Meta-Analysis

Addressing Methodological Gaps: A Systematic Review and Meta-Analysis of Beetroot Juice and Exercise Capacity in Chronic Obstructive Pulmonary Disease

Gaspar R. Chiappa[1,2,‡,*]; Alberto S. Sá Filho[2,3,‡]; Juliene Sá[2]; Amanda G. Duarte[4]; Gerson Ferrari[1,5]; Adriana Meira G. Chiappa[6]; Leticia de Araújo Morais[7]; Paulo T. Muller[8]; Luis Puente-Maestu[9]; Francisco Valdez Santos[10]; Rodolfo P. Vieira[2,3]; Davi A. Caixeta[2]; Vicente Aprigliano*[,11]; Victor Renault Vaz[12]

[1]Faculty of Health Sciences, Universidad Autónoma de Chile, Providencia, 7500912, Santiago, Chile; [2]Graduate Program in Human Movement and Rehabilitation, Evangelical University of Goiás, Anápolis, Brazil; [3]Graduate Program in Pharmaceutical Sciences, Pharmacology and Therapeutics, Evangelical University of Goiás, Anápolis, Brazil; [4]Universidade Federal de Minas Gerais, Departamento de Medicina, Belo Horizonte, Minas Gerais, Brazil; [5]Escuela de Ciencias de la Actividad Física, el Deporte y la Salud, Universidad de Santiago de Chile (USACH), Santiago 9170022, Chile; [6]Hospital de Clínicas de Porto Alegre, Physical Therapy Department, Porto Alegre, Brazil; [7]Physiotherapy Department, Estácio de Sá University Center of Goiás, Goiânia, Brazil; [8]Respiratory Physiopathology Laboratory, Federal University of Mato Grosso do Sul, Maria Aparecida Pedrossian Hospital, Campo Grande, Brazil; [9]Hospital General Universitario Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain; [10]Clinical Research Department, Cancer Institute of São Paulo, São Paulo, Brazil; [11]Escuela de Ingeniería de Construcción y Transporte, Pontificia Universidad Católica de Valparaíso, Valparaíso 2362804, Chile; [12]Medicine Department, Mount Auburn Hospital—Harvard Medical School, Cambridge, MA, United States

[‡]Author Contributions: Contributed equally to the development and finalization of the manuscript

*Corresponding Authors: Gaspar R. Chiappa, Faculty of Health Sciences, Universidad Autónoma de Chile, Providencia, 7500912, Santiago, Chile (Gaspar.chiappa@gmail.com) and Vicente Aprigliano, Escuela de Ingeniería de Construcción y Transporte, Pontificia Universidad Católica de Valparaíso, Avda Brasil 2147, Valvaraíso 2362804, Chile (Vicente.aprigliano@pucv.cl)

Background: *Despite numerous meta-analyses examining the effects of beetroot juice (BJ) supplementation on exercise capacity in patients with chronic obstructive pulmonary disease (COPD), significant methodological shortcomings persist, including failure to stratify findings by study design.*

Objective: *In this meta-analysis we aimed to assess the effects of BJ supplementation on exercise capacity and cardiovascular parameters in COPD patients, identifying methodological gaps by stratifying the results of parallel and crossover randomized clinical trials (RCTs).*

Data Sources: *We conducted a systematic search in Scopus, Lilacs, PubMed, Embase, Web of Science, CENTRAL, and Science Direct from database inception until December 30, 2024. We identified studies of the effects on of nitrate-rich BJ supplementation on exercise capacity and cardiovascular parameters in COPD patients.*

Data Extraction: *Data extraction was performed independently by 2 reviewers, who collected information on participant characteristics, supplementation protocol, exercise capacity outcomes, and*

https://doi.org/10.1093/nutrit/nuag013

cardiovascular parameters. Data synthesis included subgroup and sensitivity analyses, meta-regression, and stratified random effects meta-analyses. Bias risk was assessed using the revised tool to assess risk of bias in randomized trials (RoB2), and evidence certainty was evaluated via Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

Data Analysis: *The data extraction yielded 12 studies (357 participants) that were included in this study. Supplementation with BJ significantly improved the exercise capacity (standardized mean difference [SMD], 0.31; 95% CI, 0.10-0.53; $I^2 = 0\%$). Stratified analyses revealed greater benefits in parallel RCTs (standardized mean difference [SMD], 0.52; 95% CI, 0.23-0.81; $I^2 = 0\%$) compared with crossover trials (SMD, 0.06; 95% CI, −0.25 to 0.38; $I^2 = 0\%$). Beetroot juice (BJ) reduced systolic (mean difference [MD], −5.33 mmHg; 95% CI, −6.45 to −4.21) and diastolic blood pressure (MD, −3.01 mmHg; 95% CI, −4.39 to −1.63; $I^2 = 0\%$).*

Conclusion: *This meta-analysis provides robust evidence that BJ improves exercise capacity and key cardiovascular parameters in COPD patients. By addressing critical methodological limitations and stratifying the results by study design, this study established a reliable foundation for clinical application. Standardized long-term studies are essential to confirm these findings and elucidate dose-response relationships.*

Systematic Review Registration: *PROSPERO registration No. [CRD42024540181].*

Key words: blood pressure, inorganic nitrate, nitrate supplementation, exercise tolerance, dietary nitrates.

INTRODUCTION

Exercise capacity in patients with chronic obstructive pulmonary disease (COPD) is often compromised due to a combination of pulmonary abnormalities, mechanical inefficiencies, and impairments in muscle bioenergetics, which collectively reduce nitric oxide (NO)-mediated vasodilation.[1] NO is critical for vascular homeostasis, blood pressure (BP) regulation, vascular tone, and oxygen utilization during physical activity.[2] Interventions that enhance NO bioavailability are promising for addressing exercise limitations in COPD patients. Dietary nitrate can be obtained from several sources, including green leafy vegetables, capsules, and beetroot juice (BJ). Among these, BJ, a nitrate-rich functional food, has gained considerable interest in recent years.[3]

Supplementation with BJ enhances NO production via the nitrate-nitrite-NO pathway, which has been shown to improve endothelial function and vascular responses. Previous systematic reviews and meta-analyses in the general population[4–6] and in hypertensive patients[7–9] have demonstrated that nitrate supplementation may reduce blood pressure and improve vascular outcomes. Building upon this broader evidence, systematic reviews and meta-analyses have also suggested potential benefits of BJ supplementation in COPD populations.[10–12] These findings included enhanced exercise capacity, reduced BP, and improved oxygen delivery during exertion. Moreover, previous studies have also reported increased circulating nitrate and nitrite levels following BJ supplementation, supporting its role in enhancing NO bioavailability. However, despite the encouraging data, existing meta-analyses exhibit significant methodological shortcomings, particularly a lack of stratification by study design, which limits the robustness and reliability of their conclusions.

Methodological heterogeneity between parallel and crossover randomized controlled trials (RCTs) is a critical factor often overlooked in previous reviews. According to Cochrane guidelines, stratifying analyses by study design is essential to ensure accurate and unbiased interpretation of pooled results.[13] Among the available studies on BJ supplementation in COPD, three studies were parallel,[14–16] and nine studies were crossover studies.[17–25] The imbalance in the study design necessitates a more nuanced analytical approach to prevent bias and misrepresentation.

This meta-analysis addressed these gaps by stratifying the analysis based on study design, as recommended by Cochrane,[13] and incorporated rigorous quality assessment frameworks, including Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology[26] for evaluating evidence certainty. This comprehensive approach ensures that our findings provide a reliable foundation for understanding the therapeutic potential of nitrate-rich BJ for COPD management. By clarifying the efficacy of BJ supplementation through a stratified lens, in this study we aimed to inform future research and clinical applications, offering insights into optimizing interventions to improve patient outcomes.

METHODS

We conducted a systematic review and meta-analysis of randomized controlled trials , following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[27] This manuscript was registered in the PROSPERO database (CRD42024540181).

Eligibility Criteria

Study Design, Intervention, Comparison, and Outcomes. The research question and eligibility criteria were defined according to the PICOS framework (participants, interventions, comparisons, outcomes, and study design). Accordingly, the following were included:

(P): Participants were adult patients diagnosed with mild-to-moderate COPD without severe comorbidities, such as pulmonary hypertension, chronic heart failure, or asthma, according to international guidelines.[28]

(I): Intervention assessed was the consumption of nitrate-rich BJ, as opposed to other nitrate sources, compared to placebo.

