes in lean  
223 mass or muscle strength. Six of nine studies measured lean mass and seven of nine measured  
224 changes in muscle strength. The six trials measuring lean mass had a total of 175 participants

225 (n = 86 in the INT group and n = 89 in the CON) while the six trials measuring strength had a  
226 total of 159 participants (n = 80 in the INT group and n = 79 in the CON). Four of the trials  
227 were in older adults ( $\geq 60$  years) (Bjørnsen et al., 2015; Bobeuf, Labonte, Dionne, & Khalil,  
228 2011; Bobeuf, Labonte, Khalil, & Dionne, 2010; Labonte et al., 2008) with the rest in  
229 participants  $< 30$  years. All trials were randomized, double-blind, controlled designs; however,  
230 2 studies did not have a placebo plus RT group as their comparator group (RT only group)  
231 (Bobeuf et al., 2011; Bobeuf et al., 2010). All studies provided both vitamin C ( $1000 \text{ mg} \cdot \text{day}^{-1}$ )  
232 and vitamin E ( $400 \text{ IU} \cdot \text{day}^{-1}$ ) for the duration of the RT program. Three studies were 24  
233 weeks in duration; the remaining six were less than 12 weeks and the shortest was 4 weeks (n  
234 = 2). Two studies provided supplements 5 weeks prior to and 2 weeks following the RT  
235 program (Theodorou et al., 2011; Yfanti et al., 2017). In all trials, both those assessing AE and  
236 RT adaptations, the supplements were taken orally.

### 237 **Risk of bias**

238 Overall, the level of evidence for the AE trials was high, with seven of the nine studies  
239 considered to have a low risk of bias for all bias variables (Figures 2 and S1). One study was  
240 considered to have a high risk of bias because the supplementation was not double blinded  
241 (Nalbant et al., 2009) and another study an unclear risk of bias for allocation concealment  
242 because the comparator was a AE only group, as opposed to a placebo plus AE exercise group  
243 (Gomez-Cabrera et al., 2008). However, there was a low risk of bias in all studies for random  
244 sequence allocation, incomplete outcome data, selective reporting and other bias. With regards  
245 to the trials examining adaptations to RT, overall the study quality was high, with five of the  
246 nine studies having low risk of bias for all variables (Figures 3 and S2). Two studies did not  
247 include a placebo plus RT group (a RT group only) (Bobeuf et al., 2011; Bobeuf et al., 2010)  
248 and therefore had an unclear risk of bias for allocation concealment but a low risk of bias for  
249 the remaining variables, while one study was rated high risk because supplementation was not

250 double blinded (Yfanti et al., 2017) and another study had an unclear risk of bias because  
251 whether the study was randomized or not was unclear (Theodorou et al., 2011). However, the  
252 bias variables: incomplete outcome data, selective reporting and other bias were low risk for  
253 100% of the studies. From visual inspection of the funnel plots (Figure S3-S6) there was little  
254 evidence of reporting bias; however, as acknowledged in the methods, these should be  
255 interpreted with caution given the low number of studies included.

### 256 *Meta-analysis*

257 Vitamin C or E did not attenuate training-induced improvements in  $\dot{V}O_{2\max}$  (SMD -0.14, 95%  
258 CI: -0.43 to 0.15,  $P = 0.35$ ) and there was low heterogeneity between studies ( $\text{Chi}^2 = 2.65$ ;  $I^2 =$   
259  $0\%$ ,  $P = 0.92$ ) (Figure 4). Similarly, in the four studies that assessed endurance performance  
260 we found no differences between INT and CON groups (SMD -0.01, 95% CI: -0.38 to 0.36,  $P$   
261  $= 0.97$ ) and no heterogeneity between the trials ( $\text{Chi}^2 = 0.40$ ;  $I^2 = 0\%$ ,  $P = 0.94$ ; Figure 5). There  
262 were also no differences between the INT and CON groups in our sub-group analysis of studies  
263 of aerobic exercise adaptations in older adults ( $\geq 60$  years of age) (SMD: -0.08, 95% CI: -0.54  
264 to 0.38,  $P = 0.75$ ) and low heterogeneity ( $\text{Chi}^2 = 0.41$ ;  $I^2 = 0\%$ ,  $P = 0.81$ ) (Figure S7).

265 Vitamin C or E did not attenuate training-induced improvements in lean mass (SMD -0.07,  
266 95% CI: -0.36 to 0.23,  $P = 0.67$ ) or muscle strength (SMD -0.15, 95% CI: -0.16 to 0.46,  $P =$   
267  $0.35$ ) and there was no heterogeneity between studies for either outcome ( $\text{Chi}^2 = 0.64$  &  $1.75$ ;  
268  $I^2 = 0\%$ ,  $P > 0.05$ ) (Figures 6 and 7). There were also no group differences in our sub-group  
269 analysis of trials performed in older adults evaluating changes in lean mass (SMD: -0.05, 95%  
270 CI: -0.41 to 0.31,  $P = 0.79$ ,  $\text{Chi}^2 = 0.55$ ;  $I^2 = 0\%$ ,  $P = 0.91$ ) (Figure S8). As only two of the  
271 studies in older adults measured muscle strength we did not perform a separate meta-analysis  
272 for this outcome.

