ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE DELLA RICERCA

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

The effect of tyrosine supplementation on whole-body endurance performance in physically active population: A systematic review and meta-analysis including GRADE qualification

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:
Solon-Júnior, L.J.F., Boullosa Alvarez, D.A., Martinez Gonzalez, B., da Silva Machado, D.G., de Lima-Junior, D., de Sousa Fortes, L. (2023). The effect of tyrosine supplementation on whole-body endurance performance in physically active population: A systematic review and meta-analysis including GRADE qualification. JOURNAL OF SPORT SCIENCES, 41(22), 2045-2053 [10.1080/02640414.2024.2309434].

Availability:
This version is available at: https://hdl.handle.net/11585/960349 since: 2024-04-25

Published:
DOI: http://doi.org/10.1080/02640414.2024.2309434

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (https://cris.unibo.it/).
When citing, please refer to the published version.

(Article begins on next page)

07 May 2026

Title: The Effect of Tyrosine Supplementation on Whole-Body Endurance Performance in Physically Active Population: A Systematic Review and Meta-Analysis including GRADE qualification

Running Head: Effect of Tyrosine Supplementation on endurance performance

Authors: Luiz José Frota Solon-Júnior[1], Daniel Alexandre Boullosa Alvarez[2,3,4], Borja Martinez Gonzalez[5], Daniel Gomes da Silva Machado[6], Dalton de Lima-Junior[5], and Leonardo de Sousa Fortes[7].

Affiliations:

[1] Federal University of Paraíba. Department of Physical Education, João Pessoa, Paraíba, Brazil.

[2] Faculty of Physical Activity and Sports Sciences, Universidad de León, 24007 León, Spain.

[3] Integrated Institute of Health, Federal University of Mato Grosso do Sul, Campo Grande, Brazil.

[4] College of Healthcare Sciences, James Cook University, Townsville, Australia.

[5] University of Bologna. Department for Life Quality Studies, Rimini, Italy.

[6] Federal University of Rio Grande do Norte. Department of Physical Education, Brazil.

[7] Federal University of Paraíba. Department of Physical Education, João Pessoa, Paraíba, Brazil.

Corresponding author:

Luiz José Frota Solon-Júnior

Department of Physical Education.

Federal University of Paraíba, João Pessoa, Paraíba, Brazil.

Avda. Josiara Telino 370. Bancários, João Pessoa, Paraíba, Brazil.

Phone: +55 88996881388

E-mail: sluis424@gmail.com

Title: The Effect of Tyrosine Supplementation on Whole-Body Endurance Performance in Physically Active Population: A Systematic Review and Meta-Analysis including GRADE qualification

Abstract

Although tyrosine supplementation is well recognized to improve cognitive function, its impact on endurance performance is debatable and needs to be clarified further. The purpose of this systematic review and meta-analysis was to evaluate the effects of tyrosine supplementation on whole-body endurance performance in physically active population. The search strategy follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), using four databases (Cochrane Library, Web of Science, Scopus, PsycINFO, and PubMed) until August 3, 2023. The effect of tyrosine (experimental condition) was compared against placebo (control condition). The methodological quality of the included studies was evaluated using the Physiotherapy Evidence Database (PEDro) scale. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE Pro software) System was also used to assess the quality of evidence. A total of 10 interventions from 8 studies were included. The sub-group analysis revealed no significant differences between tyrosine and placebo conditions for time to exhaustion (SMD = 0.02; p = 0.94) and time trial performance (SMD = -0.04; p = 0.85). The level of evidence as qualified with GRADE was moderate. In conclusion, moderate-quality evidence suggests that tyrosine supplementation is ineffective on endurance performance in the physically active population, independently of the endurance task (TTE or ETT).

Keywords: dietary supplement; exercise; endurance performance; sport nutrition

Clinical Trial Registration: The study protocol was registered in the Prospective Register of Systematic Review (PROSPERO) with the following registration number: (CRD42023386871).

Introduction

The amino acid L-tyrosine (TYR), usually present in protein-rich foods, is the biochemical precursor of catecholamines such as dopamine (DA) and norepinephrine (NE). Physiologically, oral consumption of TYR leads to peak plasma levels between one and two hours after ingestion,, which can remain significantly elevated for up to four hours (Coull et al., 2016). Once passed through the blood-brain barrier (BBB) and then absorbed by the neuronal cells, TYR is converted to L-DOPA through an enzyme called tyrosine hydroxylase (TH) (Daubner et al., 2011). Subsequently, L-DOPA is converted to DA, increasing the DA level in the brain. Additionally, DA can be converted to NE through the enzyme dopamine beta-hydroxylase (DBH) (Daubner et al., 2011). Notably, TH activity increases with oral supplementation of TYR; however, feedback inhibition regulates its activity to prevent significant increases in catecholamine release (Daubner et al., 2011). Over the past few decades, TYR has been used as a supplement to increase the levels of these catecholamines in the brain and potentially providing beneficial effects on cognitive and behavioral performances, which depends on the neurotransmitter's function (Jongkees et al., 2015).

The effects of TYR supplementation on cognitive and behavioral performances involve various aspects, including working memory (Colzato et al., 2013), inhibitory control (Colzato et al., 2015), cognitive flexibility (Steenbergen et al., 2015), reaction time, and vigilance (Banderet & Lieberman, 1989). However, the findings regarding the efficacy of TYR supplementation on these outcomes varied considerably, with some studies reporting beneficial effects (Colzato et al., 2013, 2015), while others did not (Chinevere et al., 2002; Sutton et al., 2005). A review by Jongkees et al. (2015), it was reported that TYR supplementation could reverse cognitive decline in short-term stressful situations and cognitively demanding tasks (e. g., heat exposure, cold exposure, cognition challenge, and auditory stress); nevertheless, the efficacy of supplementation may be influenced by the clinical outcomes assessed (e.g., cold exposure, cognition challenged, sleep deprivation, heat exposure) and participant's characteristics (e.g., healthy, parkinson's, depressive, and schizophrenia patients).