(C): Comparators were placebo or nitrate-depleted BJ, matched for volume, appearance, and taste when reported.

(O): Outcomes primarily included exercise capacity evaluated using the 6-minute walk test (6MWT, distance, meters), incremental shuttle walk test (ISWT, distance, meters), and endurance shuttle walk test (ESWT, distance, meters). Secondary outcomes included levels of nitrate (NO_3^-, μM), nitrite (NO_2^-, μM), and exhaled NO fraction (FeNO, ppb, μg/L in aqueous solutions), which were assessed as biomarkers of NO bioavailability; systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), mean arterial pressure (MAP; mmHg), and heart rate (HR; bpm), which were evaluated as complementary physiological parameters related to cardiovascular function during exercise.

(S): Study designs included parallel and crossover RCTs.

Exclusion criteria were as follows: (1) individuals aged >80 years; (2) study participants with other associated cardiovascular diseases; (3) nonrandomized, observational, and cohort studies; (4) conference abstracts without a full published article; and (5) studies with inconsistencies or those that did not provide enough data to calculate the effect size (ES). Title/abstract and full-text screenings were conducted in duplicate by 2 independent reviewers (G.R.C. and J.S.). If necessary, a third author (W.A.S.) resolved disagreements, establishing a consensus.

Search Strategy

We systematically searched for published studies in SCOPUS, LILACS, PubMed, Embase, Web of Science, Cochrane Library and Science Direct from database inception to December 30, 2024 (see item 1.1, Online Supplemental, for more details on the search strategy).

Study Selection

Using Rayyan Platform Professional software,[29] 2 reviewers (G.R.C. or A.S.S.F.) independently screened all identified references for inclusion based on the study title and abstract. Two reviewers (G.R.C. or A.S.S.F.) independently assessed the full text to include potentially eligible studies, with disagreements resolved by consensus or, if necessary, consultation with a third reviewer (L.A.M. or A.M.G.).

Data Collection

Two reviewers (G.R.C. and A.S.S.F.) independently extracted the data from each study using a standardized data collection form. Discrepancies were resolved by consensus or, if necessary, by consultation with a third reviewer (A.D.). Available data were extracted as outlined in the protocol, including the characteristics of the included studies, study design, demographic and clinical details of the study population, details of the intervention and comparison groups (BJ and placebo), and study outcomes. Attempts were made to contact the corresponding authors of the included studies to obtain the essential aggregate-level data. No imputation was performed for missing data.

Risk of Bias Assessment

The risk of bias in the studies was analyzed using version 2 of the Cochrane risk of bias tool for RCTs.[13,30] Two authors (L.A.M. and G.R.C.) independently assessed the risk of bias. The risk of bias was assessed for all outcomes of interest.

Any discrepancies were resolved by consensus or, if necessary, consultation with a third reviewer (F.V.L.).

Certainty of Evidence

The included studies were assessed using the GRADE[26] method to examine the quality of evidence according to the Cochrane Handbook[31] using a desktop version of the GRADEpro Guideline Development Tool (www.gradepro.org; McMaster University and Evidence Prime, Canada) to generate evidence profiles.

Data Synthesis

We performed random-effects meta-analyses, with the pooled mean difference (MD) for measures within the same study design or the standardized mean difference (SMD) for comparisons across different study designs, following the recommendations outlined in the *Cochrane Handbook*, as pooled-effect size and 2-sided 95% CI.[31]

For data presented in figures (such as mean and SD or SE), webPlotDigitizer software was used, following the guidelines outlined in the Cochrane Handbook.[31] Data presented as medians and IQRs were converted to mean and SD. Heterogeneity was assessed using I^2 statistics. The random-effects model was applied because of the considerable variability in several experimental factors (eg, test, dose duration, and dose amount) across trials. To minimize potential bias from repeated measures in crossover trials, we prioritized data from the first intervention period whenever available, thereby reducing the risk of carryover effects. When first-period data were not reported, outcomes were extracted from the postintervention period and analyzed as if the trial had a parallel design. This conservative approach, in line with Cochrane recommendations, underestimates rather than inflates effect sizes, ensuring consistency and clinical relevance across studies (Cochrane Handbook, Section 16.4.4).

Subgroup and Sensitivity Analyses

Subgroup analyses were conducted for exercise capacity categorized by study design and BJ dose frequency. Sensitivity analyses were performed to assess the impact of crossover study inclusion on overall effect estimates and heterogeneity. Sensitivity analyses for SBP and DBP were performed using the leave-one-out method to evaluate the impact of each study on pooled analysis. For sensitivity analysis, we created 2 subgroup analyses that have not been explored in studies, which are the analysis of the number of doses consumed during the protocol divided by the ideal dose (recommended nitrate dose [3.05 μM per day] used for blood pressure outcomes [SBP and DBP], high dose >10, low dose <10 recommended doses/d). Sensitivity analyses for exercise capacity were conducted based on the dosage consumed, the intervention duration (during the short term, <7 days, or long term, >30 days), and the type of exercise test used (6 MWT, ISWT, or ESWT) to evaluate the distance covered. All statistical analyses were performed using the "meta" (version 7.0.0) and "metaphor" (version 4.6.0) packages of R studio software version 2023.12.1 + 402 for Mac (R Foundation, Vienna, Austria). Forest plots were created using R Studio, incorporating R.

RESULTS

Study Description

The initial search yielded 490 results for December 30, 2024. After removing duplicate entries and applying the eligibility criteria, 12 records were selected for full-text review, all of which were included in this meta-analysis (flow diagram of the systematic search—Flowchart 1). Two studies were parallel and 10 were crossover. These studies encompassed 357 participants, of whom 243 (68%) were randomized to receive BJ (either nitrate rich or nitrate depleted). The follow-up duration ranged from 1 to 12 weeks. The mean patient age was 66.8 years (SD, 2.28 years), with forced expiratory volume in 1 second (FEV_1) values ranging from 39.6% to 69.2% of the predicted value of 55.5% (5.80). The individual study characteristics and definitions of BJ and placebo are shown in **Tables 1 and 2**. Variations in BJ definitions across studies have been attributed to differences in juice quantity, nitrate concentrations, and intake frequency. Four studies used a single dose,[18,19,21,22] whereas 8 employed multiple doses.[14–17,20,23–25]

Main Outcomes

Exercise Capacity. The pooled standardized mean difference (SMD) for exercise capacity with BJ supplementation compared to placebo is summarized in **Figure 1A**, stratified by study design, intervention duration, exercise test types, and BJ dosages. BJ supplementation significantly improved exercise capacity (SMD = 0.31; 95% CI, 0.10-0.53; $P < .01$, $I^2 = 0\%$). Parallel RCTs ($n = 2$ studies) with long-term (≥56 days) interventions demonstrated marked improvements (SMD = 0.52; 95% CI, 0.23-0.81; $I^2 = 0\%$), whereas short-term (<30 days) interventions in 6 crossover studies yielded no effects (SMD = 0.06; 95% CI, −0.25 to 0.38; $I^2 = 0\%$). In parallel RCTs, both the 6MWT and the ISWT significantly improved exercise capacity (6MWT: SMD = 0.60; 95% CI, 0.12-1.08; ISWT: SMD = 0.47; 95% CI, 0.11-0.83, **Figure 1B**). In crossover trials, no significant effects were observed across the

Table 1. Included studies comparing nitrate supplementation of the beetroot juice vs placebo group.[a]