273 Our sensitivity analysis, in which studies that did not have a passive placebo group (an exercise  
274 only control group instead) or were not double blind did not significantly affect the result of  
275 the meta-analysis for  $\dot{V}O_{2\max}$  (n = 1 removed; SMD: -0.09, 95% CI: -0.39 to 0.21, P = 0.55, I<sup>2</sup>  
276 = 0%, P = 0.99), endurance performance (n=1 removed; SMD: 0.01, 95% CI: -0.42 to 0.40, P  
277 = 0.97, I<sup>2</sup> = 0%, P = 0.82), lean mass (n = 2 removed; SMD: 0.08, 95% CI: -0.44 to 0.28, P =  
278 0.67, I<sup>2</sup> = 0%, P = 0.96), muscle strength (n = 1 removed; SMD: 0.03, 95% CI: -0.31 to 0.38,  
279 P = 0.85, I<sup>2</sup> = 0%, P = 0.99).

## 280 **Discussion**

281 The primary finding of this meta-analysis is that vitamin C and E, taken alone or in  
282 combination, did not attenuate adaptations to either aerobic exercise or resistance training.  
283 Neither  $\dot{V}O_{2\max}$ , endurance performance, lean mass or muscle strength were negatively affected  
284 by vitamin C and/or E supplementation. These findings suggest that while some individual  
285 studies indicate that vitamin C and/or E can blunt protein signaling following acute exercise  
286 (Morrison et al., 2015; Paulsen et al., 2014a) or physiological adaptations (Bjørnsen et al.,  
287 2015; Paulsen et al., 2014b), when the totality of evidence is considered, there is little evidence  
288 to suggest they significantly affect exercise induced changes in physiological function.  
289 Nonetheless, the relatively few studies conducted to date, at least in comparison to the effects  
290 of other nutrients on physiological function (e.g., protein), coupled with the low samples sizes  
291 in almost all studies, mean that these findings should be interpreted with caution and not seen  
292 as definitive.

293 It is interesting to note that in individual studies, the effects on skeletal muscle cell signaling  
294 and physiological function don't necessarily correlate. For instance, in three studies antioxidant  
295 vitamins blunted the increase in the activity of molecular pathways associated with  
296 mitochondrial biogenesis (Morrison et al., 2015; Paulsen et al., 2014a) and muscle hypertrophy

297 (Paulsen et al., 2014b); yet, despite this, these changes did not translate to an attenuation in  
298 physiological function. Whilst these findings may be unclear, it is possible that there was  
299 insufficient power to detect differences in physiological function (Paulsen et al., 2014b). There  
300 may also exist multiple regulatory molecular pathways to maintain physiological function  
301 (Morrison et al., 2015). Irrespective of the mechanistic underpinnings, this meta-analysis  
302 indicates that consuming vitamin C and E does not inhibit exercise-induced changes in  
303 physiological function.

304 Overall, our analysis suggested that the risk of bias for the included studies was low, suggesting  
305 most studies were of a high quality. Only two studies were considered to have a high risk of  
306 bias because they did not have a double-blinded design; however, removing these from the  
307 analysis did not affect the overall findings (data not shown). There were four studies that opted  
308 not to provide a placebo to their control group, performing direct comparisons between an  
309 intervention and exercise group and a non-supplemented exercise group. Considering the well-  
310 known influence of placebo and belief on exercise performance this may have introduced  
311 participant bias (Beedie & Foad, 2009). Future studies should ensure control groups are  
312 designed to include a placebo.

313 One of the primary limitations of the studies examined in this meta-analysis were low sample  
314 sizes. Only four of the eighteen trials included reported a *priori* power analysis for the primary  
315 outcome variables (Bjørnsen et al., 2015; Bobeuf et al., 2011; Dutra et al., 2018; Dutra, Alex,  
316 Silva, Brown, & Bottaro, 2019) and one of those failed to reach their target number of  
317 participants for adequate power (Dutra et al., 2019). In the AE and RT trials, the average  
318 number of participants per group was twelve and fourteen, respectively. Given the relatively  
319 low samples sizes, it would be reasonable that the risk of type II errors was high in the majority  
320 of studies and that future trials should look to increase their samples size and ensure they are  
321 sufficiently powered to detect meaningful group differences.