On the other hand, the consumption of TYR as an ergogenic resource has also been proposed as a potential strategy for improving physical performance and delaying fatigue (Roelands et al., 2015). From a neurochemical perspective, it has been reported that an increase in cerebral dopaminergic activity during prolonged physical exercise can directly activate the motor pathways and delay fatigue by inhibiting brain serotonin synthesis (Meeusen & Roelands, 2018). In addition to its impact on motor areas, dopamine also plays a role in various regions of the prefrontal cortex (PFC), including the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), which also play an essential role in decision-making related to pace regulation and exercise cessation during prolonged whole-body endurance (Robertson & Marino, 2016).

Previous studies suggested that dopaminergic neurons projecting into the prefrontal cortex may be influenced by the availability of TYR under certain circumstances (Milner & Wurtman, 1986; Tarn & Roth, 1997). Therefore, considering the importance of dopaminergic (mesocorticolimbic) and noradrenergic (locus coeruleus) pathways for motivation and physical performance (McMorris, 2020), nutritional interventions targeting this dopamine precursor could be an interesting strategy to improve endurance performance.

However, studies investigating TYR supplementation to improve whole-body endurance performance could not have confirmed this hypothesis, and the available results are conflicting despite an increasing number of publications. For example, Tumilty et al. (2011) demonstrated that TYR administration increased the time to exhaustion in heat cycling. In contrast, the positive effect of this supplement disappeared when the exercise mode was changed to a time trial (Tumilty et al., 2014). Therefore, it is still unknown whether the effect of TYR could be task-dependent, specifically whole-body endurance tasks because many sports situations are based on dynamic movements involving various joints and muscles; therefore, supplementation of TYR could be more advantageous. Also, the literature suggests that these inconsistent findings may be attributed to factors such as the exercise protocol and dosage of TYR supplementation (Tumilty et al., 2014, 2020). Additionally, possibly even more important is that studies in sports nutrition are frequently conducted with small samples and, therefore, may have low statistical power (Maughan et al., 2018; Tumilty et al., 2020). Thus, conducting a systematic review and meta-analysis utilizing the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach may help clarify the inconsistent findings on this topic.

Therefore, this systematic review focused on the following research question: "Is TYR supplementation advantageous for improving endurance performance in physically active population?". So, this article aimed to conduct a systematic review of studies examining the effects of tyrosine supplementation on whole-body endurance performance in physically active adults.

Materials and methods

This systematic review was performed following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) and was prospectively registered in PROSPERO (ID: CRD42023386871). The PICOS model, outlined in Table 1, was utilized to define the inclusion criteria.

*****Insert table 1*****

Search Strategy

The search strategy is described in Figure 1. A comprehensive examination was conducted on all randomized controlled trials (RCTs) that involved a comparison between a group receiving TYR supplementation and a group receiving a placebo, employing double-blind assignments. A structured search was conducted in the following databases until August 3, 2023: PubMed, Cochrane Library, Web of Science (WoS), Scopus, and PsycINFO. The study incorporated the following search terms: “Tyrosine” AND “Dietary Supplements” OR “Supplement” OR “Supplementation” AND “Exercise” OR “Exercise Tolerance” OR “Exercise Test” OR “Aerobic Exercise” OR “Time Trial” OR “Time To Exhaustion” OR “Endurance” OR “Physical Endurance” OR “Endurance Training” OR “Physical Fitness” OR “Time To Task Failure” AND “Performance” OR “Athletic Performance”. Search strategies were modified to meet the specific requirements of each database. The search was not limited to specific years. The search was supplemented manually by (a) examining the reference lists of the included studies and (b) examining the studies that cited the included studies (i.e., forward citation tracking). The search for studies was performed independently by two authors (Luiz José Frota Solon-Júnior and Borja Martinez Gonzalez).

Inclusion and Exclusion Criteria

To be included, the control group was required to receive a placebo during the supplementation period. The search strategy included studies of healthy men or women, regardless of their level of training, age, supplementation dose, and duration (acute or chronic). Furthermore, in the context of whole-body endurance performance (i.e., cardiorespiratory or aerobic endurance), the exercise duration for performance assessment had to exceed 75 seconds and be conducted at the maximum achievable intensity (McCormick et al., 2015). This review adopted this eligibility criterion because it is estimated that the relative contribution of the aerobic energy system generally predominates after 75 s of maximum-effort exercise (McCormick et al., 2015). The dependent variables included in this systematic review were the following data (absolute values): (A) time to exhaustion (TTE): endurance exercise at a constant intensity until participants could no longer continue with the effort; and (B) endurance time trial (ETT): completing a set distance in the shortest possible time or target work as quickly as possible. Consequently, the primary outcomes (O) were measured in minutes. Moreover, only original studies and research were included, and studies involving TYR supplementation in conjunction with other supplements (such as caffeine, probiotics, BCAA or any other supplement that alters endurance performance) were excluded.

Data Extraction and Analysis

The authors extracted the following data from the included studies: author and year of publication; sample size (n) and participants characteristics (sex, age, and training status); details of the TYR supplementation protocol, including dosage, timing, and method of administration; the specific tests employed to assess endurance performance; outcome variables (TTE or ETT); main findings related to the effects of TYR on whole-body endurance performance; and side effects. The authors of the studies included in this review were contacted if crucial data were missing from the original publication. We contacted the authors of the one article (Tumilty et al., 2020) in which endurance performance values were not described.

Quality Assessment of Included Studies

The quality assessment of the included studies was conducted using the PEDro scale of 11 items, which includes a "Yes/No" response scale related to the study design (Moher et al., 2009; Verhagen et al., 1998). According to the PEDro checklist, all items except the first one contribute to calculating a summary score ranging from 0 to 10. The PEDro scale was used because it can objectively and reliably assess the internal validity of a randomized controlled trial (RCTs) (Maher et al., 2003). On the basis of the summative scores, the studies were categorized as "excellent quality" (9 to 10 points), "good quality" (6 to 8 points), "fair quality" (4–5 points), or "poor" methodological quality (3 points) (Grgic et al., 2020). Two review authors (Luiz José Frota Solon-Júnior and Borja Martinez Gonzalez) conducted the quality assessment independently; any discrepancies between authors' scores were resolved through discussion and consensus.

