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# Creatine supplementation and VO<sub>2</sub>max: a systematic review and meta-analysis

Damien Gras

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UNIVERSITÉ CLERMONT AUVERGNE  
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES  
THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

**GRAS Damien**

Présentée et soutenue publiquement le 29 avril 2021

**Supplémentation en créatine et VO<sub>2</sub>max :  
Revue systématique et méta-analyse**

**Président du jury :** Monsieur COUDEYRE Emmanuel, Professeur, CHU Clermont-Ferrand, Médecine Physique et Réadaptation

**Directeur de thèse :** Monsieur DUTHEIL Frédéric, Professeur, CHU Clermont-Ferrand, Santé Travail Environnement

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**A notre Président de thèse :**

**Monsieur le Professeur Emmanuel COUDEYRE,**

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## Liste des abréviations

**CI95%:** 95% confidence interval

**Cr:** Cr

**CrP:** Cr Phosphate

**CS:** CS

**ES:** Effect Size

**SD:** Standard Deviation

**SEM:** Standard Error of the Mean

**VO<sub>2</sub>max:** Maximal Oxygen Consumption

# 1. Introduction

---

La créatine est un composé organique azoté présent principalement dans les muscles et le système nerveux dont les stocks cellulaires sont entretenus par une alimentation carnée et par la synthèse endogène à partir d'acides aminés tels que la glycine, l'arginine et la méthionine [1]. La créatine est l'un des compléments alimentaires sportifs les plus populaires sur le marché et largement utilisé chez les athlètes professionnels et de loisir avec plus de 400 millions de dollars de ventes annuelles [2]. La popularité de la supplémentation en créatine peut s'expliquer par un marketing intensif sur ses effets bénéfiques dans le sport. Il est bien connu que la supplémentation en créatine améliore la performance lors d'exercices courts à haute intensité tels que les sprints [3] et la force musculaire [4,5] et aurait un intérêt en usage thérapeutique pour promouvoir la santé dans des domaines variés qui sont résumés dans une récente revue de la littérature [6]. Malgré cela, la littérature scientifique actuelle diverge sur les conséquences d'une supplémentation en créatine sur la performance en endurance [7,8]. Le gold-standard pour évaluer les capacités en endurance est la  $VO_{2max}$  [9]. Celle-ci est définie comme la consommation d'oxygène atteinte à l'intensité maximale de l'exercice ne pouvant être dépassée malgré de nouvelles augmentations de la charge de travail [10]. La  $VO_2$  est le flux d'oxygène capté par les poumons, transporté dans la circulation sanguine couplé à l'hémoglobine et utilisé pour l'oxydation des substrats énergétiques (glucose et acides gras) dans la chaîne respiratoire des mitochondries aboutissant à la resynthèse de l'ATP [11]. Il a été démontré que la  $VO_{2max}$  est un indice valide mesurant les limites du système cardiorespiratoire [12] et l'un des principaux résultats permettant d'évaluer la capacité cardiorespiratoire et de prédire la performance d'un athlète dans les sports d'endurance [13,14]. De plus, l'évaluation de la  $VO_{2max}$  par un test d'effort incrémental semble être l'une des mesures de performance la plus reproductible indépendamment des protocoles utilisés [15]. Certaines études se sont intéressées à évaluer l'effet de la supplémentation en créatine sur la  $VO_{2max}$  [16,17]. L'apport d'énergie



sous la forme d'ATP à partir de la liaison phosphate riche en énergie de la phosphocréatine se produit pendant les premières secondes d'un effort intense en anaérobie en raison des réserves limitées de phosphocréatine nécessitant une période de récupération de plusieurs minutes avant sa régénération [18]. L'intérêt de la créatine dans des efforts prolongés pourrait être dû à plusieurs mécanismes moins connus tels qu'une facilitation du transport de l'ATP des mitochondries vers le cytosol où l'ATP est consommée pour la contraction musculaire [19], un rôle dans le stockage du glycogène par une augmentation des transporteurs du glucose GLUT4 [20,21] ainsi que des modifications du volume cellulaire par un effet osmotique de la créatine [22]. Outre son rôle dans la régulation et l'homéostasie du métabolisme énergétique, la supplémentation en créatine pourrait améliorer l'activation musculaire [23] et diminuer la consommation d'oxygène par l'organisme à une même intensité d'effort [24,25] pouvant être bénéfique pour la performance en endurance. Outre son utilisation courante dans le sport, la supplémentation en créatine a également été testée chez les personnes âgées et dans certaines conditions pathologiques [26,27]. Malgré ces considérations, les effets de la supplémentation en créatine sur la performance aérobie restent incertains et, à ce jour, aucune méta-analyse n'a spécifiquement étudié son rôle sur la  $VO_2max$ .

Ainsi, notre objectif était de mener une revue systématique et une méta-analyse de tous les essais contrôlés randomisés comparant les effets de la supplémentation en créatine par rapport à un placebo sur la  $VO_2max$ . Nos objectifs secondaires étaient de déterminer l'influence des caractéristiques de la population, de la supplémentation et de l'entraînement associé sur la  $VO_2max$  ainsi que d'évaluer les effets de la supplémentation en créatine sur les mesures aérobies associées à  $VO_2max$  au cours des tests d'effort incrémentaux [28].

## 2. Article

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### 2.1 Title page

#### **Creatine supplementation and VO<sub>2</sub>max:**

#### **A systematic review and meta-analysis**

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**Running title:** CS and Aerobic Performance

## 2.2 Abstract

**Background:** Despite creatine is well-known to increase performance in acute high intensity exercises, its role in aerobic performance based on  $\text{VO}_2\text{max}$  is more controversial.

**Objectives:** To perform a systematic review and meta-analysis on the effects of creatine supplementation on  $\text{VO}_2\text{max}$ .

**Method:** PubMed, Cochrane, Embase and ScienceDirect were searched for randomized controlled trials (RCTs) reporting  $\text{VO}_2\text{max}$  in both a creatine supplementation and placebo group, after and before supplementation. We computed random-effects meta-analysis on  $\text{VO}_2\text{max}$  at baseline, within groups following supplementation, on changes in  $\text{VO}_2\text{max}$  between groups, as well after supplementation between groups. Sensitivity analyses were conducted after exclusion of studies outside funnel plots and on young and healthy individuals. Metaregressions were computed to search for influential factors of  $\text{VO}_2\text{max}$ .

**Results:** We included 19 RCTs for a total of 424 individuals (mean age 30 years old, 82% men).  $\text{VO}_2\text{max}$  did not differ at baseline between groups (creatine and placebo). Both groups had a training in most studies (80%). Using changes in  $\text{VO}_2\text{max}$ ,  $\text{VO}_2\text{max}$  increased in both groups but increased less after creatine than placebo (effect size -0.32, CI95% -0.51 to -0.12). Comparisons after supplementation confirmed a lower  $\text{VO}_2\text{max}$  in the creatine group compared to the placebo group (-0.20, -0.39 to -0.001). Meta-analysis after exclusion from meta-funnel gave similar results, as well as in a subgroup of young and healthy participants. Meta-regressions on characteristics of supplementation, physical training, or sociodemographic were not significant.

**Conclusion:** Creatine supplementation has negative effect on  $\text{VO}_2\text{max}$ , regardless of the characteristics of training, supplementation, or population characteristics.

**Keywords:** dietary supplement, endurance, cardiorespiratory fitness,  $\text{VO}_2\text{peak}$ , ventilatory threshold.

## 2.3 Introduction

Creatine (Cr) is one of the most popular sport dietary supplement on the market widely used among recreational and professional athletes, with more than \$400 million in annual sales [1]. The popularity of Cr supplementation (CS) can be explained by an intensive marketing about its ergogenic effects particularly in sport performance. It is largely admitted that CS improves performance in acute and high intensity exercises such as sprints [2] and muscle strength [3,4] and have health and potential therapeutic benefits [5]. Despite this, the current scientific literature diverges on its potential effects on endurance performance [6,7]. The gold standard to assess endurance capacities is  $VO_{2max}$  [8].  $VO_{2max}$  is defined as the oxygen uptake attained during maximal exercise intensity that could not be increased despite further increases in exercise workload [9].  $VO_2$  is the oxygen flow taken by the lungs, transported through the blood circulation coupled with hemoglobin, and used for the oxidation of energy substrates (glucose and fatty acids) in the respiratory chain of mitochondria resulting in ATP resynthesis [10]. It was demonstrated that  $VO_{2max}$  is a valid index measuring the limits of the cardiorespiratory system [11] and one of the main outcome that can predict performance in endurance sports [12,13]. Moreover, the assessment of  $VO_{2max}$  through an incremental exercise test seems to be one of the most reproducible measurement independently of protocols used [14]. Some studies had investigated the effect of CS on  $VO_{2max}$  [15,16]. The ATP energy supply by the energy-rich phosphate bond of phosphocreatine (CrP) occurs during the first seconds of an high intensity exercise in anaerobic condition due to the limited CrP stores requiring a recovery period of several minutes before its regeneration [17]. In prolonged efforts, Cr could interact with aerobic metabolism through several lesser known mechanisms with a Cr phosphate shuttle facilitating the ATP transport from the mitochondria to the cytosol within the cell needing ATP for muscle contraction [18] and a role in increasing glycogen storage with an increase in GLUT4 transporters [19,20] as well as changes in cell volume with osmotic effect of Cr [21]. In addition

to its role in the regulation and homeostasis of energy metabolism, CS could improve muscle activation [22] and VO<sub>2</sub> kinetics at same workloads [23,24] which may be beneficial for endurance performance. Besides its common use in sports, CS has also been tested in elderly and in certain pathological conditions [25,26]. Despite these considerations, the effects of CS on aerobic performance remain uncertain and, to date, no meta-analysis has specifically focused on its effects in changes in VO<sub>2</sub>max levels.

Thus, we aimed to conduct a systematic review and meta-analysis of all randomized controlled trials (RCTs) comparing the effects of CS versus placebo on VO<sub>2</sub>max. Secondary aims were to determine the influence of population characteristics, supplementation, and physical training associated on VO<sub>2</sub>max levels as also as to assess the effects of CS on aerobic measures associated with VO<sub>2</sub>max during incremental exercise tests [27].

