

TITLE: EFFECTS OF HMB ON ENDURANCE PERFORMANCE IN A HEALTHY
POPULATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

BRIEF RUNNING HEAD: META-ANALYSIS: HMB ON ENDURANCE
PERFORMANCE

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JFL and NT: designed and conceived the systematic review and meta-analysis, interpreted and analyzed the data, drafted the paper, and approved the final version submitted for publication. ASG, SMO and JMA: interpreted and analyzed the data, critically reviewed the manuscript and approved the final version submitted for publication. JCG and DS: critically reviewed the paper and approved the final version submitted for publication.

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ABSTRACT

β -Hydroxy- β -Methylbutyrate (HMB) has been used extensively as a dietary supplement for athletes and physically active people. However, the ergogenic effect of HMB supplementation on endurance performance is still unclear. Therefore, this systematic review and meta-analysis (SRMA) aimed to assess HMB supplementation on endurance performance and VO₂ max. This SRMA followed PRISMA guidelines. Three electronic databases were searched (PubMed/Medline, Web of Science (WOS), and Scopus) from inception until the 3rd of April of 2023. In this SRMA, human experimental trials, controlled with a placebo group, assessing the effect of HMB supplementation on endurance performance in a healthy population were included. The quality of the studies was assessed by the Physiotherapy Evidence Database (PEDro) scale. The study protocol was registered in the Prospective Register of Systematic Review (PROSPERO): CRD42022341790. Eleven studies involving 279 participants met the inclusion criteria. The results displayed a significant improvement on endurance performance (pooled SMD=0.58[0.28–0.87]) and VO₂ max (pooled SMD=0.58[0.21–0.95]) after HMB ingestion. Moreover, after the exclusion of the studies not evenly distributed around the base of the funnel plot, the results continued to be significantly positive in endurance performance (pooled SMD=0.38[0.22–0.53]) and VO₂ max (pooled SMD=0.25[0.09–0.42]). In conclusion, HMB (3 g/day) ingestion during 2-12 weeks significantly improves endurance performance and VO₂ max.

KEYWORDS: athletes; aerobic; supplementation; nutrition; β -Hydroxy- β -Methylbutyrate

INTRODUCTION

β -Hydroxy- β -Methylbutyrate (HMB) is naturally produced in animals and humans from the essential amino acid leucine (32). However, only ~5% of the ingested leucine is converted into HMB (48). As a result, it is practically unfeasible to consume the recommended dose of HMB (~3 daily grams) associated with ergogenic effects solely from dietary sources (47). Therefore, the unique method to obtain the recommended HMB dose is taking it via sports supplement form. In order to optimize the chronic effects of HMB, the most common recommendation is to consume 3 grams of HMB daily, divided into three equal servings (47). Most studies take HMB with breakfast, lunch, and dinner, regardless of the training time (47). In addition, this is a safe supplement, and there is no evidence of any adverse effects caused by this supplement (47).

Even though this supplement has been studied as a possible ergogenic aid to improve strength, increase muscle mass or reduce muscle damage, the up to now published systematic reviews and meta-analyses (SRMA) have not shown any significant effects on the previously mentioned parameters (26,27,41,44). Nevertheless, there is still limited evidence stating the effects of HMB on endurance performance. Endurance performance is affected by parameters such as maximum rate of oxygen consumption ($VO_{2\text{ max}}$), lactate/ventilatory thresholds, and exercise economy, among other factors (3,29). Specifically, $VO_{2\text{ max}}$, which is the oxygen uptake reached during maximal exercise intensity that cannot be increased despite a rise in exercise workload (3,25,29), is one of the main outcomes that are able to predict endurance performance (20). In addition, other measurements such as time to exhaustion (when the same intensity is maintained) or distance (when the time is limited) can also determine endurance performance (3).

1 There are several physiological pathways to hypothesize that HMB supplementation may
2 improve endurance performance (16,30). Firstly, this supplement could potentially
3 increase the gene expression of peroxisome proliferator-activated receptor gamma co-
4 activator 1-alpha (PGC-1 α), which in turn could increase mitochondrial biogenesis
5 increasing the oxidative metabolism capacity (22). Another pathway by which HMB
6 could influence endurance performance may be through an enhancement of glycogen
7 synthesis due to an increase of insulin-like growth factor-1 (IGF-1) and consequently the
8 inhibition of glycogen synthase kinase 3 (GSK3), which negatively regulates glycogen
9 synthesis (9,38). Increasing glycogen storage is essential for improving performance in
10 endurance sports events (28).

11
12 On the other hand, many authors hypothesized that HMB could increase muscle mass
13 because of its effects on increasing muscle protein synthesis (19,39,48). Consequently,
14 muscle mass increase could lead to an augmentation of body mass. In this sense, the
15 increase in body mass, might negatively affect endurance performance, increasing the
16 energy cost during exercise and consequently impairing performance (5). However, the
17 meta-analysis carried out by Holland et al. showed that HMB does not affect body mass
18 (26). Not increasing body mass could, hence, be advantageous for endurance athletes.

19
20 The previously mentioned HMB-induced physiological mechanisms could be beneficial
21 for athletes who have the aim to improve their endurance performance. Nevertheless, to
22 the best of the authors' knowledge, none of the previous SRMAs investigated the HMB's
23 effectiveness on endurance performance. Therefore, the primary purpose of this SRMA
24 is to assess the HMB supplementation's effect on endurance performance and on $\text{VO}_{2\text{ max}}$.

METHODS

The study protocol of this SRMA was registered in the International Prospective Register of Systematic Review (PROSPERO): CRD42022341790. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines (2) was followed to assess the effects of HMB on endurance performance and $\text{VO}_{2\text{ max}}$.

Literature search

Literature queries were performed using the electronic databases Web of Science (WOS), PubMed/MEDLINE, and Scopus (all: until the 3rd of April of 2023). The following Boolean search was used to identify the records: (("β-Hydroxy-β-Methylbutyrate" OR "Beta-Hydroxy-Beta-Methylbutyrate" OR "HMB") AND (endurance OR aerobic OR VO_2)). Further, the snowball strategy (21) was carried out to obtain a more precise search. The search was individually carried out by two authors (XX and XX), and disagreements were solved by third-party adjudication (XX).

Eligibility criteria

The a priori inclusion criteria for study inclusion were as follows: (1) HMB supplementation protocol; (2) participants had to be healthy, human adolescents or adults; (3) endurance performance assessments, (4) human experimental trial; (5) controlled with a placebo group. Studies were excluded when: (1) HMB was mixed with another ergogenic aid; (2) studies without pre-and post-supplementation data.

Text screening

Two authors (XX and XX) independently evaluated all abstracts and full text for eligibility. If necessary, a third author (XX) was consulted for potential discrepancies between authors.

Data extraction

All the extracted data was added to a spreadsheet (Microsoft Excel, Microsoft Corporation, Washington, DC, USA). For each study, data were extracted regarding the study authors and publication year, study design, participant's sex and age, ingested HMB type, supplementation dosage, duration of the study, and endurance performance outcomes (pre- and post-data). The outcome measures were: distance, individual anaerobic threshold, 4 mmol/L lactate threshold, 8 mmol/L lactate threshold, time to exhaustion, VO_2 at 2 mmol blood lactate, $\text{VO}_{2\text{ max}}$, peak oxygen consumption ($\text{VO}_{2\text{ peak}}$), and ventilatory threshold. When numerical data were absent, and the data were expressed in graphs, each image's means and standard deviations were calculated by measuring the pixel length by Image J software (National Institutes of Health, Bethesda, MD, USA). In addition, if there was insufficient information, the respective corresponding author was contacted.