The Grading of Recommendations, Development, and Evaluation (GRADE) method was used to evaluate the overall quality of the evidence gathered with the GRADE pro (Version 20) software developed by McMaster University in 2014. The quality of evidence for RCTs was graded into four levels: very low, low, moderate, or high (Higgins & Green, 2008).

Statistical considerations

Statistical analyses were performed using the Review Manager software (RevMan 5.3.5; Cochrane Collaboration, Oxford, UK). The effect size of each study was calculated as the difference in performance between the experimental (i.e., TYR) and control (i.e., placebo) conditions. It was calculated the mean difference and 95% confidence interval (CI) to measure the intervention effect on continuous outcomes. The raw difference was divided by the within-group standard deviation to standardize the mean differences (SMD). The mean differences and CI weighted by the inverse variance method were measured using a random-effects model. Heterogeneity between studies was assessed using I^2 statistics, as well as the visual inspection of the forest plot. According to Cohen's guidelines, SMD values of 0.2, 0.5, and 0.8 represent small, moderate, and large effect sizes. Statistical significance was set at $P \leq 0.05$. Due to the limited number of studies (≤ 10 trials) available for each comparison, the risk of publication bias was not assessed using funnel plots, as they have low statistical power (Egger et al., 1997).

Results

Overview of Studies Included

A total of 214 papers were initially identified based on the combined descriptors. Initially, 135 original research articles were selected from the 214 papers. Of these 135 articles, 31 were removed due to duplication. From the remaining 104 articles screened, Ten articles were excluded because they did not solely investigate TYR supplementation (e.g., combined use of caffeine, theanine, and TYR; Multi-Ingredient Pre-Workout Supplement; Probiotic; Amino Acids) or involved the use of other supplements (e. g., Methylphenidate, Zinc, glutamine, and alanine). Additionally, two articles were excluded as they focused on patients with specific diseases (e.g., Parkinson's disease and anorexia nervosa patients), and six articles were excluded as they did not evaluate physical performance as an outcome (e.g., response execution, inhibitory control, and working memory).

In addition, one article was excluded because it involved animal testing, and seventy-five were out of context and did not match the search criteria. Ten full-text papers were then read. One of the ten articles did not assess whole-body endurance performance, and another did not assess the maximal nature of exercise. However, only eight original English-language papers were declared eligible for inclusion in this review.

*****Insert figure 1*****

Characteristics of Subjects

There were a total of 83 male participants included in the studies that were evaluated. No study included samples of both sexes or women. The number of trial participants ranged from seven (Tumilty et al., 2014) to twenty (Sutton et al., 2005), with a mean sample size of 9.75 ± 4.23. The mean ages of the participants ranged from 20 (Tumilty et al., 2014) to 32 (Sutton et al., 2005; Tumilty et al., 2011) years old. Included in the studies were endurance-trained males (Chinevere et al., 2002; Strüder et al., 1998; Tumilty et al., 2014), as well as physically active or recreationally trained men (Coull et al., 2016; Sutton et al., 2005; Tumilty et al., 2020; Watson et al., 2012).

*****Insert table 2*****

Tyrosine Administration

Regarding the delivery of TYR, most of the studies chose to either suspend it in drinks (such as flavored water sugar-free) or dissolved in water. There was a considerable variation in the dosage of TYR administered per dose. Out of the eight included studies, one study used a TYR dose of 20 g (Strüder et al., 1998), another used a dose of 25 mg/kg (Chinevere et al., 2002), and five studies used a dose of 150 mg/kg (Coull et al., 2016; Sutton et al., 2005; Tumilty et al., 2011, 2014; Watson et al., 2012). One study employed three distinct concentrations, including 150, 300, and 400 mg/kg (Tumilty et al., 2020). The timing of TYR ingestion ranged from 15 minutes to up to 120 minutes before exercise. In some studies, the TYR dose was administered at a single time point, while other divided the total dose and administered it multiple times (e.g., 120, 60, 30, and 15 min pre-exercise; see Table 2 for details). All of the included studies utilized an acute intervention protocol.

Quality of Articles

The mean PEDro score of the included studies was 9.37 ± 1.06 out of 10, indicating a high methodological quality. Among the studies, seven were classified as excellent and one as good quality. None of the studies were rated as fair or poor regarding methodological quality (Table 3).

*****Insert table 3*****

GRADE

Based on the overall analysis, the evidence quality was assessed as moderate, indicating that TYR is ineffective compared to placebo in enhancing endurance performance. The level of evidence for randomized controlled trials (RCTs) was downgraded due to imprecision, i.e., less than 400 participants in the comparison for continuous outcomes. In summary, the analysis shows moderate confidence in the metanalysis quality of evidence. More studies are needed to increase the number of participants in the GRADE analysis, altering from moderate to high-quality evidence (see Table 4).

*****Insert table 4*****

Outcome and Aim of the Studies

All studies shared similar results but with different objectives. The critical dependent variables of the studies were TTE (Strüder et al., 1998; Sutton et al., 2005; Tumilty et al., 2011; Watson et al., 2012) and ETT (Chinevere et al., 2002; Coull et al., 2016; Tumilty et al., 2014, 2020). Five out of the eight included studies aimed to investigate the effects of this supplement on the endurance task in a warm environment (Coull et al., 2016; Tumilty et al., 2011, 2014, 2020; Watson et al., 2012), while three studies were conducted in temperature-controlled ambient conditions (Chinevere et al., 2002; Strüder et al., 1998; Sutton et al., 2005).

Effect of TYR Supplementation on Whole-Body Endurance Performance

The systematic search uncovered a total of ten interventions within eight studies that investigated the effects of TYR supplementation on endurance performance (TTE or ETT). As shown in Figure 2, there was no overall effect favoring the TYR condition (standardized mean difference [SMD] = -0.01; 95% CI = -0.32, 0.29; P = 0.93), without significant heterogeneity (P = 0.85 and I^2 = 0%). Subgroup analysis also revealed no significant differences between the TYR and placebo conditions for TTE (SMD = 0.02; 95% CI = -0.45, 0.49; P = 0.94) and ETT (SMD = -0.04; 95% CI = -0.44, 0.37; P = 0.85). These results suggest that TYR supplementation does not improve whole-body endurance performances.