## **2.4 Methods**

### **Literature search**

We search for all RCTs with CS versus placebo, with a measure of VO<sub>2</sub>max before and after supplementation. PubMed, The Cochrane Central Register of Controlled Trials (CENTRAL), Excerpta Medica Database (EMBASE), and ScienceDirect were searched until March 1<sup>st</sup> 2020 using the keywords “VO<sub>2</sub>max” AND “creatine supplementation” (see detailed search strategy in [S1 Appendix](#)). The search was not limited to specific years. No language restrictions were applied. Reference lists of all publications meeting the inclusion criteria were manually searched to identify any further studies not found through electronic searching. Two authors (DG and CL) conducted all literature searches, separately reviewed and collated the abstracts, and based on the selection criteria decided the suitability of the articles for inclusion. A third author (FD) was asked to review the article when consensus on suitability was not met. Then,

all authors reviewed the eligible articles ([Figure 1](#)). We followed the PRISMA guidelines ([S7 Appendix](#)).

## **Data collection**

The data collected included first author's name, publication year, study design, periods of studies, aims and outcomes of included articles, sample size, characteristics of individuals (age, gender, physical activity, health status), supplementation protocol (type of Cr, total time of supplementation, total dose), physical training during supplementation period, VO<sub>2</sub>max (values in each unit, and measurement method), and performance associated with the incremental test (ventilatory threshold, time to exhaustion, maximal power output).

## **Outcomes**

The main outcome for our meta-analysis was VO<sub>2</sub>max. Our secondary outcomes were ventilatory threshold, time to exhaustion and maximal power output from incremental exercise tests if measures were available.

## **Quality of assessment**

The Scottish Intercollegiate Guidelines Network (SIGN) checklist for RCTs was used to assess the quality of reporting ([Figure 2](#)) [28]. Through 11 items, the SIGN checklist evaluates internal validity and study quality. Additionally, the PEDro scale was assessed for each study ([S2 Appendix](#)) [29]. Methodological quality of articles was evaluated by two independent reviewers.

## Statistical considerations

Data were analysed using Stata (v16, Texas, USA). When not available, standard deviation (SD) were calculated by multiplying the Standard Error of the Mean (SEM) by the square root of the sample size [30], or estimated from interval quartiles or minimum and maximum intervals [31]. The main meta-analysis compared changes in VO<sub>2</sub>max between groups (CS versus placebo). Changes were calculated using the method from Borenstein et al. [32]. Results were expressed as effect size (ES) [33]. A decreased ES denoted a lower improvement in VO<sub>2</sub>max in the Cr group compared to the placebo group. A scale for ES has been suggested with -0.2 reflecting a small effect, -0.5 a moderate effect, and -0.8 a large effect [34]. In order to verify the strength of our results, we also computed random-effects meta-analysis on VO<sub>2</sub>max 1) at baseline between groups (CS versus placebo) to verify that groups were comparable, 2) within groups after supplementation, 3) as well after supplementation between groups. Each meta-analysis was stratified by type of exercise (running, cycling or rowing), and by units of measure (L/min or mL/kg/min). Finally, we also conducted meta-analyses on ventilatory threshold, maximal power output and time to exhaustion on the incremental exercise tests. For all aforementioned meta-analyses, sensitivity analyses were conducted after exclusion of studies outside funnel plots and on young and healthy individuals. Heterogeneity between studies was also evaluated using I<sup>2</sup> statistic, ranging from 0 (no heterogeneity) to 100% (high heterogeneity). Metaregressions were computed to search for putative influential factors of VO<sub>2</sub>max, such as characteristics of population (age, gender, training and health), characteristics of supplementation (loading dose, total duration of supplementation and total dose) and characteristics of training during supplementation (none, aerobic or HIIT). Results were expressed as regression coefficients and 95%CI. P values less than 0.05 were considered statistically significant.



## 2.5 Results

An initial search produced a possible 4985 articles. Removal of duplicates and use of the selection criteria reduced the number of articles reporting VO<sub>2</sub>max assessment at baseline and following CS or placebo to nineteen articles, among them one study reported two independent gender groups [35]. All articles were written in English (Figure 1).

### Quality of articles

Risk of bias in included studies was mostly low (Figure 2 and S2 Appendix). However, most studies did not describe the randomization method. Some studies matched subjects based on the baseline measurements. Two studies used a single-blind design [25,36], but all of the participants were blind about supplementation. Three studies declared to have more than twenty percent of dropped out [16,36,37]. All studies mentioned ethical approval.

### Study designs and aims of included articles

All studies were double blind randomized placebo-controlled trials. Only one study had a cross-over design [37]. All the studies were monocentric. Five studies were conducted in Europe (Germany [37], Netherlands [38,39], Poland [40] and Sweden [15]), one in Brazil [26,41], eight in North America (Canada [42] and USA [16,24,25,35,43,44,45]), and four in Australia [23,36,46,47]. The duration between baseline and measures after supplementation ranged from 4 [46] to 180 days [26]. The nineteen included studies aimed to evaluate the effect of CS on performance or quality of life in elderly and patients with heart failure [25,26,37,45], among which nine studies aimed specifically at assessing aerobic performance

[15,16,23,24,35,36,42,43,47]. If seventeen studies were on healthy individuals, two studies recruited patients with heart failure [26,37] (Table 1).

## Population

**Sample size** ranged from 10 [40] to 46 [39], for a total of 424 participants (216 in the CS group and 208 individuals in the placebo group).

**Gender** was reported in all studies. Mean proportion of males was 81.7%, with 160 males and 56 females in the CS group versus 155 males and 53 females in the placebo group. Eleven studies included only men [15,23,24,26,38,39,41,43,45,46], three only women [25,42,44].

**Age** was reported as mean values in all studies except for three studies that reported age in min-max interval [15,36,41]. Mean age was 29.7 years old, ranging from 20.5 [46] to 68 [25] years old. Most studies (79%) had participants aged between 18 and 40 years old.

**Physical activity at baseline** was reported in all studies. We classified individuals as competitive or highly trained athletes (15.6%) [15,40,41,47], recreationally trained (54.2%) [16,23,24,35,36,42,43,44,45,46], and sedentary or have low daily physical activity (30.2%) [25,26,37,38,39].

**Additional outcomes** were seldomly reported such as echocardiographic measures [23,37] or cellular changes using muscular biopsy [24,36,38,39,44] (Table 1).

### Aerobic outcomes: VO<sub>2</sub>max and other parameters

Measurements of maximal oxygen consumption were reported in VO<sub>2</sub>max [15,23,24,35,37,38,41,45] or VO<sub>2</sub>peak [16,25,26,36,39,40,42,43,44,46,47]. We chose to use VO<sub>2</sub>max as a generalization in this article. Nine studies measures VO<sub>2</sub> in L/min [16,23,24,38,39,42,43,46,47] and eleven in mL/min/kg [15,25,26,35,36,37,40,41,42,44,45] –

among them one study reported both L/min and mL/kg/min [42]. Most studies measured  $\text{VO}_2$  with gas exchange analysis during incremental exercise tests such as bicycle ergometer test [16,23,24,25,26,36,38,39,42,43,44,46], treadmill test [15,35,37,40,45] or rowing ergometer test [47]. The incremental tests were as close as possible to the training habitus of participants.  $\text{VO}_{2\text{max}}$  was also extrapolated from sub-maximal measures of  $\text{VO}_2$  in two studies [45,48] and estimated through a 12-minute Cooper test in one study [41]. Ten studies also assessed ventilatory threshold, using the V-slope method [49] in six studies [16,26,37,39,42,43] – i.e. the point where  $\text{VCO}_2$  production increases more than  $\text{VO}_2$  consumption –, the “Wasserman” method [50] in three studies [25,35,44] – i.e. the point where  $\text{VE}/\text{VO}_2$  increases without a concomitant increase in  $\text{VE}/\text{VCO}_2$  –, and without further information in one study [40]. Six studies reported time to exhaustion [23,35,43,44] or maximal power output [25,38,39] at the incremental tests (Table 1 and S3 Appendix).

## **Creatine supplementation**

Cr monohydrate was used in 74% of studies, Cr citrate in two studies [35,43], Cr malate in one study [40], and not reported in two studies [26,37]. A loading dose was used in twelve studies i.e. a dose  $\geq 20$  g/day or 0.3 g/kg which had shown the greatest effectiveness for increasing muscle total Cr content with minimal Cr losses through renal excretion [51], splitted in two [42], three [25,41,45] or four [16,23,35,36,37,38,44,47] intakes per day, during 4 to 7 days for all studies except one that used a loading dose for a prolonged period [37]. A maintenance dose ranging from 2 [23] to 10 g/day [23] was used in six studies, once daily except for one study [23]. Seven studies did not used a loading dose and supplemented only with a low dose of Cr [15,24,26,39,40,43,46]. In total, the CS was 285 g in average, ranging from 42 g [46] to 912 g [39], over a period of 42 days, ranging from four days [46] to six months [39] (Table 1).

## Training during supplementation

In all studies, all participants performed the same physical training and differed only by the supplementation (Cr or placebo). A standardized training program was proposed in six studies: high-intensity interval training (HIIT) [42,43], resistance [45], aerobic [36], or mixed training [39,41]. Nine studies maintained the usual physical activity of participants i.e. running [15], cycling [24] rowing [47], team sports [23], judo [40] or other recreational activities [16,35,44,46]. Four studies included sedentary participants without exercise intervention [25,26,37,38]. We classified exercise training as “aerobic” (68.9%), “anaerobic” (11.8%), and “none” (19.3%) ([Table 1](#)).

## Meta-analysis

There were no differences in any outcomes at baseline between group Cr and placebo groups ([S4 Appendix](#)). Using changes from baseline to after the supplementation,  $VO_{2max}$  increased less in the Cr group compared to the control group (ES = -0.30, CI95% -0.50 to -0.11,  $p=0.003$ ). Stratification showed a lower increase in the Cr group for  $VO_{2max}$  in L/min (-0.39, -0.67 to -0.12,  $p=0.005$ ), and for cycling (-0.33, -0.58 to -0.09,  $p=0.007$ ). Other aerobic outcomes (ventilatory threshold, time to exhaustion, maximal power output) did not differ between groups ([Figure 3](#)).

