# **RESEARCH ARTICLE**

# The effects of dietary nitrate supplementation on endurance exercise performance and cardiorespiratory measures in healthy adults: a systematic review and meta-analysis

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# Abstract

**Background:** Nitrate supplementation is thought to improve performance in endurance sports.

Objective: To meta-analyze studies evaluating the effect of nitrate supplementation on endurance sports performance among adults.

Data sources: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Web of Science and CINAHL without language restrictions.

Methods: We included studies that: 1) compared nitrate supplementation with placebo; 2) enrolled adults engaging in an endurance-based activity; and 3) reported a performance measure or surrogate physiologic outcome. We evaluated risk of bias using the Cochrane Collaboration tool and pooled data with a random-effects model. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate confidence in estimates.

**Results:** We included 73 studies (n = 1061). Nitrate supplementation improved power output (MD 4.6 watts, P < 10000.0001), time to exhaustion (MD 25.3 s, P < 0.00001), and distance travelled (MD 163.7 m, P = 0.03). We found no significant difference on perceived exertion, time trial performance and work done. Nitrate supplementation decreased VO<sub>2</sub> (MD – 0.04 L/min, P < 0.00001) but had no significant effect on VO<sub>2max</sub> or blood lactate levels.

**Conclusion:** The available evidence suggests that dietary nitrate supplementation benefits performance-related outcomes for endurance sports.

Keywords: Nitrate supplementation, Endurance exercise, Systematic review and meta-analysis

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# Strengths and limitations of this study

- Systematic review and meta-analysis of randomized studies with a comprehensive search strategy and pre-specified protocol
- Rigorous methods and systematic evaluation of randomized data
- Insufficient details on randomization procedures in study reports, leading to unclear risk of bias
- Heterogeneity in study methodologies and outcome reporting

# Background

Endurance capacity is an important component of physical fitness that relates to the ability of the circulatory and respiratory systems to support sustained physical activity [1]. The performance of athletes training and competing in sports such as distance running, triathlons, swimming, biking and rowing depends on their endurance capacity [2, 3]. Different macronutrients and micronutrients have been used as ergogenic aids to potentially improve performance [4]. Specifically, nitrates are thought to potentially improve athletic performance. Beetroot juice, pomegranate extract and green leafy vegetables such as collard greens, lettuce, and spinach constitute substantial sources of dietary nitrate [5]. While the exact mechanism underlying the ergogenic benefits of nitrate supplementation has not yet been established, it has been proposed that dietary nitrate, once ingested, is reduced to nitric oxide (NO). Classically, NO was thought to be generated by

oxidation of L-arginine, resulting in endogenous production of nitrate (NO3-) and nitrite (NO2-). A vasodilator, it is believed to influence muscle function by modulating skeletal muscle function through its role in blood flow regulation, contractility, glucose and calcium homeostasis, and mitochondrial biogenesis [5]. Increased levels of NO in tissues and peripheral circulation may lead to improved oxygen transport and uptake in muscles during exercise [3, 6]. Figure 1 gives details on the potential mechanisms that nitrate supplementation can, eventually, result in improved physical performance.

While animal studies (in dogs, cats and horses) have demonstrated that reduction in endogenous NO production increases oxygen consumption (VO2), controversy remains in human performance. In fact, recent research suggesting nitrate supplementation may have performance benefits has resulted in its increased popularity among individuals attempting to improve their athletic performance [7]. However, the results of primary investigations examining nitrate supplementation have been inconsistent, with some studies suggesting a benefit ([8– 11]) and others no effect ([12–15]). In reviewing these studies, along with input from elite athlete (co-author, RC), we decided to focus on power output, time to exhaustion, and VO2, among others as metrics of athletic performance.

This systematic review and meta-analysis aimed to summarize the placebo-controlled trials evaluating dietary nitrate supplementation's effect on endurance exercise performance.



# Methods

# Identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Web of Science and CINAHL from inception to February 2021 without language restrictions (Search strategy – Supplementary Table 1).

### Study inclusion and selection

We included comparative studies that examined the effect of dietary nitrate supplementation on endurance activities. We performed title and abstract screening independently and in duplicate using the Covidence online software (Veritas Health Innovation, Melbourne, Australia). If either reviewer deemed a study relevant, we retrieved it for full-text review. We resolved disagreements between reviewers regarding eligibility through discussion or third-party arbitration. Eligible studies had to meet the following criteria:

The population of interest was healthy adults (over the age of 18) participating in endurance-based activities, including: distance running, rowing, cycling, swimming, kayaking, and triathlon. The study had to examine at least one source of dietary nitrate, to compare it to no exposure, and to report on any one of the outcomes of interest: power output, time to exhaustion, rating of perceived exertion, time trial performance, distance travelled, work done, VO<sub>2</sub>, VO<sub>2max</sub>, or blood lactate.