Description of protocol								
Studies, (y)	**Design**	**Nitrate dose**	**Placebo dose**	**Condition dose**	**Duration**	**Number dose (vol of nitrate)**	**Washout**	**Outcomes**
Alasmari et al., 2024[12]	RCT	70 mL NR-BJ (400 mg nitrate [4.71 mmol])*	70 mL water ND-BJ	Multiple	1/d for 90 d	90 (423.9 mmol nitrate)	–	↓ SBP, AIx75%, ↑ 6MWT, RHI
Behnia et al., 2018[13]	RCT	70 mL BJ (400 mg nitrate)*	70 mL water + (180 mL currant)	Multiple	1×/d for 8 days	8 (37.68 mmol)	–	No difference in VO_2, HR, DBP, ↓ SBP
Beijers et al., 2018[15]	Crossover	8 mmol of sodium nitrate	NaCl ingestion	Multiple	1×/d for 7 d	7 (56 mmol of nitrate)	7 d	No difference in VO_2, time, SBP, DBP, HR; ↑ nitrate, and nitrite
Berry et al., 2015[16]	Crossover	140 mL BJ (7.78 mmol nitrate)	163 mL prune juice (0.01 mmol nitrate)	Simple	1×/d for 1 d	1 (7.78 mmol of nitrate)	7 d	No difference in VO_2, HR, StO2; ↓ DBP, resting SBP, ↑ nitrate and nitrite
Curtis et al., 2015[17]	Crossover	140 mL BJ (0,8 g or 12.9 mmol nitrate)	140 mL ND-BJ	Simple	1×/d for 1 d	1 (12.9 mmol of nitrate)	7 d	No difference in HR, StO2; ↓ DBP, VO2, ↑ nitrate
Friis et al., 2017[18]	Crossover	140 mL BJ (300 mg nitrate or 3.52 mmol)**	140 mL ND-BJ	Multiple	2×/d for 7 d	14 (49.28 mmol)	7 d	No difference VO_2, 6MWT, HR, SBP; ↓ DBP; ↑ nitrite
Kerley et al., 2015[19]	Crossover	140 mL BJ (12.9 mmol nitrate)	140 mL water + 200 mL currant juice	Simple	1×/d for 1 d	1 (12.9 mmol of nitrate)	7 d	↓ SBP, DBP, MAP, ↑ ISWTD; no difference in HR, StO2; ↑ nitrate and nitrite
Kerley et al., 2019[20]	Crossover	140 mL BJ (12.9 mmol nitrate)	140 mL ND-BJ (0.5 mmol nitrate)	Simple	1×/d for 1 d	1 (12.9 mmol of nitrate)	NA	↑ ISWTD; ↑ nitrate and nitrite
Leong et al., 2015[21]	Crossover	70 mL BJ (4.8 mmol nitrate)	140 mL ND-BJ (0.0056-0.02 mmol nitrate)	Multiple	2×/d for 3.5 d	7 (33.6 mmol nitrate)	4 d	No difference in ESWTD, ESWTT; ↓ resting SBP

(continued)

Table 1. Continued

Description of protocol								
Studies, (y)	**Design**	**Nitrate dose**	**Placebo dose**	**Condition dose**	**Duration**	**Number dose (vol of nitrate)**	**Washout**	**Outcomes**
Pavitt et al., 2020[14]	RCT	140 mL BJ (12.9 mmol nitrate)	140 mL ND-BJ (0.002 mmol nitrate)	Multiple	56 d	56 (722.4 mmol nitrate)	No	↓ SBP, DBP, MAP; no difference in physical activity; ↑ FMD
Pavitt et al., 2022[22]	Crossover	140 mL NR-BJ, (12.9 mmol nitrate)	140 mL ND-BJ (0.002 mmol nitrate)	Multiple	7 d	NA	7-30 d	No difference in SBP, DBP, MAP, ↑FMD, ↑exhaled nitric oxide, nitrate and nitrite
Shepherd et al., 2015[23]	Crossover	70 mL BJ, (6.77 mmol nitrate)	140 mL ND-BJ (0.004 mmol nitrate)	Multiple	2× for 2.5 d	5 (33.85 mmol de nitrate)	7 d	No difference in VO_2, 6MWT, SBP, DBP; ↑nitrate

Abbreviations: AIx75%, augmentation index normalized to a heart rate of 75 beats/min; BJ, beetroot juice; DBP, diastolic blood pressure; ESWT, endurance shuttle walk test; FMD, flow-mediated dilatation; ISWT, incremental shuttle walk test; MAP, mean arterial pressure; ND, nitrate depleted; NR, nitrate-rich; RHI, reactive hyperemia index; SBP, systolic blood pressure; StO_2, arterial O_2 saturation; VO_2, oxygen consumption; 6MWT, 6-minute walk test.

[a]Python-based calculations were used to convert nitrate dose from milligrams to millimoles using the molecular weight of sodium nitrate (85.00 g/mol). Thus, 400 mg corresponds to 4.71 mmol. The same approach was applied to the 300-mg dose.

Table 2. Characteristics of included studies.

Studies	Design of study	Sample	Description functional					BJ		Placebo	
			FEV_1 (% pred)	FVC (% pred)	FEV_1/FVC (%)	*n*	Male, *n* (%)	*n*	Age, y (mean ± SD)	*n*	Age, y (mean ± SD)
Alasmari et al., 2024[12]	RCT	Moderate to severe COPD, SBP ≥ 130 mmHg	BJ 45.2 ± 14.9; PL 39.6 ± 15.2	–	–	70	–	36	62.5 ± 7.4	34	64.5 ± 7.4
Behnia et al., 2018[13]	RCT	Mild to severe COPD	–	–	57 ± 10	25	12 (48)	12	67 ± 8	13	68 ± 10
Beijers et al., 2017[15]	Crossover	Mild-to-moderate COPD patients	69.2 ± 16.3	97.8 ± 18.5	54.2 ± 9.8	18	13 (72)	18	66.6 ± 7.5	18	–
Berry et al., 2015[16]	Crossover	COPD	61.8 ± 17.2	–	55.4 ± 10.3	15	11 (73.3)	15	69.6 ± 8.5	15	–
Curtis et al., 2015[17]	Crossover	Moderate to severe COPD	50.1 ± 21.6	–	–	21	16 (76.2)	21	68 ± 7	21	–
Fris et al., 2017[18]	Crossover	Moderate to severe COPD	44.7 ± 15.1	74.2 ± 14.7	61 ± 19	15	9 (60)	15	63 ± 13	15	–
Kerley et al., 2015[19]	Crossover	Moderate COPD	43.4 ± 18.9	70.1 ± 16.5	43.4 ± 20.6	11	5 (45.5)	11	69 ± 7	11	–
Kerley et al., 2019[20]	Crossover	Moderate COPD	55 ± 19	91 ± 10	48 ± 15	8	8 (100)	8	62.9 ± 7.1	8	–
Leong et al., 2015[21]	Crossover	Moderate COPD patients	62 ± 6.9	91.6 ± 12.9	66 ± 7.6	19	5 (26.3)	19	67 ± 7.9	19	–
Pavitt et al., 2020[14]	RCT	Moderate COPD	BJ 65.2 ± 7.5; PL 48 ± 7.5	–	–	122	69 (56.5)	57	70.5 ± 3.5	65	68 ± 3
Pavitt et al, 2022[22]	Crossover	COPD	–	–	–	20	12 (60)	20	67.7 ± 2.7	20	68.5 ± 3
Shepherd et al., 2015[23]	Crossover	COPD	57 ± 9	–	41 ± 16	13	13 (100)	13	64.7 ± 7.7	13	–

Abbreviations: BJ, beetroot juice; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume; FVC, forced vital capacity; FEV_1/FVC, ratio; PL, placebo; RCT, randomized controlled trial.

6MWT, ISWT, and ESWT ($P = .27$). Higher BJ doses in RCTs yielded significant benefits (SMD = 0.52; 95% CI, 0.23-0.81, $I^2 = 0\%$, **Figure 1C**), while crossover studies, regardless of the doses, demonstrated no effect.

The dose-dependent subgroup analysis highlighted a critical trend: Higher doses of BJ in parallel RCTs significantly improved exercise capacity (SMD = 0.52; 95% CI, 0.23-0.81; $I^2 = 0\%$), while both higher and lower doses in crossover studies showed negligible effects with no impact, demonstrating a satisfactory difference between the groups (SMD = 0.31; 95% CI, 0.10-0.53; $I^2 = 0\%$, $P = .08$).