## Sensitivity analyses

Meta-analyses comparing  $VO_{2max}$  after supplementation between groups demonstrated similar results than meta-analyses on changes i.e. a significant lower  $VO_{2max}$  in the Cr compared with the placebo group (-0.2, -0.39 to -0.001,  $p=0.049$ ), as well as for  $VO_{2max}$  expressed in L/min (-0.32, -0.59 to -0.04,  $p=0.022$ ), and a tendency for cycling (-0.22, -0.46 to 0.02,  $p=0.074$ ) ([S4 Appendix](#)). We also computed meta-analyses on  $VO_{2max}$  changes within groups:  $VO_{2max}$

increased in the placebo group (0.35, 0.15 to 0.54,  $p=0.001$ ), with only a tendency within the the Cr group (0.18, -0.01 to 0.37,  $p=0.060$ ). Despite a very limited number of studies ( $n=3$ ) for this parameter, maximal power output increased in the Cr group (0.45, 0.03 to 0.88,  $p=0.038$ ). All aforementioned meta-analysis were repeated after exclusion of studies not evenly distributed around the base of the metafunnel, and demonstrated similar findings ([S5 Appendix](#)). Lastly, we also repeated all meta-analyses in the subgroup of young and healthy participants and results were similar i.e. a lower  $VO_2\text{max}$  increase in the creating compared to the placebo group using changes between groups (-0.26, -0.49 to -0.02,  $p=0.031$ ), a lower  $VO_2\text{max}$  after supplementation in the creating compared to the placebo group (-0.26, -0.49 to -0.02,  $p=0.031$ ), an increase in  $VO_2\text{max}$  within the placebo group (0.25, 0.02 to 0.48,  $p=0.035$ ) and not within the Cr group (0.10, -0.13 to 0.32,  $p=0.41$ ). Using changes between groups, ventilatory threshold increased in the Cr compared to the control group (0.66, 0.23 to 1.1,  $p=0.003$ ) ([Figure 3 and S6 Appendix](#)).

## Metaregressions

The meta-regressions failed to show any influencing variables on the  $VO_2\text{max}$  i.e. the putative influence of individuals, supplementation, or training characteristics. The limited number of patients with heart failure precluded analyses on the influence of health status on  $VO_2\text{max}$  ([Figure 4](#)).

## 2.6 Discussion

The main findings were that CS is detrimental to  $VO_2\text{max}$ , especially for cycling. If CS was also not beneficial on the maximal aerobic parameters associated with  $VO_2\text{max}$ , ventilatory threshold seemed to be improved. Results were independent of sociodemographic or supplementation characteristics.

## **Creatine and VO<sub>2</sub>max**

Cr is well-known for ergogenic effects in acute high intensity exercises. However, current results of our meta-analysis led to adverse effects of CS on endurance capacity assessed with VO<sub>2</sub>max which increased in the placebo group but not in the Cr group. VO<sub>2</sub>max limiting factors are shared between central factors for ~70% and peripheral factors for ~30% [52]. Thus, O<sub>2</sub> delivery and particularly maximal cardiac output are known as primary limiting factors for VO<sub>2</sub>max in exercising humans [10]. Cr is known to induce water retention in tissues increasing their Cr content after supplementation such as skeletal muscle [53] and potentially cardiomyocytes [54]. However, knowledge of the effects of cardiomyocytes swelling on contractile function and consequences on blood flow during exercise are lacking and still questionable. Several methods exist to determine maximal cardiac output during exercise [55] but none of them was applied among included studies. Echocardiography found no change in ejection fraction and left ventricular diameters after CS at rest [23,37] and during maximal exercise [56]. In addition to the cardiac function, O<sub>2</sub> delivery to working muscles also depends on arterial oxygen content. Thus, hemoglobin and hematocrit levels are not modified at rest following CS [7,24,57]. However, it was observed that CS can alter plasma volume during exercise [24] but negative consequences on muscles oxygen supply and VO<sub>2</sub>max levels were not demonstrated. Changes in oxygen saturation during exercise after CS was not reported among studies. Finally, the Cr effect on central limiting factors of VO<sub>2</sub>max does not appear to be essential. This can be explained by the fact that CS rather acts at the peripheral muscle level and as Cr is well-known to improve anaerobic performances through the hypertrophy and the higher recruitment in fast-twitch muscle fibers [53], changes in skeletal muscle energy metabolism could have explain our negative findings on VO<sub>2</sub>max. This hypothesis is supported by the lack of improvement in muscle oxidative capacity following CS [38,58]. Some studies reported improvement in muscular glycogen content following CS when associated with

carbohydrates intake and physical training but this effect on energy storage can help to maintain prolonged effort but not affect  $\text{VO}_2\text{max}$  level. CS has negative effect on  $\text{VO}_2\text{max}$  which should be considered for its application in cardiovascular disease involving a decrease in  $\text{VO}_2\text{max}$ , in elderly patients despite potential effects to prevent sarcopenia or bone loss [5], and in endurance athletes for which  $\text{VO}_2\text{max}$  is a determining factor of performance more than the ability to achieve a longer distance at submaximal intensity. At this intensity, the increase in the ventilatory threshold found in young subjects could be an asset for performance.

### **Creatine and secondary outcomes (time to exhaustion, maximal power output and ventilatory threshold)**

The ventilatory threshold refers to the point during exercise at which ventilation starts to increase at a faster rate than  $\text{VO}_2$  related to onset lactate accumulation [50]. The ventilatory threshold occurs at a higher percentage of  $\text{VO}_2\text{max}$  in well-trained endurance athletes [59] and can predict endurance performance as well as in sedentary or recreationally trained [60] and endurance athletes [61]. The increase in the ventilatory threshold found after CS in young and healthy is in accordance with greater exercise efficiency at submaximal workloads resulting in a decrease of  $\text{O}_2$  consumption [16,23,24] relative to a reduction in the work performed by the cardiovascular system at these intensities [16]. Hypothesis are that CrP hydrolysis consumes hydrogen ions and might contribute to the buffering of intracellular acidosis when ATP resynthesis occurs from CrP stores [62]. Moreover, an increase in muscle CrP levels due to CS could delayed the decrease in the ATP/ADP ratio needed to stimulate mitochondrial respiration and  $\text{VO}_2$  [49]. Also, an increase in mechanical efficiency could also participate [16,22]. Improvement in ventilatory threshold is given for young subjects and why this result was not observed in the elderly population even without patients with heart failure remains unclear.

No statistical change occurred in maximal power output and exercise time to exhaustion following CS. While CS increased peak power during sprints [38], no improvement in maximal aerobic power was found among limited number of studies [25,38,39]. As maximal power output for cycling, we could not conduct analysis on maximal aerobic speed or velocity at  $\text{VO}_2\text{max}$  ( $v\text{VO}_2\text{max}$ ) because this measurement was not provided by studies [63]. Here, we used time to exhaustion which refers to the time measured from the start of the incremental treadmill test until  $\text{VO}_2\text{max}$  was reached with the same protocol at baseline and T1 within studies. A higher time to exhaustion means a better performance on the aerobic test. This measurement has a certain limitation because it depends even more on the protocol of the incremental test. Besides these considerations and the greater number of studies reporting time to exhaustion than maximal power output we found no significant change in this parameter after CS compared to placebo. As describe above, the lack of improvement in muscle oxidative capacity after CS could explain these results on maximal aerobic power and time to exhaustion which mainly depends on the work of oxidative muscle fibers [63]. Finally, CS seems to not increase maximal aerobic performances more than training alone.

### **Supplementation protocols and characteristics of individuals**

Monohydrate form of Cr was mostly used without influence on  $\text{VO}_2\text{max}$  of one or other forms of Cr. Whey proteins added to Cr seems to have no additional benefits on  $\text{VO}_2\text{max}$  in older adults [45]. A Cr loading dose is admitted at a dosage about 0.3 g/kg/day which had shown the greatest effectiveness to increase muscle total Cr content with minimal Cr losses through renal excretion [51]. A meta-analysis not presented in this paper found less changes in  $\text{VO}_2\text{max}$  levels immediately after Cr loading compared to placebo. A maintenance dose of 0.06 g/kg is necessary to raise plasma Cr concentration required for the uptake of Cr by skeletal muscle [47]. Among studies included, only three employed lower daily Cr doses [24,38,41] but



muscular biopsies for two of them also found significant increase in total muscle Cr content. Conversely, two studies with higher Cr doses [36,44] did not find significant increase in muscle Cr content. These results could be explained by different responder profiles. Indeed, better responder profiles have lower initial Cr muscle levels [64] and/or higher proportion of fast-twitch muscle fibers [53]. The limited number of muscular biopsies in studies did not allow to assess changes in aerobic performance based on the response profile. Heterogeneity was also found in the supplementation duration which varied from 4 days to 6 months but did not appear to be a determining factor for  $VO_2$ max changes.

CS has been most extensively studied in young and trained males. Few studies had reported sex-based differences for strength gains with greater improvement in men [64,65]. Reasons are lower proportion of lean mass, higher baseline Cr muscle content [65] and lower training adaptations in women [66]. Only one study assessed changes in  $VO_2$ max levels with gender comparisons and did not find difference in response to CS on this outcome and time to exhaustion [35].

In an elderly population, despite improvement in muscle strength [67] and in ability to perform functional living tasks, CS did not improve endurance capacity even when combined with resistance or aerobic training [25,39,45].

Patients with heart failure appeared to increase muscle strength as much as healthy [37,56] but not  $VO_2$ max and functional capacity such as walking distance [26,37] or quality of life [37]. Furthermore, no major change in ejection fraction at rest or during exercise occurs [37,56].

CS increases more muscle mass and muscle strength when combined with resistance training by acting both rather on fast-twitch muscle fibers [68]. Endurance performance depends more of the proportion and the oxidative capacity of low-twitch muscle fibers [53] that could explain the less evident results of CS on aerobic measurements. While HIIT partly involves anaerobic capacities and shows interesting results on  $VO_2$ max [69], no influence of this type of training was found on  $VO_2$ max when associated with CS. CS limited more  $VO_2$ max on cycling than running or rowing that could be explained by the greatest number of subjects performing cycling.

It is known that CS causes body mass gain [70] but the adverse effect of Cr on VO<sub>2</sub>max does not appear to be explain with changes in body mass in a meta-analysis we have not presented here. Also, only three studies reported body mass index without significant increase after CS [38,40,47]. Furthermore, if body mass gain had influenced VO<sub>2</sub>max levels, its measurements in mL/kg/min should have been lower than the measurements in L/min which was not observed.

