Systematic Review and Meta-Analysis

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Efficacy and safety of nitrate supplementation on exercise tolerance in chronic obstructive pulmonary disease

A systematic review and meta-analysis

Hongkuan Yang, MMed[a], Shuifeng He, BD[b], Fang Chen, PhD[c], Linbao Liang, BD[a], Junjie Pan, PhD[d,*]

Abstract

Background: Exercise intolerance was prevalent in people with chronic obstructive pulmonary disease (COPD) and had a detrimental effect on the quality of life. We aimed to evaluate the efficacy and safety of nitrate supplementation in exercise tolerance of people with COPD.

Methods: We searched medical databases including Cochrane Library, EMBASE, and PubMed from inception to October 2020 for randomized control trials in treating COPD with nitrate supplementation.

Results: Nine trials were identified. Compared with placebo, nitrate supplementation has no significant effect on the following variables: exercise endurance time (standard mean difference [SMD]: 0.06; 95% confidence interval [CI]: –0.39 to 0.52; $P = .79$), exercise capacity (SMD: 0.30; 95% CI: –0.21 to 0.80; $P = .25$), oxygen consumption (SMD: –0.04; 95% CI: –0.33 to 0.25; $P = .80$), resting systolic blood pressure (MD: –2.84; 95% CI: –8.46 to 2.78; $P = .32$), systolic blood pressure after exercise (MD: –4.66; 95% CI –15.66 to 6.34; $P = .41$), resting diastolic blood pressure (MD: 0.89; 95% CI: –4.41 to 6.19; $P = .74$), diastolic blood pressure after exercise (MD: –0.21; 95% CI: –5.51 to 5.10; $P = .94$), heart rate (MD: –2.52; 95% CI: –7.76 to 2.73; $P = .35$), and arterial oxygen saturation (MD: –0.44; 95% CI: –2.38 to 1.49; $P = .65$). No severe adverse effects from nitrate supplementation were reported in the included trails.

Conclusion: Current evidence suggests that nitrate supplementation may be safe but ineffective for improving exercise tolerance in people with COPD.

Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, DBP = diastolic blood pressure, HR = heart rate, IND = inspiratory neural drive, ISWTD = incremental shuttle walk test distance, MD = mean difference, NA = not available, NO = nitric oxide, RCTs = randomized control trials, SaO_2 = arterial oxygen saturation, SBP = systolic blood pressure, SMD = standard mean difference, V_E/V_{CO2} = ventilation relative to carbon dioxide production, VO_2 = oxygen consumption.

Keywords: chronic obstructive pulmonary disease, exercise tolerance, nitrate

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide disease with a global prevalence of 11.7%, causing a great burden to the global medical system with annual death of 3 million.[1,2] People with COPD experience persistent respiratory symptoms such as breathlessness and dyspnea. Dyspnea occurs when there is a mismatch between increased inspiratory neural drive (IND) and inadequate mechanical response of the respiratory system.[3]

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Data Availability: The numeric data supporting this meta-analysis are from previously reported studies, which have been cited. The processed data are available from the corresponding author upon request.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Respiratory Intensive Care Unit, The People's Hospital of Gaozhou, Maoming, China, [b] The First Section of Department of Pulmonary and Critical Care Medicine, The People's Hospital of Gaozhou, Maoming, China, [c] Pulmonary Function Room, Zhejiang Hospital of Traditional Chinese Medicine, Hangzhou, China, [d] Pulmonary and Critical Care Medicine Department, Hangzhou Hospital of Traditional Chinese Medicine (Dingqiao District), Hangzhou, China.

[*] Correspondence: Junjie Pan, Pulmonary and Critical Care Medicine Department, Hangzhou Hospital of Traditional Chinese Medicine (Dingqiao District), 310021, China (e-mail: 516606020@qq.com).

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Airflow limitation caused by destruction and remodeling of the lung tissue, as well as skeletal muscle dysfunction, contribute to inadequate mechanical response of the respiratory system when gas exchange abnormality caused by pulmonary blood flow shunting contribute to increased IND.[4,5] Dyspnea results in fatigue and exercise intolerance, lowering the quality of life in people with COPD.[6] Promoting exercise tolerance has always been a therapeutic priority in COPD therapy guidelines.[7]