*****Insert figure 2*****

Side effects

Information on side effects was reported in three of the eight studies (see Table 5 for details). Overall, no side effects or gastric discomfort were reported across the three studies.

*****Insert table 5*****

Study Limitations

Although the authors did not identify any critical defects in the eight included RCTs, they did identify some general concerns. When conducting repeated measures trials to determine the effect of nutritional treatment interventions on endurance performance, dietary control is of the uttermost importance. One study did not address dietary control (Strüder et al., 1998), whereas seven studies required participants to replicate their diet for the days preceding performance testing based on dietary records obtained during baseline testing. However, these seven studies that mentioned dietary control did not report the results of the dietary records collected. Also, it is worth noting that only one study (Sutton et al., 2005) requested a list of tyrosine-rich foods for participants to avoid 24 hours before testing. Another consideration that should be addressed is the "Concealed allocation" (item 3 of the PEDro scale) of the participants. Only five studies clearly described the allocation method.

Discussion

Despite the fact that tyrosine supplementation may not enjoy the same level of popularity as other supplements, such as caffeine and creatine, it is essential to emphasize the need for exhaustive and rigorous research on this topic. The main result from the current systematic review with meta-analysis was that TYR supplementation is inefficient for whole-body endurance performance in physically active adults. Existing reviews have investigated the effects of TYR in different contexts (Jongkees et al., 2015; Meeusen & Decroix, 2018; Meeusen & Roelands, 2018), but none focused on this topic or proposed to evaluate the methodological quality of the included studies when formulating their results, resulting in low confidence in their findings. Previous literature has demonstrated that combining findings from studies without considering their methodological quality can lead to bias (Egger et al., 2002; Schulz et al., 1995). Therefore, to the best of our knowledge, this is the first systematic review with meta-analysis using GRADE to gather the available evidence about the effects of TYR supplementation on whole-body endurance performance (TTE and ETT). Overall, the quality of evidence, as assessed by GRADE, was moderate, indicating that further research is likely to impact our confidence in the estimated effect significantly and will likely change the current estimate (Higgins & Green, 2008).

This systematic review and meta-analysis examined the effects of tyrosine supplementation on whole-body endurance performances using ten interventions from eight studies. Although the effects of supplementation with TYR to improve endurance performance are based on its ability to increase circulating concentrations of adrenaline, noradrenaline, and dopamine in the central and periphery nervous systems (Meeusen & Decroix, 2018), our analyses failed to reveal a significant effect of tyrosine on endurance performance when all tasks were combined or when TTE and ETT were used to separate them.

Surprisingly, only one study (with high methodological quality) reported a successful outcome (Tumilty et al. 2011). In this study, Tumilty et al. (2011) showed that supplementing with a nutritional dopamine precursor one hour before exercise increased exercise capacity in the heat. On the other hand, the remaining 7 observed no significant effects of TYR supplementation on endurance performance (Table 5). Six studies were classified as excellent quality tests, and only one was considered a good quality test trial. These studies, therefore, did not suggest that TYR supplementation improves performance and delays fatigue during prolonged exercise (Meeusen & Decroix, 2018), regardless of the presence of stressful conditions. On the other hand, Jongkees et al. (2015) suggest that TYR supplementation may promote improvement in physical performance; however, this positive effect occurs only under specific conditions that activate catecholaminergic neurons and involve high cognitive demands, such as attention and cognitive control. Therefore, future studies should consider using TYR supplementation as a potential countermeasure against mental or central fatigue and its subsequent impact on endurance performance.

The majority of research examined in this review focused on investigating and observing elevated levels of TRY in plasma or serum following consumption. However, it is essential to note that while peripheral markers are necessary for manipulation checks in sports nutrition, none of the included studies in this review evaluated central markers. Recent literature proposes incorporating electrophysiological and imaging techniques to understand better TYR ingestion's effects on the brain (Meeusen & Roelands, 2018). Such approaches could help researchers to gain insights into the neurological changes following TYR supplementation. Additionally, future studies of TYR could also include indirect behavioral measures (e.g. eye blink rate and pupil diameter) to quantity dopaminergic activity (Dave et al., 2021).

This review has some possible limitations, including those within the included RCTs (see session “Study Limitations”). While the PEDro scale has been widely used in systematic review studies involving supplementations and nutritional ergogenic resources (Grgic et al., 2020; McMahon et al., 2017; Quesnele et al., 2014), it is argued that the scale may need to be revised to adequately address methodological issues specific to studies involving supplementation (Quesnele et al., 2014). Some of these methodological issues include the source of obtaining supplementation and details of participants' dietary reports, which also contribute as limitations to our review. Another limitation was the inclusion of only a small number of subjects in most studies, and this makes difficult the estimation of the actual effect.

Conclusions and practical implications

In conclusion, the current systematic review and meta-analysis indicate that supplementation with tyrosine did not significantly enhance the endurance performance of physically active individuals. However, further research is needed to explore potential benefits in specific populations and understand the underlying action mechanisms. Specifically, future studies should investigate which subgroups of individuals are more likely to benefit from TYR supplementation, the specific brain areas that are activated with TYR use, and the context of fatigue (whether central, cognitive, or mental) in which supplementation may have a meaningful effect. These areas of investigation will contribute to a deeper understanding of tyrosine's potential role in enhancing endurance performances.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgement

Luiz José Frota Solon-Júnior was supported by Fundação de Apoio à Pesquisa do Estado da Paraíba.

Daniel Alexandre Boullosa Alvarez was supported by Grant RYC2021-031098-I funded by MCIN/AEI/10.13039/501100011033, by “European Union NextGenerationEU/PRTR”, and by a productivity research grant (PQ1D) from CNPq (Brazil).

