

THE EFFECT OF NITRATE SUPPLEMENTATION ON EXERCISE TOLERANCE AND PERFORMANCE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Van De Walle, GP and Vukovich, MD. The effect of nitrate supplementation on exercise tolerance and performance: a systematic review and meta-analysis. *J Strength Cond Res* 32(6): 1796–1808, 2018—The purpose of this article was to systematically review the current literature and evaluate the overall efficacy of nitrate supplementation on exercise tolerance and performance by meta-analysis. Studies were eligible for inclusion if they met the following criteria: (a) were an experimental trial published in an English peer-reviewed journal; (b) compared the effects of inorganic nitrate consumption with a non-bioactive supplement control or placebo; (c) used a quantifiable measure of exercise performance; and (d) was carried out in apparently healthy participants without disease. A total of 29 studies were identified that investigated the effects of nitrate supplementation on exercise tolerance or performance in accordance with the criteria outlined. Analysis using time to exhaustion as the outcome variable revealed a significant effect of nitrate supplementation on exercise tolerance ($ES = 0.28$; 95% confidence interval [CI]: 0.08–0.47; $p = 0.006$) compared with placebo. Analysis using time to complete a specific distance as the outcome variable revealed no significant effect of nitrate supplementation on exercise performance ($ES = -0.05$; 95% CI: -0.28 to 0.17 ; $p = 0.64$) compared with placebo. Nitrate supplementation is likely to improve exercise tolerance and capacity that may improve exercise performance. More research is required to determine the optimal dose and duration of nitrate supplementation. It would also be important to consider the type of athlete performing the exercise and the duration, intensity, and mode of the exercise performed because these factors are likely to influence the efficacy of nitrate supplementation.

KEY WORDS inorganic nitrate, time to exhaustion, athlete

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INTRODUCTION

Nitric oxide (NO) is a signaling molecule that plays an important role in several cellular functions, including vasodilation, cellular respiration, and angiogenesis (39). Elevated NO availability may positively augment oxygen and nutrient delivery to the working muscle, thereby lowering the ATP cost of muscle contractile force production and oxygen costs of aerobic exercise. The mechanisms attributed to these effects are linked to mitochondrial respiration and biogenesis (26,39). This gives athletes reason to believe that enhancing NO bioavailability may favorably influence exercise performance. To this effect, several “NO stimulating supplements” (e.g., L-arginine, arginine- α -ketoglutarate) have been marketed to the fitness community as NO boosters claiming to improve performance. However, these supplements have little effect on NO-related physiological processes or exercise performance (46).

More recently, nitrate (NO_3^-) supplementation via beetroot juice has gained popularity as a means of increasing NO bioavailability. Beetroot is high in inorganic nitrate, which when consumed is converted to bioactive nitrite (NO_2^-) in part by facultative anaerobic bacteria on the dorsal surface of the tongue. The nitrite then enters the systematic circulation and is subsequently reduced in blood vessels, the heart, and skeletal muscle to form NO (23). The reduction of nitrite to NO is facilitated by hypoxia and low pH, conditions that may be present during exercise. On a per-weight basis, other green leafy vegetables like spinach and arugula contain more nitrate than beetroot. However, beetroot juice is a much more palatable option. Other sources of nitrate in the diet include sodium nitrate (NaNO_3^-) in cured and processed meats and is found in minute amounts of drinking water (22).

Aside from nitrate, beetroot contains several bioactive compounds (Figure 1), including phenolics, ascorbic acid, carotenoids, and betalains (17). Betaine supplementation is reported to increase power output and endurance, possibly through its role as an osmolyte, in which increased intracellular concentrations can increase resistance to stress (38). Additionally, beetroot is rich in the bioflavonoids, quercetin, and resveratrol, which are associated with induced mitochondrial biogenesis and aerobic capacity. For this reason, the physiological effects associated with exercise performance may not be consequent to the high

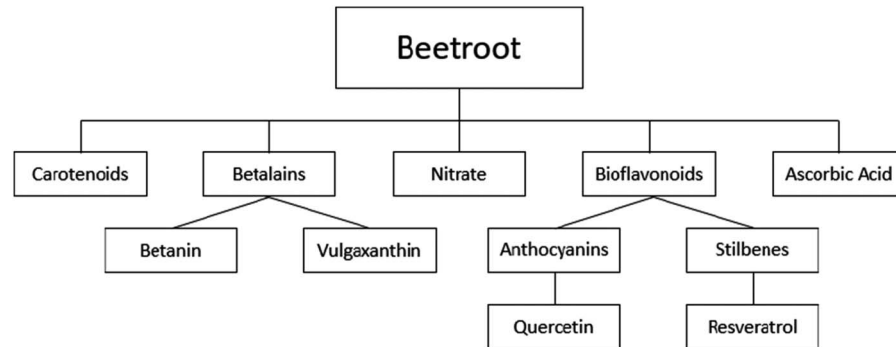


Figure 1. Bioactive compounds of beetroot.

nitrate content of beetroot. Testing this theory, however, Lansely et al. (25) observed no reduction in $\dot{V}O_2$ when control subjects were supplemented with depleted nitrate beetroot juice placebo using an ion-exchange resin, confirming that nitrate is the primary constituent responsible for the physiological effects following beetroot juice supplementation.

A meta-analysis by Hoon et al. (20) reported a significant benefit of nitrate supplementation on performance for time-to-exhaustion (TTE) tests and a small but insignificant benefit on performance for time-trial (TT) and graded exercise tests (GXT). Because of the small number of studies ($n = 17$), Hoon et al. concluded that further research was required to determine the overall efficacy of dietary nitrate supplementation on exercise performance. Moreover, the authors did not perform sub-analyses on parameters likely to affect the efficacy of nitrate supplementation, such as training status, nitrate dose, and duration. To this effect, the ergogenic effects of nitrate supplementation seems to selectively benefit primarily recreationally active and moderately trained individuals with minimal benefit, if any, observed in well-trained individuals (7,9,16,34). Interestingly, there may be individual variability in the response to nitrate supplementation, resulting in responders and nonresponders based on individual variances (9,16,45). Therefore, the purpose of this article was to systematically review the current literature and evaluate the overall efficacy of nitrate supplementation on exercise tolerance and performance by meta-analysis. We also investigated whether the effect of nitrate on effect size (ES) was modified by training status, supplementation duration, and dose. The findings should further enhance our understanding of the ergogenic influence dietary nitrate supplementation has on exercise tolerance and performance, with efforts focused on providing usage recommendations.