322 None of the studies included in the analysis were performed in elite athletes, with most  
323 participants described as being healthy, sedentary, recreationally or physically active (Tables  
324 1 and 2). The lack of research in elite athletes is perhaps for ethical reasons, given the growing  
325 concern that vitamin C and E could negate training-induced adaptations (Gomez-Cabrera et al.,  
326 2012). Notwithstanding, because no studies were performed in elite or at least well-trained  
327 athletes, there was not enough studies to evaluate whether training status influences the  
328 effectiveness of vitamin C and/or E on training adaptations. Thus, despite the calls encouraging  
329 athletes to limit or avoid consuming high doses of these supplements (Gomez-Cabrera et al.,  
330 2012; Paulsen et al., 2014b), the body of available evidence suggests their effects in elite  
331 athletes is still largely unknown.

332 A number of studies have suggested that while non-steroidal inflammatory drugs (NSAIDs)  
333 can attenuate training adaptations in younger adults, they might actually potentiate them in  
334 older adults, owing to their ability to attenuate the low grade inflammatory response in ageing  
335 muscles (Lundberg & Howatson, 2018; Trappe et al., 2016). It has been speculated that vitamin  
336 C and E might have similar effects; that is, they might be beneficial for older adults but  
337 detrimental in younger adults — owing to their antioxidant function and ability to attenuate the  
338 age associated increase in RS (Gomez-Cabrera et al., 2013). However, our study did not  
339 provide any evidence that age is a modifying factor in the efficacy of vitamin C and/or E  
340 supplementation when combined with an exercise training program. It is important to note that  
341 of the 18 studies evaluated, only 7 were in older adults (>60 years old); thus, additional research  
342 is needed before any definitive conclusions can be made on the potentially differing effects of  
343 vitamin C and/or E supplementation on exercise training adaptations in older and younger  
344 adults.

345 The studies examining adaptations to AE were mostly performed with male participants (n =  
346 5) or a combination of males and females (n = 4) with no studies or analysis performed in

347 females only. In those assessing adaptations to RT, two were performed just in females (Dutra  
348 et al., 2018; Dutra et al., 2019), but the rest were either in males ( $n = 4$ ) or males and females  
349 ( $n = 3$ ). Females are underrepresented in sports and exercise nutrition science research  
350 (Costello, Bieuzen, & Bleakley, 2014) so the sex imbalance in participants in these studies is  
351 not surprising. However, it would be useful for future research to explore if there are sex  
352 differences in response to these antioxidant vitamins, especially given the suggestion that  
353 females might be more protected against exercise-induced RS production, owing to the  
354 antioxidant effects of estrogen (Kendall & Eston, 2002).

355 Due to the low number of studies assessing vitamin C or E alone ( $n = 2$  of each), or for longer  
356 than 12 weeks, we were unable to assess, at least with any confidence, whether the type of  
357 supplement provided or duration of supplementation significantly influenced the findings.  
358 Furthermore, no studies compared the effects of vitamin C and vitamin E, or different doses of  
359 the two (either alone or combined), or over different durations (e.g., 4 vs. 24 weeks). Thus, it  
360 remains unclear what, if any, influence the type, dose and duration of these two commonly  
361 consumed antioxidant supplements has on the adaptive responses to exercise.

362 It is important to acknowledge that a limitation of this analysis is that we did not consider the  
363 intake of other dietary supplements purported to have antioxidant effects (e.g., co-enzyme Q10,  
364 selenium, or any polyphenols) on exercise-induced training adaptations. This is for several  
365 reasons. Firstly, we excluded studies containing polyphenols because there is a large body of  
366 evidence to suggest they are not just antioxidants but in fact have a wide range of biological  
367 effects that differ to those of vitamin C and E (Myburgh, 2014; Scalbert, Johnson, & Saltmarsh,  
368 2005). Furthermore, the wide discrepancy in the types and doses of polyphenols provided in  
369 studies examining their effects on exercise performance has the potential to introduce bias and  
370 ambiguity to our analysis. Studies that included selenium, co-enzyme Q10 or any other  
371 molecules that have antioxidant properties were not included because, firstly, we were not



372 aware of any studies that recommend avoiding these supplements due to potentially negative  
373 effects on exercise-induced training adaptations, which was the chief motivation for this  
374 review. Indeed, the controversy in recent decades has solely focused on vitamin C and/or E.  
375 Secondly, co-enzyme Q10, selenium and other nutrients with antioxidant activity are not  
376 consumed as frequently as vitamin C and E (Bailey et al., 2013; Knapik et al., 2016). Thus,  
377 limiting our analysis to these nutrients would be more pertinent. Finally, similar to the above  
378 reasoning with polyphenols, by including these additional nutrients we would introduce further  
379 heterogeneity into the analysis, given the different dosages, bioavailability, and biochemical  
380 effects of these supplements. Another limitation of our analysis, although inherent in all  
381 systematic reviews, is the quality of the available studies. Overall, the studies were generally  
382 of high quality in terms of study design and outcomes; however, they were limited by low  
383 samples sizes. As such, our findings should be considered preliminary, pending additional high  
384 quality studies with larger sample sizes.