Nitric oxide (NO) has been used to improve exercise tolerance in people with COPD. NO is a potent arterial vasodilator and plays a vital role in the relaxation of smooth muscle cells in blood vessel walls.[8] Inhaled or oral vasodilator therapy may improve pulmonary blood flow, improve ventilation-perfusion mismatch, and reduce IND.[9] As a result, NO may relieve dyspnea in people with COPD. Moreover, NO holds a significant function in skeletal muscle contraction and mitochondrial oxidative phosphorylation efficiency,[10,11] which may promote mechanical efficiency. Several studies revealed that nitrate supplementation, which converts into NO through entero-salivary pathway in vivo,[12] could improve exercise tolerance in people with COPD. Berry et al[13] found that acute dietary nitrate supplementation improved exercise performance and reduced blood pressure in people with COPD. Curtis et al[14] found that nitrate-rich beetroot juice caused reduced oxygen consumption (VO_2) at isotime. However, other researchers made different results. Beijers et al[15] discovered that sodium nitrate supplementation did not modulate mechanical efficiency in people with COPD. Leong et al[16] stated that dietary nitrate supplementation as beetroot juice did not enhance exercise endurance in people with COPD. The contradictory results make it difficult to determine the efficacy of nitrate supplementation on exercise tolerance in people with COPD.

We wonder whether nitrate supplementation may improve exercise tolerance in people with COPD. Herein, we systematically review the evidence and perform a meta-analysis on efficacy and safety of nitrate supplementation in COPD to establish a reference for clinical practice.

2. Materials and methods

This study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[17]

2.1. Literature search

We searched medical databases including Cochrane Library, EMBASE, and PubMed from inception until October 2020. The details of search strategy are included in Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G586 for the details of the search strategy in databases including Cochrane Library, EMBASE, and PubMed. Additionally, we reviewed the references of included studies to prevent missing any eligible studies and increase the recall ratio.

2.2. Inclusion criteria

(1) People with COPD diagnosed with international guidelines.[7]
(2) Comparison of nitrate supplementation with control.
(3) Randomized controlled trials (RCTs).
(4) Full-text papers published in peer-reviewed journals.
(5) Studies published in English language.

2.3. Exclusion criteria

(1) Protocols or conference abstracts.
(2) Data could not be extracted from articles for meta-analysis.

2.4. Quality assessment

The qualities of included randomized studies were evaluated for the risk of bias by the Cochrane Collaboration's tool.[18]

2.5. Data extraction

Two authors, HY and SH, independently screened the literature and extracted data. Different opinions from the 2 authors were resolved through consensus or consultation with a third author, FC. Information in the included studies such as study design, sample size, age, sex ratio, intervention, control, and outcome was extracted with a pre-set data extract table piloted by Kun Zhao.

2.6. Data synthesis and analysis

Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK) was employed for statistical analysis. Statistical heterogeneity in studies was assessed using I^2 method, with $I^2 > 50\%$ or $P < .1$, suggesting significant heterogeneity. The results were expressed as standardized mean difference (SMD) or mean difference (MD) with a corresponding 95% confidence interval (CI). $P < .05$ was considered statistically significant. Sensitivity analysis was performed to determine the robustness of results by excluding any single study. Subgroup analysis was conducted to evaluate efficacy of nitrate supplementation on resting systolic blood pressure and systolic blood pressure after exercise, as well as resting diastolic blood pressure and after exercise.

3. Ethical statement

This study did not require ethical approval because it is based on previously conducted studies and does not contain any studies with human participants or animals performed by any author.

4. Results

4.1. Literature search

After searching databases, 277 studies were obtained. After removing duplicates and studies that did not match inclusion criteria, 16 were reserved for full-text review. Finally, we identified 9 studies after excluding studies including conference abstracts, protocols, or studies that lack available data. The process of literature search is depicted in Fig. 1.

4.2. Study characteristics and quality assessment

The study characteristics are detailed in Table 1.

The studies were performed from 2014 to 2018 and in different countries, including Netherlands (n = 1), USA (n = 2), UK (n = 4),

