FOOD STANDARDS Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

Supporting document 2

Assessment of the health effects – Application A1102

L-carnitine in food

Executive summary

The stated purpose of adding L-carnitine or L-carnitine-L-tartrate to foods, according to the application, is to maintain the normal carnitine status of the body, particularly in vegetarians and in people that may be nutritionally deficient, such as elderly people or those who may have an increased requirement for L-carnitine such as athletes. The application also indicated that several clinical trials have shown that L-carnitine supplementation, in conjunction with dietary modification and/or exercise, can be beneficial for weight management.

The concentration of carnitine in blood plasma is commonly used as an indicator of body carnitine status, both in healthy people and in those with medical conditions. However, greater than 95% of total body carnitine resides in muscle, and the correlation between plasma and muscle carnitine concentrations is low. Therefore, plasma carnitine concentration is not a good marker of body status even though it can be increased by approximately two-fold from the intake of L-carnitine in supplementation studies. Muscle carnitine concentration is therefore considered to be the most suitable indicator of body carnitine status. No evidence has been identified that muscle carnitine concentration ranges differ between the general healthy population and population sub-groups of relevance to the application, i.e. otherwise healthy overweight, elderly, vegetarians/vegans, and athletes/exercise-trained individuals.

Human supplementation studies with L-carnitine and L-carnitine-L-tartrate have investigated a large number of parameters of relevance to this application. This assessment has considered 43 studies investigating the potential favourable effects of oral L-carnitine supplementation in healthy subjects, including population sub-groups identified in the application. Most studies used daily dosing at levels of around 2000–3000 mg per day and most were conducted with male participants and used small subject numbers. In most studies L-carnitine or L-carnitine-L-tartrate were provided as tablets or capsules, however no information has been identified that would indicate a difference in the absorption of L-carnitine from food compared to oral supplements. All repeat-dose studies have given carnitine at least once per day. No studies were found which examined the effect of less frequent intakes such as several times per week.

Findings for most parameters show a lack of consistency between studies. These studies show a lack of reproducible effects on protein, fat, or carbohydrate metabolism; bodyweight and composition (excluding subjects over 70 years); exercise performance (e.g. swimming, cycling, and running time trials); maximal oxygen uptake; blood and muscle lactate; muscle

glycogen; blood glucose; hormone responses to exercise; muscle fibre composition; and mitochondrial enzyme activity.

There is inconsistent evidence that muscle carnitine concentration can be increased slightly in vegetarians. For example, supplementation with a high intake of L-carnitine (4000 mg/day as tablets) for 3 months to adult males resulted in a 2-fold increase in plasma total carnitine, however muscle carnitine concentration was unaffected (Wächter et al. 2002). On the other hand, in a study in 16 adult male vegetarians and 8 adult male omnivores, supplementation with L-carnitine (2000 mg/day as capsules) for 12 weeks resulted in increased plasma carnitine concentration in both groups (by 24% in omnivores and 31% in vegetarians) while muscle total carnitine was increased only in vegetarians (by 13%, and remained within the normal range) (Novakova et al. 2016). However, neither of these studies included a placebo control group and there were no effects on the other parameters investigated by Novakova et al. (2016) [biochemical parameters including skeletal muscle ATP, phosphocreatinine, glycogen and lactate; exercise performance (sustained maximum cycling power) and aerobic capacity (VO2max)].

Favourable effects of supplementary L-carnitine intake have been reported in studies in elderly subjects (70 years and over). These studies, which used L-carnitine doses of 1500 to 4000 mg/day for 4 weeks to 6 months, reported increases in muscle mass, loss of fat, and improved physical function following L-carnitine supplementation. However, of the two studies which tested 1500 mg/day, only one reported a favourable effect. L-carnitine has not been shown to improve body composition (i.e. increase muscle mass and/or decrease fat mass) in adults under 70 years.

For athletes and others undertaking regular exercise training, three randomised, placebo-controlled trials (RCTs) have reported that L-carnitine reduces post-exercise muscle soreness. All three studies found an effect on the first day but there was variation in the duration of the effect after that. It has been suggested that L-carnitine supplementation can result in increased muscle carnitine concentrations, and that this may aid post-exercise muscle recovery. Increased muscle carnitine concentrations in omnivorous humans have only been reliably demonstrated in a study where L-carnitine (2720 mg/day for 24 weeks) was co-ingested with large amounts of carbohydrate (2 x 80 g per day of a glucose polymer mixture), however post-exercise muscle soreness was not investigated in this study.

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1 Introduction

The purpose of adding L-carnitine or L-carnitine L-tartrate to foods, as stated in the application, is:

> *"to maintain the normal carnitine status of the body, particularly among individuals avoiding meat like vegetarians, vegans or people with reduced appetite for meat or inadequate supply of nutrients, such as elderly populations or people who might have an increased requirement of L-carnitine like athletes"*

The application also states that:

> *"for weight management initiatives which include body weight reduction, several clinical trials have shown that L-carnitine supplementation in conjunction with dietary modification and/or exercise can be beneficial"*

Studies in humans supplemented with L-carnitine or L-carnitine-L-tartrate were provided with the application as scientific evidence claimed to support the above statements. FSANZ also searched the literature and identified additional relevant human studies. Following a request from FSANZ for additional information, the applicant provided further studies in January 2017, including an unpublished study report. In March 2018, the applicant provided FSANZ with a newly published review on L-carnitine supplementation in recovery after exercise (Fielding et al. 2018)[1]. This review cited additional relevant studies which are also assessed here.

Human studies that investigated supplementation with carnitine compounds other than L-carnitine or L-carnitine-L-tartrate were considered, but those using routes of administration other than oral were not considered in this assessment.

A total of 43 human studies in which L-carnitine or L-carnitine-L-tartrate was provided as oral supplements (e.g. in tablet or capsule form) or added to beverages were considered for the present assessment.

2 Assessment of the effect of adding L-carnitine to foods

FSANZ formulated a set of questions to be addressed in order to assess the effects which might follow from the addition of L-carnitine or L-carnitine-L-tartrate to food, including beverages. Responses to these questions are provided in section 2.1, with further discussion in section 2.2.

A summary of human intervention trials with L-carnitine or L-carnitine-L-tartrate that were considered relevant for assessing the application is provided in Appendix 1. These studies were conducted in healthy subjects including those relevant to the applicant's stated purpose of adding L-carnitine or L-carnitine-L-tartrate to foods (elderly, vegetarians, athletes/ exercise-trained subjects, and people who are overweight or obese).

[1] FSANZ alerted the journal editor to errors in this publication and an erratum was subsequently published on the journal website on 26 April 2018: http://www.mdpi.com/2072-6643/10/5/541/htm

Information on the biochemistry, physiology and pharmacokinetics of L-carnitine is provided in Supporting Document 1, and relevant aspects are referred to here.

2.1 Responses to questions on the stated purpose of adding L-carnitine or L-carnitine-L-tartrate to food

Question 1 To what extent is L-carnitine plasma concentration an indicator of L-carnitine status for healthy people? If insufficient as an indicator, what other indicators of L-carnitine status are more reliable?

Response

Plasma/serum carnitine concentration is commonly used as an indicator of body carnitine status, both in healthy people and in those with medical conditions (Reuter et al. 2008).[2,3] Plasma carnitine concentrations can be increased following increased dietary intake of foods containing carnitine or from the use of L-carnitine supplements; however, greater than 95% of total body carnitine resides in muscle, and there is a poor correlation between concentrations in plasma and muscle (Starling et al. 1995).

Studies indicate that plasma carnitine concentration ranges for the elderly, athletes and overweight do not differ from those of the general population. Vegetarians have been shown to have lower plasma carnitine concentrations on average, but still within the range observed for non-vegetarians.

A study published in 2008 examined carnitine plasma levels in 60 healthy males and females using three analytical methods (Reuter et al. 2008). The dietary habits and body mass index of the subjects were not reported. The three analytical methods were based on methods used in 22 previously published studies on healthy subjects. Plasma L-carnitine concentrations (mean ± standard deviation; µmol/L) determined using each of the three methods were 38 ± 8 (radioimmunoassay), 43.3 ± 8.6 (high performance liquid chromatography), and 41.2 ± 10.1 (electrospray tandem mass spectrometry). The ranges for female and male subjects were 24–54 and 28–66 µmol/L, respectively. Analysis of two age groupings of subjects (group 1: 18–40 years, mean 27 years; group 2: >40 years, mean 51 years) showed that age had no impact on plasma carnitine concentrations. For the purposes of this assessment, plasma L-carnitine concentrations within the above ranges are considered to be 'normal'.

Plasma L-carnitine levels in 32 centenarians (mean age 101 years) were reported to be 41.8 ± 7.7 µmol/L (mean ± standard deviation), which is within the ranges reported for younger subjects above (Malaguarnera et al. 2007).

A number of studies have investigated plasma carnitine levels in athletes/exercise-trained individuals (e.g. sprinters and long distance runners, i.e. anaerobically and aerobically trained) and no consistent differences to non-athletes/sedentary individuals are apparent

[2] In this document the term "carnitine", when used alone, includes L-carnitine (often termed free carnitine) and esters of L-carnitine (which are also present in food and in the body). The application requests approval for the addition of the specific substances L-carnitine and L-carnitine-L-tartrate to a range of foods.

[3] Carnitine concentrations are more commonly measured in blood plasma than in serum. Choice of plasma or serum does not appear to affect the quantitative values obtained.

(e.g. Wall et al. 2002; Appendix 1). Limited data in subjects that are overweight or obese also do not indicate a difference in plasma carnitine concentration range compared to healthy subjects of normal body weight (e.g. Cederblad 1976).

Vegetarians have a substantially lower dietary intake of carnitine compared to non-vegetarians, but this is compensated by a greater rate of endogenous carnitine synthesis (from the amino acids methionine and lysine) and lower urinary excretion (Rebouche and Chenard 1991; Rebouche et al. 1993; Reuter and Evans 2012). Slightly lower plasma carnitine concentrations have been reported in vegetarians compared to omnivores (Delanghe et al. 1989; Lombard et al. 1989), however this has not been consistently associated with lower muscle carnitine concentrations. For example, Stephens et al. (2011) reported a 17% lower muscle total carnitine concentration in 7 male vegetarians compared to 14 male non-vegetarians. However, in a study in 16 adult male vegetarians (dietary carnitine intake ~4 mg/day) and 8 adult male omnivores (dietary carnitine intake ~50 mg/day), the vegetarian group had a 10% lower plasma carnitine concentration while muscle carnitine concentration did not differ between the two groups (Novakova et al. 2016).

In conclusion, muscle carnitine concentration, not plasma carnitine concentration, is the most suitable indicator of body carnitine status.

Question 2 What is the normal carnitine concentration range in human muscle for the general population and for the four target groups (elderly, athletes, overweight, vegetarians)?