References

Banderet, L. E., & Lieberman, H. R. (1989). Treatment with tyrosine, a neurotransmitter precursor, reduces environmental stress in humans. *Brain Research Bulletin*, *22*(4), 759–762. https://doi.org/10.1016/0361-9230(89)90096-8

Chinevere, T. D., Sawyer, R. D., Creer, A. R., Conlee, R. K., & Parcell, A. C. (2002). Effects of L -tyrosine and carbohydrate ingestion on endurance exercise performance. *Journal of Applied Physiology*, *93*(5), 1590–1597. https://doi.org/10.1152/japplphysiol.00625.2001

Colzato, L. S., de Haan, A. M., & Hommel, B. (2015). Food for creativity: Tyrosine promotes deep thinking. *Psychological Research*, *79*(5), 709–714. https://doi.org/10.1007/s00426-014-0610-4

Colzato, L. S., Jongkees, B. J., Sellaro, R., & Hommel, B. (2013). Working Memory Reloaded: Tyrosine Repletes Updating in the N-Back Task. *Frontiers in Behavioral Neuroscience*, *7*. https://doi.org/10.3389/fnbeh.2013.00200

Coull, N., Chrismas, B., Watson, P., Horsfall, R., & Taylor, L. (2016). Tyrosine Ingestion and Its Effects on Cognitive and Physical Performance in the Heat. *Medicine & Science in Sports & Exercise*, *48*(2), 277–286. https://doi.org/10.1249/MSS.0000000000000757

Daubner, S. C., Le, T., & Wang, S. (2011). Tyrosine hydroxylase and regulation of dopamine synthesis. *Archives of Biochemistry and Biophysics*, *508*(1), 1–12. https://doi.org/10.1016/j.abb.2010.12.017

Dave, A. A., Lehet, M., Diwadkar, V. A., & Thakkar, K. N. (2021). Ocular measures during associative learning predict recall accuracy. *International Journal of Psychophysiology*, *166*, 103–115. https://doi.org/10.1016/j.ijpsycho.2021.05.010

Egger, M., Ebrahim, S., & Smith, G. D. (2002). Where now for meta-analysis? *International Journal of Epidemiology*, *31*(1), 1–5. https://doi.org/10.1093/ije/31.1.1

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, *315*(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

Grgic, J., Rodriguez, R. F., Garofolini, A., Saunders, B., Bishop, D. J., Schoenfeld, B. J., & Pedisic, Z. (2020). Effects of Sodium Bicarbonate Supplementation on Muscular Strength and Endurance: A Systematic Review and Meta-analysis. *Sports Medicine*, *50*(7), 1361–1375. https://doi.org/10.1007/s40279-020-01275-y

Higgins, J. P., & Green, S. (2008). *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*.

Jongkees, B. J., Hommel, B., Kühn, S., & Colzato, L. S. (2015). Effect of tyrosine supplementation on clinical and healthy populations under stress or cognitive demands—A review. *Journal of Psychiatric Research*, *70*, 50–57. https://doi.org/10.1016/j.jpsychires.2015.08.014

Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., & Elkins, M. (2003). Reliability of the PEDro Scale for Rating Quality of Randomized Controlled Trials. *Physical Therapy*, *83*(8), 713–721. https://doi.org/10.1093/ptj/83.8.713

Maughan, R. J., Burke, L. M., Dvorak, J., Larson-Meyer, D. E., Peeling, P., Phillips, S. M., Rawson, E. S., Walsh, N. P., Garthe, I., Geyer, H., Meeusen, R., van Loon, L., Shirreffs, S. M., Spriet, L. L., Stuart, M., Vernec, A., Currell, K., Ali, V. M., Budgett, R. G. M., … Engebretsen, L. (2018). IOC Consensus Statement: Dietary Supplements and the High-Performance Athlete. *International Journal* *of Sport Nutrition and Exercise Metabolism*, *28*(2), 104–125. https://doi.org/10.1123/ijsnem.2018-0020

McCormick, A., Meijen, C., & Marcora, S. (2015). Psychological Determinants of Whole-Body Endurance Performance. *Sports Medicine*, *45*(7), 997–1015. https://doi.org/10.1007/s40279-015-0319-6

McMahon, N. F., Leveritt, M. D., & Pavey, T. G. (2017). The Effect of Dietary Nitrate Supplementation on Endurance Exercise Performance in Healthy Adults: A Systematic Review and Meta-Analysis. *Sports Medicine*, *47*(4), 735–756. https://doi.org/10.1007/s40279-016-0617-7

McMorris, T. (2020). Cognitive Fatigue Effects on Physical Performance: The Role of Interoception. *Sports Medicine*, *50*(10), 1703–1708. https://doi.org/10.1007/s40279-020-01320-w

Meeusen, R., & Decroix, L. (2018). Nutritional Supplements and the Brain. *International Journal of Sport Nutrition and Exercise Metabolism*, *28*(2), 200–211. https://doi.org/10.1123/ijsnem.2017-0314

Meeusen, R., & Roelands, B. (2018). Fatigue: Is it all neurochemistry? *European Journal of Sport Science*, *18*(1), 37–46. https://doi.org/10.1080/17461391.2017.1296890

Milner, J. D., & Wurtman, R. J. (1986). Catecholamine synthesis: Physiological coupling to precursor supply. *Biochemical Pharmacology*, *35*(6), 875–881. https://doi.org/10.1016/0006-2952(86)90071-7

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & for the PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ*, *339*(jul21 1), b2535–b2535. https://doi.org/10.1136/bmj.b2535

Quesnele, J. J., Laframboise, M. A., Wong, J. J., Kim, P., & Wells, G. D. (2014). The Effects of Beta-Alanine Supplementation on Performance: A Systematic Review of the Literature. *International Journal of Sport Nutrition and Exercise Metabolism*, *24*(1), 14–27. https://doi.org/10.1123/ijsnem.2013-0007

Robertson, C. V., & Marino, F. E. (2016). A role for the prefrontal cortex in exercise tolerance and termination. *Journal of Applied Physiology*, *120*(4), 464–466. https://doi.org/10.1152/japplphysiol.00363.2015

Roelands, B., De Pauw, K., & Meeusen, R. (2015). Neurophysiological effects of exercise in the heat: Exercise and the brain. *Scandinavian Journal of Medicine & Science in Sports*, *25*, 65–78. https://doi.org/10.1111/sms.12350

Schulz, K. F., Chalmers, I., Hayes, R. J., & Altman, D. G. (1995). Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*, *273*(5), 408–412. https://doi.org/10.1001/jama.273.5.408