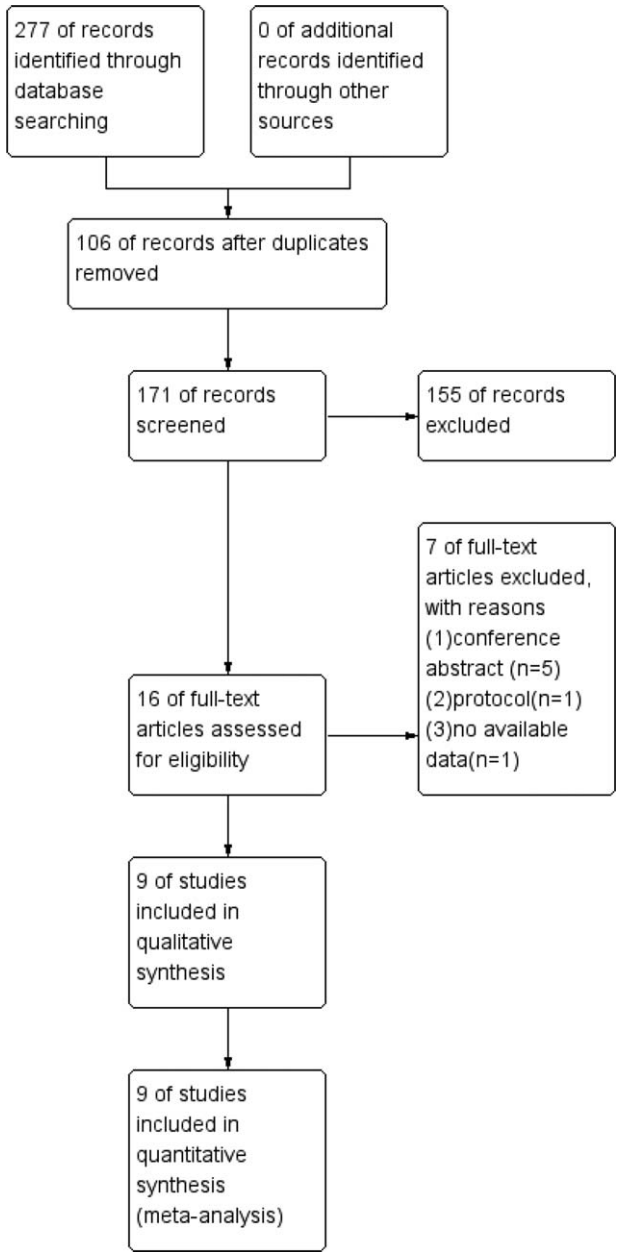

Figure 1. The process of literature search.

Denmark (n = 1), and Australia (n = 1).[13–16,19–23] The sample sizes in studies ranged from 8 to 25 subjects with 145 subjects in total. Most studies were crossover trials except for 1 study, which was a parallel group trial.[19] Most studies used beetroot juice for nitrate supplementation except 1 study, which used inorganic sodium nitrate.[15]

The quality assessment is detailed in Fig. 2.

5. Efficacy

5.1. Exercise endurance time

Two RCTs,[15,16] involving 74 subjects, evaluated exercise endurance time in nitrate supplementation and control groups, indicating low heterogeneity ($P = .92$, $I^2 = 0\%$). SMD was employed in these 2 studies since cycling time and endurance shuttle walk test time were used. In overall analysis, nitrate did not significantly increase endurance time (SMD: 0.06; 95% CI: –0.39 to 0.52; $P = .79$, Fig. 3).

5.2. Exercise capacity

Five RCTs,[16,20–23] involving 132 subjects, evaluated exercise capacity in nitrate intervention and control groups, demonstrating high heterogeneity ($P = .09$, $I^2 = 50\%$). SMD was employed in these studies since 6-minute walk test distance, endurance shuttle walk test distance, and incremental shuttle walk test distance were utilized. In overall analysis, nitrate did not significantly increase exercise capacity (SMD: 0.30; 95% CI: –0.21 to 0.80; $P = .25$, Fig. 4).

5.3. Oxygen consumption

Six RCTs,[13–15,19,20,23] including 185 subjects, evaluated VO_2 in the nitrate intervention and control groups, revealing low heterogeneity ($P = 1.00$, $I^2 = 0\%$). SMD was employed in these studies since different measure units (mL/min or mL/kg/min) were utilized. In overall analysis, nitrate did not significantly decrease VO_2 (SMD: –0.04; 95% CI: –0.33 to 0.25; $P = .80$, Fig. 5).

5.4. Systolic blood pressure

Preset subgroup analysis was performed for systolic blood pressure (SBP). Five RCTs,[13,16,20,21,23] involving 146 subjects, evaluated resting SBP in nitrate intervention and control groups, demonstrating low heterogeneity ($P = .34$, $I^2 = 11\%$). In overall analysis, nitrate did not significantly decrease resting SBP (MD: –2.84; 95% CI: –8.46 to 2.78; $P = .32$, Fig. 6). Four RCTs,[13,15,19]

Table 1

Characteristics of the included studies.