## **Limitations**

This is the first meta-analysis that has focused on the effect of CS on VO<sub>2</sub>max levels. Many studies did not report all the results to be include in the meta-analysis. For instance, studies reported baseline measurement without measurement after supplementation for VO<sub>2</sub>max or without its change expression [16,71] or did not expressed dispersion of its measurement [72]. Our study has some limitations inherited of all meta-analyses [73] but the use of rigorous inclusion criteria i.e. double blind randomized controlled trials limited the publication bias. A bias of reporting due to the scarcity of publications with negative findings is common to all systematic review and meta-analyses but could reinforce our main findings. A publication bias was also assessed according to funnel plots and sensitivity analyses gave similar results on the main outcome. Not all studies employed measurements of VO<sub>2</sub> with gas exchange analysis during incremental exercise tests which could have led to a measurement bias. In fact, the rigorous determination of VO<sub>2</sub>max depends on the met of different criterion (plateau in oxygen consumption, respiratory exchange ratio > 1,1, heart rate greater than age-predicted maximal heart rate, blood lactates > 6-8 mmol or physical exhaustion [74]). In our meta-analysis, VO<sub>2</sub>max was report through rigorous determination by three studies [23,24,35]. Four studies [16,25,42,43]assessed VO<sub>2</sub>peak as the highest average VO<sub>2</sub> obtained for any period of time between 15-second [43] and 1-minute [25] without specifying if a VO<sub>2</sub>plateau was obtained. Ten studies did not provide additional information for the determination of the maximum

oxygen uptake and mentioned  $\text{VO}_2\text{max}$  [15,38] or  $\text{VO}_2\text{peak}$  [26,36,37,39,40,44,46,47] without precision and two studies had estimated  $\text{VO}_2\text{max}$  [41,45]. The fact that most studies assessed  $\text{VO}_2\text{peak}$  instead of  $\text{VO}_2\text{max}$  can question the maximality of the incremental tests and the measures reproducibility at baseline and following supplementation within these studies [27]. To assess the impact of training associated with the CS, we used a clearly imperfect classification of the type of training performed during the supplementation and the physical level of participants. Unfortunately, this last classification was not possible mainly because of the variations of  $\text{VO}_2\text{max}$  with gender.

Most of the performance variables included in this meta-analysis were measured in a laboratory setting and field-based endurance performance must be assessed.

## **2.7 Conclusion**

Creatine supplementation has negative effect on  $\text{VO}_2\text{max}$ , regardless of the supplementation protocols, physical training and population characteristics. Considering that creatine is the most widely used dietary supplement in sport, a particular attention towards its used should be paid for endurance athletes.

## **2.8 Supporting information**

**S1 Appendix. Details for the search strategy used within each database**

**S2 Appendix. PEDro scale**

**S3 Appendix. Meta-analyses of aerobic measures at baseline and at T1 between groups, and between T0 and T1 within groups for all studies**

**S4 Appendix. Meta-analyses of aerobic measures at baseline and at T1 between groups, and between T0 and T1 within groups after exclusions from meta-funnels.**

**S5 Appendix. Meta-analyses of aerobic measures at baseline and at T1 between groups, and between T0 and T1 within groups in young and healthy.**

**S6 Appendix. PRISMA Checklist**

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### **Competing Interests**

No conflicting relationship exists for any author.

### **Author contributions**

Conceived and designed the study: FD. Conducted the systematic literature search: DG, CL. Final approval of eligible articles: all authors. Analyzed the data: DG, FD. Wrote the first draft of the article: DG, FD. Critical revision of the article: all authors. Integrity of the data analysis: DG, FD.

### **Data availability statement**

All relevant data are within the paper.

## 2.9 References

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## **2.10 Figures and tables**

**Fig 1. Search strategy**

**Fig 2. Quality of articles – SIGN checklist**

**Fig 3. Meta-analysis of aerobic changes after supplementation period between groups**

**Fig 4. Meta-regressions for the main outcome (VO<sub>2</sub>max)**

**Fig 5. Funnel plots of aerobic changes after supplementation period between groups**

**Table 1. Characteristics of included studies.**

Figure 1. Search strategy

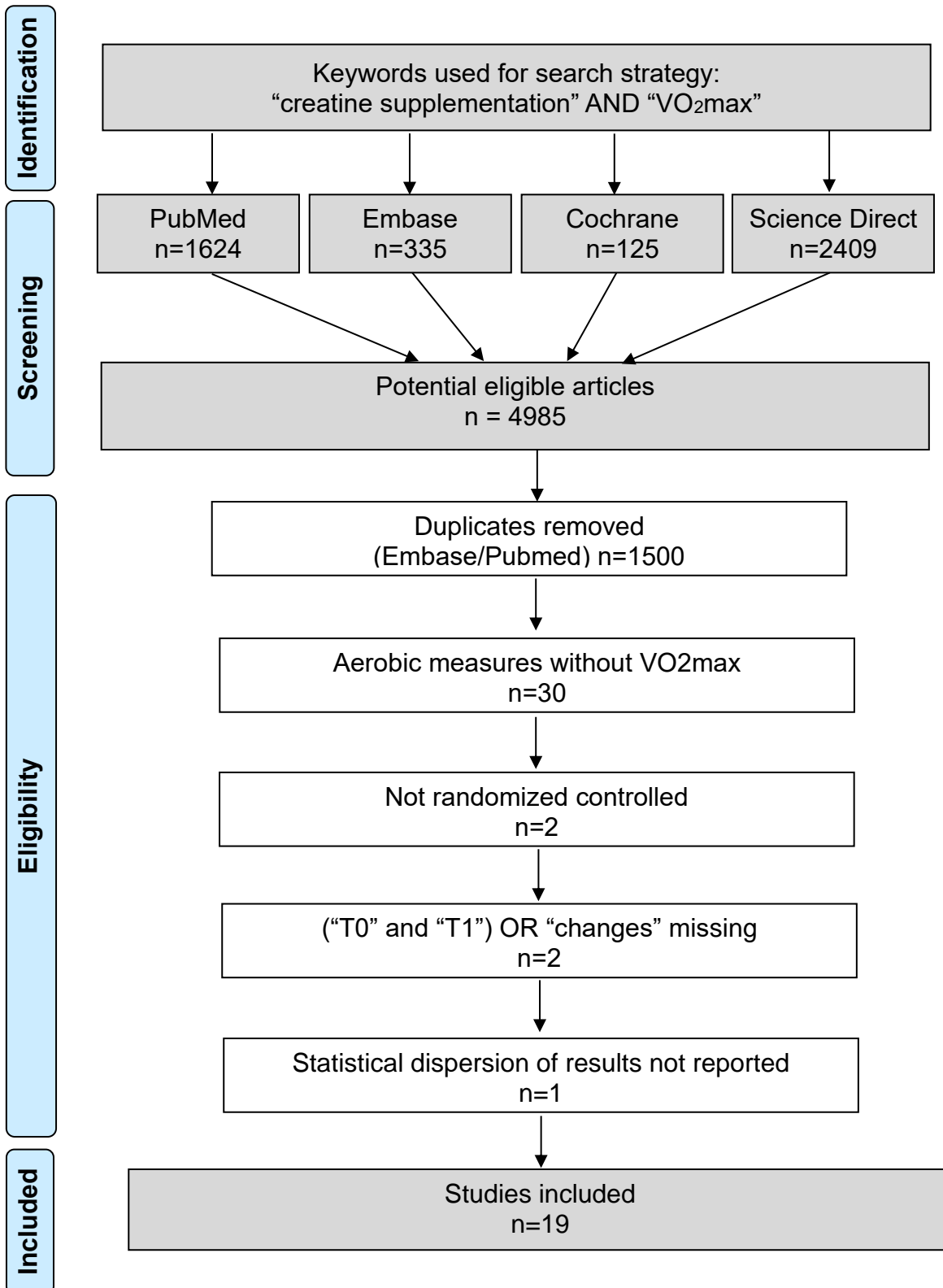
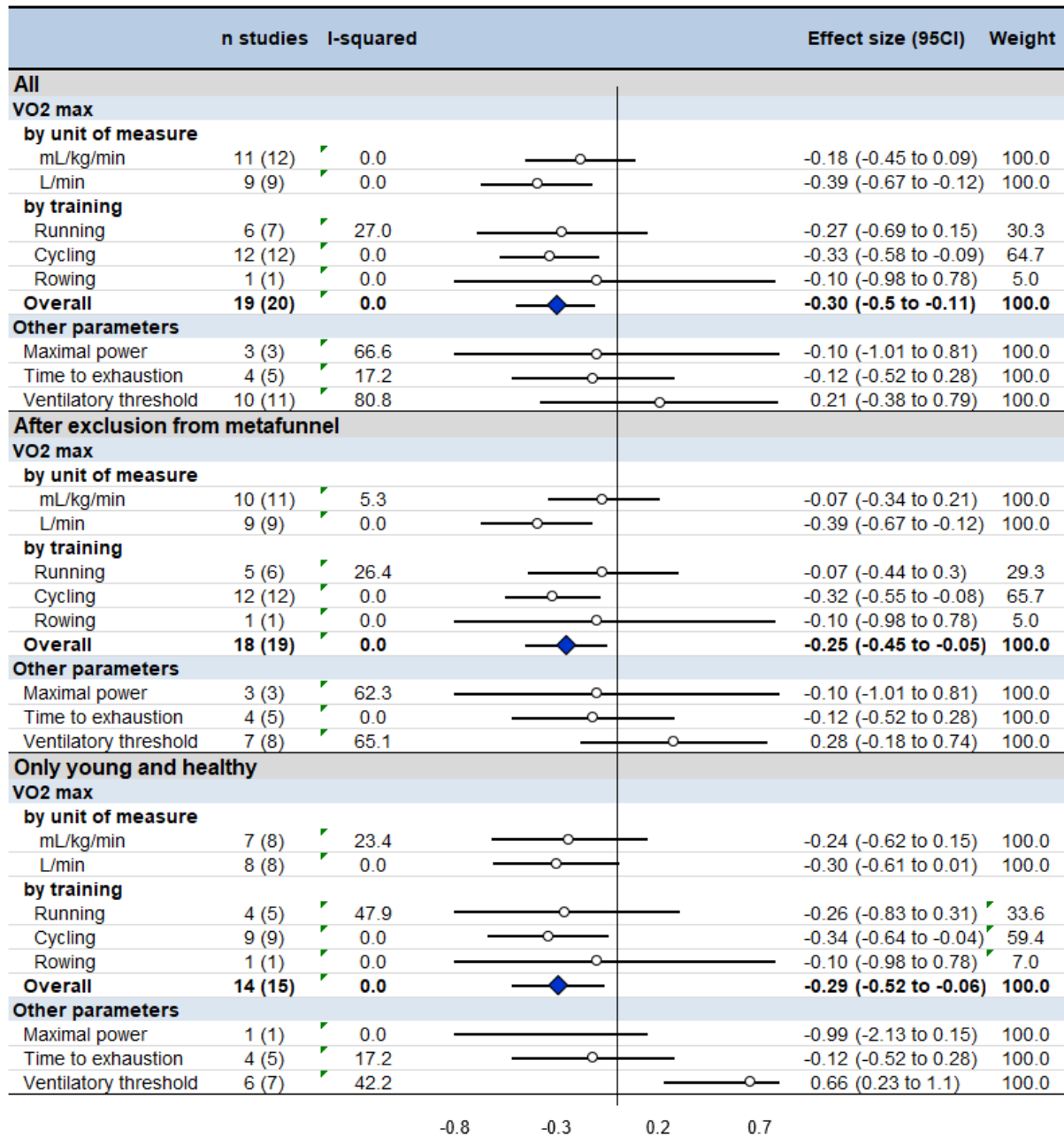