Quality Assessment of included studies

The quality of the studies was assessed through the Physiotherapy Evidence Database (PEDro) scale (35). The studies can obtain the mark of excellent quality (when the score is 9 or 10 points), good quality (when the score is between 6 and 8 points), fair quality (when the score is between 4 and 5 points), or poor quality (when the score is under 3 points) (6). Two independent researchers (XX and XX) conducted the evaluation, and discrepancies were resolved through discussion.

Meta-analysis calculation

The statistical analyses were performed using R software's "metafor" package (R Foundation for Statistical Computing, Vienna, Austria). Most of the studies in the SRMA showed more than one relevant outcome evaluating endurance performance. However, when more than one outcome per study is included in a meta-analysis, the final results could affect the weight of the studies in the meta-analysis results (4). In order to reduce the errors affecting the weight the meta-analysis gives to each study, "MAAd" package in R software (R Foundation for Statistical Computing, Vienna, Austria) was used. In that way, it was obtained a unique effect size estimate per study (8). The within-study correlation utilized for this analysis was 0.70 (18). Therefore, each study of the SRMA received a weighted estimation of standardized mean difference (SMD) and variance calculated as Hedges' G (23), using the inverse variance random-effects model by the DerSimonian & Laird method (10). The correlation coefficient used to obtain the variance was 0.70 (43).

For the estimation of the endurance performance meta-analysis, all of the outcomes included were taken into account (distance, individual anaerobic threshold, 4 mmol/L lactate threshold, 8 mmol/L lactate threshold, time to exhaustion, VO_2 at 2 mmol blood lactate, $\text{VO}_{2 \text{ max}}$, $\text{VO}_{2 \text{ peak}}$, and ventilatory threshold), while for $\text{VO}_{2 \text{ max}}$ meta-analysis calculation, $\text{VO}_{2 \text{ max}}$ and $\text{VO}_{2 \text{ peak}}$ outcomes were included. The $\text{VO}_{2 \text{ peak}}$ was included in the $\text{VO}_{2 \text{ max}}$ meta-analysis when the authors' provided data was obtained by measuring the maximal oxygen consumption during graded exercise tests to volitional exhaustion.

The calculations of the effects of HMB supplementation vs. placebo were assessed using the SMD with a 95% of confidence interval (95% CIs; [lower bound–upper bound]), and the significance was set at $p < 0.05$. The SMD was evaluated through the Cohen criteria,

and it was classified as trivial (SMD <0.2), small (SMD was between 0.2-0.3), moderate (SMD was between 0.4- 0.8), and large (SMD>0.8) (7).

The heterogeneity between trials was evaluated using the I^2 statistic and was calculated based on the restricted maximum-likelihood estimator of tau-square. I^2 values of <25%, 25–50%, and >50% are considered to represent small, medium, and large amounts of inconsistency (24).

The funnel plot asymmetry was visually evaluated to determine the potential publication bias. Furthermore, funnel plot asymmetry was as well assessed using Egger's regression test (15) and Duval and Tweedie's trim and fill method (14). With the aim of reducing publication bias and the heterogeneity of the analysis, the meta-analysis was repeated after excluding studies not evenly distributed around the base of the funnel plot.

RESULTS

Literature search

Three hundred sixty articles met the objectives after the database search. Finally, 11 studies (1,11–13,17,31,34,36,40,42,45) involving 279 participants were extracted from the first search and were included in the SRMA. The detailed steps of the article selection process for the SRMA are shown as a flow diagram in figure 1.

****[Figure 1 about here]****

Study characteristics

The most important information about the studies included in this SRMA is summarized in table 1. All participants in the experimental groups ingested 3 g of HMB and took the

same daily amount of HMB (1,11–13,17,31,34,36,40,42,45). In most of the analyzed studies, HMB-induced improvements were found (11–13,17,34,42,45). Only four of the investigations could not find improvements in any of the endurance performance markers that the authors had analyzed (1,31,36,40). The improvements were found in the individual anaerobic threshold (17), 8 mmol/L lactate threshold (17), time to exhaustion (11–13), VO_2 at 2 mmol blood lactate (45), $\text{VO}_{2\text{ max}}$ (11,12,34), $\text{VO}_{2\text{ peak}}$ (42), and ventilatory threshold (11–13,42).

****[Table 1 about here]****

Level of quality of the studies

The PEDro scale showed that the study quality of the investigations included in this SRMA was excellent, with an average score of 9.28 points. Ten (1,11–13,17,31,34,40,42,45) of the eleven studies included in this SRMA were categorized as excellent quality, while only one study (36) was classified as fair quality. The results are shown in table 2.

****[Table 2 about here]****

Endurance performance outcomes

The supplementation with HMB showed a significant ($p<0.01$) and moderate effect on endurance performance (pooled $\text{SMD}=0.58[0.28 - 0.87]$) (figure 2a). The measurements of heterogeneity showed a significant and large inconsistency ($I^2=61.19\%$; $p<0.01$). In addition, the visual analysis of the funnel plot showed possible publication bias (figure 3a); however, Egger's regression test did not find funnel plot asymmetry ($df=9$; $p=0.05$),

and there were not any missing studies on either side of the plot after Duval and Tweedie trim and fill test.

****[Figure 2 about here]****

After excluding the studies not evenly distributed around the base of the funnel plot (36,45) (figure 3b), the heterogeneity between studies was drastically reduced ($I^2=0\%$; $p=0.96$), and the effect of HMB supplementation on endurance performance was slightly reduced (pooled SMD=0.38[0.22 – 0.53]) (figure 2b).

****[Figure 3 about here]****

VO₂ max outcomes

Similar trends were observed on VO₂ max meta-analysis obtaining a significant ($p<0.01$) and moderate effect after HMB ingestion (pooled SMD=0.58[0.21 – 0.95]) (figure 4a). The heterogeneity evaluation revealed a significant and large inconsistency ($I^2=70.22\%$; $p<0.01$). Moreover, possible publication bias was found after the visual analysis of the funnel plot (figure 5a) and Egger's regression test ($df=7$; $p=0.03$). After Duval and Tweedie trim and fill test, there were three missing studies on the left side of the plot.

****[Figure 4 about here]****

The heterogeneity between studies was considerably reduced ($I^2=0\%$; $p=0.89$) when the studies not evenly distributed around the base of the funnel plot (36,45) were eliminated (figure 5b), and Egger's regression test did not find funnel plot asymmetry ($df=4$; $p=0.40$) after the correction. The effect size after the correction continued to be significant ($p<0.01$) with a small effect size (pooled SMD=0.25[0.09 – 0.42]) (figure 4b).

