β-alanine supplementation to improve exercise capacity and performance: a systematic review and meta-analysis

Review Article

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ABSTRACT

Objective: To conduct a systematic review and meta-analysis of the evidence on the effects of β-alanine supplementation on exercise capacity and performance.

Design: This study was designed in accordance with PRISMA guidelines. A three level mixed effects model was employed to model effect sizes and account for dependencies within data.

Data sources: Three databases (PubMed, Google Scholar, Web of Science) were searched using a number of terms ("β-alanine" and "beta-alanine" combined with "supplementation", "exercise", "training", "athlete", "performance", and "carnosine").

Eligibility criteria for selecting studies: Inclusion/exclusion criteria limited articles to double-blinded, placebo-controlled studies investigating the effects of β-alanine supplementation on an exercise measure. All healthy participant populations were considered, whilst supplementation protocols were restricted to chronic ingestion. Crossover designs were excluded due to the long washout period for skeletal muscle carnosine following supplementation. A single outcome measure was extracted for each exercise protocol and converted to effect sizes for meta-analyses.

Results: Forty individual studies employing 65 different exercise protocols and totalling 70 exercise measures in 1461 participants were included in the analyses. A significant overall effect size of 0.18 (95%CI: 0.08, 0.28) was shown. Meta-regression demonstrated that exercise duration significantly (P=0.004) moderated effect sizes. Subgroup analyses also identified the type of exercise as a significant (P=0.013) moderator of effect sizes within an exercise timeframe of 0.5-10 min with greater effect sizes for exercise capacity [0.4998 (95%CI: 0.246, 0.753)] *vs.* performance [0.1078 (95%CI: -0.201, 0.416)]. There was no moderating effect of training status (P=0.559), intermittent or continuous exercise (P=0.436) or total amount of β-alanine ingested (P=0.438). Co-supplementation with sodium

bicarbonate resulted in the largest effect size when compared to placebo [0.43 (95%CI: 0.22, 0.64)]. **Summary/Conclusions**: β-alanine had a significant overall effect while sub-group analyses revealed a number of modifying factors. These data allow individuals to make informed decisions as to the likelihood of an ergogenic effect with β-alanine supplementation based upon their chosen exercise modality.

Key points:

- Carnosine (β-alanyl-L-histidine) is abundant in skeletal muscle suggesting it plays an important role during exercise, with a key physiological role considered to be intracellular pH regulation;
- β-alanine supplementation can increase muscle carnosine concentration and improve exercise capacity and performance;
- There may be a number of confounding factors, including exercise type, duration and mode and population, that may influence the effects of β-alanine supplementation;

Novel findings from the current study:

- There was an overall ergogenic effect of β-alanine supplementation on exercise;
- Exercise duration was the greatest factor influencing effect sizes: a duration of 0.5 to 10 min results in the greatest gains while very short duration exercise (<0.5 min) clearly results in no benefits;
- Effect sizes for exercise capacity were larger than for performance, particularly during exercise lasting from 0.5 to 10 min in duration;
- The effect of β-alanine on trained individuals showed smaller effect sizes than non-trained individuals, while isolated limb and whole body exercise were shown to equally benefit from β-alanine;

- Co-supplementation of β-alanine and sodium bicarbonate, to increase both intracellular and extracellular buffering capacity, was shown to result in additional improvements above β-alanine alone.

Keywords: Beta-alanine supplementation; muscle carnosine; exercise capacity; exercise performance; acidosis; buffering capacity; sodium bicarbonate; co-supplementation

Introduction

The purported pleiotropic effects of carnosine (β-alanyl-L-histidine) have attracted interest in this histidine-containing dipeptide in recent years due to its potential ergogenic and therapeutic benefits.[1] Its abundance in skeletal muscle suggests it plays an important role during exercise, with a key physiological role considered to be intracellular acid-base regulation, although further roles for carnosine have also been suggested, such as protection against oxidative damage, glycation and regulation of calcium sensitivity (for review, see [2]). The rate limiting factor to muscle carnosine synthesis is the availability of β-alanine from the diet,[3] with supplementation shown to increase skeletal muscle concentrations in both upper and lower limbs.[3-9] This has led to investigations into the effects of β-alanine supplementation, and thus increased muscle carnosine concentration, on capacity and performance within a variety of exercise tests and sample populations.

A previous meta-analysis [10] showed the efficacy of β-alanine supplementation on exercise with a significant effect on capacity but not performance tests; although the authors acknowledged that this might have been due to the lack of studies employing a performance measure at the time. The exercise timeframe in which β-alanine was most effective was 1 to 4 min, with no effect on exercise of less than 1 min in duration. Although a positive effect was shown on exercise of more than 4 min in duration, there was a lack of protocols employing long-duration continuous exercise; the majority of the longer duration exercise studies employed incremental protocols of such low intensity during the initial stages that they were unlikely to produce any significant changes that result in fatigue. Therefore, the duration of such tests is somewhat deceiving since it is only the latter stages that may be susceptible to changes in muscle carnosine with supplementation. Furthermore, in line with the primary suggested role of muscle carnosine, a 0.5 to 10 min timeframe may be more appropriate since

acidosis following 20 s of exercise may already contribute to fatigue,[11] while exercise of 7-8 min in duration has been shown to have a high contribution from glycolytic energy sources.[12] Thus, determination of the effect of β-alanine within these different exercise durations would further contribute to the evidence base as to the main physiological role of carnosine in skeletal muscle during exercise.

It would be of interest to investigate the ability of β-alanine to improve exercise measures in different sample populations (*i.e.*, trained and non-trained) and exercise modes (*i.e.*, whole body and isolated limb exercise) since its efficacy for trained individuals [13 14] and whole body exercise has been questioned.[15] Furthermore, since over half of professional footballers reported taking β-alanine,[16] determination of its effect on intermittent, as well as continuous, exercise is warranted. Additionally, since muscle carnosine increases are dose-dependent,[17] it appears reasonable to suggest that the total amount ingested or supplementation duration may influence any exercise gains. Co-supplementation of β-alanine with sodium bicarbonate may lead to additive gains via increased intracellular (from increased muscle carnosine concentrations) and extracellular (from increased blood bicarbonate concentrations) buffering capacity.[18] Therefore, it would be of interest to determine the effect of co-supplementation of β-alanine with sodium bicarbonate to determine whether any improvements are additive and exceed those with β-alanine alone.

The aim of this study was to perform a systematic review and meta-analysis on the effects of β-alanine supplementation, accounting for a number of potential modifying factors including exercise duration, type and mode, sample population, total dose employed and study length. Furthermore, the combined effects of sodium bicarbonate and β-alanine were also investigated.

Methods

Study Eligibility:

The protocol for this study was designed in accordance with PRISMA guidelines,[19] and the question determined in respect of PICO (Population, Intervention, Comparator and Outcomes). The ***population*** included healthy human males and females of any age. Recreationally active and professional athletes were considered for inclusion. Studies conducted with diseased-state participants were excluded. The ***intervention*** must have employed a chronic (>1 day) β-alanine supplementation protocol. Since the net retention of β-alanine used for muscle carnosine synthesis over 4 weeks of supplementation is 6.0 – 6.5% over the dose range 3.2 to 6.4 $g \cdot day^{-1}$ (estimated from [3 20]), acute supplementation protocols were not included since a single dose of β-alanine would not result in any meaningful increases in muscle carnosine. No cross-over designs were included in the analyses if they did not demonstrate a complete washout of muscle carnosine, given the long washout period for muscle carnosine (up to 16 weeks) following doses of between 1.6 and 4.8 $g \cdot day^{-1}$ of β-alanine.[6 17] Although Danaher, et al. [21] reported no significant differences in muscle carnosine concentration following 12 weeks of washout, a lack of a statistical significance does not exclude the possibility that carnosine remained elevated in some individuals. Thus, following a discussion and agreement between all reviewers, this study was not included in any of the analyses. In relation to the ***comparator***, the protocol for this study determined that only double-blinded, placebo-controlled studies were included. Studies that reported on ***outcomes*** based on exercise performance and capacity were considered for inclusion. For the purpose of this review, exercise capacity tests were defined as those requiring exertion to the point of volitional fatigue, whilst performance based tests were defined as those requiring pacing strategies that may not necessarily elicit maximal exertion. Only peer-reviewed, original human studies published between 2002 and February

2016 were included within this review. We applied a date restriction of 2002 to coincide with the publication of the first paper to investigate the association between muscle carnosine and exercise.[22] Where data were incomplete, authors were contacted to obtain the relevant information. Data from one study was not received,[23] meaning that this study was not included in the analyses.

