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REVIEW

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Plasma nitrate, dietary nitrate, blood pressure, and vascular health biomarkers: a GRADE-Assessed systematic review and dose-response meta-analysis of randomized controlled trials

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Abstract

Background Hypertension and vascular dysfunction are major health concerns, and studies have suggested different interventions, including dietary nitrate (NO3), to improve it. We sought to elucidate the effects of dietary NO3 on plasma NO3 and nitrite (NO2) levels and to determine the shape of the effect of dietary NO3 on blood pressure (BP) and vascular health biomarkers.

Methods PubMed, Scopus, and Web of Science were searched up to February 2024 for eligible randomized controlled trials (RCTs). The pooled results were reported as weighted mean differences (WMD) and 95% confidence intervals (CIs).

Results Our analysis of 75 RCTs involving 1823 participants revealed that per each millimole (mmol) increase in the administered NO3 dose, both acute (WMD: 32.7µmol/L; 95%CI: 26.1, 39.4) and chronic-term (WMD: 19.6µmol/L; 95%CI: 9.95, 29.3) plasma NO3 levels increased. Per each mmol increase in NO3 intake, a reduction in systolic BP levels was observed in the acute (WMD: -0.28mmHg; 95%CI: -0.40, -0.17), short-term (WMD: -0.24mmHg; 95%CI: -0.40, -0.07), and medium-term (WMD: -0.48mmHg; 95%CI: -0.71, -0.25) periods. Furthermore, a decrease in diastolic BP for each mmol increase in NO3 intake (WMD: -0.12 mmHg; 95% CI: -0.21, -0.03) was shown. Moreover, a linear dose-response relationship was indicated between each mmol of NO3 intake and medium-term pulse wave velocity (WMD:

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-0.07 m/s; 95%CI: -0.11, -0.03), medium-term flow-mediated dilation (WMD: 0.30%; 95%CI: 0.15, 0.46), and medium-term augmentation index (WMD: -0.57%; 95%CI: -0.98, -0.15).

Conclusion We observed dose-dependent increases in plasma NO3 and NO2 levels, along with consequent reductions in BP and enhancements in vascular health following dietary NO3 supplementation. Future high-quality, population-specific studies with optimized dietary NO3 dosages are needed to strengthen the certainty of the evidence.

Registration The protocol for this systematic review was registered in PROSPERO under the registration number CRD42024535335.

Keywords Nitrates, Hypertension, Vascular stiffness, Cardiometabolic risk factors, Controlled clinical trial, Preventive cardiology

Introduction

Elevated blood pressure (BP) contributes to the incidence, mortality, and disability associated with cardiovascular diseases (CVDs) [1, 2]. It is estimated that the upward trend in the prevalence of hypertension (HTN) will continue and reach 1.5 billion people worldwide by 2025 [3].

Meanwhile, arterial stiffness measured by pulse wave velocity (PWV) [4–6] or augmentation index (AI) [7], and endothelial function measured by flow-mediated dilation (FMD) [8] is an independent predictor of future cardiac events [9, 10] and plays a significant role in the pathogenesis of atherogenesis and HTN [11, 12]. Considering the bidirectional relationship between BP and vascular health, therapeutic strategies for improving them are needed to prevent cardiovascular morbidity and mortality [13–16].

Pharmacotherapy has a significant effect in lowering BP [17] but also has side effects and medication resistance [18], in which only a third of individuals undergoing pharmacological treatment achieve adequate BP control [19]. Effective, low-cost, sustainable strategies are needed to manage BP and vascular dysfunction. Meanwhile, nonpharmacologic interventions, including dietary approaches, are a cornerstone for managing high BP [20].

Dietary interventions showed promise in reducing BP levels and improving vascular dysfunction [21–24], offering safe, affordable options easily integrated into daily life [25, 26]. Dietary recommendations include sodium-restricted diets [27], and adopting the Dietary Approach to Stop Hypertension (DASH) diet, which emphasizes increasing fruits and vegetable consumption [28]. Previous clinical trials have utilized dietary vegetables such as beetroot and lettuce as rich sources of nitrate (NO3) (>2500 mg NO3/kg) [29]. The ingestion of dietary NO3 can lead to the production of nitric oxide (NO), which in turn causes vasodilation [30–32]. Additionally, dietary NO3 demonstrates anti-inflammatory and anti-aggregation properties and may impact energy production performance [33–35].

Previous studies have extensively explored the efficacy of dietary NO3 in reducing BP levels and improving vascular health markers, but some limitations should be addressed. Prior meta-analyses have failed to adequately differentiate between NO3 salts and dietary NO3 effects [36–40] and have mainly focused on NO3 from beetroot, leaving the consumption of NO3 from other dietary sources unexplored [41–44]. An umbrella review indicated that the effects of dietary NO3 on BP levels become more pronounced with higher doses, yet they did not clarify the shape of the association between dietary NO3 dosage and BP levels [22]. Additionally, previous studies have highlighted vasodilation due to elevated serum NO3 and nitrite (NO2) levels. Still, the extent of this effect and the relationship between dietary NO3 dosage and serum NO3 and NO2 levels remain uncertain. Some studies suggested that the impact of dietary NO3 on BP levels can be independent of the quantity of NO3 consumed [44]. Conversely, others proposed that this effect depends on the NO3 content in dietary sources [22].

We undertook a systematic review and meta-analysis to elucidate the potential dose-dependent impacts of dietary NO3 on plasma NO3 and NO2 as reservoirs for NO. We also aimed to determine the optimal dosage of dietary NO3 that positively affects BP levels and vascular health markers and stratify results based on the source of dietary NO3 and HTN status. Furthermore, we conducted a safety analysis to evaluate the risk of adverse events following dietary NO3 supplementation.

Materials and methods

The present dose-response meta-analysis has been conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [45] and also followed the guidelines of the Declaration of Helsinki. The protocol for this systematic review was registered in PROSPERO under the registration number CRD42024535335.

Systematic search

We systematically searched PubMed, Scopus, and ISI Web of Science up to February 2024. We employed keywords related to intervention, outcome, and study design to identify potential eligible randomized controlled trials (RCTs). A detailed search strategy is provided in Supplementary Table 1. We manually reviewed the reference lists of existing related reviews to augment the database search. Our search was restricted to studies published in English. Teams of two reviewers independently screened titles and abstracts according to pre-defined inclusion and exclusion criteria to identify potentially eligible RCTs.