The outcome of time to exhaustion is one of significant complexity. Studies varied in use of constant exercise versus incremental/gradual exercise test; this information was not readily available in all studies. As such, whenever possible, we recorded time to exhaustion for controls and nitrate supplementation for available increments and meta-analysed them together. This allowed a comparison (with limitations) of no nitrate to nitrate on time to exhaustion at all potential power outputs. Unfortunately, not enough studies explicitly stated incremental versus constant to conduct a sensitivity analysis.

#### Data collection and management

We performed data extraction independently and in duplicate using pre-piloted extraction forms. If there was a discrepancy, a third party reviewed the data.

# Risk of bias assessment for RCTs

We judged risk of bias as "low, "high" or "unclear" using the Cochrane Collaboration Risk of Bias Tool [16]. Two independent reviewers evaluated each trial for six aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting and other sources of bias. If all aspects were considered to have "low" risk of bias, we considered the study at "low" risk. If even one aspect or more was considered to have "unclear" risk of bias, we considered the paper at "unclear" risk. Studies with at least one aspect considered to have "high" risk of bias were considered at "high" risk.

# Summary measures of treatment effect and unit of analysis

We analysed data using RevMan 5.3. Expecting heterogeneity among studies, we used a random effects model to pool results and summarize evidence. We evaluated the clinical, methodological and statistical heterogeneity of the included studies to assess whether pooling data was appropriate. We pooled studies using the DerSimonian and Laird method and planned to analyse RCTs and observational studies separately. We presented point estimates as mean difference (MD), with 95% confidence interval (CI).

# Summary measures of treatment effect and unit of analysis

We performed analyses using Review Manager 5.3 (RevMan 5.3). We expected heterogeneity among studies and applied a random effects model to pool relevant results and review the evidence. We presented all outcomes as mean differences (MD) with 95% confidence intervals (CI).

#### Assessment of heterogeneity

We used the chi-squared test for homogeneity and the  $I^2$  statistic to analyse for heterogeneity. We performed subgroups analyses (described later) to explain any heterogeneity observed.

#### **Publication bias**

We inspected the funnel plots for potential publication bias.

# Subgroups

We prespecified the following possible subgroups to explain possible heterogeneity within data:

- Dose: less than ~ 4 mmol per day versus more than ~ 4 mmol per day;
- 2. Duration of supplementation: single day versus multiple days;
- 3. Athletic level: sedentary, recreational athletes, and national–/international-level or elite athletes;
- 4. Source of dietary nitrate: beetroot juice, nitrate tablet/capsule/beetroot crystals, non-beet foods (pomegranate extract, watercress, red radish) and other (dissolved betaine, high nitrate diet, nitrate-rich gels, sodium nitrate dissolved in water);
- 5. Age profile: under 20 years of age, 20–29 years of age, and older than 30 years of age;

6. Study design: Randomized or non-randomized comparative study design.

In addition, we evaluated the following subgroups post-hoc:

- Co-supplementation with one of the following substances: L-arginine, sodium phosphate, caffeine, ultraviolet light A, sodium bicarbonate, N-acetylcysteine (NAC);
- 2. Risk of bias: high and unclear versus low risk of bias.

#### Assessment of confidence in pooled effect estimates

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate confidence in effect estimate s[17]. In the GRADE framework, RCTs are considered high-quality evidence, but they can be rated down for risk of bias, imprecision, inconsistency, indirectness or publication bias.

# Results

Figure 2 summarizes the screening and study selection process. We identified 17,048 citations for title and abstract screening and we reviewed the full-text of 449 studies. Seventy-three RCTs (n = 1061) met inclusion criteria, which we pooled [references provided in Supplemental Table 2]. Supplemental Table 2 summarizes the characteristics of the included studies. These trials were all placebo-controlled, single-centre, and examined nitrate-containing substances in a total of 1061 participants undergoing various endurancebased exercise tests. The participants ranged from sedentary to elite athletes in their level of athletic involvement, with the majority of participants characterized as recreationally active, healthy adults. The trials reported power output (28 studies), time to exhaustion (20 studies), rating of perceived exertion (20 studies), time trial performance (28 studies), distance travelled (2 studies), work done (4 studies), VO<sub>2</sub> (42 studies), VO<sub>2max</sub> (10 studies), and blood lactate (23 studies).



Three trials were at low risk of bias, while the remaining trials were at high risk of bias due to unclear descriptions of random sequence generation and/or allocation concealment. Table 1 presents the quality of evidence assessment for each outcome.

# Power output (Fig. 3)

Nitrates led to an increase in power output compared placebo (MD 4.59 watts, 95% CI [2.6, 6.58], 95%CI, P < 0.0001,  $I^2 = 0\%$ , low-quality evidence). We downgraded the quality of evidence for serious risk of bias and suspected publication bias (Table 1).

## Time to exhaustion (Fig. 4)

Nitrates increased the time to exhaustion compared to placebo (MD 25.27 s, 95% CI [12.69, 37.84], P < 0.00001,  $I^2 = 38\%$ , low-quality evidence). We downgraded the quality of evidence for serious risk of bias and suspected publication bias (Table 1).