Search Strategy and Quality Assessment:

An electronic search of the literature was undertaken by BS using three databases (PubMed, Google Scholar and Web of Science) to identify all relevant articles. The search terms "β-alanine" and "beta-alanine" were individually concatenated with "supplementation", "exercise", "training", "athlete", "performance", and "carnosine"; search terms were restricted to the title of the articles. Following the removal of duplicates, a 2-phase search strategy was subsequently employed by three independent reviewers (BS, GGA and KES). Phase one assessed the eligibility of the title and abstract of every hit generated from the search terms against the inclusion/exclusion criteria. Studies that had questionable suitability were included at this stage and the final decision was reached at the next phase (phase two). In phase two, full articles were retrieved and assessed against the eligibility criteria. Reference lists of relevant original and review articles were screened to ensure all relevant studies were included. Any differences of opinion relating to study eligibility were resolved through discussion. The search strategy is summarised in Figure 1. The final search was completed in February 2016.

A funnel plot (Supplementary Figure 1) was used to visually determine publication bias; BS and BG performed this according to standard recommendations.[24] Some data appeared to contribute to some asymmetry in the plot, with one study having a very low sample size (BA

= 5, PL = 2;[25]). High standard errors shown for the other two [26 27] are likely due to high inter-individual responses within the respective studies. It was concluded that there was no publication bias and inclusion of all study estimates was warranted. BS and KES independently reviewed the strength of the evidence provided by all studies using the criteria outlined in the Consolidated Standards of reporting Trials (CONSORT statement;[28 29] Supplementary Table 1). Any differences between reviewers were resolved by discussion until an agreement was reached. Items 3b, 6b, 7b, 14a, 14b, 17b, 18, 23 and 24 were removed, as they were not applicable to any of the studies. The results of the CONSORT assessment were not used to exclude any study that did not meet the standards or requirements but provide an objective measure of each study's adherence to the minimum set of recommendations for reporting randomised trials as determined by CONSORT.

Data Extraction and Variable Categorisation:

Data extraction was conducted by BS using a standardised and pre-piloted data extraction form. A number of protocols resulted in several outcome measures of the same exercise test; in order to avoid duplication bias, only a solitary outcome measure from each exercise protocol was included. Thus, where a single exercise protocol resulted in one or more outcome measures, the outcome measure included was based upon a hierarchy agreed upon by all reviewers to ensure consistency in data extraction. Data were extracted according to availability, prioritising exercise measures over physiological measures, according to the following hierarchical profile:

1. Total work done
2. Mean output throughout the test (*i.e.*, mean power output; mean velocity; mean height)
3. Time to completion (performance test)/time to exhaustion (capacity test)

4. Oxygen consumption (*i.e.*, VO_{2max} or VO_{2peak})

Where multiple time points following supplementation existed (*i.e.*, 0 - 4 and 0 - 10 weeks), post-supplementation outcome data were extracted from the final time point available. This was performed to ensure the highest possible accumulation of muscle carnosine due to β-alanine supplementation and thus, theoretically, the most likely time point to show any effect.

Following extraction, data were allocated into categories to allow for sub-group analyses. This included separating data by exercise duration according to the approach of Hobson et al.[10] [*duration 1*], namely 0 to 1 min, 1 to 4 min and in excess of 4 min, which were chosen to consider the proposed physiological mechanisms of carnosine, in particular pH buffering. Additional sub-group analyses were performed according to exercise duration using the following categories [*duration 2*]: 0-0.5 min; 0.5-10 min; 10 min+. The lower limit was chosen since Bogdanis et al.[11] suggested that sprint performance may be affected by the acidosis that occurred during the initial 20 s of exercise. Although maximal H^+ accumulation in blood occurs after approximately 4 min,[30] total anaerobic energy contribution during 4 km cycling time-trial (lasting ~6 min) is ~25%,[31] while Stellingwerff et al.[12] showed non-oxidative glycolysis contributes approximately 12% towards total energy contribution during 2000 m rowing (lasting in excess of 7 min). Thus, to ensure inclusion of all exercise with a substantial contribution from anaerobic energy sources, an upper limit of 10 min was determined. All exercise in excess of 10 min, with a likely predominantly aerobic energy contribution, made up the final category.

Exercise protocols were categorised according to whether they measured exercise capacity or performance [*exercise type*]. Capacity tests require exertion to the point of volitional exhaustion, resulting in a maximal production of H^+, whereas performance tests rely more

upon pacing strategies that might not elicit maximal exertion.[32] Analyses also separated investigations according to the sample populations recruited to the study [*training status*], since it has been suggested that trained individuals may be less responsive to β-alanine supplementation.[13 14] Studies were categorised as using trained individuals if the sample population was engaged in a structured training programme and whose training plan was relevant for the exercise task employed to study the effects of β-alanine; those individuals who did not fit this description (*i.e.*, recreationally active; non-trained) were categorised as non-trained. Exercise tests were additionally categorised according to whole-body or isolated limb exercise [*exercise mode*], since differences in exercise mode influence energy substrate utilisation [33] and oxygen uptake kinetics.[34] Differences in whole-body and isolated muscle recruitment have also been suggested to contribute to the efficacy of β-alanine due to differences in whole body *versus* local muscle acidosis.[15] Exercise tests were similarly categorised according to whether they employed an intermittent or continuous exercise protocol [*intermittent*]. Since increases in muscle carnosine appear to be dose dependent,[17] we analysed the effect of total dose [*total amount*] and study length [*study length*] as continuous variables (in grams and days). Further sub-analysis was performed on studies that investigated the effect of co-supplementation of β-alanine and sodium bicarbonate on exercise [*co-supplementation*].

Data Analysis

Data were converted to observed effect sizes (d) and their variances (σ_r^2) calculated according to Morris [35]:

$$d = C\left[\frac{\left(M_{post,T} - M_{pre,T}\right) - \left(M_{post,P} - M_{pre,P}\right)}{SD_{pre}}\right]$$

Where T refers to the BA group and P refers to PL. SD_{pre} is the pooled standard deviation and defined as:

$$SD_{pre} = \sqrt{\frac{(n_T - 1)SD_{pre,T}^2 + (n_P - 1)SD_{pre,P}^2}{n_T + n_P - 2}}.$$

C is a bias correction and equal to:

$$C = 1 - \frac{3}{4(n_T + n_P - 2) - 1}.$$

The effect size variance σ_r^2 was calculated as

$$\sigma_r^2 = 2(1 - r_{pre-post})\left(\frac{n_T + n_P}{n_T n_P}\right)\left(\frac{n_T + n_P - 2}{n_T + n_P - 4}\right)\left(1 + \frac{d^2}{2(1 - r_{pre-post})\left(\frac{n_T + n_P}{n_T n_P}\right)}\right) - \left(\frac{d^2}{C^2}\right).$$

To calculate the observed effect size variance, the correlation between pre- and post-supplementation outcomes ($r_{pre-post}$) was required. A single correlation value was estimated for all observed effect sizes. Raw data were obtained for 9 of the 40 included studies, comprising a total of 12 outcomes. The average pre- to post-supplementation correlation value obtained was 0.877 $\pm$ 0.20; a weighted average pre- to post-supplementation correlation value of 0.95 (0.88, 0.97) was obtained. Therefore, a single pre- to post-supplementation correlation value of 0.9 was used to calculate σ_r^2. Sensitivity analyses were also carried out using a single pre- to post-supplementation correlation value of 0.7.

A three level mixed effects model was used to model effect sizes and account for dependencies within the data. The basic model consisted of three regression equations, one for each level [36]:

$$d_{jk} = \beta_{jk} + r_{jk} \text{ with } r_{jk} \sim N(0, \sigma_{rjk}^2) \text{ (level 1: sample)}$$

The equation at the first level states that d_{jk} the j-th observed effect size from study k is equal to the corresponding population value β_{jk} plus a random deviation, r_{jk}, that is normally distributed with mean zero and variance obtained as described above. The second level equation represents the outcome level and states that the population effects for the different outcomes within a study can be decomposed into a study mean (θ_{0k}) and random residuals v_{jk}.

$$\beta_{jk} = \theta_{0k} + v_{jk} \text{ with } v_{jk} \sim N(0, \sigma_v^2) \text{ (level 2: outcome)}$$

The third level is an extension of the common random effects model and states that mean study effects θ_{0k} can vary around an overall mean γ_{00} with the random variation μ_{0k}:

$$\theta_{0k} = \gamma_{00} + \mu_{0k} \text{ with } \mu_{0k} \sim N(0, \sigma_\mu^2) \quad \text{(level 3: study)}$$

The between study variance in the mean effect, σ_μ^2, reflects the covariance between two effect sizes from the same study. Van den Noortgate, et al. [36] previously demonstrated that the three-level model can provide appropriate mean effect size estimates and standard error estimates across a variety of realistic situations. The model was then extended by incorporating fixed effects in an attempt to further explain the variation in observed effects sizes. The fixed effects assessed included characteristics of the outcomes ([*exercise duration*], [*exercise type*], [*training status*], [*exercise mode*]) and studies ([*total dose*], [study length]). Subgroup analyses performed on outcomes from studies providing a co-supplementation group comprising β-alanine and sodium bicarbonate were performed using a two-level meta-analysis due to limited nesting of outcomes within studies. Additionally, effect sizes were computed comparing the co-supplementation group (BASB) relative to the placebo group (PL) and the co-supplementation group relative to the β-alanine only (BA) group. All data were analysed using the rma and rma.mv functions in the metafor package

[37] in R (R Foundation for Statistical Computing, Vienna Austria) and significance level was previously set at $P < 0.05$.

