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

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Abstract

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

Introduction

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

Notwithstanding, evidence for beneficial effects of vitamin C and E on any aspect of exercise performance is equivocal. In fact, some recent studies report negative effects with these vitamins, suggesting that the typical dose found in supplements (often ≥10 x the recommended daily allowance) can actually impair recovery or blunt exercise-induced training adaptations (Bjørnsen et al., 2015; Close et al., 2006; Gomez-Cabrera et al., 2008). Indeed, the last decade has seen a growing concern that dampening exercise-induced RS could actually mitigate or at least lessen some of the physiological adaptations evoked by exercise training (Gomez-Cabrera et al., 2008; Paulsen et al., 2014a). A key function of the RS produced during exercise is to stimulate molecular pathways via proteins such as peroxisome proliferator-activated receptor-γ coactivator (PGC1-α) and mitogen-activated protein kinases (MAPK), that lead to improvements in aerobic capacity and muscle hypertrophy, respectively (Gomez-Cabrera et 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 ($\dot{V}O_{2max}$), 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 $\dot{V}O_{2max}$ and PGC-1α — a key marker of mitochondrial biogenesis.
84 Furthermore, in the human participants, $\dot{V}O_{2max}$ 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^{-1}) and E (400 IU·day^{-1}) improved $\dot{V}O_{2max}$ 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^{-1}) and E (400 IU·day^{-1}) 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 al., 2014b). Another study from the same group
97 (Bjørnsen et al., 2015) examined vitamin C and E supplementation in older adults (≥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

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

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

Methods

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

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

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

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

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

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

Heterogeneity, risk of bias, and sensitivity analyses

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

Statistical Analysis

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

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

Results

Search results

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

Aerobic capacity

Studies characteristics

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

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

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

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

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

Risk of bias

Overall, the level of evidence for the AE trials was high, with seven of the nine studies considered to have a low risk of bias for all bias variables (Figures 2 and S1). One study was considered to have a high risk of bias because the supplementation was not double blinded (Nalbant et al., 2009) and another study an unclear risk of bias for allocation concealment because the comparator was a AE only group, as opposed to a placebo plus AE exercise group (Gomez-Cabrera et al., 2008). However, there was a low risk of bias in all studies for random sequence allocation, incomplete outcome data, selective reporting and other bias. With regards to the trials examining adaptations to RT, overall the study quality was high, with five of the nine studies having low risk of bias for all variables (Figures 3 and S2). Two studies did not include a placebo plus RT group (a RT group only) (Bobeuf et al., 2011; Bobeuf et al., 2010) and therefore had an unclear risk of bias for allocation concealment but a low risk of bias for 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 $\dot{V}O_{2max}$ (SMD -0.14, 95%
258 CI: -0.43 to 0.15, P = 0.35) and there was low heterogeneity between studies ($Chi^2 = 2.65$; $I^2 =$
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 ($Chi^2 = 0.40$; $I^2 = 0\%$, 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 (≥60 years of age) (SMD: -0.08, 95% CI: -0.54
264 to 0.38, P = 0.75) and low heterogeneity ($Chi^2 = 0.41$; $I^2 = 0\%$, 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 ($Chi^2 = 0.64$ & 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, $Chi^2 = 0.55$; $I^2 = 0\%$, 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.