****[Figure 5 about here]****

DISCUSSION

Eleven studies fulfilled the inclusion criteria to be included in this SRMA, and a total of 279 participants took part in the study. Every participant in the intervention group ingested the recommended dose of 3 daily grams of HMB so as to maximize this supplement's effects. The main purpose of this SRMA was to analyze and summarize the current scientific literature in order to assess the efficacy of HMB supplementation on endurance performance. The primary discovery of this SRMA was that HMB supplementation had significant positive effects on endurance performance. The meta-analysis results showed significant change ($p < 0.01$) with a moderate positive effect ($ES = 0.58$ [0.28-0.87]; $I^2 = 61.19\%$) to improve endurance performance compared with placebo. With the aim of reducing publication bias, the same analysis was performed after excluding two studies (36,45) not evenly distributed around the base of the funnel plot. Following the exclusion of both investigations, the result of the meta-analysis was similar ($ES = 0.38$ [0.22-0.53]; $p < 0.01$; $I^2 = 0\%$). Moreover, this SRMA also displayed a significant improvement of HMB on $VO_{2\max}$ capacity of the participants before ($ES = 0.58$ [0.21-0.95]; $p < 0.01$; $I^2 = 70.22\%$) and after the correction of publication bias ($ES = 0.25$ [0.09-0.42]; $p < 0.01$; $I^2 = 0\%$).

In this SRMA, after a close observation of the results obtained in table 1 (effect section) and the meta-analyses results, an illogic result was detected in O'Connor & Crowe et al. study (36). These authors did not find any significant effect in $VO_{2\max}$ measurement; however, a large effect size was observed in the meta-analysis. Therefore, in order to find an explanation for the results obtained, it is possible that O'Connor & Crowe et al. could have made a mistake when reporting the data or used an inadequate statistical analysis.

Consequently, publication bias was detected in that study after the evaluation of the funnel plot asymmetry. Hence, O'Connor & Crowe et al. study (36) was excluded in the corrected meta-analysis in both $\text{VO}_{2\text{ max}}$ and endurance performance meta-analyses in order to reduce possible bias.

Otherwise, another interesting result was observed when assessing endurance and $\text{VO}_{2\text{ max}}$ meta-analyses. The effect size obtained in the endurance meta-analysis was considerably higher than $\text{VO}_{2\text{ max}}$ meta-analysis. These outcomes can be explained because HMB supplementation may enhance endurance performance through multiple mechanisms beyond $\text{VO}_{2\text{ max}}$ improvement. Endurance performance involves several factors, such as lactate/ventilatory thresholds and movement economy, in addition to $\text{VO}_{2\text{ max}}$ (3). Therefore, HMB supplementation may affect these alternative physiological mechanisms and lead to a more significant improvement in endurance performance than $\text{VO}_{2\text{ max}}$ alone. This explanation could explain why the endurance performance meta-analysis showed a higher effect size than the $\text{VO}_{2\text{ max}}$ meta-analysis.

The results found in this SRMA showed that the ingestion of HMB in the adequate dose (3g/days) and duration (2 to 12 weeks) of supplementation influences endurance capacity positively. Furthermore, the point that most of the participants included in this SRMA combined the supplementation protocol with a training protocol, mainly aerobic training, might have influenced the results (1,11,13,17,34,36,40,42,45). Hence, there could be a synergistic effect between training and HMB to improve endurance performance. In order to explain the positive results found in this SRMA, there are different HMB-induced physiological pathways that can elucidate the results.

This ergogenic aid could increase the gene expression of PGC-1 α (22). Consequently, HMB supplementation could increase mitochondrial biogenesis, and play a role in the

transformation of muscle fibers shifting muscle fibers to type I, the ones rich in mitochondria, increasing the oxidative metabolism capacity (22). The enhancement of the oxidative capacity obtained throughout this pathway could explain the enhancements of aerobic parameters such as VO_2 max, VO_2 peak, ventilatory threshold, or individual thresholds. Likewise, the increase of oxidative capacity could save muscle glycogen during exercise and reduce lactate production during exercise (45).

In addition, HMB enhances glycogen storage through a sequential process: first, it elevates IGF-1 levels, followed by the inhibition of GSK3, resulting in increased glycogen synthesis (9,38). This pathway, in conjunction with the previously noted upregulation of PGC-1 α gene expression (22), could explain the results found in time to exhaustion outcome, which was measured in four studies. Three of the four studies (11–13) demonstrated statistically significant effects on this parameter, while only one failed to detect any significant effect (42). Enhancing glycogen availability is crucial in increasing endurance capacity, ensuring greater energy accessibility, and thereby contributing to improved time to exhaustion.

Furthermore, HMB may play a role in the post-training recovery period (19). This ergogenic aid might inhibit the ubiquitin-proteasome proteolytic pathway, which is responsible for the specific degradation of intracellular proteins (46). Concretely, few investigations showed that HMB was able to decrease muscle damage and improve recovery after high-intensity training (31,37). Improving recovery after training could enhance exercise-induced muscular adaptation and, consequently, sports performance.

On the other hand, there is one pathway that HMB could negatively affect endurance capacity (5). This supplement has been studied as an ergogenic aid to increase muscle mass and, in consequence, body mass (26,27,41,44). The increase in body mass can

negatively affect endurance performance, augmenting the energy cost during exercise and, thus, decreasing performance (5). It has been hypothesized that HMB could augment muscle mass by increasing protein synthesis by upregulation of mammalian target of rapamycin (mTOR) (33). However, there is no evidence supporting this hypothesis due to the results found in previous meta-analyses (26,27,41,44). Hence, the incapacity of this supplement to increase body mass could be positive for endurance performance.

It is important to state that this study is not exempt from potential limitations. Thus, the results of this SRMA should be cautiously interpreted. The number of studies included in this SRMA could have influenced the final results of the pooled meta-analysis, mainly after the publication bias correction, where the number of studies was reduced. Nevertheless, that reduction in the studies included in the analyses (endurance performance and $\text{VO}_2 \text{ max}$) reduced the publication bias and the heterogeneity to 0 %. In addition, the only study with a lower score on the PEDro scale, with a score of 5 points (fair quality), was removed after publication bias correction. Therefore, in the end, only studies with excellent quality (9 or more points on the PEDro scale) were included in the analyses.

PRACTICAL APPLICATIONS

HMB supplementation influences several physiological pathways that enhance endurance performance and VO_2 capacity, as observed in the meta-analysis results. This supplement may increase oxidative capacity, augment muscle glycogen storage, and accelerate recovery without increasing body mass. Therefore, sports scientists, nutritionists, dietitians, coaches, and athletes must keep in mind the results found in this SRMA when the main objective is to enhance endurance performance.

CONCLUSION

In conclusion, the current SRMA indicates that the supplementation of 3 daily grams of HMB for 2-12 weeks significantly improves endurance performance and $\text{VO}_2 \text{ max}$. Nonetheless, in order to confirm the positive association of HMB effects on endurance performance and further contribute to current knowledge in the HMB supplementation field, more double-blinded, randomized, placebo-controlled trials are necessary.