Results

Included Study Characteristics

Forty published studies met the criteria for inclusion in the analyses (Table 1). A total of 65 exercise tests were employed across the various studies resulting in 70 exercise outcome measures in 1461 participants (BA: N = 746; PL: N = 715). Grouping of studies and exercise protocols for the various sub-analyses performed is presented in Table 2.

Meta-analysis

Overall

Results from the meta-analysis showed a small significant mean effect size of 0.180 (95%CI: 0.078, 0.284). Substantial heterogeneity was noted with systematic variance (level 2 and level 3 variance) accounting for ~72% of the total variance (Table 3). Sensitivity analysis using a pre- to post-supplementation correlation of 0.7 resulted in a small main effect estimate of 0.180 (95%CI: 0.076, 0.292) with a concomitant increase in sampling variance that resulted in systematic variance accounting for ~36% of the total variance.

Univariate Meta-regressions

There was a significant moderating effect of [*duration 1*] (P = 0.003) with results showing small significant effect sizes for durations of 1-4 min [0.210 (95%CI: 0.057, 0.362) and 4+ min [0.233 (95%CI: 0.059, 0.407), but not 0-1 min [0.016 (95%CI: -0.223, 0.254). Similarly, there was a significant moderating effect of [*duration 2*] (P = 0.004, Figure 2) with results showing a small significant effect size for durations of 0.5-10 min [0.224 (95%CI: 0.088, 0.361). There was a tendency towards significance for 10+ min [0.174 (95%CI: -0.030, 0.377) but effect size was not significant for 0-0.5 min [0.040 (95%CI: -0.220, 0.300).

There was no moderation effect distinguishing between the different levels of [*exercise type*] (P = 0.256), [*training status*] (P = 0.559), [*exercise mode*] (P = 0.931) and [*intermittent*] (P = 0.436). Similarly, no moderation effect was obtained for the continuous variable [*total amount*] (P = 0.438) on effect sizes. However, there was a moderation effect of [*study length*] (P = 0.005) with an apparent 0.011 increase in effect size each day beyond 20 days of supplementation (Table 3). However, this result appeared to be driven by the presence of two outliers (Cook's distance 1.8 and 0.7), and when a sensitivity analysis was performed without these data points, [*study length*] no longer had a significant effect (P = 0.685).

Further analyses

Due to the strong effect of [*duration 2*] on effect sizes, further meta-regressions were performed using [*duration 2*]. Sub group analyses were completed for the outcomes within 0.5-10 min (N = 41) only. No moderation effects were shown for [*total amount*] (P = 0.831), [*study length*] (P = 0.309), and the different levels of [*exercise mode*] (P = 0.507), [*intermittent*] (P = 0.255) or [*training status*] (P = 0.874). However, there was a significant moderation effect distinguishing between the two levels of [*exercise type*] (P = 0.01) with higher effect sizes for exercise capacity than performance [0.4998, medium effect (95%CI: 0.246, 0.753) *vs.* 0.1078, small effect (95%CI: -0.201, 0.416).

Analysis of [*co-supplementation*] showed that, in comparison to PL, BASB resulted in a significant effect size of 0.433 (0.230, 0.637; P < 0.001). Furthermore, compared to BA, BASB also resulted in a significant effect size of 0.242 (0.071, 0.412; P = 0.006; Figure 3).

Discussion

The results of this meta-analysis showed a significant positive overall effect of β-alanine supplementation on exercise, supporting the efficacy of increased muscle carnosine to improve exercise. Exercise duration was the greatest influencing factor regarding the efficacy of β-alanine supplementation. Replicating the duration timeframes of Hobson, et al. [10] yielded similar results; significant effect sizes were shown for exercise 1 to 4 min in duration, supporting previous evidence that β-alanine is beneficial for this exercise timeframe. No effect was shown for exercise protocols lasting less than 1 min, and considering a mechanism of action relating to increased intracellular buffering, this would make sense given that this duration of exercise is unlikely to be limited by intracellular H^+ accumulation.[38] This finding also provides some indirect evidence in opposition to the influence of increased muscle carnosine content on calcium sensitivity of the contractile apparatus or calcium release from the sarcoplasmic reticulum. This is in agreement with the recent data of Hannah, et al. [39] who showed no effect of β-alanine on maximal explosive voluntary contractions suggesting that calcium sensitivity and release might not be the primary mechanisms by which increased carnosine improves whole muscle exercise in humans. Exercise of longer than 4 min in duration was improved with β-alanine supplementation, with greater effect sizes than exercise 1-4 min in duration (0.233 *vs.* 0.210), though we speculate that this may be due to shorter duration protocols (6-7 min,[7 40]), which may be more susceptible to increases in muscle carnosine if its primary mechanism is considered to be that of pH buffering, being grouped with those of longer duration (30-60 min,[41 42]).

Although results reported within the current study agree somewhat with the categorisation of exercise durations employed by Hobson, et al. [10], we further explored the effect of exercise duration using adapted criteria. Short duration exercise (≤0.5 min) was not benefited from

supplementation (d = 0.040), while effect sizes for moderate duration exercise (0.5-10 min) were significant (d = 0.224). However, β-alanine was no longer shown to be effective for longer duration exercise (>10 min), although there was still a moderate effect size (d = 0.174). It was supposed that these data may have been influenced by incremental protocols with a low intensity during the initial stages that were unlikely to induce fatigue. Therefore, the duration of such tests is somewhat deceiving since it is only the latter stages, conducted at higher exercise intensities, that may be susceptible to changes in muscle carnosine content. Although individual studies appear to confirm this hypothesis, there were no differences in effect sizes between continuous and incremental protocols (data not shown). Nonetheless, here we provide novel evidence to suggest that exercise of 0.5 to 10 min in duration to be the exercise timeframe in which β-alanine supplementation is most influential.

Exercise capacity and performance were both improved by supplementation, although effect sizes suggested β-alanine to be almost twice as effective at improving exercise capacity. Further meta-regressions were performed on outcomes within 0.5-10 min due to the strong effect of duration on effect sizes, and showed higher effect sizes for exercise capacity than performance indicating that exercise capacity tests within this timeframe will likely elicit the greatest improvements with β-alanine supplementation. It has previously been suggested that performance tests, such as time-trials, may be influenced by intrinsic pacing,[32] potentially making them less likely to be influenced by increased muscle carnosine concentration. The majority of capacity tests included in the analyses were performed until exhaustion, likely resulting in a maximal production of H^+, and thus are sensitive to changes in buffering capacity. As such, current data suggest that exercise capacity tests provide greater scope to identify significant effects of β-alanine supplementation, particularly within a 0.5 to 10 min timeframe.

There has been doubt raised as to the efficacy of β-alanine in well-trained participants,[13 14], perhaps due to adaptions to training such as increased buffering capacity, which may minimise the contribution of increased muscle carnosine content in these individuals. The findings of the current study showed significant effect sizes for non-trained individuals only, suggesting they may be more susceptible to exercise improvements than their well-trained counterparts. This appears in contrast to Painelli, et al. [43], who directly compared the efficacy of β-alanine supplementation on training status using a trained and non-trained population and showed it to be equally effective in both sets of participants. Nonetheless, there were no differences in effect sizes between trained and non-trained populations in this study, while effect sizes for the trained group were close to the overall effect of β-alanine (0.144 vs. 0.180). Although it appears trained athletes might experience smaller gains, such changes may translate into worthwhile improvements in an applied setting (*i.e.*, competition). Thus, this meta-analysis provides some evidence to support the efficacy of β-alanine in non-trained and trained populations, though improvements are likely to be greater in non-trained individuals.