Eligibility criteria

We employed the PICOS framework (population, intervention, comparator, outcome, and study design) to establish our inclusion and exclusion criteria. Eligible for inclusion in the present meta-analysis were published human interventional studies that met the following criteria: (1) RCTs, whether with parallel or crossover design, conducted on adults aged 18 years or older; (2) Investigating the effect of dietary NO3 on systolic BP (SBP), diastolic BP (DBP), ambulatory SBP, ambulatory DBP, mean arterial pressure (MAP), heart rate (HR), ambulatory HR, PWV, FMD, and AI, or measured plasma NO2 and NO3 levels. (3) Investigating the effect of various doses of dietary NO3 on BP, HR, vascular health biomarkers, or plasma NO2 and NO3 levels, compared to a placebo; (4) Considering changes in BP, HR, vascular health biomarkers, or plasma NO2 and NO3 levels as either primary or secondary outcomes; (5) Presenting mean and standard deviation (SD) of changes in BP, HR, vascular health biomarkers, or plasma NO2 and NO3 levels across study arms, or provided adequate information for estimation; and (6) Reporting the number of participants in each study arm. Studies with a non-randomized design, quasi-experimental trials, those involving adolescents (under 18 years old), pregnant and lactating women, and trials incorporating exercise plans alongside dietary NO3 interventions were excluded from the analysis.

Data extraction

Two reviewers (MHR and AMH), working independently and in duplicate, screened the full texts of eligible RCTs and extracted the following data: author and year of publication, location of the population, study design, duration of the study, characteristics of the population (sex and health status), total sample size, intervention details (type and dose of dietary NO3), comparison groups, and studied outcomes. Any discrepancies between the two reviewers were resolved through discussion.

Risk of bias assessment

Two reviewers (MHR and SGH), independently and in duplicate conducted the risk of bias assessments using the Cochrane risk of bias tool [46]. RCTs were assigned an overall quality score based on bias domains: good (≤ 1 item was unclear and none were high), fair (≤ 2 items were unclear or at least one was high), and high risk of bias (≥ 2 items were high). Any discrepancies in the risk of bias assessment were resolved through discussion.

Statistical analysis

We calculated the weighted mean difference (WMD) and 95% confidence interval (CI) of change to report the meta-analysis results. To conduct our meta-analysis, we used a random effect model [47] and followed a comprehensive method previously described [48]. We performed a random-effects pairwise meta-analysis to examine the impact of dietary NO3 supplementation on plasma NO3 and NO2 levels, considering both acute (within a few hours of supplementation) and chronic (after several days of supplementation) levels [47]. Additionally, we utilized the one-stage approach introduced by Crippa and Orsini et al. [49] to compute the mean difference and its corresponding SD for changes in the studied outcomes across various dietary NO3 dosages within the intervention group compared to the control group in each trial. We examined other studied outcomes across three supplementation durations: acute (within a few hours of supplementation), short-term (1–7 days of supplementation), and medium-term (more than a week of supplementation) [22].

The potential publication bias was evaluated through Egger's test [50], Begg's test [51], and visual examination of funnel plots. We quantitatively assessed heterogeneity using the I^2 statistic and conducted a $\chi 2$ test for homogeneity (P-heterogeneity > 0.10) [52]. For the safety analysis (comparative effects of dietary NO3 on adverse events and withdrawal due to intervention), we calculated relative effects based on the number of participants and events in both the intervention and control groups.

We conducted a one-stage weighted mixed-effects meta-analysis to elucidate the effect of various doses of dietary NO3 on BP, HR, vascular health biomarkers, or plasma NO2 and NO3 levels [49]. Nonlinear dose-response relationships were assessed using restricted cubic splines with 3 knots at Harrell's recommended centiles (10%, 50%, and 90%). The fitness of the non-linear model was determined by the significance of the Wald test [49, 53]. Finally, we conducted a sensitivity analysis to assess the impact of dietary NO3 on BP separately in hypertensive individuals and in studies that supplemented beetroot. Statistical analyses were performed using STATA software version 17.0, with significance set at a two-tailed *P* value of less than 0.05.

Grading the evidence

We employed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to assess the overall certainty of the evidence (CoE) for each outcome [54] based on a minimally contextualized and null effect approach [55]. Two pairs of authors, MN and MHR, independently conducted the GRADE assessment, and any discrepancies were resolved through consensus to reach a unified conclusion.

There are sets of criteria responsible for downgrading or upgrading the evidence. These criteria include limitations of the study (based on the risk of bias as assessed by the Cochrane Risk of Bias tool) [56], inconsistency (referring to substantial unexplained heterogeneity between studies; $I^2 \geq 50\%$ and P heterogeneity < 0.10) [57], indirectness (pertaining to factors related to population, intervention, comparator, or outcome that limit the generalizability of the findings) [58], imprecision (indicated by small sample size, wide 95% CIs for the WMDs or when the point estimate was not statistically significant. Of note, we used linear dose-response point estimate for the BP and vascular health biomarkers.) [59], and potential evidence of publication bias. However, a large effect size and dose-response gradient contribute to upgrading the CoE. Therefore, given that our study is a dose-response meta-analysis, we could upgrade the CoE when the dose significantly influenced the outcomes. The GRADE system categorizes CoE as high, moderate, low, or very low, as follows: (1) Very low: The actual effect is highly uncertain and may significantly deviate from the estimated effect; (2) Low: The actual effect may substantially deviate from the estimated effect, and further research is highly likely to impact both our CoE in the estimated effect and the effect estimate itself; (3) Moderate: CoE levels when the estimated effect closely approximates the actual effect. Further research can significantly influence our confidence in the estimated effect and may alter the estimate; and (4) High: CoE levels when there is a substantial degree of certainty that the actual effect aligns with the estimated effect. Additional research is unlikely to alter our confidence in the estimated effect.

Results

Study selection

The flow diagram for study selection is presented as Fig. 1. Initially, our systematic search in databases yielded 6061 results, of which 1493 were duplicates. The remaining records ($n = 4568$) underwent initial screening based on the title and abstract review. Out of these, 141 records required full-text review, leading to the inclusion of 75 RCTs [30, 60–133] and the exclusion of 66 studies due to added exercise plan to the main intervention ($n = 21$), did not report pre/post-intervention data ($n = 35$), did not illustrate clear diagram ($n = 2$), not suitable control group ($n = 7$) and conducted on pregnant women ($n = 1$).

Study characteristics

Supplementary Table 2 outlines the primary characteristics of the included RCTs. Our inclusion of 75 RCTs encompassed 86 studies, accounting for variations in follow-up duration or NO3 supplementation dosage among participants. Across all the RCTs included, there were 1823 participants.