Steenbergen, L., Sellaro, R., Hommel, B., & Colzato, L. S. (2015). Tyrosine promotes cognitive flexibility: Evidence from proactive vs. reactive control during task switching performance. *Neuropsychologia*, *69*, 50–55. https://doi.org/10.1016/j.neuropsychologia.2015.01.022

Strüder, H., Hollmann, W., Platen, P., Donike, M., Gotzmann, A., & Weber, K. (1998). Influence of Paroxetine, Branched-Chain Amino Acids and Tyrosine on Neuroendocrine System Responses and Fatigue in Humans. *Hormone and Metabolic Research*, *30*(04), 188–194. https://doi.org/10.1055/s-2007-978864

Sutton, E. E., Coll, M. R., & Deuster, P. A. (2005). Ingestion of Tyrosine: Effects on Endurance, Muscle Strength, and Anaerobic Performance. *International Journal* *of Sport Nutrition and Exercise Metabolism*, *15*(2), 173–185. https://doi.org/10.1123/ijsnem.15.2.173

Tarn, S.-Y., & Roth, R. H. (1997). Mesoprefrontal dopaminergic neurons: Can tyrosine availability influence their functions? *Biochemical Pharmacology*, *53*(4), 441–453. https://doi.org/10.1016/S0006-2952(96)00774-5

Tumilty, L., Davison, G., Beckmann, M., & Thatcher, R. (2011). Oral tyrosine supplementation improves exercise capacity in the heat. *European Journal of Applied Physiology*, *111*(12), 2941–2950. https://doi.org/10.1007/s00421-011-1921-4

Tumilty, L., Davison, G., Beckmann, M., & Thatcher, R. (2014). Failure of Oral Tyrosine Supplementation to Improve Exercise Performance in the Heat. *Medicine & Science in Sports & Exercise*, *46*(7), 1417–1425. https://doi.org/10.1249/MSS.0000000000000243

Tumilty, L., Gregory, N., Beckmann, M., & Thatcher, R. (2020). No Influence of Low-, Medium-, or High-Dose Tyrosine on Exercise in a Warm Environment. *Medicine & Science in Sports & Exercise*, *52*(6), 1404–1413. https://doi.org/10.1249/MSS.0000000000002245

Verhagen, A. P., de Vet, H. C., de Bie, R. A., Kessels, A. G., Boers, M., Bouter, L. M., & Knipschild, P. G. (1998). The Delphi list: A criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *Journal of Clinical Epidemiology*, *51*(12), 1235–1241. https://doi.org/10.1016/s0895-4356(98)00131-0

Watson, P., Enever, S., Page, A., Stockwell, J., & Maughan, R. J. (2012). Tyrosine Supplementation Does Not Influence the Capacity to Perform Prolonged

Exercise in a Warm Environment. *International Journal of Sport Nutrition and Exercise Metabolism*, *22*(5), 363–373. https://doi.org/10.1123/ijsnem.22.5.363

Table 1. Description of the PICOS strategy (Population, Intervention, Comparison, Outcome, and Study design).

PICOS COMPONENTS	**DETAIL**
Participants	Physically active (men or women)
Interventions	Tyrosine supplementation
Comparisons	Same conditions with placebo
Outcomes	Endurance performance, ETT, and TTE
Study designs	Double-blind and randomized controlled trials with crossover design or counterbalanced design

Table 2. Characteristics of the studies included.

Study	Participants characteristics	Age	Supplement protocol	Changes in plasma/serum concentration of tyrosine	Exercise protocol (endurance task)
(Strüder et al., 1998)	10 endurance-trained male cyclists	25.5±2.1	10g of TYR 15 min pre-exercise (12:45a.m.) dissolved in water + 10g of TYR after 60 min of exercise duration	Plasma tyrosine increased significantly 30 minutes after the start of exercise	Cycling to exhaustion (unable to maintain a frequency of 50 rpm on the ergometer)
(Chinevere et al., 2002)	9 male competitive cyclists	25 ± 1	25 mg/kg (TYR) 60 min pre-exercise suspended in 5 ml/kg drink	Tyrosine ingestion significantly raised plasma tyrosine after supplementation and before exercise when compared to placebo	Cycled at 70% peak oxygen uptake for 90 min + a time trial [completion of an individual work target as rapidly as possible, that is, Total amount of work for time trial (J) 0.70*Wmax*1,800].
(Sutton et al., 2005)	20 men (Healthy and moderately to highly physically fit)	32 ± 1.1	150 mg/kg 1-crystalline tyrosine in 70 g of apple sauce 30 min pre-exercise	Tyrosine ingestion significantly raised plasma tyrosine after supplementation and before exercise when compared to placebo	Load carriage exercise test (backpack weighted to 30% of his body weight)
(Tumilty et al., 2011)	8 healthy male (regular exercisers involved in competitive team and endurance sports)	32 ± 11	150 mg/kg (TYR) 60 min pre-exercise suspended in 500 mL drink	Plasma tyrosine concentrations increased significantly after supplementation and before	Cycling to exhaustion at a constant exercise intensity (@ 68%$\dot{V}O_{2peak}$) in 30°C and 60% relative humidity.
(Watson et al., 2012)	8 trained male (physically active and took part in competitive team or endurance sports)	23 ± 3	75 mg/kg (TYR) 30 min pre-exercise suspended in 150 mL drink + 150 ml consumed every 15 min throughout exercise (total TYR dose: 150 mg/kg)	Serum tyrosine concentrations increased significantly after supplementation and before exercise when compared to placebo	Cycling to exhaustion at 70% VO_{2peak}.
(Tumilty et al., 2014)	7 endurance-trained male (level 3)	20 ± 0	150 mg/kg (TYR) 60 min pre-exercise suspended in 500 mL drink	Plasma tyrosine concentrations increased significantly after supplementation and before exercise when compared to placebo	60 min cycling at 57% ± 4% peak oxygen uptake (VO2peak) + a simulated time trial in 30°C and 60% relative humidity (completion of an individual work target as quickly as possible).