Figure 2. Quality of articles – SIGN checklist

	Internal validity							Quality			
	Appropriate and clearly focused question	Assignment of subjects is randomised	Adequate concealment method is used	Subjects and investigators blind about treatment	Treatment and control groups are similar	Only difference between group is treatment	Outcomes measured in a standard and valid way	Number of dropped outs (%)	Analyses in randomly allocated groups	Results are comparable for all sites	General level of evidence
Balsom 1993	+	+	+	+	+	+	+	0	+	NA	++
Barnett 1996	+	?	?	+	+	+	+	0	+	NA	++
Canete 2006	+	?	+	-	+	+	+	0	+	NA	++
Carvalho 2012	+	?	+	+	+	+	+	0	+	NA	++
Da Silveira 2014	+	?	?	+	+	+	-	8	+	NA	+
Eijnde 2003	+	?	+	+	+	+	+	0	+	NA	++
Forbes 2017	+	+	+	+	+	+	+	6	+	NA	++
Graef 2009	+	?	?	+	+	+	+	0	+	NA	++
Hickner 2010	+	?	?	+	+	+	+	0	+	NA	++
Kresta 2014	+	?	?	+	+	+	+	9	+	NA	++
Kueth 2006	+	?	?	+	+	+	+	35	+	NA	+
Lawrence 1996	+	?	?	+	+	+	+	0	+	NA	++
Murphy 2005	+	?	?	+	+	+	+	0	+	NA	++
Nelson 2000	+	?	?	+	+	+	+	28	+	NA	+
Reardon 2006	+	?	?	-	+	+	+	23	+	NA	+
Smith 2011	+	?	?	+	+	+	+	0	+	NA	++
Sterkowicz 2012	+	?	?	+	-	+	+	0	+	NA	+
Van Loon 2003	+	+	+	+	+	+	+	5	+	NA	++
Villanueva 2014	+	?	?	+	+	+	-	0	+	NA	+

**Figure 3. Meta-analyses of changes between groups**



**Figure 3. Meta-analysis of changes between groups for all studies and sensitivity analyses: VO<sub>2</sub>max (stratified by unit of measure and by type of training), maximal aerobic performances (time to exhaustion and maximal power output) and ventilatory threshold. Cr group as reference.**

**Figure 4. Meta-regressions**

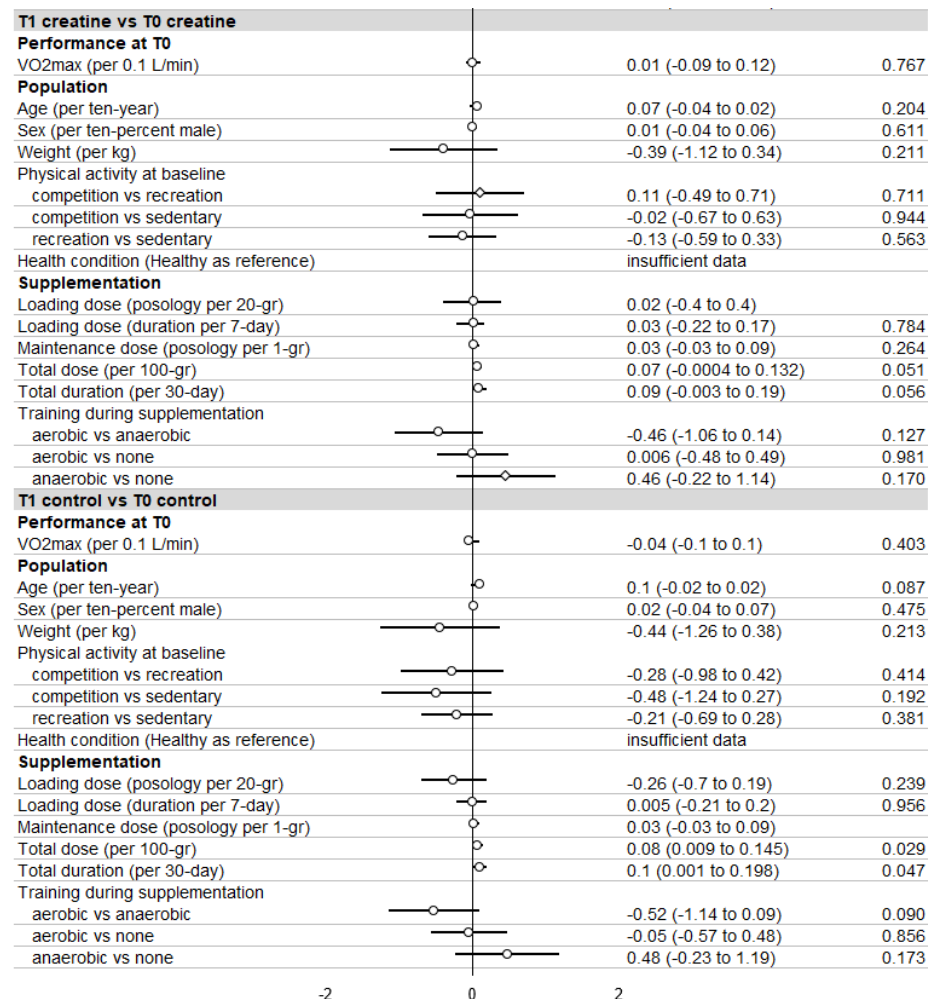
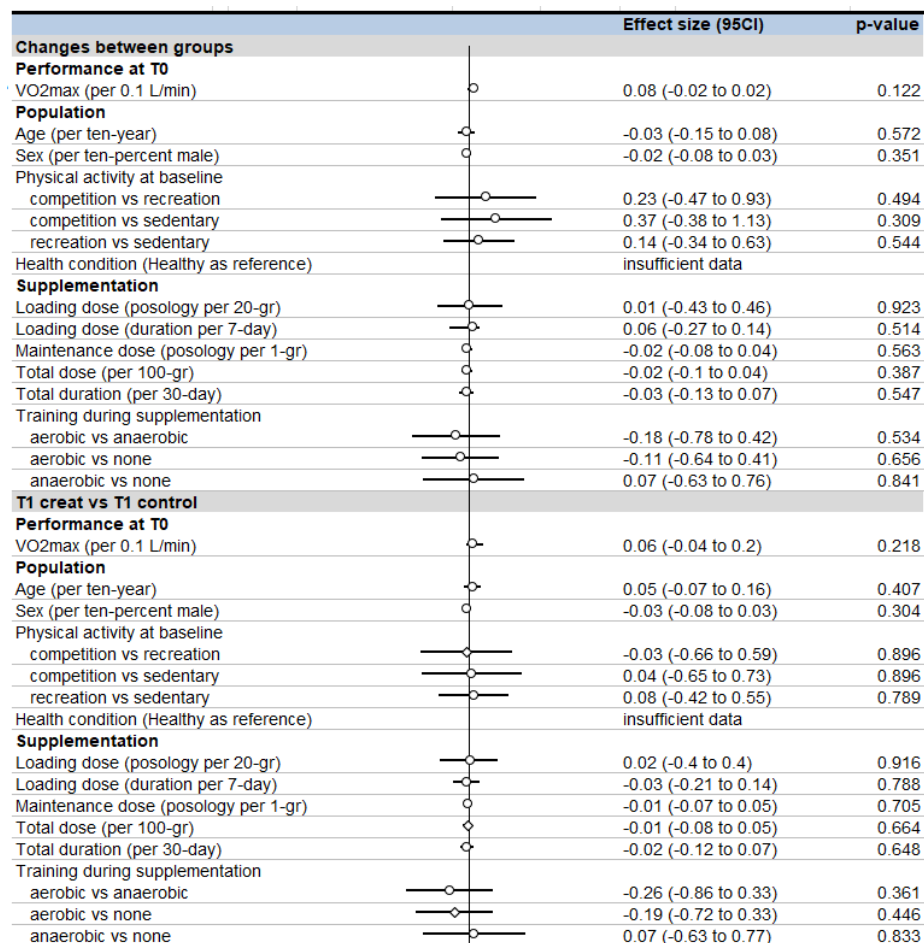
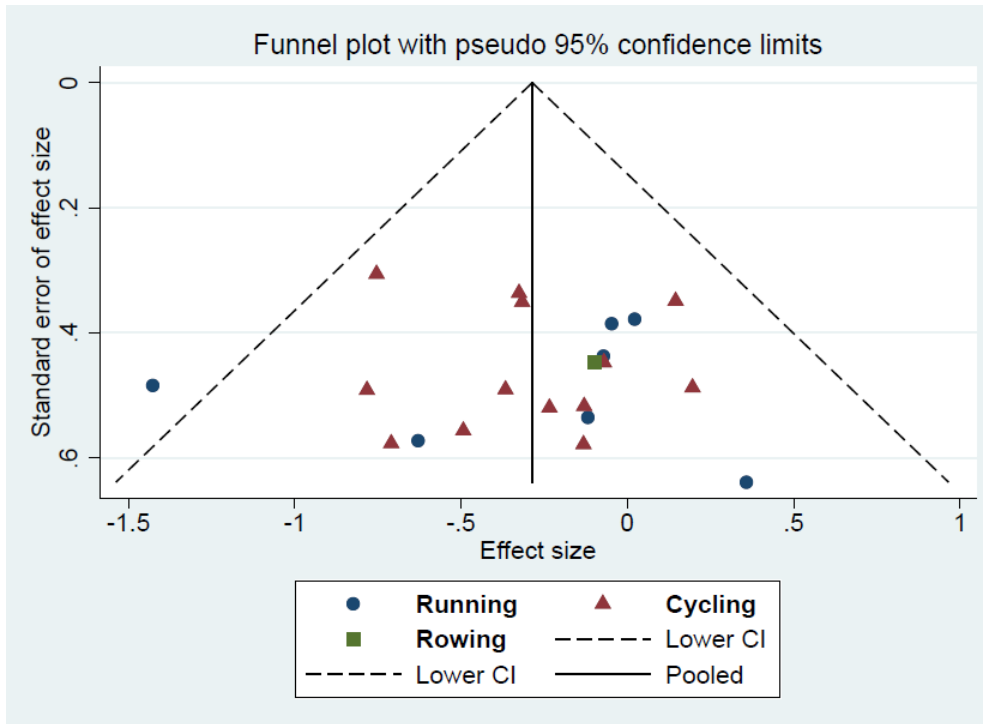
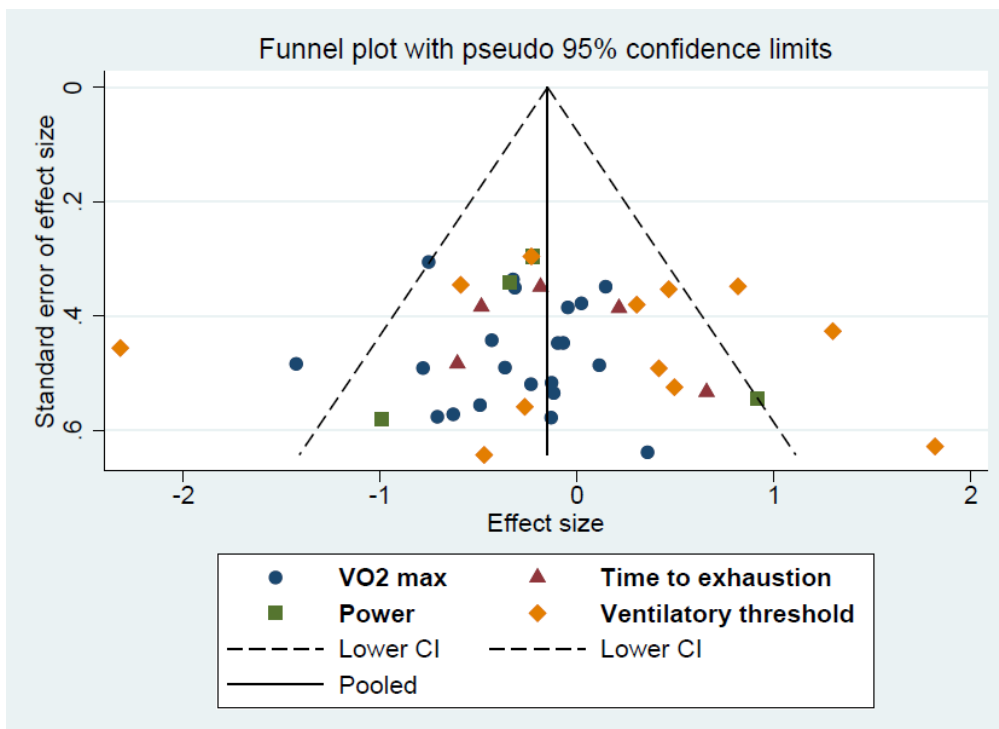