Response

The concentration of total carnitine in skeletal muscle of healthy adults has been reported to range from approximately 15 to 30 mmol/kg muscle (dry weight) (Starling et al. 1995; Novakova et al. 2016). No evidence has been identified that would indicate concentration ranges unique to any of the four target population groups.

Question 3 What is the evidence that an increased oral intake of L-carnitine (above baseline L-carnitine intake from food) would be consistent with the stated purpose of maintaining normal carnitine status for the general population?

Response

The majority of L-carnitine supplementation regimens that have been tested in human trials have not resulted in increased muscle carnitine levels. This is explained by the large concentration gradient (plasma concentration is only ~2% of muscle concentration; Stanley 2004) and the increased urinary excretion of carnitine as intake increases. Carnitine homeostasis is achieved physiologically regardless of L-carnitine intake due to a marked increase in carnitine excretion in urine at high intakes, while at low intakes excretion is correspondingly reduced (Evans and Fornasini 2003). To illustrate this, healthy vegetarians/vegans maintain normal carnitine plasma and muscle concentrations despite dietary intakes of only a few milligrams per day (Novakova et al. 2016). Also, there are studies reporting that people who have lost large amounts of muscle and fat due to anorexia nervosa maintain normal carnitine muscle concentrations (Sandstedt et al. 1986; Morton et al. 1999).

While plasma carnitine concentrations can be increased following supplemental intake of L-carnitine at doses of ≥ 2000 mg/day, most studies show that muscle carnitine concentrations do not change following L-carnitine supplementation. The scientific evidence base supports

the conclusion that increasing the oral intake of L-carnitine does not aid the maintainance of normal carnitine status in healthy adults.

Question 4 What is the evidence for an increased oral intake of L-carnitine being associated with beneficial health effects, specifically for:

(i) improved muscle, joint, and cardiovascular health in the elderly;

(ii) various muscle-related processes in exercise recovery in athletes;

(iii) assisting weight management or weight loss in the overweight; and

(iv) improved plasma, breast milk, muscle stores/function in vegetarians.

Response

(i) Four relevant studies in healthy elderly subjects were identified and are summarised in Appendix 1. The mean age of subjects in each study was > 65 years. Three of these studies reported favourable effects from L-carnitine supplementation, as summarised below.

A 4-week double-blind, parallel, randomised, placebo-controlled trial (RCT) was conducted in male and female subjects (n = 42 per group, mean age 81 years), who experience onset of fatigue following slight physical activity. At the end of 4 weeks, compared to the placebo group the L-carnitine group (4000 mg/day) lost more body fat mass (-3.1 vs -0.5), gained more muscle mass (+2.1 kg vs +0.2 kg), and showed improvements in serum total cholesterol (-1.2 vs +0.1 mmol/L), low density lipoprotein (LDL) cholesterol (-1.1 vs -0.2 mmol/L), high density lipoprotein (HDL) cholesterol (+0.2 vs +0.01 mmol/L), triglycerides (-0.3 vs 0.0 mmol/L), apolipoprotein A1 (apoA1, -0.2 vs 0.0 g/L), apoliprotein B (apoB, -0.3 vs -0.1 g/L), mental fatigue score (-3.5 vs -0.6), and physical fatigue score (-5.3 vs -1.4) (Pistone et al. 2003).

A subsequent double-blind, parallel RCT from the same research group investigated the potential benefical favourable effects of acetyl L-carnitine (2000 mg/day for 6 months) in centenarians (n = 34 and 32 in the placebo and L-carnitine groups, respectively). At the end of 6 months, the L-carnitine-treated centenarians, compared with the placebo group, showed improvements in total fat mass (-1.8 vs 0.6 kg), total muscle mass (3.8 vs 0.8 kg), total cholesterol (-0.69 vs -0.15 mmol/L), physical fatigue score (-4.1 vs -1.1), mental fatigue score (-2.7 vs 0.3), fatigue severity score (-23.6 vs 1.9), and cognitive function score (4.1 vs 0.6) There were no differences between placebo and L-carnitine for body mass, plasma triglycerides, HDL- and LDL-cholesterol (Malaguarnera et al. 2007).

A double-blind, parallel RCT investigated the potential effects of L-carnitine (1500 mg/day for 10 weeks) on males and females, mean age 69 years. All subjects were defined as pre-frail based on the Fried criteria in which frailty is defined as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (4.5 kg or more) in the past year, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity (Fried et al. 2001). Frailty Index score and hand grip strength were improved (by ~30% and 3%, respectively) in the L-carnitine group as compared to no changes in the placebo group. Four of the 50 subjects (three from the L-carnitine group and one from the control group) transitioned from pre-frail status to robust by the end of the study. There were no differences between placebo and L-carnitine for cognitive function, shoulder strength, 2-minute step test, timed up and go, walking speed, standing time from seated position, daily activity level or peak expiratory flow rate (Badrasawi et al. 2016).

Finally, in a study in healthy women, age 65–70 years, L-carnitine supplementation at 1500 mg/day for 24 weeks resulted in no changes in any of the the parameters assessed, namely body mass, body composition, and knee extensor and flexor muscle strength (Sawicka et al. 2018).

In all four of the above studies, L-carnitine was administered in tablet/capsule/vial form, not in a food or beverage.

(ii) A total of 19 studies in athletes/physically-trained subjects supplemented with L-carnitine (12 studies) or L-carnitine-L-tartrate (7 studies[4]) are summarised in Table 2 of Appendix 1. Doses in these studies, expressed as L-carnitine, ranged from 1000 to 5000 mg/day for durations of up to 24 weeks. Most of these studies used a small number of participants (typically 8 to 15) and mostly males.

Findings from these studies are summarised below (with studies cited in chronological order).

- **Body composition**
  Drăgan et al. 1988 – reduced body fat and muscle mass;
  Stephens et al. 2013 – no effect on lean body mass.

- **Protein, fat, and carbohydrate metabolism**
  Soop et al. 1988 – no effect on free fatty acid utilisation;
  Gorostiaga et al. 1989 – no effect on plasma free fatty acid or glycerol concentrations;
  Colombani et al. 1996 – no effect on plasma glucose, carbohydrate metabolites, or fat metabolites;
  Broad et al. 2005 – no effect on carbohydrate or fat oxidation;
  Kraemer et al. 2006 – no effect on plasma glucose;
  Spiering et al. 2007 – no effect on plasma glucose;
  Broad et al. 2008 – decreased plasma ammonia but no effect on carbohydrate oxidation, nitrogen excretion, branched-chain amino acid oxidation, or plasma urea;
  Broad et al. 2011 – decreased blood glucose but no effect on carbohydrate or fat oxidation;
  Stephens et al. 2013 – no effect on carbohydrate and fat oxidation during exercise.

- **Exercise performance**
  Trappe et al. 1994 – no effect on swimming performance;
  Colombani et al. 1996 – no effect on running performance;
  Broad et al. 2005 – no effect on cycling performance;
  Wall et al. 2011 – no effect on work output after 12 weeks L-carnitine (2720 mg/day) + carbohydrate (160 g glucose polymer mixture per day), but increased after 24 weeks;
  Burrus et al. 2018 – no effect on time to exhaustion.

[4] One study was described in two publications: Wall et al. (2011) and Stephens et al. (2013).

- **Muscle strength and power output**
  Drăgan et al. 1988 – increased muscle strength;
  Vecchiet et al. 1990 – increased cycling power output;
  Maggini et al. 2000 – highly variable cycling power output results;
  Wächter et al. 2002 – no effect on power output;
  Spiering et al. 2007 – no effect on grip strength;
  Burrus et al. 2018 – no effect on power output.

- **Exercise heart rate**
  Soop et al. 1988 – no effect;
  Wächter et al. 2002 – no effect;
  Broad et al. 2011 – lower.

- **Maximal oxygen uptake (VO_2max)**
  Soop et al. 1988 – no effect;
  Drăgan et al. 1989 – inconsistent effects across six trials;
  Gorostiaga et al. 1989 – no effect;
  Vecchiet et al. 1990 – increased;
  Wächter et al. 2002 – no effect.

- **Vasodilation**
  Spiering et al. 2008 – no effect on plasma prostacyclin.

- **Blood and muscle lactate concentration**
  Siliprandi et al. 1990 and Vecchiet et al. 1990 – decreased plasma lactate;
  Trappe et al. 1994 and Wächter et al. 2002 – no effect on blood lactate;
  Colombani et al. 1996 – no effect on lactate dehydrogenase;
  Volek et al. 2002 – no effect on plasma lactate;
  Wächter et al. 2002 – no effect on blood lactate;
  Kraemer et al. 2006 – no effect on plasma lactate;
  Spiering et al. 2007 – no effect on plasma lactate;
  Wall et al. 2011 – no effect on muscle lactate after 12 weeks L-carnitine (2720 mg/day) + carbohydrate (160 g glucose polymer mixture per day), decreased muscle lactate after 24 weeks.
  Burrus et al. 2018 – decreased blood lactate.

- **Muscle glycogen**
  Vukovich et al. 1994 – no effect;
  Wall et al. 2011 – no effect after 12 weeks of L-carnitine (2720 mg/day) + carbohydrate (160 g/day), increased after 24 weeks.

- **Hormone responses to exercise**
  Colombani et al. 1996 – no effect on insulin, glucagon, or cortisol;
  Kraemer et al. 2003 – no effect on growth hormone, testosterone, insulin-like growth factor-1, small and variable effect on insulin-like growth binding protein-3;
  Kraemer et al. 2006 – no effect on muscle androgen receptor concentration or follicle stimulating hormone, variable effects on testosterone, luteinizing hormone, sex-hormone binding globulin, adrenocorticotrophic hormone, and cortisol.

- **Biomarkers of oxidative stress**
  Volek et al. 2002 – reduced exercise-induced increases in plasma xanthine oxidase and malondialdehyde;
  Spiering et al. 2007 – decreased post-exercise serum hypoxanthine, xanthine oxidase and myoglobin;
  Spiering et al. 2008 – decreased plasma malondialdehyde.

- **Muscle fibre composition**
  Wächter et al. 2002 – no effect.

- **Activities of respiratory-chain enzymes**
  Huertas et al. 1992 – no change for succinate dehydrogenase, decrease for citrate synthase, increases for rotenone-sensitive NADH cytochrome c reductase, succinate cytochrome c reductase, and cytochrome c oxidase;
  Wächter et al. 2002 – no effect for citrate synthase or cytochrome c oxidase.
  Wall et al. 2011 – no effect on muscle citrate synthase, pyruvate dehydrogenase, phosphocreatine, phosphocreatine/ATP ratio after 12 weeks of L-carnitine (2720 mg/day) + carbohydrate (160 g glucose polymer mixture per day), increase in some parameters after 24 weeks.