# Distance travelled (Fig. 5)

Participants in the nitrate group had a travelled 163.7 m further compared to participants in the placebo group (MD 163.73 m, 95% CI [18.4, 309.1], P = 0.03,  $I^2 = 0\%$ ,

Table 1 Quality of Evidence - GRADE Assessment

very low-quality evidence). We downgraded the quality of evidence for serious risk of bias and very serious imprecision (Table 1).

# VO<sub>2</sub> (Fig. 6)

Participants in the nitrate group had a significant decrease in VO<sub>2</sub> compared to participants in the placebo group (MD – 0.04 L/min, 95% CI [– 0.05, – 0.02], P < 0.0001,  $I^2 = 0\%$ , low-quality evidence). We downgraded the quality of evidence for serious risk of bias and serious indirectness (Table 1).

# VO<sub>2max</sub> (Fig. 7)

Nitrates did not increase  $VO_{2max}$  compared with placebo (MD 0.04 L/min, 95% CI [-0.02, 0.10], P = 0.23,  $I^2 = 0\%$ , very low-quality evidence). We downgraded the quality of evidence for serious risk of bias, serious indirectness, and serious imprecision (Table 1).

# Rating of perceived exertion (Supplemental Fig. 1)

Nitrates did not affect the rating of perceived exertion (Borg scale) (MD -0.11, 95% CI [-0.34, 0.12], P = 0.36,  $I^2 = 62\%$ , very low-quality evidence). We downgraded the

Certainty assessment							Nº of p	atients	Effe	ct		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Power Outp	ut											
28	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected	535	527	-	MD 4.59 higher (2.6 higher to 6.58 higher)		
Blood Lacta	te											
23	randomised trials	serious	not serious	serious	serious	publication bias strongly suspected	424	424	•	MD 0.08 lower (0.21 lower to 0.05 higher)	⊕ VERY LOW	
Time to exh	austion											
20	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected	302	302		MD 26.04 higher (13.46 higher to 38.62 higher)		
VO2							-	-				
42	randomised trials	serious	not serious	serious	not serious	none	780	783	-	MD 0.04 lower (0.05 lower to 0.02 lower)		
Rating of Pe	erceived Exertion	ı										
20	randomised trials	serious	serious	not serious	serious	none	487	487	-	MD 0.11 lower (0.33 lower to 0.12 higher)	€ VERY LOW	
Time Trial P	erformance											
28	randomised trials	serious	not serious	not serious	serious	none	497	515	•	MD 1.98 lower (4.37 lower to 0.41 higher)		
Distance Tr	avelled											
2	randomised trials	serious	not serious	not serious	very serious	none	24	27	-	MD 163.73 higher (18.42 higher to 309.05 higher)		
Work Done												
4	randomised trials	serious	serious	not serious	not serious	none	48	40	-	MD 0.02 higher (0 to 0.04 higher)		
VO2 Max												
10	randomised trials	serious	not serious	serious	serious	none	143	143	-	MD 0.04 higher (0.02 lower to 0.1 higher)	URY LOW	