Plasma NO_3^-, NO_2^- Levels, and FeNO

Figure 2 illustrates the effects of BJ on NO_3^-, NO_2^- (μM), and FeNO levels (ppb). BJ supplementation significantly increased NO_3^- levels in 7 crossover studies (MD = 445.59 μM; 95% CI, 272.10-619.07; $I^2 = 99\%$; $P < .01$) and NO_2^- levels in 5 crossover studies (MD = 372.00 μM; 95% CI, 297.16-446.85; $I^2 = 22\%$; $P < .01$). FeNO levels showed no significant changes in 3 studies (SMD = 1.47; 95% CI, −0.56 to 3.51; $I^2 = 97\%$; $P = .16$).

Blood Pressure–Stratified Analysis and Heart Rate

The pooled results for SBP, DBP, MAP, and HR are summarized in **Figure 3**. BJ supplementation significantly reduced SBP overall (SMD = −0.44; 95% CI, −0.85 to −0.03; $I^2 = 76\%$; $P = .04$). Subgroup analyses indicated that heterogeneity in SBP responses was primarily influenced by variability in BJ dosage and intervention duration, with greater inconsistency in shorter protocols and lower-dose interventions. DBP demonstrated a modest but significant reduction (SMD = −0.21; 95% CI, −0.40 to −0.02; $I^2 = 0\%$; $P = .03$), with crossover studies administering low BJ doses showing the clearest reductions (SMD = −0.50; 95% CI, −0.90 to −0.10; $I^2 = 0\%$). MAP showed the most pronounced reduction across cardiovascular outcomes (SMD = −0.47; 95% CI, −0.71 to −0.22; $I^2 = 0\%$; $P < .01$). In contrast, HR did not differ significantly across subgroups ($P = .64$).

Quality of Studies and Grading the Strength of Evidence

When the RoB2 tool was used to evaluate both study designs (crossover and parallel RCTs), a wide range of bias risks was observed among the outcomes analyzed, with a predominance of high-risk studies. Key sources of bias included incomplete blinding, selective outcome reporting, and variability in intervention protocols. The results of the RoB2 assessment and grading of the strength of evidence are presented in **Tables 3 and 4**. Based on the GRADE framework, evidence for exercise capacity outcomes was rated with moderate certainty, while evidence for SBP and DBP outcomes ranged from low to moderate certainty, reflecting both the high heterogeneity and risk of bias in some studies (Online Supplementary Material, Table S1).

DISCUSSION

This systematic review and meta-analysis provides updated insights into the effects of nitrate supplementation from BJ on exercise capacity and blood pressure responses in COPD patients. Our findings indicate that nitrate-rich BJ significantly enhances exercise capacity and improves physiological parameters, such as SBP, DBP, and MAP, while increasing circulating NO_3^- and NO_2^- levels. These results offer substantial evidence for nitrate-rich BJ as a potential adjunctive therapy in COPD management, particularly concerning cardiovascular and exercise-related outcomes.

Comparisons With Previous Studies

Previous systematic reviews[3,4,11,12] have yielded conflicting results regarding the impact of BJ on exercise capacity in COPD patients, mainly due to methodological limitations. Most notably, these reviews did not stratify analyses by study design, which may have introduced bias. In contrast, our study adhered to the Cochrane guidelines[13] by stratifying data based on the study design, thus providing a more robust interpretation of the effects of BJ supplementation. We found that while crossover trials yielded inconsistent effects,[17,19,23–25] parallel RCTs[14–16] demonstrated significant improvements in exercise capacity, especially with long-term interventions and higher doses of BJ. This stratification clarifies the ambiguity surrounding earlier findings.

Mechanistic Pathways

The beneficial effects of BJ are primarily attributed to its high NO_3^- content, which undergoes biotransformation via the enterosalivary pathway. Upon ingestion, dietary nitrate is absorbed by the upper gastrointestinal tract and circulates to the salivary glands, where it is concentrated and converted to NO_2^- by commensal oral bacteria. NO_2^- is then swallowed and reduced to NO under acidic gastric conditions or enzymatically within hypoxic tissues.[32–34] This bioconversion significantly enhances the bioavailability of NO, which is crucial for its vasodilatory, anti-inflammatory, and mitochondrial efficiency–enhancing effects.

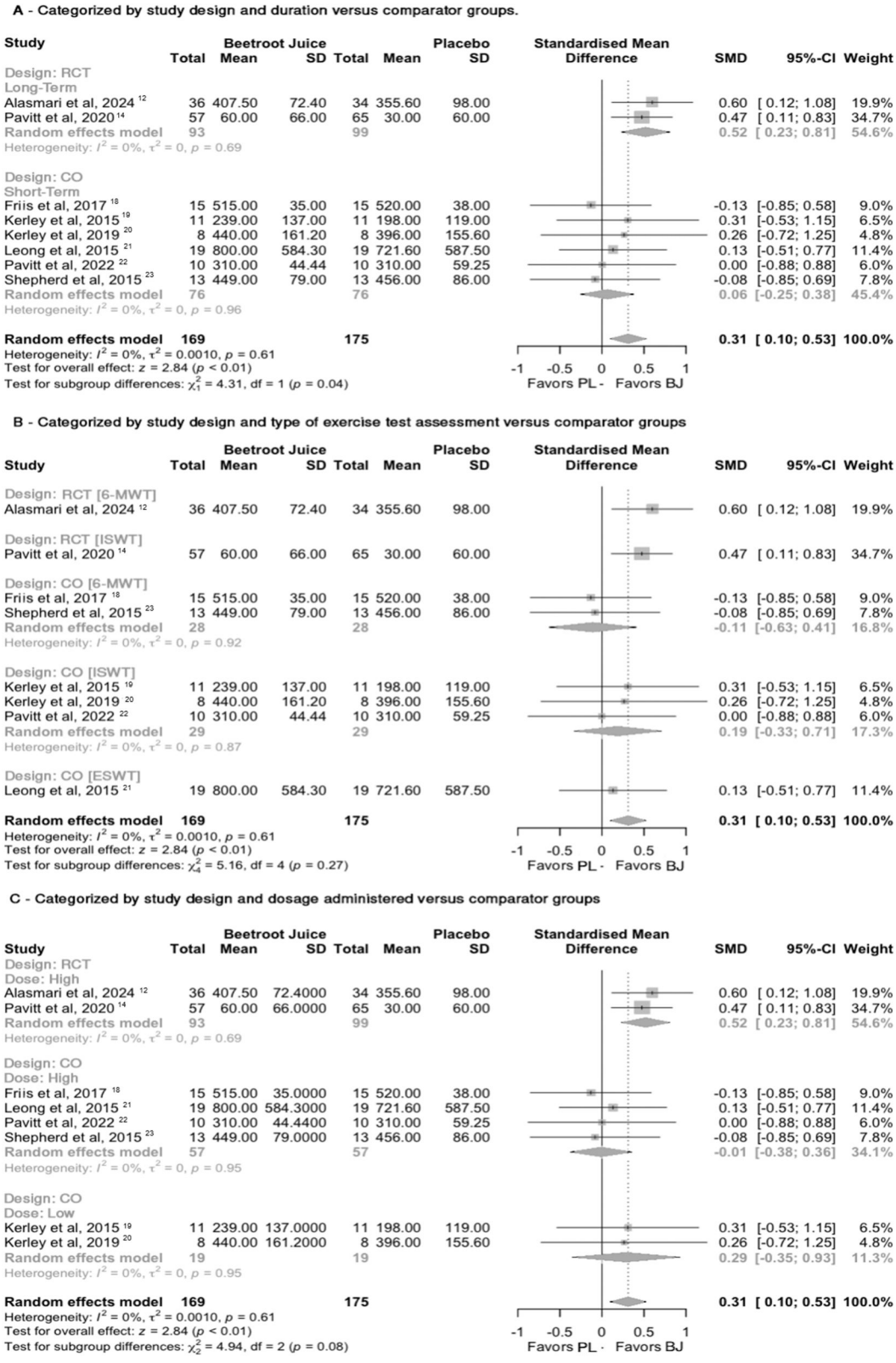


Figure 1. Pooled standardized mean differences for exercise capacity categorized according to the following: (A) by study design and duration vs comparator groups; (B) by study design and type of exercise test assessment vs comparator groups, and (C) by study design and dosage administered vs comparator groups.