METHODS

Experimental Approach to the Problem

Studies were eligible for inclusion if they met the following criteria: (a) were an experimental trial published in an English peer-reviewed journal; (b) compared the effects of

inorganic nitrate consumption with a non-bioactive supplement control or placebo; (c) used a quantifiable measure of exercise performance; and (d) was carried out in apparently healthy participants without disease.

Subjects

Participants in the included studies consisted of males and females who were physically active or well trained (Table 1). Studies reported that subjects were healthy, free from injury and illness and were not using prescription medications, illicit social drugs, tobacco, or dietary supplements. Subjects participated in recreational team sports (soccer, field hockey, rugby), competitive running, cycling, cross-country skiing, rowing, kayak, and triathlons.

Procedures

A systematic search of the literature was conducted in reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (31). To carry out this review, the computer databases—PubMed, Science Citation Index of Web of Knowledge, EBSCOhost, and ProQuest—were searched up until May 18, 2016. The keywords used as search terms were “nitrate” AND “exercise.” The reference lists of the retrieved articles were subsequently screened for additional articles that were of relevance. A total of 1,986 studies were evaluated based on the keywords searched. An additional 8 studies were then identified as potentially being eligible for inclusion, leaving a total of 1,993 studies screened for inclusion. Of the studies reviewed, 35 were determined to be potentially relevant based on the abstracts. The full text of these articles were then screened, in which 29 were identified for inclusion (Figure 2). Table 1 summarizes the studies analyzed.

Studies were individually coded for the following variables: subject’s characteristics by group, including sex and training status; supplement intervention, including nitrate source, dose, delivery, and duration; and type of exercise test data. Outcome variables were coded for tolerance and performance variables. Exercise tests using TTE and GXT trials

TABLE 1. Summary of studies meeting inclusion criteria.*†

Reference	Subjects, <i>n</i>	Nitrate supplementation	Exercise test	Outcome	Trial result (mean $\pm$ SD)
Arnold et al. (2)	Well-trained runners, <i>n</i> = 10 (men)	7 mmol single dose as BR	Incremental treadmill TTE @ 4,000 m (a)	Did not alter TTE or time to complete a 10-km TT	N = 402 $\pm$ 80 (a)
		2.5 h pretest	Stimulated altitude 12.9% O ₂	3 runners experienced a "likely, probable" performance improvement	P = 393 $\pm$ 62
			10 km treadmill TT @ 2,500 m (b)		N = 2,862 $\pm$ 233 s (b)
			Stimulated altitude 15.4% O ₂		P = 2,874 $\pm$ 265 s
Aucouturier et al. (3)	Recreationally active, <i>n</i> = 12 (men)	5.5 mmol·d ⁻¹ for 3 d as BR	15-s exercise periods at 170% of maximal aerobic power using a cycle ergometer	Enhanced exercise tolerance at supramaximal intensity	N = 26.1 $\pm$ 10.7 reps
Bailey et al. (6)	Recreationally active, <i>n</i> = 8 (men)	5.5 mmol·d ⁻¹ for 6 d as BR	Cycling TTE @ 70% between GET and $\dot{V}O_{2\max}$	Increased TTE by 16% compared with placebo	P = 21.8 $\pm$ 8.0 reps
					N = 675 $\pm$ 203 s
Bailey et al. (4)	Recreationally active, <i>n</i> = 7 (men)	5.1 mmol·d ⁻¹ for 6 d as BR	Leg extension TTE @ 15 and 30% MVC	Increased TTE by 25% compared with placebo	P = 583 $\pm$ 145 s
					N = 734 $\pm$ 288 s
Bailey et al. (5)	Recreationally active, <i>n</i> = 7 (men)	8.4 mmol·d ⁻¹ for 9 d as BR	Cycling TTE @ 80% between GET and $\dot{V}O_{2\max}$ 115 RPM 35 RPM	Extended exercise tolerance by 22% when cycling at a high, but not a low pedal cadence	P = 586 $\pm$ 212 s
					N = 362 $\pm$ 137 s (a)
					P = 297 $\pm$ 79 s
					N = 344 $\pm$ 74 s (b)
Bescos et al. (8)	Well-trained cyclists and triathletes, <i>n</i> = 11 (men)	10 mg·kg ⁻¹ single dose as NaNO ₃ ⁻	Cycle incremental TTE	No improvement in the tolerance of high-intensity cycling	P = 341 $\pm$ 99 s
					N = 416 $\pm$ 106 s
Bescos et al. (7)	Well-trained cyclists and triathletes, <i>n</i> = 13 (men)	3 h pretest 10 mg·kg ⁻¹ for 3 d as NaNO ₃ ⁻	40-min cycle distance TT	No improvement in 40-min distance TT performance	P = 409 $\pm$ 90 s
					N = 26.4 $\pm$ 1.1 km
Boorsma et al. (9)	Elite distance runners, <i>n</i> = 8 (men)	19.5 mmol single dose as BR (a)	1,500-m TT acute (a)	No improvement in TT performance after acute or chronic supplementation; 2 responders to BR were identified	P = 26.3 $\pm$ 1.2 km
		2.5 h pretest	1,500-m TT chronic (b)		N = 250.7 $\pm$ 4.3 s (a)
		13 mmol·d ⁻¹ for 8 d as BR (b)			P = 250.4 $\pm$ 7.0 s
					N = 250.5 $\pm$ 6.2 s (b)