CI Confidence interval, MD Mean difference

		Vitrate		P	lacebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Aucouturier 2015	472.5	42.5	8	468.8	43.4	8	0.2%	3.70 [-38.39, 45.79]	
Bescos 2011	258	28	13	257	28	13	0.9%	1.00 [-20.53, 22.53]	
allahan 2017	388	54	8	386	55	8	0.1%	2.00 [-51.41, 55.41]	
allahan 2017	393	54	8	394	52	8	0.1%	-1.00 [-52.95, 50.95]	
ermak1 2012	275	7	20	278	7	20	21.0%	-3.00 [-7.34, 1.34]	
ermak2 2012	294	12	12	288	12	12	4.3%	6.00 [-3.60, 15.60]	+
hristensen 2013	630	84	10	630	92	10	0.1%	0.00 [-77.21, 77.21]	•
hristensen 2013	746	111	10	745	121	10	0.0%	1.00 [-100.77, 102.77]	•
hristensen 2013	290	43	10	285	44	10	0.3%	5.00 [-33.13, 43.13]	
rum 2018	262	49	8	265	49	8	0.2%	-3.00 [-51.02, 45.02]	
rum 2018	270	48	8	272	62	8	0.1%	-2.00 [-56.33, 52.33]	
loon 2014	400	48	26	396	57	26	0.5%	4.00 [-24,64, 32,64]	
loon 2014	396	45	26	397	56	26	0.5%	-1.00[-28.61.26.61]	
loriuchi 2017	257	22	9	233	25	ģ	0.8%	24 00 [2 24 45 76]	
loriuchi 2017	105	17	á	105	13	ă	2.0%	0.00[-13.98, 13.98]	
n 2017	152.3	30.9	14	146.9	373	14	0.7%	5 40 [-18 01 28 81]	
0 2017	148.8	40.4	15	146.6	42.8	15	0.4%	2 20 [-27 95 32 35]	
ally 2012	270.0	70.1	-1- G	218	75.0		0.7%	2.20 [-27.35, 32.35]	
romor 2016	049.09	196.9	12	210	157 22	12	0.0%	42 09 [-05 07 191 22]	
ramer 2016	77750	110 02	12	776 09	05 21	12	0.0%	1 50 1 94 72 97 721	
namer 2010	757.20	110.95	12	750.00	90.51 41	12	0.1%	1.50 [-04.75, 07.75]	•
ane 2014	298	30	12	303	41	12	0.4%	-5.00 [-35.50, 25.50]	
ane 2014	207	31	12	207	29	12	0.7%	0.00 [-24.02, 24.02]	
ane 2014	314	44	12	313	38	12	0.4%	1.00 [-31.89, 33.89]	
ane 2014	212	27	12	216	34	12	0.7%	-4.00 [-28.56, 20.56]	
arsen 2007	360.6	32.8	9	358.9	32.3	9	0.4%	1.70 [-28.38, 31.78]	
IcQuillan 2017	423	31	9	429	31	9	0.5%	-6.00 [-34.64, 22.64]	
IcQuillan 2017	380	41	9	375	40	9	0.3%	5.00 [-32.42, 42.42]	
IcQuillan 2018	337	50	8	336	45	8	0.2%	1.00 [-45.61, 47.61]	
leamarbashi 2014	139.5	21	22	130	26	14	1.5%	9.50 [-6.70, 25.70]	
luggeridge 2013	108	23	8	108	22	8	0.8%	0.00 [-22.06, 22.06]	
luggeridge 2013	420	23	8	404	24	8	0.7%	16.00 [-7.03, 39.03]	
luggeridge 2014	224	6	9	216	6	9	12.9%	8.00 [2.46, 13.54]	
lumford 2018	231.6	36.2	28	225.3	35.8	28	1.1%	6.30 [-12.56, 25.16]	
orcelli 2016	74	5	7	74	5	7	14.4%	0.00 [-5.24, 5.24]	
uype 2015	147	5	11	134	5	11	22.6%	13.00 [8.82, 17.18]	-
ienks 2015	106	18	9	104	21	9	1.2%	2.00 [-16.07, 20.07]	
imer 2016	1,229	317	13	1,213	300	13	0.0%	16.00 [-221.25, 253.25]	•
okkedal-Lausch 2019	269.3	13.2	12	264.4	13.2	12	3.5%	4.90 [-5.66, 15.46]	
okkedal-Lausch 2019	315.8	13.2	12	311.3	13.2	12	3.5%	4.50 [-6.06, 15.06]	- <del>-</del>
anhatalo 2010	331	68	8	323	68	8	0.1%	8.00 [-58.64, 74.64]	· · · · · · · · · · · · · · · · · · ·
/ilkerson 2012	238	22	8	235	27	8	0.7%	3.00 [-21.13, 27.13]	<del></del>
Mie 2016	374	57	10	375	59	10	0.2%	-1.00 [-51.85, 49.85]	
ylie 2016	568	136	10	539	136	10	0.0%	29.00 [-90.21, 148.21]	•
Vie 2016	792	159	10	782	154	10	0.0%	10.00 [-127.19, 147.19]	•
Mie 2016	768	157	10	776	142	10	0.0%	-8.00 [-139.20, 123.20]	• •
Vylie 2016	558	95	10	562	94	10	0.1%	-4.00 [-86.83, 78.83]	• •
otal (95% CI)			535			527	100.0%	4.59 [2.60, 6.58]	• .
ieterogeneity: Tau4 = 0. 'est for overall effect: Z	00; Chi <sup>2</sup> = = 4.52 (P	< 0.0000	df = 45 01)	(P = 0.7	$0); 1^{2} = 0$	6			-50 -25 0 25 50

studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data

quality of evidence for serious risk of bias, serious inconsistency, and serious imprecision (Table 1).

Time trial performance (Supplemental Fig. 2)

Time trials appeared unchanged with and without nitrates (MD – 1.98 s, 95% CI [– 4.37, 0.41], P = 0.1,  $I^2 = 8\%$ , low-quality evidence). We downgraded the quality of evidence for serious risk of bias and serious imprecision (Table 1).

# Work done (Supplemental Fig. 3)

Nitrates did not significantly increase work done compared with placebo (MD 0.02 kJ, 95% CI [0.0, 0.03], p = 0.09,  $I^2 = 0\%$ , low-quality evidence). We downgraded the

# Blood lactate (Supplemental Fig. 4)

Nitrates did not significantly decrease blood lactate compared with placebo (MD – 0.08 mM, 95%CI [– 0.21, 0.05], P = 0.22,  $I^2 = 12\%$ , very low-quality evidence). We downgraded the quality of evidence for serious risk of bias, serious indirectness, serious imprecision, and suspected publication bias (Table 1).

quality of evidence for serious risk of bias and serious in-

# Subgroup analyses

consistency (Table 1).