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

Conclusions

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

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Figure Legends

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

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

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

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

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

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

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

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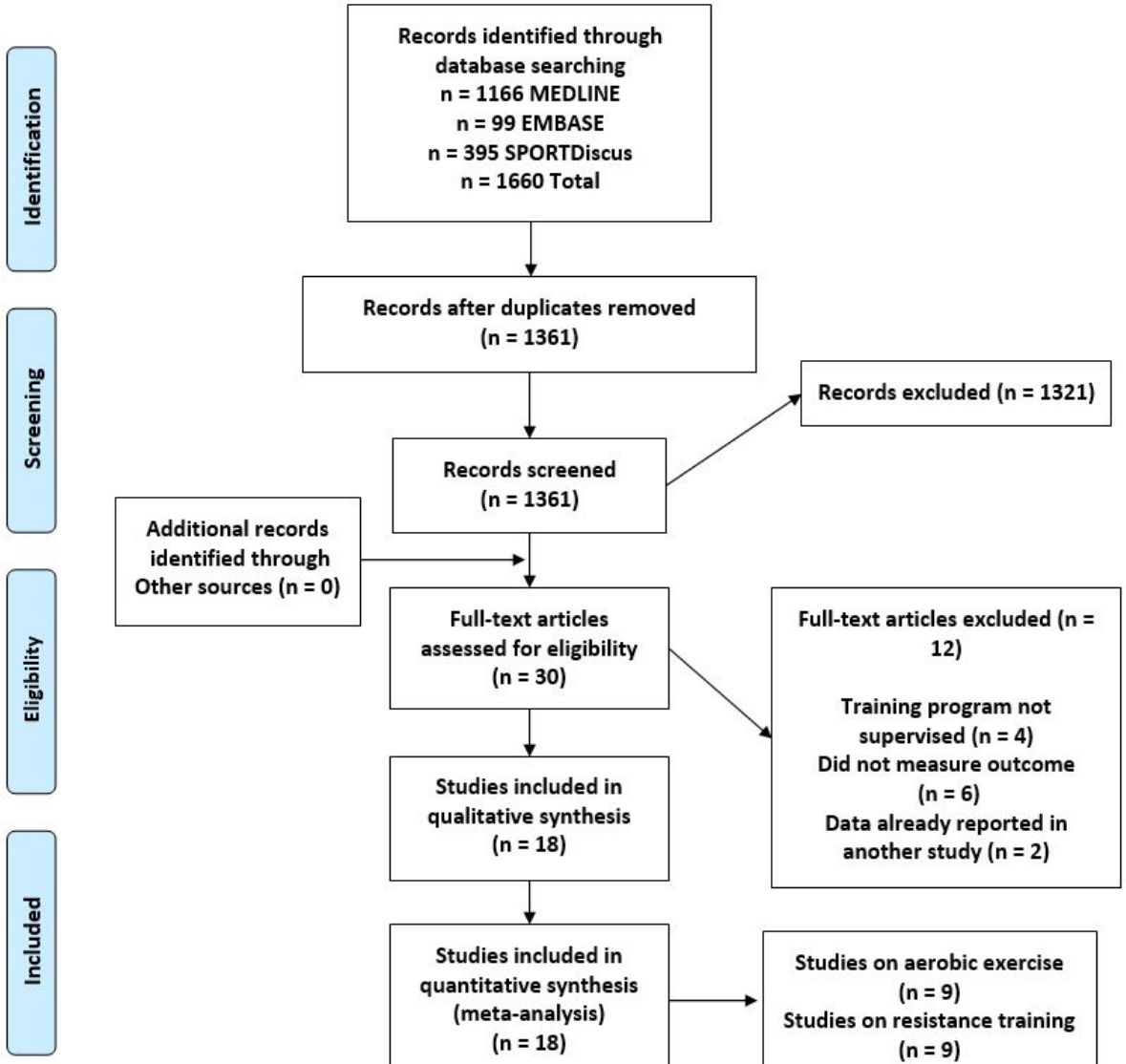
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Additional records identified through Other sources (n = 0)
Full-text articles assessed for eligibility (n = 30)
Full-text articles excluded (n = 12)
Training program not supervised (n = 4)
Did not measure outcome (n = 6)
Data already reported in another study (n = 2)
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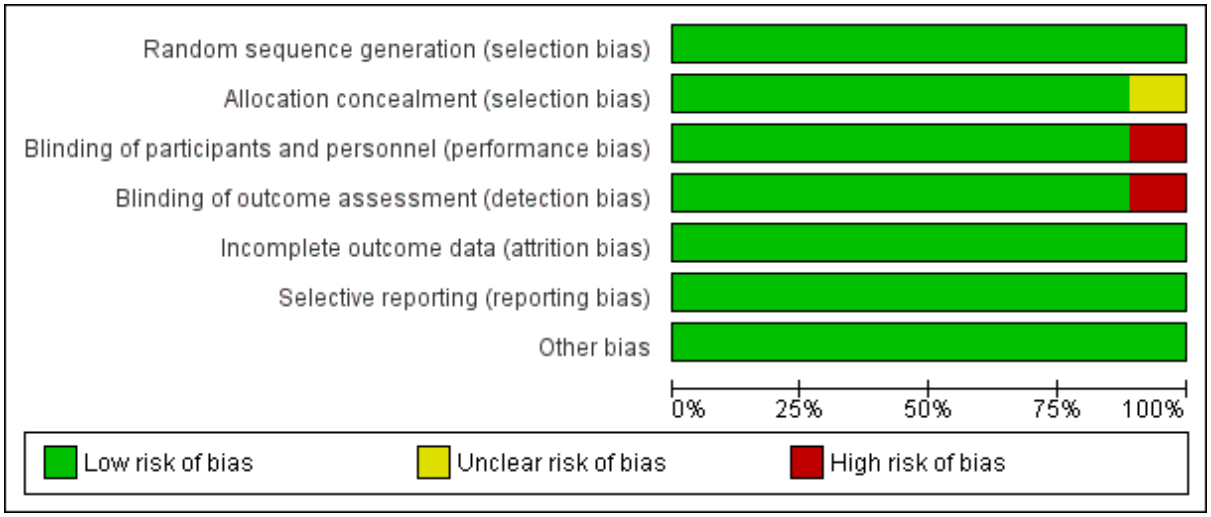
Studies on aerobic exercise (n = 9)
Studies on resistance training (n = 9)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Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
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Unclear risk of bias
High risk of bias