Fig 5. Funnel plots

### VO<sub>2</sub>max changes stratified by training



### “Aerobic” changes



**Table 1. Characteristics of included studies**

Study			Population				Outcome measurement	Intervention					Other assessments
Author	Year	Country	Total (n)	Men (%)	Age (mean or interval)	Physical level activity	Incremental test	Training intervention	Type Cr	Loading dose (g/day - n/day - n days)	Maintenance dose (g/day - n/day - n days)	Total dose	
Balsom	1993	Sweden	14	100	19-37	Competition (mid-distance runners)	Running	Aerobic	Cr monohydrate	0	5 - 1 - 6	30	
Barnett	1996	Australia	17	100	20,5	Recreation	Cycling	Aerobic	Cr monohydrate	0	5 - 4 - 4	20	
Canete	2006	USA	16	0	68	Sedentary	Cycling	None	Cr monohydrate	19 - 3 - 7	0	130	
Carvalho	2012	Brazil	33	100	55,7	Sedentary (heart failure)	Cycling	None	No information	0	5 - 1 - 180	900	
Da Silveira	2014	Brazil	22	100	18-30	Competition (military)	Running	Aerobic (MTP)	Cr monohydrate	25 - 3 - 7	2,5 - 1 - 86	385	
Eijnde	2003	Netherlands	46	100	55-75	Sedentary	Cycling	Aerobic (FTP)	Cr monohydrate	0	5 - 5 - 182	910	muscle biopsy, body composition
Forbes	2017	Canada	17	0	23	Recreation	Cycling	Anaerobic (HIIT)	Cr monohydrate	19 - 2 - 5	6,5 - 1 - 23	245	body composition
Graef	2009	USA	33	100	22,6	Recreation	Cycling	Anaerobic (HIIT)	di-Cr citrate	0	10 - 2 - 30	300	
Hickner	2010	USA	12	100	27,2	Recreation (cyclists)	Cycling	Aerobic	Cr monohydrate	0	3 - 1 - 28	84	muscle biopsy, body composition
Kresta	2014	USA	15	0	21,5	Recreation	Cycling	Aerobic	Cr monohydrate	18 - 4 - 7	6 - 1 - 21	252	muscle biopsy, body composition
Kuethe	2006	Germany	13	75	58,2	Sedentary (heart failure)	Walking	None	No information	20 - 4 - 42	0	840	
Lawrence	1996	Australia	20	50	21,2	Competition (elite rowers)	Rowing	Aerobic	Cr monohydrate	18 - 4 - 5	0	92	
Murphy	2005	Australia	18	100	24	Recreation (team sports)	Cycling	Aerobic	Cr monohydrate	20 - 4 - 7	10 - 2 - 21	350	
Nelson	2000	USA	36	55	23,5	Recreation	Cycling	Aerobic	Cr monohydrate	20 - 4 - 7	0	140	
Reardon	2006	Australia	13	70	19-22	Recreation	Cycling	Aerobic	Cr monohydrate	20 - 4 - 7	5 - 1 - 21	168	muscle biopsy, body composition
Smith	2011	USA	27	100	22,2	Recreation	Running	Aerobic	di-Cr citrate	20 - 4 - 5	0	100	
Smith	2011	USA	28	0	21,2	Recreation	Running	Aerobic	di-Cr citrate	20 - 4 - 5	0	100	
Sterkowicz	2012	Poland	10	100	21,2	Competition (judoists)	Running	Aerobic	Cr malate	0	5 - 1 - 42	210	body composition

Van Loon	2003	Netherlands	20	100	20,6	Sedentary	Cycling	None	Cr monohydrate	20 - 4 - 5	2	174	muscle biopsy, body composition
Villanueva	2014	USA	14	100	68,1	Recreation	Cycling	Aerobic	Cr monohydrate	24 - 3 - 5	5,5 - 1 - 79	552	body composition

*FTP=fitness training program; HIIT=high intensity interval training; MTP=military training program*



## **S1 Appendix. Details for the search strategy used within each database.**

### **Pubmed**

("Cr"[MH] OR "Cr"[TW]) AND ("physical conditioning, human"[MH] OR "physical conditioning"[TW] OR "physical training"[TW] OR "training"[Title] OR "physical endurance"[MH] OR "physical endurance"[TW] OR "endurance, physical"[TW] OR "endurance"[Title] OR "physical stamina"[TW] OR "Sports"[Mesh] OR Sport\*[TW] OR "Sports Nutritional Sciences"[Mesh] OR "exercise test"[MESH] OR "exercise"[MH] OR exercise\*[TW] OR "activities, physical"[TW] OR "activity, physical"[TW] OR "physical activities"[TW] OR "physical activity"[TW] OR "athletes"[MH] OR "athletes"[TW] OR "athlete"[TW] OR "athletic performance"[MH] OR (performance\*[TW] AND (Athlet\*[TW] OR sport\*[TW] OR fitness[TW] OR physical\*[TW])) OR "physical fitness"[MH] OR "fitness, physical"[TW] OR "physical fitness"[TW] OR "oxygen consumption"[MH] OR "oxygen consumptions"[TW] OR "oxygen consumption"[TW] OR "oxygen requirement"[TW] OR "consumption, oxygen"[TW] OR VO2[TW] OR VO2max[TW] OR VO2peak[TW]) AND ("dietary supplements"[MH] OR supplement\*[TW] OR "nutraceuticals"[TW] OR "nutraceutical food"[TW] OR "trace elements"[TW]) NOT (animals[MeSH Terms] NOT humans[MeSH Terms])

Filter Language = none ; Filter Dates = none

*Results = 1624*

### **Cochrane Library (combining searching on Embase databases)**

#1 "Cr":ti,ab,kw

#2 "physical conditioning":ti,ab,kw OR "physical training":ti,ab,kw OR "training":ti OR "physical endurance":ti,ab,kw OR "endurance, physical":ti,ab,kw OR "endurance":ti OR "physical stamina":ti,ab,kw OR Sport\*:ti,ab,kw OR exercise\*:ti,ab,kw OR "activities, physical":ti,ab,kw OR "activity, physical":ti,ab,kw OR "physical activities":ti,ab,kw OR "physical activity":ti,ab,kw OR "athletes":ti,ab,kw OR "athlete":ti,ab,kw OR (performance\*:ti,ab,kw AND (Athlet\*:ti,ab,kw OR sport\*:ti,ab,kw OR fitness:ti,ab,kw OR physical\*:ti,ab,kw)) OR "fitness, physical":ti,ab,kw OR "physical fitness":ti,ab,kw OR "oxygen consumptions":ti,ab,kw OR "oxygen consumption":ti,ab,kw OR "oxygen requirement":ti,ab,kw OR "consumption, oxygen":ti,ab,kw OR VO2:ti,ab,kw OR VO2max:ti,ab,kw OR VO2peak:ti,ab,kw

#3 supplement\*:ti,ab,kw OR "nutraceuticals":ti,ab,kw OR "nutraceutical food":ti,ab,kw OR "trace elements":ti,ab,kw

#4 #1 AND #2 AND #3

Filter Language = not available in CENTRAL ; Filter Dates = none

*Results = 956*

### **ScienceDirect:**

"CS" AND ("VO2max" OR "VO2peak" OR "maximal oxygen consumption")