We attempted to perform subgroup analyses according to the length of dosing, athletic level, source of dietary nitrate, mean age profile, co-supplementation, and risk



of bias. The available data were insufficient to perform subgroup analyses based on the daily dose of nitrate. We identified only one statistically interaction – an interaction (p = 0.005) between athletic level and treatment on VO<sub>2</sub>, with no significant effect of nitrate supplementation in elite (MD 0.01, 95% CI [- 0.02, 0.04]) or sedentary athletes (MD 0.06, 95% CI [- 0.16, 0.29]), but a significant effect in recreational athletes (MD -0.05, 95% CI [- 0.07, - 0.03]) (Supplemental Figure 5).

# Discussion

We meta-analyzed the results of 73 trials including participants undergoing various endurance-based exercise tests either with or without nitrate supplementation. Nitrate supplementation improved power output, time to exhaustion, and distance travelled, but did not impact perceived exertion, time trial performance, work done generation of lactate, or  $VO_{2max}$ . Nitrates led to a reduction in VO2 at different exercise intensities. Therefore, the existing randomized data suggests that nitrate supplementation improves endurance exercise performance by reducing the oxygen cost of the exercise.

Dietary nitrate supplementation may enhance muscle function and exercise performance through the nitratenitrite-NO pathway. Dietary inorganic nitrate intake increases circulating nitrate levels, which is then reduced to bioactive nitrite by facultative anaerobic bacteria in the saliva, and subsequently converted into NO in the acidic environment of the stomach. The NO generated via this pathway supplements endogenous NO, produced by oxidation of circulating L-arginine. Further, after nitrate ingestion, plasma nitrate and nitrite concentrations peak after a few hours, and both gradually fall to baseline values in approximately 24 h. Subsequently, many