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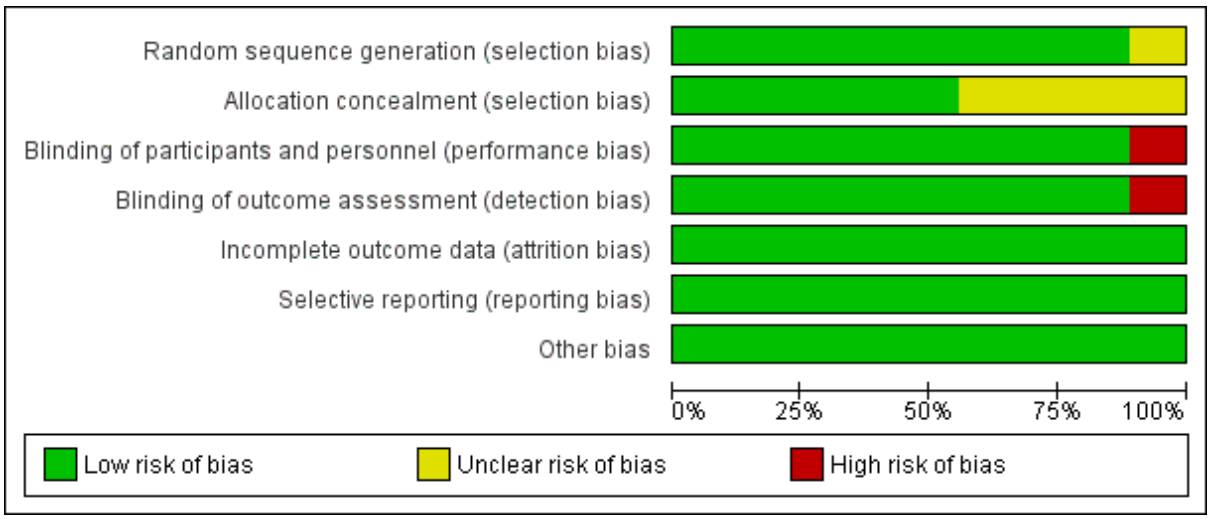