Among the 86 studies, 12 followed a parallel design, while the remaining used a crossover design. Additionally, 2 studies were triple-blind, 62 were double-blind, 7 were single-blind, and 15 were open-label. Of all included studies, 47 were on healthy participants, 14 were on individuals with HTN or pre-HTN, 6 were on hypertensive individuals with heart failure (HF), type 2 diabetes mellitus (T2DM), or chronic obstructive pulmonary disease (COPD), and the remaining studies ($n = 19$) focused on other medical conditions. Of note, the mean age of study participants ranged from 18.6 to 72.5 years. Dietary NO3 supplementation was administered in various forms, including beetroot ($n = 70$), spinach ($n = 5$), lettuce ($n = 1$), or a NO3-rich diet ($n = 10$). Additionally, the intervention types were varied and included juice ($n = 68$), gel ($n = 1$), cereal bar ($n = 1$), extract ($n = 2$), or dietary plan ($n = 14$). Additionally, the daily dose of dietary NO3 intake ranged from 0.35 to 27.84 mmol. The study duration ranged from a minimum of 30 min in the acute phase to a maximum of 91 days in the chronic phase. Except for three studies, where participants received water [110] or had no intervention [130, 134], in all the other studies, individuals in the control groups consumed specified placebos (such as usual or low NO3 diet, NO3-depleted juice, cereal bar, or gel) compared to the intervention groups.

Meta-analysis

Pair-wise analysis for the effect of dietary NO3 on plasma levels of NO2 and NO3

As indicated in Supplementary Fig. 1, our findings revealed that dietary NO3 supplementation significantly influenced plasma NO2 levels both in acute (WMD: 0.25 μmol/L; 95% CI: 0.10, 0.40; I^2: 97.8) and chronic (WMD: 0.46 μmol/L; 95% CI: 0.23, 0.69; I^2: 99.7) terms. Additionally, dietary NO3 supplementation had a significant effect on acute (WMD: 390 μmol/L; 95% CI: 333, 446; I^2: 99.5) and chronic (WMD: 175 μmol/L; 95% CI: 88.0, 262; I^2: 99.9) plasma NO3 levels.

Dose-response analysis for the effect of dietary NO3 on plasma levels of NO2 and NO3

Our study showed a dose-response relationship between dietary NO3 and plasma NO3 and NO2 levels. As indicated in Fig. 2 and Supplementary Table 3, up to a dose

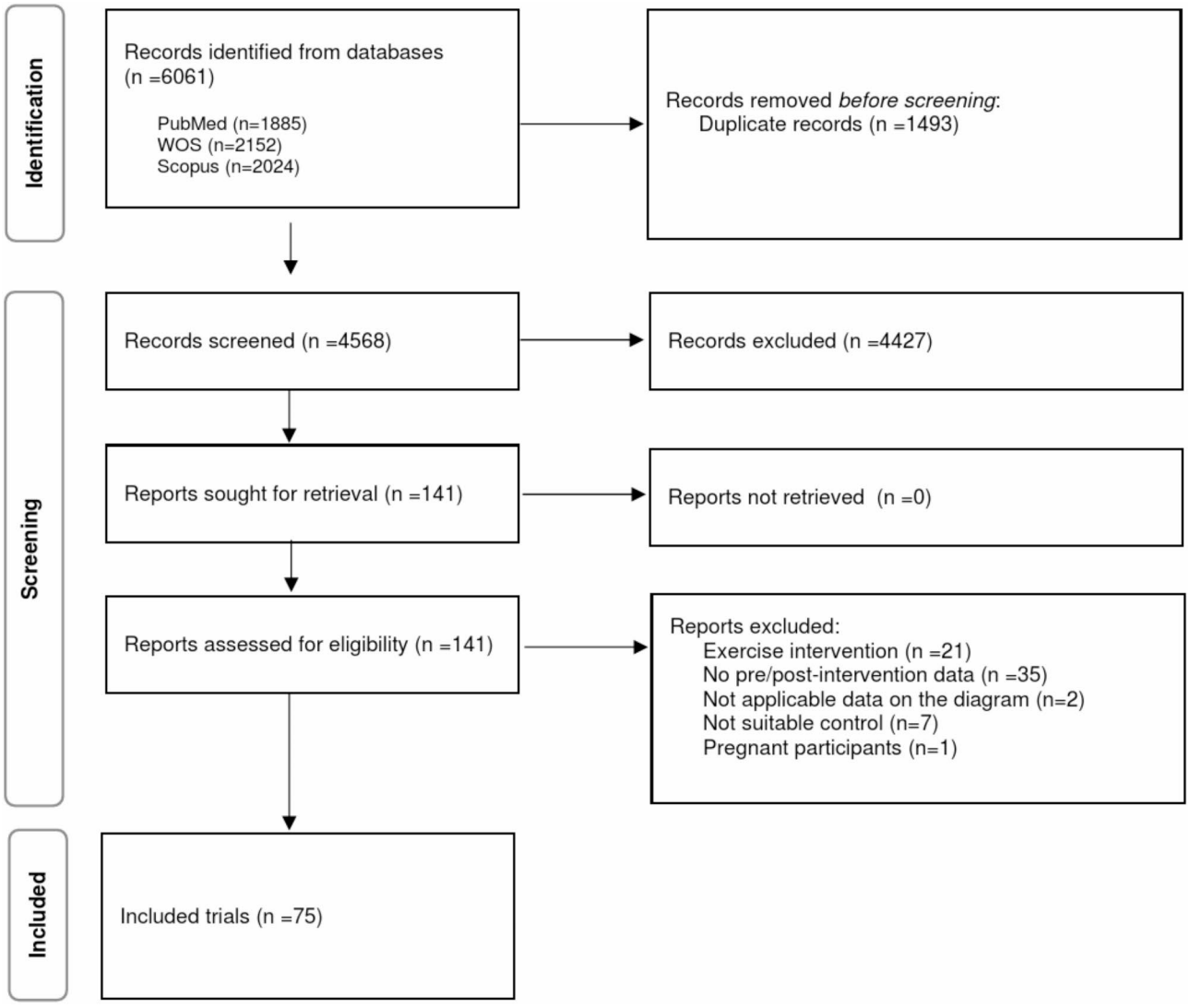

Fig. 1 The PRISMA flow diagram for the selection of the included studies

of 2 mmol of NO3 per day, there were no significant changes in plasma NO3 levels. However, at doses higher than 2 mmol per day, plasma NO3 levels increased linearly. Moreover, as depicted in Supplementary Fig. 2, for each mmol increase in NO3 dose, plasma NO3 levels increased both in acute (WMD: 32.7 µmol/L; 95% CI: 26.1, 39.4; I^2: 99.3) and chronic (WMD: 19.6 µmol/L; 95% CI: 9.95, 29.3; I^2: 99.8) terms. It has also been observed that per each mmol increase in NO3 intake, plasma NO2 levels changed both in acute (WMD: 0.02 µmol/L; 95% CI: 0.02, 0.03; I^2: 93.9) and chronic (WMD: 0.06 µmol/L; 95% CI: 0.02, 0.09; I^2: 99.7) terms.