Bourdillon et al. (10)	Well-trained cyclists, $n = 12$ (men)	0.1 mmol·kg ⁻¹ for 3 d as NaNO ₃ ⁻	15-km TT in normoxia	No improvement in TT performance during exercise in normoxia and hypoxia	$P = 251.4 \pm 7.6$ s $N = 1,597 \pm 96$ s (a)
			15-km TT in normobaric hypoxia		$P = 1,581 \pm 63$ s $N = 2,155 \pm 687$ (b)
Breese et al. (11)	Recreationally active, $n = 9$ (4 men, 5 women)	8 mmol·d ⁻¹ for 6 d as BR	Cycling TTE @ 70% between GET and V _O ₂ max	Increased TTE during moderate- to severe-intensity cycling by 22% over placebo	$P = 2,005 \pm 309$ s $N = 635 \pm 258$ s
Cermak et al. (14)	Trained cyclists and triathletes, $n = 20$ (men)	8.7 mmol single dose as BR	1-h TT	No improvement in TT performance compared with placebo	$P = 521 \pm 158$ s $N = 65.5 \pm 4.9$ min
Cermak et al. (15)	Trained cyclists and triathletes, $n = 12$ (men)	2.5 h pretest 8 mmol for 6 d as BR	10-km TT	Time to complete TT was 1.2% lower with BR	$P = 65.0 \pm 4.9$ min $N = 953 \pm 72.7$ s
Hoon et al. (19)	Well-trained rowers, $n = 10$ (men)	4.2 mmol single dose as BR (a) 2 h pretest 8.4 mmol single dose as BR (b)	2,000-m rowing ergometer T	A high but not moderate dose improved 2,000-m rowing performance	$P = 965 \pm 72.7$ s $N = 383.4 \pm 8.7$ s (a) $P = 383.5 \pm 9.0$ s $N = 381.9 \pm 9.0$ s (b)
Lansley et al. (24)	Trained cyclists, $n = 9$ (men)	2 h pretest 6.2 mmol single dose as BR 2.5 h pretest	4-km cycling TT 16.1-km cycling TT	Improved 4 and 16.1 km completion time by 2.8 and 2.7% over placebo	$P = 383.5 \pm 9.0$ s $N = 6.27 \pm 0.35$ min (a) $P = 6.45 \pm 0.42$ min $N = 26.9 \pm 1.8$ min (b) $P = 27.7 \pm 2.1$ min $N = 563 \pm 90$ s
Larsen et al. (27)	Healthy subjects, $n = 9$ (7 men, 2 women)	0.1 mmol·kg ⁻¹ for 2 d as NaNO ₃ ⁻	Incremental arm crank and cycle TTE	A trended increase in TTE was noted	
MacLeod et al. (28)	Trained cyclists, $n = 11$ (men)	6.5 mmol single dose as BR 2.5 h pretest	10-km TT normoxia 10-km TT normobaric hypoxia	No improvement in TT performance during exercise in normoxia and hypoxia	$P = 524 \pm 93$ s $N = 961 \pm 54$ s (a) $P = 954 \pm 47$ s $N = 1,018 \pm 52$ s (b)
Masschelein et al. (29)	Physically active, $n = 15$ (men)	0.07 mmol·kg ⁻¹ for 6 d as BR 2.5 h pretest	Cycle incremental TTE @ 5,000 m	Increased TTE by 5%	$P = 1,023 \pm 49$ s $N = 597 \pm 85$ s $P = 568 \pm 89$ s (continued on next page)

Muggeridge et al. (32)	Well-trained cyclists, $n = 9$ (men)	5 mmol single dose as BR 3 h pretest	16.1-km TT @ 2,500 m Stimulated altitude 15% O_2	Improved 16.1-km TT performance by 2.9%	$N = 1,664 \pm 42$ s $P = 1,702 \pm 45$ s
Murphy et al. (33)	Healthy subjects, $n = 11$ (5 men, 6 women)	8 mmol as whole BR 1.25 h pretest	5-km running TT	Increased velocity by 3%	$N = 12.3 \pm 2.7$ km·h ⁻¹ $P = 11.9 \pm 2.6$ km·h ⁻¹
Peacock et al. (34)	Well-trained cross-country skiers, $n = 10$ (men)	9.9 mmol single dose as KNO_3^- (pill)	5-km running TT	No effect on exercise performance	$N = 1,005 \pm 53$ s
Peeling et al. (35)	National-level kayak athletes, $n = 6$ (men)	2.5 h pretest 4.8 mmol single dose as BR (a)	7 × 4-min step test kayak (a)	(a) Distance covered was (+0.7%) greater in BR trial	$P = 966 \pm 49$ s $N = 989 \pm 31$ m (a)
	International-level kayak athletes, $n = 5$ (women)	2.5 h pretest 9.6 mmol single dose as BR (b)	Ergometer 500-m paddle TT (b)	(b) Performance was (-1.7%) faster in BR	$P = 982 \pm 36$ m $N = 114.6 \pm 1.5$ s (b)
Porcelli et al. (36)	Distance runners, $n = 21$ (men)	2 h pretest 5.5 mmol for 6 d as $NaNO_3^-$	3-km treadmill TT	Low and moderate trained subjects improved task 1–4% faster; no benefit in high trained	$P = 116.7 \pm 2.2$ s $N = 886 \pm 74$ s (a)
	Low trained, $n = 8$				$P = 910 \pm 82$ s
	Moderate trained, $n = 7$				$N = 723 \pm 90$ s (b)
	High trained, $n = 6$				$P = 734 \pm 93$ s
					$N = 627 \pm 30$ s (c) $P = 629 \pm 28$ s
Thompson et al. (40)	Recreationally active, $n = 16$ (men)	5 mmol as BR	TTE at 90% $\dot{V}O_{2peak}$	TTE was 16% longer with nitrate compared with placebo	$N = 185 \pm 122$ s
Thompson et al. (41)	Recreational team-sport players, $n = 16$ (men)	1.5 h pretest 12.8 mmol for 7 d as BR	Intermittent sprint test	Increased total work done by 3.5%	$P = 160 \pm 109$ s $N = 123 \pm 19$ kJ
		Final dose ingested 2.5 h pretest			$P = 119 \pm 17$ kJ
Vanhatalo et al. (42)	Recreationally active, $n = 8$ (5 men, 3 women)	4.84 mmol single dose as BR (a)	Cycle incremental TTE	Peak power output was higher after 15 d of BR supplementation but not 2.5 h or 5 d	$N = 325 \pm 71$ Wmax (a)