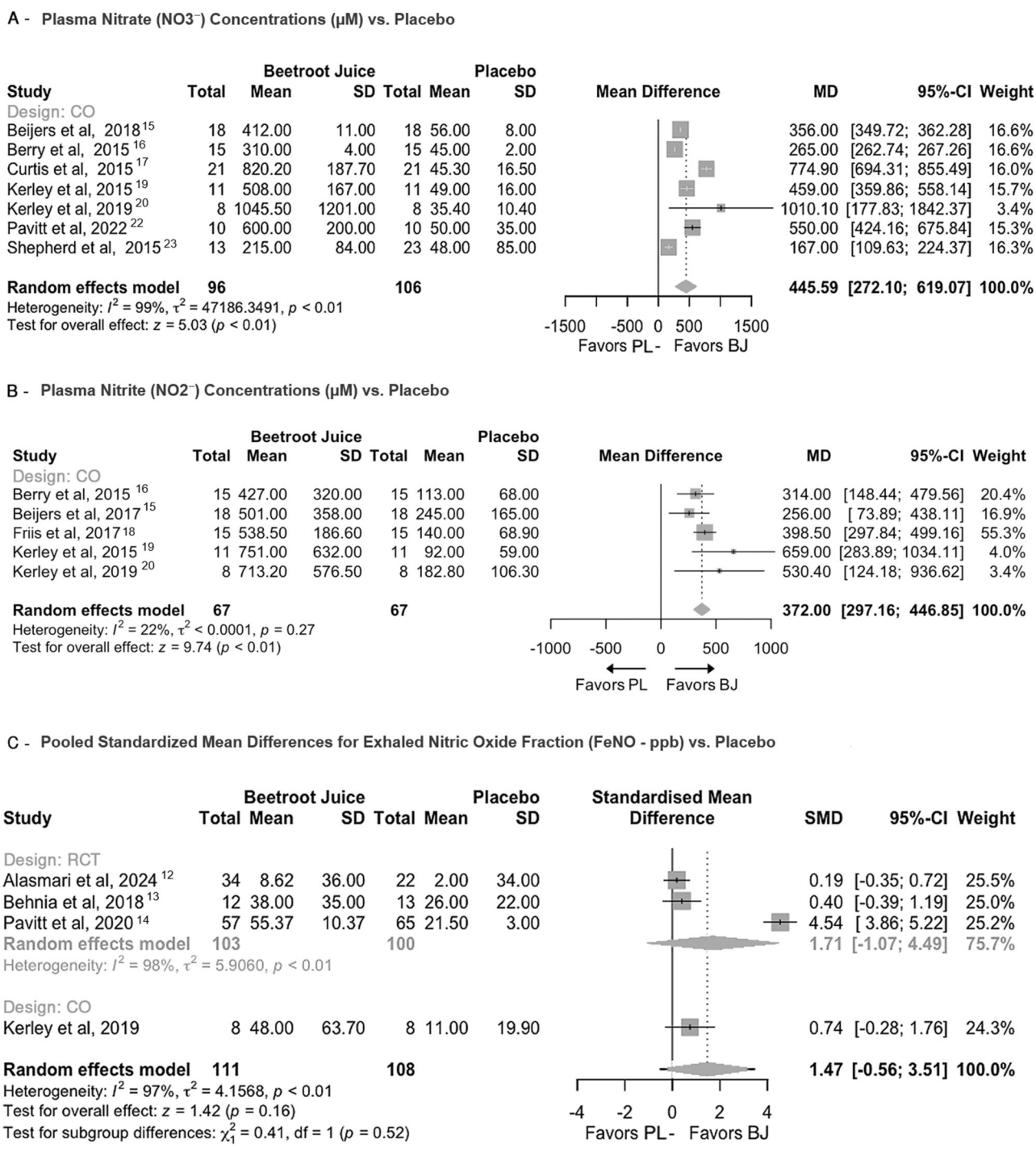


Figure 2. Pooled mean differences for: (A) nitrate (NO_3^-) vs comparator groups, (B) nitrite (NO_2^-) vs comparator groups, and (C) pooled standardized mean differences for exhaled nitric oxide fraction (FeNO) vs comparator groups.

1. Vascular Effects: NO acts as a potent vasodilator by stimulating soluble guanylyl cyclase in vascular smooth muscle cells, increasing cyclic guanosine monophosphate (cGMP) levels, and promoting relaxation.[35,36] This mechanism improves endothelial function, reduces systemic vascular resistance, and enhances blood flow, particularly in exercising the muscles. These effects are amplified in patients with COPD, who often experience endothelial dysfunction and impaired oxygen delivery.
2. Mitochondrial Efficiency: NO improves mitochondrial efficiency by modulating oxygen consumption through competitive inhibition of cytochrome c oxidase in the electron transport chain.[37] This cascade

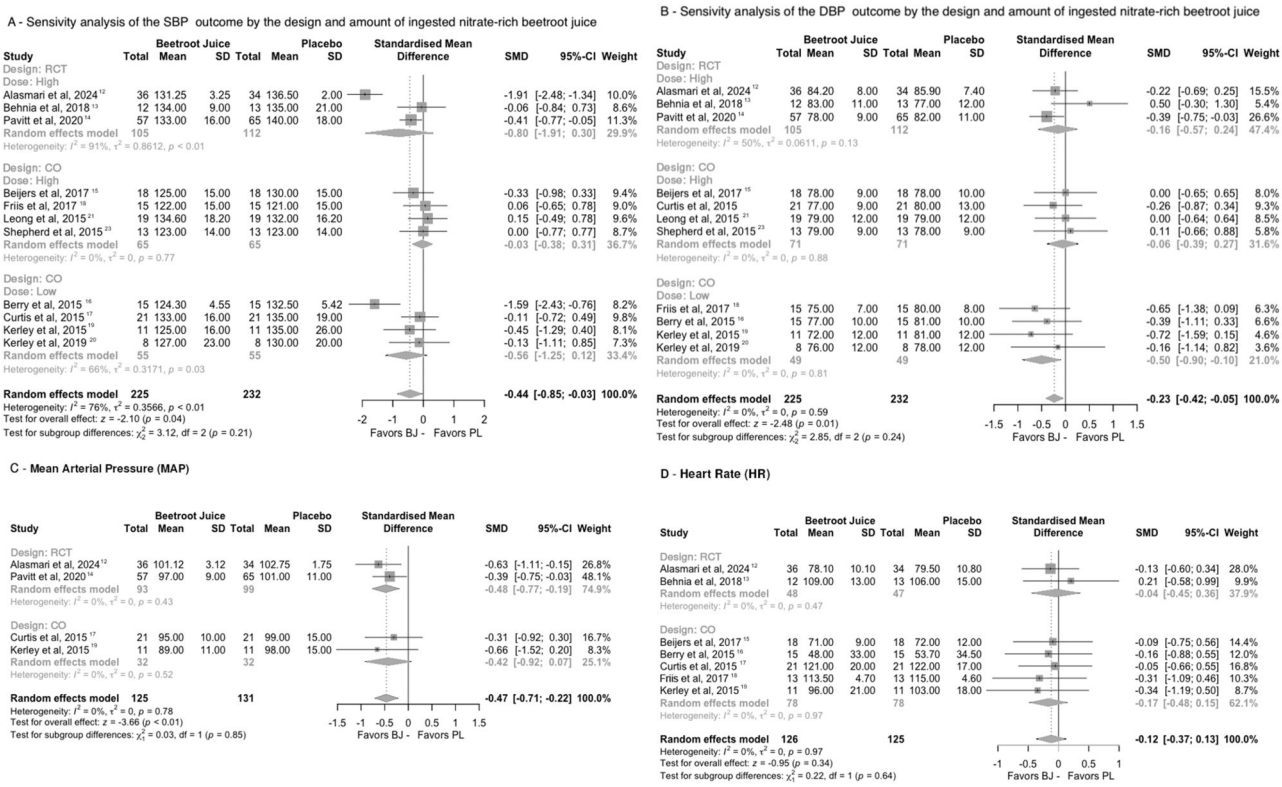


Figure 3. Sensitivity analysis categorized by study design type and quantity of beetroot juice consumed according to the evaluated outcome: (A) systolic blood pressure compared to placebo groups; (B) diastolic blood pressure compared to placebo groups; (C) mean arterial pressure (MAP), and (D) heart rate (HR).

reduces the oxygen cost of ATP production, particularly under hypoxic conditions, which is critical for COPD patients during exercise.