Dose-response analysis for the effect of beetroot on plasma levels of NO2 and NO3

Our study showed a dose-response relationship between beetroot consumption and plasma NO3 and NO2 levels. As depicted in Fig. 3 and Supplementary Table 4, the most significant increase in chronic plasma NO3 levels was observed at a dosage of 250 ml per day (WMD: 202 µmol/L; 95% CI: 102, 303), beyond which the effect plateaued. Additionally, per each 70 ml dose of beetroot intake (Supplementary Fig. 3), acute (WMD: 188 µmol/L; 95% CI: 161, 215; I^2: 99.5) and chronic (WMD: 73.3 µmol/L; 95% CI: 59.6, 87.1; I^2: 98.6) plasma NO3 levels were increased. Moreover, the dose of beetroot intake exhibits a non-linear relationship with plasma NO2 levels. The maximum change in chronic plasma NO2 levels was observed at a daily dose of 250 ml of beetroot intake (WMD: 0.36 µmol/L; 95% CI: 0.15, 0.57), beyond which the effect declined. Acute plasma NO2 levels were increased up to a dose of 160 ml of beetroot per day (WMD: 0.25 µmol/L; 95% CI: 0.17, 0.33), after which the effect plateaued. Additionally, per each 70 ml increase in

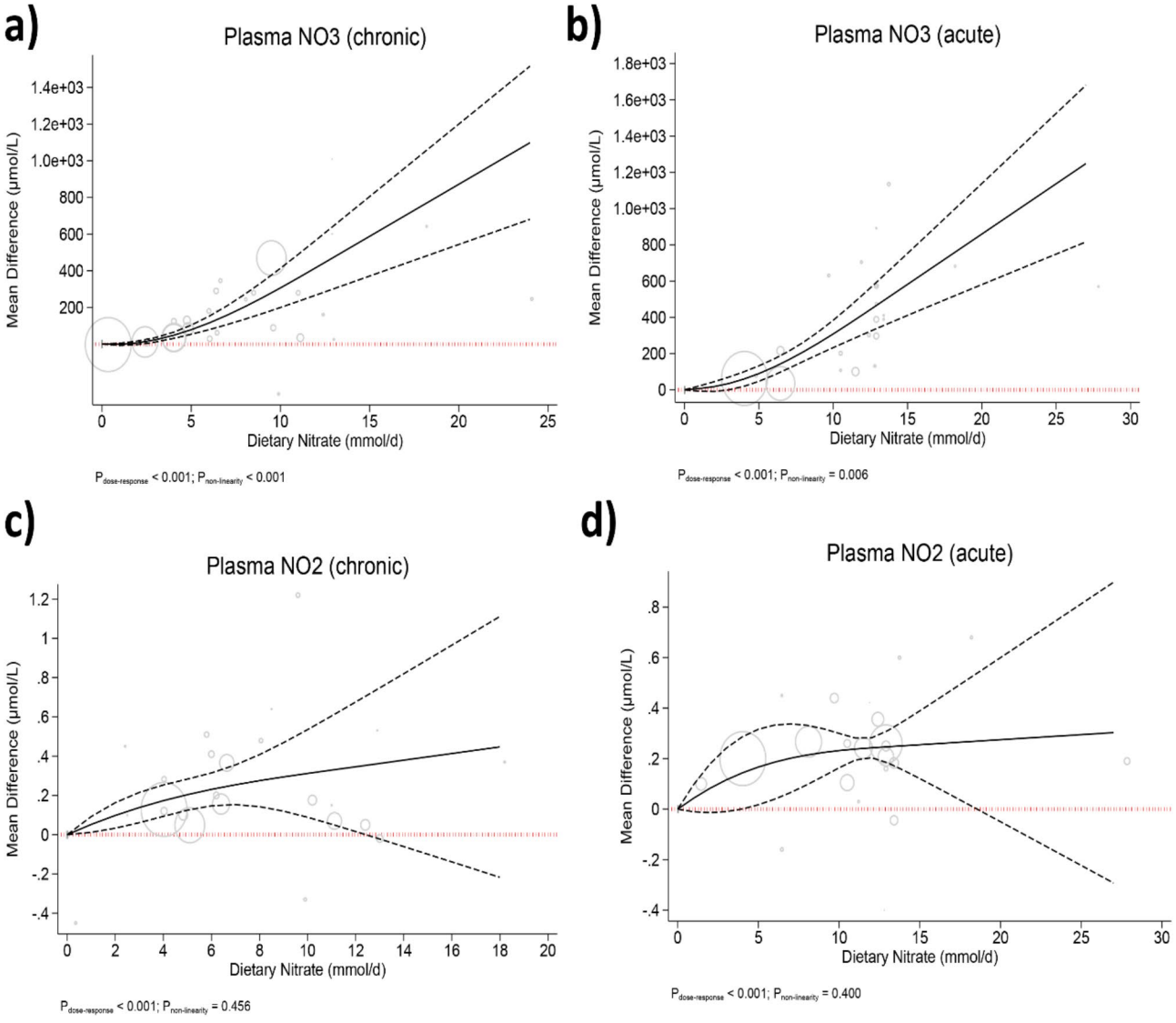

Fig. 2 Non-linear dose-response analysis for the effects of dietary nitrate (mmol/day) on WMDs of plasma levels of (**a**) chronic NO3, (**b**) acute NO3, (**c**) chronic NO2, and (**d**) acute NO2

beetroot intake, we observed an increase in acute (WMD: 0.10 µmol/L; 95% CI: 0.08, 0.12; I^2: 95.2) and chronic (WMD: 0.11 µmol/L; 95% CI: 0.08, 0.13; I^2: 97.6) plasma NO2 levels.