The efficacy of β-alanine may be influenced by the mode of exercise performed, specifically whole-body *versus* isolated limb activity. Smaller muscle groups, such as upper-body muscles, may be more subjected to local acidosis than whole body exercise.[44] In addition, increased muscle tension imposed by the type of muscle contraction can mechanically reduce peripheral blood flow and oxygen extraction,[45] which may lead to an increased muscle acidosis. Therefore, it has been suggested that differences in muscle recruitment between activities such as cycling and running may lead to discrepancies in the apparent efficacy of the supplement.[15] The current data suggest, however, that the efficacy of β-alanine is not

affected by the mode of exercise and that both isolated limb and whole-body exercise are equally likely to benefit. Indeed, individual studies do provide evidence that whole-body type tasks can be improved by β-alanine supplementation.[40 46 47] Nonetheless, well-controlled experiments specifically designed to address whether there is a greater effect of local *versus* whole body acidosis are warranted. Additionally, intermittent and continuous protocols were both equally improved with β-alanine. However, most intermittent tests were not sport-specific protocols and thus, further research investigating the effect of β-alanine within applied sport-specific settings is warranted.

Neither the total amount ingested, nor supplementation duration, mediated the effect of β-alanine supplementation on exercise outcomes. These results may be due to the wide range of dosing strategies employed, meaning individuals performed exercise at various stages of increased muscle carnosine content. Although Stellingwerff et al. [17] showed that increases in muscle carnosine concentration were dependent on the total amount of β-alanine consumed, their study employed two low doses (1.6 and 3.2 $g \cdot day^{-1}$), whereas most studies included in this meta-analysis employed higher doses. The time course of carnosine accumulation with doses in excess of 3.2 $g \cdot day^{-1}$ is yet to be determined and given that most studies did not directly measure muscle carnosine content, it is not possible to determine whether individuals performed exercise following similar increases in muscle carnosine, although this would seem unlikely. This meta-analysis showed that the total amount of β-alanine ingested does not directly influence its efficacy, making it difficult to make specific recommendations as to the optimal dosing strategy for individuals. Nonetheless, supplementation of 1.6 $g \cdot day^{-1}$ for as little as two weeks has been shown to increase muscle carnosine,[17] while improvements in exercise have been shown at doses ranging from 3.2 – 6.4 $g \cdot day^{-1}$ for 4 – 12 weeks.[4 26] Further research should determine the required dosing

strategy to attain maximal carnosine accumulation in muscle and whether maximal exercise improvements occur at an identical time point.

It has been suggested that co-supplementation of β-alanine with sodium bicarbonate may result in further exercise gains over β-alanine alone, due to an increase in both intracellular and extracellular buffering capacity. Six of the nine studies encountered in our search strategy investigating co-supplementation were included in the analysis. The majority of studies that employed acute doses of sodium bicarbonate have shown co-supplementation to result in non-significant effects on performance.[13 18 47] The only study that employed a chronic (7 d) sodium bicarbonate supplementation phase showed a significant effect of the additional sodium bicarbonate supplementation with β-alanine over β-alanine alone.[48] This may be due to the multiple-bout nature of the test, which likely resulted in a higher acidosis than the continuous exercise protocols employed in other studies;[30 49] or due to the chronic supplementation protocol employed, which may have resulted in a more pronounced blood alkalosis,[50] although the authors did not measure this directly. Nonetheless, the current meta-analytic data suggest that co-supplementation of β-alanine with sodium bicarbonate can lead to additional gains over those with β-alanine alone. The reason for the apparent disparity between our findings and the individual study results may be due to the statistical power of the studies undertaken. Studies investigating the effects of combined supplementation have used relatively small samples sizes, which may have hindered standard analytical approaches, with many of these studies also including a magnitude based inferences approach,[51] showing small but meaningful additional improvements with co-supplementation.[18 40] Taken together, these data suggest that the co-supplementation of β-alanine with sodium bicarbonate results in further benefits than supplementation with β-alanine alone.

Nonetheless, further investigation is required since the current data are based upon the results of six individual studies only.

This study is not without its limitations. All outcome measures were converted to effect sizes to standardise the data and subsequently perform our meta-analyses. It has previously been suggested that converting data to mean power may be more appropriate so that meta-analysed performance effects could be applied directly to athletic performance and practical recommendations for coaches and athletes.[52] However, the sheer variety of exercise protocols included in this analysis meant that it was not possible to convert all available data into power output. Furthermore, we feel that our analytical approach provides a comprehensive and clear analysis of the data, clarifying its significance to different athletic populations. Although our choice of sub-analyses and categorisation of exercise tests revealed insightful information on ergogenic properties of β-alanine supplementation, we acknowledge that alternative sub-analyses could have been performed and that our definitions to categorise studies into these sub-analyses may differ from other authors. However, we believe our choices to be relevant from a practical standpoint (*i.e.*, in a sport context) and we have attempted to support this with an evidence base.

In conclusion, β-alanine supplementation had a significant overall ergogenic effect on exercise. Exercise duration was the greatest influencing factor on the efficacy of β-alanine supplementation, with a timeframe of 0.5 to 10 min likely to result in the greatest gains, while very short duration exercise clearly results in no benefits. Exercise capacity resulted in greater effect sizes than exercise performance; this was particularly apparent for exercise lasting 0.5 to 10 min. The efficacy of β-alanine for non-trained individuals was clearly demonstrated, while lower effect sizes were shown for trained populations, though these may

still translate into competitive gains. Isolated limb *versus* whole body exercise benefitted equally from β-alanine supplementation. The co-supplementation of β-alanine and sodium bicarbonate resulted in the largest effect sizes and also resulted in greater gains than β-alanine alone.

From a practical standpoint, these data allow individuals to make informed decisions as to the likelihood of an ergogenic effect with β-alanine supplementation based upon their chosen exercise modality (e.g. 400, 800 and 1500 m running; 4 km cycling; 100, 200 and 400 m swimming) and coaches can support claims as to the efficacy of this supplement to their athletes. Athletic individuals can also save time and resources if they are unlikely to obtain any exercise gains due to their preferred sport (e.g. 100 m running; 25 m swimming; >30 min cycling), although improvements with supplementation during training should not be dismissed since this will likely incorporate repeated exercise bouts and activity of longer duration than competition. Individuals are advised to supplement daily with β-alanine for a minimum of 2 – 4 weeks at a dose of 3.2 – 6.4 $g \cdot day^{-1}$ ingested at several timepoints throughout the day (0.8 – 1.6 g every 3 – 4 h) to avoid acute side-effects. Although the current data support the efficacy of β-alanine supplementation during certain types of exercise, the exact mechanisms by which increased carnosine contributes to improved exercise outcomes remains to be experimentally demonstrated. Further studies should aim to determine the exact contribution of carnosine to buffering capacity and the changes therein following dietary supplementation of β-alanine. Additionally, it would be of interest to determine the greatest exercise gains due to increased muscle carnosine concentration using more prolonged supplementation protocols, and whether gains directly mirror changes in intracellular carnosine. The current meta-analysis provides support to design the most

appropriate protocols to determine changes in muscle carnosine concentration with β-alanine (*i.e.*, exercise capacity test of 0.5 to 10 min).

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COMPETING INTERESTS

The authors declare no conflicts and financial competing interests.

AUTHOR'S CONTRIBUTIONS

BS, BG and CS contributed to the conception and design of the study. BS, KES and GGA contributed to the development of the search strategy analysis and to the acquisition of data. BS, PAS, ED and HR performed the data analysis and interpretation of data. BS was the principal writer of the article while all authors contributed to drafting the article and revising it critically. All authors approved the final version to be submitted.

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Table 1. All studies included in the meta-analysis.