## 385 **Conclusions**

386 In conclusion, vitamin C and/or E supplementation did not attenuate exercise-induced training  
387 adaptations, as measured by changes in aerobic capacity, endurance performance, lean mass or  
388 muscle strength. Our findings therefore do not support the notion that vitamin C and/or E  
389 supplementation blunts exercise-induced adaptations in physiological function, irrespective of  
390 age. However, given that supplementation did not benefit these adaptations, it is unclear why,  
391 in the absence of deficiency, these supplements would be consumed for this purpose.  
392 Notwithstanding, many of the included trials had small sample sizes and were therefore likely  
393 underpowered to detect more subtle group differences. Thus, this review highlights that there  
394 is a need for studies with larger sample sizes to better understand the potential effects of these  
395 vitamin supplements on exercise adaptations.



397 **Financial Disclosure:** None reported.

398 **Funding/Support:** No funding or support was received for this work.

399

#### 400 **Figure Legends**

401 **Figure 1:** Flow diagram of the process used in selection of the randomized controlled trials  
402 included in this systematic review and meta-analysis.

403

404 **Figure 2:** Risk of bias graph from studies examining adaptations to aerobic exercise.

405

406 **Figure 3:** Risk of bias graph from studies examining adaptations to resistance training.

407

408 **Figure 4:** Forest plots showing the effect of vitamin C and/or E on  $\dot{V}O_{2\max}$ .

409

410 **Figure 5:** Forest plots showing the effect of vitamin C and/or E on endurance performance. Data  
411 from Roberts et al. (2011) is a pooled average of the 3 performance tests described in Table 1.

412

413 **Figure 6:** Forest plots showing the effect of vitamin C and/or E on lean mass.

414

415 **Figure 7:** Forest plots showing the effect of vitamin C and/or E on muscle strength. Data from  
416 Bobeuf et al. (2011), Bjørnsen et al. (2015), and Dutra et al. (2019) is a pooled average of the  
417 tests shown in Table 2.