Dose-response analysis for the effect of dietary NO3 on BP and vascular health biomarkers

As depicted in Fig. 4 and Supplementary Figs. 4 and 5, there was a dose-response relationship between dietary NO3 dosage and levels of SBP (acute, short, and medium-term), DBP (acute-term), MAP (medium-term), PWV (medium-term), FMD (acute and medium-term), and AI (medium-term). For each mmol increase in NO3 intake (Supplementary Fig. 6), there was a decrease in SBP levels in the acute (WMD: -0.28 mmHg; 95% CI: -0.40, -0.17; I^2: 31.0), short-term (WMD: -0.24 mmHg; 95% CI: -0.40, -0.07; I^2: 32.5), and medium-term (WMD: -0.48 mmHg; 95% CI: -0.71, -0.25; I^2: 53.6) periods. Additionally, a linear relationship was observed between NO3 intake and acute-term DBP, with a decrease in DBP for each mmol increase in NO3 intake (WMD: -0.12 mmHg; 95% CI: -0.21, -0.03; I^2: 43.4). There was a non-linear dose-response relationship between dietary NO3 with medium-term MAP, that the greatest effect observed at a dose of 3 mmol dietary NO3 per day (WMD: -4.43 mmHg; 95% CI: -7.84, -1.03). However, there was no significant decrease in medium-term MAP at doses higher than 5 mmol dietary NO3 per day (Supplementary Table 5). Furthermore, for each mmol increase in dietary NO3 dosage, a linear dose-response relationship was observed between NO3 dose and medium-term PWV (WMD: -0.07 m/s; 95% CI: -0.11, -0.03; I^2: 0.00), medium-term

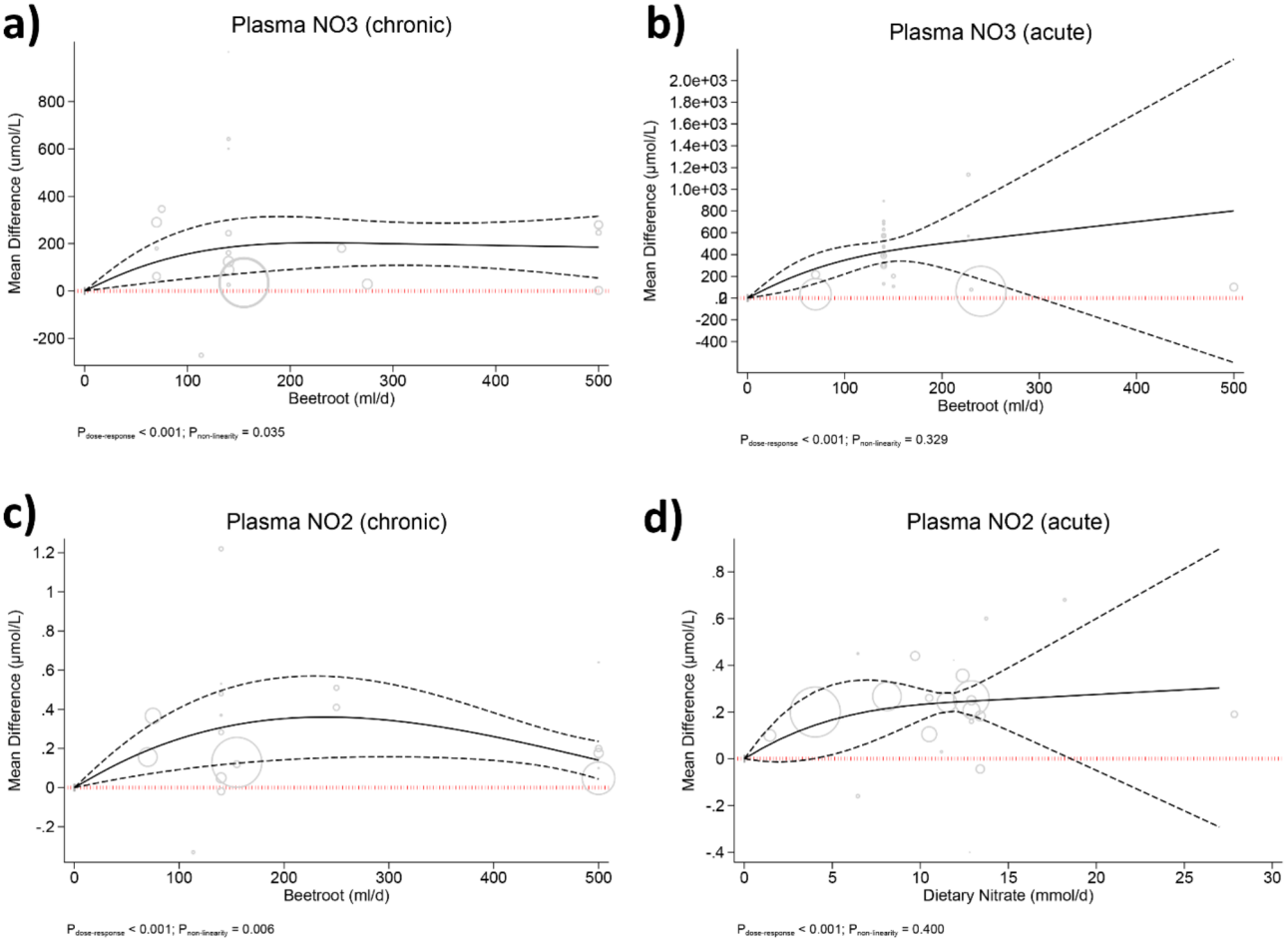

Fig. 3 Non-linear dose-response analysis for the effects of beetroot (ml/day) on WMDs of plasma levels of (**a**) chronic NO3, (**b**) acute NO3, (**c**) chronic NO2, and (**d**) acute NO2