- **Muscle carnitine concentration**
  Arenas et al. 1991 – increased by ~10%;
  Huertas et al. 1992 – increased by ~10%
  Wächter et al. 2002 – no effect;
  Wall et al. 2011 – no effect after 12 weeks L-carnitine (2720 mg/day) + carbohydrate (160 g glucose polymer mixture per day), increased muscle total carnitine (by 30%) after 24 weeks.

- **Muscle tissue damage**
  Colombani et al. 1996 – no effect on creatine kinase;
  Volek et al. 2002 – decreased according to MRI assessment and blood levels of cytosolic proteins.

- **Muscle tissue oxygenation**
  Spiering et al. 2008 – decreased during and after resistance exercise.

- **Gene expression in muscle**
  Stephens et al. 2013 – increased expression of genes involved in insulin signalling and fatty acid metabolism after 24 weeks of L-carnitine (2720 mg/day) + carbohydrate (160 g glucose polymer mixture per day).

- **Self assessment of level of exertion during exercise**
  Wall et al. 2011 – no effect after 12 weeks L-carnitine (2720 mg/day) + carbohydrate (160 g glucose polymer mixture per day), decreased perceived exertion after 24 weeks.

- **Self assessment of post-exercise muscle soreness**
  Volek et al. 2002 – soreness rated lower;
  Spiering et al. 2007 – soreness rated lower;
  Ho et al. 2010 – soreness rated lower.

For most of the parameters summarised above there is a lack of reproducibility between studies for favourable effects. These parameters include protein, fat, and carbohydrate metabolism; bodyweight and composition; exercise performance (e.g. swimming, cycling, and running time trials); maximal oxygen uptake; blood and muscle lactate; muscle glycogen; blood glucose; hormone responses to exercise; muscle fibre composition; and mitochondrial enzyme activity.

There were four studies in athletes investigating whether L-carnitine supplementation could increase muscle carnitine concentration (Arenas et al. 1991; Huertas et al. 1992; Wächter et al. 2002; Wall et al. 2011). In three of these studies increases in muscle carnitine concentration were reported (Arenas et al. 1991; Huertas et al. 1992; Wall et al. 2011). Arenas et al. (1991) reported 8-10% increases in muscle free carnitine in endurance runners and sprinters following supplementation with L-carnitine at 2000 mg/day for 120 days, however plasma L-carnitine concentrations were unexpectedly unaffected. Huertas et al. (1992) reported that L-carnitine supplementation (2000 mg/day for 4 weeks) was associated with increased muscle carnitine concentration (by ~10%), which was accompanied by increased activities of several respiratory chain enzymes. However, in the placebo group, muscle carnitine levels inexplicably decreased by ~10% over the 4-week study period, but the same respiratory chain enzyme activities were unaffected by this apparent decrease in muscle carnitine. In Wall et al. 2011, increased muscle total carnitine (by 30%) was observed after 24 weeks of daily L-carnitine supplementation in combination with a high carbohydrate dose (2 x 80 g per day of a high molecular weight glucose polymer), but not after 12 weeks. In a 3-month study, supplementation to physically-trained males with 4000 mg/day L-carnitine resulted in a 2-fold increase in plasma carnitine; however, muscle carnitine levels were unaffected (Wächter et al. 2002). The increased muscle carnitine concentrations reported in these studies were still within the normal range [15–30 mmol/kg muscle (dry weight), see response to Question 2].

Three studies, in a total of 36 subjects, investigated whether L-carnitine supplementation can reduce post-exercise muscle soreness. Muscle carnitine concentrations were not measured in these studies. These studies used essentially the same design and were conducted by an overlapping group of investigators (Volek was an author on all three studies). This effect on muscle soreness has not been replicated by a different research group and Volek's group have not reported whether the effect can be achieved with a pre-exercise supplement period of less than 3 weeks.

Decreased post-exercise muscle soreness was reported by Volek et al. (2002), Spiering et al. (2007), and Ho et al. (2010). These were crossover RCTs in weight-trained adult males (Volek et al. 2002; Spiering et al. 2007) or recreationally active adult males and females (Ho et al. 2010). L-carnitine-L-tartrate (equivalent to 2000 mg/day L-carnitine) given in a divided dose (breakfast and lunch) for 21 days, with washout periods of one week, were used in Volek et al. (2002) and Ho et al. (2010), and these were double-blind studies. Volek et al. (2002) reported that muscle soreness was rated lower after L-carnitine treatment (on days 1, 2 and 4 after the exercise test which was a series of leg squats, but not on day 3) compared to placebo. Ho et al. (2010) reported that perceived muscle soreness was lower for men immediately after exercise and during recovery days 1 and 2, and for women during recovery days 1 and 2.

Spiering et al. (2007) used two L-carnitine dose levels (1000 and 2000 mg/day for 21 days) with washout periods of 21 days, however it was not stated if the study was blinded. Compared to placebo, supplementation with 1000 mg/day reduced perceived muscle soreness at 24 and 72 hours after exercise, but not at 48 hours; and compared to placebo supplementation with 2000 mg/day reduced perceived muscle soreness at all three post-

exercise timepoints assessed (24, 48 and and 72 hours after exercise). Compared to 1000 mg/day, supplementation with 2000 mg/day reduced perceived muscle soreness at 48 hours after exercise but not at 24 and 72 hours.

In each study, muscle soreness was self-rated using a continuous scale ranging from 0 (representing no pain) to 10 (extreme pain). In Volek et al. (2002), compared to placebo, L-carnitine-L-tartrate supplementation was associated with lower muscle soreness on day 1 (mean soreness rating of 4.2 vs. 5.8), day 2 (4.9 vs. 5.5) and day 4 (1.0 vs. 1.8) after a squat exercise protocol, but not on day 3. In Spiering et al. (2007), compared to placebo, supplementation with 1000 mg/day was associated with lower muscle soreness ratings at 24 hours (3.2 vs. 6.2) and 72 hours (2.8 vs. 4.5), but not at 48 hours after a squat exercise protocol; and compared to placebo supplementation with 2000 mg/day reduced perceived muscle soreness at all three timepoints after exercise [24 hours (4.5 vs. 6.2), 48 hours (4.3 vs. 6.2) and 72 hours (3.1 vs. 4.5). Compared to 1000 mg/day, supplementation with 2000 mg/day reduced perceived muscle soreness at 48 hours (4.3 vs. 5.2) after exercise but not at 24 and 72 hours. In Ho et al. (2010), L-carnitine was associated with lower muscle soreness in men immediately after a squat/leg-press protocol, and on recovery days 1 and 2 (mean soreness ratings were ~1 vs. ~2 for placebo); and for women on recovery day 1 (rating of ~1.3 vs. 3 for placebo) and day 2 (0.7 vs. 1.6).

Several studies reported potentially favourable effects of L-carnitine supplementation on biomarkers of muscle recovery and oxidative stress[5] following exercise. However, recent reviews highlight that there is a lack of consensus concerning the validation, standardization, and reproducibility of the various analytical methods used for the measurement of such biomarkers. Also, a growing body of research indicates that reactive oxygen species may act as signalling molecules involved in the activation of protective adaptive responses. Transiently increased levels of oxidative stress, as may occur during and immediately after exercise, may therefore be beneficial to health (Alleman et al. 2014; Nikolaidis et al. 2015; Pingitore et al. 2015; Boccatonda et al. 2016; Powers et al. 2016; Gomes et al. 2017; Webb et al. 2017; Tan et al. 2018). Large increases in the dietary intake of a substance which results in decreased production of reactive oxygen species may therefore not be desirable. Consequently there does not appear to be a consensus on whether this effect, if it is shown to be real, would be favourable or adverse.

(iii) A recently published systematic review and meta-analysis examined the potential effects of L-carnitine on body weight in adults (Pooyandjoo et al. 2016). Six studies were included in the meta-analysis of body weight change, however only one of these studies was in healthy (but obese) subjects (Villani et al. 2000; summarised in Appendix 1). The authors reported that subjects who received L-carnitine lost more body weight compared with the control group (mean difference: -1.33 kg; 95% confidence interval: -2.09 to -0.57 kg). However, a subsequent publication identified that the meta-analysis had mixed studies using L-carnitine alone and L-carnitine in combination with pharmacological therapy and/or diet and lifestyle interventions. An analysis of studies that used treatments consisting exclusively of L-carnitine concluded that supplementation had no effect on body weight (Del Vecchio et al. 2017).

(iv) Supplementation with L-carnitine has been shown to increase plasma carnitine concentrations to a similar degree in both vegetarians and non-vegetarians. There is inconsistent evidence that muscle carnitine concentration can be increased slightly in vegetarians. For example, supplementation with a high intake of L-carnitine (4000 mg/day as

[5] Oxidative stress relates to an imbalance between the production and degradation of reactive oxygen species.

tablets) for 3 months to adult males resulted in a 2-fold increase in plasma total carnitine, however muscle carnitine concentration was unaffected (Wächter et al. 2002). On the other hand, in a study in 16 adult male vegetarians and 8 adult male omnivores, supplementation with L-carnitine (2000 mg/day as capsules) for 12 weeks resulted in increased plasma carnitine concentration in both groups (by 24% in omnivores and 31% in vegetarians) while muscle total carnitine was increased only in vegetarians (by 13%, and remained within the normal range) (Novakova et al. 2016). However, neither of these studies included a placebo control group and there were no effects on the other parameters investigated by Novakova et al. (2016) [biochemical parameters including skeletal muscle ATP, phosphocreatinine, glycogen and lactate; exercise performance (sustained maximum cycling power) and aerobic capacity (VO2max)].

No studies were located that investigated carnitine levels in the breast milk of vegetarians. However, Cederblad and Svenningsen (1986) reported that otherwise healthy premature infants maintain plasma carnitine levels despite a 9-fold range in their mothers' breast milk carnitine levels (17–148 µmol/L). Also, Rovamo et al. (1986) reported that the carnitine concentrations in serum and breast milk of mothers were not correlated. In another study, breast milk concentrations of all carnitine fractions examined (free, acid-soluble acyl-, acid-insoluble acyl-, or total carnitine) did not correlate with dietary carnitine intake or with the duration of lactation (1–10 months) (Mitchell and Snyder 1991).

Question 5 Is there any difference in absorption of L-carnitine from food compared to supplements?

Response

No information has been identified that would indicate a difference in the absorption of L-carnitine from food compared to supplements. Absorption is however dose-dependent. At low carnitine intakes, typical for vegans/vegetarians, carnitine bioavailability is high (up to 87%) while bioavailability is low when carnitine intake is high (14–18% at intakes of 0.5–6 g/day (Rebouche 2004).

2.2 Discussion

Human dietary intake of carnitine varies over a large range – from as low as ~1 mg/day for vegetarians to ~500 mg/day or more for regular meat eaters. Dietary protein provides an additional source of carnitine via biosynthesis from the amino acids methionine and lysine. Estimates of carnitine dietary intake for Australia/New Zealand population groups are provided in Supporting Document 1 (SD1). SD1 also contains information on the biochemistry, physiology and pharmacokinetics of carnitine, including specific information on L-carnitine and L-carnitine-L-tartrate.