		4.84 mmol for 5 d as BR (b)			P = 322 ± 68 Wmax N = 328 ± 68 Wmax (b)
		4.84 mmol for 15 d as BR (c)			P = 323 ± 67 Wmax N = 331 ± 68 Wmax (c)
Vanhatalo et al. (43)	Recreationally active, n = 9 (7 men, 2 women)	9.3 mmol 24 h, 12 h, and 2.5 h as BR	Leg extension TTE @ 14.5% O ₂	Increased high-intensity exercise by 21%	P = 323 ± 68 Wmax N = 477 ± 200 s
Wilkerson et al. (45)	Well-trained cyclists, n = 8 (men)	6.1 mmol single dose as BR	50-mile cycle TT	Mean reduction in time of 0.8% or 1.2 min	P = 393 ± 169 s N = 136.7 ± 5.6 min
Wylie et al. (47)	Recreationally active, n = 10 (men)	2.5 h pretest 4.2 mmol single dose as BR (a)	Cycling TTE @ 75% between GET and $\dot{V}O_{2\max}$	Increased TTE with 8.4 and 16.8 mmol by 14 and 12% but not with 4.2 mmol	P = 137.9 ± 6.4 min N = 508 ± 102 s (a)
		8.4 mmol single dose as BR (b)			P = 470 ± 81 s N = 570 ± 153 s (b)
		16.8 mmol single dose as BR (c)			P = 498 ± 113 s N = 552 ± 117 s (c)
Wylie et al. (48)	Recreational team-sport players, n = 14 (men)	2.5 h pretest 8.2 mmol day before in morning	Yo-Yo intermittent recovery test	Improved distance covered in intermittent exercise by 4.2%	P = 493 ± 114 s N = 1,704 ± 304 m
		8.2 mmol day before in evening			P = 1,636 ± 288 m
		8.2 mmol 2.5 h pretest			
		4.1 mmol 1.5 h pretest			

*BR = beetroot juice; TTE = time to exhaustion; TT = time trial; N = nitrate trial; P = placebo trial; GET = gas exchange threshold; RPM = revolutions per minute; MVC = maximum voluntary isometric contract; Wmax = peak power output.
†(a), (b), and (c) indicate when more than one exercise test or supplementation protocol was used in one study.

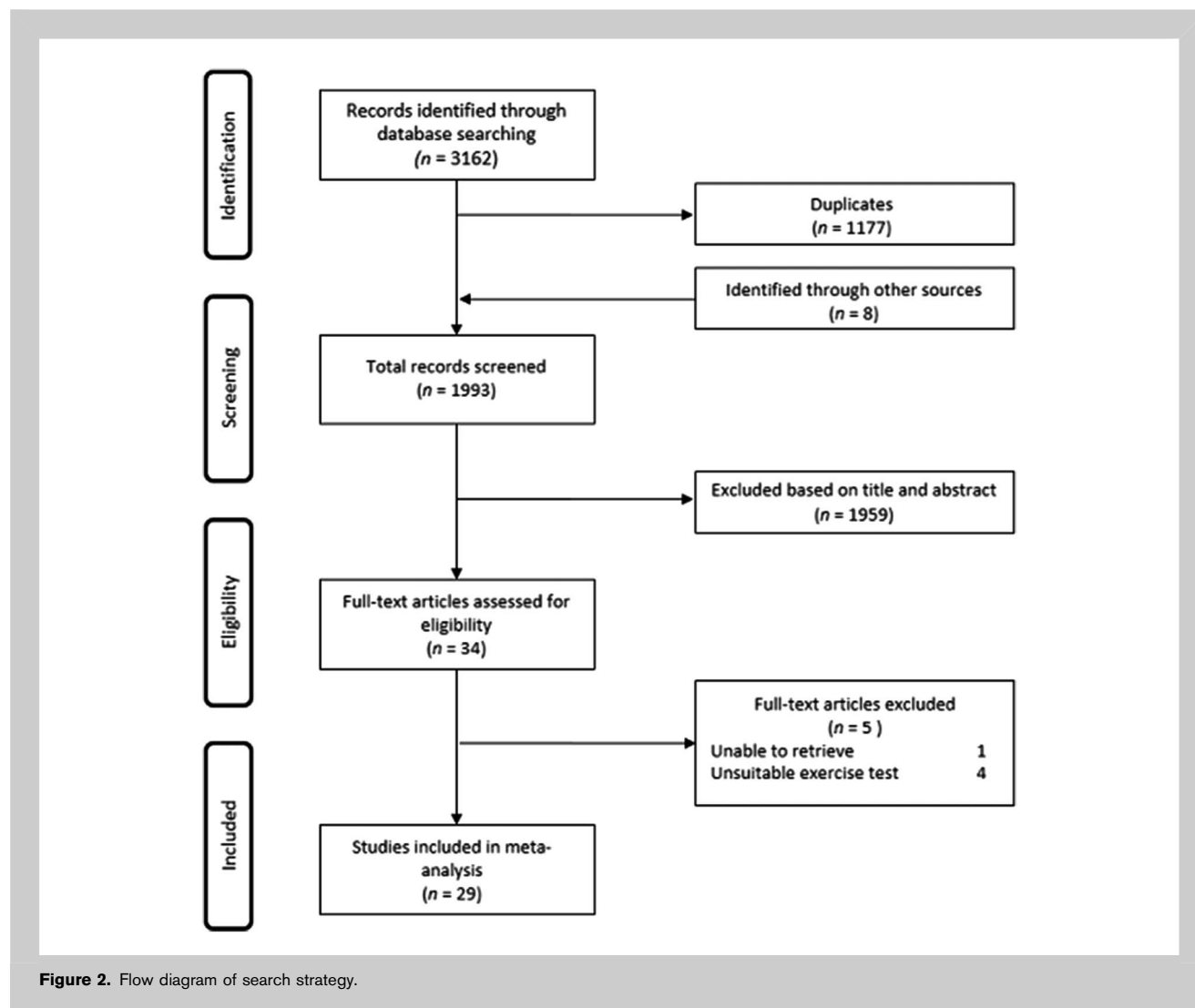
were classified as tests of exercise tolerance, whereas TT were classified as tests of exercise performance. A TTE trial was defined as a single step increment in work rate continued to exhaustion. A GXT was defined as a multiple or continuous ramp incremental TTE. A TT was defined as the time to complete a specific distance or course. Studies that included more than one supplement intervention, tolerance, or performance variable were coded as separate results.

