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# Extracellular buffering supplements to improve exercise capacity and performance: a comprehensive systematic review and meta-analysis.

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**Extracellular buffering supplements to improve exercise capacity and performance: a comprehensive systematic review and meta-analysis**

Review Article

Running head: Extracellular buffering supplements for exercise: meta-analysis

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**ABSTRACT**

**Background: E**xtracellular buffering supplements (sodium bicarbonate [SB], sodium citrate [SC], sodium/calcium lactate [SL/CL]) are ergogenic supplements though questions remain about factors which may modify their effect.

**Objective:** To quantify the main effect of extracellular buffering agents on exercise outcomes, and to investigate the influence of potential moderators on this effect using a systematic review and meta-analytic approach.

**Methods** This study was designed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Three databases were searched for articles which were screened according to inclusion/exclusion criteria. Bayesian hierarchical meta-analysis and meta-regression models were used to investigate pooled effects of supplementation and moderating effects of a range of factors on exercise and biomarker responses.

**Results** 189 articles with 2019 participants were included, 158 involving SB supplementation, 30 with SC, and seven with CL/SL; four studies provided a combination of buffering supplements together. Supplementation led to a mean estimated increase in blood bicarbonate of +5.2 mmol·L$^{-1}$ [95%CrI: 4.7 to 5.7 mmol·L$^{-1}$]. The meta-analysis models identified a positive overall effect of supplementation on exercise capacity and performance compared to placebo ($ES_{0.5}$ = 0.17 [95%CrI: 0.12 to 0.21]) with potential moderating effects of exercise type, duration and mode, training status and when the exercise test was performed following prior exercise. The greatest ergogenic effects were shown for exercise durations of 0.5–10 min ($ES_{0.5}$=0.18 [0.13–0.24]) and >10 min ($ES_{0.5}$=0.22 [0.10–0.33]). Evidence of greater effects on exercise were obtained when blood bicarbonate increases were medium (4–6 mmol·L$^{-1}$) and large (>6 mmol·L$^{-1}$) compared with small (≤4 mmol·L$^{-1}$) ($\beta_{Small:Medium}$=0.16 [95%CrI: 0.02–0.32], $\beta_{Small:Large}$=0.13 [95%CrI: -0.03–0.29]). SB (192 outcomes) was more effective for performance compared to SC (39 outcomes) ($\beta_{SC:SB}$ = 0.10 [95%CrI: -0.02 to 0.22]).

**Conclusions** Extracellular buffering supplements generate large increases in blood bicarbonate concentration leading to positive overall effects on exercise, with sodium bicarbonate being most effective. Evidence for several group-level moderating factors were identified. These data can guide an athlete's decision as to whether supplementation with buffering agents might be beneficial for their specific aims.

## Key points

1. This systematic review and meta-analysis provided strong evidence that extracellular buffering agents are effective at improving exercise capacity and performance ($ES_{0.5}$ = 0.17 [95%CrI: 0.12 to 0.21]).
2. Exercise duration was identified as the strongest factor influencing the ergogenic effect, with exercise ≥30 s in duration showing greater improvements than exercise less than 30 s.
3. Individuals should aim to reach an increase of at least +4 $mmol \cdot L^{-1}$ in blood bicarbonate concentration to ensure an optimal chance of a performance improvement.
4. Sodium bicarbonate was identified as the most effective buffering supplement when compared to sodium citrate ($\beta_{SC:SB}$ = 0.10 [95%CrI: -0.02 to 0.22]).

## 1. Introduction

Sodium bicarbonate (SB), sodium citrate (SC), calcium (CL) and sodium lactate (SL) are ergogenic supplements that augment the body's extracellular buffering capacity via an increase in bicarbonate concentration [1]. This blood alkalosis leads to a greater efflux of the intramuscular hydrogen ions ($H^+$) that are generated during high-intensity exercise out of the working muscle. Accumulation of $H^+$ within the intracellular environment can interfere with several metabolic and contractile processes [2-5], ultimately leading to a reduction in force and power production and the onset of fatigue during exercise. Thus, it follows that improved maintenance of acid-base balance can positively favour exercise tasks limited by muscle acidosis through accelerating removal of $H^+$, and these extracellular buffering supplements have all been independently demonstrated to be effective ergogenic aids [1]. Nonetheless, substantial between and within-participant variation has been shown regarding the exercise response to some of these supplements [6, 7]. Thus, intriguing questions remain related to how the use of these buffering agents can be optimised, and addressing these questions has substantial potential to advance their efficacy in practice.

The landscape of nutritional supplementation to improve exercise performance and training is constantly advancing and adapting, and the same is true of extracellular buffering supplements. Determination of factors that might modify the responses to supplementation is gaining traction and interest in recent years [1]. Several moderating factors that appear to influence the individual response to extracellular buffering supplements include supplementation timing and the absolute changes in circulating bicarbonate concentration, the exercise task performed, training status, gender, genetics and associated side-effects [1, 8]. Nonetheless, evidence to support the contribution of these factors to variability in the supplementation response is still incipient or lacking. While previous meta-analyses have investigated the ergogenic effect of these individual buffering supplements [9-11], most have not determined the extent to which modifying factors influence their efficacy. None have pooled data from all supplements that increase extracellular buffering capacity. It is vital that the impact of these factors is determined to identify more targeted and evidence-based dosing recommendations.

Speculation exists as to the minimum increase in circulating bicarbonate necessary to elicit an ergogenic effect, which has been suggested to be +5-6 $mmol \cdot L^{-1}$ [1, 12] although this claim is yet to be validated. It would be of interest to confirm these currently unsubstantiated thresholds and determine if performance improvements are indeed related to the change in circulating bicarbonate following supplementation and exceeding certain thresholds. A recent trend in extracellular buffering supplementation is the concept of time-to-peak, where the moment at which an individual's blood bicarbonate peaks following supplementation is determined, and this information is used in subsequent sessions to ensure that the exercise task coincides with each individual's peak blood bicarbonate concentration [13, 14]. Theoretically, this gives the greatest chance of a performance improvement since blood buffering capacity will be at its maximum, although this assumes a linear dose-response relationship between blood bicarbonate and performance, which is yet to be experimentally confirmed. Certainly, it appears logical that greater bioavailability of circulating bicarbonate will provide a greater chance of a performance improvement, and evidence exists demonstrating this strategy to be effective [13, 14]. One study has shown that using time-to-peak is more effective for rowing performance than supplementing sixty minutes prior to exercise [15] while others have suggested that there may be a long-lasting window of ergogenic opportunity considering bicarbonate increases above five to six $mmol \cdot L^{-1}$ following SB ingestion [16], It remains unclear if more blood bicarbonate as would occur at peak bicarbonate concentration elicits greater performance improvements.

The aim of this study was to address contemporary questions regarding the efficacy of extracellular buffering supplements on exercise capacity and performance using a systematic review and meta-analytic approach, while accounting for several potential modifying factors including: exercise duration, type, sample population, supplementation strategy, and changes in blood bicarbonate concentration.

## 2. Methods

### *2.1. Study Eligibility*

Only peer-reviewed, original human studies in English were included within this review. The protocol for this study was designed in accordance with PRISMA guidelines [17] (see PRISMA checklist, Supplementary Material Appendix S1) and the question and eligibility criteria were determined according to PICOS (***Population, Intervention, Comparison, Outcomes*** and ***Study Design***). The ***population*** included healthy human males and females of any age, studies conducted with diseased-state participants were excluded. The ***intervention*** must have employed an acute (<1 day) or chronic (>1 day) supplementation protocol with either sodium bicarbonate, sodium citrate, calcium lactate or sodium lactate prior to performing an exercise test. In relation to the ***comparison***, the protocol for this study determined that both single and double blinded, placebo-controlled studies were included. Studies that reported on ***outcomes*** based on exercise performance and capacity were considered for inclusion. ***Study design*** allowed for crossover or parallel group designs. This study was not pre-registered.

### *2.2. Search Strategy*

An electronic search of the literature was undertaken by LFO using three databases (MEDLINE, Embase, SPORTDiscus) to identify all relevant articles. The search terms “sodium bicarbonate”, “sodium citrate”, “calcium lactate”, “sodium lactate” and “alkalosis” were individually concatenated with “supplementation”, “exercise”, “training”, “athlete” and “performance”. An example search is included in Supplementary Material Appendix S2. Following the removal of duplicates, a two-phase search strategy was subsequently employed by two independent reviewers (LFO and ED) using freely available software (Rayyan QCRI; [18]). Phase one assessed the eligibility of the title and abstract of every paper retrieved from the search terms against the inclusion/exclusion criteria. Studies that had unclear suitability were included at this stage and the final decision was reached at the next phase. In phase two, full articles were assessed against the eligibility criteria. Reference lists of included articles were screened using a snowballing approach to ensure all studies meeting the inclusion criteria were included. Any differences of opinion relating to study eligibility were resolved through discussion and consensus, with a third reviewer (BS) invited to mediate when necessary. The search strategy is summarised in Fig 1. No date limitations were included within the search, and a final updated search was completed in June 2021.

### *2.3. Certainty in cumulative outcomes*

Certainty in outcomes was determined according to the framework provided by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) working group [19]. The approach considers eight factors which determine the level of certainty in each review outcome, five of which can be used to downgrade certainty in outcomes (risk of bias, imprecision, inconsistency, indirectness and publication bias). Certainty can also be upgraded if there is evidence of large effects; a dose-response; or the presence of plausible residual confounding factors. All included studies were initially provided an *a-priori* rating of "high" since they were all blinded, placebo-controlled trials. This rating was either maintained or downgraded following application of the strategy, with certainty in outcomes graded as "high", "moderate", "low" or "very low".

Risk of bias was assessed using the most recent Cochrane tool for assessing risk of bias in randomized trials (RoB 2) [20]. An additional question was included to address potential topic-specific sources of bias deemed particularly relevant to this investigation, namely in Domain 4 (Was there a familiarisation to the exercise protocol?). Evaluation of risk of bias was performed by three reviewers (LFO, ED and BS).

*2.4. Data Extraction and Variable Categorisation*

Data extraction was conducted by LFO using a standardized and pre-piloted Microsoft Excel spreadsheet and extraction was verified by BS. Where numerical data was not directly available, data were extracted from figures using software (DigitizeIt; [21]). Authors of articles whose data could not be extracted from writing or figures were contacted for data. Blood pH, bicarbonate and lactate values were extracted from three moments where available: i) pre-supplementation, ii) post-supplementation (and immediately pre-exercise), iii) immediately post-exercise. A single outcome measure was extracted from each exercise test according to availability and the hierarchical profile of Saunders et al. [22]. For repeated-bout exercise protocols, only data from the first bout were included in the overall meta-analytical model and subsequent bouts were included in a further analysis (detailed below).

Several factors that might modify the blood and exercise response to supplementation were identified *a priori*, and categorised as follows:

1) The size of change in blood pH and bicarbonate concentration from pre-supplementation to pre-exercise, and the change in blood pH, bicarbonate and lactate concentrations from pre-exercise to post-exercise.
2) Exercise protocols were separated by exercise duration [*Exercise duration 1*] according to the approach of Saunders et al. [22], namely <0.5 min; 0.5–10 min; >10 min. A further sub-analysis was performed within the 0.5–10 min timeframe [*Exercise duration 2*], according to the following timeframes: 0.5–<1.5 min, 1.5–<5 min and 5–10 min. These timeframes were based on the distinct energy system contribution during exercise of different durations [23], subsequent $H^+$ accumulation and the proposed physiological mechanisms of $H^+$ buffering agents.

3) The effect of supplement dose [*Supplement dose*] on exercise outcomes was investigated here (Low, <0.3 $g \cdot kg^{-1}$ of body mass (BM); Mid, 0.3 $g \cdot kg^{-1}$BM; High, >0.3 $g \cdot kg^{-1}$BM). The effect of supplementation strategy [*Supplement strategy*], as a single or split dose strategy; supplementation provided acutely (<1 day) vs. chronically (>1 day) [*Acute/Chronic*]; and supplement form [*Supplement form*], as a solution or capsule, on exercise outcomes was determined. The relationship between blood bicarbonate increases prior to exercise and exercise [*Bicarbonate increase*] were also evaluated.

4) Studies were separated according to the sample population recruited [*Training status*], since trained individuals may be less responsive to supplementation with buffering agents [10, 22]. Individuals were categorised into one of three groups: top-level, trained and non-trained. Participants who were described as "elite" and Olympic- or international-level in their area were categorised as top-level. Trained individuals were considered those engaged in a structured training programme with a training plan relevant to the exercise task employed in the study, but not elite or international standard. All remaining populations that did not fit these two previous descriptions (*i.e.*, recreationally active) were categorised as non-trained.

5) Exercise protocols were categorised according to whether they measured exercise capacity or performance [*Exercise type*] [24]. Capacity tests require exertion to the point of volitional exhaustion (*e.g.,* time-to-exhaustion text) whereas performance tests rely more on pacing strategies that might not elicit maximal exertion (*e.g.*, time-trial).

6) Prior exercise can induce $H^+$ accumulation which may affect subsequent exercise performance [25], thus, the influence of prior exercise [*Prior exercise*] as a moderating factor was determined.

7) Exercise tests were similarly categorised according to whether they employed an intermittent exercise protocol [*Intermittent*] and the effect on increasing numbers of exercise bouts was investigated.

### *2.5. Statistical Analysis*

All analyses were performed within a Bayesian framework to provide a more flexible modelling approach and enable results to be interpreted intuitively through reporting of subjective probabilities [26]. Three-level hierarchical models were conducted on aggregate data to pool effects and investigate moderators whilst including random effects to account for within study variation, between study variation and covariance of multiple outcomes reported in the same study. The analysis was split into four stages. For the first stage, the effects of supplementation and exercise on biomarker outcomes (bicarbonate, pH and lactate) were investigated. Meta-analyses were performed on mean difference effect sizes calculated based on absolute values (*e.g.*, $mmol \cdot L^{-1}$) to facilitate interpretation across three time points (pre-supplementation, pre-exercise and post-exercise). To fully describe the biomarker response across the three time points, effect sizes were calculated for both the supplement condition only, and by subtracting the mean difference from the placebo group (controlling for the placebo). Within-study variance of effect sizes were calculated according to standard distributions. However, such distributions are influenced by pre-post correlations ($\rho$) that are generally not reported. It was assumed that correlations were likely to range between 0.5 and 0.9 [27], and to meet this assumption an additional error term was included with informative prior included to model the range. Meta-regressions were used to explore potential moderating effects of factors such as supplement dose, exercise type and exercise duration.

The effect of supplementation on exercise outcomes was investigated in the second stage of the analysis. To pool results across a range of exercise outcomes (*e.g.*, performance tests, time-to-exhaustion tests, and fatiguing resistance protocols), standardized mean difference effect sizes between supplementation and placebo were calculated. Due to the repeated measures nature of the data, within-study variances were calculated as described above using informative priors to account for uncertainty in unknown correlations. Meta-regressions were used to explore the potential moderating effects of exercise type, exercise duration and prior exercise. A sub-analysis was then completed on studies comprising up to three exercise bouts to investigate whether the effects of supplementation increased with subsequent bouts. In the third stage of the analysis the effects of different supplementation protocols (*e.g.*, supplement form [gelatine capsules, solution, tablets], dose [Low (<0.3 $g \cdot kg^{-1}$BM), Mid (0.3 $g \cdot kg^{-1}$BM) or High (>0.3 $g \cdot kg^{-1}$BM)] and supplementation strategy [single or split-dose]) on exercise outcomes were investigated. Influential moderators identified in stage 2 of the analysis (exercise characteristics) were included in meta-regressions to control for confounding factors. In the final stage of the analysis the relationship between changes in blood bicarbonate concentration and exercise outcomes were investigated by meta-regression and categorising changes as small (<4 $mmol \cdot L^{-1}$ increase), moderate (4–6 $mmol \cdot L^{-1}$ increase) and large (>6 $mmol \cdot L^{-1}$ increase) and controlling for the same influential moderators identified in stage 2 of the analysis.

Inferences from all analyses were performed on posterior samples generated using the Hamiltonian Markov Chain Monte Carlo method (five chains, 100,000 iterations and 50,000 warmup). Interpretations were based on the median value ($ES_{0.5}$: 0.5-quantile), the 95% credible interval (CrI) for location parameters, and the 75% CrI for variance parameters. To assist with interpretation of standardized effect sizes, threshold values of 0.01, 0.2, 0.5 and 0.8 were used to describe effect sizes as very small, small, medium and large [28]. Meta-regressions were presented by selecting one level of the factor as a reference to make comparisons ($\beta_{Reference:Comparison}$ = Median [95%CrI: LB to UB], such that $\beta > 0$ indicates an increased effect of the comparison relative to the reference). Between-study variance ($\tau$) and the intraclass correlation (ICC) calculated as the ratio of the between-outcomes variance relative to the total variance [29] were also presented for primary meta-analyses. Outlier values were identified by the method proposed by Verardi and Vermandele [30], adjusting the data by a Tukey g-and-h distribution to remove outliers from potentially skewed and heavy tailed distributions. Analyses were performed using the R wrapper package brms interfaced with Stan to perform sampling [31]. Convergence of parameter estimates was obtained for all models with Gelman-Rubin R-hat values below 1.1 [32]. Small-study effects (publication bias, etc.) were visually inspected with funnel plots.

# 3. Results

## *3.1. Study search*

The literature search initially identified a total of 3621 potential studies, with 3142 remaining following removal of duplicates. After title and abstract screening, 293 full articles were evaluated according to the inclusion/exclusion criteria. A total of 189 studies including 2019 participants (Minimum: N=4; Maximum: N=49; Median: N=10; IQR: 8-12) met the inclusion criteria and were included in the meta-analysis (Fig 1) (Table of all include studies can be found in Supplementary Material Appendix S3). Studies included 158 involving SB supplementation (226 outcomes), 30 with SC (45 outcomes) and seven with CL or SL (7 outcomes); four studies (4 outcomes) provided a combination of buffering supplements together (*e.g.*, SB and SC).