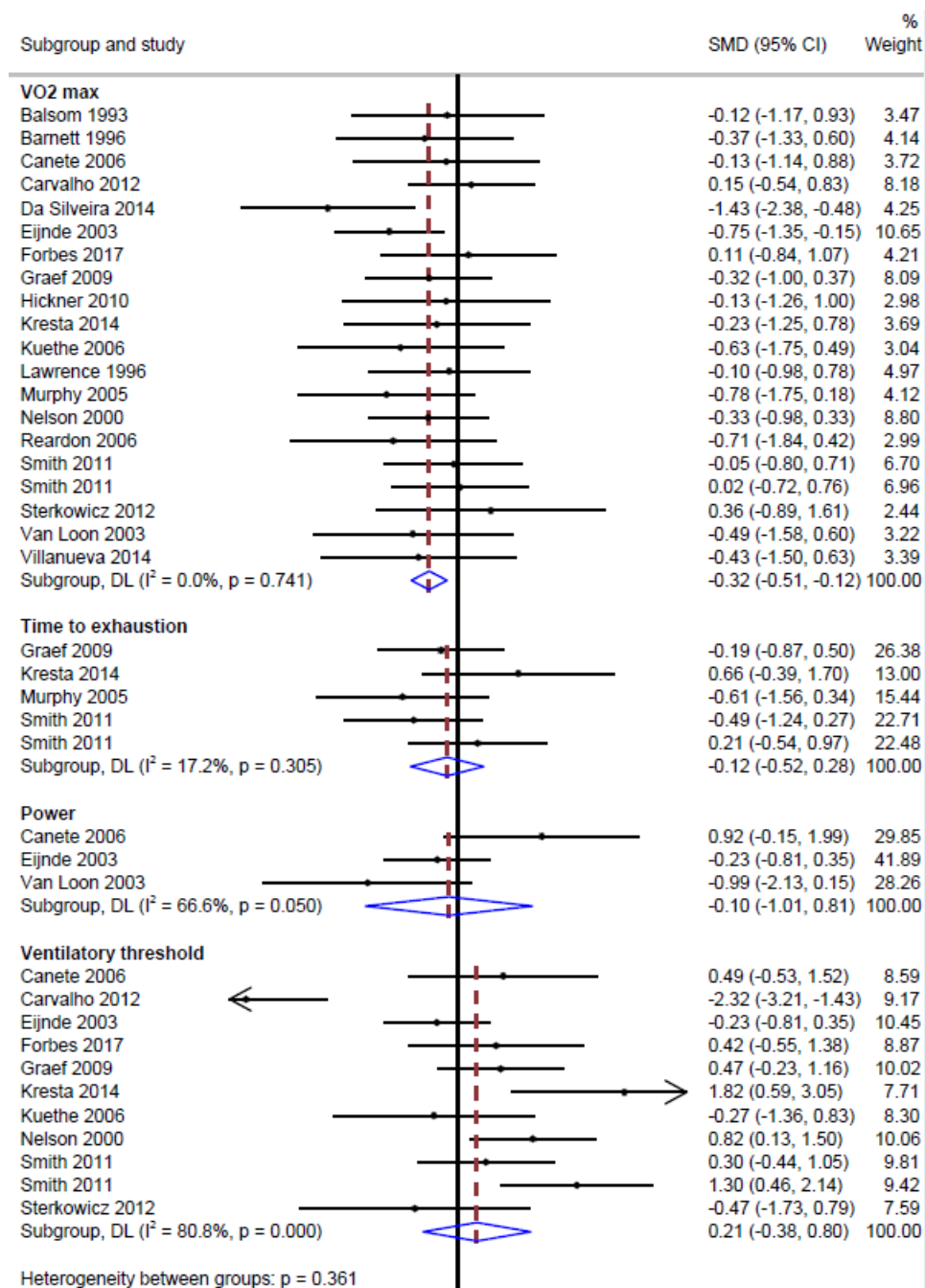
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*Results = 2409*

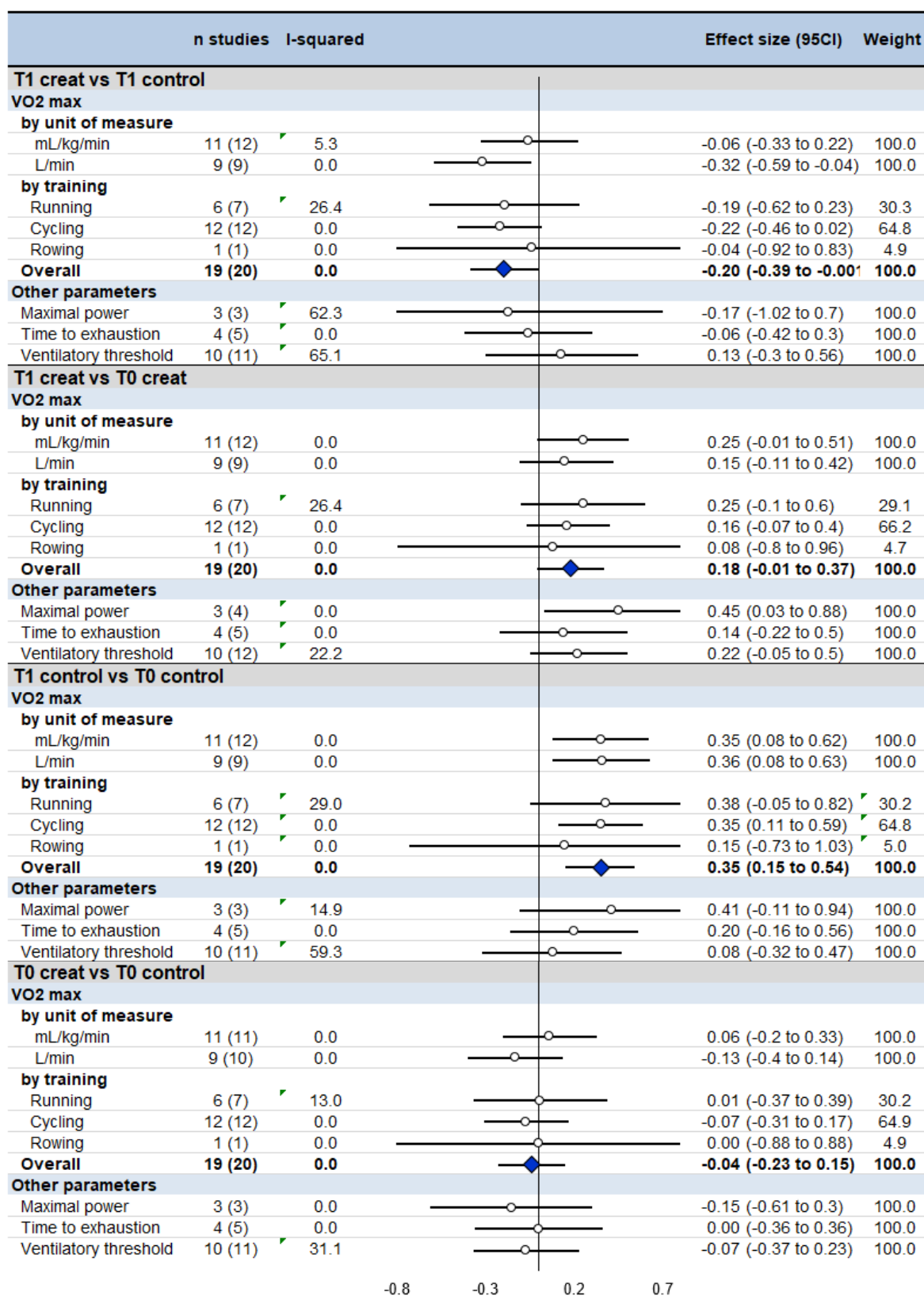
## S2 Appendix. Quality of articles – PEDro scale for RCTs

	External validity		Internal validity					Statistical information			
	eligibility criteria were specified	subjects were randomly allocated to groups	allocation was concealed	the groups were similar at baseline regarding the most important prognostic indicators	there was blinding of all subjects	there was blinding of all therapists	there was blinding of all assessors	key outcome obtained from > 85% of the subject	all subjects received the allocated treatment or outcomes analysed by "intention to treat"	the results of between-group statistical comparisons are reported for at least one key	the study provides both point measures and measures of variability for at least one key
Balsom 1993	+	+	-	+	+	+	+	+	+	+	+
Barnett 1996	+	+	-	+	+	+	+	+	+	+	+
Canete 2006	+	+	+	+	+	-	+	+	+	+	+
Carvalho 2012	+	+	-	-	+	+	+	+	+	+	+
Da Silveira 2014	+	+	-	-	+	+	+	+	+	+	+
Eijnde 2003	+	+	+	+	+	+	+	+	+	+	+
Forbes 2017	+	+	+	+	+	+	+	+	+	+	+
Graef 2009	+	+	-	+	+	+	+	+	+	+	+
Hickner 2010	+	-	-	+	+	+	+	+	+	+	+
Kresta 2014	+	+	-	+	+	+	+	+	+	+	+
Kueth 2006	+	-	-	+	+	+	+	+	+	+	+
Lawrence 1996	+	-	-	+	+	+	+	+	+	+	+
Murphy 2005	+	+	-	+	+	+	+	+	+	+	+
Nelson 2000	+	+	+	+	+	+	+	-	+	+	+
Reardon 2006	+	-	-	+	+	-	-	-	+	+	+
Smith 2011	+	+	-	+	+	+	+	+	+	+	+
Sterkowicz 2012	+	+	-	-	+	+	+	+	+	+	+
Van Loon 2003	+	+	+	+	+	+	+	+	+	+	+
Villanueva 2014	+	+	+	+	+	+	+	+	+	+	+