Authors & Location	Participants	Supplementation protocol	Total dosage (g)	Exercise protocol
Baguet et al. [7] Belgium	Elite male rowers PL = 9; BA = 8	5.0 g·day^{-1} for 49 days	245	2000 m rowing ergometry
Bellinger et al. [13] Australia	Trained male cyclists PL = 7; BA = 7	65 mg·kg^{-1}BM·day^{-1} for 4 weeks	~129.4	4 min maximal cycle bout
Bellinger and Minhan [53] Australia	Trained male cyclists PL = 7; BA = 7	6.4 g·day^{-1} for 4 weeks	179.2	1 km cycling TT 4 km cycling TT 10 km cycling TT
Carpentier et al. [54] Belgium	Physically active males and females PL = 13; BA = 14	5.6 g·day^{-1} for 8 weeks	313.6	Squat jump CMJ 45 CMJ Fatigue test
Chung et al. [55] Australia	Elite/sub-elite male/female swimmers PL = /; BA = /	4.8 g·day^{-1} for 4 weeks followed by 3.2 g·day^{-1} for 6 weeks	268.8	50 – 400 m swimming: Training performance Competition performance
Chung et al. [42] Belgium/Australia	Trained male cyclists PL = 13; BA = 14	6.4 g·day^{-1} for 6 weeks	268.8	1 h cycling TT
Cochran et al. [56] Canada	Healthy young males PL = 12; BA = 12	3.2 g·day^{-1} for 6 weeks	134.4	Incremental cycle test 250 kJ cycling TT Repeated sprint cycle test
Del Favero et al. [46] Brazil	Elderly males and females PL = 6; BA = 12	3.2 g·day^{-1} for 12 weeks	268.8	Constant load submaximal test Incremental treadmill test
Derave et al. [5] Belgium	Sprint trained competitive athletes PL = 7; BA = 8	2.4 g·day^{-1} for 4 days, 3.6 g·day^{-1} for 4 days, 4.8 g·day^{-1} up to 5 weeks	153.6	400 m sprint Isometric endurance Maximal isokinetic knee extensions
Ghiasvand et al. [57] Iran	Recreational males PL = 19; BA = 20	2.0 g·day^{-1} for 42 days	84	Graded exercise test

Glenn et al. [58] USA	Female masters athletes PL = 11; BA = 11	3.2 g·day^{-1} for 4 weeks	89.6	Lower body ISO strength Hand grip strength
Gross et al. [9] Switzerland	Recreational males PL = 9; BA = 9	3.2 g·day^{-1} for 38 days	121.6	Maximal incremental cycle
Gross et al. [25] Switzerland	Elite male alpine skiers PL = 4; BA = 5	4.8 g·day^{-1} for 5 weeks	168	Counter movement jump 90 s box jump test
Hill et al. [4] UK	Recreational males PL = 8; BA = 7	4.0 g·day^{-1} in week 1 rising to 6.4 g·day^{-1} by week 4 till week 10	414.4	Cycling capacity test at 110% of PowerMax
Hobson et al. [40] UK	Trained male rowers PL = 10; BA = 10	6.4 g·day^{-1} for 28 days	179.2 - 192	2000 m rowing ergometry
Hoffman et al. [59] USA	Elite male soldiers PL = 9; BA = 9	6.0 g·day^{-1} for 4 weeks	168	4 km run 5 countermovement jumps 120 m sprint
Hoffman et al. [60] USA	Elite male soldiers PL = 9; BA = 9	6.0 g·day^{-1} for 30 days	180	2.5 km run 1-min sprint 50 m casualty carry Repeated 30 m sprints
Howe et al. [61] Australia	Highly trained male cyclists PL = 8; BA = 8	65 mg·kg^{-1}BM·day^{-1} for 4 weeks	127.4	4 min maximal cycle bout
Jagim et al. [62] USA	Anaerobically trained athletes PL = 11; BA = 10	4.0 g·day^{-1} for 1 week followed by 6.0 g·day^{-1} for 4 weeks	196	Run to exhaustion at 115% VO_{2max} Run to exhaustion at 140% VO_{2max}
James et al. [41] UK	Trained male cyclists PL = 9; BA = 10	6.4 g·day^{-1} for 4 weeks	179.2	20 km cycling TT
Jordan et al. [63] USA	Recreational males PL = 9; BA = 8	6.0 g·day^{-1} for 4 weeks	168	Incremental treadmill run to exhaustion
Okudan et al. [64] Turkey	Untrained healthy males PL = 11; BA = 11	3.2 g·day^{-1} for 22 days and 6.4 g·day^{-1} for 6 days	108.8	3 x 30 s Wingates

Painelli et al. [47] Brazil	Male and female swimmers PL = 7; BA = 7	3.2 g·day^{-1} for 1 week and 6.4 g·day^{-1} for 3 weeks	156.8	100 m swimming 200 m swimming
Painelli et al. [43] Brazil	Trained male cyclists and recreational males PL = 19; BA = 20	6.4 g·day^{-1} for 4 weeks	179.2	4 x 30 s cycle Wingates
Sale et al. [18] UK	Recreational males PL = 10; BA = 10	6.4 g·day^{-1} for 4 weeks	179.2	Cycling capacity test at 110% of PowerMax
Sale et al. [65] UK	Recreational males PL = 6; BA = 7	6.4 g·day^{-1} for 4 weeks	179.2	IKET
Saunders et al. [66] UK	Elite/non-elite male games players PL = 18; BA = 18	6.4 g·day^{-1} for 4 weeks	179.2	Loughborough Intermittent Shuttle Test
Saunders et al. [26] UK	Amateur male footballers PL = 8; BA = 9	3.2 g·day^{-1} for 12 weeks	268.8	YoYo Intermittent Recovery Test Level 2
Saunders et al. [67] UK	16 recreational males PL = 8; BA = 8	6.4 g·day^{-1} for 4 weeks followed by 3.2 g·day^{-1} for 1 week	179.2 – 201.6	3 sets of 5 x 6 s repeated sprints
Smith et al. [68] USA	Recreational males PL = 18; BA = 18	6.0 g·day^{-1} for 3 weeks followed by 3.0 g·day^{-1} for 3 weeks	189	Cycle capacity at 110% VO_{2max}
Smith et al. [69] USA	Recreational women PL = 11; BA = 13	4.8 g·day^{-1} for 4 weeks	134.4	Graded exercise test
Smith-Ryan et al. [70] USA	Recreational males PL = 24; BA = 26	4.8 g·day^{-1} for 4 weeks	134.4	Run to exhaustion at 90% PV Run to exhaustion at 100% PV Run to exhaustion at 110% PV
Smith-Ryan et al. [71] USA	Recreational males and females PL = 15; BA = 15	6.4 g·day^{-1} for 4 weeks	179.2	Graded exercise test
Stout et al. [72] USA	Males PL = 13; BA = 12	6.4 g·d^{-1} for 6 days, then 3.2 g·d^{-1} for 22 days	108.8	Incremental cycle to exhaustion
Stout et al. [73]	Females	3.2 g·d^{-1} for 7 days, then	156.8	Incremental cycle to exhaustion

USA	PL = 11; BA = 11	6.4 $g \cdot d^{-1}$ for 21 days		
Stout et al. [27] USA	Elderly males and females PL = 14; BA = 12	2.4 $g \cdot d^{-1}$ for 90 days	216	Discontinuous incremental exercise protocol
Tobias et al. [48] Brazil	Martial arts male athletes PL = 9; BA = 10	6.4 $g \cdot day^{-1}$ for 4 weeks	179.2	4 x 30 s upper body Wingates
van Thienen et al. [74] Belgium	Well-trained male cyclists PL = 8; BA = 9	2 $g \cdot day^{-1}$ for 2 weeks, 3 $g \cdot day^{-1}$ for 2 weeks, then 4 $g \cdot day^{-1}$ for 4 weeks	182	Incremental cycle to exhaustion 10 minute cycling TT 30 s cycle sprint
Walter et al. [75] USA	Recreational females PL = 19; BA = 14	6.0 $g \cdot day^{-1}$ for 3 weeks followed by 3.0 $g \cdot day^{-1}$ for 3 weeks	189	Graded exercise test
Zoeller et al. [76] USA	Healthy males PL = 13; BA = 12	6.4 $g \cdot day^{-1}$ for 6 days followed by 3.2 $g \cdot day^{-1}$ for 22 days	108.8	Incremental cycle to exhaustion

TT = Time trial; CMJ = Countermovement jump; ISO = Isokinetic strength; IKET = Isometric knee extension test at 45% of maximum voluntary contraction; PV = Peak velocity;

Table 2. Categorisation of studies for sub-analyses.