(Coull et al., 2016)	8 recreationally active males (7.1 ± 1.8 h/wk)	23 ± 1	2x 75 mg/kg or 2x 150 mg/kg (TYR) 60 min pre-exercise suspended in 250 mL drink	Not assessed	60-min walk (6.5 km/h) + a 2.4-km time trial carrying a 25-kg backpack (40°C; relative humidity, 30%) (to complete as fast as possible).
(Tumilty et al., 2020)	8 healthy recreationally trained male (level 2)	23 ± 4	150 (TYR), 300 (TYR) and 400 (TYR) mg/kg 60 to 120 min pre time trial suspended in 300 mL drinks.	Plasma tyrosine concentrations increased significantly after supplementation and before exercise when compared to placebo.	60 min constant intensity cycling + a simulated time trial in 30°C and 60% relative humidity (completion of an individual work target as quickly as possible).

PLA = placebo; TYR = Tyrosine; *=difference of the condition PLA

Table 3. Results of the methodological quality assessment using the Physiotherapy Evidence-Based Database (PEDro) scale ratings of the included studies.

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Struder et al. (1998)	No	1	U	1	1	1	1	1	1	1	1	9
Chinevere et al. (2001)	No	1	1	1	1	1	1	1	1	1	1	10
Sutton et al. (2005)	U	1	1	1	1	1	1	1	1	1	1	10
Tumilty et al. (2011)	U	1	1	1	1	1	1	1	1	1	1	10
Watson et al. (2012)	U	1	U	1	1	U	U	1	1	1	1	7
Tumilty et al. (2014)	U	1	1	1	1	1	1	1	1	1	1	10
Coull et al. (2016)	U	1	U	1	1	1	1	1	1	1	1	9
Tumilty et al. (2020)	U	1	1	1	1	1	1	1	1	1	1	10

All but one study had a score of ≥ 7 which indicates good to excellent quality.

Note: 1 = criterion is satisfied; 0 = criterion is not satisfied; U = Unclear (unable to rate).

1, eligibility criteria were specified; 2, volunteers were randomly allocated to groups; 3, allocation was concealed; 4, the groups were similar at baseline regarding the most important prognostic indicators; 5, blinding of all participants; 6, blinding of all therapists who administered the therapy; 7, blinding of all assessors who measured at least one key outcome; 8, measures of one key outcome were obtained from 85% of participants initially allocated to groups; 9, all participants for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by “intention to treat”; 10, the results of between-group statistical comparisons are reported for at least one key outcome; 11, the study provides both point measures and measures of variability for at least one key outcome.

Table 4. GRADE table RCTs.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Tyrosine]**	**[Placebo]**	**Relative (95% CI)**	**Absolute (95% CI)**		
8	Randomized trials	Not serious	Not serious	Not serious	Serious*	None	83	83	-	SMD **0.01 SD lower** (0.32 lower to 0.29 higher)	⊕⊕⊕◯ Moderate	CRITICAL

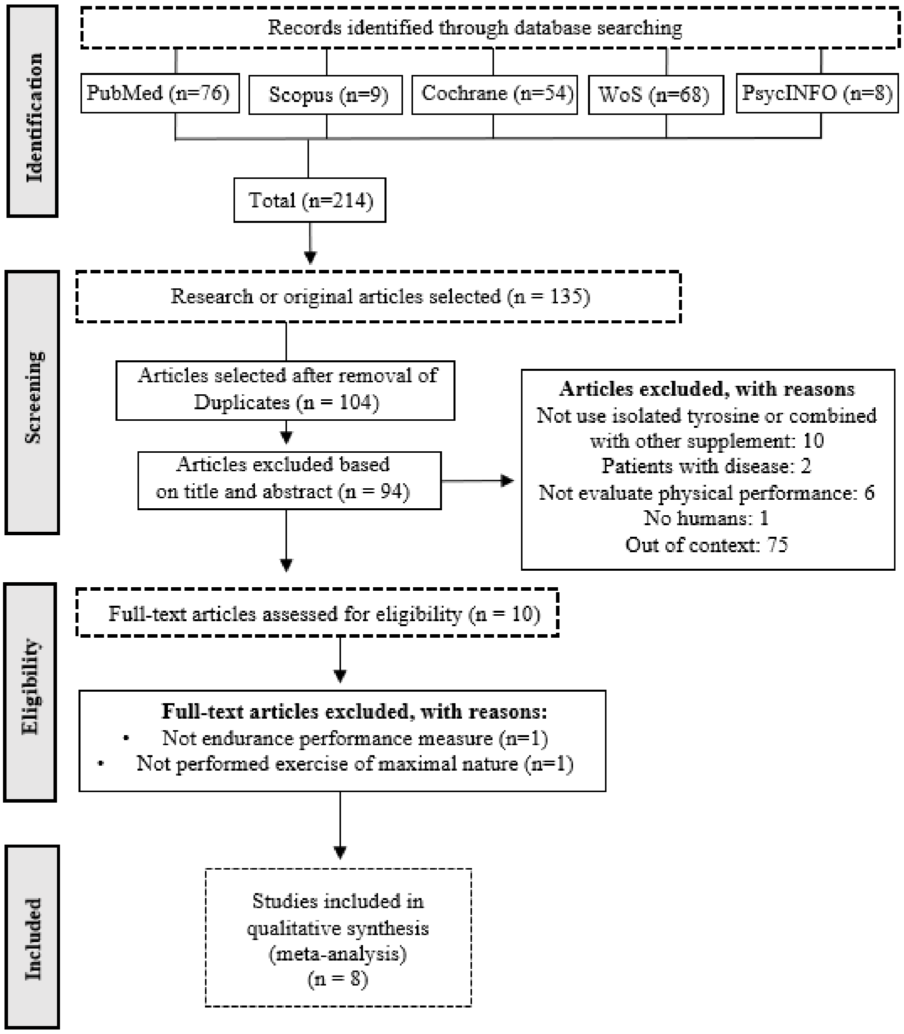
CI: confidence interval; **SMD:** standardised mean difference.

*. The total number of total participants in this comparision is lower than the Optimal Information Size.

Table 5. Main results and side effects.