		litrate		Placebo				Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Arnold 2015	2.0878	0.1606	10	2.0878	0.1606	10	1.4%	0.00 [-0.14, 0.14]			
Aucouturier 2015	2.735	0.345	12	2.787	0.346	12	0.4%	-0.05 [-0.33, 0.22]			
Bailey 2009 Bailey 2009	2.40	0.13	8	1.52	0.12	8	1.8%	-0.07 [-0.19, 0.05]			
Bescos 2011	3.63	0.33	13	3.63	0.26	13	0.5%	0.00 [-0.23, 0.23]			
Betteridge 2016	2.325	0.075	8	2.33	0.07	8	5.4%	-0.00 [-0.08, 0.07]	-+-		
Bourdillon 2015	0.367	0.065	12	0.339	0.093	12	6.6%	0.03 [-0.04, 0.09]			
Bourdillon 2015	0.404	0.06	12	0.402	0.044	12	15.4%	0.00 [-0.04, 0.04]	+		
Breese 2013 Breese 2017	3.09	0.51	9	3.12	0.51	9	0.1%	-0.03 [-0.50, 0.44]			
Cermak2 2012	1.93	0.05	12	2.50	0.07	12	11.6%	-0.07 [-0.12, -0.02]			
Cermak2 2012	2.94	0.1	12	3.1	0.09	12	4.7%	-0.16 [-0.24, -0.08]			
Christensen 2013	4.083	0.297	10	4.106	0.359	10	0.3%	-0.02 [-0.31, 0.27]			
Crum 2017	5.37207	0.42559	8	5.07496	0.44968	8	0.1%	0.30 [-0.13, 0.73]	· · · · · · · · · · · · · · · · · · ·		
Crum 2017	5.50055	0.57816	12	5.621	0.50589	8	0.1%	-0.12 [-0.65, 0.41]			
Cholami 2019	2.9	0.5	10	2.9	0.4	10	0.3%	-0.09[-0.28, 0.28]	·		
Glaister 2015	2.69	0.42	14	2.77	0.32	14	0.4%	-0.08 [-0.36, 0.20]			
Glaister 2015	2.67	0.32	14	2.63	0.41	14	0.4%	0.04 [-0.23, 0.31]			
Handzlik 2013	3.9	0.45	14	4	0.4	14	0.3%	-0.10 [-0.42, 0.22]			
Handzlik 2013	2.9	0.4	14	2.8	0.3	14	0.4%	0.10 [-0.16, 0.36]			
Handzlik 2013	2.8	0.4	14	2.8	0.4	14	0.3%	0.00 [-0.30, 0.30]			
Horiuchi 2017	1.382	0.225	9	2.442	0.185	9	0.8%	-0.06 [-0.25, 0.13]			
Kelly 2013	4 369	0.337	9	4 382	0.277	9	0.3%	-0.01[-0.29_0.27]			
Kelly 2013	4.222	0.32	9	4.115	0.425	9	0.2%	0.11[-0.24, 0.45]			
Kelly 2013	4.18	0.39	9	4.119	0.42	9	0.2%	0.06 [-0.31, 0.44]			
Kelly 2013	4.499	0.371	9	4.405	0.476	9	0.2%	0.09 [-0.30, 0.49]			
Kelly 2014	4.721	0.434	12	4.814	0.47	12	0.2%	-0.09 [-0.45, 0.27]			
Kelly 2014 Kelly 2014	1.905	0.275	12	2.049	0.247	12	0.6%	-0.14 [-0.35, 0.07]			
Kelly 2014 Kelly 2014	3.751	0.249	12	3.986	0.5	12	0.5%	-0.24 [-0.46, -0.01]			
Lansley 2014	2.908	0.34	9	2.26	0.251	9	0.3%	-0.16[-0.41_0.09]			
Lansley 2011	3.5	0.62	9	3.77	0.57	9	0.1%	-0.27 [-0.82, 0.28]	←		
Larsen 2007	4.49	0.44	9	4.61	0.28	9	0.2%	-0.12 [-0.46, 0.22]			
Larsen 2011	1.89	0.1	14	1.95	0.09	14	5.5%	-0.06 [-0.13, 0.01]			
Masschelein 2012	1.95	0.06	15	2.03	0.06	15	14.8%	-0.08 [-0.12, -0.04]			
Masschelein 2012	2.79	0.11	15	2.88	0.14	15	3.4%	-0.09 [-0.18, 0.00]			
McQuillari 2017 Meamarhashi 2014	4.7	0.55	11	3.05	0.34	14	0.2%	0.06 [-0.36, 0.48]			
Muggeridge 2013	2.85868	0.20075		2.95504	0.19272	8	0.7%	-0.10 [-0.29, 0.10]			
Muggeridge1 2014	2.9	0.209	9	2.924	0.181	9	0.8%	-0.02 [-0.20, 0.16]			
Muggeridge1 2014	2.919	0.179	9	2.972	0.171	9	1.0%	-0.05 [-0.21, 0.11]			
Nyback 2017	4.09	0.81	8	4.17	0.81	8	0.0%	-0.08 [-0.87, 0.71]	· · · · · · · · · · · · · · · · · · ·		
Nyback 2017 Nyback 2017	3.47	0.54	8	3.D 270	0.58	8	0.1%	-0.03 [-0.58, 0.52]			
Nyback 2017	3.48	0.57	8	3.47	0.55	8	0.1%	0.01 [-0.54, 0.56]			
Nyback 2017	2.94	0.51	8	2.94	0.53	8	0.1%	0.00 [-0.51, 0.51]			
Nyback 2017	2.92	0.48	8	2.9	0.49	8	0.1%	0.02 [-0.46, 0.50]			
Porcelli 2015	5.51	0.64	6	5.57	0.64	6	0.1%	-0.06 [-0.78, 0.66]	· · · · · · · · · · · · · · · · · · ·		
Porcelli 2015 Porcelli 2015	2.13	0.4	8	2.04	0.38	8	0.2%	0.09 [-0.29, 0.47]			
Porcelli 2015 Porcelli 2016	1 178	0.47	7	1 2 6 9	0.49	7	1.3%	-0.03 [-0.33, 0.47]			
Rienks 2015	1.5	0.2	9	1.51	0.23	9	0.7%	-0.01 [-0.21, 0.19]			
Rokkedal-Lausch 2019	4.443	0.139	12	4.364	0.14	12	2.2%	0.08 [-0.03, 0.19]	+		
Rokkedal-Lausch 2019	3.948	0.142	12	3.855	0.142	12	2.1%	0.09 [-0.02, 0.21]			
Rossetti 2017	1.7	0.3	20	1.69	0.29	20	0.8%	0.01 [-0.17, 0.19]			
Sandbakk 2015 Sandbakk 2015	3.825 7.97	0.55	9	3.8/	0.46	9	0.1%	-0.04 [-0.51, 0.42]			
Shannon 2016	1.47752	0.9636	12	1.63812	1.01178	12	0.0%	-0.16[-0.95, 0.63]	· · · · · · · · · · · · · · · · · · ·		
Shannon 2017	1.38116	0.31317	10	1.45343	0.31317	10	0.4%	-0.07 [-0.35, 0.20]			
Shannon 2017	2.77838	0.50589	10	2.73823	0.43362	10	0.2%	0.04 [-0.37, 0.45]			
Shannon 2017	2.409	0.31317	10	2.38491	0.41756	10	0.3%	0.02 [-0.30, 0.35]			
Shannon 2017	1.41328	0.3212	10	1.48555	0.33726	10	0.3%	-0.07 [-0.36, 0.22]			
Van Hoorebeke 2016	2.01	0.50027	13	0.347105	0.4/38/	13	0.4%	-0.00 [-0.27, 0.26]			
Vanhatalo 2010	1.37	0.23		1.43	0.23	8	0.5%	-0.06 [-0.29, 0.17]			
Wickham 2019	1.259	0.161	12	1.254	0.157	12	1.7%	0.00 [-0.12, 0.13]			
Wickham 2019	1.252	0.144	12	1.267	0.155	12	1.9%	-0.01 [-0.13, 0.10]			
Wilkerson 2012	3.6	0.4	8	3.7	0.4	8	0.2%	-0.10 [-0.49, 0.29]			
Wylle 2016	3.23	0.28	10	3.22	0.24	10	0.5%	0.01 [-0.22, 0.24]			
Wyle 2016	1.76 7 99	0.16	10	1.74	0.15	10	1.5%	-0.02 [-0.12, 0.16]			
THE EVEN	2.99	0.29	10	5.02	V.10	10	0.070	0.00 [ 0.27, 0.10]			
Total (95% CI)			765			768	100.0%	-0.04 [-0.05, -0.02]	•		
Heterogeneity: $Tau^2 = 0.09$	0; Chi <sup>2</sup> = 53	3.85, df =	72 (P =	0.95); l <sup>2</sup> =	0%				-05 -025 0 025 05		
Test for overall effect: Z =	4.31 (P < 0	0.0001)							Favours Nitrate Favours Placebo		