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FIGURE LEGENDS

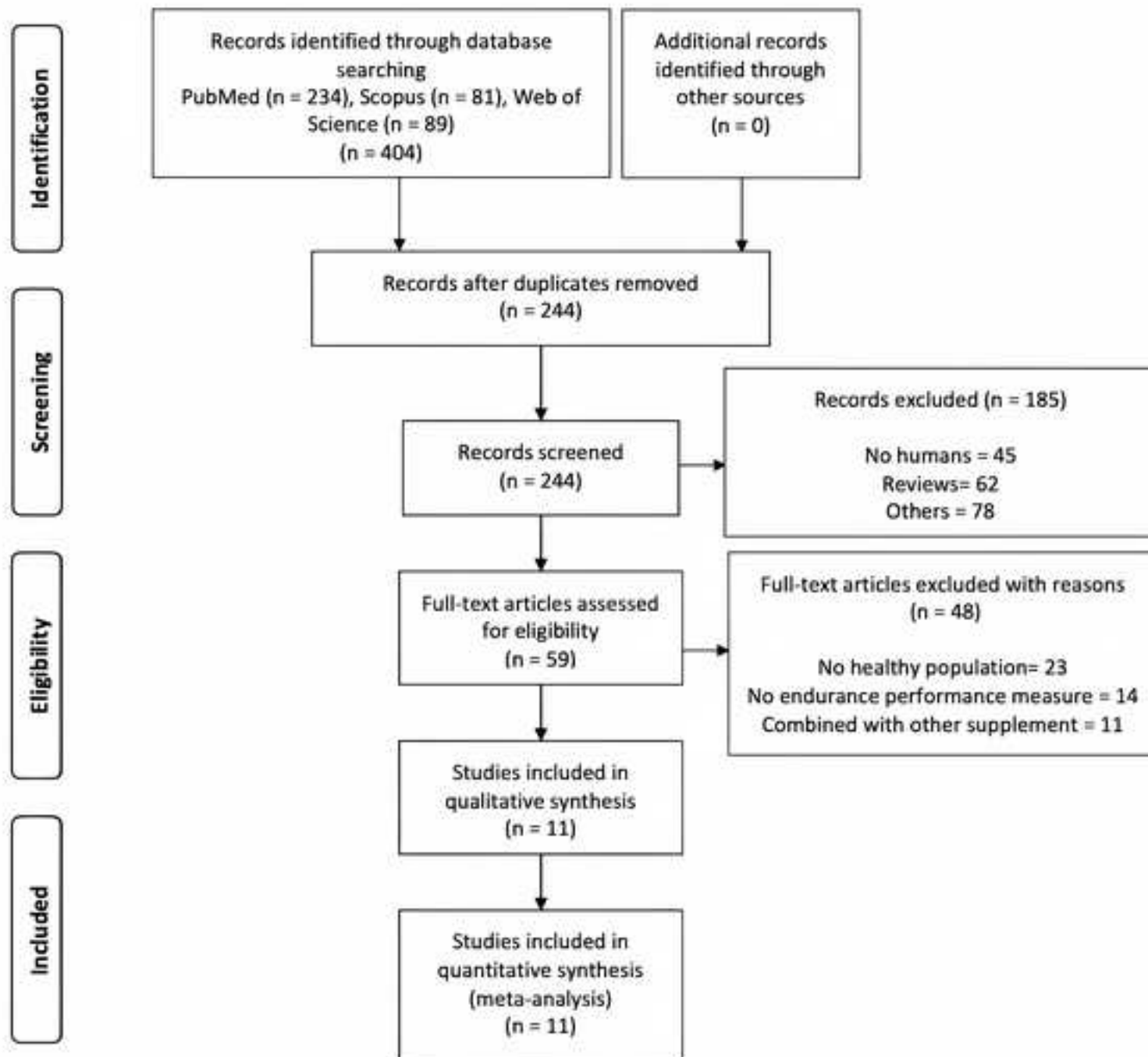
Figure 1. PRISMA flow diagram.

Figure 2. Pooled meta-analysis of the effects of HMB on endurance performance. a) before the correction; b) after the correction.

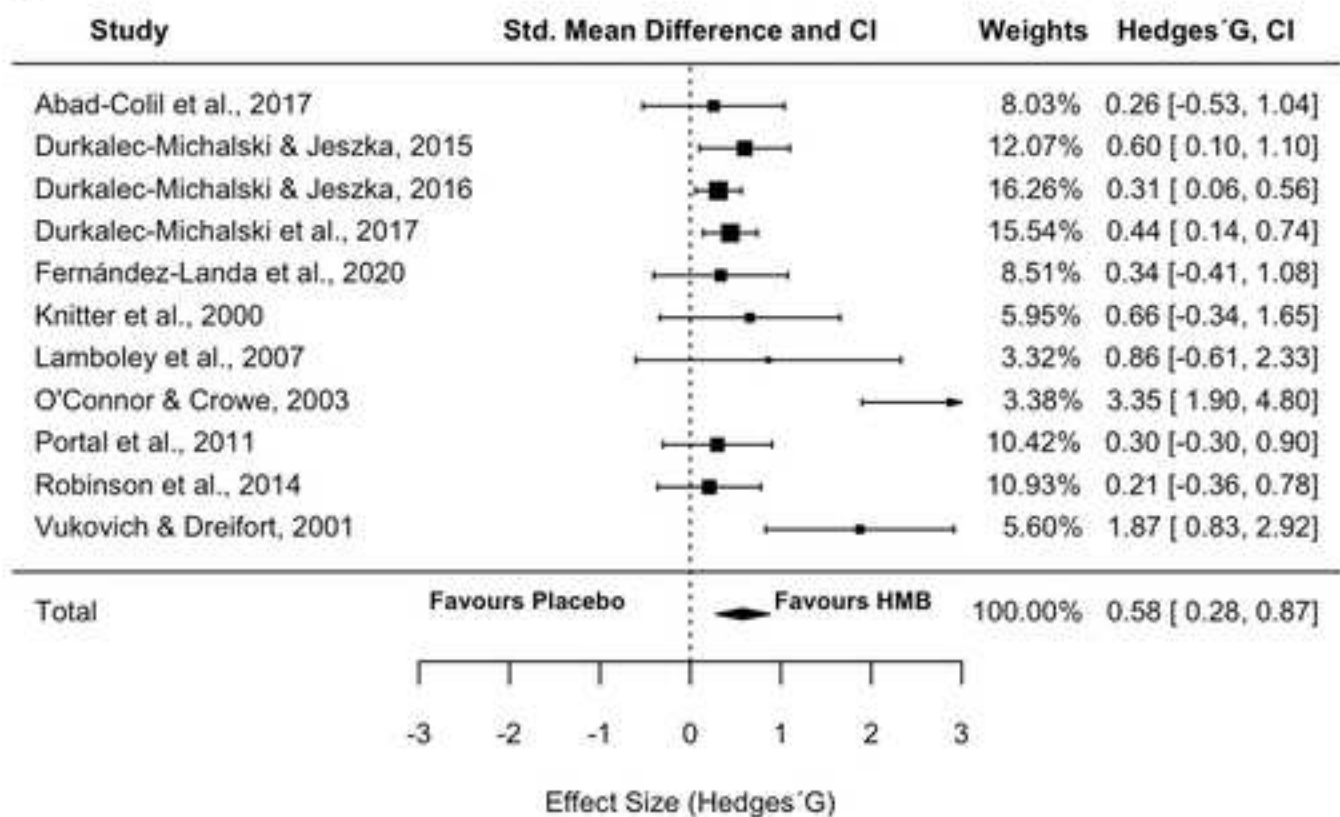
Figure 3. Funnel plot of the studies evaluating the effects of HMB on endurance performance. a) before the correction; b) after the correction.

Figure 4. Pooled meta-analysis of the effects of HMB on $VO_{2\max}$. a) before the correction; b) after the correction.