When dietary intake of carnitine is low, physiological adaptations occur to ensure that muscle carnitine levels remain adequate for normal muscle function. For example, vegetarians have a greater rate of endogenous carnitine synthesis and also excrete less carnitine in urine. A recent study in omnivorous women that changed to a vegetarian diet showed no change in plasma and muscle carnitine concentrations (Blancquaert et al. 2018). There is inconsistent evidence that muscle carnitine concentration can be increased slightly in vegetarians supplemented with L-carnitine, however suitable evidence for other effects is lacking. Clinical carnitine deficiencies are predominantly due to disorders that result in specific enzyme deficiencies rather than dietary insufficiencies, except in cases of severe protein malnutrition.

The concentration of carnitine in plasma is commonly used as an indicator of body carnitine status, both in healthy people and in those with medical conditions. However, greater than 95% of total body carnitine resides in muscle, and the correlation between plasma and muscle carnitine levels is low (Lennon et al. 1986; Starling et al. 1995). Therefore, plasma carnitine concentration is not a good marker of body status even though it can be increased by approximately two-fold from the intake of L-carnitine in supplementation studies. Muscle carnitine concentration is therefore considered to be a more reliable suitable indicator of body carnitine status. No evidence has been identified that muscle carnitine concentration ranges differ between the general healthy population and population sub-groups identified in the application, i.e. otherwise healthy overweight, elderly, vegetarians/vegans, and athletes/exercise-trained individuals (Starling et al. 1995; Wächter et al. 2002; Malaguarnera et al. 2007; Novakova et al. 2016). It is noted that during and after exercise, alterations in skeletal muscle carnitine metabolism can result in changes in the relative concentrations of various carnitine species in muscle, including increased acylcarnitines and decreased free carnitine (Hiatt et al. 1989; Decombaz et al. 1992).

Summaries of 43 studies investigating the potential favourable effects of oral L-carnitine supplementation in healthy subjects, including population sub-groups relevant to the application, are provided in Tables 1 and Table 2 of Appendix 1. Many of these trials report increases in plasma carnitine, which supports compliance with the study protocols.

These studies do not show reproducible effects on protein, fat, or carbohydrate metabolism; bodyweight and composition; exercise performance (e.g. swimming, cycling, and running time trials); maximal oxygen uptake; blood and muscle lactate; muscle glycogen; blood glucose; hormone responses to exercise; muscle fibre composition; and mitochondrial enzyme activity.

Favourable effects of supplementary L-carnitine intake have been reported in studies in elderly subjects (70 years and over). These studies, which used L-carnitine doses of 1500 to 4000 mg/day for 4 weeks to 6 months, reported increases in muscle mass, loss of fat, and improved physical function following L-carnitine supplementation. However, of the two studies which tested 1500 mg/day, only one reported a favourable effect. L-carnitine has not been shown to improve body composition in adults under 70 years. Muscle carnitine concentrations were not investigated in studies in elderly subjects.

Regarding the effects of L-carnitine on muscle recovery following exercise, two randomised, placebo-controlled trials (RCTs) in weight-trained adult males and one RCT in recreationally active adult males and females reported that supplementation with L-carnitine (2000 mg/day as a supplement, in a divided dose for 21 days) was associated with decreased muscle soreness following a leg squat protocol. All three studies found an effect on the first day but there was variation in the duration of the effect after that. One of these RCTs reported that an L-carnitine dose of 2000 mg/day was more effective than 1000 mg/day in reducing post-exercise muscle soreness, however it was not stated if this study was blinded. These three studies all used essentially the same protocol and were done by an overlapping set of investigators. The effect has not been tested by other research groups or for exercises other than leg squats/leg presses, or for a pre-exercise supplementation period of less than 3 weeks. It has been suggested L-carnitine supplementation can result in increased muscle carnitine concentrations, and that this may aid post-exercise muscle recovery. Increased muscle total carnitine concentrations in omnivorous humans have been reported in a study where L-carnitine was co-ingested with large amounts of carbohydrate (2 x 80 g per day of a glucose polymer mixture), however post-exercise muscle soreness was not investigated in this study. The increased muscle carnitine concentrations in this study remained within the normal range of 15–30 mmol/kg muscle (dry weight).

3 Conclusion

Human supplementation studies with L-carnitine and L-carnitine-L-tartrate have investigated a large number of parameters of relevance to this application. Most studies used daily dosing at levels of around 2000–3000 mg per day. Most studies were conducted with male participants and used small subject numbers. In most studies L-carnitine or L-carnitine-L-tartrate were provided as tablets or capsules, however no information has been identified that would indicate a difference in the absorption of L-carnitine from food compared to oral supplements. All repeat-dose studies have given carnitine at least once per day. No studies were found which examined the effect of less frequent intakes such as several times per week.

Findings for most parameters show a lack of consistency between studies. The studies show a lack of reproducible effects on protein, fat, or carbohydrate metabolism; bodyweight and composition (excluding subjects over 70 years); exercise performance (e.g. swimming, cycling, and running time trials); maximal oxygen uptake; blood and muscle lactate; muscle glycogen; blood glucose; hormone responses to exercise; muscle fibre composition; and mitochondrial enzyme activity.

There is inconsistent evidence that muscle carnitine concentration can be increased slightly in vegetarians. Favourable effects of supplementary L-carnitine intake have been reported for elderly subjects (70 years and over), namely increases in muscle mass, loss of fat, and improved physical function. These studies used L-carnitine doses of 1500–4000 mg/day for 4 weeks to 6 months, however, of the two studies which tested 1500 mg/day, only one reported an effect. Therefore the evidence in the elderly is inconclusive. L-carnitine has not been shown to improve body composition (i.e. increase muscle mass and/or decrease fat mass) in adults under 70 years.

For athletes and others undertaking regular exercise training, three RCTs reported that L-carnitine reduces post-exercise muscle soreness. All three studies found an effect on the first day but there was variation in the duration of the effect after that. It has been suggested that L-carnitine supplementation can result in increased muscle carnitine concentrations, and that this may aid post-exercise muscle recovery. Increased muscle carnitine concentrations in omnivorous humans have only been reliably demonstrated in a study where L-carnitine (2720 mg/day for 24 weeks) was co-ingested with large amounts of carbohydrate (2 x 80 g per day of a glucose polymer mixture), however post-exercise muscle soreness was not investigated in this study. The increased muscle carnitine concentrations in this study remained within the normal range of 15–30 mmol/kg muscle (dry weight).

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Appendix 1

Tables 1 and 2 contain information on studies with L-carnitine or L-carnitine-L-tartrate in healthy subjects who are physically-untrained or physically-trained, respectively.

Table 1: Studies investigating the effects of L-carnitine or L-carnitine-L-tartrate in healthy, physically-untrained subjects.

Reference and study design	Parameters measured	Results
Greig et al. (1987) Two trials were conducted to investigate the effects of L-carnitine supplementation on maximum and sub-maximum exercise capacity. Two groups of healthy, untrained subjects were studied in two double-blind cross-over trials. L-carnitine (2000 mg/day) was provided as a supplement for 2 weeks (trial 1) or 4 weeks (trial 2). There was no control group in either trial.	Maximum heart rate, maximum oxygen uptake (VO_2max), and heart rate at 50% of VO_2max were assessed during a continuous progressive cycle ergometer exercise test. Plasma concentrations of lactate and β-hydroxybutyrate (a metabolite of fatty acids and ketogenic amino acids) were measured pre- and post-exercise.	L-carnitine had no effect[6] on VO_2max or maximum heart rate in either trial. In trial 1, there was a small decrease in heart rate at 50% VO_2max, however this was not observed in trial 2. L-carnitine had no effect on plasma lactate or β-hydroxybutyrate in either trial.
Oyono-Enguelle et al. (1988) Study in ten males receiving L-carnitine (2000 mg/day) for 4 weeks. There was no control group.	Indicators of carbohydrate, protein, lipid, and ketone body metabolism. Measurements were made on blood samples collected during each experiment at fixed time intervals before exercise, during 60 min of bicycle exercise performed near 50% VO_2max, and during a 120 min recovery period.	Free and total plasma carnitine levels reached a plateau corresponding to an average rise of 25% for both fractions, 9–10 days after the beginning of L-carnitine supplementation. Levels returned to initial values 6–8 weeks after L-carnitine cessation. L-carnitine did not significantly modify any indicators of fuel metabolism.
Vukovich et al. (1994) Eight healthy males (mean age 27 years) completed exercise trials before L-carnitine supplementation and at 7 and 14 days after L-carnitine-L-tartrate supplementation (administered in orange juice; 3 x 3000 mg/day, equivalent to 6000 mg/day of L-carnitine). There was no control group.	VO_2max; respiratory exchange ratio; heart rate; rate of carbohydrate oxidation; rate of fat oxidation; serum total acid soluble and free carnitine; muscle carnitine and glycogen. Muscle biopsies were obtained pre-exercise and after 30 and 60 min of exercise. Blood samples were taken prior	There were no differences in VO_2max, respiratory exchange ratio, heart rate, rate of carbohydrate oxidation, or rate of fat oxidation. Serum total acid soluble and free carnitine increased with L-carnitine supplementation, however muscle carnitine and glycogen concentrations were

[6] In Tables 1 and 2, differences in parameters between groups/treatments are indicated if $p < 0.05$.