Study	Outcome variables	Main results	Side effects?
Struder et al. (1998)	TTE	No significant difference was found in the TTE between the PLA (157 ± 53 min) and TYR (150 ± 42 min) trials.	There was no gastric discomfort
Chinevere et al. (2001)	ETT (work load)	No significant differences were found in time to complete the ETT for PLA (34.44 ± 2.89 min) vs. TYR (32.64 ± 3.05 min).	None reported
Sutton et al. (2005)	TTE	Ingestion of tyrosine did not significantly lengthen total time on the treadmill: 118.9 ± 1.4 min for tyrosine as compared to 119.2 ± 1.2 min for placebo treatment.	There was no gastric discomfort
Tumilty et al. (2011)	TTE	Subjects exercised for 15 ± 11% longer in TYR compared to PLA (80.3 ± 19.7 min vs. 69.2 ± 14.0 min).	None reported
Watson et al. (2012)	TTE	TYR ingestion had no effect on exercise capacity (PLA 61.4 ± 13.7 min, TYR 60.2 ± 15.4 min).	None reported
Tumilty et al. (2014)	ETT (distance)	ETT performance (34.8 ± 6.5 and 35.2 ± 8.3 min in TYR and PLA, respectively) were similar between trials.	None reported
Coull et al. (2016)	ETT (distance)	No significant difference was observed in ETT completion time between the TYR (19.78 ± 3.44 min) and PLA (20.29 ± 3.55 min) condition.	There was no gastric discomfort
Tumilty et al. (2020)	ETT (distance)	The ETT performance relative to PLA was unaffected by tyrosine ingestion (p = 0.579). PLA 34.3 ±2.5 min LOW (150mg) 35.7 ±5.9 min MED (300mg) 35.5 ±5.1 min HIGH (400mg) 36.6 ±6.0 min	None reported

PLA = placebo; TYR = tyrosine. TTE = Time to exhaustion; ETT= Time trial.



Identification
Records identified through database searching
PubMed (n=76)
Scopus (n=9)
Cochrane (n=54)
WoS (n=68)
PsycINFO (n=8)
Total (n=214)
Screening
Research or original articles selected (n = 135)
Articles selected after removal of Duplicates (n = 104)
Articles excluded based on title and abstract (n = 94)
Articles excluded, with reasons
Not use isolated tyrosine or combined with other supplement: 10
Patients with disease: 2
Not evaluate physical performance: 6
No humans: 1
Out of context: 75
Eligibility
Full-text articles assessed for eligibility (n = 10)
Full-text articles excluded, with reasons:
Not endurance performance measure (n=1)
Not performed exercise of maximal nature (n=1)
Included
Studies included in qualitative synthesis (meta-analysis) (n = 8)

Figure 1.

Study or Subgroup	Tyrosine Mean	Tyrosine SD	Tyrosine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
1.1.1 TTE									
Struder et al. (1998)	150	42	10	157	53	10	12.2%	-0.14 [-1.02, 0.74]	1998
Sutton et al. (2005)	118.9	1.4	9	119.2	1.2	9	11.0%	-0.22 [-1.15, 0.71]	2005
Tumilty et al. (2011)	80.3	19.7	8	69.2	14	8	9.2%	0.61 [-0.40, 1.62]	2011
Watson et al. (2012)	60.2	15.4	8	61.4	13.7	8	9.8%	-0.08 [-1.06, 0.90]	2012
Subtotal (95% CI)			**35**			**35**	**42.3%**	**0.02 [-0.45, 0.49]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.75, df = 3 (P = 0.63); I² = 0%									
Test for overall effect: Z = 0.08 (P = 0.94)									
1.1.2 ETT									
Chinevere et al. (2002)	-32.64	3.05	9	-34.44	2.89	9	10.5%	0.58 [-0.37, 1.53]	2002
Tumilty et al. (2014)	-34.8	6.5	7	-35.2	8.3	7	8.6%	0.05 [-1.00, 1.10]	2014
Coull et al. (2016)	-19.78	3.44	8	-20.29	3.55	8	9.8%	0.14 [-0.84, 1.12]	2016
Tumilty et al. (2020)	-35.7	5.9	8	-34.3	2.5	8	9.7%	-0.29 [-1.28, 0.69]	2020
Tumilty et al. (2020)*	-35.5	5.1	8	-34.3	2.5	8	9.7%	-0.28 [-1.27, 0.70]	2020
Tumilty et al. (2020)**	-36.6	6	8	-34.3	2.5	8	9.5%	-0.47 [-1.47, 0.52]	2020
Subtotal (95% CI)			**48**			**48**	**57.7%**	**-0.04 [-0.44, 0.37]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.99, df = 5 (P = 0.70); I² = 0%									
Test for overall effect: Z = 0.19 (P = 0.85)									
Total (95% CI)			**83**			**83**	**100.0%**	**-0.01 [-0.32, 0.29]**	
Heterogeneity: Tau² = 0.00; Chi² = 4.77, df = 9 (P = 0.85); I² = 0%									
Test for overall effect: Z = 0.09 (P = 0.93)									
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%									

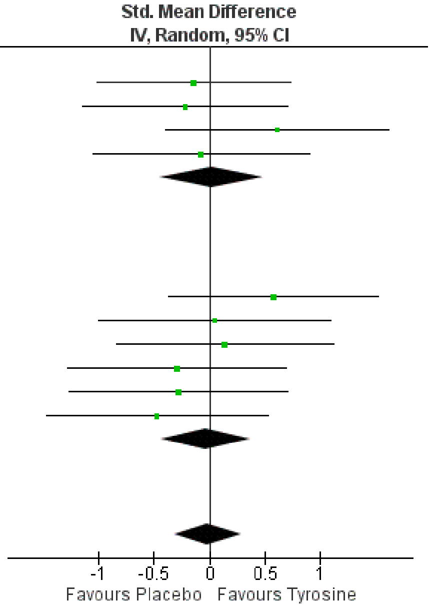


Figure 2.

Figure captions

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. After reviewing a total of 204 search records, 8 studies were included in the review. WoS = Web of science.

Figure 2. Forest plot with endurance performance comparison analyses between placebo and tyrosine. Note: Tumilty et al (2020): group that received a dose of 150mg of tyrosine; Tumilty et al (2020) *: group that received a dose of 300mg of tyrosine; Tumilty et al (2020) **: group that received a dose of 400mg of tyrosine. The values for TTE were multiplied by -1 in order to invert the values because the shorter the time in the time trial, the better the performance.