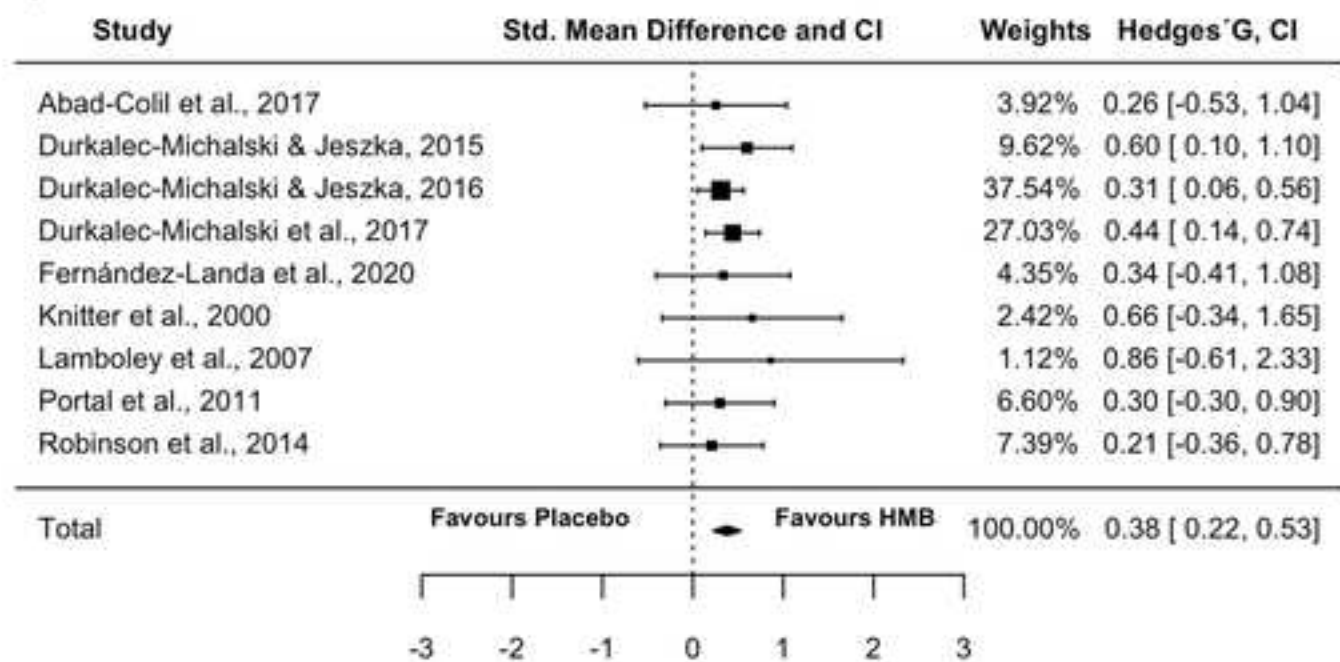
Figure 5. Funnel plot of the studies assessing the effects of HMB on $VO_{2\max}$. a) before the correction; b) after the correction.

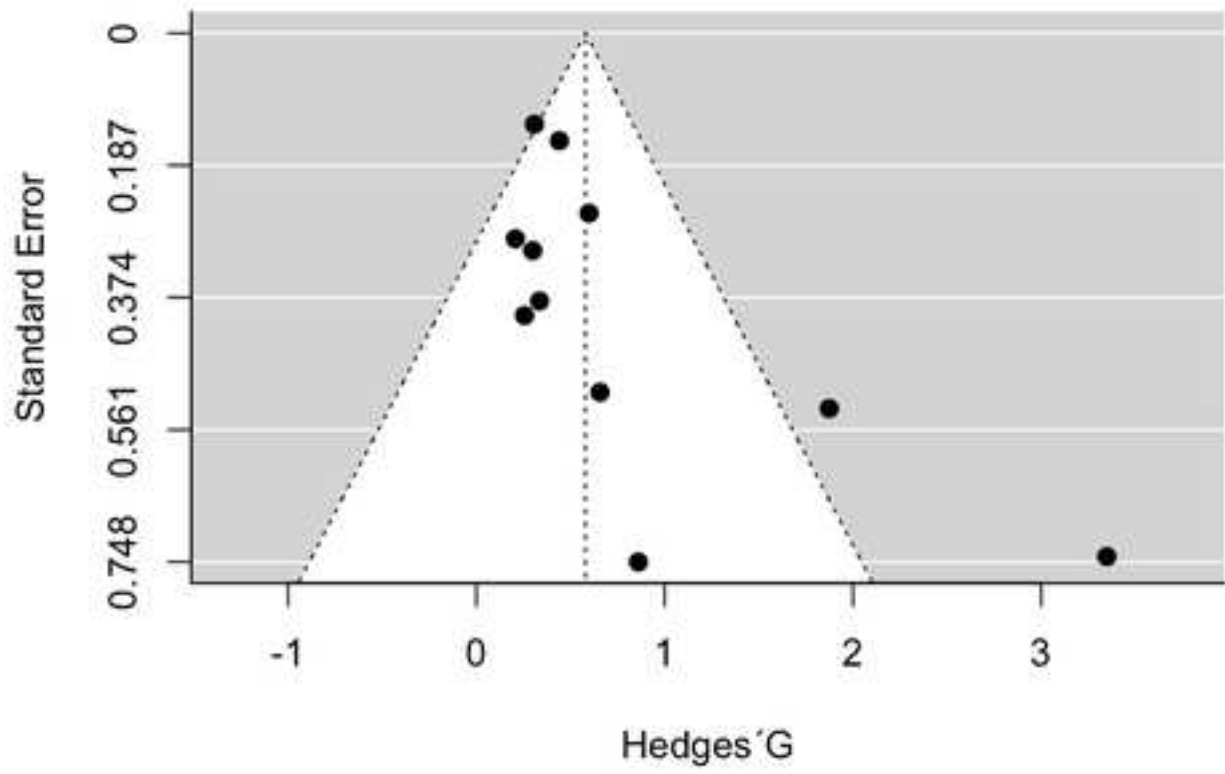
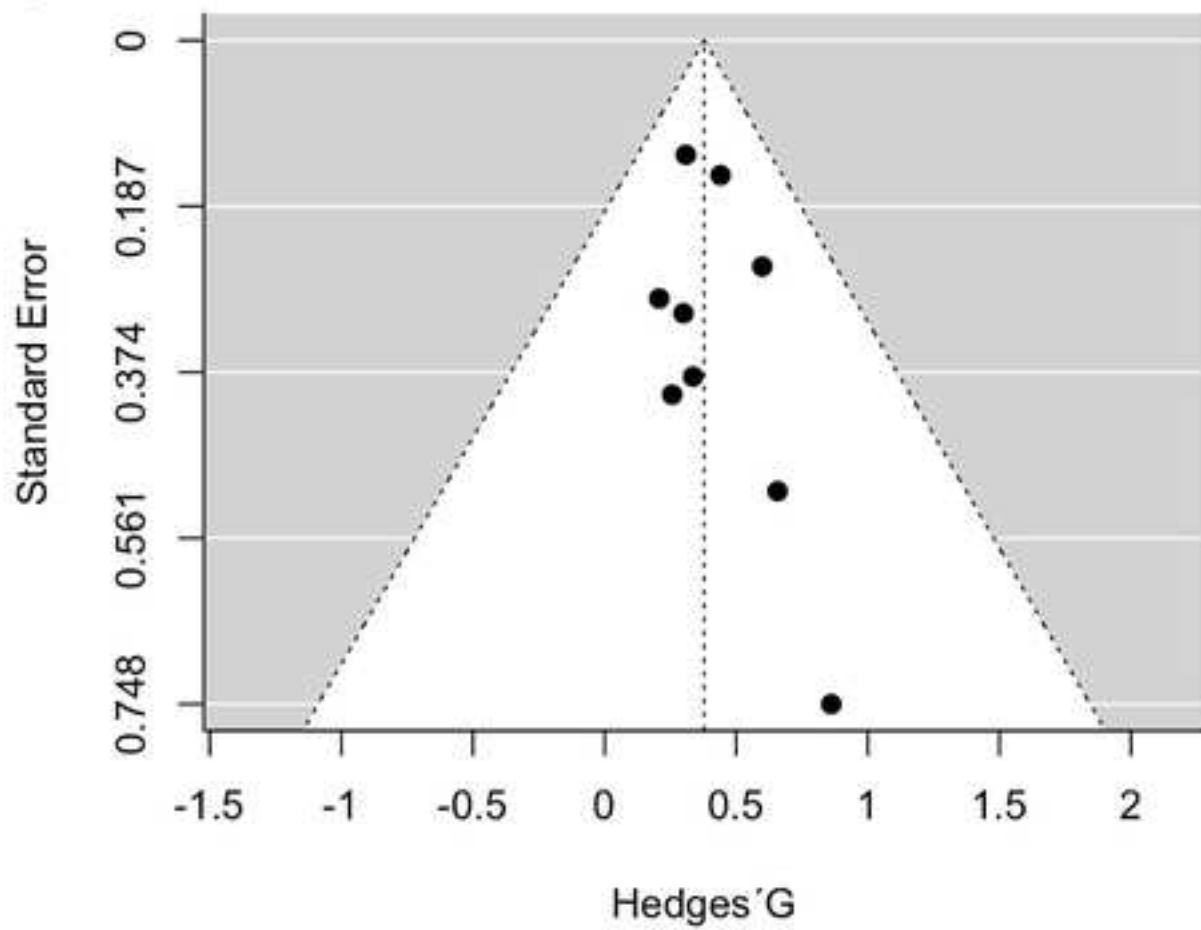