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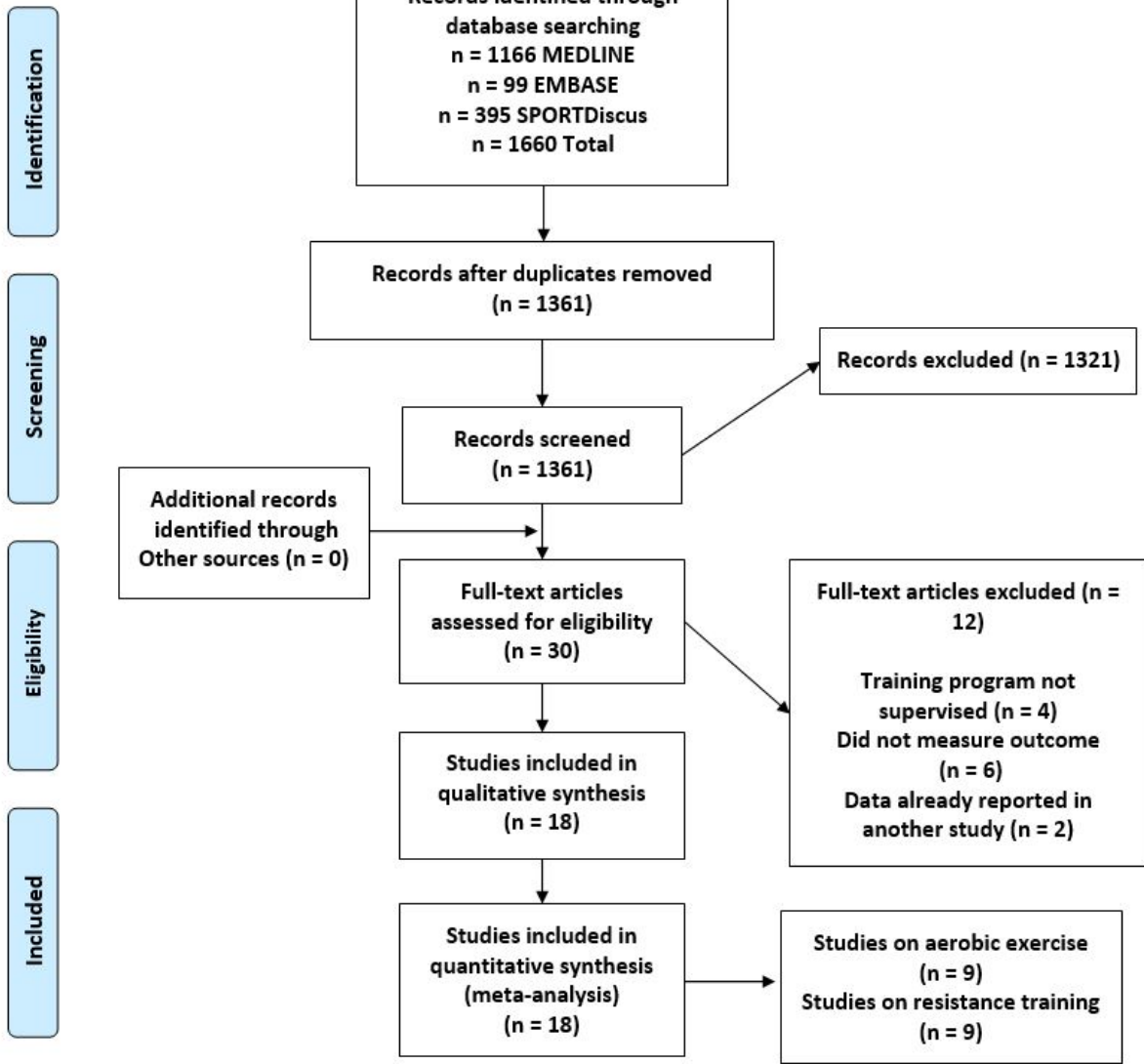
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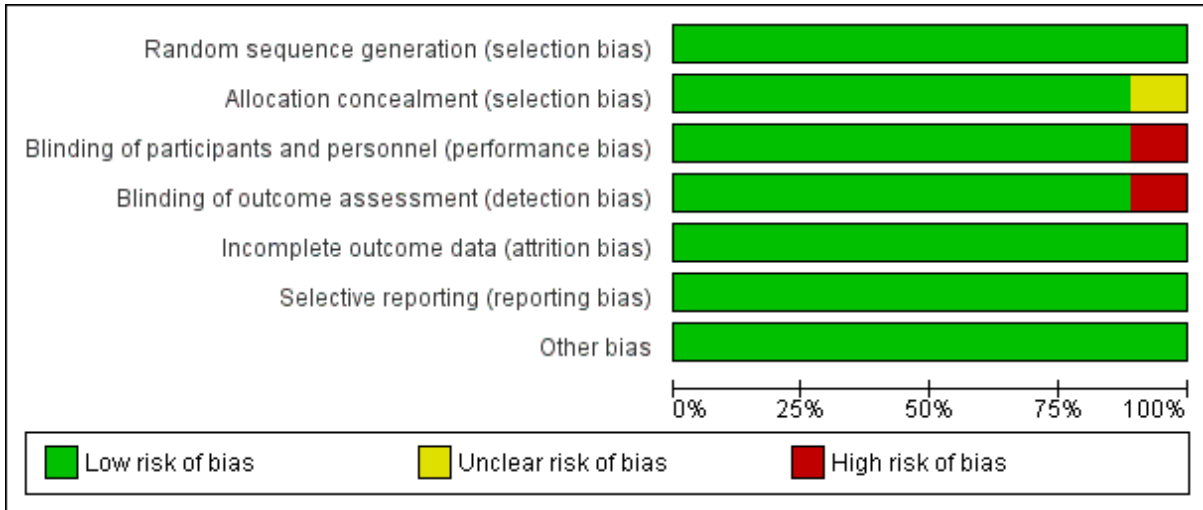
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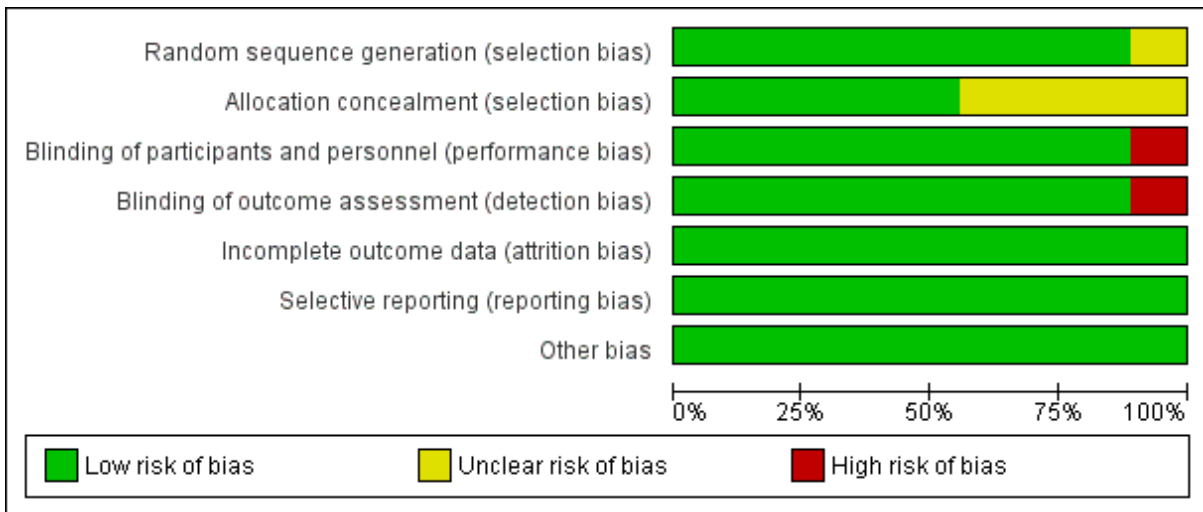
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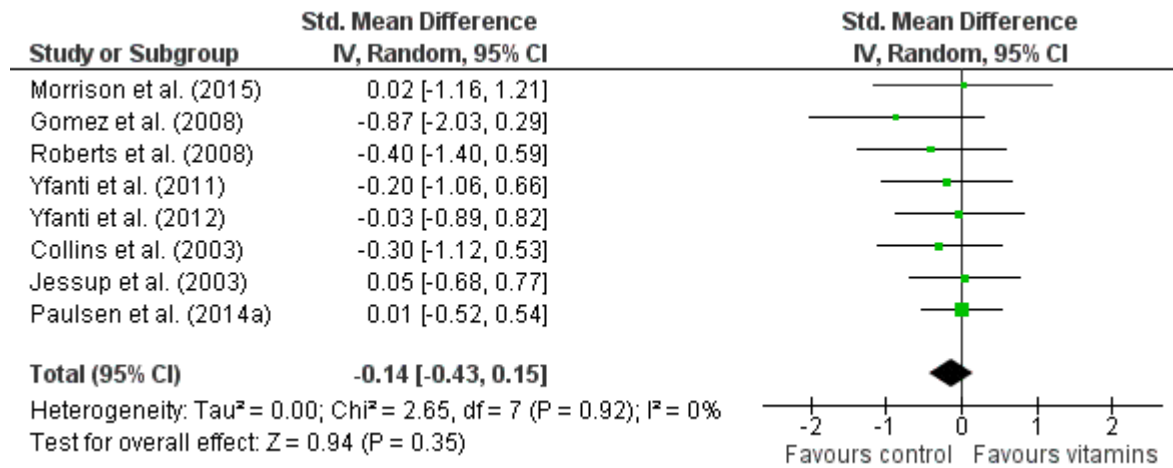
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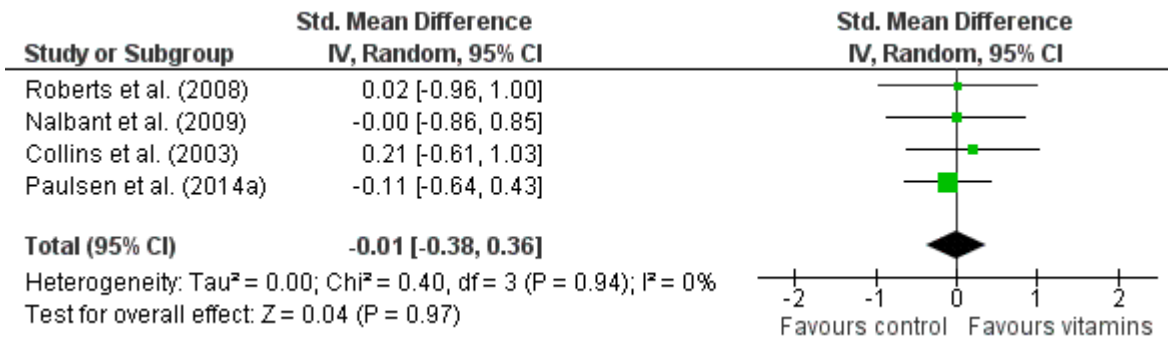
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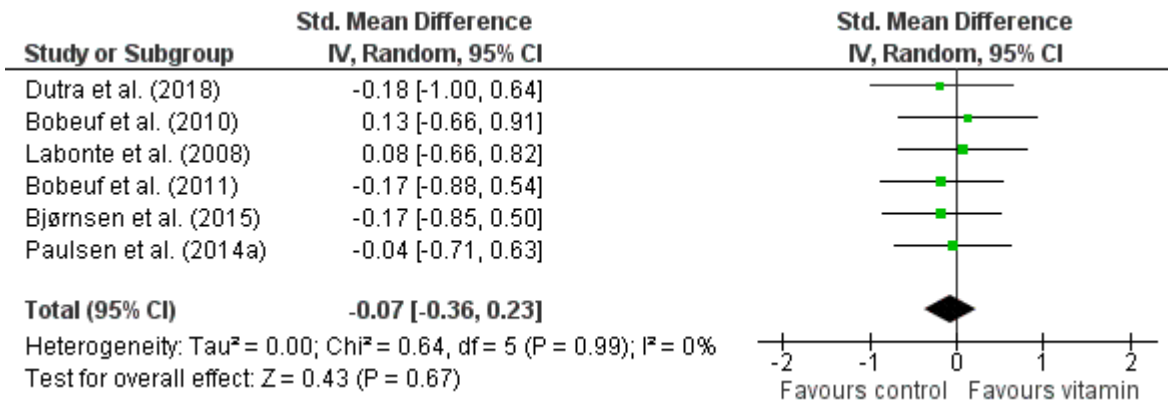
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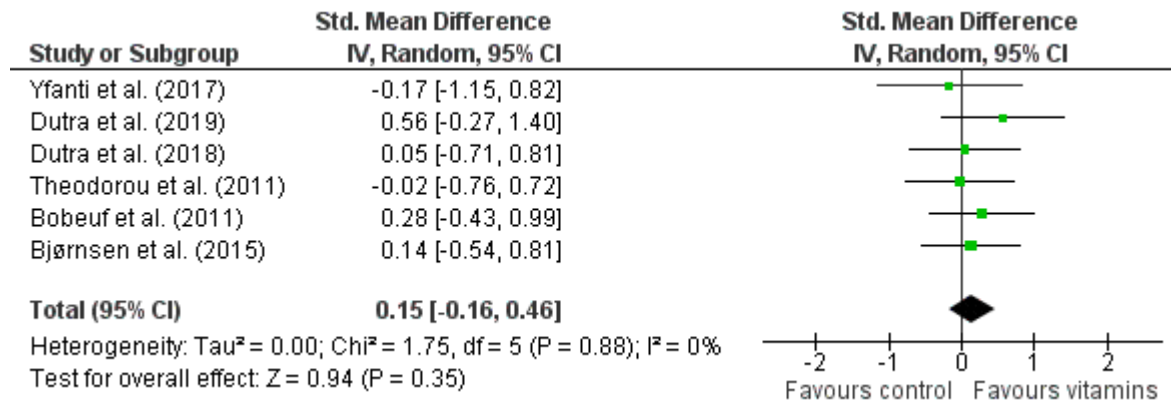
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708 **Table 1** – An overview of studies included in the systematic review and meta-analysis that measured adaptations to aerobic exercise (AE) training.