Reference and study design	Parameters measured	Results
	to exercise and every 15 min during exercise.	unaffected.
Giamberardino et al. (1996) Single-blind, non-randomised, crossover study in 6 healthy males (not physically trained; age 22–33 years). Subjects received placebo daily for 3 weeks followed by a one week break then L-carnitine (via oral phial; 3 x 1000 mg/day) for 3 weeks. Step tests (20-min eccentric effort of the quadriceps muscle) were performed on the first day of the 3rd and 7th week.	Pain after leg exercise test (assessed using visual analogue scale, however details not provided); pain thresholds to pressure and electrical stimulation; muscle creatine kinase, as a marker of muscle damage.	L-carnitine was associated with reduced pain after exercise. Pressure pain thresholds were higher for L-carnitine at 48, 72 and 96 hours after exercise and electrical pain thresholds were higher for L-carnitine at 48 and 72 hours. Muscle creatine kinase was lower for L-carnitine at 24 hours after eccentric exercise, but did not differ from placebo at 48, 72 and 96 hours.
Maggini et al. (2000) Double-blind, crossover RCT in 12 healthy adults (mean age 26 years). Six subjects (1 female, 5 males) were described as trained and six (1 female, 5 males) as untrained. Subjects received either placebo or L-carnitine-L-tartrate (equivalent to 2000 mg/day L-carnitine) for 5 days and then crossed over to the other treatment for 5 days. The form of supplementation was not stated (e.g. capsule, beverage).	Mean power output measured during 3 sets of 10 leg extensions separated by 60 seconds. Testing was conducted at 5, 10, 15, 20 and 25 min after commencement of a cycling protocol that was stated to have been conducted at anaerobic threshold.	Supplementation with L-carnitine-L-tartrate was associated with an 11–14% increase in mean power output ($p < 0.005$) during leg extension exercise sets. However, inter-subject variability was large (changes in mean power output ranged from -6% to +42%) suggesting that the intensity during the cycling trials conducted prior to leg power testing may not have been well controlled.
Villani et al. (2000) Double-blind, parallel RCT in healthy women (n = 18 per group, age 19–48 years) for 8 weeks. The treatment group received L-carnitine (4000 mg/day; mixed in a beverage). 33 subjects were considered moderately obese because body fat mass was greater than 30% of body mass, however mean body mass index (BMI) was in the normal range (24.7 ± 0.7 kg/m^2).	Body composition (body mass, fat mass, fat-free mass, average skinfold measurements), and resting metabolic indicators (respiratory quotient, non-protein respiratory quotient, absolute resting energy expenditure, resting energy expenditure per kg body mass).	L-carnitine had no effect on any of the investigated parameters.
Müller et al. (2002) Ten healthy untrained subjects (5 men, 5 women, age 22–56 years) consumed 1 g of $^{13}CO_2$-labelled palmitic acid with breakfast and $^{13}CO_2$ in exhaled breath was measured. Subjects were then supplemented for 10 days with L-carnitine [in ampules, 3 x 1000 mg/day (with breakfast, lunch and dinner)]. On day 10, 1 g of ^{13}C-labelled palmitic acid was given 30 minutes after the breakfast L-carnitine dose and CO_2 exhalation was measured. There was no control group.	$^{13}CO_2$ in exhaled breath (every 15 minutes for 15 hours after consumption of 1 g of ^{13}C-labelled palmitic acid); 24-hour urine for determination of L-carnitine; serum total carnitine, L-carnitine, glucose, haemoglobin A_{1c}, triglycerides, cholesterol, HDL- and LDL-cholesterol.	Compared to baseline values, the following were higher after L-carnitine supplementation: cumulative $^{13}CO_2$ exhalation (7.0% vs 5.1%); serum total L-carnitine levels (placebo: 47.1 ± 6.8 mol/l v L-carnitine: 59.9 ± 9.5 mol/L); urinary excretion of total carnitine (placebo: 36.8 ± 33.3 mg/24 h v L-carnitine: 367 ± 202 mg/24 h). L-carnitine did not effect the other serum parameters.

Reference and study design	Parameters measured	Results
Pistone et al. (2003) Double-blind, parallel RCT for 4 weeks in otherwise heathy elderly males and females with onset of fatigue following slight physical activity. Placebo group (n = 42, 57% male, age 80.7 ± 6.9 years). L-carnitine group (4000 mg/day in vials; n = 42, 52% male, age 81.5 ± 6.7 years).	Body mass, total fat mass and total muscle mass (estimated by bioelectrical impedance analysis), serum triglyceride, total cholesterol, high- and low-density lipoprotein cholesterol (HDL-C, LDL-C), apolipoprotein A1 (apoA1) and apoB. Physical and mental fatigue tests, conducted at the beginning and end of the study period.	At the end of 4 weeks, compared to the placebo group the L-carnitine group (4000 mg/day) lost more body fat mass (-3.1 vs -0.5; $p < 0.01$), gained more muscle mass (+2.1 kg vs +0.2 kg; $p < 0.01$), and showed improvements in serum total cholesterol (-1.2 vs +0.1 mmol/L; $p < 0.01$), LDL-cholesterol (-1.1 vs -0.2 mmol/L; $p < 0.01$), HDL-cholesterol (+0.2 vs +0.01 mmol/L; $p < 0.02$), triglycerides (-0.3 vs 0.0 mmol/L; $p < 0.02$), apoA1 (-0.2 vs 0.0 g/L; $p < 0.05$), apoB (-0.3 vs -0.1 g/L; $p < 0.05$), mental fatigue score (-3.5 vs -0.6; $p < 0.001$), and physical fatigue score (-5.3 vs -1.4; $p < 0.001$). Body mass was not affected by L-carnitine treatment.
Wutzke and Lorenz (2004) Crossover study in 12 healthy subjects (7 females, 5 males; age 18–30 years; BMI 24–27 kg/m^2) receiving a standardised diet either with or without L-carnitine-L-tartrate (equivalent to 3000 mg/day L-carnitine; form of supplementation not stated) for 10 days. Information on blinding was not provided.	Protein turnover, fat oxidation, body fat mass, total body water, and lean body mass.	Fat oxidation was slightly greater with L-carnitine supplementation (19.3% v 15.8%; $p = 0.02$), however body fat mass, lean body mass, total body water, and protein synthesis and breakdown rates were unchanged.
Stuessi et al. (2005) Double-blind, crossover RCT in 12 healthy males, age 25 ± 3 years. Subjects received either a single dose of L-carnitine (2000 mg) or placebo. Two hours after administration, subjects performed a constant-load exercise test by cycling at their individual anaerobic threshold to exhaustion. Three hours later this test was repeated. After 4–14 days, each subject performed the same cycling tests after swapping treatments.	Exercise time to exhaustion; heart rate; oxygen consumption; respiratory exchange ratio; blood lactate.	There were no differences between placebo and L-carnitine for any parameters.
Malaguarnera et al. (2007) Double-blind, parallel RCT in male and female centenarians. Subjects received either placebo or acetyl L-carnitine (2000 mg/day, in vials) for 6 months. Placebo group: 11 males, 23 females, age 101 ± 1.4 years. L-carnitine group: 10 males, 22 females, age 101 ± 1.3 years.	Plasma free carnitine and total carnitine; physical fatigue score; mental fatigue score; cognitive function (mini mental state evaluation, MMSE; Tombaugh and McIntyre 1992); body mass; fat and muscle mass (estimated using bioelectrical impedance analysis); plasma triacylglycerols, total cholesterol, HDL and LDL cholesterol.	Plasma free carnitine (µmol/L) before and after L-carnitine supplementation was 41.8 ± 7.7 and 49.2 ± 17.6, respectively (difference not statistically significant). Plasma total carnitine (µmol/L) was 55.2 ± 9.9 before treatment and 67.8 ± 29.9 after treatment), $p < 0.05$. At the end of 6 months, the L-carnitine treated centenarians, compared with the placebo group, showed improvements in total fat mass (-1.8 vs 0.6

Reference and study design	Parameters measured	Results
		kg; p < 0.01), total muscle mass (3.8 vs 0.8 kg; p < 0.01), physical fatigue score (-4.1 vs -1.1; p < 0.01), mental fatigue score (-2.7 vs 0.3; p < 0.001), fatigue severity score (-23.6 vs 1.9; p < 0.001), and cognitive function score (4.1 vs 0.6; p < 0.001). Body mass, plasma triacylglycerols, HDL- and LDL-cholesterol were not affected by L-carnitine treatment.
Ho et al. (2010) Double-blind, crossover RCT in healthy males (n = 9, mean age 45 years) and females (n = 9, mean age 52 years). Subjects were considered recreationally active but not resistance trained. Subjects received either placebo or 2944 mg/day L-carnitine-L-tartrate (equivalent to 2000 mg L-carnitine, as capsules) divided into 2 doses (at breakfast and lunch) for 24 days. An acute resistance exercise challenge (squats for males, leg presses for females) was performed after 21 days of supplementation (day 0) and recovery was assessed on day 1, day 2, and day 4. After a 1-week washout, subjects crossed-over to the other treatment for 24 days and the same protocol was repeated.	Serum L-carnitine; plasma lactate, hypoxanthine and xanthine oxidase (markers of purine metabolism); malondialdehyde (a marker of lipid peroxidation/cell membrane damage: Tsikas 2017); myoglobin and creatine kinase (markers of muscle tissue disruption); perceived muscle soreness [visual analogue scale ranging from 0 (no pain) to 10 (extreme pain)]; physical performance and functional mobility (vertical jump, handgrip strength, timed “up and go” test, stairclimbing, anterior reach test, step-down test).	There were no statistically significant differences between L-carnitine-L-tartrate and placebo for plasma lactate at all time-points; hypoxanthine at 6 time-points for both males and females; xanthine oxidase at 6 time-points for males and 7 time-points for females; malondialdehyde at 1 time-point for males and 5 time-points in females; myoglobin in males and females at 5 time-points; creatine kinase at 4 time-points for males and 5 time-points for females; physical performance/functional mobility tests. The following were higher for L-carnitine-L-tartrate compared to placebo: serum total L-carnitine concentrations at all time-points measured (~2-fold increases, with no differences between men and women). The following were lower for L-carnitine-L-tartrate compared to placebo: hypoxanthine at 2 time-points for both males and females; xanthine oxidase at 3 time-points for males and 2 time-points for females; malondialdehyde at 8 time-points for males and 5 time-points for females; myoglobin in males and females at 4 time-points; creatine kinase at 5 time-points for males and 4 time-points for females; perceived muscle soreness for men immediately after exercise and during recovery days 1 and 2 (mean soreness ratings were ~1 vs. ~2 for placebo), and for women during recovery days 1 (rating of ~1.3 vs. 3 for placebo) and 2 (0.7 vs. 1.6).