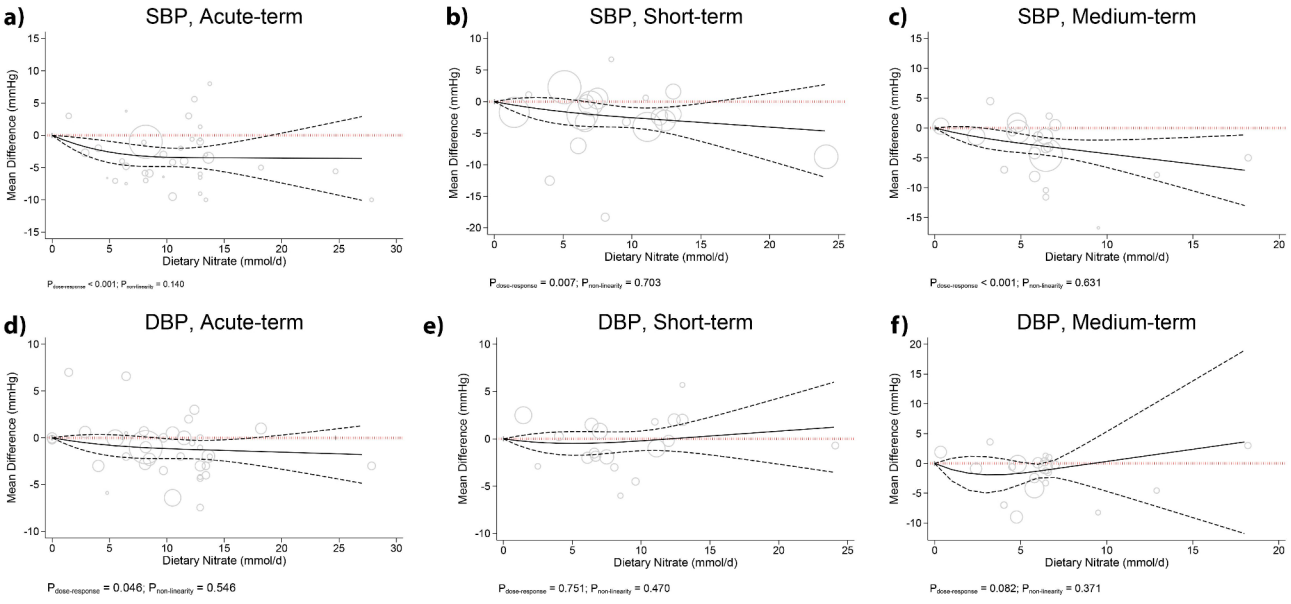

Fig. 4 Non-linear dose-response analysis for the effects of dietary nitrate (mmol/day) on the WMDs of (**a**) acute-term SBP, (**b**) short-term SBP, (**c**) medium-term SBP, (**d**) acute-term DBP, (**e**) short-term DBP, and (**f**) medium-term DBP

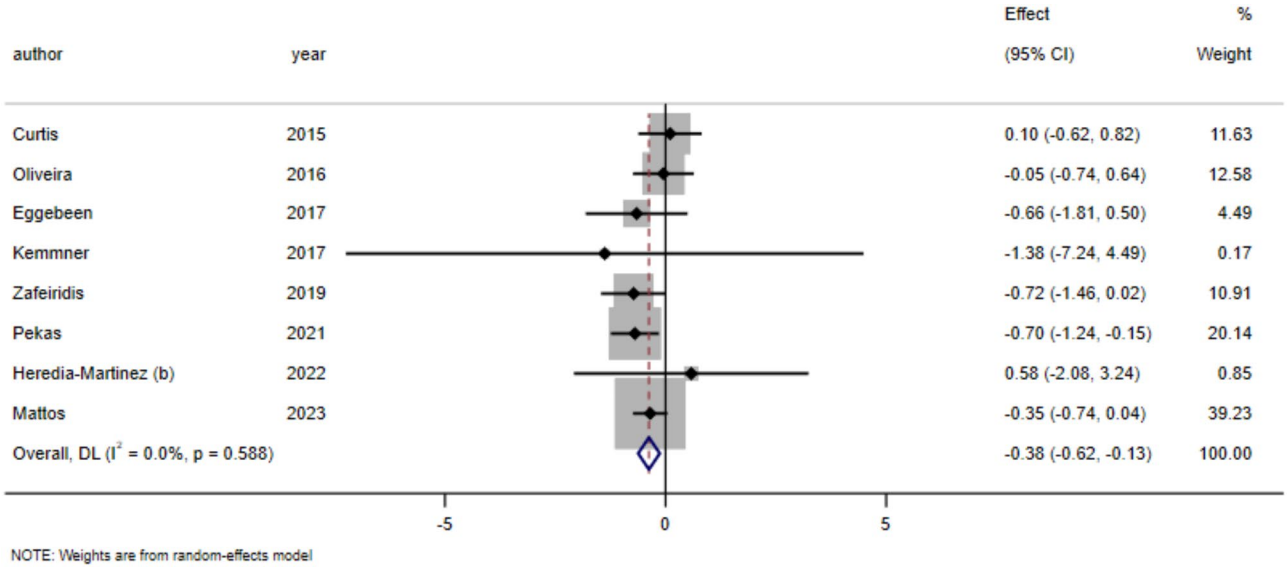

Fig. 5 Forest plot of the linear dose-response analysis indicating WMDs and the 95% CI for the impact of each mmol increase in dietary nitrate dosage on acute-term SBP among hypertensive individuals

FMD (WMD: 0.30%; 95% CI: 0.15, 0.46; I^2: 67.2), and medium-term AI (WMD: -0.57%; 95% CI: -0.98, -0.15; I^2: 82.3).

We also performed a dose-response analysis in hypertensive individuals (Fig. 5 and Supplementary Fig. 7). Dietary NO3 had a linear dose-response relationship with acute-term SBP, indicating that for each one mmol increase in NO3 intake, acute-term SBP decreased linearly (WMD: -0.38 mmHg; 95% CI: -0.62, -0.13; I^2: 0.00).

Dose-response analysis for the effect of beetroot on BP

A significant dose-response relationship was observed between the dietary beetroot intake and levels of SBP (acute, short, and medium-term), DBP (acute-term), and MAP (acute-term) (Supplementary Figs. 8 and 9). A significant linear relationship was indicated between dietary beetroot intake and acute-term SBP, DBP, and MAP, such that for every 70 ml increase in the beetroot intake, acute-term SBP (WMD: -1.23 mmHg; 95% CI: -1.80, -0.66; I^2: 39.3), acute-term DBP (WMD: -0.57 mmHg; 95% CI: -0.96, -0.17; I^2: 46.3), and acute-term MAP (WMD: -0.82 mmHg; 95% CI: -1.54, -0.10; I^2: 72.0) decreased linearly (Supplementary Fig. 10). Also, there was a non-linear relationship between dietary beetroot intake and short and medium-term SBP (Supplementary Table 6). Specifically, short-term SBP showed the greatest reduction up to the use of a dose of 100 ml dietary beetroot per day (WMD: -2.68 mmHg; 95% CI: -4.43, -0.93), beyond which the observed reduction effect minimized and was insignificant. Similarly, there was a non-linear relationship between dietary beetroot intake and medium-term SBP; the most significant reduction was observed at a dose of 150 ml beetroot per day (WMD: -4.56 mmHg; 95% CI: -6.42, -2.71), after which the effect plateaued.