Authors	Exercise protocol	[*duration 1*]	[*duration 2*]	[*exercise type*]	[*training status*]	[*exercise mode*]	[*intermittent*]	[*study length*]	[*total dose*]
		1 = 0-1 min 2 = 1-4 min 3 = 4 min+	1 = 0-0.5 min 2 = 0.5-10 min 3 = 10 min+	1 = Capacity 2 = Performance	1 = Trained 2 = Non-trained	1 = Isolated limb 2 = Whole body	1 = Intermittent 2 = Continuous	(days)	(g)
Baguet et al. [7]	2000 m rowing	3	2	2	1	2	2	49	245
Bellinger et al. [13]	4 min maximal cycle	2	2	2	1	1	2	28	129.4
Bellinger and Minhan [53]	1 km cycling TT	2	2	2	1	1	2	28	179.2
	4 km cycling TT	3	2	2	1	1	2	28	179.2
	10 km cycling TT	3	3	2	1	1	2	28	179.2
	Supramaximal cycle	2	2	1	1	1	2	28	179.2
Carpentier et al. [54]	Squat jump	1	1	1	2	1	2	56	313.6
	CMJ	1	1	1	2	1	2	56	313.6
	45 CMJ Fatigue test	2	2	2	2	1	2	56	313.6
Chung et al. [55]	Swimming Training	2	2	2	1	2	2	70	268.8
	Swimming Competition	2	2	2	1	2	2	70	268.8
Chung et al. [42]	1 h cycling time trial	3	3	2	1	1	2	42	268.8
Cochran et al. [56]	Incremental cycle	3	3	1	2	1	2	42	134.4
	250 kJ cycle TT	3	3	2	2	1	2	42	134.4
	Repeated cycle sprints	2	2	2	2	1	1	42	134.4
Del Favero et al. [46]	Incremental treadmill test	3	3	1	2	2	2	84	268.8
	Treadmill test	3	2	1	2	2	2	84	268.8
Derave et al. [5]	Isometric endurance	2	2	1	1	1	2	36	153.6
	400 m running	1	2	2	1	2	2	36	153.6
	Maximal isokinetic knee extensions	1	1	1	1	1	2	36	153.6
Ghiasvand et al. [57]	Incremental cycle test	3	3	1	2	1	2	42	84
Glenn et al. [58]	Isokinetic strength – Flexion	2	2	2	1	1	2	28	89.6
	Isokinetic strength – Extension	2	2	2	1	1	2	28	89.6
	Hand grip test	1	1	1	1	1	2	28	89.6
Gross et al. [9]	Incremental cycle test	3	3	1	2	1	2	38	121.6
Gross et al. [25]	CMJ	1	1	1	1	1	2	35	168

	90-s box jump test	2	2	2	1	1	2	35	168
Hill et al. [4]	$CCT_{110\%}$	2	2	1	2	1	2	70	414.4
Hobson et al. [40]	2000 m rowing	3	2	2	1	2	2	35	192
Hoffman et al. [59]	4 km run	3	3	2	2	2	2	28	168
	CMJ (x5)	1	1	2	2	1	2	28	168
	120 m running sprint	1	1	2	2	2	2	28	168
Hoffman et al. [60]	2.5 km running sprint	3	3	2	2	2	2	30	180
	1 min running sprint	1	2	2	2	2	2	30	180
	Repeated 30 m sprints	1	1	2	2	2	1	30	180
	50 m casualty carry	1	1	2	2	2	2	30	180
Howe et al. [61]	4 min maximal cycle	2	2	2	1	1	2	28	127.4
Jagim et al. [62]	Run at 115% VO_{2max}	2	2	1	2	2	2	35	196
	Run at 140% VO_{2max}	2	2	1	2	2	2	35	196
James et al. [41]	20 km cycling TT	3	3	2	1	1	2	28	179.2
Jordan et al. [63]	Incremental treadmill test	3	3	1	2	2	2	28	168
Okudan et al. [64]	3 bouts of 30 s cycling	2	2	2	2	1	1	28	108.8
Painelli et al. [47]	100 m swimming	2	2	2	1	2	2	28	156.8
	200 m swimming	2	2	2	1	2	2	28	156.8
Painelli et al. [43]	4 bouts of 30 s cycling	2	2	2	1	1	1	28	179.2
		2	2	2	2	1	1	28	179.2
Sale et al. [18]	$CCT_{110\%}$	2	2	1	2	1	2	28	179.2
Sale et al. [65]	Isometric endurance	2	2	1	2	1	2	28	179.2
Saunders et al. [66]	LIST	2	2	2	1	2	1	28	179.2
		2	2	2	2	2	1	28	179.2
Saunders et al. [26]	YoYo IR2	3	2	1	1	2	1	84	268.8
Saunders et al. [67]	5 x 6 s sprints	1	1	2	2	1	1	35	201.6
Smith et al. [68]	Cycle at 110% VO_{2max}	2	2	1	2	1	2	42	189
Smith et al. [69]	Incremental treadmill test	3	2	1	2	2	2	28	134.4
Smith-Ryan et al. [70]	Run to exhaustion at 110% peak velocity	2	2	1	2	2	2	28	134.4
	Run to exhaustion at 100% peak velocity	2	2	1	2	2	2	28	134.4
	Run to exhaustion at 90% peak velocity	2	2	1	2	2	2	28	134.4

Smith-Ryan et al. [71]	Incremental cycle test	3	3	1	2	1	2	28	179.2
Stout et al. [72]	Incremental cycle test	3	3	1	2	1	2	28	108.8
Stout et al. [73]	Incremental cycle test	3	3	1	2	1	2	28	156.8
Stout et al. [27]	Incremental cycle test	3	3	1	2	1	2	90	216
Tobias et al. [48]	Upper-body Wingates	2	2	2	1	1	1	28	179.2
van Thienen et al. [74]	Incremental cycle test	3	3	1	1	1	2	56	182
	10 min cycling TT	3	2	2	1	1	2	56	182
	30 s cycle sprint	1	1	2	1	1	2	56	182
Walter et al. [75]	Incremental cycle test	3	3	1	2	1	2	42	189
Zoeller et al. [76]	Incremental cycle test	3	3	1	2	1	2	28	108.8

TT = Time-trial; CMJ = Countermovement jump; VO_{2max} = Maximal oxygen uptake; $CCT_{110\%}$ = Cycling capacity test at 110% Powermax; LIST = Loughborough Intermittent Shuttle Test; YoYo IR2 = YoYo Intermittent Recovery Test Level 2

Table 3. Results of univariate meta-regressions. Parameter estimates and model outputs.

Moderator		Parameter Estimate	Standard Error	QM_{df}	Between outcome variance σ_v^2 (% of total variance)	Between study variance σ_μ^2 (% of total variance)	QE_{df}
[*duration 1*]	0 - 1 min	0.016	0.122	14.1_3	0.144 (71.9%)	0.001 (0.5%)	240.8_{67}
	1 - 4 min	0.210*	0.078				
	4+ min	0.233*	0.089				
[*duration 2*]	0 - 0.5 min	0.040	0.132	13.3_3	0.146 (72.1%)	0.001 (0.5%)	242.2_{67}
	0.5 - 10 min	0.224*	0.070				
	10+ min	0.174	0.104				
[*exercise type*]	Capacity	0.244*	0.076	13.0_2	0.142 (71.2%)	0.003 (1.5%)	243.4_{68}
	Performance	0.126	0.084				
[*training status*]	Trained	0.144	0.083	12.1_2	0.145 (72.4%)	0 (0%)	244.4_{68}
	Non-Trained	0.207*	0.068				
[*exercise mode*]	Isolated	0.185*	0.068	11.7_2	0.146 (72.1%)	0 (0%)	244.8_{68}
	Whole body	0.176*	0.084				
[*intermittent*]	Intermittent	0.284*	0.142	12.4_2	0.145 (72.4%)	0 (0%)	243.7_{68}
	Continuous	0.165*	0.057				
[*total dose*]	Intercept	0.060	0.171	0.60_1	0.141 (69.4%)	0.006 (3.4%)	245.1_{68}
	Gradient	0.001	0.001				
[*study length*]	Intercept	-0.217	0.160	8.06_1	0.108 (52.9%)	0.041 (20.1%)	240.8_{68}
	Gradient	0.011*	0.004				