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Study	Subjects	Age (years)	Intervention	Comparator	Training program	Duration	Outcome measures
Jessup et al. (2003)	INT: 14 SED M & F CON: 15 SED M & F	INT: 76.1 ± 5.0 CON: 75.9 ± 3.3	Vitamin E (800 IU·d <sup>-1</sup> )	Placebo	AE, 2 x 1 h·wk <sup>-1</sup>	16 weeks	$\dot{V}O_{2\max}$
Collins et al. (2003)	INT: 12 M & F with claudication pain CON: 11 M & F with claudication pain	INT: 67.5 ± 5.8 CON: 63.6 ± 7.8	Vitamin E (400 IU·d <sup>-1</sup> )	Placebo	Pole striding, 1 x ~45 min·wk <sup>-1</sup>	24 weeks	$\dot{V}O_{2\max}$
Gomez et al. (2008)	INT: 5 SED M CON: 9 SED M	INT: 28 ± 1 CON: 31 ± 6	Vitamin C (1000 mg·d <sup>-1</sup> )	No placebo	AE, 3 x 40 min·wk <sup>-1</sup>	8 weeks	$\dot{V}O_{2\max}$
Nalbant et al. (2009)	INT: 10 SED M & F CON: 11 SED M & F	INT: 73 ± 5 CON: 70 ± 9	Vitamin E (900 IU·d <sup>-1</sup> )	No placebo	AE, 3 x 90 min·wk <sup>-1</sup>	24 weeks	6 min walk test
Roberts et al. (2011)	INT: 8 M R/A CON: 8 M R/A	INT: 21.0 ± 3.0 CON: 23.0 ± 2.0	Vitamin C (1000 mg·d <sup>-1</sup> )	Placebo	HIIT, 4 x 30 min·wk <sup>-1</sup>	4 weeks	$\dot{V}O_{2\max}$ 10 km TT YoYoIRT 1 YoYoIRT 2