Author	Year	Study design	Sample size (n)	Age, yr	Gender (M/F)	Intervention	Control	Duration	Outcome
Shepherd[23]	2015	Crossover study	13	64.7 ± 7.7	NA	70 mL beetroot juice (6.77 mmol nitrate)	Placebo	Twice a day for 2.5 days	No difference in VO_2, 6MWTD, SBP, DBP.
Leong[16]	2015	Crossover study	19	67 ± 7.9	5/14	70 mL beetroot juice (4.8 mmol nitrate)	Placebo	Twice a day for 3.5 days	No difference in ESWTD, ESWTT. Decreased resting SBP.
Kerley[22]	2018	Crossover study	8	62.9 ± 7.1	5/3	140 mL beetroot juice (12.9 mmol nitrate)	Placebo	Once a day for 14 days	Increased ISWTD.
Kerley[21]	2015	Crossover study	11	69 ± 7	5/6	140 mL beetroot juice (12.9 mmol nitrate)	Placebo	Once a day for 1 day	Decreased SBP, DBP. Increased ISWTD. No difference in HR, SaO_2.
Friis[20]	2017	Crossover study	15	63 ± 13	9/6	140 mL beetroot juice (600 mg nitrate)	Placebo	Twice daily for 7 days	No difference in VO_2, 6MWTD, HR, SBP. Decreased DBP.

(*continued*)

Table 1

(continued).

Author	Year	Study design	Sample size (n)	Age, yr	Gender (M/F)	Intervention	Control	Duration	Outcome
Curtis[14]	2015	Crossover study	21	68 ± 7	16/5	140 mL beetroot juice (0.8 g or 12.9 mmol nitrate)	Placebo	Once a day for 1 day	No difference in HR, SaO_2. Decreased DBP, VO_2.
Berry[13]	2014	Crossover study	15	69.6 ± 8.5	12/3	140 mL beetroot juice (7.58 mmol of NO_3^-)	Placebo	Once a day for 1 day	No difference in HR, VO_2, SaO_2. Decreased DBP, resting SBP.
Beijers[15]	2017	Crossover study	18	66.6 ± 7.5	13/5	140 mL water with 680 mg NaNO3 (496 mg or 8 mmol nitrate)	Placebo	Once a day for 7 days	No difference in VO_2, Cycling time, SBP, DBP, HR.
Behnia[19]	2018	Parallel group study	Nitrate (n = 12) placebo (n = 13)	Nitrate 67 ± 8 placebo 68 ± 10	Nitrate 6/6 placebo 7/6	250 mL juice (made of 70 mL of beetroot juice plus 180 mL of black currant juice).	Placebo	Once a day for 8 days	No difference in VO_2, HR, DBP. Decreased SBP.

6MWTD = six-minute walk test distance, DBP = diastolic blood pressure, ESWTD = endurance shuttle walk test distance, ESWTT = endurance shuttle walk test time, HR = heart rate, ISWTD = incremental shuttle walk test distance, NA = not available, SaO_2 = arterial O_2 saturation, SBP = systolic blood pressure, VO_2 = oxygen consumption.

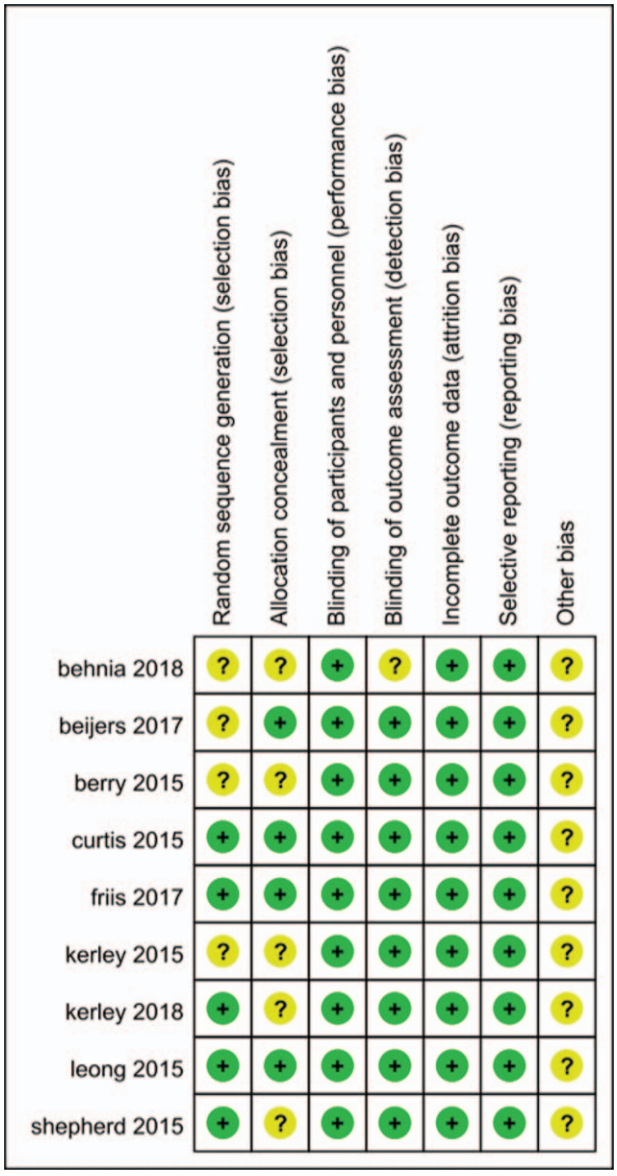

Figure 2. Risk of bias summary.

including 129 subjects, evaluated SBP after exercise in nitrate intervention and control groups, revealing low heterogeneity ($P = .19$, $I^2 = 37\%$). In overall analysis, nitrate did not significantly decrease SBP after exercise (MD: –4.66; 95% CI: –15.66 to 6.34; $P = .41$, Fig. 6).