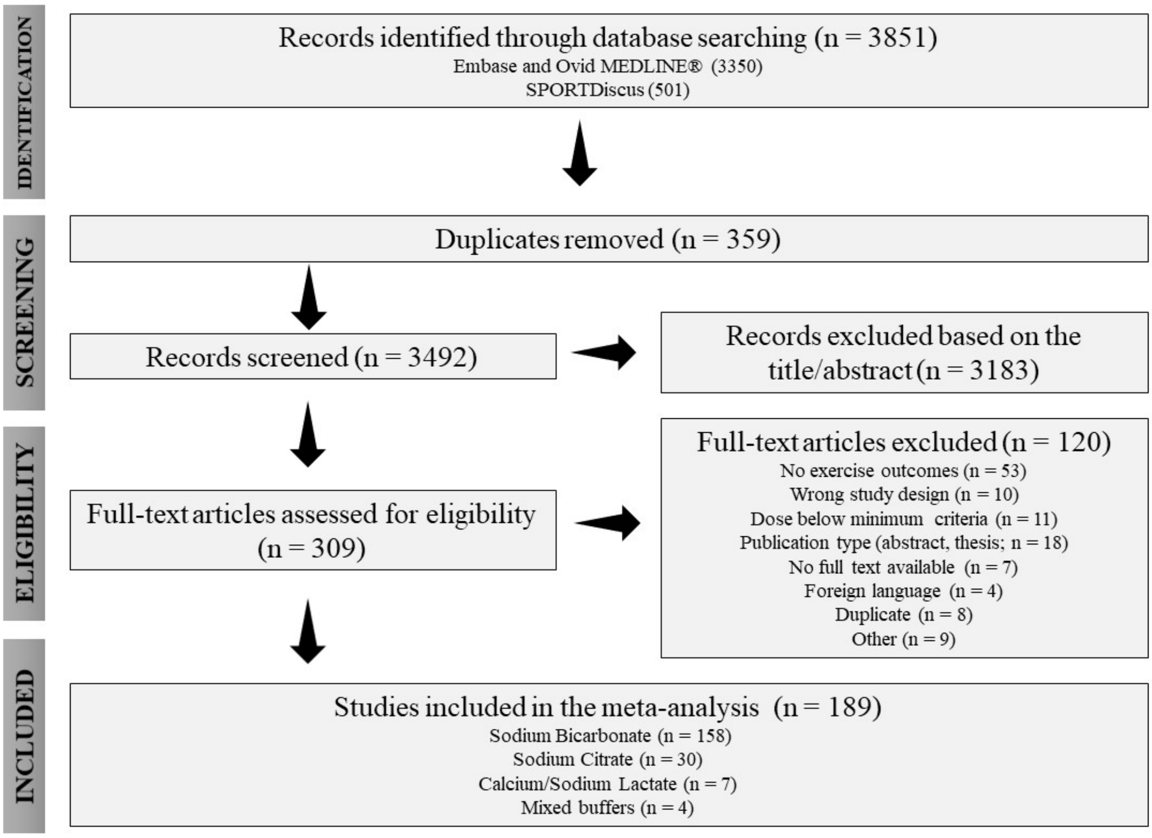


**Fig 1** Flow diagram of search and study selection. *Note: Several studies investigated more than one supplement, therefore, summing studies of individual supplements will lead to duplication and not accurately reflect the true number of studies.*

### 3.2. Meta-analysis

#### 3.2.1. Biomarker Outcomes

##### 3.2.1.1. Pre-supplementation to Pre-exercise

The primary meta-analysis was completed on 131 outcomes from 87 studies. Supplementation was estimated to lead to a median increase in blood bicarbonate of 5.2 mmol·L$^{-1}$ [95%CrI: 4.7 to 5.7 mmol·L$^{-1}$] relative to placebo. Moderate between-study variation ($\tau_{0.5}$ = 1.5 [75%CrI: 0.9 to 2.0 mmol·L$^{-1}$]) and covariance between multiple outcomes reported from the same study (ICC: 0.58 [75%CrI: 0.41 to 0.79]) were identified. Due to the large number of studies and outcomes, visual presentations of meta-analysis results are included in funnel plots and not forest plots. The funnel plot of blood bicarbonate changes from pre-supplementation to pre-exercise provided no visual evidence of small-study effects, such as publication bias (Fig 2, Panel A). Most outcomes were obtained from SB supplementation (N=109), followed by SC (N=19) and CL/SL (N=3). All supplement types were capable of increasing blood bicarbonate, although some evidence was obtained to indicate greater post-supplementation increases in blood bicarbonate from SB compared with SC ($\beta_{SB:SC}$ = -1.3 mmol·L$^{-1}$ [95%CrI: -2.7 to 0.3 mmol·L$^{-1}$]) (Table 1). The average supplement dose was 0.3 g·kg$^{-1}$BM and ranged from 0.1 to 0.5 g·kg$^{-1}$BM. Evidence of a moderation effect of supplement dose was shown, with an estimated increase in blood bicarbonate of 1.1 mmol·L$^{-1}$ [95%CrI: 0.7 to 1.7 mmol·L$^{-1}$] per every additional 0.1 g·kg$^{-1}$BM of supplement (Table 1). Similar general results were obtained for blood pH and are presented in Supplementary Material Appendix S4.

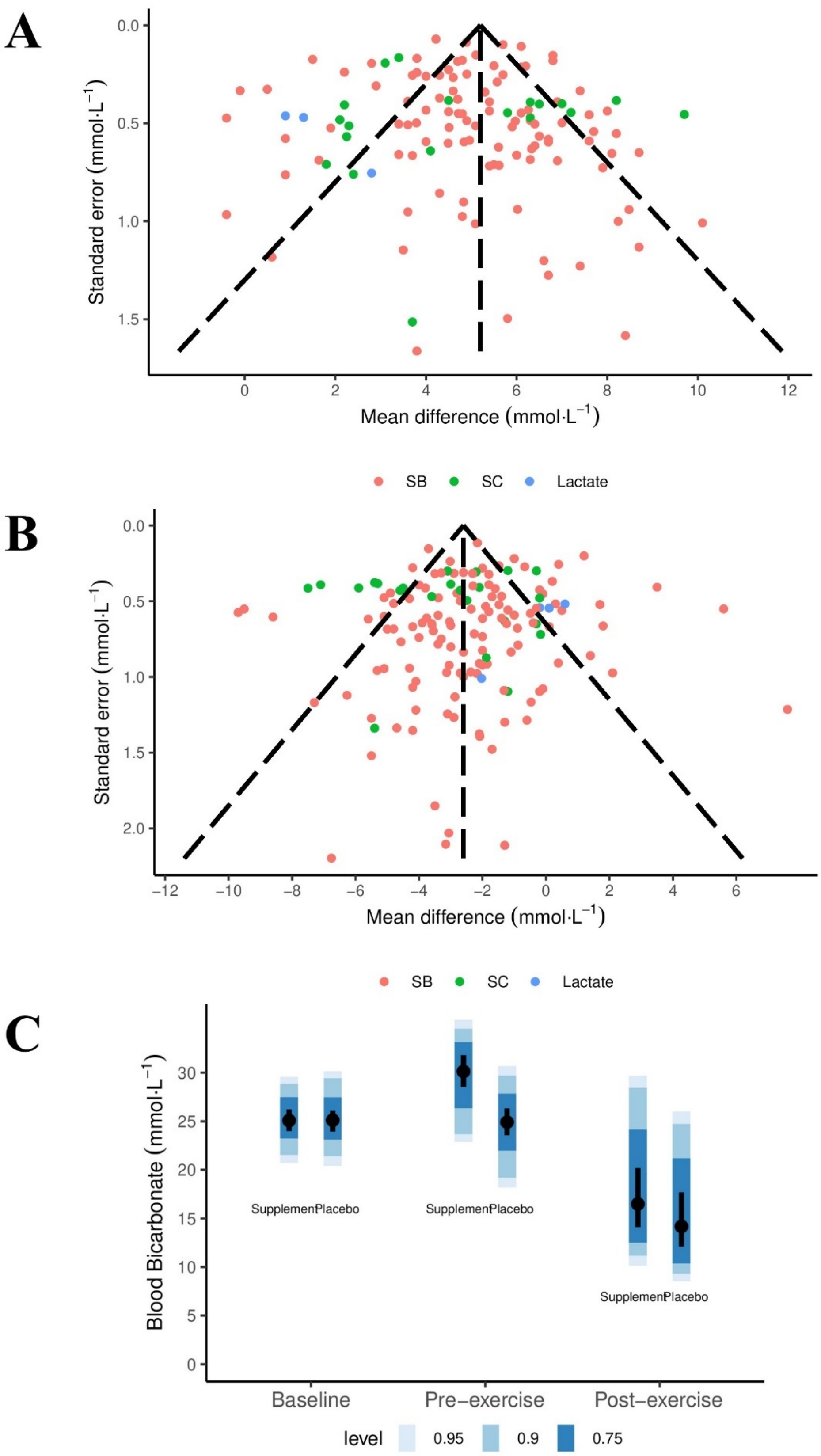


**Fig 2** Panel A/B: Funnel plots illustrating mean difference effects of blood bicarbonate relative to placebo (A: Pre-supplementation to pre-exercise; B: Pre-exercise to post-exercise). Panel C: Plot illustrating prediction (blue) and 50% fitted intervals (black) of group mean supplementation and placebo blood bicarbonate values across three time points. SB = Sodium bicarbonate, SC = Sodium citrate.

*3.2.1.2. Pre-exercise to Post-exercise*

A large decrease in the blood bicarbonate pooled estimate (153 outcomes from 104 studies) was identified ($ES_{0.5}$ = -12.0 mmol·L$^{-1}$ [95%CrI: -13.0 to -10.9 mmol·L$^{-1}$]) in the non-placebo-controlled effect sizes. Substantive between-study variation ($\tau_{0.5}$ = 5.2 [75%CrI: 4.7 to 5.7 mmol·L$^{-1}$]) and limited covariance between multiple outcomes reported from the same study (ICC: 0.09 [75%CrI: 0.06 to 0.11]) were also identified. The magnitude of the decrease in blood bicarbonate was influenced by [*Exercise type*], with performance tests estimated to cause an additional drop compared to capacity tests ($\beta_{Capacity:Performance}$ = -4.1 mmol·L$^{-1}$ [95%CrI: -5.9 to -2.3 mmol·L$^{-1}$]) (Table 1). A moderating effect of [*Exercise duration*] was also identified, with the greatest decreases in blood bicarbonate estimated for tests lasting between 0.5 and 10 minutes ($\beta_{0.5\text{-}10min:<0.5min}$ = 0.90 mmol·L$^{-1}$ [95%CrI: -1.0 to 2.8 mmol·L$^{-1}$]; $\beta_{0.5\text{-}10min:>10min}$ = 5.5 [95%CrI: 2.6 to 8.5 mmol·L$^{-1}$]) (Table 1). When investigating the change relative to placebo, a greater decrease in blood bicarbonate following exercise was obtained in the supplementation condition ($ES_{0.5}$ = -2.6 mmol·L$^{-1}$ [95%CrI: -3.3 to -2.0 mmol·L$^{-1}$]; $\tau_{0.5}$ = 3.0 [75%CrI: 2.7 to 3.4 mmol·L$^{-1}$]; ICC: 0.15 [75%CrI: 0.10 to 0.22]). Funnel plot provided no visual evidence of small-study effects (Fig 2, Panel B). Similar general results for both placebo-controlled and non-controlled effects sizes were obtained for blood pH and are presented in Supplementary Material Appendix S4.

Blood lactate data were meta-analysed across the exercise period. The non-controlled mean difference effect sizes (139 outcomes from 104 studies) estimated a pooled increase of $ES_{0.5}$ = 11.1 mmol·L$^{-1}$ ([95%CrI: 10.1 to 12.0 mmol·L$^{-1}$]; $\tau_{0.5}$ = 3.9 [75%CrI: 3.4 to 4.5 mmol·L$^{-1}$]; ICC: 0.32 [75%CrI: 0.18 to 0.40]), which was found to be greater than the increase obtained in the placebo condition ($ES_{0.5}$ = 1.5 mmol·L$^{-1}$ [95%CrI: 1.3 to 1.8 mmol·L$^{-1}$]; $\tau_{0.5}$ = 0.5 [75%CrI:

0.2 to 0.8 mmol·L$^{-1}$]; ICC: 0.57 [75%CrI: 0.42 to 0.70]). Similar to other biomarkers investigated, moderating effects of [*Exercise type*] and [*Exercise duration*] were identified, with the supplement condition demonstrating greater blood lactate increases with performance tests compared to capacity tests ($\beta_{Capacity:Performance}$ = 2.5 mmol·L$^{-1}$ [95%CrI: 0.9 to 4.4 mmol·L$^{-1}$]), and the greater increases for tests lasting between 0.5 to 10 minutes ($\beta_{<0.5min:0.5\text{-}10min}$ = 3.5 mmol·L$^{-1}$ [95%CrI: 1.2 to 5.7 mmol·L$^{-1}$]; $\beta_{0.5\text{-}10min:>10min}$ = -3.6 mmol·L$^{-1}$ [95%CrI: -5.9 to -1.2 mmol·L$^{-1}$] (Table 1).

### 3.2.2. *Exercise Outcomes*

There were 256 exercise outcomes across 173 individual studies. Two negative outliers (effect size <-1.0) and thirteen positive outliers (effect size >1.9) were identified and removed from subsequent analyses. The pooled standardized mean difference identified a very small to small effect of supplementation on exercise outcomes compared to placebo ($ES_{0.5}$ = 0.17 [95%CrI: 0.12 to 0.21]; $\tau_{0.5}$ = 0.13 [75%CrI: 0.09 to 0.17]; ICC: 0.04 [75%CrI: 0.00 to 0.13]). Probabilities of the pooled effect size exceeding very small and small were p>0.999 and *p*=0.085. A funnel plot provided evidence of small-study effects (*i.e.*, publication bias) with substantive asymmetry and many large positive effect sizes far from the central cluster (Fig 3). Potential moderating effects (Table 2) were identified for [*Exercise type*], [*Exercise duration*] and [*Exercise duration 2*] with greater improvements for capacity tests ($\beta_{Capacity:Performance}$ = -0.06 [95%CrI: -0.15 to 0.02]), and exercise durations greater than 0.5 min ($\beta_{<0.5min:0.5\text{-}10min}$ = 0.12 [95%CrI: 0.00 to 0.24]; $\beta_{<0.5min:>10min}$ = 0.16 [95%CrI: 0.01 to 0.31]). Largest effects within [*Exercise duration 2*] were shown for exercise 5–10 min in duration ($\beta_{0.5\text{-}1.5min:5\text{-}10min:}$ = 0.02 [95%CrI: -0.13 to 0.18]; $\beta_{1.5\text{-}5min:5\text{-}10min:}$ = 0.10 [95%CrI: -0.04 to 0.25]) (Table 2). Exercise performed following prior exercise [*Prior exercise*] showed evidence of greater improvements with supplementation compared with no prior exercise ($\beta_{PriorExercise:NoPriorExercise}$ = -0.12

[95%CrI: -0.29 to 0.02]) (Table 2). In support of the moderating effects of prior exercise, analysis of research investigating multiple exercise bouts (143 outcomes from 41 studies) demonstrated that compared to placebo a greater pooled effect size was obtained in the second exercise bout compared to the first ($\beta_{Bout1:Bout2}$ = 0.07 [95%CrI: -0.04 to 0.17]), and an even greater pooled effect size obtained in the third ($\beta_{Bout1:Bout3}$ = 0.16 [95%CrI: 0.04 to 0.27]) (Table 2).

Most outcomes from a single bout of exercise were conducted on trained individuals (139 outcomes), followed by non-trained (80 outcomes) and top-level (21 outcomes) individuals. The greatest uncertainty in the pooled estimate was obtained for top-level athletes ($ES_{0.5}$ =0.12 [95%CrI: -0.03 to 0.27]), with similar values obtained across all groups but the highest estimates obtained for non-trained individuals ($\beta_{Non\text{-}trained:Top\text{-}level}$ = -0.07 [95%CrI: -0.24 to 0.09]; $\beta_{Non\text{-}trained:Trained}$ = -0.03 [95%CrI: -0.13 to 0.07]) (Table 2). When all potential moderators were included in the same regression, large uncertainty with wide credible intervals were obtained for all factors except for exercise duration where consistent evidence was obtained for exercise of longer durations ($\beta_{<0.5min:0.5\text{-}10min}$ = 0.13 [95%CrI: 0.00 to 0.25]; $\beta_{<0.5min:>10min}$ = 0.15 [95%CrI: 0.01 to 0.32]). Analysis of exercise outcomes were repeated for studies supplementing with SB only based on analyses demonstrating differences in blood biomarker response compared with sodium citrate. No substantive differences were identified in any of the moderator analyses however, effect sizes were increased systematically with SB by very small amounts (~0 to 0.05) (Supplementary Material Appendix S5).

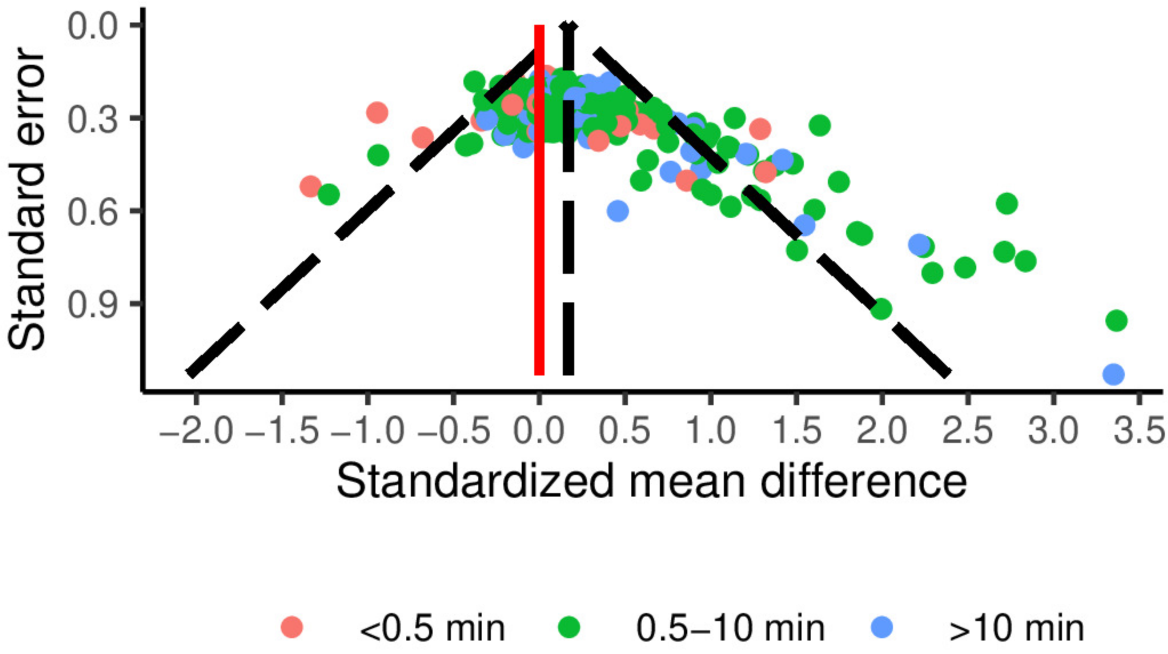


**Fig 3** Funnel plot illustrating standardized mean difference effect sizes for exercise outcomes relative to within-study standard errors. Centre dashed black line and blue region represent the mean pooled estimate and 95% credible interval.