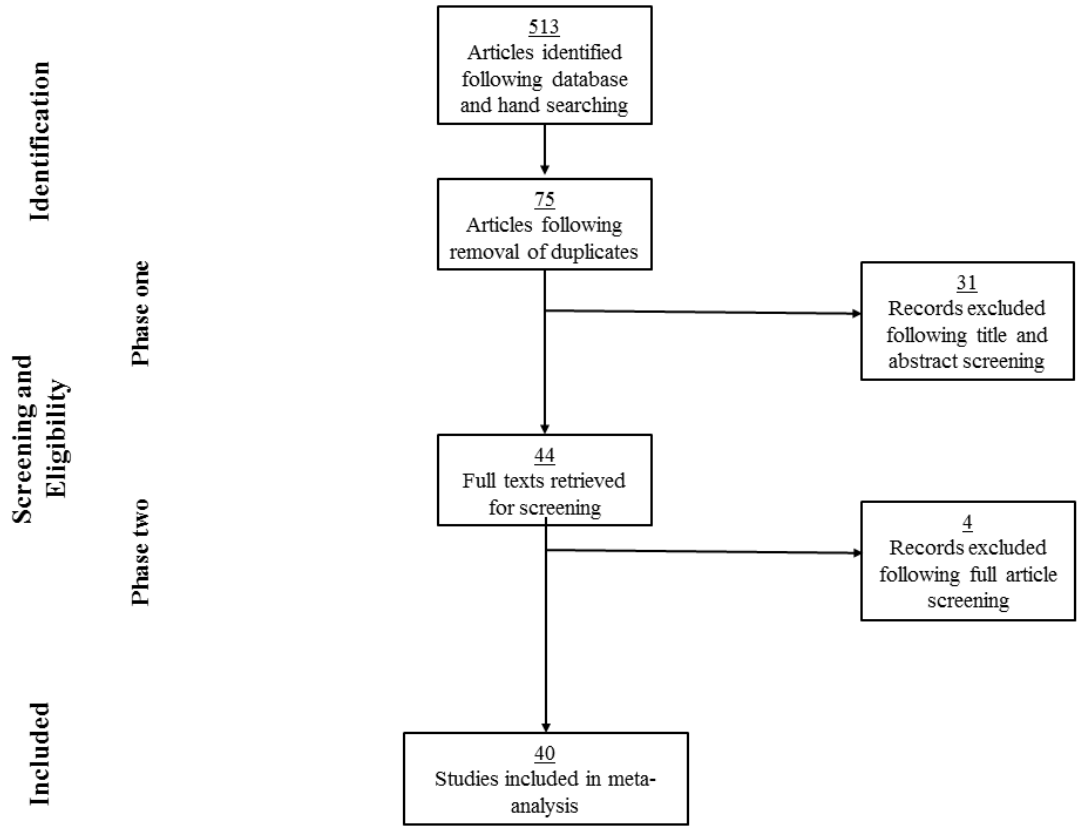
* $P \leq 0.05$. †. QM_{df}: Omnibus moderator test statistic. QE_{df}: Residual heterogeneity test statistic.

Figures

Figure 1. Search strategy summery.

Figure 2. Forest plot of the results of the random-effects meta-analysis shown as mean effect sizes with 95% CIs. Data are separated according to [*duration 2*]. The diamonds below each section represent the overall mean effect within the various sub-groups; the diamond below the graph represents the overall effect of BA *vs.* PL.

Figure 3. Forest plot of the results of the random-effects meta-analysis for BASB *vs.* PL (Panel A) and BASB *vs.* BA (Panel B). Data points are shown as mean effect sizes with 95% CIs. The diamonds represent the overall mean effect within the sub-groups.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Phase two
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Records excluded following title and abstract screening
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Full texts retrieved for screening
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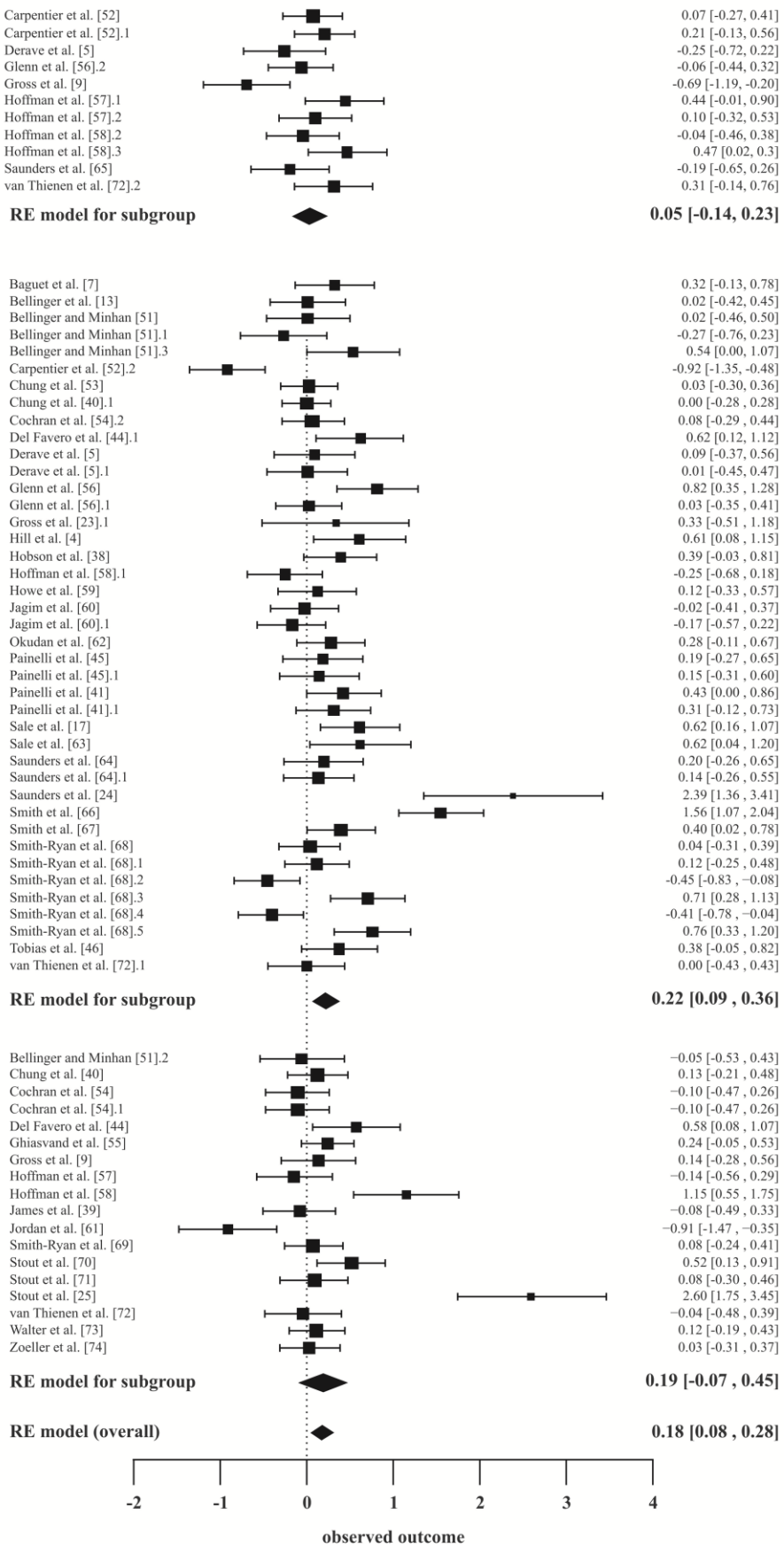
Records excluded following full article screening
40
Studies included in meta-analysis