5.5. Diastolic blood pressure

Preset subgroup analysis was performed for diastolic blood pressure (DBP). Four RCTs,[14,20,21,23] involving 120 subjects, evaluated the resting DBP in the nitrate intervention and control groups, revealing high heterogeneity ($P = .07$, $I^2 = 58\%$). In overall analysis, nitrate did not significantly decrease resting DBP (MD: 0.89; 95% CI: –4.41 to 6.19; $P = .74$, Fig. 7). Three RCTs,[13,15,19] including 91 subjects, evaluated DBP after exercise in nitrate intervention and control groups, manifesting low heterogeneity ($P = .31$, $I^2 = 16\%$). In overall analysis, nitrate did not significantly decrease DBP after exercise (MD: –0.21; 95% CI: –5.51 to 5.10; $P = .94$, Fig. 7).

5.6. Heart rate

Six RCTs,[13–15,19–21] involving 189 subjects, evaluated the heart rate (HR) in nitrate intervention and control groups, indicating low heterogeneity ($P = .67$, $I^2 = 0\%$). In overall analysis, nitrate did not significantly decrease HR (MD: –2.52; 95% CI: –7.76 to 2.73; $P = .35$, Fig. 8).

5.7. Arterial O_2 saturation

Three RCTs,[13,14,21] including 94 subjects, evaluated arterial O_2 saturation (SaO_2) in nitrate intervention and control groups, revealing high heterogeneity ($P = .11$, $I^2 = 55\%$). In overall analysis, nitrate did not significantly decrease SaO_2 (MD: –0.44; 95% CI: –2.38 to 1.49; $P = .65$, Fig. 9).

5.8. Safety

No severe adverse effects from nitrate supplementation were reported in included trials. The adverse effects are shown in Table 2.

5.9. Sensitivity analysis

For exercise capacity, heterogeneity disappeared when a study from Kerley was omitted, but statistical significance remained the

Figure 3. Forest plot of exercise endurance time.

same.[21] For resting DBP, heterogeneity disappeared when a study from Kerley or Curtis was excluded, but statistical significance remained unchanged.[14,21] For SaO_2, heterogeneity disappeared when a study from Kerley was omitted, but statistical significance remained the same.[21]

6. Discussion

Our study aimed to evaluate the efficacy and safety of nitrate supplementation on exercise tolerance in people with COPD. We found that nitrate supplementation may be safe but does not significantly affect exercise capacity, exercise endurance time, oxygen cost, blood pressure, oxygen saturation, or HR in people with COPD.

Dyspnoea is a symptom of COPD which contributes to exercise intolerance in patients with COPD. Dyspnea has been shown to result from disruption of normal relationship between IND to breathe and the dynamic response of the respiratory system.[3] Nitrate acquired from beetroots juice or sodium nitrate consumption can be converted into NO in vivo, which is an important regulator of vascular blood flow, mitochondrial function, skeletal muscle contractility, and calcium handling.[24] It has been postulated that nitrate supplementation may improve pulmonary blood flow, improve ventilation-perfusion mismatch, and reduce IND.[9] As a result, NO can relieve dyspnea in people with COPD. In our study, nitrate supplementation did not induce any effects on exercise tolerance in COPD. We speculate that, may be nitrate supplementation did not affect respiratory mechanics. The study by Behnia et al[19] included in this review found that nitrate supplementation did not affect markers of ventilation/perfusion matching (i.e., ventilation relative to carbon dioxide production, V_E/V_{CO2} ratio) nor ventilation during exercise in people with COPD, although it increased the level of exhaled NO by 200%. This phenomenon may explain why nitrate supplementation did not have any effect on COPD. A recent study done by Phillips et al[25] showed that inhaled NO increased peak oxygen uptake, secondary to reduced ventilation relative to carbon dioxide production (V_E/V_{CO2}) and dyspnoea, which improved exercise capacity in people with mild COPD. The differences in these findings may result from the nature of subjects included. In the study by Phillips et al, the subjects had mild COPD whereas subjects included in the studies involved in