a)

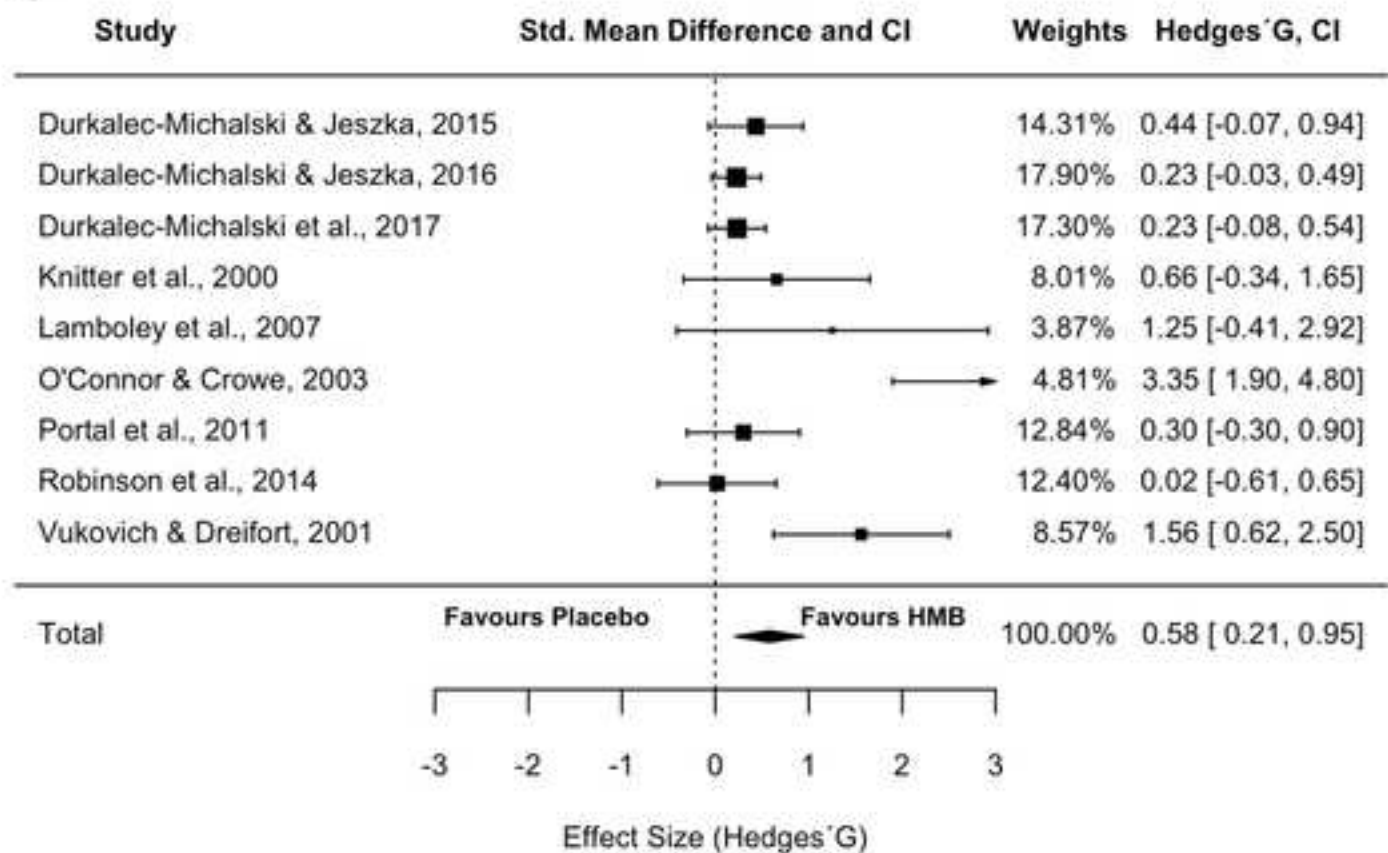


b)