Using a continuous measure, the variance within each intervention group was calculated as the standardized mean difference (SMD) between nitrate and placebo exercise toler-

ance performance outcomes using the Hedges *g* statistic under the fixed effects model (18), which was calculated using the following equation:

$$g = \frac{\bar{x}_1 - \bar{x}_2}{s_{\text{pooled}}}$$

The effect sizes were based on Cohen's definition of small (≤ 0.2), moderate (~ 0.5), and large (≥ 0.8). A negative ES for an exercise performance variable suggests an ergogenic effect. Where *SE* was reported, the *SD* was calculated as $SD = SE \times \sqrt{n}$, where *n* represents the sample size.



Statistical Analyses

Meta-analyses were performed using hierarchical data structures, with a sample bias adjustment for small samples. The observations were weighted by the inverse of the reported sampling variance. It was assumed the effects varied between studies, and the total effect is the weighted average of the effects reported. Separate analyses were performed for exercise tolerance (TTE and GXT) and performance tests (TT). When sample size was not limited, subgroup analyses were performed on the following factors: training status (classified as “untrained” or “trained” populations as defined by the author), supplement dose (low ≤ 7 mmol or high > 8 mmol), duration (short ≤ 3 days or long > 3 days) and experimental conditions (hypoxia). Statistical analyses were performed using Review Manager (RevMan) computer program (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Data are presented as SMD for the performance outcomes with 95% confidence interval (CI) and are presented in forest plots.

The SMD was considered statistically significant ($p \leq 0.05$) if the value of 0 was not within the 95% CI. The marker size is relative to study weight, and the pooled effects are represented using a diamond in which the location represents the ES and the width reflects the precision of the estimate.

RESULTS

Exercise Tolerance

The analysis on exercise tolerance compromised 200 subjects and 20 ESs, nested within 15 studies. Analysis using TTE and GXT as the outcome variables revealed a significant impact of nitrate supplementation on exercise tolerance (ES = 0.28; 95% CI: 0.08–0.47; $p = 0.006$) (Figure 3). Subgroup analysis on training status showed a significant effect of nitrate supplementation on exercise tolerance in untrained subjects (ES = 0.32; 95% CI: 0.10–0.53; $p = 0.004$) (Figure 3A) but not in trained subjects (ES = 0.1; 95% CI: –0.41 to

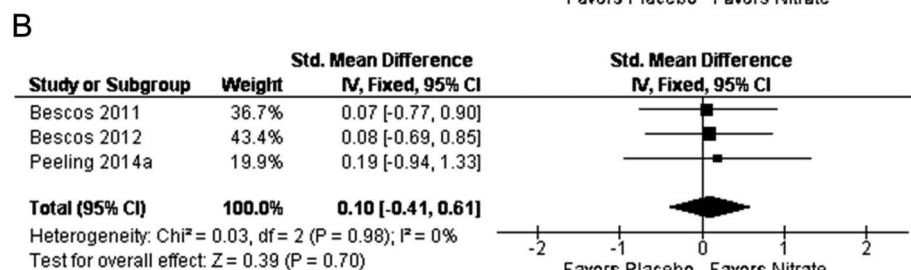
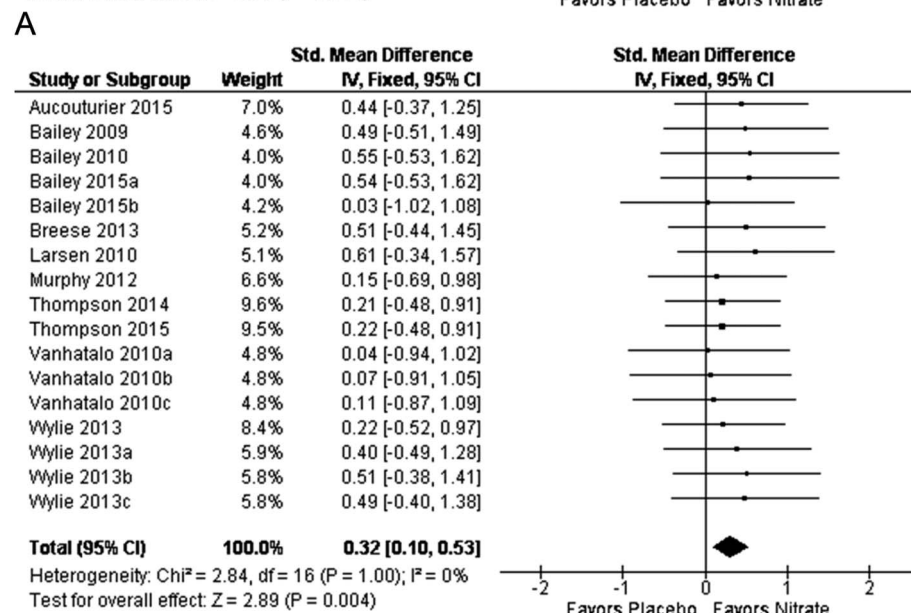
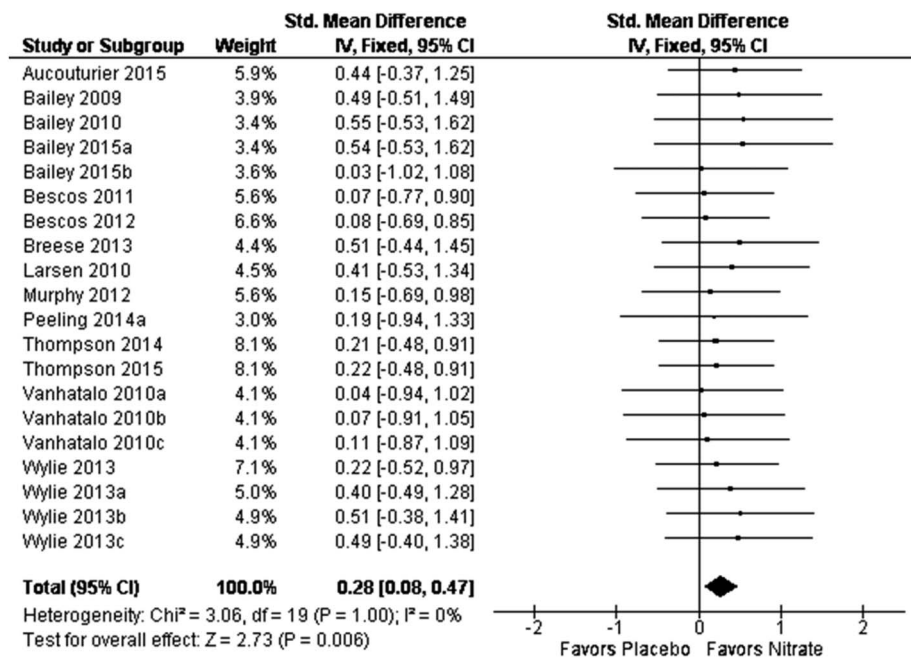


Figure 3. Forest plot of the impact of nitrate supplementation on exercise tolerance. A) Forest plot of the impact of nitrate supplementation on exercise tolerance in untrained subjects. B) Forest plot of the impact of nitrate supplementation on exercise tolerance in trained subjects.