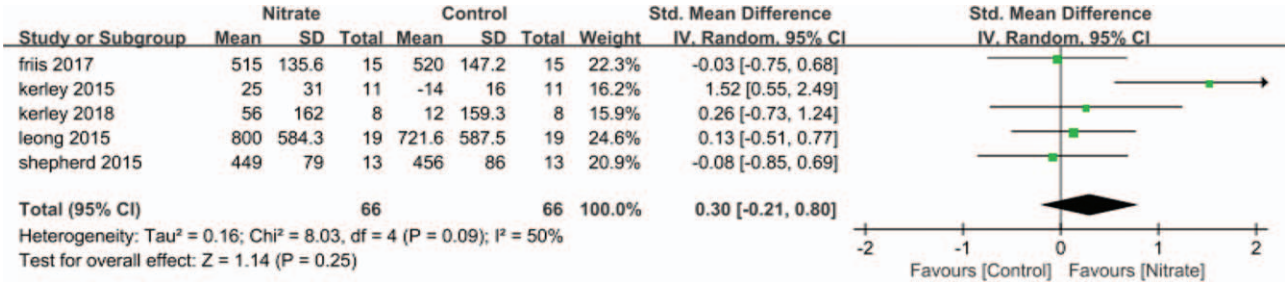

Figure 4. Forest plot of exercise capacity.

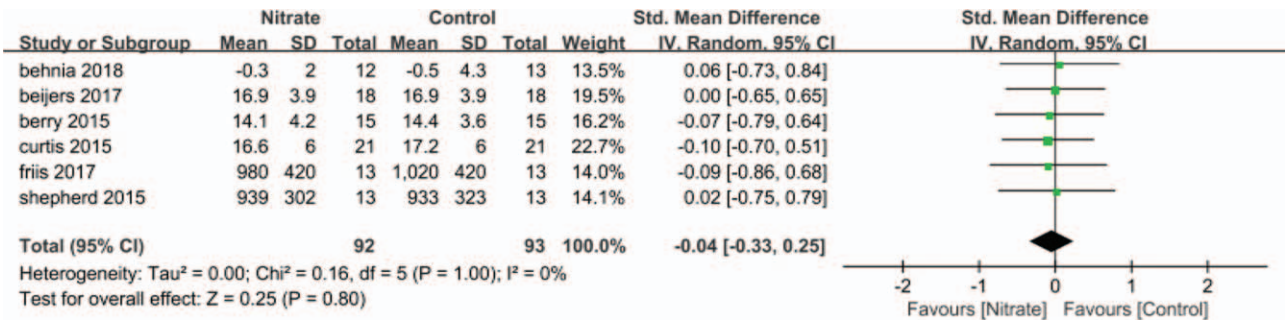

Figure 5. Forest plot of oxygen consumption.