### *3.2.3. Supplementation protocols and Exercise Outcomes*

To assess the effect of supplement dose on exercise outcomes (Table 3), the dose provided was categorised as low (< 0.3 $g \cdot kg^{-1}$BM, 33 outcomes), moderate (0.3 $g \cdot kg^{-1}$BM, 162 outcomes) or high (>0.3 $g \cdot kg^{-1}$BM, 43 outcomes). Whilst controlling for exercise duration and the existence of prior exercise, no moderating effect of dose was identified ($\beta_{<0.3:0.3}$ = 0.03 [95%CrI: -0.10 to 0.17]; $\beta_{0.3:>0.3}$ = -0.01 [95%CrI: -0.13 to 0.10]). In contrast, some evidence was obtained to indicate greater effects when the dose was consumed in a single preparation (162 outcomes) compared to split dose strategies (77 outcomes) ($\beta_{Split:Single}$ = 0.11 [95%CrI: 0.01 to 0.20]); when the dose was consumed in solution (123 outcomes) compared with capsules (100 outcomes) ($\beta_{Capsule:Solution}$ = 0.09 [95%CrI: 0.01 to 0.18]); and when SB (192 outcomes) was consumed compared with SC (39 outcomes) ($\beta_{SC:SB}$ = 0.10 [95%CrI: -0.02 to 0.22]). There was some evidence that chronic supplementation was more effective than acute supplementation ($\beta_{Acute:Chronic:}$ = 0.08 [95%CrI: -0.11 to 0.26]) (Table 3), although credible intervals were wide.

### 3.2.4. *Blood Biomarkers and Exercise Outcomes*

The effects of change in blood bicarbonate ([*Bicarbonate increase*]; pre-supplementation to pre-exercise) on exercise performance were investigated by categorising changes as small (≤4 $mmol \cdot L^{-1}$ increase, 44 outcomes), medium (4–6 $mmol \cdot L^{-1}$ increase, 51 outcomes) and large (>6 $mmol \cdot L^{-1}$ increase, 30 outcomes) and controlling for the effects of prior exercise and exercise duration. Evidence of greater effects of exercise were obtained for medium and large changes in blood bicarbonate compared with small changes ($\beta_{Small:Medium}$ = 0.16 [95%CrI: 0.02 to 0.32], $\beta_{Small:Large}$ = 0.13 [95%CrI: -0.03 to 0.29]). There was no evidence of increased performance effects comparing medium and large blood bicarbonate changes ($\beta_{Medium:Large}$ = -0.05 [95%CrI: -0.20 to 0.12]; Fig 4). Prediction intervals were calculated for the different categories, with probabilities of modelled effect size exceeding standard thresholds equal to: very small effect (small changes: $p$=0.553, medium changes: $p$=0.727, large changes: $p$=0.688); small effect (small changes: $p$=0.359; medium changes: $p$=0.536; large changes: $p$=0.496); medium effect (small changes: $p$=0.136; medium changes: $p$=0.242; large changes: $p$=0.225); and large effect (small changes: $p$=0.042; medium changes: $p$=0.081; large changes: $p$=0.086).

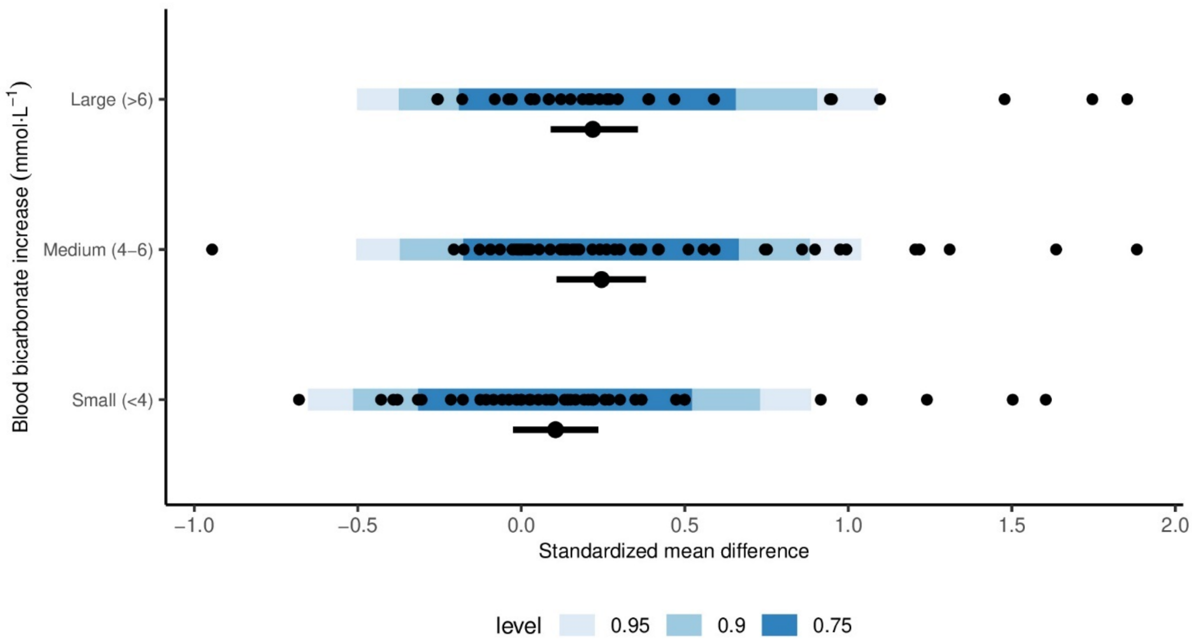


**Fig 4** Relationship between increased blood bicarbonate concentration following supplementation and exercise performance ([*Bicarbonate increase*]). Mean changes in blood bicarbonate (y-axis) following supplementation were separated into small (≤4 mmol·L$^{-1}$), medium (4–6 mmol·L$^{-1}$), and large (>6 mmol·L$^{-1}$) increases. Standardized mean difference effects size is presented on the x-axis. Blue interval scale provides prediction intervals for the different categories. Black intervals represent the 50% fitted interval. Black points equal calculated standardized intervals from studies.

### *3.3. Certainty in cumulative outcomes*

Blood and exercise outcomes were assigned an *a-priori* certainty rating of "high" because they were all based on blinded, placebo-controlled trials (as defined by the eligibility criteria). All studies included in the meta-analysis were classified as having at least "some concerns" according to ROB2 (Fig 5). Almost all studies were classified as having at least some concerns in Domain 1 due to a lack of detailed information regarding randomisation and allocation concealment, while all studies received some concerns due to a lack of a pre-specified analysis plan (as outlined in Domain 5). This was not deemed to pose an undue risk to outcome measures, thus no outcome was downgraded based on risk of bias (see Supplementary Material Appendix S6). The overall analysis of extracellular buffers on exercise outcomes received a "moderate" GRADE rating due to indirectness, while individual sub-analyses received ratings of "low" to "high" (Table 1, 2 and 3). Blood values generally received a "high" GRADE rating except pre-supplementation to pre-exercise changes in bicarbonate per increase per 0.1 $g \cdot kg^{-1}$BM (Moderate) which was downgraded due to heterogeneity of results (Inconsistency; Table 1). Some exercise moderators were similarly downgraded due to heterogeneity of results (Inconsistency) while all were downgraded because of publication bias (Table 2). All moderator analyses of supplement protocols on exercise outcomes were graded as "low" due to heterogeneity of results (Inconsistency) and publication bias (Table 3).

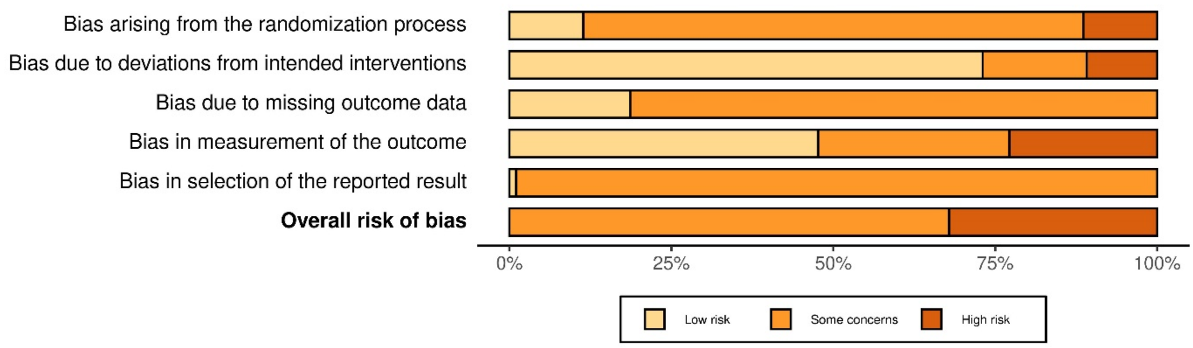


**Fig 5** Risk of bias assessment of the ten studies included in the meta-analysis (Plot was created using *robvis* [33] and is in a colour-blind-friendly colour scheme).

## 4. Discussion

The results of this systematic review and meta-analysis identified large increases in blood bicarbonate and pH with extracellular buffering supplements leading to an overall positive effect on exercise outcomes. The two most researched buffering supplements were SB and SC, with evidence that sodium bicarbonate generated both greater biomarker responses and larger improvements in exercise outcomes. Several factors moderating the blood biomarker and exercise response were identified, including exercise duration, exercise type, prior exercise and training status. Specifically, greater performance benefits can be expected for exercise lasting >0.5 min while trained athletes might expect smaller gains compared to non-trained individuals. Exercise capacity tests showed greater improvements with supplementation than performance tests, while larger effects on outcomes were shown when exercise protocols were performed following prior exercise. A positive chain of association was identified between supplement dose, circulating blood bicarbonate concentration, and exercise performance.

### *4.1. Exercise duration*

The strongest modifying factor that influenced the ergogenic effect of these buffering supplements was exercise duration, with exercise equal to or greater than thirty seconds duration showing greater improvements than exercise less than thirty seconds. These findings are in general consistent with previous results that showed induced alkalosis to be most effective for exercise lasting one to ten minutes [9]. Exercise tasks lasting thirty seconds to ten minutes were further sub-categorised (0.5–<1.5 min; 1.5–<5 min; 5–10 min) considering that glycolytic energy contribution, and concomitant $H^+$ accumulation which can limit exercise capacity and performance [2-5], follows a hyperbolic curve with anaerobic contribution reducing as exercise duration increases [23]. Supplementation led to positive effects across all three categories, with some evidence to suggest exercise 30 – 90 s (*e.g.*, 400 m running, 100 m swimming) and 5 – 10 min (*e.g.*, 4-km cycling, 2000 m rowing) was most susceptible to improvements with supplementation. Athletes whose main exercise modality fits into these categories should be aware that extracellular buffering agents may be effective within these types of events.

Exercise lasting less than thirty seconds is thought to be of insufficient duration to result in substantial $H^+$ accumulation meaning that muscle acidosis is unlikely to affect performance [34]. The data here support this notion with evidence to support the use of extracellular buffering supplements for this type of short duration exercise. This supports previous meta-analytical data showing sodium bicarbonate to be effective for muscle endurance but not muscle strength [35]. This meta-analysis provides novel data that extracellular buffering supplements improve exercise greater than ten minutes in duration, which is somewhat in contrast with previous evidence on the efficacy of increased buffering capacity for endurance exercise [36]. This is thought to be because endurance exercise is not generally performed at an intensity that generates large $H^+$ accumulation that will limit performance, highlighted by lower blood lactate concentration during exercise lasting less than ten minutes shown here. Nonetheless, during most endurance training and competition there are periods of increased intensity that might benefit from supplementation, including a sprint finish in cycling [37], or a final lap sprint as seen in 5000 and 10 000 m running [38, 39]. Improved overall performance during endurance activity following extracellular buffers supplementation might be due to the improved ability to transiently increase intensity at various moments throughout although no study has directly measured this and is an avenue worth investigating.

### *4.2. Training status*

The ergogenic effect with buffering supplements was greater for non-trained individuals compared to trained individuals. A novelty in the current meta-analysis was that we could further separate sixteen studies that recruited top-level athletes, namely international-, Olympic- and elite-level competitors. However, the effect of extracellular buffers on exercise outcomes in top-level athletes was less clear due to substantive study heterogeneity. The training status of the individual has long been purported to modify the effect of buffering supplements on exercise outcomes [9, 10, 36, 40], albeit with contrasting opinion. Some have suggested that greater glycolytic capacity, as commonly seen in trained individuals [41], might allow for a greater performance benefit following induced alkalosis [40], while others suggest that training adaptations, including increased muscle buffering capacity [42], might leave athletes closer to their upper limit for improvements and minimising the effects of any ergogenic aid such as buffering supplements. It must be recognised that different training intensities will lead to distinct glycolytic and buffering adaptations [43, 44] making such generalisations difficult. Whatever the mechanistic reason for this difference, the current data provide support for the notion that less trained individuals experience greater improvements in exercise performance with extracellular buffering supplements compared to trained individuals. The necessity for supplementation in this untrained population is an important caveat to highlight, given that non-competitive athletes have less need for performance enhancing supplements, whereas the marginal gains for competitive athletes might be sufficient to affect medal or qualifying positions [45]. More work regarding extracellular buffers and top-level athletes is required.

### *4.3. Moderating factors*

Improvements in both exercise capacity and performance tests were shown here, with the greatest improvements obtained for capacity tests supporting our previous meta-analysis investigating increased intracellular buffering capacity via beta-alanine supplementation [36]. Capacity tests (i.e., those that require maximal effort or exertion until exhaustion) have previously been shown to be more susceptible to improvement following increases in buffering capacity [24, 36]. This is of relevance to athletes such as cycling domestiques who are sometimes required to exert themselves to the point of exhaustion for their team leader, or athletics athletes trying to maintain the pace of a faster opponent. The current analyses also showed a greater pooled effect of extracellular buffers on exercise performed following prior exercise, namely when a high-intensity or endurance bout of exercise was performed prior to the measured exercise outcome. This has important practical application since certain long-distance events, including endurance cycling and athletics, might be decided by whoever can maintain a higher intensity during the closing stages or final sprint. This was demonstrated by a study from Dalle et al. [37] who showed final sprint performance following 3-h simulated cycling was improved with SB supplementation.

### *4.4. Repeated-bout activities*

The finding that prior exercise generated greater effects with supplementation were further supported by the results for repeated-bout intermittent activities, which showed larger effects with each additional exercise bout. This finding seems to be physiologically plausible, given that sodium bicarbonate supplementation has been reported to improve acid-base recovery kinetics following high-intensity exercise [46, 47], and also enhance phosphorylcreatine resynthesis which is impaired at low muscle pH [48]. Thus, supplementation may accelerate recovery between repeated high-intensity bouts and could be important for individuals involved in sports that require repeated high-intensity bouts with intermittent rest or recovery periods that do not allow for complete restoration of acid-base balance (*e.g.*, team sports players, boxers or track cyclists), although no study has directly measured this with short recovery bouts. This information could also be crucial for athletes engaged in repeated high-intensity training since supplementation with extracellular buffers prior to their training might lead to improved session quality, theoretically generating greater adaptations and gains over time. This may also be relevant to athletic groups whose competitions involves exercise less than thirty seconds in duration. Although results suggest that events less than 30 seconds are unlikely to benefit directly from extracellular buffers, athletes involved in such events likely perform a substantial proportion of their training undertaking high-intensity intermittent activities. Supplementation throughout training could indirectly lead to performance gains for their short duration event irrespective of supplementation prior to competition. This supports data from individual studies demonstrating that SB throughout short-term training (up to 8 weeks) might augment the response to training leading to improved performance even when the exercise test is performed without prior supplementation [49, 50]. However, supplementation and training studies are scarce and further experimental studies should look to determine how to implement these buffering agents throughout training and their longer-term impact on training adaptations.

### *4.5. Supplementation strategies*

The importance of individualised supplement timing has gained traction in recent years with studies suggesting that coinciding the onset of exercise with peak bicarbonate leads to greater gains than standardized timing [13-15]. Conversely, several studies have suggested that a minimum increase of 5–6 $mmol \cdot L^{-1}$ in circulating bicarbonate is required to elicit likely and almost certain exercise improvements with buffering supplements [12, 16, 51], although it remained uncertain whether increases above these thresholds further enhance performance. The results of this meta-analysis provide support for a threshold hypothesis, with smaller performances improvements shown when the average increase in circulating bicarbonate was $<4$ $mmol \cdot L^{-1}$compared with increases $\geq 4$ $mmol \cdot L^{-1}$. There was no evidence of a greater effect on exercise outcomes with bicarbonate increases greater than 6 mmol·L$^{-1}$ compared with increases of 4-6 mmol·L$^{-1}$, indicating a non-linear dose-response relationship which questions the necessity of time-to-peak or any other strategy that aims to increase blood bicarbonate above this 4-6 mmol·L$^{-1}$ threshold. Although this suggests that more blood bicarbonate is not necessarily better, some caution is advised since these analyses were performed using group data for blood bicarbonate and exercise outcomes. Experimental studies specifically designed to investigate the existence of this theoretical threshold and whether peak blood bicarbonate is necessary on an individual-participant basis are required to confirm or refute these data. We herein show that even small increases in circulating bicarbonate (<4 mmol·L$^{-1}$) contribute to performance gains, but individuals should ideally aim to ensure they reach an increase of at least 4-6 mmol·L$^{-1}$ to ensure an optimal chance of an exercise performance improvement.