**Fig. 6** Forest plot for VO<sub>2</sub> in litres/minute for nitrate supplementation versus placebo. Square markers represent mean difference for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data

		Nitrate		F	lacebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Arnold 2015	3.8544	0.3212	10	3.8544	0.4015	10	3.9%	0.00 [-0.32, 0.32]	
Balsalobre-Fernandez 2018	5.62903	0.5621	12	6.01447	0.48983	12	2.2%	-0.39 [-0.81, 0.04]	·
Cocksedge 2020	3.83	0.44	10	3.82	0.53	10	2.2%	0.01 [-0.42, 0.44]	
Gholami 2019	3.55	0.36	10	3.59	0.36	10	3.9%	-0.04 [-0.36, 0.28]	
Nyback 2017	4.56	0.95	8	4.68	0.97	8	0.4%	-0.12 [-1.06, 0.82]	• • • •
Nyback 2017	4.13	0.87	4	4.15	0.79	4	0.3%	-0.02 [-1.17, 1.13]	• • • • • • • • • • • • • • • • • • • •
Perez 2019	4.1	0.491436	20	4.0519	0.4866	20	4.3%	0.05 [-0.25, 0.35]	
Puype 2015	5.26768	0.16863	11	5.12314	0.12848	11	25.0%	0.14 [0.02, 0.27]	<b>_</b>
Rokkedal-Lausch 2019	4.895	0.15	12	4.925	0.151	12	27.1%	-0.03 [-0.15, 0.09]	
Rokkedal-Lausch 2019	4.305	0.152	12	4.225	0.152	12	26.6%	0.08 [-0.04, 0.20]	+
Torregrosa-Garcia 2019	3.87135	0.60634	26	3.95775	0.61271	26	3.6%	-0.09 [-0.42, 0.24]	
Vanhatalo 2010	3.5	0.82	8	3.42	0.88	8	0.6%	0.08 [-0.75, 0.91]	•
Total (95% CI)			143			143	100.0%	0.04 [-0.02, 0.10]	•
Heterogeneity: $Tau^2 = 0.00$ ; Test for overall effect: $Z = 1.2$	Chi <sup>2</sup> = 9.31, 20 (P = 0.23	, df = 11 (P 3)	= 0.59	9); I <sup>2</sup> = 0%					-0.5 -0.25 0 0.25 0.5 Favours Placebo Favours Nitrate

confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data

enzymes and proteins, such as deoxyhemoglobin catalyze nitrite to NO in blood and other tissues. This process is facilitated in conditions of low oxygen availability (ischemia and hypoxia), enabling NO production where it is most required; these conditions may exist in skeletal muscle during endurance exercis e[18]. By mediating smooth muscle relaxation, NO promotes vasodilation, increasing oxygen delivery to skeletal muscles [19]. The subsequent improvements in type II muscle fiber function and efficiency have been implicated in dietary nitrate's positive effects on cardiorespiratory endurance [20].

This postulated mechanism for nitrates to improve muscle contraction efficiency is supported by our finding (albeit with low certainty) that dietary nitrate reduced VO<sub>2</sub>, or the oxygen cost of physical activity. These findings are also congruent with studies suggesting that dietary nitrate supplementation (pure sodium nitrate or beetroot juice) in young, healthy volunteers reduces the submaximal oxygen cost of a given intensity of muscle contractions [21]. Evidence also supports that nitrate supplementation may improve mitochondrial efficiency [21], calcium handling and contractile function [22], translating into higher fraction of oxygenated hemoglobin in muscle, as well as lower rate of whole-body oxygen uptake  $(VO_2)$ in endurance exercise. Our findings indicate that nitrate supplementation's effect is independent of the maximal oxygen uptake (VO2max), which is regarded as one of the best indicators of an athlete's physical capacity to work at a higher intensity for a longer period of time, among other factors [23]. As mentioned previously, assessing time to exhaustion is a nuanced outcome. While some studies may test the difference in time over a set distance traveled, others may test distance traveled over increments of time (as seen in graded or incremental exercise testing); both would produce significant differences in absolute values. For instance, an improvement of 25 s might be beneficial over 10 km, but may be even more important at 5 km. Even so, our approach to meta-analysing this outcome at all reported power outputs, along with lack of heterogeneity ( $I^2 = 0\%$ ), does demonstrate that the increase in time to exhaustion with nitrates is of note.