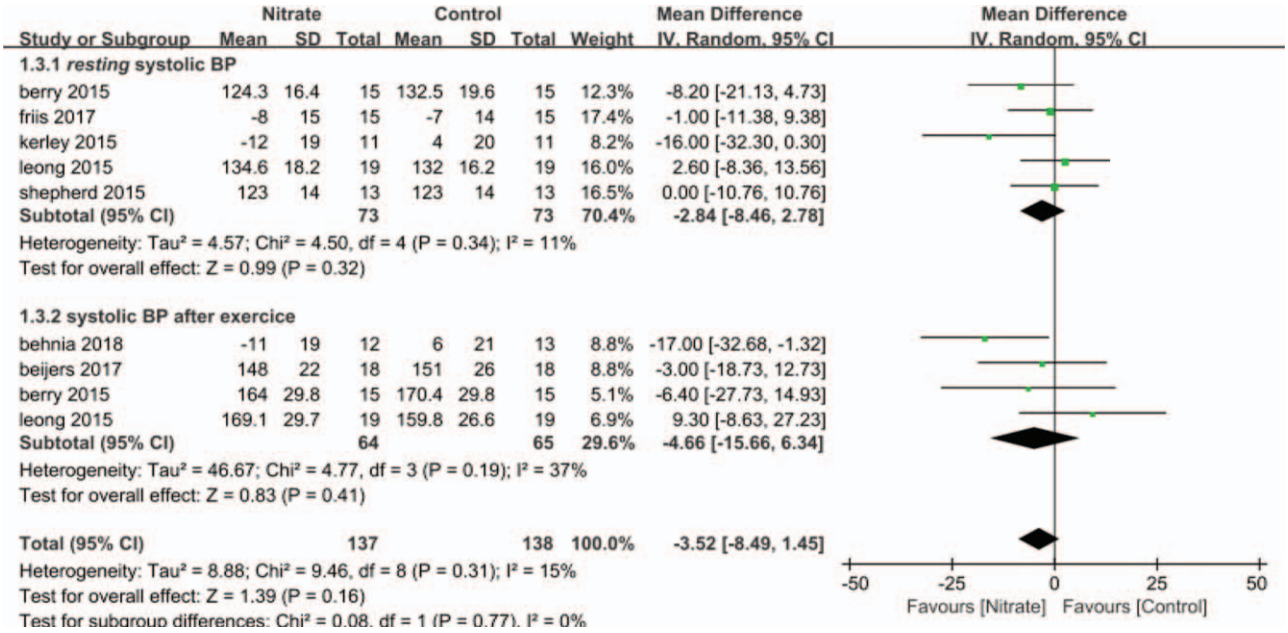

Figure 6. Forest plot of systolic blood pressure.

our review had moderate to severe COPD. The progression of COPD is accompanied by damage to the pulmonary capillaries due to emphysema as well as pulmonary vasoconstriction caused by hyoxemia. In people with moderate to severe COPD, application of pulmonary vasodilators may regulate hypoxic pulmonary vasoconstriction and redirect perfusion to poorly ventilated alveoli. This will cause low ventilation–perfusion ratio and negatively affect pulmonary gas exchange.[26,27] This may partly explain the results reported by Phillips et al.[25]

Our meta-analysis revealed no decrease in SBP or DBP. A meta-analysis revealed that vascular aging might reduce tissue-specific responses to nitrate supplementation and the capacity to convert inorganic nitrate into nitrite,[28] which may partly explain why nitrate supplementation is ineffective in lowering blood pressure, given that included subjects in our meta-analysis were elderly. Another possible explanation may be using anti-hypertensive medication in included subjects in clinical trials. Numerous studies found no significant reduction in blood pressure in older hypertension subjects receiving anti-hypertensive medication.[29,30] It was supposed that anti-hypertensive agents might mitigate NO-mediated reduction in blood pressure by an unknown mechanism. In our meta-analysis, people with COPD receive anti-hypertensive medication, which may cause anti-hypertensive agents to mitigate NO-mediated reduction in blood pressure.

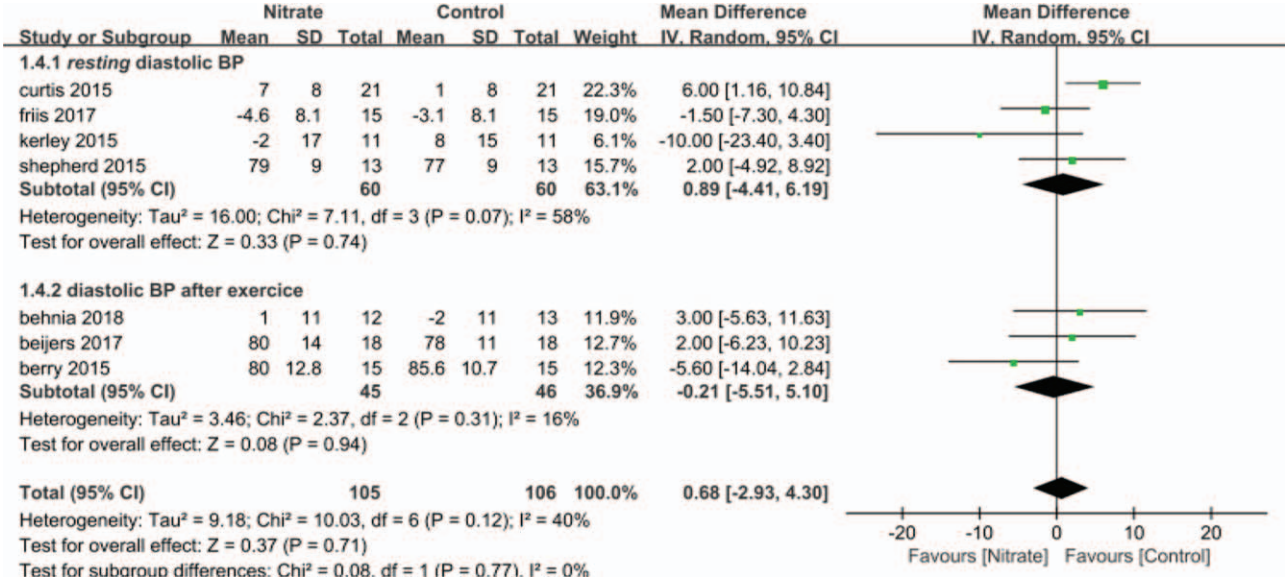

Figure 7. Forest plot of diastolic blood pressure.