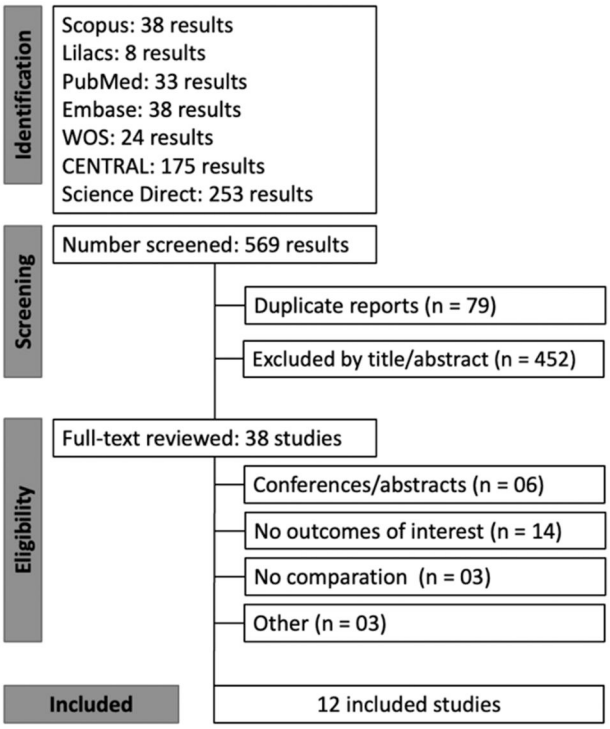
3. Reduced Oxygen Cost of Exercise: By enhancing the matching of oxygen delivery to oxygen demand and improving vasodilation, BJ supplementation reduced the oxygen cost of exercise. This effect is particularly beneficial for COPD patients who frequently experience dynamic hyperinflation and inefficient oxygen utilization during physical activity.[1,37]
4. Anti-inflammatory Properties: NO exerts anti-inflammatory effects by inhibiting leukocyte adhesion to the endothelium and reducing the production of pro-inflammatory cytokines.[38,39] These properties may mitigate the chronic systemic inflammation observed in COPD and contribute to improved cardiovascular and pulmonary outcomes.
5. Pulmonary Hemodynamics: NO derived from BJ also demonstrates promising effects on pulmonary hemodynamics. It improves pulmonary vascular resistance and promotes vasodilation within the pulmonary circulation, potentially reducing pulmonary artery pressure. These effects are critical for COPD patients, who often experience elevated pulmonary vascular resistance and pulmonary hypertension.[40] Improved oxygen uptake and optimized ventilation-perfusion matching in the lungs may also contribute to enhanced exercise tolerance and reduced dyspnea. Additionally, increased NO availability can mitigate hypoxia-induced vasoconstriction, which exacerbates pulmonary hypertension during exercise or at rest.

Cardiovascular Benefits

In addition to enhancing exercise capacity, BJ supplementation significantly improved blood pressure outcomes. The overall analysis demonstrated significant reductions in the SBP, DBP, and MAP. Specifically, SBP decreased by an SMD of −0.44, while DBP showed a smaller but statistically significant reduction (SMD = −0.21). These findings align with the understanding that increased NO availability from dietary nitrate improves endothelial function, reduces vascular resistance, and enhances blood flow.[16,36,41] This effect is particularly beneficial in COPD patients, who often face increased cardiovascular risk due to systemic inflammation and endothelial dysfunction.[40]

Clinical Applications

The clinical relevance of these findings lies in the potential of BJ to complement the current COPD management strategies. As a dietary intervention, BJ offers a cost-



Flowchart 1. Flow diagram of the systematic search.

effective, noninvasive approach that can be integrated into rehabilitation programs to enhance exercise tolerance and cardiovascular health. The blood pressure–lowering effects observed with BJ supplementation may also benefit COPD patients with concurrent hypertension or increased cardiovascular risk. Moreover, the potential role of BJ in mitigating pulmonary hypertension offers a dual advantage in improving systemic and pulmonary vascular health.

By providing additive benefits without significant adverse effects, BJ supplementation can also serve as an adjunct to pharmacological therapies. The role of BJ in promoting endothelial health and reducing systemic inflammation may also slow disease progression and improve the quality of life of COPD patients. However, further research is needed to standardize dosing regimens, identify optimal treatment durations, and evaluate long-term outcomes.

Comparison with Other Populations

Studies on BJ have extensively documented its blood pressure–lowering effects in the cardiac and respiratory populations. BJ contains a high concentration of NO_3^-, with 6.2 mmol of NO_3^- per 0.5 L juice.[5] Studies have reported favorable results in reducing blood pressure in healthy individuals,[42–44] heart failure patients,[33,45] and COPD patients.[14–25] A reduction of approximately 3.55 mmHg for SBP and 1.32 mmHg for DBP is typically expected in these populations,[4] consistent with findings from aerobic exercise studies,[46] in which SBP and DBP were reduced by −3.84 mmHg (95% CI, −4.97 to −2.72 mmHg) and −2.58 mmHg (95% CI, −3.35 to −1.81 mmHg), respectively. The reduction in SBP and DBP related to the administered dosage did not differ by subgroup analysis, showing that high doses favor SBP reduction. In contrast, both high and low doses favor DBP reduction.

Risks of Long-Term BJ Use

Although BJ supplementation offers several benefits, its long-term use is not without potential risks. Excessive NO_3^- intake may lead to methemoglobinemia, a condition in which elevated methemoglobin levels impair blood oxygen delivery. Although this condition is rare, individuals with predisposing conditions or genetic enzyme deficiencies may be more susceptible to infection.[47]

Moreover, chronic high-dose NO_3^- supplementation may affect the balance of the oral microbiota. Disruptions in nitrate-reducing bacteria can alter the enterosalivary nitrate-nitrite-NO pathway and diminish the efficacy of supplementation over time.[48] There is also concern regarding interactions with medications, such as phosphodiesterase inhibitors or antihypertensives, which may amplify the blood pressure-lowering effects and lead to hypotension.[49]

Additionally, the long-term use of BJ may contribute to excessive caloric intake if consumed in large quantities, potentially leading to weight gain, particularly in COPD patients with reduced physical activity levels. Patients with comorbidities such as diabetes may also need to monitor the sugar content of commercially available BJ products.[50]

Last, NO_3^- supplementation has raised theoretical concerns regarding the formation of carcinogenic N-nitroso compounds, especially when combined with high-protein diets. Although no conclusive evidence links dietary nitrate to increased cancer risk, further research is warranted to ensure the safety of chronic BJ use.[51,52]

Methodological Limitations

Although our meta-analysis provided valuable insights, several limitations must be acknowledged. First, there was considerable heterogeneity across the included trials, particularly in crossover designs. Variability in BJ dosage, intervention duration, and exercise test type contributed to this heterogeneity. These differences influenced the pooled effect sizes and limited the ability to identify consistent patterns across the studies.

Table 3. Risk of bias according to study design: RoB2 for RCT parallels

Study	Randomization Process	Intervention Bias	Incomplete outcome data	Outcome measurement	Outcome reporting	Overall risk of bias
Alasmari et al., 2024[12]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Behnia et al., 2018[13]	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Some concerns
Pavitt et al., 2020[14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Abbreviations: RCT, parallel-group randomized controlled trial; RoB 2, revised tool for assessing risk of bias in randomized trials.

Table 4. Risk of bias according to study design: RoB2 for crossover design

Study	Randomization Process	Carryover Effect	Intervention Bias	Incomplete Outcome Data	Outcome Measurement	Outcome Reporting	Overall Risk of Bias
Beijers et al., 2017[15]	Some concerns	Some concerns	Some concerns	Low Risk	Some concerns	Low Risk	Some concerns
Berry et al., 2015[16]	Low Risk	Low Risk	Some concerns	Low Risk	Low Risk	Low Risk	Low Risk
Curtis et al., 2015[17]	Some concerns	Some concerns	Some concerns	Low Risk	Low Risk	Some concerns	Some concerns
Friis et al., 2017[18]	Low Risk	Some concerns	Some concerns	Some concerns	Low Risk	Low Risk	Some concerns
Kerley et al., 2015[19]	Some concerns	Some concerns	Some concerns	Low Risk	Low Risk	Low Risk	Some concerns
Kerley et al., 2019[20]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Leong et al., 2015[21]	Some concerns	Some concerns	Some concerns	Low Risk	Some concerns	Some concerns	Some concerns
Pavitt et al., 2020[14]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Pavitt et al., 2022[22]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns

Abbreviations: RoB 2, revised tool for assessing risk of bias in randomized crossover trials.