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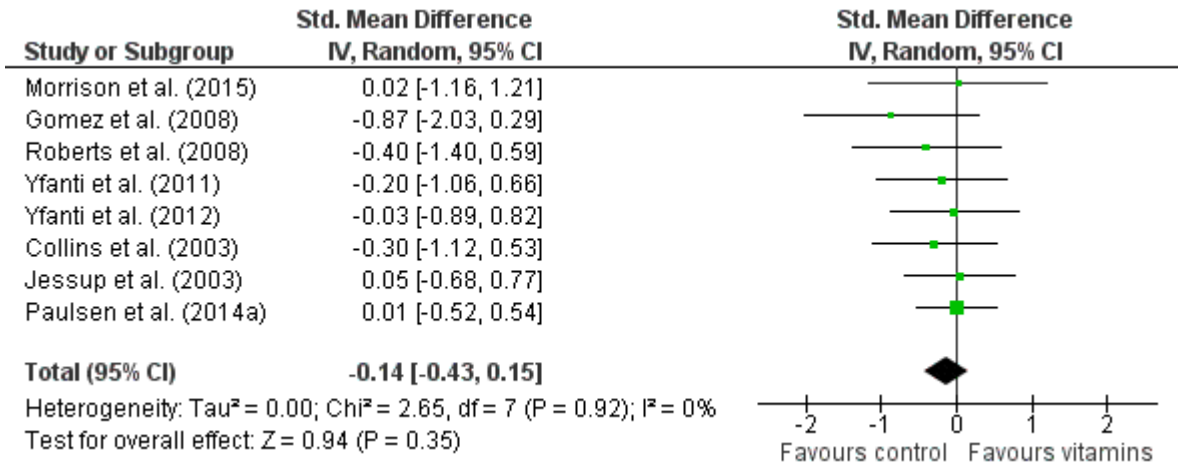
Std. Mean Difference
Study or Subgroup
IV, Random, 95% CI
Std. Mean Difference
IV, Random, 95% CI
Morrison et al. (2015) 0.02 [-1.16, 1.21]
Gomez et al. (2008) -0.87 [-2.03, 0.29]
Roberts et al. (2008) -0.40 [-1.40, 0.59]
Yfanti et al. (2011) -0.20 [-1.06, 0.66]
Yfanti et al. (2012) -0.03 [-0.89, 0.82]
Collins et al. (2003) -0.30 [-1.12, 0.53]
Jessup et al. (2003) 0.05 [-0.68, 0.77]
Paulsen et al. (2014a) 0.01 [-0.52, 0.54]
Total (95% CI) -0.14 [-0.43, 0.15]
Heterogeneity: Tau² = 0.00; Chi² = 2.65, df = 7 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)
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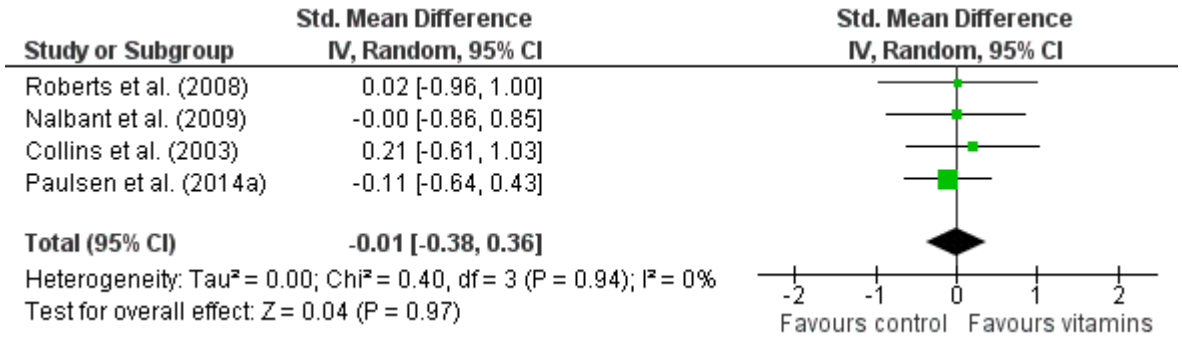
Favours vitamins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IV, Random, 95% CI
Std. Mean Difference
IV, Random, 95% CI
Roberts et al. (2008) 0.02 [-0.96, 1.00]
Nalbant et al. (2009) -0.00 [-0.86, 0.85]
Collins et al. (2003) 0.21 [-0.61, 1.03]
Paulsen et al. (2014a) -0.11 [-0.64, 0.43]
Total (95% CI) -0.01 [-0.38, 0.36]
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 3 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)
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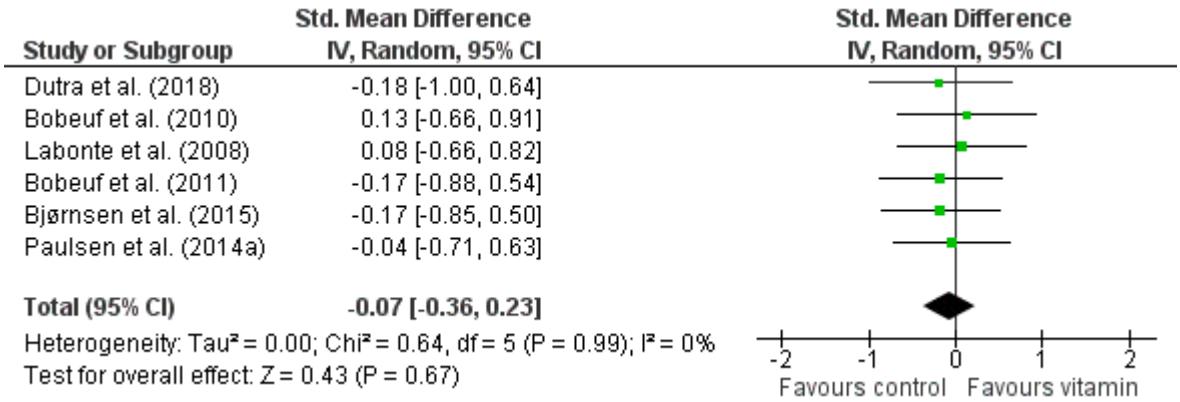
Favours control
Favours vitamins