The significant interaction between athletic level and nitrate treatment may be a spurious finding or may relate to the benefit of nitrates being less dependent on muscle fibre efficiency in elite athletes which may already be optimized. In particular, we cannot draw conclusive inferences from this potential interaction as subgroup analyses are prone to type II errors, especially in a meta-analysis where subgroup analyses are not adjusted for multiplicity.

#### Strengths and limitations

Our systematic review and meta-analysis has several strengths: a comprehensive search strategy, the inclusion of randomized data, and a rigorous evaluation of the quality of evidence. However, it also has limitations. First, many studies lacked sufficient methodological details, which led us to adjudicate them at unclear or high risk of bias for evaluated outcomes. Second, the methods of included studies varied in terms of type of exercise test (wide variability in performance variables - in some cases time to exhaustion was a constant load, while in others, it was graded), participants' athletic background, forms and quantities of nitrate supplementation (wide variability of doses, dose routines and sources used), and cointerventions such as caffeine and ultraviolet-A light. Third, this included trials had small, select study populations and well-monitored adherence, which may limit external validity. Lastly, while we discuss dietary nitrates, with vegetables comprising 80% of naturally available sources, the included trials used a variety of commercially available nitrate supplementary products. These products contain a blend of nitrate-rich foods, extracts and other

ingredients, which may modulate nitrate bioavailabilit y[24]. As such, our results should be interpreted in context of commercial nitrate supplementation, rather than ingestion of natural foods.

# Athletes experience and perspective (Reid Coolsaet, Olympic Marathon 2012, 2016)

In 2011 I used beetroot juice in training and in five competitions. My protocol was to drink at least 500 ml of beetroot juice approximately 2–3 h before a competition or run. The competitions all went well as I met or exceeded expectations. Of course, it's impossible to credit beetroot supplementation alone as there are many variables that lead to successful competitions. I did experience GI distress, which was not problematic in the 10 km distance, slightly problematic competing in the half marathon distance, and problematic over the marathon distance. It was the GI distress that led me to stop supplementing with beetroot juice.

World Athletics lists 5 supplements that improve performance; caffeine, nitrate, creatine, B-alanine and bicarbonate [4]. For endurance sports, the two believed to be most effective are caffeine and nitrate. This metaanalysis suggests that the improvement in endurance activities from nitrates is significant, supporting the endorsement by the World Athletics Organization.

With the knowledge that multiple-day ingestion is effective and high nitrate doses are available commercially in smaller volumes, as an elite athlete I am interested in testing nitrate supplementation again. Future research should establish the best dosing strategy including how long before competition one can stop supplementing without losing the benefit.

# Conclusions

Based on very low- to moderate-quality, RCT data, this systematic review and meta-analysis suggests that dietary nitrate supplementation improves performance during endurance sports. This is especially evident when evaluating important outcomes, such as power output, time to exhaustion and distance traveled. However, given its mixed effects on explanatory variables, like blood lactate and VO<sub>2</sub>, further research is needed to determine the specific means by which nitrate supplementation impacts physical endurance and establish the optimal dosing strategy accounting for adverse GI effects that may accompany some formulations.

#### Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12970-021-00450-4.

Additional file 1: Supplemental Figure 1. Forest plot for rating of perceived exertion for nitrate supplementation versus placebo. Square

markers represent mean difference for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all metaanalyzed data. Supplemental Figure 2. Forest plot for time trial performance of nitrate supplementation versus placebo. Square markers represent mean difference for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all metaanalyzed data. Supplemental Figure 3. Forest plot for work done of nitrate supplementation versus placebo. Square markers represent mean difference for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data. Supplemental Figure 4. Forest plot of blood lactate levels with nitrate supplementation versus placebo. Square markers represent mean difference for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data. Supplemental Figure 5. Forest plot with subgroup analysis of VO2 with nitrate supplementation versus placebo, based on athletic level. Square markers represent mean difference for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data

Additional file 2: Supplementary Table 1. Search strategies and search terms used with various databases.

Additional file 3: Supplemental Table 2. Study Characteristics of Included Randomized Controlled Trials

#### Authors' contributions

Chloe Gao, Richard Whitlock, Emilie Belley-Cote developed the study question and study protocol; they also drafted the manuscript. Saurabh Gupta, Taranah Adli, Winston Hou, Reid Coolsaet, Abigail Hayes, Kevin Kim Arjun Pandey, Jacob Gordon and Gurneet Chahil provided the critical input on the protocol, collected data. Chloe Gao and Saurabh Gupta performed the analysis. All authors provided critical input on the final manuscript. The authors read and approved the final manuscript.

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#### Availability of data and materials

The authors will consider written requests for data.

### Declarations

#### Ethics approval and consent to participate

Ethics approval was not required for this systematic review.

#### Consent for publication

All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with ICMJE criteria.

#### **Competing interests**

Dr. Whitlock reports grants from Bayer, Roche, and Boeringer-Ingelheim outside the submitted work. He also reports speaker honorarium from Boeringer-Ingelheim and consultancy for AtriCure and PhaseBio outside the submitted work.

Dr. Belley-Cote reports grants from Bayer and Roche outside this submitted work.

The other authors have no conflict of interest.

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