There was evidence that SB was the most effective supplement both for increasing blood bicarbonate and for improving exercise outcomes. It has been suggested that supplementation protocols with SC are suboptimal [52], with commonly employed supplementation protocols leading to exercise initiating at the moment of maximal side-effects and minimal bicarbonate changes. More work with more optimal dosing strategies [53] are warranted and the efficacy of SC should be revisited once more novel data has been accrued [54]. There was insufficient data on CL/SL to provide any clear estimates. There was some evidence that increasing supplement dose leads to greater increases in bicarbonate concentration, although there was little evidence of an effect of dose on exercise outcomes, an effect likely lost due to the heterogeneity in exercise tests. Single dose ingestion strategies appear to lead to greater exercise improvements than split-dose ingestion strategies, while ingestion in solution was more beneficial for exercise outcomes than in gelatine capsules although certainty in these outcomes was low. Greater improvements with solution could be due, in part, to placebo effects associated with its ingestion [55], since it might be easier to identify the intervention condition due to its distinct salty taste and correct supplement identification can lead to greater ergogenic effects [56]. There was weak evidence that chronic ingestion led to greater performance improvements than acute supplementation. Previous work showed no differences in performance improvements between chronic and acute sodium bicarbonate supplementation strategies [57], while only acute but not chronic sodium citrate supplementation improved swim performance [58]. Thus, since these meta-analytical data were based upon few chronic (n=14) compared to acute (n=227) supplementation protocols, caution is advised, and individuals should adopt and trial their preferred supplementation strategy.

Supplementation with buffering agents results in a large increase in blood bicarbonate, and more bicarbonate is also subsequently used during exercise compared with placebo, leading to performance improvements. These data suggest that improvements in exercise outcomes are due to an increased buffering of $H^+$ that are removed from the muscle. One might expect that the greater buffering capacity would allow an individual to exert themselves for longer eventually reaching the same acidotic endpoint (i.e., equally depleted bicarbonate and low pH), particularly during capacity tests to exhaustion. Nonetheless, the results show that at the end of exercise, supplemented conditions still have higher blood pH and bicarbonate values which suggests that individuals do not make full use of all this additional buffering capacity. Although acidosis can contribute to fatigue [2-5], not all exercise tests have a specific endpoint that is solely limited by this acidosis while the causes of fatigue during exercise are multifactorial. This means that although increased bicarbonate via supplementation may improve performance, it does not necessarily follow that blood bicarbonate will be further reduced compared to a placebo session. This supports the prior notion that time-to-peak may not be a necessary strategy since bicarbonate availability may not be fully used, and that moderate increases in bicarbonate concentration are sufficient to bring about performance gains.

### *4.6. Limitations*

One of the limitations of this meta-analysis is that we did not determine the influence of side-effects associated with supplementation of these buffering agents on subsequent exercise performance. Symptoms of gastric discomfort including bloating and abdominal pain, nausea and vomiting are commonly reported side-effects following supplementation with alkalizing agents [12, 53] and these could negatively impact performance [7]. However, there is a distinct lack of reporting of side-effects in many studies, while those that do are inconsistent in their reporting methods. Additionally, studies do not generally provide information as to whether side-effects were associated with changes in exercise outcomes. For these reasons, side-effects were not considered as moderators within the analysis. Despite their efficacy, coaches and athletes should be aware that supplementation with these ergogenic aids could generate uncomfortable side-effects that might negatively impact performance. Athletes are encouraged to trial these supplements away from competition first to determine their individual tolerance and performance effects which can then guide their own personal decision making as to their implementation. Further work in this area should aim to standardize the reporting of side-effects with these supplements using validated questionnaires and provide detailed analysis of whether this impacted exercise performance. We also urge better reporting of participant flow throughout the study since associated side-effects could lead to dropouts, but these appear to be substantially underreported in the literature. Underreporting of participants dropouts or exclusion of individuals from data analysis due to complications [59] could skew data in favour of these buffering supplements.

Exercise comparisons here were made to a placebo session/group, however, real-world effects of supplements include both the active component of the supplement in addition to placebo effects [55]. Athletes might expect slightly greater effects than those shown here when ingesting these supplements due to the physiological and psychological components associated with supplementation [55]. Finally, studies here were predominantly performed with men, but we have previous shown that women can similarly expect to benefit from supplementation [8]. The existence of small-study effects was investigated by creating and interpreting funnel plots. For the biomarker response no asymmetry was detected. However, for exercise outcomes substantive asymmetry was detected with many very large positive effect sizes beyond the central cluster and very few correspondingly large negative effect sizes. The difference in funnel plot characteristics obtained for biomarkers and exercise performance may be explained by the greater range of outcomes available in the exercise domain and the ability of researchers to retrospectively select values which demonstrate the largest effects. Similar findings of small-study effects were obtained from a large meta-analysis investigating exercise performance following high intensity interval training [60] where researchers also commonly assess a range of outcome measures. All studies were deemed to have at least some risk of potential bias, although this was primarily due to underreporting of information relating to study randomisation and allocation sequence concealment, missing data and dropouts and a lack of preregistration. We encourage all future studies to better report their study proceeding relating to domains 1 (Randomisation), 3 (Missing outcome data) and 5 (Selection of reported results) to improve transparency and thus certainty in the strength of outcomes.

### *4.7. Practical Implications*

The current systematic review and meta-analysis highlights important aspects that can guide athletes and coaches' decisions to consider supplementation with extracellular buffering agents. Current evidence suggests individuals should preferentially supplement with SB over any other extracellular buffering supplement, as it leads to the largest increases in blood bicarbonate and the clearest exercise effects. A 0.3 $g \cdot kg^{-1}$BM dose ingested in solution 60 to 180 min prior to starting exercise should lead to increases above 4 $mmol \cdot L^{-1}$ in blood bicarbonate concentration which is what athletes should aim for to improve various exercise outcomes. Supplementation was shown to be most effective for capacity tests which is important information for individuals required to exert themselves maximally to the point of near or complete exhaustion (*e.g.*, cycling domestiques, athletics athletes trying to maintain race pace), although exercise performance was also improved (*e.g.*, time-trials). Athletes whose training and/or competitive event involves high-intensity activity lasting greater than 30 seconds or involving repeated-bout activity (*e.g.*, team and combat sports, tennis, high intensity functional/cross training) should consider supplementing prior to competition. Some athletes involved in intermittent activities interspersed throughout the day (*e.g.*, judo) might wish to supplement between bouts to accelerate recovery and optimise performance in subsequent bouts. Supplementation may also be advantageous throughout high-intensity training for athletes involved in all types of exercise, allowing more work and/or greater intensities to be performed, providing greater adaptations and performance gains even when competition is performed without prior acute supplementation. It is important to note that extracellular buffers can improve the capacity to undertake these high intensity efforts but will only likely be effective when the effort is maximal and limited by acidosis. Supplementation during training or competition that is sub-maximal will likely make little or no difference.

### *4.8. Conclusion*

Extracellular buffering supplements generate large increases in circulating bicarbonate concentration leading to small positive overall effects on exercise, with sodium bicarbonate being the most effective. Several potential moderating factors were identified (Fig 6), including exercise duration, exercise type and prior exercise, that appeared to modify the size of the ergogenic effect. These data can be used to guide an individual's decision as to whether supplementation with buffering agents might be beneficial for their specific aims.

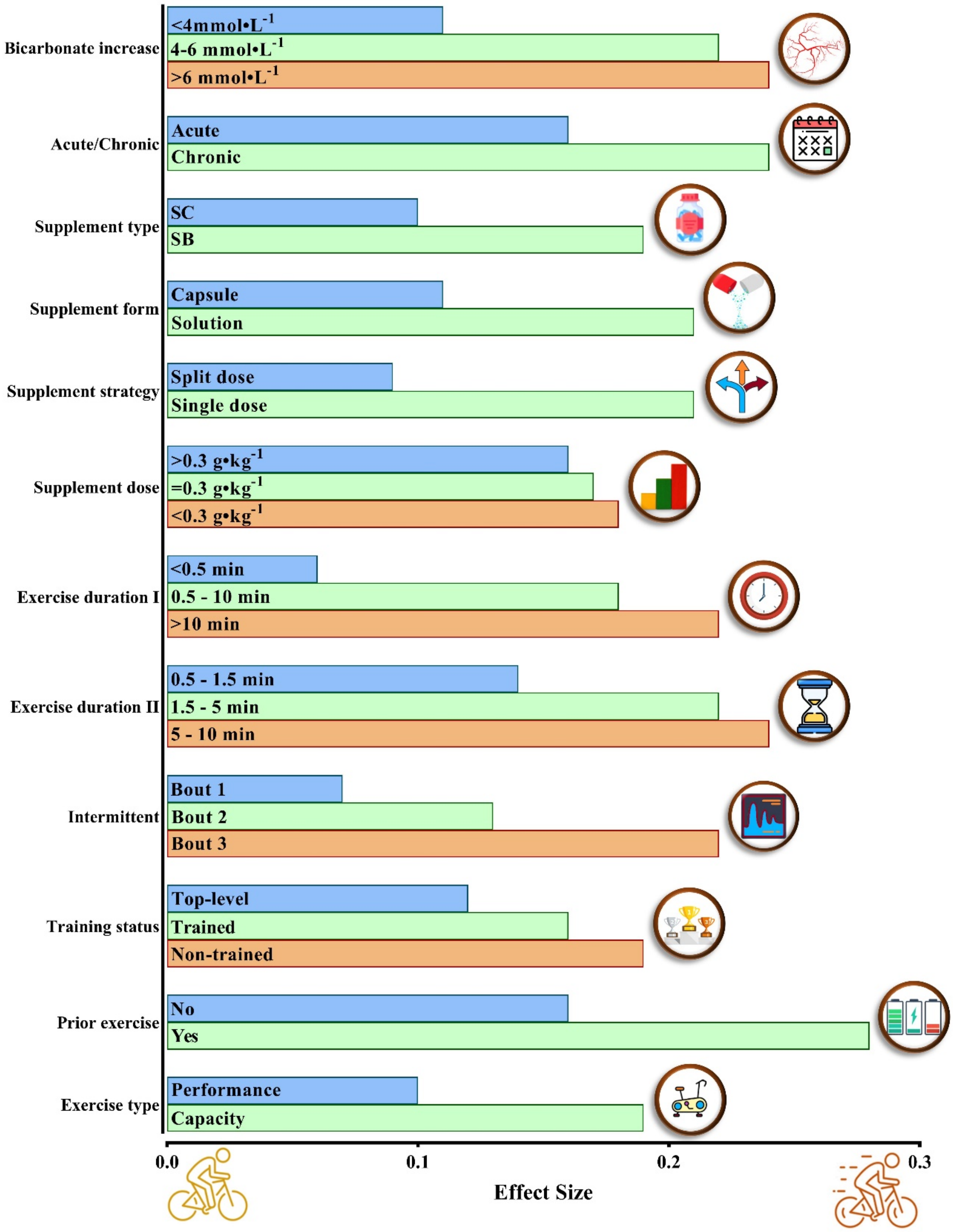


**Fig 6** Overview of the factors that may moderate the ergogenic effect of extracellular buffering supplements on exercise outcomes. SB = Sodium bicarbonate, SC = Sodium citrate. The x-axis reflects mean effect sizes; note that the figure does not include credible intervals.

## Declarations

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### Competing Interests

Several of the authors (LFO, GGA, BS) have previously received sodium bicarbonate, sodium citrate and calcium lactate supplements at no cost from a national supplement company (Farmácia Analítica, Rio de Janeiro, Brazil) for work unrelated to the current article. Farmácia Analítica have not had any input (financial, intellectual, or otherwise) into this review. The remaining authors report no conflict of interest.

### Authors Contributions

LFO, ED and BS are responsible for the conception of the work. LFO and ED performed the literature search, article selection and data extraction. PS performed all data analysis. LFO and BS drafter the first version of the manuscript, ED, KD-M, GGA and LRM critically revised the work and content. All authors read and approved the final version.

### Data Availability Statements

Extracted data and analysis codes are available upon reasonable request.

## Ethics approval, Consent to participate and Consent for publication

Not applicable

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Table 1. Moderator analyses conducted on biomarker data (blood bicarbonate and lactate) across supplementation and exercise periods.

| Moderator | | Parameter Estimate [95% CrI] | Probabilities | Between study SD $\tau$ [75%CrI] | Intraclass Correlation Coefficient [75%CrI] | Grade |
|---|---|---|---|---|---|---|
| **Bicarbonate** | | | | | | |
| *Pre-supplementation to Pre-exercise* | | | | | | |
| **[*Supplement type*]** | SB (n=109) | 5.5 [4.9 to 6.0] | *P*(SB > SC) = 0.932 | 1.5 [1.0 to 1.9] | 0.58 [0.41 to 0.78] | High |
| | SC (n=19) | 4.2 [2.2 to 5.9] | | | | High |
| **[*Supplement dose*]** | Intercept (0.3 g·kg$^{-1}$BM) | 5.2 [4.8 to 5.8] | | 1.9 [1.5 to 2.2] | 0.36 [0.23 to 0.56] | Moderate |
| | Increase per 0.1 g·kg$^{-1}$BM (n=128) | 1.1 [0.7 to 1.7] | *P*(Increase > 0) > 0.999 | | | |
| *Pre-exercise to Post-exercise (non-placebo controlled)* | | | | | | |
| **[*Exercise duration*]** | <0.5 min (n=14) | -11.8 [-13.9 to -9.9] | *P*(<0.5 min > 0.5–10min) = 0.818 | 4.8 [4.5 to 5.3] | 0.10 [0.07 to 0.14] | High |
| | 0.5–10min (n=122) | -12.8 [-13.9 to -11.7] | *P*(0.5–10min < +10min) = 0.999 | | | High |
| | >10min (n=12) | -7.3 [-10.1 to -4.5] | *P*(<0.5 min < +10min ) = 0.995 | | | High |
| **[*Exercise type*]** | Performance (n=101) | -13.5 [-14.6 to -12.3] | *P*(Capacity > Performance) > 0.999 | 4.7 [4.3 to 5.2] | 0.11 [0.08 to 0.15] | High |
| | Capacity (n=52) | -9.4 [-10.9 to -7.9] | | | | High |
| **Lactate** | | | | | | |
| *Pre-exercise to Post-exercise (non-placebo controlled)* | | | | | | |
| **[*Exercise duration 1*]** | <0.5 min (n=16) | 8.5 [6.5 to 10.6] | *P*(<0.5 min < 0.5–10min) = 0.999 | 4.1 [3.6 to 4.6] | 0.20 [0.13 to 0.30] | High |
| | 0.5–10min (n=104) | 12.1 [11.0 to 13.0] | *P*(0.5–10min > +10min) = 0.998 | | | High |
| | >10min (n=19) | 8.5 [6.2 to 10.8] | *P*(<0.5 min > +10min ) = 0.532 | | | High |
| **[*Exercise type*]** | Performance (n=95) | 11.9 [10.9 to 12.9] | *P*(Capacity<Performance) = 0.998 | 3.7 [3.2 to 4.3] | 0.30 [0.21 to 0.44] | High |
| | Capacity (n=44) | 9.3 [7.9 to 10.7] | | | | High |

SD: Standard deviation; n: Number of outcomes for covariate or factor level; SB: Sodium bicarbonate; SC: Sodium *citrate; g·kg$^{-1}$BM: grams per kilogram body mass: CrI: Bayesian credible interval. Note: The intercept value for [Supplement dose] provides the best estimate of the most common dose (~0.3 g·kg$^{-1}$BM).*

Table 2. Exercise outcomes moderator analyses conducted on placebo controlled standardized effect sizes.

| Moderator | | Parameter Estimate [95% CrI] | Probabilities | Between study SD (τ) [75%CrI] | Intraclass Correlation Coefficient [75%CrI] | Grade |
|---|---|---|---|---|---|---|
| **Exercise outcomes** | | | | | | |
| [*Exercise duration 1*] | <0.5 min (n=36) | 0.06 [-0.05 to 0.17] | *P*(<0.5 min < 0.5–10min) = 0.978 | 0.13 [0.08 to 0.17] | 0.04 [0.00 to 0.13] | Low |
| | 0.5–10min (n=168) | 0.18 [0.13 to 0.24] | *P*(0.5–10min > +10min) = 0.700 | | | Moderate |
| | >10min (n=37) | 0.22 [0.10 to 0.33] | *P*(<0.5 min < +10min ) = 0.974 | | | Moderate |
| [*Exercise duration 2*] | 0.5-1.5 min (n=55) | 0.22 [0.13 to 0.31] | *P*(0.5-1.5 min > 1.5–5min) = 0.915 | 0.11 [0.05 to 0.17] | 0.04 [0.00 to 0.15] | Moderate |
| | 1.5–5 min (n=82) | 0.14 [0.06 to 0.21] | *P*(1.5–5min < 5-10 min) = 0.930 | | | Moderate |
| | 5-10 min (n=31) | 0.24 [0.12 to 0.36] | *P*(0.5-1.5 min < 5-10 min) = 0.622 | | | Moderate |
| [*Exercise type*] | Performance (n=149) | 0.14 [0.08 to 0.19] | *P*(Capacity > Performance) = 0.871 | 0.13 [0.08 to 0.17] | 0.04 [0.00 to 0.14] | Moderate |
| | Capacity (n=92) | 0.20 [0.13 to 0.28] | | | | Moderate |
| [*Prior exercise*] | Prior (n=28) | 0.28 [0.15 to 0.42] | *P*(Prior > No Prior) = 0.956 | 0.13 [0.08 to 0.17] | 0.03 [0.00 to 0.13] | Low |
| | No Prior (n=213) | 0.16 [0.11 to 0.20] | | | | Moderate |
| [*Training status*] | Top-level (n=21) | 0.12 [-0.03 to 0.27] | *P*(Top-level < Trained) = 0.700 | 0.13 [0.08 to 0.18] | 0.05 [0.00 to 0.14] | Low |
| | Trained (n=139) | 0.16 [0.11 to 0.23] | *P*(Trained < Non-trained) = 0.701 | | | Moderate |
| | Non-trained (n=80) | 0.19 [0.11 to 0.28] | *P*(Top-level < Non-trained) = 0.788 | | | Moderate |
| [*Intermittent*] | Bout 1 (n=51) | 0.07 [-0.03 to 0.17] | *P*(Bout 2 > Bout 1) = 0.886 | 0.19 [0.15 to 0.23] | 0.00 [0.00 to 0.01] | Moderate |
| | Bout 2 (n=51) | 0.13 [0.03 to 0.23] | *P*(Bout 3 > Bout 2) = 0.941 | | | Moderate |
| | Bout 3 (n=42) | 0.22 [0.11 to 0.33] | *P*(Bout 3 > Bout 1) = 0.996 | | | Moderate |

SD: Standard deviation; n: Number of outcomes for covariate or factor level; CrI: Bayesian credible interval.