Yfanti et al. (2011)*	INT: 11 M P/A CON: 10 M P/A	INT: 29 ± 5 CON: 31 ± 5	Vitamin C (500 mg·d <sup>-1</sup> ) & Vitamin E (400 IU·d <sup>-1</sup> )	Placebo	AE & HIIT, 5 x 60 – 155 min·wk <sup>-1</sup>	12 weeks	$\dot{V}O_{2max}$
Yfanti et al. (2012)*	INT: 11 M P/A CON: 10 M P/A	INT: 29 ± 5 CON: 31 ± 5	Vitamin C (500 mg·d <sup>-1</sup> ) & Vitamin E (400 IU·d <sup>-1</sup> )	Placebo	AE & HIIT, 5 x 30 – 120 min·wk <sup>-1</sup>	12 weeks	$\dot{V}O_{2max}$
Paulsen et al. (2014a)	INT: 27 E/T & R/A M & F CON: 27 E/T & R/A M & F	INT: 25 ± 5 CON: 24 ± 6	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (235 mg·d <sup>-1</sup> )	Placebo	AE & HIIT, 2 x 30- 60 min·wk <sup>-1</sup>	10 weeks	$\dot{V}O_{2max}$ 20 m shuttle run test
Morrison et al. (2015)	INT: 6 M CON: 5 M	INT: 23 ± 1 CON: 22 ± 2	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (800 IU·d <sup>-1</sup> )	Placebo	HIIT, 3 x 60 min·wk <sup>-1</sup>	4 weeks	$\dot{V}O_{2peak}$