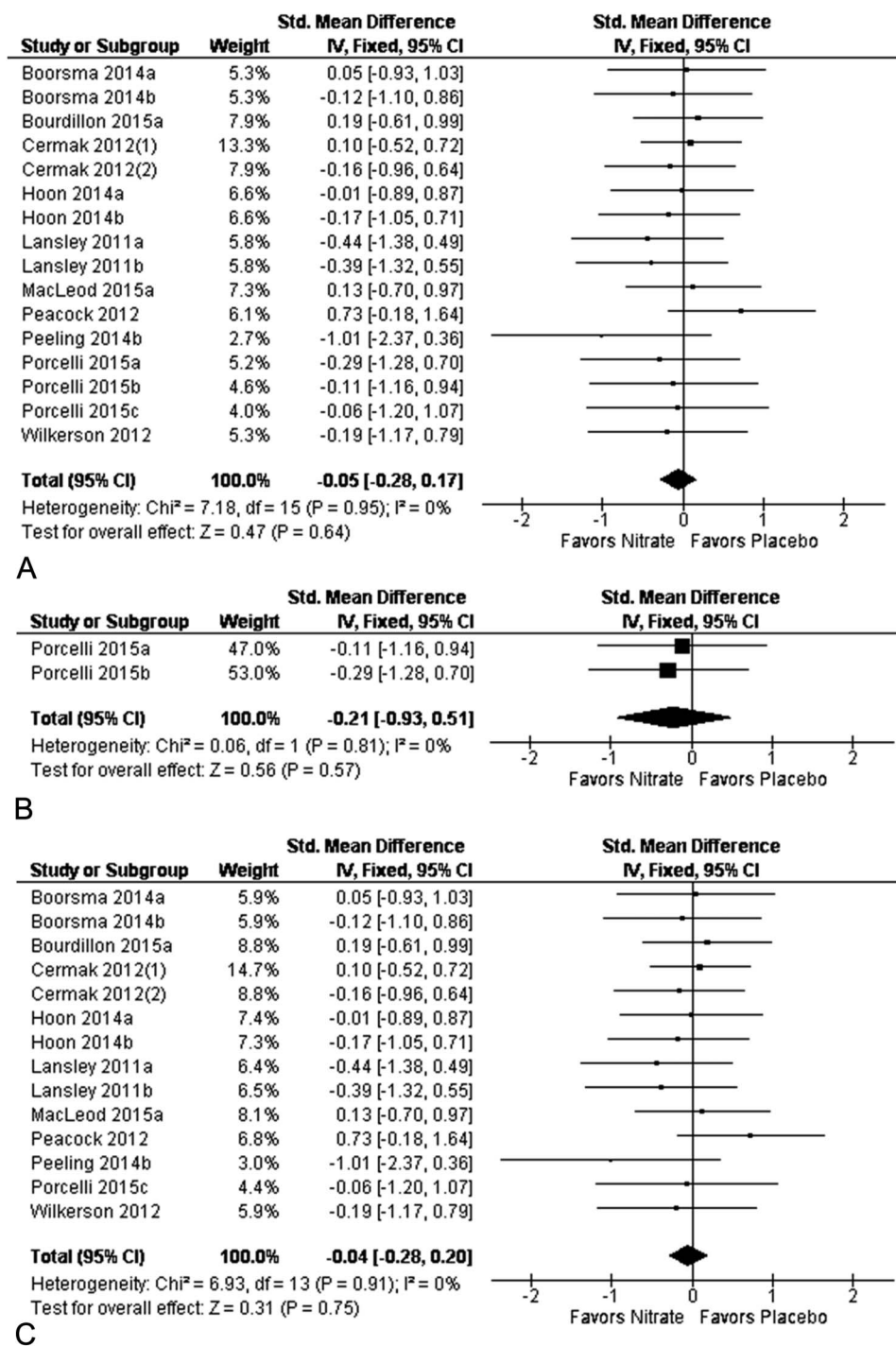


Figure 4. Forest plot of the impact of nitrate supplementation on exercise performance. A) Forest plot of the impact of nitrate supplementation on exercise performance in trained subjects. B) Forest plot of the impact of nitrate supplementation on exercise performance in untrained subjects.

0.61; $p = 0.70$) (Figure 3B). Subgroup analysis by dose showed that a larger nitrate dose significantly improved exercise tolerance (ES = 0.27; 95% CI: 0.01–0.53; $p = 0.04$)

but not a smaller dose (ES = 0.28; 95% CI: –0.03 to 0.58; $p = 0.08$). Surprisingly, the supplementation duration had little impact on exercise tolerance, with a longer supplementation

duration showing a similar, albeit nonsignificant, effect ($ES = 0.32$; 95% CI: -0.03 to 0.68 ; $p = 0.07$) as a shorter duration ($ES = 0.25$; 95% CI: 0.02 – 0.49 ; $p = 0.04$).

Exercise Tolerance in Hypoxia

The analysis on exercise tolerance in hypoxia compromised 34 subjects and 3 ESs, nested within 3 studies. Analysis using TTE and GXT as the outcome variables revealed a small but insignificant effect of nitrate supplementation on exercise tolerance in hypoxia compared with placebo ($ES = 0.29$; 95% CI: -0.19 to 0.77 ; $p = 0.23$).