Table 3. Moderator analyses for supplement protocols conducted on placebo controlled standardized exercise effect sizes.

| Moderator | | Parameter Estimate [95% CrI] | Probabilities | Between study SD ($\tau$) [75%CrI] | Intraclass Correlation Coefficient [75%CrI] | Grade |
|---|---|---|---|---|---|---|
| *Exercise Outcomes* | | | | | | |
| [*Supplement dose*] | Low (<0.3 g·kg$^{-1}$BM; n=33) | 0.18 [0.06 to 0.30] | *P*(Low > Mid) = 0.527 | 0.13 [0.08 to 0.18] | 0.04 [0.00 to 0.14] | Low |
| | Mid (=0.3 g·kg$^{-1}$BM; n=162) | 0.17 [0.12 to 0.23] | *P*(Mid > High) = 0.574 | | | Low |
| | High (>0.3 g·kg$^{-1}$BM; n=43) | 0.16 [0.06 to 0.27] | *P*(Low > High) = 0.581 | | | Low |
| [*Supplement strategy*] | Single dose (n=162) | 0.21 [0.15 to 0.27] | *P*(Single > Split) = 0.994 | 0.12 [0.07 to 0.17] | 0.04 [0.01 to 0.10] | Low |
| | Split dose (n=77) | 0.09 [0.02 to 0.17] | | | | Low |
| [*Acute / Chronic*] | Acute (n=227) | 0.16 [0.12 to 0.21] | *P*(Acute < Chronic) = 0.741 | 0.14 [0.09 to 0.18] | 0.04 [0.00 to 0.13] | Moderate |
| | Chronic (n=14) | 0.24 [0.06 to 0.43] | | | | Moderate |
| [*Supplement form*] | Solution (n=123) | 0.21 [0.15 to 0.27] | *P*(Solution > Capsule) = 0.984 | 0.09 [0.03 to 0.14] | 0.06 [0.02 to 0.13] | Low |
| | Capsule (n=100) | 0.11 [0.05 to 0.18] | | | | Low |
| [*Supplement type*] | SB (n=192) | 0.19 [0.14 to 0.24] | *P*(SB > SC) = 0.881 | 0.13 [0.08 to 0.18] | 0.05 [0.01 to 0.11] | Low |
| | SC (n=39) | 0.10 [0.00 to 0.23] | | | | Low |
| [*Bicarbonate increase*] | Small (≤4 mmol·L$^{-1}$; n=44) | 0.11 [0.00 to 0.22] | *P*(Med > Small) = 0.967 | 0.28 [0.09 to 0.49] | 0.27 [0.15 to 0.38] | Low |
| | Medium (4–6 mmol·L$^{-1}$; n=51) | 0.24 [0.15 to 0.35] | *P*(Med > Large) = 0.612 | | | Low |
| | Large (>6 mmol·L$^{-1}$; n=30) | 0.22 [0.09 to 0.35] | *P*(Large > Small) = 0.909 | | | Low |

Parameter values are obtained from unadjusted meta-regressions. SD: Standard deviation; n: Number of outcomes for covariate or factor level; CrI: Bayesian credible interval. SB: Sodium bicarbonate; SC: Sodium citrate.

# PRISMA 2009 Checklist

**Article title**: Extracellular buffering supplements to improve exercise capacity and performance: a comprehensive systematic review and meta-analysis.
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| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4-5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 7 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7-8 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 9 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 9 |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8-9 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 11-13 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8,11-13 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 11-13 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 14 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 14. Supplementary Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 22-23 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 15-21 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 15-21 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 22-23 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 15-21 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 24-33 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 29-30 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 32 |
| **FUNDING** | | | |

| | | | |
|---|---|---|---|
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 34 |

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

For more information, visit: **www.prisma-statement.org**.

**Article title**: Extracellular buffering supplements to improve exercise capacity and performance: a comprehensive systematic review and meta-analysis.

**Corresponding author**: Dr Bryan Saunders. Applied Physiology and Nutrition Research Group, School of Physical Education and Sport; Rheumatology Division; Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, BR, University of São Paulo, SP, BR.

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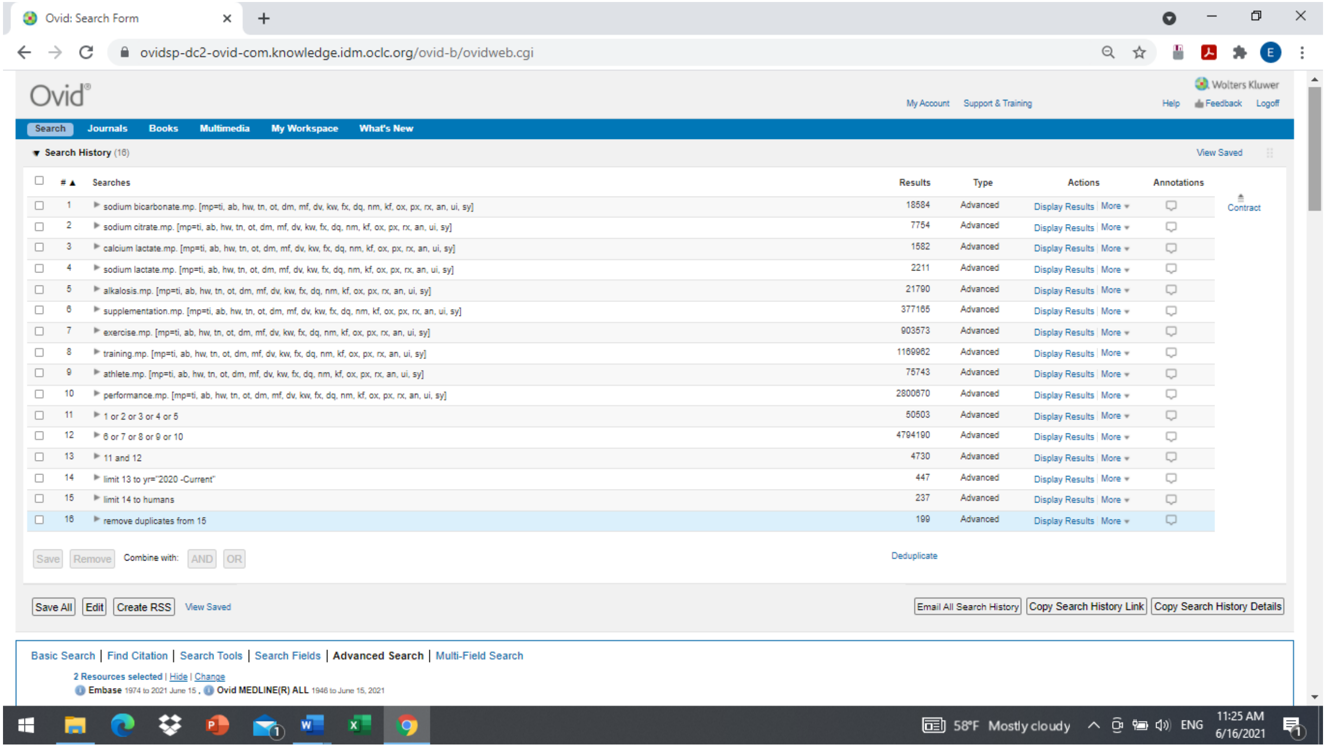
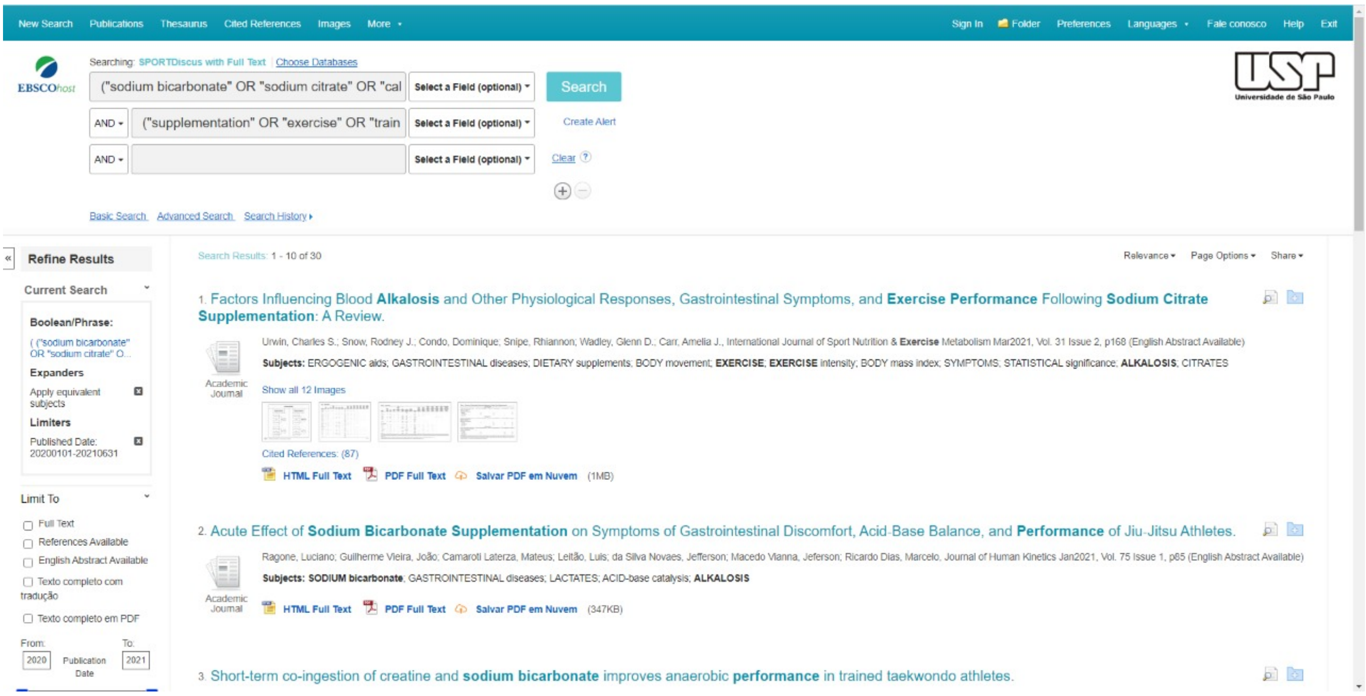
Supplementary Material Appendix S3. Literature searches on 16/06.2021

Medline + Embase (deduplicated using OVID option). N = 199



| # | Searches | Results | Type |
|---|---|---|---|
| 1 | sodium bicarbonate.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 18584 | Advanced |
| 2 | sodium citrate.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 7754 | Advanced |
| 3 | calcium lactate.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 1582 | Advanced |
| 4 | sodium lactate.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 2211 | Advanced |
| 5 | alkalosis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 21790 | Advanced |
| 6 | supplementation.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 377165 | Advanced |
| 7 | exercise.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 903573 | Advanced |
| 8 | training.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 1169962 | Advanced |
| 9 | athlete.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 75743 | Advanced |
| 10 | performance.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] | 2800670 | Advanced |
| 11 | 1 or 2 or 3 or 4 or 5 | 50503 | Advanced |
| 12 | 6 or 7 or 8 or 9 or 10 | 4794190 | Advanced |
| 13 | 11 and 12 | 4730 | Advanced |
| 14 | limit 13 to yr="2020 -Current" | 447 | Advanced |
| 15 | limit 14 to humans | 237 | Advanced |
| 16 | remove duplicates from 15 | 199 | Advanced |

Sport Discus. N = 30



**Article title**: Extracellular buffering supplements to improve exercise capacity and performance: a comprehensive systematic review and meta-analysis.

**Corresponding author**: Dr Bryan Saunders. Applied Physiology and Nutrition Research Group, School of Physical Education and Sport; Rheumatology Division; Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, BR, University of São Paulo, SP, BR.

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Supplementary Material Appendix S3. Table of all included studies.

| | **STUDY** | **SAMPLE** | **STUDY DESIGN** | **SUPLEMENTATION** | **EXERCISE** |
|---|---|---|---|---|---|
| | **Authors (Year) Location** | Population (N) | Design Blinding | Form (dose [in g·kg$^{-1}$BM]) Ingestion time prior to exercise | Protocol (Familiarisation) |
| | | | **SODIUM BICARBONATE** | | |
| **1** | AbuMoh'd (2021) Jordan | Well-trained sprinting athletes (N = 13) | Crossover Double-blind | Solution (0.3) 60 min | Intermittent sprint test on treadmill, with repeated 60-s sprint bouts until volitional exhaustion with 30s recovery between bouts. (Familiarisation = Yes) |
| **2** | Afman (2014) UK | Well-trained male basketball players (N = 7) | Crossover Double-blind | Solution (0.2) 90 min; (0.2) 20 min | 4 blocks of the modified LIST (Familiarisation = Yes) |
| **3** | Ansdell (2017) UK | Healthy and active male basketball players (N = 10) | Crossover Double-blind | Solution (0.2) 90 min; (0.2) 20 min | 4 blocks of the modified LIST (Familiarisation = Yes) |
| **4** | Araújo Dias (2015) Brazil | Recreationally active males (N = 15) | Crossover Double-blind | Capsule (0.3) 90 min | 4 SB sessions of the $CCT_{110\%}$ (Familiarisation = Yes) |
| **5** | Artioli (2007) Brazil | Experienced judo competitors (N = 9) | Crossover Double-blind | Capsule (0.3) 120 min | Special judo fitness test (Familiarisation = No) |
| | | Experienced judo competitors | | | Wingate Test for Upper Limbs (4 bouts) |

| | | | | | |
|---|---|---|---|---|---|
| | | (N = 14) | | | (Familiarisation = No) |
| **6** | Aschenbach (2000)<br>USA | Members of the Virginia Tech NCAA Division I varsity wrestling team<br>(N = 8) | Crossover<br>Double-blind | Solution<br>(0.15) 90 min; (0.15) 60 min | 8 x 15 s arm cranks<br>(Familiarisation = No) |
| **7** | Ball (1996)<br>UK | Healthy males<br>(N = 6) | Crossover<br>Double-blind | Capsule<br>(0.3) 180 - 60 min | Cycle to exhaustion at 95% $VO_{2max}$ on a normal and low carbohydrate diet<br>(Familiarisation = Yes) |
| **8** | Bellinger (2012)<br>Australia | Highly trained male cyclists<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(03) 90 - 30 min | Maximal 4 min cycling performance trial<br>(Familiarisation = Yes) |
| **9** | Bird (1995)<br>UK | Male distance runners<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.15) 120 min; (0.15) 60 min | Two SB sessions of a 1500 m running<br>(Familiarisation = Yes) |
| **10** | Bishop (2004)<br>Australia | Recreational, team-sport playing females<br>(N = 10) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | 5 x 6 s repeated sprint cycling test<br>(Familiarisation = Yes) |
| **11** | Bishop (2005)<br>Australia | Female team-sport athletes<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.2) 110 - 90 min; (0.2) 50 - 20 min | Intermittent sprint test 2x 36 min of 4s sprint 100s recovery active +20s recovery passive<br>(Familiarisation = Yes) |
| **12** | Bouissou (1988)<br>France | Healthy male volunteers<br>(N = 6) | Crossover<br>Single-blind | Capsule<br>(0.3) 120 min | A supramaximal cycle bout at 125% of peak aerobic power<br>(Familiarisation = No) |
| **13** | Brien (1989)<br>Canada | Oarsmen from the National rowing team<br>(N = 6) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | 4 min rowing at 80% following 2 min maximal effort<br>(Familiarisation = No) |
| **14** | Brisola (2015)<br>Brazil | Healthy and moderately active<br>(N = 15) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | Supramaximal effort at 110% $VO_{2max}$ in the treadmill<br>(Familiarisation = No) |
| **15** | Callahan (2016)<br>Australia | Well-trained cyclists<br>(N = 8) | Crossover<br>Double-blind | Capsule<br>(0.3) 150 - 75 min | 4 km cycling TT<br>(Familiarisation = Yes) |

| | | | | | |
|---|---|---|---|---|---|
| **16** | Campos (2012)<br>Brazil | Swimmers (minimum 2 y experience in competitive swimming)<br>(N = 10) | Crossover<br>Double-blind | Capsule<br>(0.3) 60 min | 6 maximal 100 m swims<br>(Familiarisation = No) |
| **17** | Carr (2011)<br>Australia | Well-trained rowers<br>(N = 8) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | 2000m rowing ergometer TT<br>(Familiarisation = Yes) |
| **18** | Carr (2012)<br>Australia | Well-trained rowers<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.3) 120 min<br>Capsule<br>$(0.5)^{-1}$day for 3 days | 2 SB sessions of a 2000m rowing ergometer TT<br>(Familiarisation = Yes) |
| **19** | Carr (2013)<br>USA | Healthy, resistance-trained<br>(N = 12) | Crossover<br>Double-blind | Capsule<br>(0.075) 80 min; (0.075) 70 min; (0.075) 60 min; (0.075) 50 min; | Back squats<br>(Familiarisation = Yes)<br>Inclined leg press<br>(Familiarisation = Yes)<br>Knee extension<br>(Familiarisation = Yes)<br>Knee extension at 50% of 1RM until exhaustion<br>(Familiarisation = Yes) |
| **20** | Casarin (2019)<br>Brazil | Healthy<br>(N = 12) | Crossover<br>Double-blind | Capsule<br>(0.3) 60 min | Isometric knee extension during 8 min or exhaustion at 70% RM<br>(Familiarisation = Yes) |
| **21** | Christensen (2014)<br>Denmark | International level rowers<br>(N = 12) | Crossover<br>Double-blind | Capsule<br>(0.3) 60 min | 6 min maximal rowing test<br>(Familiarisation = No) |
| **22** | Coombes (1993)<br>Australia | Healthy physical education university students<br>(N = 9) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | Isokinetic leg extension/flexion exercise<br>(Familiarisation = No) |
| **23** | Coppoolse (1997)<br>USA | Healthy<br>(N = 5) | Crossover<br>NI | Solution<br>(0.3) 60 min | Cycling test with a work rate increment of 25 or 30 W/min<br>(Familiarisation = Yes) |
| **24** | Correia-Oliveira (2017) | Recreationally trained cyclists | Crossover | Capsule | 4 km TT cycling |