710 INT, intervention; CON, control; M, male; F, female; SED, sedentary; R/A, recreationally active; P/A physically active; E/T, endurance trained; mg, milligrams; IU,  
711 international units; AE, aerobic exercise; HIIT, high intensity interval training;  $\dot{V}O_{2max}$ , maximal aerobic capacity;  $\dot{V}O_{2peak}$ , peak aerobic capacity; YoYoIRT 1, yo yo  
712 intermittent recovery tests level 1; YoYoIRT 2, yo yo intermittent recovery test level 2. Data presented as means ± SD. \*supplementation started 4 weeks before the exercise  
713 program.

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717 Table 2 – An overview of studies included in the systematic review and meta-analysis that measured adaptations to resistance training (RT).

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<b>Study</b>	<b>Subjects</b>	<b>Age (years)</b>	<b>Intervention</b>	<b>Comparator</b>	<b>Training program</b>	<b>Duration</b>	<b>Outcome measures</b>
Labonte et al. (2008)	INT: 15 M & F CON: 19 M & F	INT: 65 ± 4 CON: 66 ± 3	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (600 mg·d <sup>-1</sup> )	Placebo	RT, 3x·wk <sup>-1</sup>	6 months	Fat free mass
Bobeuf et al. (2010)	INT: 12 SED M & F CON: 12 SED M & F	INT: 65 ± 4 CON: 66 ± 3	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (600 mg·d <sup>-1</sup> )	No placebo	RT, 3x·wk <sup>-1</sup>	6 months	Fat free mass
Bobeuf et al. (2011)	INT: 14 SED M & F CON: 17 SED M & F	INT: 64 ± 4 CON: 67 ± 4	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (600 mg·d <sup>-1</sup> )	No placebo	RT, 3x·wk <sup>-1</sup>	6 months	Fat free mass Strength gain in 8 exercises
Theodorou et al. (2011)*	INT: 14 R/A M CON: 14 R/A M	INT: 26 ± 2 CON: 26 ± 1	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (400 IU·d <sup>-1</sup> )	Placebo	RT, 2x·wk <sup>-1</sup>	4 weeks	Isometric strength
Bjørnsen et al. (2015)	INT: 17 U/T M CON: 17 U/T M	INT: 69 ± 7 CON: 67 ± 5	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (400 IU·d <sup>-1</sup> )	Placebo	RT, 3x·wk <sup>-1</sup>	12 weeks	Lean mass 1 RM leg extension 1 RM leg press 1 RM bicep curl

Paulsen et al. (2014a)#	INT: 17 R/A M & F CON: 15 R/A M & F	INT: 27 ± 6 CON: 24 ± 3	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (400 IU·d <sup>-1</sup> )	Placebo	RT, 3x·wk <sup>-1</sup>	10 weeks	Lean mass 1 RM upper body 1 RM lower body
Yfanti et al. (2017)*	INT: 8 R/A M 8 CON: 8 R/A M 8	INT: 25 ± 3 CON: 26 ± 6	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (400 IU·d <sup>-1</sup> )	Placebo	RT, 2x·wk <sup>-1</sup>	4 weeks	Isometric strength
Dutra et al. (2018)	INT: 15 F CON: 12 F	INT: 24 ± 2 CON: 24 ± 3	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (400 IU·d <sup>-1</sup> )	Placebo	RT, 2x·wk <sup>-1</sup>	10 weeks	Isometric strength
Dutra et al. (2019)	INT: 12 U/T F CON: U/T 11 F	INT: 23 ± 2 CON: 23 ± 2	Vitamin C (1000 mg·d <sup>-1</sup> ) & Vitamin E (400 IU·d <sup>-1</sup> )	Placebo	RT, 2x·wk <sup>-1</sup>	10 weeks	Fat free mass Deadlift strength Lunge strength

719 INT, intervention; CON, control; M, male; F, female; SED, sedentary; R/A, recreationally active; P/A physically active; U/T, un-trained; mg, milligrams; IU, international  
720 units; RT, resistance training; RM, repetition maximum. Data presented as means ± SD. \*supplementation started 5 weeks prior to exercise training and continued for 2  
721 weeks post-training. #muscle strength data not used in meta-analysis.

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