Figure 1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Glenn et al. [56].2 -0.06 [-0.44, 0.32]
Gross et al. [9] -0.69 [-1.19, -0.20]
Hoffman et al. [57].1 0.44 [-0.01, 0.90]
Hoffman et al. [57].2 0.10 [-0.32, 0.53]
Hoffman et al. [58].2 -0.04 [-0.46, 0.38]
Hoffman et al. [58].3 0.47 [0.02, 0.3]
Saunders et al. [65] -0.19 [-0.65, 0.26]
van Thienen et al. [72].2 0.31 [-0.14, 0.76]
RE model for subgroup 0.05 [-0.14, 0.23]
Baguet et al. [7] 0.32 [-0.13, 0.78]
Bellinger et al. [13] 0.02 [-0.42, 0.45]
Bellinger and Minhan [51] 0.02 [-0.46, 0.50]
Bellinger and Minhan [51].1 -0.27 [-0.76, 0.23]
Bellinger and Minhan [51].3 0.54 [0.00, 1.07]
Carpentier et al. [52].2 -0.92 [-1.35, -0.48]
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Cochran et al. [54].2 0.08 [-0.29 , 0.44]
Del Favero et al. [44].1 0.62 [0.12, 1.12]
Derave et al. [5] 0.09 [-0.37, 0.56]
Derave et al. [5].1 0.01 [-0.45, 0.47]
Glenn et al. [56] 0.82 [0.35 , 1.28]
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Gross et al. [23].1 0.33 [-0.51 , 1.18]
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Hobson et al. [38] 0.39 [-0.03 , 0.81]
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Howe et al. [59] 0.12 [-0.33 , 0.57]
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Smith-Ryan et al. [68].5 0.76 [0.33 , 1.20]
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van Thienen et al. [72].1 0.00 [-0.43 , 0.43]
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Bellinger and Minhan [51].2 −0.05 [-0.53 , 0.43]
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James et al. [39] −0.08 [-0.49 , 0.33]
Jordan et al. [61] −0.91 [-1.47 , −0.35]
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Stout et al. [70] 0.52 [0.13 , 0.91]
Stout et al. [71] 0.08 [-0.30 , 0.46]
Stout et al. [25] 2.60 [1.75 , 3.45]
van Thienen et al. [72] −0.04 [-0.48 , 0.39]
Walter et al. [73] 0.12 [-0.19 , 0.43]
Zoeller et al. [74] 0.03 [-0.31 , 0.37]
RE model for subgroup 0.19 [-0.07 , 0.45]
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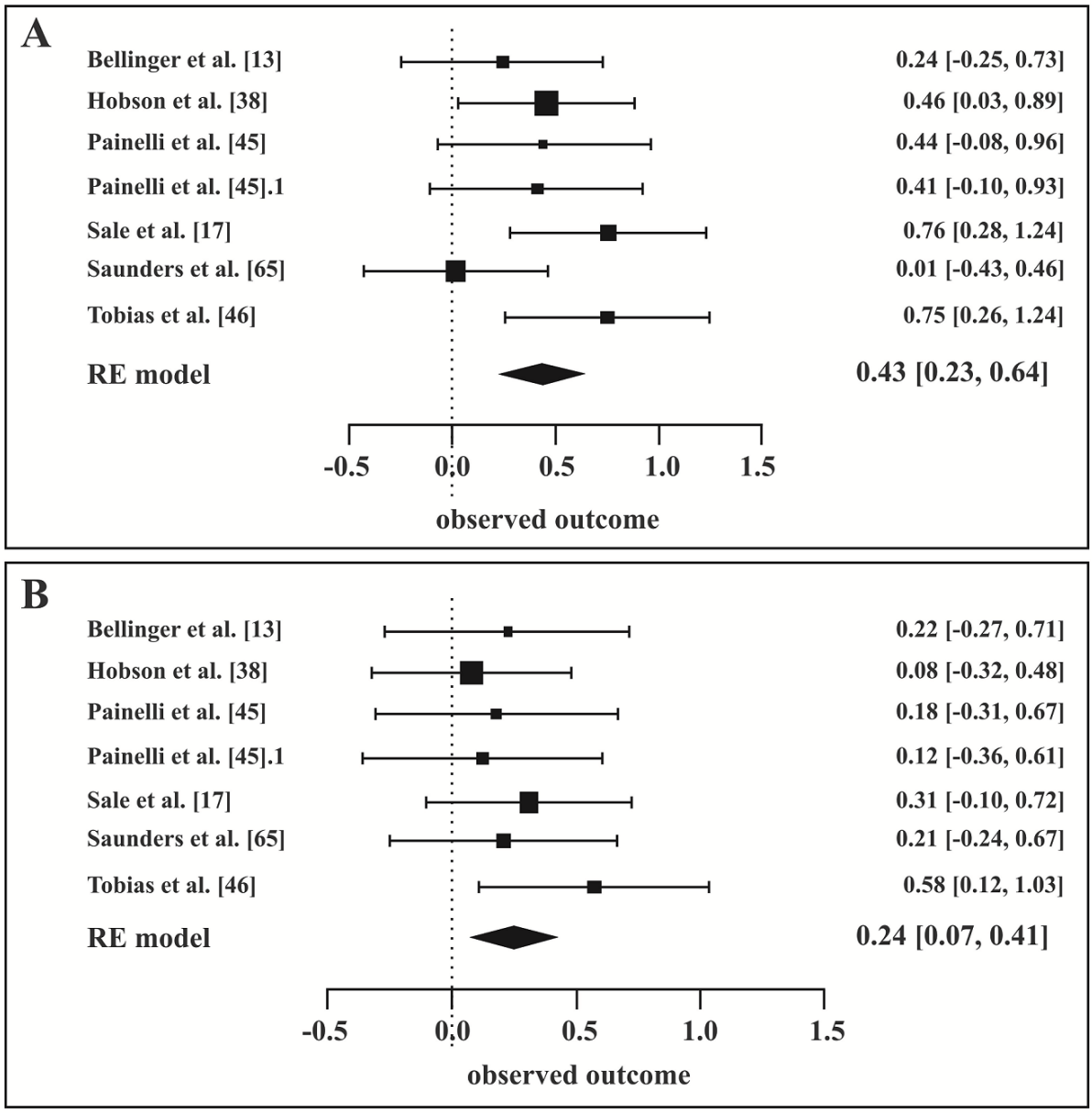
-2
-1
0
1
2
3
4
observed outcome

Figure 2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Tobias et al. [46]
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0.5
1.0
1.5
observed outcome
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Hobson et al. [38]
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Painelli et al. [45].1
Sale et al. [17]
Saunders et al. [65]
Tobias et al. [46]
RE model
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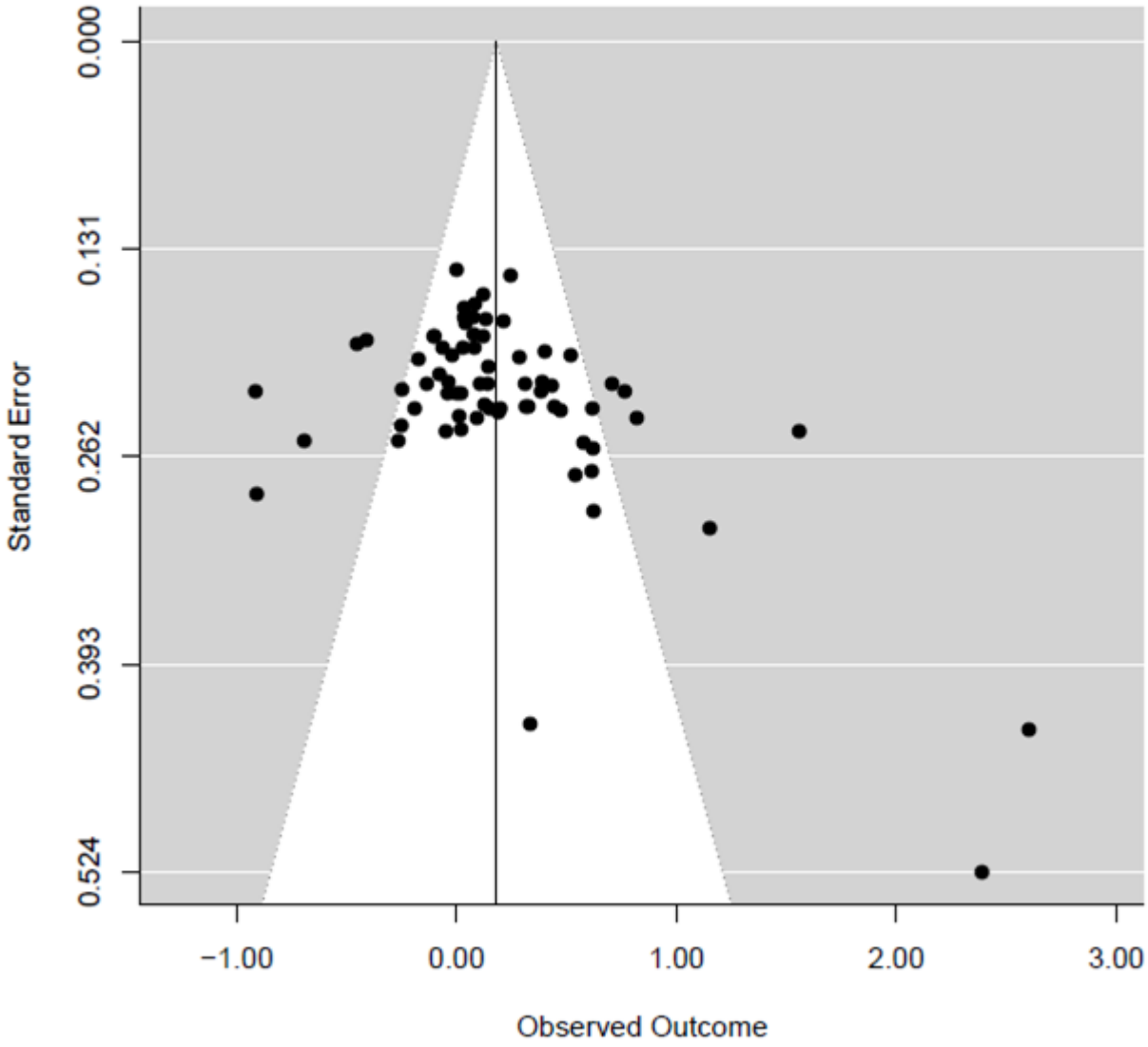
0.5
1.0
1.5
observed outcome

Figure 3



Supplementary Figure 1