| | | | | | |
|---|---|---|---|---|---|
| | Brazil | (N = 15) | Double-blind | (0.3) 90 min | (Familiarisation = Yes) |
| 25 | Costill (1984)<br>Netherlands | "No description"<br>(N = 11) | Crossover<br>Double-blind | Solution<br>(0.2) 60 min | 4 x sprints cycling bouts of 1 min at 125% $VO_{2max}$ with 1 min recovery and the fifth bout until exhaustion<br>(Familiarisation = No) |
| 26 | Dalle (2019)<br>Belgium | Physically actives<br>(N = 12) | Crossover<br>Double-blind | Capsule<br>(0.43) 540 - 60 min | 2 min all-out cycling bouts 3 h intervals<br>(Familiarisation = Yes) |
| 27 | Dalle (2020)<br>Belgium | Cyclists<br>(N = 11) | Crossover<br>Double-blind | Solution<br>(0.15) 120; (0.15) 30 min | 3-h intermittent exercise bout aimed to simulate a cycling race followed by a 90-s all-out'sprint'.<br>(Familiarisation = Yes) |
| 28 | Danaher (2014)<br>Australia | Apparently healthy, recreationally active<br>(N = 8) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 - 50 min | $CCT_{110\%}$<br>(Familiarisation = Yes) |
| | | | | Capsule<br>(0.3) 90 min | Repeated sprint ability test 5x 6s maximal cycling bouts<br>(Familiarisation = Yes) |
| 29 | Deb (2017)<br>UK | Trained cyclists<br>(N = 11) | Crossover<br>Single-blind | Solution<br>(0.3) ITTP | 2 SB sessions (normoxia, hypoxia) of the 3 min Critical power cycling test<br>(Familiarisation = Yes) |
| 30 | Deb (2018)<br>UK | Recreationally active males<br>(N = 11) | Crossover<br>Double-blind | Solution<br>(0.3) ITTP | Intermittent cycling test 60s with 20s recovery until exhaustion<br>(Familiarisation = Yes) |
| 31 | Delextrat (2018)<br>UK | University basketball players<br>(N = 15) | Crossover<br>Double-blind | Capsule<br>$(0.4)^{-1}$day for 3 days | Basketball exercise simulation test<br>(Familiarisation = Yes) |
| 32 | Do Valle Bargieri (2013)<br>Brazil | High performance athletes<br>(N = 8) | Parallel<br>NI | Capsule<br>$(0.3)^{-1}$day for 5 days | Incremental treadmill cardiopulmonary exercise test<br>(Familiarisation = Yes) |
| 33 | Douroudos (2006)<br>Greece | Healthy<br>(N = 24) | Parallel<br>Double-blind | Solution<br>$(0.3)^{-1}$day for 5 days | Wingate test at 0.075 $kg^{-1}$BM<br>(Familiarisation = Yes) |
| | | | | Solution<br>$(0.5)^{-1}$day for 5 days | Wingate test at 0.075 $kg^{-1}$BM<br>(Familiarisation = Yes) |

| | | | | | |
|---|---|---|---|---|---|
| **34** | Driller (2012)<br>Australia | Well-trained cyclists<br>(N = 8) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 - 60 min<br>Capsule<br>$(0.4)^{-1}$day for 3 days | 4 min performance test cycling<br>(Familiarisation = Yes) |
| **35** | Driller (2012)<br>Australia | Well-trained cyclists<br>(N = 8) | Crossover<br>Double-blind | Capsule<br>(0.3) 120 - 60 min | 2 SB sessions of a 2 min performance test cycling<br>(Familiarisation = Yes) |
| **36** | Driller (2013)<br>Australia | National representative rowers<br>(N = 12) | Parallel<br>Double-blind | Capsule<br>(0.3) 90 - 60 min | 2000 m rowing ergometer TT<br>(Familiarisation = Yes) |
| **37** | Ducker (2013)<br>Australia | Competitive team-sport athletes<br>(N = 12) | Parallel<br>Single-blind | Capsule<br>(0.3) 60 min | 3x (of 6x 20m run sprint with 25s recovery) 4 min recovery<br>(Familiarisation = No) |
| **38** | Duncan (2014)<br>UK | Experience resistance exercise<br>(N = 8) | Crossover<br>Double-blind | Solution<br>(0.3) 60 min | 3x back squat at 80% 1RM until failure with 3 min rest<br>(Familiarisation = Yes)<br>3x bench press at 80% 1RM until failure with 3 min rest<br>(Familiarisation = Yes) |
| **39** | Durkalec-Michalski (2018)<br>Poland | Recreationally training CrossFit<br>(N = 21) | Parallel<br>Double-blind | Tablet<br>$(0.0375)^{-1}$day for days 1 - 2;<br>$(0.075)^{-1}$day for days 3 - 4;<br>$(0.1125)^{-1}$day for days 5 - 7;<br>$(0.150)^{-1}$day for days 8 – 10 | CrossFit FGB 3x 5 multi-joint exercises<br>(Familiarisation = Yes)<br>Incremental cycling test<br>(Familiarisation = Yes) |
| **40** | Durkalec-Michalski (2018)<br>Poland | Athletes of Polish wrestling national team<br>(N = 49) | Parallel<br>Double-blind | Tablet<br>$(0.025)^{-1}$day for days 1 - 2;<br>$(0.05)^{-1}$day for days 3 - 5;<br>$(0.075)^{-1}$day for days 6 - 7;<br>$(0.1)^{-1}$day for days 8 – 10 | 2x 30s Wingate test 7.5%BM<br>(Familiarisation = Yes)<br>Wrestling-specific performance<br>(Familiarisation = Yes) |
| **41** | Durkalec-Michalski (2020)<br>Poland | Wrestlers<br>(Female, N = 18; Male, N = 33) | Parallel<br>Double-blind | Tablet<br>$(0.025)^{-1}$day for days 1 - 2;<br>$(0.05)^{-1}$day for days 3 - 5; | 2 Wingate bouts<br>(Familiarisation = Yes)<br>Dummy throw test |

| | | | | | |
|---|---|---|---|---|---|
| | | | | $(0.075)^{-1}$day for days 6 - 7;<br>$(0.1)^{-1}$day for days 8 - 10 | (Familiarisation = Yes) |
| **42** | Durkalec-Michalski (2020)<br>Poland | Field hockey players<br>(N = 24) | Crossover<br>Double-blind | Tablet<br>$(0.05)^{-1}$day for days 1 - 2;<br>$(0.1)^{-1}$day for days 3 - 4;<br>$(0.15)^{-1}$day for days 5 - 6;<br>$(0.2)^{-1}$day for days 7 - 8; | Specific hockey field test<br>(Familiarisation = Yes) |
| **43** | Egger (2014)<br>Germany | Well-trained cyclists<br>(N = 21) | Crossover<br>Double-blind | Solution<br>(0.3) 60 min | Constant load cycling test 30 min at 95% IAT then 110% until exhaustion<br>(Familiarisation = No)<br>Incremental exercise cycling test at 50W/ 3 min until fatigue<br>(Familiarisation = No) |
| **44** | Farney (2018)<br>USA | Involved in a structured exercise training program<br>(N = 11) | Crossover<br>Single-blind | Solution<br>(0.3) 60 min | 3x 5s of isometric mid-thigh pull test<br>(Familiarisation = Yes) |
| **45** | Felippe (2016)<br>Brazil | Judo athletes<br>(N = 10) | Crossover<br>Double-blind | Capsule<br>(0.1) 120 min; (0.1) 90 min;<br>(0.1) 60 min | Special judo fitness test<br>(Familiarisation = No) |
| **46** | Ferreira (2019)<br>Brazil | Cyclists<br>(N = 21) | Crossover<br>Double-blind | Solution<br>(0.1) 60 min<br>Solution<br>(0.3) 60 min | Cycling at 1kg + 5%BM until exhaustion<br>(Familiarisation = Yes) |
| **47** | Flinn (2004)<br>Australia | Recreationally trained<br>(N = 12) | Crossover<br>Double-blind | Capsule<br>(0.1) 90 min; (0.1) 60 min;<br>(0.1) 30 min | 2 SB sessions (normoxia and hypoxia)<br>120W 30s 30W 30s until exhaustion<br>(Familiarisation = Yes) |
| **48** | Freis (2017)<br>Germany | Endurance athletes<br>(N = 18) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | Constant load cycling to exhaustion<br>(Familiarisation = No)<br>Graded exercise cycle<br>(Familiarisation = No) |
| **49** | Gaitanos (1991)<br>UK | Physical education students<br>(N = 7) | Crossover<br>Single-blind | Solution<br>(0.3) 120 min | 10 x max 6s sprints with 30 s recovery<br>(Familiarisation = Yes) |

| | | | | | |
|---|---|---|---|---|---|
| **50** | Gao (1988)<br>USA | Well-trained college swimmers<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.29) 60 min | 2 SB sessions of 5 x 100-yard front crawl swimming; 2 min recovery<br>(Familiarisation = No) |
| **51** | George (1988)<br>UK | Health actively competitive sports<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.2) 180 min | Run to volitional exhaustion<br>(Familiarisation = No) |
| **52** | Goldfinch (1988)<br>Australia | Athletes<br>(N = 6) | Crossover<br>Double-blind | Solution<br>(0.4) 60 min | 400 m run<br>(Familiarisation = No) |
| **53** | Gordon (1994)<br>USA | Healthy active<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | Single-bout maximal cycle ergometry <2 min<br>(Familiarisation = Yes) |
| **54** | Gough (2017)<br>UK | Healthy active<br>(N = 9) | Crossover<br>Double-blind | Solution<br>(0.3) 60 min | Bout of cycling at 100%$W_{peak}$ until exhaustion following prior exercise<br>(Familiarisation = Yes) |
| **55** | Gough (2017)<br>UK | Cyclists<br>(N = 11) | Crossover<br>Double-blind | Solution<br>(0.2) ITTP<br>Solution<br>(0.3) ITTP | 4 km cycling TT<br>(Familiarisation = Yes) |
| **56** | Gough (2018)<br>UK | Cyclists<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.2) ITTP<br>Solution<br>(0.3) ITTP | 2x 4 km cycling TT with 40 min interval<br>(Familiarisation = No) |
| **57** | Gough (2019)<br>UK | Club-level cyclists<br>(N = 14) | Crossover<br>Single-blind | Solution<br>(0.2) ITTP<br>Solution<br>(0.3) ITTP | 4 km cycling TT<br>(Familiarisation = No) |
| **58** | Griffen (2015)<br>UK | Well-trained<br>(N = 9) | Crossover<br>Double-blind | Solution<br>$(0.3)^{-1}$day for 7 days | 6 x 10s cycling sprints 7.5%BM<br>(Familiarisation = Yes) |
| **59** | Guimarães (2020)<br>Brazil | Semi-professional adolescent soccer players<br>(N = 15) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | Running anaerobic sprint test (RAST) performing six maximal 35-m sprints, with a passive 10-s interval between runs. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | (Familiarisation = No) |
| **60** | Gurton (2020) UK | Club-level male cyclists (N = 8) | Crossover Double-blind | Solution (0.3) ITTP | 4-km cycling TT (Familiarisation = Yes) |
| **61** | Gurton (2020) UK | Recreationally active (N = 12) | Crossover Single-blind | Solution (0.3) 60 min | Three bouts of 60 s cycling (90, 95, and 100% MAP), interspersed with 90 s of active recovery (100 W) and TTE cycling at 105% MAP. (Familiarisation = Yes) |
| **62** | Gurton (2021) UK | Recreationally trained runners (N = 11) | Crossover Single-blind | Solution (0.3) 30 min | Running TTE protocol at 100% $VO_{2max}$ on the treadmill (Familiarisation = No) |
| **63** | Haug (2014) Australia | Athletes Australian national short track speed skating team (N = 8) | Crossover Double-blind | Tablet (0.3) 75 min | 1 skater racing at maximal effort for 1 lap (Familiarisation = No) |
| **64** | Higgins (2013) UK | Healthy active (N = 10) | Crossover Double-blind | Solution (0.3) 60 min | Cycling to volitional exhaustion at 100% $W_{peak}$ (Familiarisation = Yes) |
| | | | | | Cycling to volitional exhaustion at 110% $W_{peak}$ (Familiarisation = Yes) |
| | | | | | Cycling to volitional exhaustion at 120% $W_{peak}$ (Familiarisation = Yes) |
| **65** | Hilton (2020) UK | trained male cyclists (N = 11) | Crossover Double-blind | Capsules (GR) (0.3) ITTP | 4 km cycling time trial (Familiarisation = Yes) |
| **66** | Hobson (2013) UK | Competitive club-level rowers (N = 20) | Crossover Double-blind | Capsule (0.2) 240 min; (0.1) 120 min | 2000 m rowing ergometer TT (Familiarisation = Yes) |
| **67** | Hobson (2014) UK | Competitive club-level rowers (N = 20) | Crossover Double-blind | Capsule (0.2) 240 min; (0.1) 120 min | 2000 m rowing ergometer TT (Familiarisation = Yes) |
| **68** | Horswill (1988) USA | Endurance-trained cyclists (N = 9) | Crossover NI | Solution (0.3) 60 min | 2 min exercise bout cycling (Familiarisation = No) |
| | | | | Solution | |

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| | | | | (0.2) 60 min<br>Solution<br>(0.15) 60 min | |
| **69** | Hunter (2009)<br>Ireland | Club triathletes<br>(N = 8) | Crossover<br>Double-blind | Capsule<br>(0.3) 180 min | MVC<br>(Familiarisation = Yes) |
| **70** | Ibanez (1995)<br>Spain | Athletes runners 400m below 50s<br>(N = 6) | Crossover<br>Single-blind | Solution<br>(0.5) 180 min | 300m running sprint<br>(Familiarisation = No) |
| **71** | Inbar (1983)<br>Israel | Physical education students<br>(N = 13) | Crossover<br>NI | Capsule<br>(0.15) 170 min | Want sprint 30s with 4.41/BM<br>(Familiarisation = No) |
| **72** | Iwaoka (1989)<br>Japan | Physical education students<br>(N = 6) | Crossover<br>Double-blind | Capsule E<br>(0.2) 120 min | Cycling 10 min 40% $VO_{2max}$;15 min 12W; then until exhaustion at 95% $VO_{2max}$<br>(Familiarisation = Yes) |
| **73** | Joyce (2011)<br>Australia | Swimmers<br>(N = 8) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min<br>Capsule<br>$(0.3)^{-1}$day for 3 days; (0.1) 90 min | 200 m swim<br>(Familiarisation = No) |
| **74** | Katz (1984)<br>USA | Healthy<br>(N = 8) | Crossover<br>Double-blind | Solution<br>(0.2) 60 min | Cycling at 125% $VO_{2max}$ until exhaustion<br>(Familiarisation = No) |
| **75** | Kilding (2012)<br>New Zealand | Well-trained cyclists<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.3) 120 - 90 min | 3 km TT cycling<br>(Familiarisation = Yes) |
| **76** | Kowalchuk (1984)<br>Canada | Healthy<br>(N = 6) | Crossover<br>Single-blind | Capsule<br>(0.3) 180 min | Cycling until exhaustion with increase of 100 kpm/min<br>(Familiarisation = No) |
| **77** | Kozak-Collins (1994)<br>USA | Competitive cyclists<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.3) 120 min | 1 min cycling at 95% $VO_{2\ max}$; 1 min recovery at 60W; repeated until exhaustion<br>(Familiarisation = No) |
| **78** | Kraemer (2000)<br>USA | Healthy active<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.3) 75 min | Cycling sprint for 90s with 0.05kg/BM<br>(Familiarisation = No) |

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| **79** | Kumstát (2018)<br>Czech Republic | Elite level swimmers<br>(N = 6) | Crossover<br>Double-blind | Capsule<br>(0.3) 60 min | 400 m freestyle swim<br>(Familiarisation = No) |
| **80** | Kupcis (2012)<br>Australia | Nationally competitive lightweight rowers<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.1) 90 min; (0.1) 80 min; (0.1) 70 min | 2000 m rowing ergometer TT<br>(Familiarisation = Yes) |
| **81** | Lambert (1993)<br>Scotland | Healthy<br>(N = 6) | Crossover<br>Double-blind | NI<br>(0.3) 180 min | Cycle at 70, 80, 90 of $VO_{2\ max}$ by 5 min with 5 min interval between each bout then at 100% until exhaustion<br>(Familiarisation = Yes) |
| **82** | Lavender (1989)<br>UK | Members of the movement studies department<br>(N = 23) | Crossover<br>Double-blind | Solution<br>(0.3) 120 min | Ten maximal cycle sprints 10s of duration a 50 s recovery<br>(Familiarisation = Yes) |
| **83** | Light (1999)<br>USA | Normal<br>(N = 6) | Crossover<br>Double-blind | Capsule<br>$(0.3)^{-1}$day for 5 days | Maximal exercise cycling test in incremental 30W/min<br>(Familiarisation = Yes) |
| **84** | Linderman (1992)<br>USA | Cyclists<br>(N = 8) | Crossover<br>Double-blind | Tablet<br>(0.2) 90 min | Cycling at the $P_{max}$ until exhaustion<br>(Familiarisation = No) |
| **85** | Lindh (2008)<br>UK | Elite-standard swimmers<br>(N = 9) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | 200m freestyle swim<br>(Familiarisation = No) |
| **86** | Lopes-Silva (2018)<br>Brazil | Taekwondo black belt athletes<br>(N = 9) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | Simulated taekwondo combat<br>(Familiarisation = No) |
| **87** | Macutkiewicz (2018)<br>UK | Elite hockey players<br>(N = 8) | Crossover<br>Single-blind | Capsule<br>(0.2) 180 min; (0.1) 90 min | LIST<br>(Familiarisation = No) |
| **88** | Margaria (1971)<br>Italy | Athletes, sportsmen and sedentary<br>(N = 12) | Crossover<br>NI | NI<br>(0.167) 60 min | Running on treadmill at 16 km/h at 16% inclination<br>(Familiarisation = Yes) |
| **89** | Marriott (2015)<br>Sweden | Sub-elite team-sports<br>(N = 12) | Crossover<br>Single-blind | Capsule<br>(0.4) 90 min | Yo-Yo IR2 following prior upper body exercise<br>(Familiarisation = Yes) |
| **90** | Marx (2002)<br>USA | Healthy<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.3) 60 min | 90 s cycle at 0.5 N/BM<br>(Familiarisation = Yes) |
| **91** | Materko (2008) | Strength trained | Crossover | Solution | Bench press test |