Reference and study design	Parameters measured	Results
Odo et al. (2013) Double-blind, parallel RCT for four weeks in four groups of healthy males (n = 5 or 6 per group, mean age 40–44 years, mean BMI 25.8–26.6 kg/m^2). Group 1: Placebo without motivation training Group 2: Placebo with motivation training Group 3: L-carnitine (500 mg/day, as capsules) without motivation training Group 4: L-carnitine (500 mg/day, as capsules) with motivation training. For motivation training, subjects were advised of the beneficial effect of weight loss on the risk of metabolic diseases, and were encouraged to perform daily physical activities such as taking stairs instead of using escalators, and were recommended to reduce energy intake to 1500–1800 kcal per day.	Body weight, body-mass index, body fat mass, body muscle mass, basal metabolic rate.	There were no statistically significant differences between groups for body fat mass, muscle mass and basal metabolic rate. The L-carnitine with motivation group showed a decrease in mean body weight of 1.1 kg after 4 weeks (baseline: 82.0 ± 2.2 kg; at 4 weeks: 80.9 ± 1.8 kg, p = 0.007). Body weight was unchanged in the other three groups. Body weight change differed only between the L-carnitine with motivation group and the placebo without motivation group (p = 0.0019). BMI decreased slightly in the L-carnitine with motivation group (from 26.6 kg/m^2 at baseline to 26.2 kg/m^2 after 4 weeks), but was unchanged in the other 3 groups.
Parandak et al. (2014) Double-blind, parallel RCT in healthy males receiving either placebo (n = 10, mean age 22 years) or 2000 mg/day L-carnitine (n = 11, mean age 22 years) in capsules for 14 days. Groups were matched for BMI (placebo: 23.0 ± 0.6 kg/m^2; L-carnitine: 22.4 ± 0.8 kg/m^2) and VO_2max (placebo: 43.0 ± 1.0 kg/m^2; L-carnitine: 43.4 ± 0.9 kg/m^2) (mean ± standard error). On day 15 after an overnight fast, participants ran for 10 minutes at ~50% VO_2max and were then instructed to run 14 km at their maximum ability.	Plasma total antioxidant capacity (TAC, by the method of Varga et al. 1998); malondialdehyde (MDA) as a marker of lipid peroxidation/cell membrane damage; serum creatine kinase (CK) and lactate dehydrogenase (LDH) as markers of muscle damage; 14 km running time.	There were no statistically significant differences between L-carnitine and placebo for: TAC (immediately after, and 2 h after run); MDA (before, immediately after, and 2 h after run); CK (before, immediately after, and 2 h after run); LDH (immediately after, and 2 h after run); 14 km running time. The following was higher for L-carnitine compared to placebo: TAC (before and 24 h after run; by 12–18%, p = 0.02). The following were lower for L-carnitine compared to placebo: MDA (24 h after run: by 32%, p = 0.003); CK (24 h after run: by 17%, p = 0.03); LDH [2 and 24 h after run: 25% (p = 0.01) and 33% (p = 0.003) lower, respectively].
Badrasawi et al. (2016) Double-blind, parallel RCT for 10 weeks. Placebo group (n = 24, age 68.8 ± 6.5 years, 62.5% female); L-carnitine group (1500 mg/day, n = 26, age 68.2 ± 6.3 years, 46.2% female). Treatments were taken as capsules. All subjects were considered “pre-frail” based on the Fried criteria in	Frailty Index score; cognitive function; strength and physical performance parameters (hand grip strength, shoulder strength, 2-minute step test, timed up and go, walking speed, standing from seated position test); daily activity level; peak expiratory flow rate; serum interleukin-6, tumor necrosis factor-alpha, and insulin-	Frailty Index score and hand grip strength were improved (by ~30% and 3%, respectively) in the L-carnitine group as compared to no changes in the placebo group. Based on the Fried criteria, four of the 50 subjects (three from the L-carnitine group and one from the control group) transitioned from pre-frail status to

Reference and study design	Parameters measured	Results
which frailty is defined as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (4.5 kg or more) in the past year, self-reported exhaustion, weakness (based on grip strength), slow walking speed, and low physical activity (Fried et al. 2001).	like growth factor-1.	robust by the end of the study.
Novakova et al. (2016) 24 healthy males (16 vegetarians and 8 omnivores) were treated for 12 weeks with L-carnitine-L-tartrate capsules (equivalent to 2000 mg/day L-carnitine). There was no control group.	Plasma and skeletal muscle carnitine and acylcarnitines; skeletal muscle ATP, phosphocreatinine, glycogen and lactate; urine creatinine, L-carnitine and acylcarnitines; physical performance (sustained maximum cycling power); aerobic capacity (VO_2max).	Supplementation increased plasma carnitine levels in omnivores and in vegetarians, while increases in pre-exercise (11%) and post-exercise (13%) skeletal muscle total carnitine was observed only in vegetarians. There were no changes in physical performance or aerobic capacity.
Shannon et al. (2016) Randomised, single-blind, three-arm, crossover study in seven healthy non-vegetarian males (age 24.2 ± 5.0 years). Subjects ingested 4500 mg L-carnitine-L-tartrate (equivalent to 3000 mg L-carnitine) with 30 mg of tritium-labelled L-carnitine in water. After 60 minutes, subjects were given a 500 mL beverage of either 80 g carbohydrate, 40 g carbohydrate + 40 g whey protein isolate, or flavoured water. The washout period between treatments was not stated.	Net carnitine balance (arteriovenous) measured in forearm blood (used as a surrogate marker of muscle carnitine uptake). Blood samples were taken at 20 minute intervals from 80 to 180 minutes after L-carnitine-L-tartrate ingestion.	L-carnitine-L-tartrate + carbohydrate resulted in increased net carnitine balance at 100, 120, 140 and 180 minutes after ingestion, with no effect at 80 and 160 minutes. However, there was no effect on net carnitine balance at any sampling timepoint for L-carnitine-L-tartrate alone or L-carnitine-L-tartrate + carbohydrate + protein.
Evans et al. (2017) Double-blind, parallel, randomised, placebo-controlled RCT in sedentary healthy adults (14 per group) for 8 weeks. Subjects received either placebo or 2200 mg/day L-carnitine-L-tartrate (equivalent to 1500 mg/day L-carnitine). An additional group received 2200 mg/day L-carnitine-L-tartrate in combination with L-leucine and vitamin D (results for this group not summarised in this Table). Treatments were dissolved in orange juice. Placebo group: 10 f, 4 m; mean age 57 years.	Body mass; lean mass (arms, legs, trunk)[7]; arm strength; leg strength; 6 minute walking test; muscle biopsy for protein analysis (mTOR[8] and downstream effectors); and quality of life assessment (RAND SF-36 questionnaire[9]).	L-carnitine-L-tartrate had no effect on body mass; leg and trunk lean mass; arm strength, leg strength; 6 minute walking test; mTOR and downstream effectors; and 7 of 8 quality of life parameters. There was an increase in one of the 8 quality of life parameters (vitality score, by 13%, $p = 0.025$), and a decrease in arm lean mass (by 2.5%, $p < 0.001$).

[7] By dual-energy X-ray absorptiometry (DXA).

[8] mTOR: Mammalian target of rapamycin, a key regulator of mammalian metabolism and physiology (Saxton and Sabatini 2017).

[9] RAND SF-36 questionnaire: https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html

Reference and study design	Parameters measured	Results
L-carnitine-L-tartrate group: 8 f, 6 m; mean age 61 years.		
Shannon et al. (2018) Double-blind, parallel RCT for 24 weeks. Healthy untrained males (age 23 ± 2 years; n = 7 per group) received as beverages either carbohydrate (2 x 80 g/day) or the same carbohydrate dose plus 4500 mg/day L-carnitine-L-tartrate (equivalent to 3000 mg/day L-carnitine). All 14 subjects also performed high intensity interval training (HIIT) over the 24 weeks.	Exercise capacity (VO_2max and $Watt_{max}$)[10]; skeletal muscle carnitine fractions, pyruvate dehydrogenase complex activation (PDCa), phosphocreatine, lactate, glycogen, and non-mitochondrial ATP production.	HIIT resulted in a 9% increase in $VO2_{max}$, 15% increase in $Watt_{max}$ and 23% increase in training work output in both groups ($p < 0.001$) with no differences between placebo and L-carnitine-L-tartrate groups. HIIT resulted in similar increases in resting muscle glycogen in control and L-carnitine-L-tartrate treated groups (1.5 and 1.4 fold increases, respectively). After 24 weeks, L-carnitine-L-tartate + HIIT resulted in a 30% increase in free carnitine in muscle at rest compared to placebo + HIIT. ATP, PDCa, phosphocreatine, and lactate were similar in the control and L-carnitine-L-tartrate groups after 24 weeks of HIIT.
Sawicka et al. (2018) Double-blind, parallel RCT in healthy women (age 65–70 years, n = 14 per group). Subjects received placebo or 1500 mg/day L-carnitine-L-tartrate as capsules for 24 weeks.	Plasma free carnitine; serum IL-6, TNF-α, C-reactive protein, and IGF-1; body weight; body composition; knee muscle strength (extensor and flexor).	Increased plasma L-carnitine concentration was observed with L-carnitine-L-tartrate supplementation. There were no effects on the other parameters investigated.

[10] VO_2max: maximum rate of oxygen consumption. $Watt_{max}$ is defined in the paper as exercise at maximal workload.

Table 2: Studies investigating the effects of L-carnitine or L-carnitine-L-tartrate in healthy, physically-trained subjects.

Reference and study design	Parameters measured	Results
Soop et al. (1988) Non-randomised study in which 7 moderately trained male subjects, serving as their own controls, participated in two bicycle exercise sessions, each for 120 min at 50% of VO_2max. The second exercise session was preceded by 5 days of L-carnitine supplementation (5000 mg/day).	Free fatty acid utilization during exercise; carnitine levels in plasma; VO_2max; heart rate during exercise.	L-carnitine supplementation resulted in a doubling of plasma carnitine levels but had no effect on exercise-induced changes in free fatty acid utilization. Heart rate during exercise after L-carnitine supplementation decreased by ~8%. VO_2max was unchanged.
Drăgan et al. (1988) The effects of a milk-based protein/mineral mixture in combination with L-carnitine were investigated in a group of junior elite cyclists by a double-blind placebo-controlled trial for six weeks (not stated if the subjects were randomised). Subjects were supplemented with 1 g protein/kg bw per day for six weeks, and for 10 days before a competition also received L-carnitine (2000 mg/day). A separate group (n = 7) received the same regimen with placebo instead of L-carnitine.	Strength index; lean body mass; fat mass; total work performed on a cycle ergometer; serum cholesterol, creatinine, alanine transaminase (ALT), haemoglobin, and calcium.	Compared to placebo, favourable changes were reported for the protein + L-carnitine group for strength index, lean body mass, fat mass, work output, serum haemoglobin and calcium. Serum cholesterol, creatinine, and ALT did not change significantly in either group.
Drăgan et al. (1989) This paper summarised six double blind, crossover RCTs in a total of 110 elite young athletes (47 female, 63 male). Separate RCTs were conducted on rowers, kayakers-canoers, swimmers, weightlifters, and mid/long-distance runners. Subjects received a single dose of 4000 mg L-carnitine followed by 3-weeks of 2000-3000 mg/day. L-carnitine was provided in phials. Vitamin and mineral tablets were also provided to the subjects.	Appetite, fatigue; well-being (questionnaire); VO_2max, anaerobic capacity; scapular and lumbar strength; evoked muscular potential; serum free fatty acids, triglycerides, cholesterol, creatinine, and CPK; blood lactate and haemoglobin; plasma carnitine (free and acetyl); urine creatine kinase, mucoproteins, and carnitine (free).	Statistically significant differences between placebo and L-carnitine were observed for a range of parameters; however, apart from increases in plasma and urine carnitine, findings were not consistent across the different sports.
Gorostiaga et al. (1989) Ten endurance-trained subjects (gender not specified) performed a control test (45 min of cycling at 66% of VO_2max) followed by 60 min of recovery. Each subject repeated this trial after 28 days of placebo or L-carnitine (2000 mg/day) treatment (double-blind, crossover design).	Respiratory quotient (ratio of CO_2 production to O_2 consumption); oxygen uptake; heart rate; blood glycerol; and resting plasma free fatty acid concentrations.	Respiratory quotient was lower with L-carnitine treatment. There were no statistically significant differences between placebo and L-carnitine for oxygen uptake, heart rate, blood glycerol, and free fatty acid concentrations.
Siliprandi et al. (1990) Double-blind, cross-over RCT in ten moderately trained male subjects	Plasma free carnitine, carnitine esters, lactate, and pyruvate; carnitine esters in	L-carnitine supplementation resulted in increased plasma free carnitine without a change in carnitine