Std. Mean Difference
Std. Mean Difference
Study or Subgroup
IV, Random, 95% CI
IV, Random, 95% CI
Dutra et al. (2018) -0.18 [-1.00, 0.64]
Bobeuf et al. (2010) 0.13 [-0.66, 0.91]
Labonte et al. (2008) 0.08 [-0.66, 0.82]
Bobeuf et al. (2011) -0.17 [-0.88, 0.54]
Bjørnsen et al. (2015) -0.17 [-0.85, 0.50]
Paulsen et al. (2014a) -0.04 [-0.71, 0.63]
Total (95% CI) -0.07 [-0.36, 0.23]
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
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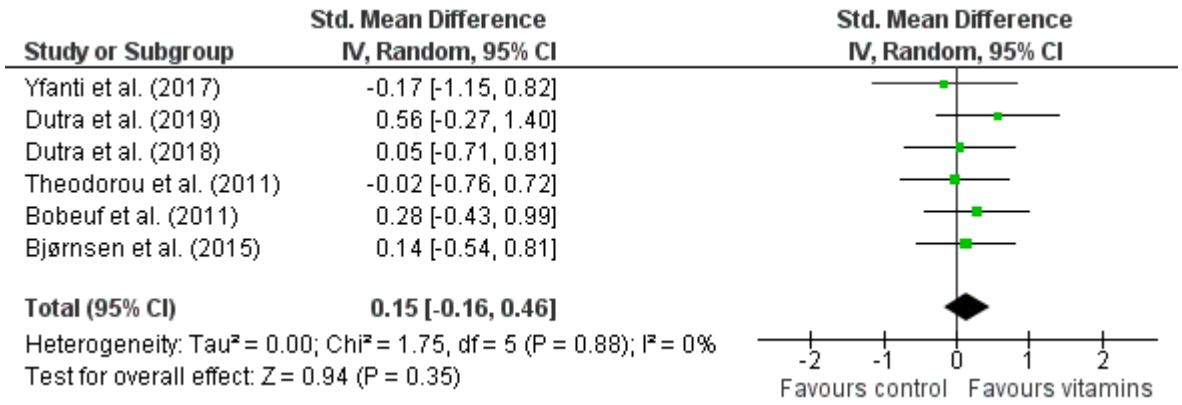
Favours control
Favours vitamin