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| | Brazil | (N = 11) | Double-blind | (0.3) 120 min | (Familiarisation = Yes)<br>Pull press test<br>(Familiarisation = Yes) |
| **92** | Matsuura (2007)<br>Japan | Undergraduate students<br>(N = 8) | Crossover<br>Single-blind | Solution<br>(0.3) 180 min | 10s cycling sprints with 30s passive recovery; with 360s recovery at 5th and 9th sprint<br>(Familiarisation = Yes) |
| **93** | McCartney (1983)<br>Canada | Healthy<br>(N = 6) | Crossover<br>NI | Capsule<br>(0.3) 180 min | Maximal force on the pedals of a constant velocity cycle ergometer at 100 rpm for 30 s<br>(Familiarisation = No) |
| **94** | McKenzie (1986)<br>Canada | Athletes<br>(N = 6) | Crossover<br>Double-blind | Solution<br>(0.15) 60 min<br>Solution<br>(0.3) 60 min | 6x 60s cycling bouts with 60s recovery at 125% $VO_{2max}$. 6[th] bout continued until exhaustion.<br>(Familiarisation = No) |
| **95** | McLellan (1988)<br>Canada | (N = 4) | Crossover<br>Single-blind | Capsule<br>(0.2) 120 min | Cycling: 10 min at 50 and 70% and 90% of $VO_{2max}$ until exhaustion<br>(Familiarisation = No) |
| **96** | McNaughton (1991)<br>Australia | Cyclists<br>(N = 8) | Crossover<br>Double-blind | Solution<br>(0.4) 60 min | Maximal 1 min cycle effort<br>(Familiarisation = No) |
| **97** | McNaughton (1991)<br>Australia | Elite rowers<br>(N = 5) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | 6 min rowing ergometer<br>(Familiarisation = No) |
| **98** | McNaughton (1992)<br>Australia | Healthy<br>(N = 9) | Crossover<br>Double-blind | Solution<br>(0.1) 90 min<br>Solution<br>(0.2) 90 min<br>Solution<br>(0.3) 90 min<br>Solution<br>(0.4) 90 min<br>Solution | Maximal 1 min cycle effort<br>(Familiarisation = No) |

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| | | | | (0.5) 90 min | |
| **99** | McNaughton (1992)<br>Australia | Males<br>(N = 8) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | Maximal 10s cycle effort<br>(Familiarisation = No)<br>Maximal 30 s cycle effort<br>(Familiarisation = No)<br>Maximal 120s cycle effort<br>(Familiarisation = No)<br>Maximal 240s cycle effort<br>(Familiarisation = No) |
| **100** | McNaughton (1997)<br>Australia | Physical active<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | Maximal 1 min cycle effort<br>(Familiarisation = No) |
| **101** | McNaughton (1999)<br>UK | Cyclists<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | 60 min cycling<br>(Familiarisation = No) |
| **102** | McNaughton (2011)<br>UK | Males<br>(N = 8) | Crossover<br>Double-blind | Solution<br>(0.3) 60 min | Running on treadmill 3x of maximal 30s with 180s recovery<br>(Familiarisation = Yes) |
| **103** | Mero (2013)<br>Filand | National and international level swimmers<br>(N = 13) | Crossover<br>Double-blind | Capsule<br>(0.3) 60 min | 2x 100m maximal freestyle sprint swimming<br>(Familiarisation = No) |
| **104** | Miller (2016)<br>UK | Active team and individual sports<br>(N = 11) | Crossover<br>Double-blind | Solution<br>(0.3) ITTP | Repeated sprint cycling 10x6s sprints with 60 recovery<br>(Familiarisation = No) |
| **105** | Mueller (2013)<br>Switzerland | Cyclists and triathletes<br>(N = 11) | Crossover<br>Double-blind | Tablet<br>(0.3) 90 min | 5 SB sessions of a Constant load cycling at critical power until exhaustion<br>(Familiarisation = No) |
| **106** | Mundel (2018)<br>New Zealand | Healthy in competitive sports and trained<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.1) 480 min; (0.1) 180 min; (0.1) 60 min | 2x 30s Wingate anaerobic test at 7.5% BM<br>(Familiarisation = Yes) |
| **107** | Northgraves (2014)<br>UK | Recreationally active non-smoking<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.3) 60 min | 40km cycling TT<br>(Familiarisation = Yes) |

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| **108** | Oliveira (2017)<br>Brazil | Athletes of rugby, judo and jiu-jitsu at university level<br>(N = 18) | Crossover<br>Double-blind | Capsule<br>$(0.5)^{-1}$day for 5 days | 4 bouts of 30s with 3 min recovery Wingate upper body anaerobic test<br>(Familiarisation = Yes) |
| **109** | Painelli (2013)<br>Brazil | Junior-standard swimmers<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | 100m swimming TT<br>(Familiarisation = No)<br>200m swimming TT<br>(Familiarisation = No) |
| **110** | Parry-Billings (1986)<br>UK | Active<br>(N = 6) | Crossover<br>Single-blind | Solution<br>(0.3) 150 min | 3x 30s Wingate test with 6 min recovery<br>(Familiarisation = Yes) |
| **111** | Peart (2011)<br>UK | Recreationally active<br>(N = 7) | Crossover<br>NI | Solution<br>(0.3) 90 min | 4-min bout of all out in cycle ergometer<br>(Familiarisation = Yes) |
| **112** | Peinado (2018)<br>Spain | Elite BMX cyclist from Spanish National team<br>(N = 12) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | 3x races in BMX Olympic trach with 15 min recovery<br>(Familiarisation = Yes) |
| **113** | Pierce (1992)<br>USA | Varsity swimmers<br>(N = 7) | Crossover<br>Double-blind | Solution<br>(0.2) 60 min | 100-yard (91,4m) swim freestyle<br>(Familiarisation = No)<br>Individual 200-yard swims<br>(Familiarisation = No)<br>Individual 200-yard swims<br>(Familiarisation = No) |
| **114** | Poffe (2021)<br>Belgium | Highly-trained male cyclists<br>(N = 12) | Crossover<br>Double-blind | Capsule<br>(0.18) 190 – 10 min | 60 min warm up + 30 min TT + all-out cycling bout at 175% of the LT<br>(Familiarisation = Yes) |
| **115** | Portington (1998)<br>USA | Involved weight training program<br>(N = 15) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | 5 maximal sets on leg press machine<br>(Familiarisation = Yes) |
| **116** | Potteiger (1996)<br>USA | Competitive distance runners<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.3) 120 min | 30 min run following by 110% of LT until exhaustion<br>(Familiarisation = No) |
| **117** | Pouzash (2012)<br>Iran | 400m runners<br>(N = 16) | Crossover<br>NI | Capsule<br>(0.3) 60 min | 400m running test<br>(Familiarisation = No) |

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| **118** | Price (2010)<br>UK | Healthy competed at University level<br>(N = 8) | Crossover<br>NI | Solution<br>(0.3) 60 min | 24x 24s runs treadmill at velocity of $VO_{2max}$, then at 120% of $VO_{2max}$ until exhaustion<br>(Familiarisation = No) |
| **119** | Price (2012)<br>UK | Healthy, recreationally active<br>(N = 9) | Crossover<br>Double-blind | Solution<br>(0.3) 60 min | Two 30 min intermittent cycling trials (repeated 3 min blocks; 90 s at 40% $VO_{2max}$, 60 s at 60% $VO_{2max}$, 14s maximal sprint, 16s rest)<br>(Familiarisation = No) |
| **120** | Pruscino (2008)<br>Australia | Highly trained elite freestyle swimmers<br>(N = 6) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | 200m TT swim<br>(Familiarisation = No) |
| **121** | Ragone (2021)<br>Brazil | Jiu-jitsu athletes blue belt graduates and affiliated to the Brazilian Jiu-Jitsu Confederation<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.3) 90 - 60 min | Maximum voluntary contraction test (MVC) handgrip force, and "Intermittent isometric contraction Test (ISO) in the largest number of successive cycles of 5 s of isometric contraction at 50% of MVC, with 5 s relaxation until fatigue."<br>(Familiarisation = Yes) |
| **122** | Raymer (2004)<br>Canada | Healthy and moderately active<br>(N = 6) | Crossover<br>NI | Capsule<br>(0.3) 90 min | 2 SB sessions of a Progressive wrist flexion until exhaustion<br>(Familiarisation = No) |
| **123** | Rezaei (2019)<br>Iran | Karateka<br>(N = 8) | Crossover<br>Double-blind | Capsule<br>$(0.3)^{-1}$day for 3 days; (0.1) 120 min; (0.1) 90 min; (0.1) 60 min | Karate specific aerobic test<br>(Familiarisation = Yes) |
| **124** | Robertson (1987)<br>USA | University students<br>(N = 10) | Crossover<br>Double-blind | Capsule<br>(0.3) 120 min | Cycling at 80% $VO_{2max}$ until exhaustion<br>(Familiarisation = No)<br>Cranking at 80% $VO_{2max}$ until exhaustion<br>(Familiarisation = No)<br>Cycling and cranking at 80% $VO_{2max}$ until exhaustion<br>(Familiarisation = No) |

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| **125** | Sale (2011)<br>UK | Physical active<br>(N = 10) | Crossover<br>Double-blind | Capsule<br>(0.2) 240 min; (0.1) 120 min | $CCT_{110\%}$<br>(Familiarisation = Yes) |
| **126** | Sarshin (2021)<br>Iran | Professional taekwondo athletes actively competing in the national taekwondo league<br>(N = 16) | Parallel<br>Double-blind | Solution<br>$(0.5)^{-1}$day for 5 days | Taekwondo Anaerobic Intermittent Kick Test (TAIKT)<br>(Familiarisation = Yes) |
| **127** | Saunders (2014)<br>UK | Recreationally active games players<br>(N = 20) | Crossover<br>Double-blind | Capsule<br>(0.2) 240 min; (0.1) 120 min | 3 sets of Repeated Running Sprints (5 × 6s)<br>(Familiarisation = Yes) |
| **128** | Saunders (2014)<br>UK | Recreationally active<br>(N = 21) | Crossover<br>Double-blind | Capsule<br>(0.2) 240 min; (0.1) 120 min | $CCT_{110\%}$<br>(Familiarisation = Yes) |
| **129** | Siegler (2008)<br>UK | Males<br>(N = 9) | Crossover<br>Double-blind | Solution<br>(0.3) 60 min | A bout of intense cycling at 120% PPO to volitional fatigue<br>(Familiarisation = Yes) |
| **130** | Siegler (2010)<br>UK | Recreationally active and healthy<br>(N = 9) | Crossover<br>Single-blind | Solution<br>(0.3) 60 min | 30s maximal efforts running with 180s walking<br>(Familiarisation = Yes)<br>30s maximal efforts running with 180s standing<br>(Familiarisation = Yes) |
| **131** | Siegler (2010)<br>UK | Members of a university swimming club<br>(N = 14) | Crossover<br>Single-blind | Solution<br>(0.3) 150 min | 8x 25m front crawl swimming maximal effort sprint<br>(Familiarisation = No) |
| **132** | Siegler (2010)<br>UK | Amateur boxers (representing country at national and international tournaments [Olympic competition]).<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.3) 60 min | Box 4x 3 min round with 1 min recovery<br>(Familiarisation = No) |
| **133** | Siegler (2013)<br>Australia | Recreationally active and healthy<br>(N = 10) | Crossover<br>Double-blind | Capsule<br>(0.1) 90 min; (0.1) 60 min; (0.1) 30 min | Cycling: 120 PPO for 30s and active recovery of 30s until exhaustion<br>(Familiarisation = Yes) |
| **134** | Siegler (2014)<br>Australia | Recreationally active and healthy<br>(N = 8) | Crossover<br>Double-blind | Capsule | Submaximal calf contractions at 55% MVC to task failure |

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| | | | | 35(0.1) 90 min; (0.1) 60 min; (0.1) 30 min | (Familiarisation = Yes) |
| **135** | Siegler (2015) Australia | Recreationally active and healthy (N = 11) | Crossover Double-blind | Capsule (0.1) 90 min; (0.1) 60 min; (0.1) 30 min | MVC (Familiarisation = Yes) |
| **136** | Siegler (2016) Australia | Resistance trained (N = 12) | Crossover Double-blind | Capsule (0.1) 90 min; (0.1) 60 min; (0.1) 30 min | Triceps surae maximal voluntary efforts (Familiarisation = Yes)<br>Triceps Brachii maximal voluntary efforts (Familiarisation = Yes) |
| **137** | Siegler (2018) Australia | Resistance trained (N = 6) | Crossover Double-blind | Capsule (0.1) 90 min; (0.1) 60 min; (0.1) 30 min | Leg extension before and after a training session (Familiarisation = Yes) |
| **138** | Siegler (2018) Australia | Healthy (N = 8) | Crossover Double-blind | Capsule (0.3) 90 min | Cycling until exhaustion at 125% $VO_{2peak}$ (Familiarisation = Yes) |
| **139** | Silva (2019) Brazil | Cyclists (N = 17) | Parallel Double-blind | Capsule (0.3) 60 min | Cycling 30 kJ TT (Familiarisation = Yes) |
| **140** | Sostaric (2005) Australia | Healthy (N = 9) | Crossover Double-blind | Capsule (0.3) 180 - 105 min | Finger flexion exercise until exhaustion (Familiarisation = Yes) |
| **141** | Stephens (2002) Australia | Cyclists, triathletes, and cross-country skier (N = 6) | Crossover Double-blind | Capsule (0.075) 120 min; (0.075) 110 min; (0.075) 100 min; (0.075) 90 min | 30 min cycling at 77% $VO_{2peak}$ then 469 kJ as quick as possible (Familiarisation = Yes) |
| **142** | Stöggl (2014) Austria | Endurance-trained (N = 12) | Crossover Double-blind | Solution (0.3) 90 min | 3x running bouts until exhaustion recovery of 25 min (Familiarisation = Yes) |
| **143** | Sutton (1981) Canada | Healthy (N = 5) | Crossover Double-blind | Capsule (0.3) 180 min | Cycling at 95% $VO_{2max}$ until exhaustion (Familiarisation = No) |
| **144** | Tan (2010) Australia | Elite players water polo squad (N = 12) | Crossover Double-blind | Capsule (0.3) 90 min | Match simulation test 59 min with sprints of 10 m (Familiarisation = Yes) |
| **145** | Thomas (2016) | Cyclists | Crossover | Capsule | 70s cycling sprint test |

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| | France | (N = 11) | Double-blind | (0.3) 90 min | (Familiarisation = Yes) |
| **146** | Thomas (2021)<br>France | World-class athletes from the French international track cycling team<br>(N = 6) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | 3 x 500m all-out sprints with 20-minute recovery per sprint, and Squat Jump Tests<br>(Familiarisation = Yes) |
| **147** | Tiryaki (1995)<br>Turkey | Track athletes and non-athletes<br>(N = 15) | Crossover<br>Double-blind | Solution<br>(0.3) 120 min | 600m running test<br>(Familiarisation = Yes) |
| **148** | Tobias (2013)<br>Brazil | Well-trained judo and jiu-jitsu<br>(N = 18) | Parallel<br>Double-blind | Capsule<br>$(0.5)^{-1}$day for 7 days | 4x 30s upper-body Wingate test at 5% BM with 3 min recovery between bouts<br>(Familiarisation = No) |
| **149** | Van Montfoort (2004)<br>Netherlands | Distance runners<br>(N = 15) | Crossover<br>Double-blind | Capsule<br>(0.3) 90 min | Treadmill run at velocity to reach exhaustion between 1-2 min<br>(Familiarisation = Yes) |
| **150** | Vanhatalo (2010)<br>UK | Habitually active<br>(N = 8) | Crossover<br>Single-blind | Solution<br>(0.3) 60 min | 3 min all-out cycling test<br>(Familiarisation = Yes) |
| **151** | Voskamp (2020)<br>Netherlands | Competitive cyclists<br>(Male, N = 16; Female, N = 16) | Crossover<br>Double-blind | Capsule<br>(0.3) 150 min | Cycling TT 2000m<br>(Familiarisation = Yes) |
| **152** | Webster (1993)<br>USA | Involved in a regular weight training program<br>(N = 6) | Crossover<br>Double-blind | Solution<br>(0.3) 105 min | 4x 12 rep with 5th set until exhaustion at 70%RM in leg press machine<br>(Familiarisation = Yes) |
| **153** | Wilkes (1983)<br>Canada | Varsity track athletes<br>(N = 6) | Crossover<br>Double-blind | Solution<br>(0.3) 120 min | 800m run race<br>(Familiarisation = No) |
| **154** | Yunoki (2009)<br>Japan | Healthy<br>(N = 7) | Crossover<br>Single-blind | Solution<br>(0.3) 60 min | Short-term intense cycling exercise (STIE) for 40 s<br>(Familiarisation = Yes) |
| **155** | Zabala (2008)<br>Spain | Elite BMX cyclist from Spanish National team<br>(N = 9) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | Vertical jump test<br>(Familiarisation = Yes)<br>3x 30s Wingate test at 0.7 $N^{-1}$BM with 3 min recovery<br>(Familiarisation = Yes) |
| **156** | Zabala (2011) | | Crossover | Capsule | Vertical jump test |

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| | Spain | Elite BMX cyclist from Spanish National team (N = 10) | Double-blind | (0.3) 90 min | (Familiarisation = Yes)<br>3x 30s Wingate test at 0.7 $N^{-1}$BM with 3 min recovery (Familiarisation = Yes) |
| **157** | Zajac (2009) Poland | Well trained competitive youth swimmers (N = 8) | Crossover Double-blind | Solution (0.3) 90 min | 4x 50m crawl swims (Familiarisation = No) |
| **158** | Zinner (2011) Germany | Well-trained healthy (N = 11) | Crossover Double-blind | Solution (0.3) 90 min | 4x 30s maximal sprints cycling with 5 min recovery (Familiarisation = No) |
| | | | **SODIUM CITRATE** | | |
| **1** | Aedma (2015) Estonia | Trained Brazilian Jiu Jitsu and Submission Wrestling practitioners (N = 11) | Crossover Double-blind | Capsule (0.9) 1020 - 30 min | 6 min Upper Body intermittent sprint performance test (Familiarisation = Yes) |
| **2** | Ball (1997) UK | Healthy males (N = 6) | Crossover Double-blind | Capsule (0.3) 180 - 60 min | 2 SC sessions of a Cycle to exhaustion at 100% $VO_2$max (Familiarisation = Yes) |
| **3** | Cox (1994) Australia | Moderately trained students (N = 8) | Crossover Double-blind | Solution (0.5) 90 min | 5x 60s all-out cycling sprints at 0.075$kg^{-1}$BM with 5 min recovery (Familiarisation = Yes) |
| **4** | Cunha (2019) Brazil | Tennis players (N = 10) | Crossover Double-blind | Capsule (0.5) 120 min | Repeated-sprint ability shuttle test (RSA): 10 x 22 m running sprints (Familiarisation = Yes) |
| **5** | Fernandez-Castanys (2002) Spain | Physical education students (N = 17) | Crossover Double-blind | Solution (0.4) 120 min | Cycling at 112% of $VO_{2max}$ until exhaustion in normoxia and hypoxia (Familiarisation = No) |
| **6** | Hausswirth (1995) France | Healthy (N = 8) | Crossover Double-blind | Solution (0.4) 120 min | Right isometric knee extension in normoxia and hypoxia (Familiarisation = Yes) |