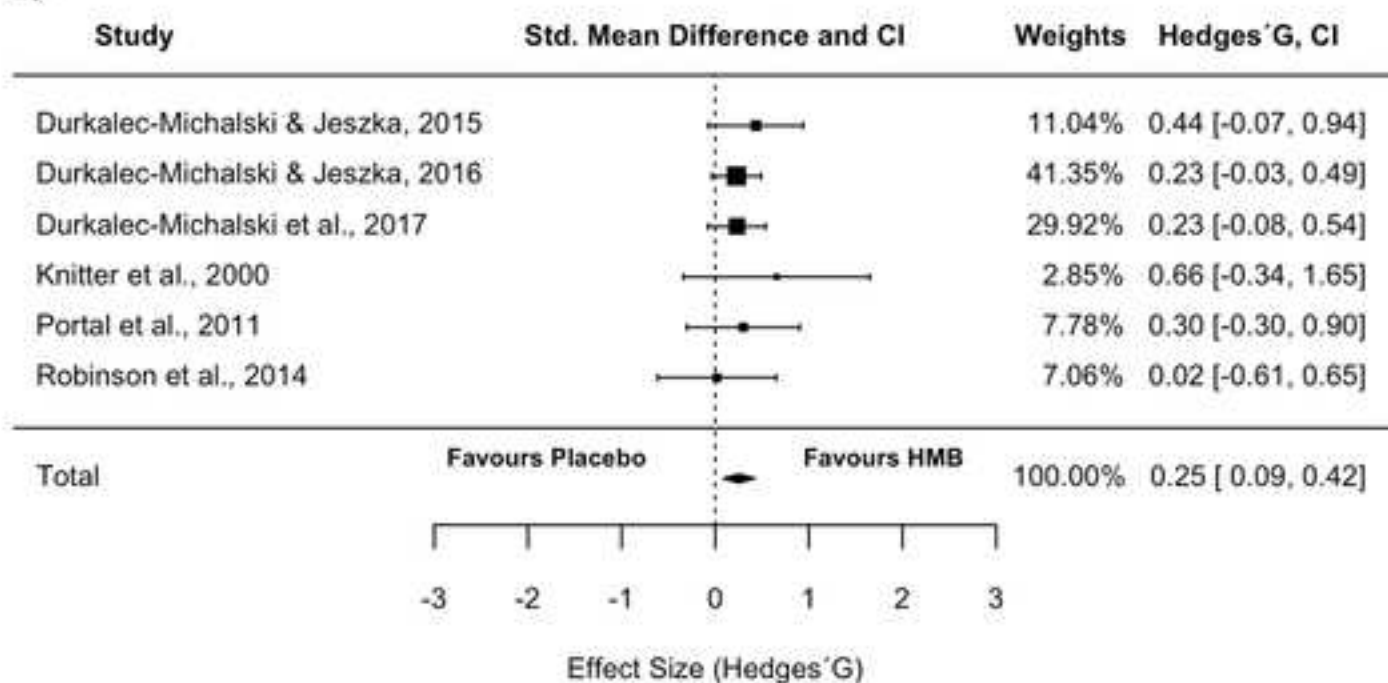


a)**b)**

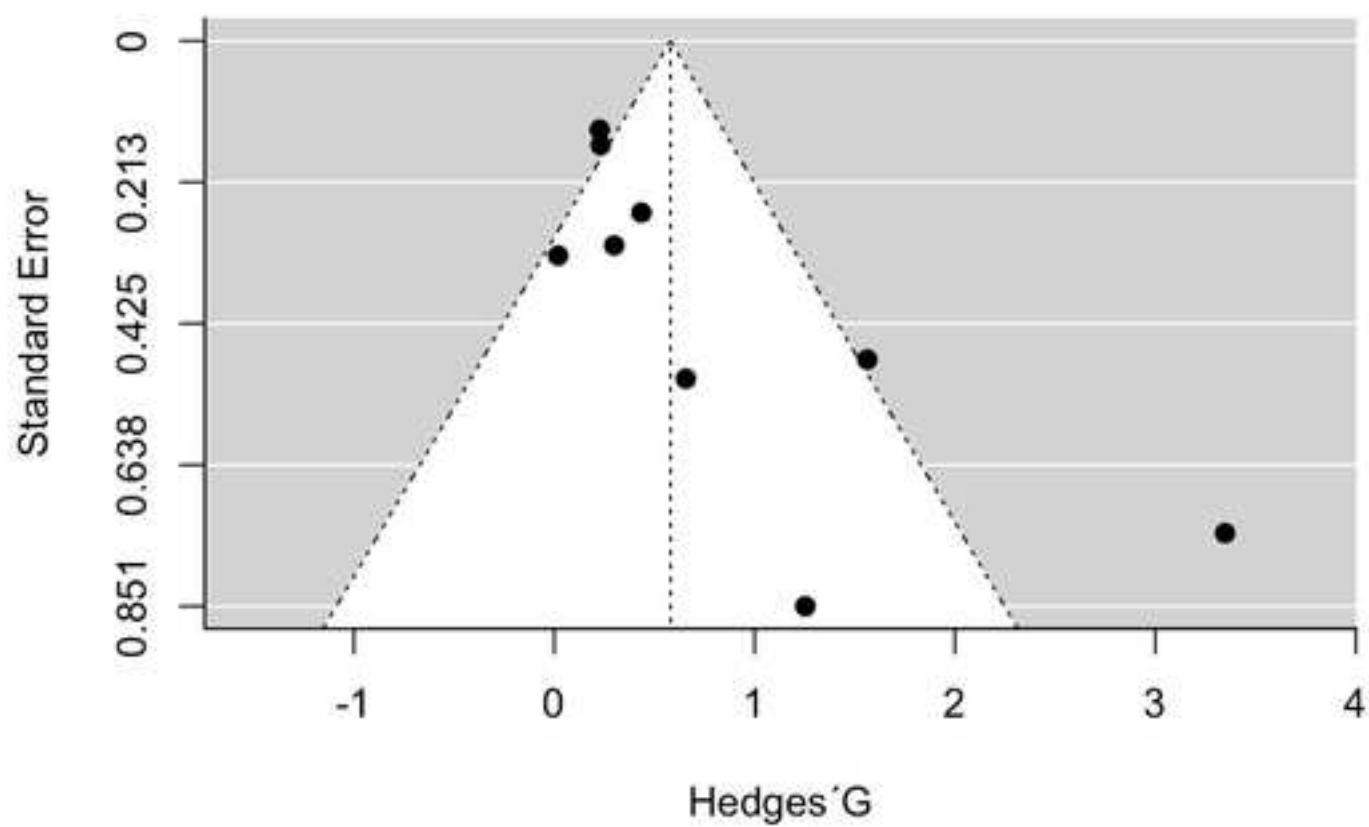
a)



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a)



b)