Publication bias

While significant publication bias was not detected concerning the impact of dietary NO3 on chronic plasma levels of NO3 ($P = 0.748$) and NO2 ($P = 0.266$), visual inspection of funnel plots and Egger's test revealed significant publication bias for acute NO3 ($P = 0.001$) and NO2 ($P = 0.019$) plasma levels. This amount of publication bias indicates that smaller, non-significant studies may be missed from the analysis (Supplementary Fig. 11).

Risk of bias assessment

As shown in Supplementary Table 7, more than 80% of the included studies (62 out of 75) had fair or good quality. Among them, 28 RCTs exhibited good quality, with a low risk of bias across most domains, although some exceptions were noted for outcome assessment blinding or the potential for missing data. Furthermore, among the RCTs with a fair quality ($n = 34$), the primary reasons for fair quality were an unclear description of outcome assessment blinding and the random sequence generation method. Additionally, among the 13 RCTs that were classified as poor quality, the predominant issues included a lack of blinding among participants and personnel or the utilization of unsuitable allocation concealment methods.

Grading the evidence

The CoE for both pairwise and linear dose-response analysis results was provided in Supplementary Table 8. Plasma NO2 and NO3 levels in the chronic term and SBP

(acute and short-term) and DBP (acute-term) were rated as Moderate due to their significant and homogeneous results. Also, acute plasma NO2 received a Low CoE due to suspected publication bias, while medium-term SBP was rated Low due to heterogeneity in results. Medium-term MAP and FMD received a Low CoE due to small sample sizes. Additionally, acute plasma NO3 was rated Very Low due to suspected publication bias, while medium-term PWV received a Very Low rating due to homogeneity in the origin of published clinical trials and small sample size. Acute FMD was rated Very Low due to non-significant results with serious heterogeneity, and medium-term AI received a Very Low rating due to serious heterogeneity and small sample size. Notably, the risk of bias was serious for all outcomes except for acute and medium-term FMD.

Safety analysis

Seventeen RCTs [69–72, 74, 76, 77, 82, 83, 85, 94, 100, 101, 108, 110, 113, 114] reported data on adverse events. Supplementary Table 9 provides detailed information on the number of adverse events observed in each trial. Adverse events typically consist of discoloration of stool and urine, commonly known as beeturia. Studies reported that this discoloration is a typical effect of beetroot supplementation, but it did not result in participant withdrawal or study discontinuation. Also, certain studies have reported side effects such as abdominal pain [70], diarrhea [69], nausea [77], and headache, along with gastrointestinal discomfort [94]. Furthermore, two studies [83, 113] indicated that some participants were excluded from the study due to reported unpalatability of the juice [113] and gastritis [83]. The safety analysis results (Supplementary Figs. 12, 13) revealed that dietary NO3 supplementation did not lead to an increase in adverse events (Risk ratio: 1.00, 95% CI 0.35, 2.82 $I^2 = 0.00\%$) or withdrawal from the study (Risk ratio: 0.42, 95% CI 0.07, 2.68; $I^2 = 0.00\%$).

Discussion

Our comprehensive analysis of 1,823 participants revealed a significant dose-response relationship between dietary NO3 dosage and plasma NO3 and NO2 levels. We also found dose-dependent effects of dietary NO3 on SBP, DBP, MAP, PWV, FMD, and AI levels. The reduction in BP was more pronounced in individuals with HTN compared to the general population. Additionally, dietary NO3 supplementation did not significantly lead to complications or withdrawals from the study.

Excessive NO3 levels in food sources are a significant concern. However, the recommended daily intake of NO3 from meats and drinking water may not apply to vegetables and requires reassessment [39]. While NO3 intake from meats can form carcinogenic compounds, vegetables are rich in polyphenols and antioxidants that prevent the formation of N-nitroso compounds by facilitating the conversion of NO2 to NO [135]. Currently, the acceptable daily limit for NO3 intake is 3.7 mg/kg of body weight per day [40]. However, the NO3 doses among included studies in our meta-analysis exceeded this acceptable daily intake (0.31 to 24.6 mg/kg for 70 kg individuals) Therefore, the optimal dosage of dietary NO3 supplementation for achieving beneficial effects on cardiovascular health parameters has yet to be firmly established.

We observed the dose-dependent effects of dietary NO3 dosage on plasma NO3 and NO2 levels, both in acute and chronic periods. Additionally, we found that the optimal dietary NO3 dose to significantly increase plasma NO3 levels is above 3 mmol per day, after which plasma NO3 levels increase linearly. This finding aligns with the established NO3–NO2–NO pathway, where dietary NO3 is converted to NO2 by bacteria in the tongue, further metabolized into NO in the stomach, and then reabsorbed into the bloodstream [136, 137]. Continuous NO3 intake sustains increased plasma NO3 levels [138, 139], consequently lowering BP and potentially mitigating the risk of atherosclerosis and all-cause mortality [140, 141].

Moreover, our results revealed linear dose-response effects of beetroot on plasma NO3 and NO2 concentrations up to 200–250 ml of beetroot per day. The definitive mechanisms underlying the observed plateauing or decline of plasma NO3 and NO2 levels after reaching peak values at specified doses remain elusive and necessitate further exploration. One plausible explanation could be that higher doses result in the saturation of absorption mechanisms, thereby diminishing the efficacy of NO3 conversion NO and reducing cellular sensitivity to NO [142–144]. The inconsistency in NO3 levels among different interventions could potentially explain this finding and may be attributed to varietal differences, cultivation methods, storage conditions, and processing techniques [145–147]. Moreover, it was mentioned that the slope of the BP curves or serum NO3 levels, following the dosage of dietary NO3, exceeded those associated with beetroot dosage. These findings may imply that the observed effects on BP reduction were primarily attributable to the NO3 content rather than other bioactive compounds present in the entire food matrix [148, 149].