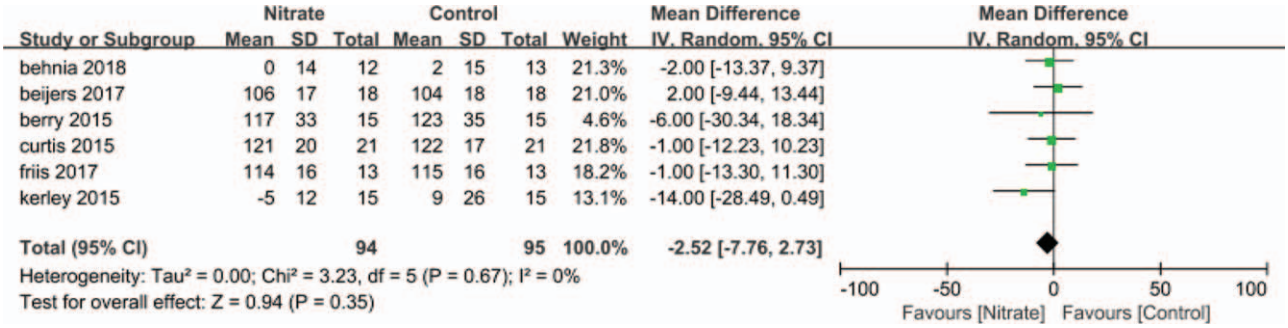

Figure 8. Forest plot of heart rate.

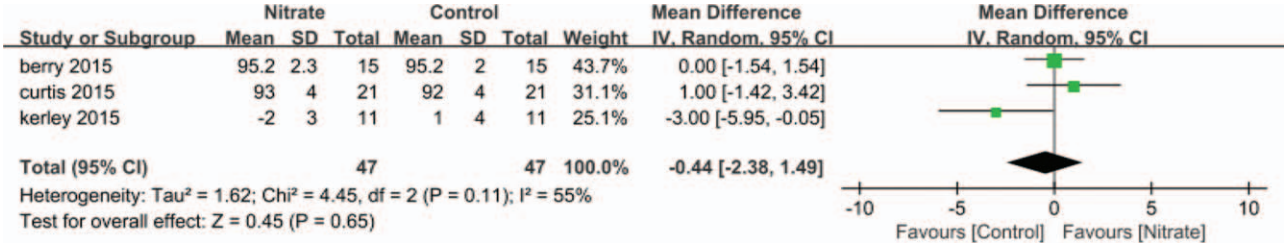

Figure 9. Forest plot of arterial oxygen saturation.

Our study also examined the safety of nitrate supplementation. Generally speaking, nitrate supplementation in the form of beetroot was well-tolerated with no reports of severe adverse effects. Specific investigations revealed gastrointestinal reactions such as nausea and color change in defecation.[14,20,22,23] The only study which utilized inorganic sodium nitrate for nitrate supplementation did not mention any adverse effect.[15]

Our study has some strengths. As far as we know, this study is the first meta-analysis evaluating efficacy and safety of nitrate supplementation on exercise tolerance in people with COPD. The included studies were all RCTs with relatively high quality of evidence. The meta-analysis was strictly conducted according to PRISMA guidelines. However, there were also some limitations. First, due to limited resources, only studies written in English were included in our meta-analysis, which may cause omission of some studies written in other languages. Second, most included studies employed a commercial beetroots juice in one company for nitrate supplementation (only 1 study used sodium nitrate). This could result in a bias due to the dosage form and its manufacturers. Third, the publication bias evaluation was unable to perform because included studies are <10.

Table 2

Adverse effect of the nitrate supplementation in patients with COPD.

Author	Adverse effect
Curtis[14]	Beeturia
Shepherd[23]	Red stools and beeturia
Friis[20]	Nausea
Kerley[22]	Intolerance to beetroots juice taste/texture

COPD = chronic obstructive pulmonary disease.

7. Conclusions

Current evidence suggests that nitrate supplementation may be safe but ineffective for improving exercise tolerance in people with COPD. The underlying mechanism is required for investigation, as is the subtype of people with COPD who benefit from nitrate supplementation.

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Author contributions

Conceptualization: Hongkuan Yang.
Data curation: Hongkuan Yang, Shuifeng He, Fang Chen.
Formal analysis: Shuifeng He, Fang Chen.
Investigation: Junjie Pan.
Methodology: Hongkuan Yang, Fang Chen, Junjie Pan.
Project administration: Hongkuan Yang.
Software: Linbao Liang.
Supervision: Hongkuan Yang.
Writing – original draft: Hongkuan Yang.
Writing – review & editing: Linbao Liang, Junjie Pan.

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