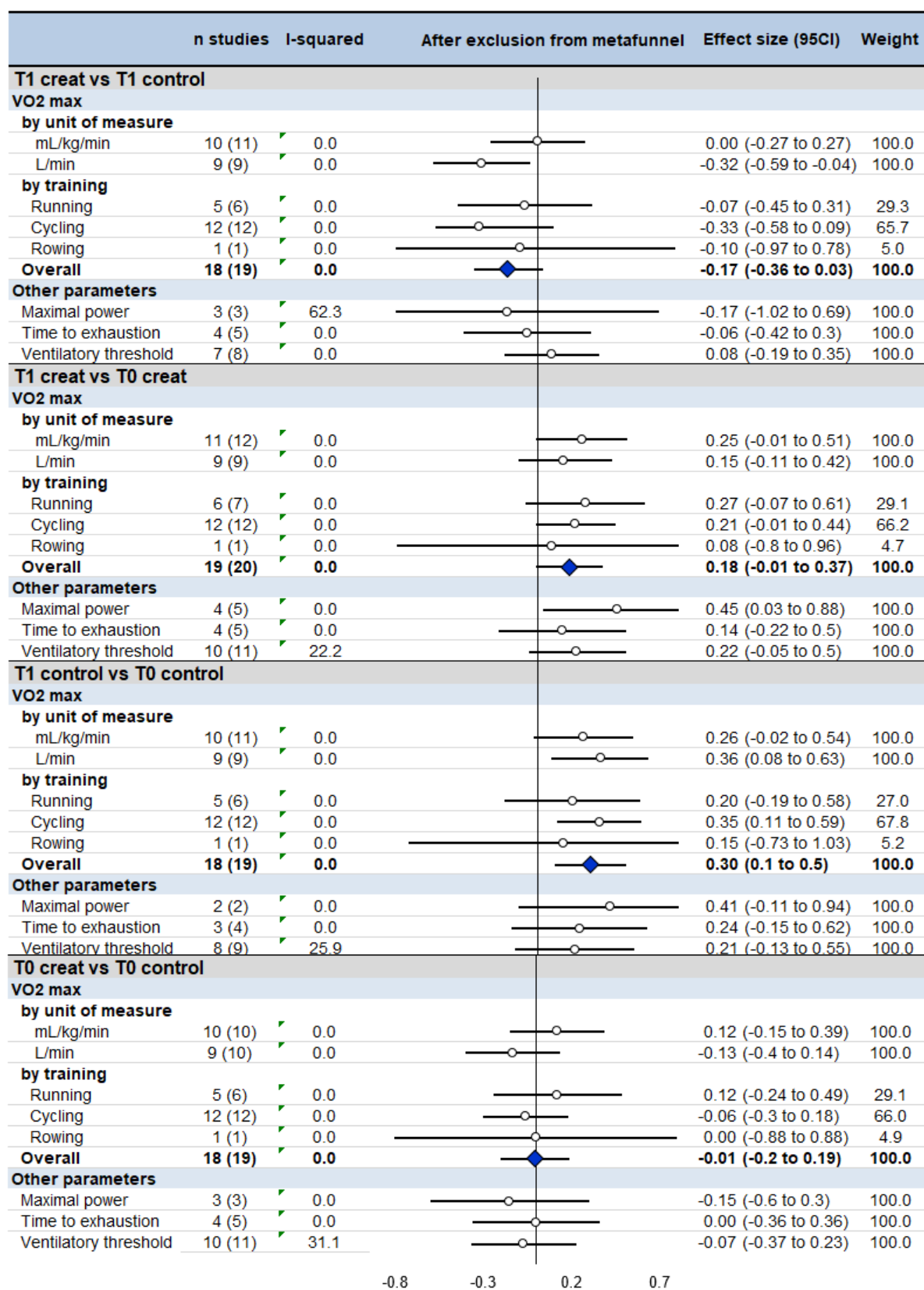
### S3 Appendix. Forest plot of aerobic changes in the Cr group compared to the control group within studies included following the supplementation period



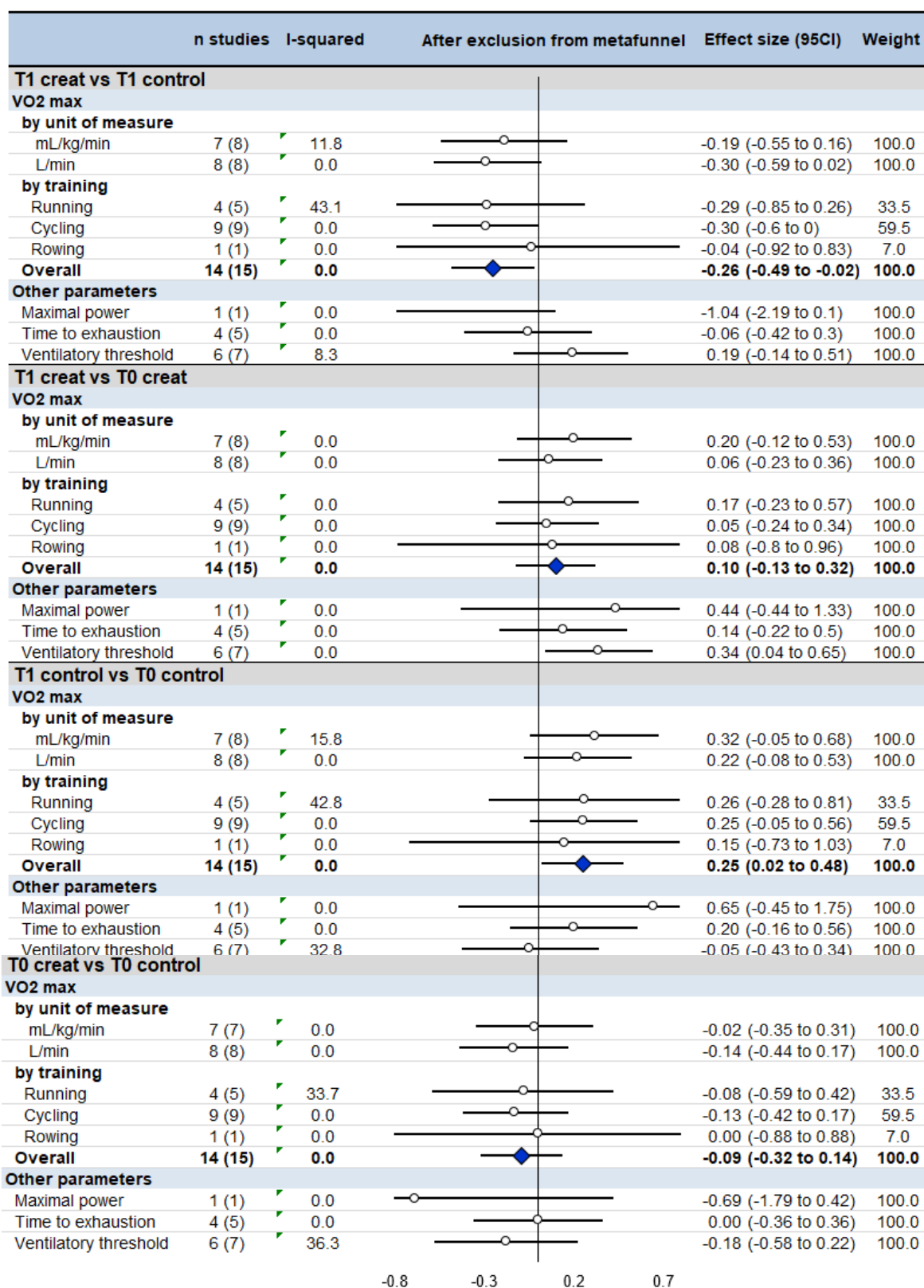
**S4 Appendix. Meta-analyses of aerobic measures at baseline and at T1 between groups, and between T0 and T1 within groups for all studies.**



**S5 Appendix. Meta-analyses of aerobic measures at baseline and at T1 between groups, and between T0 and T1 within groups after exclusions from meta funnels.**



**S6 Appendix. Meta-analyses of aerobic measures at baseline and at T1 between groups, and between T0 and T1 within groups in young and healthy.**



## S7 Appendix. PRISMA Checklist.

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	17
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	19
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	20-21
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	21
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	21
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	21
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	21 and S1 Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	21-22
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	22

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	22
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	22-23
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	23-24
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	23-24
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	23-24
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	23-24
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	24 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	24-27 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	24 and Figure 2, S2 Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	24-27 and S3 Appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	27-28 and Figures 3-4 and S4-S6 Appendix
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	27-28 and Figure 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	27-28 and S5-6 Appendix
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	28-33



Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	33-34
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	34
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	35-39

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

### 3. Conclusion

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La supplémentation en créatine a un effet négatif sur la  $VO_2\text{max}$ , indépendamment de la méthode de supplémentation, des modalités d'entraînement et des caractéristiques de la population. Considérant que la créatine est le complément diététique le plus largement utilisé dans la pratique sportive, une attention particulière doit être portée vis-à-vis de son utilisation par les sujets pratiquant une activité sportive d'endurance.

Clermont-Ferrand, le  
Pierre CLAVELOU  
Doyen - Directeur

23.6.2021



Clermont-Ferrand, le  
Le Président du Jury

22/04/2021

A handwritten signature in blue ink, consisting of several fluid, connected strokes.

## SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

## **SERMENT D'HIPPOCRATE**

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

## **Supplémentation en créatine et VO<sub>2</sub>max :**

### **Revue systématique et méta-analyse**

**Contexte:** Malgré les bénéfices admis d'une supplémentation en créatine sur la force musculaire, ses effets sur l'endurance et en particulier la VO<sub>2</sub>max sont plus controversés.

**Objectifs:** Conduire une revue systématique et une méta-analyse des effets de la supplémentation en créatine sur la VO<sub>2</sub>max.

**Méthodes:** Une recherche bibliographique des essais randomisés contrôlés (RCTs) mesurant la VO<sub>2</sub>max avant et après supplémentation en créatine ou placebo a été réalisée depuis les bases de données PubMed, Cochrane, Embase et ScienceDirect. Nous avons conduit 5 méta-analyses principales déterminant les tailles d'effet (ES) sur la VO<sub>2</sub>max de la supplémentation en créatine par rapport à un placebo avant supplémentation afin d'évaluer la comparabilité des groupes, après la supplémentation entre les groupes et sur les changements des niveaux de VO<sub>2</sub>max entre les groupes et au sein de chaque groupe. Des analyses de sensibilité ont été menées après exclusion des études pouvant présenter un biais de publication et sur un sous-groupe d'individus jeunes et sans pathologie. Des régressions ont été conduites pour identifier des facteurs pouvant influencer la VO<sub>2</sub>max.

**Résultats:** 19 RCTs ont été incluses pour un total de 424 individus (âge moyen de 29 ans, 82% d'hommes). La VO<sub>2</sub>max ne différait pas entre les groupes créatine et placebo avant le début de l'intervention. Les deux groupes bénéficiaient d'un entraînement dans la plupart des études (80%). La méta-analyse des mesures de VO<sub>2</sub>max avant et après supplémentation retrouvait une augmentation de VO<sub>2</sub>max dans les deux groupes mais une augmentation moindre avec la supplémentation en créatine par rapport au placebo (ES -0.30, IC95% -0.50 à -0.11). La comparaison de VO<sub>2</sub>max après supplémentation entre les groupes a confirmé une VO<sub>2</sub>max plus faible dans le groupe créatine (-0.20, -0.39 à -0.001). Les analyses de sensibilité ont donné des résultats similaires sur VO<sub>2</sub>max y compris dans le sous-groupe de sujets jeunes et sans pathologie. Le seuil ventilatoire est augmenté uniquement chez les sujets jeunes (0.66, 0.23 à 1.1) après supplémentation en créatine. Les méta-régressions sur les caractéristiques socio-démographiques, de l'entraînement et de la supplémentation n'étaient pas significatives.

**Conclusion:** La supplémentation en créatine a un effet négatif sur la VO<sub>2</sub>max quel que soient les caractéristiques de la population, l'entraînement pratiqué ou la méthode de supplémentation.

**Mots clés:** complément alimentaire, endurance, capacité cardio-respiratoire, VO<sub>2</sub>peak, seuil ventilatoire.