Reference and study design	Parameters measured	Results
performing two bouts of maximal cycle ergometer exercise separated by a 3 day interval. Each subject was randomly given either a single dose of L-carnitine (2000 mg) or placebo one hour before the beginning of each exercise session.	urine.	esters, decreased post-exercise plasma lactate and pyruvate, and increased acetylcarnitine. Urine acetylcarnitine and C4 esters were lower with L-carnitine treatment.
Vecchiet et al. (1990) Double-blind, crossover RCT in ten moderately trained healthy adult males. A single dose of L-carnitine (2000 mg) or placebo were administered in random order 1 h before exercise on a cycle ergometer. Exercise intensity was incrementally increased until subjects became exhausted. After 72 h recovery, subjects crossed over to the other treatment and the same exercise regimen was repeated.	Power output; VO_2max; oxygen uptake at lower exercise intensities; carbon dioxide production; pulmonary ventilation; and plasma lactate.	At maximal exercise intensity, L-carnitine was reported to increase VO_2max and power output. At lower exercise intensities, L-carnitine decreased oxygen uptake, carbon dioxide production, pulmonary ventilation, and plasma lactate.
Arenas et al. (1991) Double-blind, parallel RCT in male endurance runners (age 19-27 years) and male and female sprinters (age 19-21 years). L-carnitine dose (form not stated) was 2000 mg/day for 120 days.	Serum, muscle and urine carnitine concentrations.	L-carnitine supplementation was associated with an 8-10% increase in muscle free carnitine in endurance runners and sprinters. Serum free carnitine was unaffected while acetyl carnitine increased ~2-fold. There were large (up to 4-fold) increases in urinary carnitine excretion.
Huertas et al. (1992) Double-blind, parallel RCT in highly-trained male long-distance runners (age not stated). Subjects (n = 7/group) received either placebo or L-carnitine (2000 mg/day, form not stated) during a 4-week period of training consisting of running 130–140 km/week.	Muscle carnitine concentration; and respiratory chain enzyme activities (rotenone-sensitive NADH cytochrome c reductase, succinate cytochrome c reductase, cytochrome oxidase, succinate dehydrogenase, and citrate synthase) in muscle.	In the placebo group there were no changes in respiratory chain enzyme activities over the 4-week study period. L-carnitine supplementation was associated with a 4% decrease in citrate synthase activity, and increased activities of rotenone-sensitive NADH cytochrome c reductase (by 77%), succinate cytochrome c reductase (by 78%), and cytochrome c oxidase (by 56%). Succinate dehydrogenase activity was not affected. Total and free carnitine concentrations in muscle were increased by 11% and 12%, respectively, after L-carnitine supplementation. In the placebo group, concentrations were decreased over the 4 week study, by 10% and 12%, respectively.
Trappe et al. (1994) Twenty male collegiate swimmers completed two trials separated by seven days. Each trial consisted of five 100 yard (91.4 metre) swims with a 2 min rest interval between each bout. Following the first trial subjects	Blood pH, lactate, carnitine and carnitine fractions; swim performance times (recorded for each repeat during both trials).	Serum free and total carnitine were increased in the L-carnitine group compared to baseline. Blood pH, lactate, and performance times were similar in both groups during each trial.

Reference and study design	Parameters measured	Results
were evenly and randomly assigned to receive either L-carnitine (4000 mg/day) or placebo for 7 days.		
Colombani et al. (1996) Double-blind, crossover RCT in seven endurance trained males (age 36 ± 3 years) given L-carnitine (2000 mg as tablets) or placebo two hours before the start of a marathon run and again after 20 km of the run. After a 4 week washout/recovery period subjects crossed over to the other treatment and the protocol was repeated.	Plasma concentration of carnitine fractions, carbohydrate metabolites (glucose, lactate, pyruvate), fat metabolites (free fatty acid, beta-hydroxybutyrate, glycerol), hormones (insulin, glucagon, cortisol) and enzyme activities (lactate dehydrogenase, creatine kinase), measured 1 hour before the run, immediately after the run, 1 hour after the run, and the morning after the run; respiratory exchange ratio (before and at the end of the run); and submaximal performance test (treadmill) the morning after the run.	L-carnitine administration was associated with increases in the plasma concentrations of all carnitine fractions compared to the placebo group, but had no effects on the other parameters.
Maggini et al. (2000) Double-blind, crossover RCT in 12 healthy adults (mean age 26 years). Six subjects (1 female, 5 male) were described as trained and six (1 female, 5 male) as untrained. Subjects received either placebo or L-carnitine-L-tartrate (equivalent to 2000 mg/day L-carnitine) for 5 days and then crossed over to the other treatment for 5 days. The form of supplementation was not stated (e.g. capsule, beverage).	Mean power output measured during 3 sets of 10 leg extensions separated by 60 seconds. Testing was conducted at 5, 10, 15, 20 and 25 min after commencement of a cycling protocol that was stated to have been conducted at anaerobic threshold.	Supplementation with L-carnitine-L-tartrate was associated with an 11–14% increase in mean power output ($p < 0.005$) during leg extension exercise sets. However, inter-subject variability was large (changes in mean power output ranged from -6% to +42%) suggesting that the intensity of the cycling trials may not have been well controlled.
Volek et al. (2002) Double-blind, crossover RCT in 10 healthy, recreationally weight-trained males, mean age 24 years. Subjects received placebo or L-carnitine-L-tartrate as capsules (equivalent to 2000 mg/day L-carnitine) for 21 days followed by a 1 week washout and then received the other treatment for 21 days.	Serum carnitine fractions (free, acetyl, total). Plasma lactate, markers of purine catabolism (hypoxanthine and uric acid), and markers of free radical generation (xanthine oxidase and malondialdehyde). Muscle tissue disruption (plasma levels of myoglobin, fatty acid-binding protein, and creatine kinase; and by magnetic resonance imaging (MRI) of thigh muscles). Perceived muscle soreness after a squat exercise protocol [visual analogue scale ranging from 0 (no pain) to 10 (extreme	Serum carnitine fractions following L-carnitine-L-tartrate supplementation were approximately double the levels for placebo. There was no difference in plasma lactate between placebo and L-carnitine-L-tartrate. Exercise-induced changes in plasma hypoxanthine and uric acid were lower during L-carnitine-L-tartrate. Plasma xanthine oxidase concentrations did not vary during L-carnitine-L-tartrate but increased above pre-exercise values at 0, 15, and 180 min post-exercise during placebo. Plasma malondialdehyde peaked immediately after exercise during both L-carnitine-L-tartrate and placebo, returned to resting values by 15 min post-exercise during L-carnitine-L-tartrate, but

Reference and study design	Parameters measured	Results
	pain)].	remained elevated throughout 24 h of recovery during placebo. Muscle tissue disruption, as assessed by MRI and blood levels of cytosolic proteins, was decreased in the L-carnitine-L-tartrate group compared to placebo. Compared to placebo, muscle soreness was rated lower after L-carnitine-L-tartrate treatment on day 1 (mean soreness rating of 4.2 vs. 5.8), day 2 (4.9 vs. 5.5) and day 4 (1.0 vs. 1.8) after the squat exercise protocol, but not on day 3.
Wächter et al. (2002) Eight healthy moderately trained (VO_2max 53.1 ± 4.1 mL/kg bw/min) males (age 23–25 years) were supplemented with L-carnitine (4000 mg/day, as tablets) for 3 months. There was no control group. Exercise tests and muscle biopsies were performed before, immediately after, and 2 months after treatment. Exercise tests were performed using a bicycle ergometer for 10 min at 20%, 40%, and 60% of the maximal workload for each individual. Tests were continued with incremental increases in power output until exhaustion.	Blood lactate; free and total carnitine in plasma and muscle; renal excretion of free and total carnitine; muscle fibre composition; muscle mitochondrial enzyme activity (citrate synthase and cytochrome oxidase); exercise performance parameters (VO_2max, exercise heart rate, maximum respiratory exchange ratio, and maximum power output).	After 2 months of L-carnitine supplementation, plasma free and total carnitine were ~1.7-times and 2-times the baseline levels, respectively, with no additional increase at 3 months. Renal excretion of free and total carnitine peaked after 2 months (10-times and 6-times baseline values, respectively). L-carnitine supplementation did not affect blood lactate, muscle carnitine concentration, mitochondrial enzyme activity, muscle fibre composition, and exercise performance parameters.
Kraemer et al. (2003) Double-blind, crossover RCT in 10 healthy, recreationally weight-trained males, mean age 24 years. The same 10 subjects were used as in Volek et al. (2002). Subjects received either placebo or L-carnitine-L-tartrate as capsules (equivalent to 2000 mg/day L-carnitine) for 3 weeks. After 3 weeks, fasting morning blood samples were obtained on 6 consecutive days (D1–D6). On D2, subjects performed a squat protocol (5 sets of 15–20 repetitions), during which blood samples were obtained. After a 1-week washout, subjects crossed over to the other treatment for 3 weeks, and the same protocol was repeated.	Plasma growth hormone; serum testosterone, insulin like growth factor-1 (IGF-1), and insulin-like growth factor binding protein-3 (IGFBP-3). Blood was collected before exercise and at 15, 30, 120, and 180 minutes post-exercise.	There were no statistically significant differences between L-carnitine-L-tartrate and placebo for growth hormone, testosterone, and IGF-1 at any blood sampling time-point; and IGFBP-3 on D2 at pre-exercise, 15 min post-exercise, and on D3–D6. IGFBP-3 was higher for L-carnitine-L-tartrate on D1 (by ~6%), on D2 before the squat protocol (by ~10%), and on D2 at 30, 120 and 180 min after the squat protocol (by 4–8%).
Broad et al. (2005) Double-blind, crossover RCT in 15 endurance-trained males, age 20–46 years. Subjects undertook cycling trials during two 4-week supplementation periods with placebo or 3000 mg/day L-carnitine-L-	Carbohydrate and fat oxidation; 20 km cycling time trial performance.	L-carnitine-L-tartrate had no effect on carbohydrate or fat oxidation. After 4 weeks on placebo, there was a 5% mean reduction in time to complete the 20 km time trial. L-carnitine-L-tartrate did not affect time trial