Exercise Performance

The analysis on exercise performance compromised 153 subjects and 16 ESs, nested within 11 studies. Analysis using TT as the outcome variable revealed no significant impact of nitrate supplementation on exercise performance ($ES = -0.05$; 95% CI: -0.28 to 0.17 ; $p = 0.64$) (Figure 3). Subgroup analysis revealed no significant effect in trained subjects ($ES = -0.04$; 95% CI: -0.28 to 0.20 ; $p = 0.8$) (Figure 4A) and a small, insignificant effect ($ES = -0.21$; 95% CI: -0.93 to 0.51 ; $p = 0.6$) in untrained subjects (Figure 4B). No significant effect was found following the subgroup analyses by supplementation dose or duration. The effect size for larger dose was 0.03 (95% CI: -0.27 to 0.34 ; $p = 0.84$), whereas the ES for the smaller dose was -0.16 (95% CI: -0.50 to 0.18 ; $p = 0.35$). A longer supplementation duration had an ES of -0.16 (95% CI: -0.59 to 0.28 ; $p = 0.48$), whereas a shorter duration showed an ES of -0.02 (95% CI: -0.28 to 0.25 ; $p = 0.9$).

Exercise Performance in Hypoxia

The analysis on exercise performance in hypoxia compromised 42 subjects and 4 ESs, nested within 4 studies. Analysis using TT as the outcome variable revealed no significant impact of nitrate supplementation on exercise performance in hypoxia compared with placebo ES -0.12 (95% CI: -0.56 to 0.31 ; $p = 0.58$).

Heterogeneity and Inconsistency

No significant heterogeneity or inconsistency was observed for exercise tolerance ($Q\ 3.66$ [$p = 1.00$], $I^2 = 0.00\%$) or exercise performance ($Q\ 8.22$ [$p = 0.91$], $I^2 = 0.00\%$).

DISCUSSION

The primary purpose of this study was to systematically review the current literature and evaluate the overall efficacy of nitrate supplementation on exercise tolerance and performance by meta-analysis. The pooled analysis for the effect of nitrate supplementation on exercise tolerance using TTE and GXT protocols showed a small, significant ES compared with placebo. However, there was no significant effect of nitrate supplementation on exercise performance using TT protocols.

Hoon et al. (20) analyzed 17 studies investigating the effect of nitrate on exercise performance in 2012. Several trials on the effects of nitrate supplementation on exercise tolerance and performance have since been conducted warranting an

updated systematic review and meta-analysis. Moreover, subanalyses of factors likely to influence the efficacy of nitrate supplementation (i.e., training status) were not performed. There were also instances where Hoon et al. may have used *SE* in the calculation of ES rather than *SD* in a few of the studies.

Constant or graded work-rate tests continued to the point of exhaustion were the primary modality used to assess exercise tolerance. The demands of these tests are not always applicable to competitive sports that generally require athletes to complete a specific distance as quick as possible. However, the increased TTE of 15% demonstrated by Bailey et al. (6) may translate to a meaningful 1.0% improvement in TT performance (21). Therefore, this potential improvement in TT performance may go undetected, which may explain why the current meta-analysis found no significant benefit of nitrate supplementation relative to placebo on exercise performance.

A secondary purpose of this meta-analysis was to determine if the ES of nitrate supplementation on exercise tolerance and performance was modified by athlete training status. Results from our subgroup analysis suggested that training status may influence the effectiveness of nitrate supplementation on exercise tolerance and performance. Of the 20 ES compromising the exercise tolerance analysis, only 3 were classified as trained while the remaining 17 were considered untrained. In contrast, of the 16 ES comprising the exercise performance analysis, only 2 were classified as untrained while the remaining 14 were considered trained.

The lack of effect in trained athletes may be because under hypoxic and ischemic conditions, the reduction of nitrate to NO is enhanced. To this effect, training increases muscle capillarity, which preserves muscle oxygenation and upregulates NOS activity under most conditions, resulting in a decreased reliance on the nitrate-nitrite-NO pathway (1). Another possibility is that well-trained endurance athletes are largely adapted to their specialist discipline. This might limit the potential ergogenic effects of supplemental nitrate on mitochondrial efficiency or skeletal muscle contractility.

Finally, because training enhances the production of NO via the NOS pathway, well-trained individuals have higher baseline levels of nitrite than untrained individuals (30). On this note, Poveda et al. (37) found that plasma nitrite was 158% higher in endurance athletes compared with untrained control subjects (4.9 vs. $1.9\ \mu\text{M}$, respectively). It would also be expected that athletes consume a varied diet—including nitrate-rich vegetables—to meet caloric needs. Collectively, this means that increased endogenous production of nitrite and dietary consumption of nitrate-rich foodstuffs would leave additional nitrate through supplementation of little benefit.

Indeed, Porcelli et al. (36) evaluated the effects of nitrate supplementation on running performance in subjects with varying levels of aerobic fitness. Subjects were divided into 3 groups based on their $\dot{V}O_{2\text{peak}}$: low aerobic fitness,

$\dot{V}O_{2\text{peak}}$ range, 28.2–44.1 ml·kg⁻¹·min⁻¹; moderate aerobic fitness, $\dot{V}O_{2\text{peak}}$ range, 45.5–57.1 ml·kg⁻¹·min⁻¹; and high aerobic fitness, $\dot{V}O_{2\text{peak}}$ range, 63.9–81.7 ml·kg⁻¹·min⁻¹. After 6 days of nitrate supplementation (5.5 mmol), low and moderate aerobically trained subjects completed a 3-km TT 1–4% faster, where no improvement was found in high aerobically trained subjects compared with placebo. However, although much of evidence in trained athletes demonstrates that nitrate supplementation does not improve exercise tolerance or performance, there is evidence to suggest the existence of “responders” and “nonresponders” within trained subjects (9,16,44). Specifically, despite no significant effect for cohort means, some trained subjects improve exercise performance after nitrate supplementation. Presumably, this may be the result of variability in oral nitrate reductase activity to reduce nitrate to nitrite (23).

Because trained athletes have higher baseline plasma nitrite and nitrate levels, it has been suggested that a larger dose would be needed to elicit ergogenic effects (23). Wylie et al. (47) investigated the dose-response relationship between nitrate supplementation and the physiological effects associated with exercise. Using 3 different nitrate doses, they found that plasma nitrate and nitrite increased in a dose-dependent manner up to 16.8 mmol of nitrate. It was found that 8.4 and 16.8 mmol, but not 4.2 mmol, of nitrate administered 2.5 hours pretest increased TTE by 14 and 12%, respectively, during severe-intensity exercise. These results suggest no benefit of a small (4.2 mmol) or no further benefit with a larger (16.8 mmol) dose, at least in recreationally active men. Similarly, in a study using well-trained rowers, Hoon et al. (19) found that a high dose (8.4 mmol) resulted in a probable improvement in 2,000-m rowing performance but not a smaller (4.2 mmol) dose. Subgroup analysis by dose of our meta-analysis suggested similar findings showing that a larger nitrate dose had a significant effect on exercise tolerance ES 0.28 (95% CI: 0.04–0.52; $p = 0.02$) but not a smaller dose ES 0.27 (95% CI: –0.01 to 0.57; $p = 0.06$) despite similar ES. However, subgroup analysis on the determinants of nitrate dose on exercise performance found no significant differences between a smaller or larger dose.