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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^{-1})	Placebo	AE, 2 x 1 h·wk^{-1}	16 weeks	$\dot{V}O_{2max}$
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^{-1})	Placebo	Pole striding, 1 x ~45 min·wk^{-1}	24 weeks	$\dot{V}O_{2max}$
Gomez et al. (2008)	INT: 5 SED M CON: 9 SED M	INT: 28 ± 1 CON: 31 ± 6	Vitamin C (1000 mg·d^{-1})	No placebo	AE, 3 x 40 min·wk^{-1}	8 weeks	$\dot{V}O_{2max}$
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^{-1})	No placebo	AE, 3 x 90 min·wk^{-1}	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^{-1})	Placebo	HIIT, 4 x 30 min·wk^{-1}	4 weeks	$\dot{V}O_{2max}$ 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^{-1}) & Vitamin E (400 IU·d^{-1})	Placebo	AE & HIIT, 5 x 60 – 155 min·wk^{-1}	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^{-1}) & Vitamin E (400 IU·d^{-1})	Placebo	AE & HIIT, 5 x 30 – 120 min·wk^{-1}	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^{-1}) & Vitamin E (235 mg·d^{-1})	Placebo	AE & HIIT, 2 x 30-60 min·wk^{-1}	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^{-1}) & Vitamin E (800 IU·d^{-1})	Placebo	HIIT, 3 x 60 min·wk^{-1}	4 weeks	$\dot{V}O_{2peak}$

INT, intervention; CON, control; M, male; F, female; SED, sedentary; R/A, recreationally active; P/A physically active; E/T, endurance trained; mg, miligrams; IU, 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 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 program.

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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Study	Subjects	Age (years)	Intervention	Comparator	Training program	Duration	Outcome measures
Labonte et al. (2008)	INT: 15 M & F CON: 19 M & F	INT: 65 ± 4 CON: 66 ± 3	Vitamin C (1000 mg·d^{-1}) & Vitamin E (600 mg·d^{-1})	Placebo	RT, 3x·wk^{-1}	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^{-1}) & Vitamin E (600 mg·d^{-1})	No placebo	RT, 3x·wk^{-1}	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^{-1}) & Vitamin E (600 mg·d^{-1})	No placebo	RT, 3x·wk^{-1}	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^{-1}) & Vitamin E (400 IU·d^{-1})	Placebo	RT, 2x·wk^{-1}	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^{-1}) & Vitamin E (400 IU·d^{-1})	Placebo	RT, 3x·wk^{-1}	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^{-1}) & Vitamin E (400 IU·d^{-1})	Placebo	RT, 3x·wk^{-1}	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^{-1}) & Vitamin E (400 IU·d^{-1})	Placebo	RT, 2x·wk^{-1}	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^{-1}) & Vitamin E (400 IU·d^{-1})	Placebo	RT, 2x·wk^{-1}	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^{-1}) & Vitamin E (400 IU·d^{-1})	Placebo	RT, 2x·wk^{-1}	10 weeks	Fat free mass Deadlift strength Lunge strength

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 units; RT, resistance training; RM, repetition maximum. Data presented as means ± SD. *supplementation started 5 weeks prior to exercise training and continued for 2 weeks post-training. #muscle strength data not used in meta-analysis.