Reference and study design	Parameters measured	Results
tartrate as capsules (equivalent to 2000 mg/day L-carnitine). Washout periods for each subject ranged from 2 to 6 weeks.		performance.
Kraemer et al. (2006) Double-blind, crossover RCT in 10 healthy, recreationally weight-trained males, mean age 22 years. Subjects received either placebo or 2944 mg/day L-carnitine-L-tartrate as capsules (equivalent to 2000 mg/day carnitine), divided into 2 doses (with breakfast and lunch) for 3 weeks and then thigh muscle biopsies were taken for androgen receptor analysis. Subjects then performed two identical whole-body resistance exercises: one followed by water intake, and one followed by feeding (8 kcal/kg body mass, consisting of 56% carbohydrate, 16% protein, and 28% fat). After a 1-week washout, subjects crossed over to the opposite treatment, and all experimental procedures were repeated.	Muscle: androgen receptor concentration. Plasma: lactate, glucose. Serum: follicle stimulating hormone (FSH); luteinizing hormone (LH); sex-hormone binding globulin (SHBG); adrenocorticotrophic hormone (ACTH); total testosterone; cortisol; free androgen index (FAI = total testosterone/SHBG); total carnitine.	There were no statistically significant differences between L-carnitine-L-tartrate and placebo for muscle androgen receptor concentration; lactate; glucose; FSH, testosterone AUC[11] (feeding trial), and FAI AUC (water trial). The following were higher for L-carnitine-L-tartrate compared to placebo: testosterone AUC (water trial, by 8%); LH AUC (feeding trial, by 13%); SHBG AUC (water trial, by 18%; feeding trial, by 24%); ACTH AUC (water trial, by 19%); cortisol AUC (water trial, by 17%). The following were lower for L-carnitine-L-tartrate compared to placebo: LH (water trial, by 5%); FAI AUC (feeding trial, by 14%); ACTH AUC (feeding, by 20%); cortisol AUC (feeding, by 15%). Serum total carnitine concentrations during placebo and L-carnitine-L-tartrate treatments were 60–66 µM and 96–125 µM, respectively.
Spiering et al. (2007) Crossover RCT in 8 healthy weight-trained males (mean age 22 years). It was not stated whether the study was blinded. Subjects received either 0, 1000 or 2000 mg/day L-carnitine-L-tartrate as capsules for 21 days, followed by a 21 day washout period before crossing over to another treatment. Resistance exercise tests were conducted after each 21 day period.	Perceived muscle soreness after a squat exercise protocol [visual analogue scale ranging from 0 (no pain) to 10 (extreme pain)]; post-exercise serum hypoxanthine, xanthine oxidase, and myoglobin (as markers of metabolic stress); hand-grip strength; serum carnitine; plasma lactate, glucose, and insulin like growth factor binding protein 3 (IGF-BP3).	Compared to placebo, supplementation with 1000 mg/day reduced mean perceived muscle soreness scores at 24 hours (3.2 vs. 6.2) and 72 hours (2.8 vs. 4.5), but not at 48 hours after exercise. Compared to placebo, supplementation with 2000 mg/day reduced perceived muscle soreness at all three timepoints after exercise [24 hours (4.5 vs. 6.2), 48 hours (4.3 vs. 6.2) and 72 hours (3.1 vs. 4.5). Compared to 1000 mg/day, supplementation with 2000 mg/day reduced perceived muscle soreness at 48 hours (4.3 vs. 5.2) after exercise but not at 24 and 72 hours.

[11] AUC: Area under the concentration-time curve.

Reference and study design	Parameters measured	Results
		Compared to placebo, both dose levels similarly decreased serum hypoxanthine, xanthine oxidase and myoglobin concentrations. L-carnitine-L-tartrate treatment did not affect hand-grip strength.
Broad et al. (2008) Double-blind, parallel RCT. Twenty non-vegetarian males (actively engaged in endurance training) were pair-matched and randomly assigned to receive 2000 mg of L-carnitine-L-tartrate (as capsules) or placebo per day for 2 weeks. Participants exercised for 90 min at 70% VO_2max after 2 days of a prescribed diet (energy 13.6 ± 1.6 MJ, 57% carbohydrate, 15% protein, 26% fat, 2% alcohol) before and after supplementation.	Carbohydrate oxidation; nitrogen excretion; branched-chain amino acid oxidation; plasma urea; plasma ammonia.	Supplementation was associated with no change in carbohydrate oxidation, nitrogen excretion, branched-chain amino acid oxidation, or plasma urea during exercise. The plasma ammonia response to exercise was suppressed (baseline vs. 2 weeks: 116 ± 47 vs. 87 ± 25 µM), with no change in the placebo group.
Spiering et al. (2008) Double-blind, crossover RCT in 9 healthy resistance-trained males, age 25.2 ± 6 years. Subjects received either 3000 mg/day L-carnitine-L-tartrate (as capsules, equivalent to 2000 mg/day L-carnitine) or placebo for 23 days.	Forearm muscle tissue oxygenation during and after resistance exercise (using near infrared spectroscopy); plasma malondialdehyde (as a marker of cell membrane damage); plasma prostacyclin (vasodilation marker).	Compared to placebo, L-carnitine-L-tartrate supplementation resulted in lower muscle tissue oxygenation during and after resistance exercise, lower plasma malondialdehyde, and had no effect on plasma prostacyclin.
Broad et al. (2011) Double-blind, parallel RCT in 15 endurance-trained males. Subjects undertook exercise trials after a 2-day high-carbohydrate diet (60% CHO, 25% fat) at baseline, on day 14, and after a single day of high fat intake (15% CHO, 70% fat) on day 15. Treatment consisted of 3000 mg L-carnitine-L-tartrate (2000 mg L-carnitine/day; n = 8) or placebo (n = 7) for 15 days. Exercise trials consisted of 80 min of continuous cycling comprising 20-min periods at each of 20%, 40%, 60%, and 80% VO_2max.	Whole-body rates of carbohydrate and fat oxidation; blood glucose; heart rate.	There were no significant differences between whole-body rates of carbohydrate and fat oxidation at any workload. Blood glucose and heart rate were lower during exercise in the L-carnitine group compared to placebo.
Wall et al. (2011) Double-blind, parallel RCT in 14 healthy non-vegetarian male recreational triathletes for 24 weeks. Placebo control group (n = 7, mean age 25 years) received daily 2 x 80 g carbohydrate, and L-carnitine-L-tartrate group (n = 7, mean age 27 years) received 2 x 80 g carbohydrate and 2 x 2000 mg L-carnitine-L-tartrate (equivalent to 2720 mg/day L-carnitine). The carbohydrate was a	Skeletal muscle: glycogen, lactate, phosphocreatine (PCr), PCr/ATP ratio, pyruvate dehydrogenase activation (PDCa), citrate synthase activity, free carnitine, acetylcarnitine, acyl-carnitine, total carnitine. Perceived exertion during exercise at 50% and 80% VO_2max, self-rated every 10 min	There were no statistically significant differences between L-carnitine-L-tartrate and placebo for: all carnitine forms in muscle (after 12 weeks); acetylcarnitine and acylcarnitine in muscle (after 24 weeks); PCr; PCr/ATP ratio in muscle) (after 12 weeks); muscle glycogen (after 12 weeks, and after 24 weeks before exercise); muscle lactate (after 12 weeks); muscle PDCa (after 12 weeks); muscle

Reference and study design	Parameters measured	Results
glucose polymer mixture (Vitargo® https://www.vitargo.com/faqs/). Before commencement of dosing and at 12 and 24 weeks, volunteers exercised for 30 min on a cycle ergometer at a workload corresponding to 50% VO_2max, followed immediately by 30 min at 80% of VO_2max, then 30 min at maximal effort.	(Borg scale). Work output during maximal exercise at weeks 12 and 24.	citrate synthase; perceived exertion during exercise at 50% VO_2max (all occasions) and 80% VO_2max (before and after 12 weeks of supplementation); work output during maximal exercise at week 12. The following were higher for L-carnitine-L-tartrate compared to placebo: skeletal muscle total carnitine after 24 weeks (by 30%), free carnitine after 24 weeks and 50% VO_2max exercise (by 78%), glycogen after 24 weeks and 50% VO_2max exercise (by 35%) and 80% VO_2max exercise (by 70%), PCr/ATP ratio after 24 weeks and 80% VO_2max exercise (by 54%); and work output during maximal exercise at week 24 (by ~25%). The following were lower for L-carnitine-L-tartrate compared to placebo: skeletal muscle lactate after 24 weeks (by 44%); perceived exertion at 24 weeks (by 14%).
Stephens et al. (2013) This paper reports additional data from the study described by Wall et al. (2011) summarised above. The only data common to the two papers are total carnitine concentrations in resting muscle. The authors stated that due to tissue availability for analyses, only 12 of the original 14 subjects were included in the analyses reported in this paper.	Body composition; carbohydrate and fat oxidation during exercise; and the following determined in skeletal muscle: free-, acyl- and total carnitine; long-chain acyl-coenzyme A (CoA); carnitine palmitoyltransferase 1 (CPT1)[12] activity; and expression of fuel metabolism genes.	There were no statistically significant differences between L-carnitine-L-tartrate and placebo for lean body mass; carbohydrate and fat oxidation during exercise; and CPT1 activity. The following were higher for L-carnitine-L-tartrate compared to placebo: energy expenditure during exercise (by 6%); skeletal muscle total carnitine (by 21%) and long-chain acyl-CoA (by ~4-fold); gene expression in skeletal muscle (the largest increases were observed for genes involved in insulin signalling, fatty acid metabolism, and PPARs[13] signalling).
Burrus et al. (2018) Double-blind, randomised, crossover study in 10 healthy moderately-trained males (age 27 ± 4 years). L-carnitine was administered as a	Respiratory exchange ratio (RER); blood lactate; power output; and time to exhaustion.	RER was lower at baseline with L-carnitine ingestion (0.83 ± 0.05) compared to the placebo ingestion (0.86 ± 0.06). Blood lactate was significantly lower (p

[12] CPT1, a key enzyme in fuel metabolism (Zammit 2008).
[13] PPARs: Peroxisome Proliferator-Activated Receptors – nuclear receptor proteins that play essential roles in gene expression (Rotman and Wahli 2010).

Reference and study design	Parameters measured	Results
single dose of 3000 mg (as capsules). Washout periods were stated to be at least 3 days. Subjects cycled for 40 minutes at moderate intensity (65% of VO_2max) then continued at high intensity (85% of VO_2max) until exhausted. L-carnitine or a placebo was consumed 3 hours prior to exercise, and beverages consisting of 94 g of carbohydrate were consumed at both 2 hours, and 30 minutes prior to exercise.		= 0.02) after 10 minutes of cycling at 65% of VO_2max with ingestion of L-carnitine (35% increase from baseline) compared to placebo ingestion (53% increase from baseline). No differences were found for power output or time to exhaustion at 85% of VO_2peak.