The bioavailability of nitrate from beetroot is around 100% and plasma concentrations of nitrate peak around 1 to 2 hours (T_{max} of 1.7 ± 0.5 hours) with a plasma half-life of ~6 hours ($T_{1/2}$ of 6.1 ± 0.9 hours) demonstrating the acute effects of nitrate supplementation (44). However, it is suggested that longer durations of exposure to nitrate supplementation may favorably modify intracellular calcium handling and enhance mitochondrial protein expression (27). Vanhatalo et al. (42) looked at the effects of acute and prolonged beetroot juice supplementation (up to 15 days) containing 4.84 mmol of nitrate per day. When compared with placebo, ramp test performance remained unchanged 2.5 hours and 5 days after nitrate supplementation, but there was a significant increase in peak power output at

the gas exchange threshold after 15 days of beetroot supplementation. However, it is unknown whether long-term (<15 days) nitrate supplementation may increase (or attenuate) the physiological benefits compared with short-term (≤ 3 days) supplementation. Studies included in the present meta-analysis used acute (2–3 hours pretest), short-term (3 days), and long-term (up to 15 days) nitrate duration supplementation. Subgroup analysis of nitrate supplementation duration showed little difference between longer duration (> 3 days) compared with shorter duration (≤ 3 days) in exercise tolerance. Similarly, no significant differences in exercise performance were found with longer duration compared with shorter duration nitrate supplementation.

When sea-level residents are exposed to acute environmental hypoxic conditions, pulmonary NO significantly decreases, suggesting a maladaptive response (12). Theoretically, increasing blood flow to improve oxygen delivery could offset the low supply of oxygen in the air. To this effect, it has been suggested that supplementing with inorganic nitrate may exert ergogenic effects in hypoxic conditions. At high altitude, the L-arginine pathway is unable to optimally generate NO, making the nitrate-nitrite-NO pathway important (4). This pathway can facilitate NO production through an increase in generation and reduction of nitrate and nitrite via deoxyhemoglobin and deoxymyoglobin (39), both of which are more available when blood oxygen saturation is decreased. Although several studies favored nitrate over placebo, pooled analysis showed no significant benefit on exercise tolerance or performance under hypoxic conditions—most likely because of the wide CIs. Similar to normoxic conditions, individual training status seems to influence the effectiveness of nitrate supplementation on exercise tolerance and performance. Vanhatalo et al. (43) was among the first to report that nitrate supplementation has the potential to negate the ergolytic effects of exercise tolerance in a hypoxic environment compared with the same exercise in normoxia. More specifically, the recreationally active subjects increased TTE during high-intensity knee extensor exercise by 21% with nitrate supplementation. Masschelein et al. (29) reported that under hypoxic conditions (stimulated 5,000 m altitude) TTE during a cycle incremental test was decreased by 36%. After nitrate supplementation, this ergolytic effect was eliminated by 5% compared with placebo. In regards to the effects of nitrate supplementation on exercise performance in hypoxia, many studies (2,10,28) suggest no benefit, with one study showing improved performance (32). Nonetheless, using nitrate before high-intensity training or events may represent an effective strategy to at least offset some of the deleterious effects of a hypoxic environment on exercise performance.

In certain analyses, only 3 to 4 studies were used to determine ES. Theoretically, only 2 studies are needed to conduct a meta-analysis. With that said, however, this low number of observations may lead to inaccurate estimates in which careful interpretation of the results is warranted.

Furthermore, although no significant heterogeneity was detected in the studies included for the meta-analysis, there were considerable differences in study design. Some studies asked subjects to refrain from consuming nitrate-rich foods throughout the duration of the study, whereas other studies did not restrict the consumption of nitrate-rich foods to subjects. On this note, it is possible that restricting habitual dietary intake of nitrate-rich foods lowers baseline plasma nitrite, thereby augmenting the effects observed when nitrate is then supplemented.

For example, individuals following a vegetarian or vegan dietary pattern have low levels of intramuscular creatine because they do not consume striated tissue foods, the primary dietary source of creatine for humans. But with creatine supplementation, the ergogenic effects of creatine on sports performance are more pronounced in these individuals (13). Conversely, those who consume high amounts of meat products may already have high levels of intramuscular creatine and therefore may not respond as greatly to supplementation. Furthermore, differences in exercise mode, duration, and intensity in addition to individual subject training status made it challenging to interpret the results and devise practical recommendations.

PRACTICAL APPLICATIONS

Ergogenic aids are frequently used by athletes to maximize performance. Thus, it is prudent that athletes are informed about the legality of these supplements, acknowledge any associated risk of consumption, and understand whether the totality of the literature supports the efficacy of these products. The strength and conditioning professional is in a unique position to educate athletes in this regard because it relates to dietary nitrate supplementation.

This meta-analysis shows that nitrate supplementation increases tolerance and efficiency to high-intensity constant and maximal incremental exercise, which may increase exercise performance. Doses ranging from 5 to 9 mmol of nitrate seem to be the most effective and can be taken as either a single bolus or as multiple doses (up to 15 days). This amount (5–9 mmol) can easily be met through a normal diet consisting of vegetables, with beetroot, spinach, and rocket (roguia) representing the richest sources of dietary nitrate. Natural sources of vegetable nitrates are likely safe and should remain the primary vessel for those looking to explore the physiological effects of nitrate associated with exercise. In contrast, the uncontrolled use of organic nitrates (nitroglycerin) and nitrite salts is potentially hazardous and should be avoided. It would also be important to consider the type of athlete performing the exercise, the duration, intensity, and mode of the exercise performed as these factors are likely to influence the efficacy of nitrate supplementation.

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