Second, most of the included studies had small sample sizes, with an average effect size of 0.25, and only 2 studies reported effect sizes greater than 0.4. These small sample sizes may limit the generalizability of our findings and reduce the statistical power to detect significant differences, particularly in specific patient subgroups.

Third, although our analysis demonstrated significant improvements in exercise capacity and blood pressure, the clinical relevance of these findings, especially in patients with severe COPD, remains uncertain. Further research is needed to evaluate the long-term and clinically meaningful benefits of BJ supplementation in patients with more severe COPD. Last, the heterogeneity of protocols across studies was a notable factor.

The intervention per participant ranged from 1 to 90 days, the administered dosages varied from 3.05 to 13.5 mmol, and the number of doses ranged from 2 to 236. Our meta-analysis is to our knowledge the first to systematically account for BJ dosage, study design, and intervention duration. By incorporating these variables into our analysis, we were able to mitigate potential bias and enhance the robustness of our findings. Additionally, the potential for information bias in some reviews should be considered as it may lead to erroneous interpretation of the data. As noted in previous reviews, this bias further complicates accurate assessments of the true efficacy of BJ in patients with COPD.

CONCLUSION

Supplementation with BJ represents a promising nonpharmacological intervention for improving cardiovascular

health and exercise capacity in patients with COPD. Future research should prioritize refining dosing strategies, evaluating long-term effects, and elucidating the precise mechanisms underlying the benefits of dietary NO_3^- to maximize their therapeutic potential in this vulnerable population. Our findings indicate that BJ can significantly enhance exercise capacity, particularly in long-duration protocols, endurance exercises, and higher supplementation doses.

Author Contributions. G.R.C. and A.M.G.C. had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. A.M.G.C. and A.G.D. contributed to the concept and design of the study. G.R.C., L.A.M., and D.A.C. contributed to the data acquisition. All authors analyzed and interpreted the data. P.T.M., L.P.M., G.R.C., and V.R.V. drafted the manuscript, with critical revisions for important intellectual content from all authors. G.R.C., V.R.V., and V.A. critically reviewed the manuscript. V.R.V., G.R.C., and V.A. performed statistical analyses. V.R.V. was the study supervisor. G.R.C. and A.S.S.F., contributed equally to the development and finalization of the manuscript.

Supplementary Material

Supplementary Material is available at *Nutrition Reviews* online.

Funding. The authors have not declared a specific grant for this research from any public, commercial, or not-for-profit funding agency.

Conflicts of Interest

G.R.C., A.D.G., and V.R.V. are members of the Meta-Academy Group. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Data Availability

All data relevant to the study are included in the article or uploaded as online supplementary information. Additional details are available upon reasonable request.

Ethical Approval

Not required for Meta-Analysis.

REFERENCES

1. Chiappa GR, Queiroga F Jr., Meda E, et al. Heliox improves oxygen delivery and utilization during dynamic exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;179:1004-1010. https://doi.org/10.1164/rccm.200811-1793OC
2. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. *Nat Rev Drug Discov*. 2008;7:156-167. https://doi.org/10.1038/nrd2466
3. Alsulayyim AS, Alasmari AM, Alghamdi SM, Polkey MI, Hopkinson NS. Impact of dietary nitrate supplementation on exercise capacity and cardiovascular parameters in chronic respiratory disease: A systematic review and meta-analysis. *BMJ Open Respir Res*. 2021;8:e000948. https://doi.org/10.1136/bmjresp-2021-000948
4. Bahadoran Z, Mirmiran P, Kabir A, Azizi F, Ghasemi A. The nitrate-independent blood pressure-lowering effect of beetroot juice: a systematic review and meta-analysis. *Adv Nutr*. 2017;8:830-838. https://doi.org/10.3945/an.117.016717
5. Lansley KE, Winyard PG, Fulford J, et al. Dietary nitrate supplementation reduces the O_2 cost of walking and running: a placebo-controlled study. *J Appl Physiol*. 2011;110:591-600. https://doi.org/10.1152/japplphysiol.01070.2010
6. Siervo M, Lara J, Ogbonmwan I, Mathers JC. Inorganic nitrate and beetroot juice supplementation reduces blood pressure in adults: A systematic review and meta-analysis. *J Nutr*. 2013;143:818-826. https://doi.org/10.3945/jn.112.170233
7. Gronroos R, Eggertsen R, Bernhardsson S, Praetorius BM. Effects of beetroot juice on blood pressure in hypertension according to European Society of Hypertension Guidelines: a systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis*. 2024;34:2240-2256. https://doi.org/10.1016/j.numecd.2024.06.009
8. Benjamim CJR, Porto AA, Valenti VE, et al. Nitrate derived from beetroot juice lowers blood pressure in patients with arterial hypertension: a systematic review and meta-analysis. *Front Nutr*. 2022;9:823039. https://doi.org/10.3389/fnut.2022.823039
9. Benjamim CJR, Lopes da Silva LS, Valenti VE, et al. Effects of dietary inorganic nitrate on blood pressure during and post-exercise recovery: a systematic review and meta-analysis of randomized placebo-controlled trials. *Free Radic Biol Med*. 2024;215:25-36. https://doi.org/10.1016/j.freeradbiomed.2024.02.011
10. Alshafie S, El-Helw GO, Fayoud AM, et al. Efficacy of dietary nitrate-rich beetroot juice supplementation in patients with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *Clin Nutr ESPEN*. 2021;42:32-40. https://doi.org/10.1016/j.clnesp.2021.01.035
11. Wang J, Feng F, Zhao Y, et al. Dietary nitrate supplementation to enhance exercise capacity in patients with COPD: evidence from a meta-analysis of randomized controlled trials and a network pharmacological analysis. *Respir Med*. 2024;222:107498. https://doi.org/10.1016/j.rmed.2023.107498
12. Yang H, He S, Chen F, Liang L, Pan J. Efficacy and safety of nitrate supplementation on exercise tolerance in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Medicine*. 2022;101:e28578. https://doi.org/10.1097/MD.0000000000028578
13. Higgins J, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration. 2019; version 6.1. https://doi.org/10.1002/9781119536604.
14. Alasmari AM, Alsulayyim AS, Alghamdi SM, et al. Oral nitrate supplementation improves cardiovascular risk markers in COPD: ON-BC, a randomised controlled trial. *Eur Respir J*. 2024;63:2202353. https://doi.org/10.1183/13993003.02353-2022
15. Behnia M, Wheatley CM, Avolio A, Johnson BD. Influence of dietary nitrate supplementation on lung function and exercise gas exchange in COPD patients. *Nitric Oxide*. 2018;76:53-61. https://doi.org/10.1016/j.niox.2018.03.009
16. Pavitt MJ, Tanner RJ, Lewis A, et al. Oral nitrate supplementation to enhance pulmonary rehabilitation in COPD: ON-EPIC a multicentre, double-blind, placebo-controlled, randomised parallel