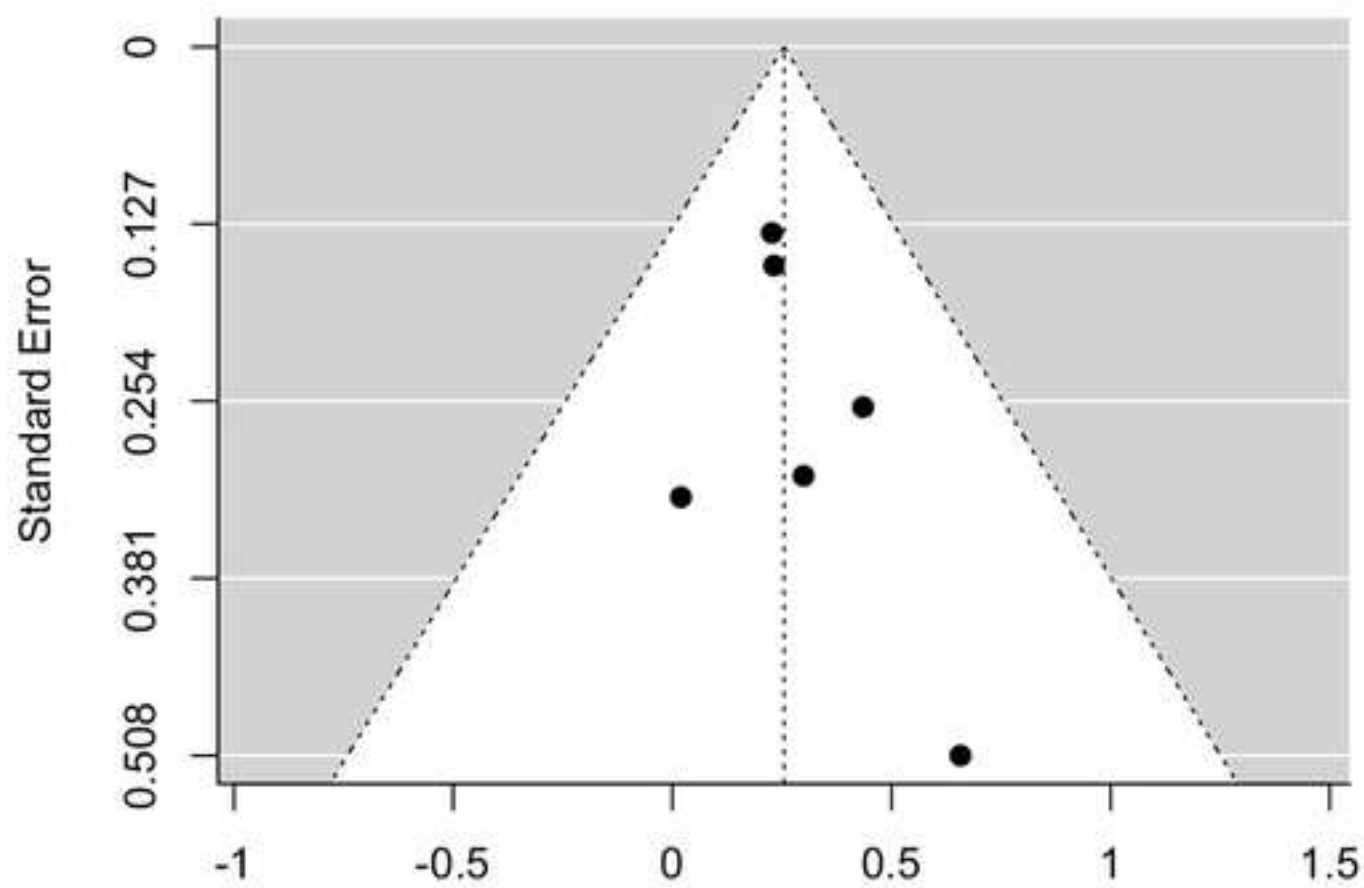


Table 1

Table 1. Summary of the studies included in the SRMA.

Study	Participants	Supplementation protocol	Duration	Form	Training program	Test	Outcome	Effect
Abad-Colil et al., 2017 (1)	16 male soccer players (EG: 18.3±1.2 years; PLA: 19.0±1.5 years)	3 g/day (divided equally into 3 parts)	4 weeks	Ca-HMB Capsules	Regular in-season soccer training	Yo-Yo endurance intermittent recovery test	Distance (m)	↔
Durkalec-Michalski & Jeszka, 2015 (11)	16 elite male rowers (19.5±1.4 years)	3 g/day (divided equally into 3 parts)	12 weeks	Capsules	Regular training	Incremental test (cycle ergometer)	VO _{2 max} (mL/min)	↔
							VO _{2 max} (mL/kg/min)	↑
							Ventilatory threshold (W)	↑
							Ventilatory threshold (W/kg)	↑
							Time to exhaustion (min)	↑
Durkalec-Michalski & Jeszka, 2016 (12)	58 male athletes (22±6 years)	3 g/day (divided equally into 3 parts)	12 weeks	Ca-HMB Capsules	No reported	Incremental test (cycle ergometer)	VO _{2 max} (mL/min)	↔
							VO _{2 max} (mL/kg/min)	↑
							Ventilatory threshold (W)	↑
							Time to exhaustion (min)	↑
Durkalec-Michalski et al., 2017 (13)	42 males trained in combat sports (22.8±6.1 years)	3 g/day (divided equally into 3 parts)	12 weeks	Ca-HMB Capsules	Minimum of 6 workout sessions/week	Incremental test (rowing ergometer)	VO _{2 max} (mL/min)	↔
							VO _{2 max} (mL/kg/min)	↔
							Ventilatory threshold (W)	↑
							Ventilatory threshold (W/kg)	↑

							Time to exhaustion (min)	↑
Fernández-Landa et al., 2020 (17)	28 elite male rowers (30.43±4.64 years)	3 g/day	10 weeks	Ca-HMB Powder	6 workout sessions/week	Incremental test (rowing ergometer)	Individual anaerobic threshold (W)	↑
							4 mmol/L lactate threshold (W)	↔
							8 mmol/L lactate threshold (W)	↑
Knitter et al., 2000 (31)	13 healthy males and females (EG: 36±2 years; PLA: 26±3 years)	3 g/day	6 weeks	Capsules	No reported	No reported	VO _{2 max} (mL/kg/min)	↔
Lambole et al., 2007 (34)	16 male and female college students (EG: 23.40±1.25 years; PLA: 23.43±0.78 years)	3 g/day (divided equally into 3 parts)	5 weeks	Ca-HMB Capsules	3 workout sessions/week	Incremental test (treadmill)	VO _{2 max} (mL/kg/min)	↑
							Ventilatory threshold (mL/kg/min)	↔
O'Connor & Crowe, 2003 (37)	27 male professional rugby players (24.9±0.7 years)	3 g/day	6 weeks	Powder	8 workout sessions/week	Multistage aerobic capacity test	VO _{2 max} (mL/kg/min)	↔
Portal et al., 2011 (41)	28 elite male and female junior volleyball players (EG: 16.1±1.3 years; PLA: 16.2±1.3 years)	3 g/day	7 weeks	Capsules	18-22 hour/week	Twenty-minute shuttle run test	VO _{2 max} (mL/kg/min)	↔
Robinson et al., 2014 (43)	34 healthy male and female (EG: 22.9±2.4 years; PLA: 23.6±0.3.7 years)	3 g/day (divided equally into 3 parts)	4 weeks	HMB-FA powder	3 workout sessions/week	Incremental test (cycle ergometer)	VO _{2 peak} (mL/kg/min)	↑
							Ventilatory threshold (mL/kg/min)	↑
							Time to exhaustion (min)	↔
		3 g/day	2 weeks	Ca-HMB Capsules	300 miles/week	Incremental test (cycle ergometer)	VO _{2 peak} (mL/min)	↔

Vukovich & Dreifort, 2001 (46)	8 male endurance-trained cyclists (34.2±2.6 years)						VO ₂ at 2 mmol blood lactate (mL/min)	↑
Legend: ↑ HMB statistically improved over placebo; ↓ HMB statistically impaired over placebo; ↔ HMB was not statistically different; EG, experimental group; g, grams; kg, kilograms; km, kilometers; L, liters; m, meters; min, minutes; mL, milliliters; mmol, millimole; PLA, placebo group; VO ₂ , oxygen uptake; VO _{2 max} , maximal oxygen uptake; VO _{2 peak} , peak oxygen uptake; W, watts.								

Table 2. Table PEDro ratings of the included studies

Study	1	2	3	4	5	6	7	8	9	10	11	TOTAL
Abad-Colil et al., 2017 (1)	Yes	0	0	1	1	1	1	1	1	1	1	10
Durkalec-Michalski & Jeszka, 2015 (11)	Yes	1	0	1	1	1	1	1	1	1	1	10
Durkalec-Michalski & Jeszka, 2016 (12)	Yes	1	1	1	1	1	1	1	1	1	1	10
Durkalec-Michalski et al., 2017 (13)	Yes	1	1	1	1	1	1	0	1	1	1	9
Fernández-Landa et al., 2020 (17)	Yes	1	1	1	1	1	1	1	1	1	1	10
Knitter et al., 2000 (31)	Yes	1	1	1	1	1	1	0	1	1	1	9
Lambole et al., 2007 (34)	Yes	1	1	1	1	1	1	1	1	1	1	10
O'Connor & Crowe, 2003 (37)	Yes	0	0	1	0	0	0	1	1	1	1	5
Portal et al., 2011 (41)	Yes	1	1	1	1	1	1	1	1	1	1	10
Robinson et al., 2014 (43)	Yes	1	1	1	1	1	1	1	1	1	1	10
Vukovich & Dreifort, 2001 (46)	Yes	1	1	1	1	1	1	0	1	1	1	9

Legend: 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 was 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.