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| | | | | | Isometric contraction at 35% MVC in normoxia and hypoxia (Familiarisation = Yes) |
| **7** | Kowalchuk (1989) Canada | Active university students (N = 9) | Crossover NI | Solution (0.3) 60 min | Cycling at 33% $VO_{2max}$ for 20 min 66% $VO_{2max}$ for 20 min 95% $VO_{2max}$ until exhaustion (Familiarisation = No) |
| **8** | Kumstát (2018) Czech Republic | Elite level swimmers (N = 6) | Crossover Double-blind | Capsule (0.3) 60 min | 400 m freestyle swim (Familiarisation = No) |
| **9** | Linossier (1997) France | Moderately active students (N = 8) | Crossover Double-blind | NI (0.5) 90 min | Cycle at 50% $VO_{2peak}$ for 15 min 15 min recovery; 60-80% $VO_{2peak}$ for 15 min and 120% $VO_{2peak}$ until exhaustion (Familiarisation = Yes) |
| **10** | Martins (2010) Brazil | Competitive rowers (N = 6) | Crossover Double-blind | Solution (0.5) 130 min | 2000 m rowing ergometer TT (Familiarisation = No) |
| | | | | Solution (0.1) 90 min | |
| | | | | Solution (0.2) 90 min | |
| **11** | McNaughton (1990) Australia | Healthy (N = 11) | Crossover Double-blind | Solution (0.3) 90 min | Maximal 1 min cycle effort (Familiarisation = No) |
| | | | | Solution (0.4) 90 min | |
| | | | | Solution (0.5) 90 min | |
| | | | | | Maximal 10s cycle effort (Familiarisation = No) |
| **12** | McNaughton (1992) Australia | Healthy (N = 10) | Crossover Double-blind | Solution (0.5) 90 min | Maximal 30s cycle effort (Familiarisation = No) |
| | | | | | Maximal 120s cycle effort (Familiarisation = No) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Maximal 240s cycle effort<br>(Familiarisation = No) |
| **13** | Messonier (2007)<br>France | Healthy<br>(N = 8) | Crossover<br>NI | NI<br>(0.5) 90 min | Cycle 120%$W_{max}$ until exhaustion<br>(Familiarisation = Yes) |
| **14** | Oöpik (2003)<br>Estonia | College runners<br>(N = 17) | Crossover<br>Double-blind | Solution<br>(0.5) 120 min | 5 km running TT<br>(Familiarisation = No) |
| **15** | Oöpik (2004)<br>Estonia | Runners<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.5) 180 min | 5 km running TT<br>(Familiarisation = No) |
| **16** | Oöpik (2008)<br>Estonia | Middle-distance runners<br>(N = 17) | Crossover<br>Double-blind | Solution<br>(0.4) 120 min | 1500m run indoor oval track<br>(Familiarisation = No) |
| **17** | Oöpik (2010)<br>Estonia | Well-trained middle- and long-distance runners<br>(N = 13) | Crossover<br>Double-blind | Solution<br>(0.5) 120 min | Continuous incremental running test to exhaustion on treadmill<br>(Familiarisation = No) |
| **18** | Parry-Billings (1986)<br>UK | Active<br>(N = 6) | Crossover<br>Single-blind | Solution<br>(0.3) 150 min | 3x 30s Wingate test with 6 min recovery<br>(Familiarisation = Yes) |
| **19** | Potteiger (1996)<br>USA | Competitive cyclists<br>(N = 8) | Crossover<br>Double-blind | Solution<br>(0.5) 90 min | 30 km TT cycling<br>(Familiarisation = No) |
| **20** | Potteiger (1996)<br>USA | Competitive distance runners<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.5) 120 min | 30 min run following by 110% of LT until exhaustion<br>(Familiarisation = No) |
| **21** | Russell (2014)<br>Canada | Well trained adolescent swimmers<br>(N = 10) | Crossover<br>Double-blind | Solution<br>(0.5) 120 min<br>Solution<br>$(0.1)^{-1}$day for 3 days; (0.3) 120 min | 200m TT swim<br>(Familiarisation = No) |
| **22** | Schabort (2000)<br>South Africa | Competitive cyclists and triathletes<br>(N = 8) | Crossover<br>Double-blind | Solution<br>(0.2) 60 min<br>Solution<br>(0.4) 60 min<br>Solution<br>(0.6) 60 min | 40 km TT cycling<br>(Familiarisation = No) |

| | | | | | |
|---|---|---|---|---|---|
| **23** | Shave (2001)<br>UK | Elite, multidisciplinary athletes (triathletes and modern pentathletes)<br>(N = 9) | Crossover<br>Double-blind | Solution<br>(0.5) 60 min | 3000m run TT<br>(Familiarisation = No) |
| **24** | Someren (1998)<br>UK | Healthy active<br>(N = 12) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | 5x 45s Wingate Anaerobic Test 4%BM<br>(Familiarisation = Yes) |
| **25** | Street (2005)<br>Denmark | Active with no health problems<br>(N = 7) | Crossover<br>NI | Solution<br>(0.3) 150 min | Constant load cycling exercise to exhaustion<br>(Familiarisation = No) |
| **26** | Suvi (2018)<br>Estonia | Endurance athletes<br>(N = 20) | Crossover<br>Double-blind | Capsule<br>(0.6) 180 min | 40 km TT cycling<br>(Familiarisation = Yes) |
| **27** | Timpmann (2012)<br>Estonia | Wrestlers<br>(N = 16) | Parallel<br>Double-blind | Capsule<br>(0.6) 960 - 120 min | Upper body intermittent sprint test at 0.04 $kg^{-1}$BM<br>(Familiarisation = Yes) |
| **28** | Tiryaki (1995)<br>Turkey | Track athletes and non-athletes<br>(N = 15) | Crossover<br>Double-blind | Solution<br>(0.3) 120 min | 600m running test<br>(Familiarisation = Yes) |
| **29** | Vaher (2014)<br>Estonia | Healthy, endurance trained<br>(N = 16) | Crossover<br>Double-blind | Capsule<br>(0.5) 120 min | 5000m run treadmill<br>(Familiarisation = Yes) |
| **30** | Van Montfoort (2004)<br>Netherlands | Distance runners<br>(N = 15) | Crossover<br>Double-blind | Capsule<br>(0.525) 90 min | Treadmill run at velocity to reach exhaustion between 1-2 min<br>(Familiarisation = Yes) |
| | | | **SODIUM /CALCIUM LACTATE** | | |
| **1** | Morris (2011)<br>USA | Competitive cyclists<br>(N = 11) | Crossover<br>Double-blind | Capsule<br>(0.12) 90 min | Cycling test until exhaustion initial at 3$w^{-1}$BM and increase 0.3 $W^{-1}$BM<br>(Familiarisation = Yes) |
| **2** | Northgraves (2014)<br>UK | Recreationally active non-smoking<br>(N = 7) | Crossover<br>Double-blind | Capsule<br>(0.014) 60 min | 40km cycling TT<br>(Familiarisation = Yes) |
| **3** | Oliveira (2017)<br>Brazil | Athletes of rugby, judo, and jiu-jitsu at university level<br>(N = 18) | Crossover<br>Double-blind | Capsule<br>$(0.5)^{-1}$day for 5 days | 4 bouts of 30s with 3 min recovery Wingate upper body anaerobic test<br>(Familiarisation = Yes) |

| | | | | | |
|---|---|---|---|---|---|
| **4** | Painelli (2014)<br>Brazil | Healthy recreationally active<br>(N = 12) | Crossover<br>Double-blind | Capsule<br>(0.15) 90 min<br>Capsule<br>(0.3) 90 min | 3x 30s upper body Wingate test at 4% BM with 3 min recovery<br>(Familiarisation = Yes) |
| **5** | Peveler (2012)<br>USA | Competitive cyclists<br>(N = 9) | Crossover<br>Double-blind | NI<br>(0.022) 60 min | 20 km TT<br>(Familiarisation = Yes) |
| **6** | Russ (2019)<br>USA | Recreationally active<br>(N = 18) | Parallel<br>Double-blind | Capsule<br>(0.016) 60 min | Graded cycling test 25W every 3 min<br>(Familiarisation = Yes) |
| **7** | Van Montfoort (2004)<br>Netherlands | Distance runners<br>(N = 15) | Crossover<br>Double-blind | Capsule<br>(0.4) 90 min | Treadmill run at velocity to reach exhaustion between 1-2 min<br>(Familiarisation = Yes) |
| | | | **MIXED BUFFERS** | | |
| **1** | Margaria (1971)<br>Italy | Athletes, sportsmen and sedentary<br>(N = 12) | Crossover<br>Double-blind | NI<br>(0.135) 60 min | Running on treadmill at 16 km/h at 16% inclination<br>(Familiarisation = Yes) |
| **2** | Obminski (2016)<br>Poland | Highly trained rowers<br>(N = 8) | Crossover<br>Double-blind | Solution<br>(0.3) 90 min | Cycling sprint at 95% $VO_{2max}$ until volitional exhaustion<br>(Familiarisation = No) |
| **3** | Parry-Billings (1986)<br>UK | Active<br>(N = 6) | Crossover<br>Single-blind | Solution<br>(0.3) 150 min | 3x 30s Wingate test with 6 min recovery<br>(Familiarisation = Yes) |
| **4** | Robergs (2005)<br>USA | Healthy competitive cyclists<br>(N = 12) | Crossover<br>NI | NI<br>(0.4) 60 min | Cycling bout at 110% $VO_{2max}$ to fatigue<br>(Familiarisation = No) |

NI = No information; SB = Sodium bicarbonate; SC = Sodium citrate; GR = Gastrorresistente; LIST = Loughborough Intermittent Shuttle Test; $CCT_{110\%}$ = Cycling capacity test at 110% of maximal power output; $VO_{2max}$ = maximal oxygen uptake; RM = Repetition maximum; TT = Time-trial; FGB = Fight Gone Bad; BM = Body mass; IAT = Individual anaerobic threshold; $W_{peak}$ = Peak power output; MVC = Maximum voluntary contraction; ; $P_{max}$ = Maximum power output; RPM = Revolutions per minute; LT = Lactate threshold; PPO = Peak power output; $VO_{2peak}$ = Peak oxygen consumption; RSA = Repeated sprint ability; $W_{max}$ = Powermax;

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Supplementary Material Appendix S4. Moderator analyses conducted on blood pH across supplementation and exercise periods.

| Moderator | | Parameter Estimate [95% CrI] | Probabilities | Between study SD $\tau$ [75%CrI] | Intraclass Correlation Coefficient [75%CrI] | Grade |
|---|---|---|---|---|---|---|
| **Bicarbonate** | | | | | | |
| *Pre-supplementation to Pre-exercise* | | | | | | |
| **[*Supplement type*]** | SB (n=97) | 0.063 [0.053 to 0.073] | *P*(SB>SC) = 0.926 | 0.027 [0.013 to 0.036] | 0.28 [0.02 to 0.78] | High |
| | SC (n=18) | 0.044 [0.023 to 0.072] | | | | High |
| **[*Supplement dose*]** | Intercept (0.3 g·kg$^{-1}$BM) | 0.060 [0.051 to 0.070] | | 0.036 [0.027 to 0.043] | 0.14 [0.01 to 0.37] | Moderate |
| | Increase per 0.1 g·kg$^{-1}$BM (n=103) | 0.012 [0.001 to 0.023] | *P*(Increase>0) = 0.979 | | | |
| *Pre-exercise to Post-exercise (non-placebo controlled)* | | | | | | |
| **[*Exercise duration*]** | <0.5 min (n=13) | -0.17 [-0.22 to -0.12] | *P*(<0.5min > 0.5–10 min) = 0.927 | 0.10 [0.09 to 0.10] | 0.04 [0.01 to 0.07] | High |
| | 0.5–10 min (n=115) | -0.21 [-0.23 to -018] | *P*(0.5–10 min < >10 min) >0.999 | | | High |
| | >10 min (n=18) | -0.08 [-0.13 to -0.02] | *P*(<0.5min < 10 min ) = 0.990 | | | High |
| **[*Exercise type*]** | Performance (n=90) | -0.21 [-0.24 to -0.19] | *P*(Capacity>Performance) >0.999 | 0.09 [0.09 to 0.10] | 0.05 [0.00 to 0.13] | High |
| | Capacity (n=56) | -0.14 [-0.17 to -0.11] | | | | High |

SD: Standard deviation; n: Number of outcomes for covariate or factor level; SB: Sodium bicarbonate; SC: Sodium citrate; g·kg$^{-1}$BM: grams per kilogram body mass: CrI: Bayesian credible interval.

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Supplementary Material Appendix S5. Table. Exercise performance moderator analyses conducted on placebo controlled standardized effect sizes with sodium bicarbonate only.

| **Moderator** | | **Parameter Estimate [95% CrI]** | **Probabilities** | **Between study SD ($\tau$) [95%CrI]** | **Intraclass Correlation Coefficient [95%CrI]** |
|---|---|---|---|---|---|
| **Exercise Performance** | | | | | |
| **[*Exercise duration 1*]** | <30s (n=33) | 0.09 [-0.03 to 0.21] | *P*(<30s > 30s–10min) = 0.055 | 0.12 [0.05 to 0.17] | 0.05 [0.00 to 0.18] |
| | 30s–10min (n=136) | 0.19 [0.13 to 0.25] | *P*(30s–10min > +10min) = 0.085 | | |
| | +10min (n=25) | 0.31 [0.16 to 0.45] | *P*(<30s > +10min ) = 0.012 | | |
| **[*Exercise type*]** | Performance (n=118) | 0.16 [0.10 to 0.22] | *P*(Capacity>Performance) = 0.927 | 0.13 [0.06 to 0.18] | 0.05 [0.00 to 0.17] |
| | Capacity (n=76) | 0.24 [0.15 to 0.32] | | | |
| **[*Prior exercise*]** | Prior (n=25) | 0.31 [0.16 to 0.46] | *P*(Prior>No Prior) = 0.957 | 0.14 [0.08 to 0.19] | 0.04 [0.00 to 0.15] |
| | No Prior (n=169) | 0.17 [0.12 to 0.22] | | | |
| **[*Training status*]** | Top-level (n=20) | 0.12 [-0.04 to 0.27] | *P* (Top-level>Trained) = 0.175 | 0.14 [0.08 to 0.19] | 0.04 [0.00 to 0.16] |
| | Trained (n=116) | 0.20 [0.13 to 0.26] | *P* (Trained>Non-trained) = 0.587 | | |
| | Non-trained (n=57) | 0.18 [0.09 to 0.28] | *P*(Top-level>Non-trained) = 0.240 | | |

SD: Standard deviation; n: Number of outcomes for covariate or factor level; CrI: Bayesian credible interval.

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Supplementary Material Appendix S6.

Table 1. Grade analysis of moderator analyses conducted on biomarker data post supplementation and post-exercise.

| Moderator | | ROB2 | Imprecision | Inconsistency | Indirectness | Publication Bias | Upgrade | Grade |
|---|---|---|---|---|---|---|---|---|
| **Bicarbonate** | | | | | | | | |
| *Pre-supplementation to Pre-exercise* | | | | | | | | |
| **[*Supplement type*]** | SB (n=97) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| | SC (n=19) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| **[*Supplement dose*]** | Increase per 0.1 $g \cdot kg^{-1}$BM (n=115) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| *Pre-exercise to Post-exercise (non-placebo controlled)* | | | | | | | | |
| **[*Exercise duration*]** | <0.5 min (n=13) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| | 0.5–10min (n=114) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| | >10min (n=12) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| **[*Exercise type*]** | Performance (n=90) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| | Capacity (n=49) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| **Lactate** | | | | | | | | |
| *Pre-exercise to Post-exercise (non-placebo controlled)* | | | | | | | | |
| **[*Exercise duration*]** | <0.5 min (n=16) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| | 0.5–10min (n=97) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| | >10min (n=14) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| **[*Exercise type*]** | Performance (n=89) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |
| | Capacity (n=42) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | High |

SB: Sodium bicarbonate; SC: Sodium citrate.

Table 2. Grade analysis for exercise performance moderator analyses conducted on placebo controlled standardized effect sizes.

| Moderator | | ROB2 | Imprecision | Inconsistency | Indirectness | Publication Bias | Upgrade | Grade |
|---|---|---|---|---|---|---|---|---|
| ***[Exercise duration 1]*** | <0.5 min | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | 0.5–10min | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| | >10min | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| ***[Exercise duration 2]*** | 0.5–1.5 min | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| | 1.5–5 min | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| | 5–10 min | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| ***[Exercise type]*** | Performance | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| | Capacity | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| ***[Acute/Chronic]*** | Acute | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| | Chronic | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| ***[Prior exercise]*** | Prior | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | No Prior | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| ***[Training status]*** | Top-level | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | Trained | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| | Non-trained | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| ***[Intermittent]*** | Bout 1 | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| | Bout 2 | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |
| | Bout 3 | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | Moderate |

Table 3. Grade analysis for the moderator analyses for supplement protocols conducted on placebo controlled standardized exercise effect sizes.

| Moderator | | ROB2 | Imprecision | Inconsistency | Indirectness | Publication Bias | Upgrade | Grade |
|---|---|---|---|---|---|---|---|---|
| *Exercise Outcomes* | | | | | | | | |
| **[*Supplement Dose*]** | Low (<0.3 g/kg) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | Mid (=0.3 g/kg) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | High (>0.3 g/kg) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| **[*Supplement Strat*]** | Single dose | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | Split dose | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| **[*Supplement Form*]** | Solution | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | Capsule | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| **[*Supplement Type*]** | SB | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | SC | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| **[*Bicarbonate increase*]** | Small (≤4 mmol·L$^{-1}$) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | Medium (4–6 mmol·L$^{-1}$) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |
| | Large (>6 mmol·L$^{-1}$) | ⊕⊕⊕⊕ | ⊕⊕⊕⊕ | ⊕⊕⊕◯ | ⊕⊕⊕◯ | ⊕⊕◯◯ | ⊕⊕◯◯ | Low |

SB: Sodium bicarbonate; SC: Sodium citrate.