group study. *Thorax*. 2020;75:547-555. https://doi.org/10.1136/thoraxjnl-2019-214278
17. Beijers R, Huysmans SMD, van de Bool C, et al. The effect of acute and 7-days dietary nitrate on mechanical efficiency, exercise performance and cardiac biomarkers in patients with chronic obstructive pulmonary disease. *Clin Nutr.* 2018;37:1852-1861. https://doi.org/10.1016/j.clnu.2017.10.011
18. Berry MJ, Justus NW, Hauser JI, et al. Dietary nitrate supplementation improves exercise performance and decreases blood pressure in COPD patients. *Nitric Oxide*. 2015;48:22-30. https://doi.org/10.1016/j.niox.2014.10.007
19. Curtis KJ, O'Brien KA, Tanner RJ, et al. Acute dietary nitrate supplementation and exercise performance in COPD: a double-blind, placebo-controlled, randomised controlled pilot study. *PLoS One*. 2015;10:e0144504. https://doi.org/10.1371/journal.pone.0144504
20. Friis AL, Steenholt CB, Lokke A, Hansen M. Dietary beetroot juice—effects on physical performance in COPD patients: a randomized controlled crossover trial. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1765-1773. https://doi.org/10.2147/COPD.S135752
21. Kerley CP, Cahill K, Bolger K, et al. Dietary nitrate supplementation in COPD: an acute, double-blind, randomized, placebo-controlled, crossover trial. *Nitric Oxide*. 2015;44:105-111. https://doi.org/10.1016/j.niox.2014.12.010
22. Kerley CP, James PE, McGowan A, Faul J, Cormican L. Dietary nitrate improved exercise capacity in COPD but not blood pressure or pulmonary function: a 2 week, double-blind randomised, placebo-controlled crossover trial. *Int J Food Sci Nutr*. 2019;70:222-231. https://doi.org/10.1080/09637486.2018.1492521
23. Leong P, Basham JE, Yong T, et al. A double blind randomized placebo control crossover trial on the effect of dietary nitrate supplementation on exercise tolerance in stable moderate chronic obstructive pulmonary disease. *BMC Pulm Med*. 2015;15:52. https://doi.org/10.1186/s12890-015-0057-4
24. Pavitt MJ, Lewis A, Buttery SC, et al. Dietary nitrate supplementation to enhance exercise capacity in hypoxic COPD: EDEN-OX, a double-blind, placebo-controlled, randomised cross-over study. *Thorax*. 2022;77:968-975. https://doi.org/10.1136/thoraxjnl-2021-217147
25. Shepherd AI, Wilkerson DP, Dobson L, et al. The effect of dietary nitrate supplementation on the oxygen cost of cycling, walking performance and resting blood pressure in individuals with chronic obstructive pulmonary disease: a double blind placebo controlled, randomised control trial. *Nitric Oxide*. 2015;48:31-37. https://doi.org/10.1016/j.niox.2015.01.002
26. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383-394. https://doi.org/10.1016/j.jclinepi.2010.04.026
27. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372:n71. https://doi.org/10.1136/bmj.n71
28. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD Executive Summary. *Am J Respir Crit Care Med*. 2017;195:557-582. https://doi.org/10.1164/rccm.201701-0218PP
29. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4
30. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366:l4898. https://doi.org/10.1136/bmj.l4898
31. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev.* 2019;10:ED000142. https://doi.org/10.1002/14651858.ED000142
32. Govoni M, Jansson EA, Weitzberg E, Lundberg JO. The increase in plasma nitrite after a dietary nitrate load is markedly attenuated by an antibacterial mouthwash. *Nitric Oxide*. 2008;19:333-337. https://doi.org/10.1016/j.niox.2008.08.003
33. Hirai DM, Zelt JT, Jones JH, et al. Dietary nitrate supplementation and exercise tolerance in patients with heart failure with reduced ejection fraction. *Am J Physiol Regul Integr Comp Physiol.* 2017;312:R13-R22. https://doi.org/10.1152/ajpregu.00263.2016
34. Lundberg JO, Carlstrom M, Larsen FJ, Weitzberg E. Roles of dietary inorganic nitrate in cardiovascular health and disease. *Cardiovasc Res.* 2011;89:525-532. https://doi.org/10.1093/cvr/cvq325
35. Cosby K, Partovi KS, Crawford JH, et al. Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. *Nat Med.* 2003;9:1498-1505. https://doi.org/10.1038/nm954
36. Kapil V, Weitzberg E, Lundberg JO, Ahluwalia A. Clinical evidence demonstrating the utility of inorganic nitrate in cardiovascular health. *Nitric Oxide.* 2014;38:45-57. https://doi.org/10.1016/j.niox.2014.03.162
37. Chiappa GR, Borghi-Silva A, Ferreira LF, et al. Kinetics of muscle deoxygenation are accelerated at the onset of heavy-intensity exercise in patients with COPD: relationship to central cardiovascular dynamics. *J Appl Physiol*. 2008;104:1341-1350. https://doi.org/10.1152/japplphysiol.01364.2007
38. Isbell TS, Gladwin MT, Patel RP. Hemoglobin oxygen fractional saturation regulates nitrite-dependent vasodilation of aortic ring bioassays. *Am J Physiol Heart Circ Physiol.* 2007;293:H2565-H2572. https://doi.org/10.1152/ajpheart.00759.2007
39. Maher AR, Milsom AB, Gunaruwan P, et al. Hypoxic modulation of exogenous nitrite-induced vasodilation in humans. *Circulation.* 2008;117:670-677. https://doi.org/10.1161/CIRCULATIONAHA.107.719591
40. Chen M, Chang S, Xu Y, Guo H, Liu J. Dietary beetroot juice—effects in patients with COPD: a review. *Int J Chron Obstruct Pulmon Dis.* 2024;19:1755-1765. https://doi.org/10.2147/COPD.S473397
41. Lara J, Ashor AW, Oggioni C, Ahluwalia A, Mathers JC, Siervo M. Effects of inorganic nitrate and beetroot supplementation on endothelial function: a systematic review and meta-analysis. *Eur J Nutr.* 2016;55:451-459. https://doi.org/10.1007/s00394-015-0872-7
42. Hobbs DA, Goulding MG, Nguyen A, et al. Acute ingestion of beetroot bread increases endothelium-independent vasodilation and lowers diastolic blood pressure in healthy men: a randomized controlled trial. *J Nutr.* 2013;143:1399-1405. https://doi.org/10.3945/jn.113.175778
43. Jonvik KL, Nyakayiru J, Pinckaers PJ, Senden JM, van Loon LJ, Verdijk LB. Nitrate-rich vegetables increase plasma nitrate and nitrite concentrations and lower blood pressure in healthy adults. *J Nutr.* 2016;146:986-993. https://doi.org/10.3945/jn.116.229807
44. Sobko T, Marcus C, Govoni M, Kamiya S. Dietary nitrate in Japanese traditional foods lowers diastolic blood pressure in healthy volunteers. *Nitric Oxide.* 2010;22:136-140. https://doi.org/10.1016/j.niox.2009.10.007
45. Borlaug BA, Anstrom KJ, Lewis GD, et al.; National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial. *JAMA.* 2018;320:1764-1773. https://doi.org/10.1001/jama.2018.14852
46. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* 2002;136:493-503. https://doi.org/10.7326/0003-4819-136-7-200204020-00006
47. Fewtrell L. Drinking-water nitrate, methemoglobinemia, and global burden of disease: a discussion. *Environ Health Perspect.* 2004;112:1371-1374. https://doi.org/10.1289/ehp.7216
48. Moran SP, Rosier BT, Henriquez FL, Burleigh MC. The effects of nitrate on the oral microbiome: a systematic review investigating prebiotic potential. *J Oral Microbiol.* 2024;16:2322228. https://doi.org/10.1080/20002297.2024.2322228
49. Prisant LM. Phosphodiesterase-5 inhibitors and their hemodynamic effects. *Curr Hypertens Rep.* 2006;8:345-351. https://doi.org/10.1007/s11906-006-0075-y
50. King DA, Cordova F, Scharf SM. Nutritional aspects of chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* 2008;5:519-523. https://doi.org/10.1513/pats.200707-092ET
51. Holtrop G, Johnstone AM, Fyfe C, Gratz SW. Diet composition is associated with endogenous formation of N-nitroso compounds in obese men. *J Nutr.* 2012;142:1652-1658. https://doi.org/10.3945/jn.112.158824
52. Seyyedsalehi MS, Mohebbi E, Tourang F, Sasanfar B, Boffetta P, Zendehdel K. Association of dietary nitrate, nitrite, and N-nitroso compounds intake and gastrointestinal cancers: a systematic review and meta-analysis. *Toxics.* 2023;11:190. https://doi.org/10.3390/toxics11020190

Nutrition Reviews, 2026, 00, 1–15
https://doi.org/10.1093/nutrit/nuag013
Meta-Analysis