According to our results, dietary NO3 supplementation leads to linear reductions in SBP (acute, short, and medium-term), as well as DBP in the acute phase, and exhibited a non-linear reduction in MAP over the medium-term. Given that a reduction of at least 2 mmHg in BP is typically considered a clinically significant unintended BP-lowering effect [17], our findings suggest that a daily NO3 dose of 8 mmol is required to achieve a

significant reduction in BP. Furthermore, our sensitivity analysis unveiled a notably robust linear dose-response association between dietary NO3 and acute SBP reduction among hypertensive individuals. For each mmol increment in dietary NO3 dosage, we observed a 0.38 mmHg reduction in acute SBP within the hypertensive subgroup, contrasting with a 0.28 mmHg reduction in the overall population analysis. This finding implies that hypertensive populations may experience more significant advantages from dietary NO3 supplementation, possibly owing to their impaired NO bioavailability [150]. As HTN frequently involves endothelial dysfunction and diminished NO synthesis [151], augmenting NO bioavailability via dietary NO3 supplementation may directly oppose the underlying mechanisms contributing to elevated BP in this demographic. NO is involved in reducing BP by inducing vasodilation, achieved through the attenuation of cardiovascular sympathetic tone and neural control modulation [102, 152–154].

The BP reduction achieved through dietary NO3 is similar to the most effective nonpharmacological and pharmacologic interventions in terms of lowering BP. A network meta-analysis has indicated that the DASH diet exhibits the most significant effect on reducing SBP (6.97 mmHg) and DBP (3.54 mmHg) among individuals with pre-HTN and HTN [155]. The advantages of adhering to the DASH diet can be attributed to including vegetables rich in NO3 [39]. The latest recommendations from the International Society of HTN highlight the potential BP-lowering effect of vegetables as a source of NO3 [156]. A meta-analysis of 68 clinical trials revealed that a single antihypertensive medication can lower SBP and DBP by 12 and 7 mmHg, respectively [17], while a combination therapy can result in a reduction of up to 18.9 mmHg in SBP [157].

Nevertheless, dietary NO3 achieved reductions in BP without adding to the number of pills patients had to take or increasing the risk of medication interactions and adverse side effects. Recent research has indicated that mineralocorticoid antagonists may not be effective in lowering BP in individuals with heart failure [158]. Contrary to dietary NO3, organic NO3s like isosorbide monoNO3 have shown ineffectiveness in enhancing the quality of life for heart failure patients and may potentially induce hypotension and endothelial dysfunction [159]. Also, nitroglycerin and other NO3-containing medications may not be optimal choices for individuals with severe valvular stenosis or heart failure due to their adverse effects and propensity to provoke tachycardia [160, 161]. Our safety analysis indicates that the rarely reported complications linked to dietary intake of NO3 are not expected to impede its utilization. Moreover, dietary NO3 shows an enhanced pathway in hypoxic and acidic environments, like ischemic tissue [159]. Consequently, the BP-lowering properties of dietary NO3 could potentially lead to a decrease in the number or dosage of common antihypertensive medications needed to attain optimal control.

Recent studies indicate that relying solely on pharmacological treatments may not always yield positive results, as some individuals may develop resistance to them [162]. Therefore, a comprehensive approach that includes a combination of pharmacological treatments, supplements, and lifestyle interventions appears to be more effective in managing BP [163]. A study comparing different treatments for resistant HTN found that combining spironolactone with triple-drug therapy significantly reduced SBP by 13.30 mm Hg [164]. Meanwhile, a clinical trial indicated that following the DASH diet, along with weight management, psychological counseling, and an exercise plan, can effectively lower both clinic and ambulatory BP by up to 12.5 mmHg and enhance endothelial function in individuals with resistant HTN [163].

Furthermore, our analysis revealed a linear dose-dependent improvement of endothelial function (increased FMD), as well as a decrease in arterial stiffness of small muscular arteries (measured by AI) and elastic aorta (measured by PWV). The simultaneous enhancements in FMD, PWV, and AI indicate that dietary NO3 could potentially yield beneficial outcomes for cardiac function. A meta-analysis showed that each 1% increase in FMD caused a 13% decrease in the risk of cardiovascular events [8]. Therefore, a 1.85% enhancement in FMD due to dietary NO3 supplementation [22] could potentially lead to a 24% decrease in cardiovascular events.

Considering the bidirectional relationship between BP and vascular health, it is unclear if lowering BP improves vascular health or vice versa [165]. In general, oxidative stress plays a significant role in causing endothelial dysfunction by reducing the NO availability [166]. This leads to changes in the structure of the arterial wall, including smooth muscle cell proliferation, collagen deposition, and elastin fragmentation [167]. The enhancement of vascular health appears to rely on additional beneficial compounds found in dietary NO3 sources. One possible explanation for these effects is the potential ability to inhibit NADPH oxidase activity and directly neutralize free radicals [168]. Furthermore, dietary NO3 supplementation enhances the levels of plasma NO3 and NO, which play a crucial role in maintaining a healthy endothelial function [169]. This is attributed to its vasodilatory, antiatherogenic, and antiproliferative properties [169]. The ability of dietary NO3 to boost NO production may be linked to the antioxidant properties of its active components such as ascorbic acid, and betalain, which help minimize the scavenging of NO by superoxide [169]. These active ingredients may also improve

collagen synthesis [170–172]. Dietary NO3 supplements have been found to enhance vascular health facilitating the relaxation of smooth muscles, stimulating potassium channels, improving the effectiveness of oxidative phosphorylation, and boosting mitochondrial respiration [41, 173, 174].

Various nutritional interventions, including potassium [175], and omega-3 [176], have been implemented for improving arterial stiffness and endothelial function. However, their impact is not as significant as the effect of dietary NO3 on vascular health markers [22]. A network meta-analysis revealed that current vitamin interventions do not significantly enhance arterial stiffness [177]. Nevertheless, prolonged vitamin D supplementation could effectively reduce PWV by 0.15 m/s [177]. Furthermore, a meta-analysis of 22 clinical trials demonstrated that a moderate weight loss of 8% of initial body weight may result in a decrease in PWV by 0.32 m/s [178]. A comprehensive analysis indicated that mineralocorticoid receptor inhibitors have a notable advantage over other antihypertensive medications in enhancing PWV (-0.75 m/s), AI (-6.74%), and FMD (1.18%), regardless of BP levels [179]; This impact is similar and nearly identical to the findings of the Norouzzadeh et al. study that focused on the effect of dietary NO3 supplementation on changes in PWV (-0.75 m/s), AI (-7.19%), and FMD (1.22%) [22].

Our study possesses numerous strengths, including a comprehensive assessment of outcomes, a dose-response analysis, an assessment of the certainty of the evidence, and a comprehensive safety analysis. However, our study had limitations, primarily due to the high heterogeneity observed among the included studies. Nevertheless, it is important to note that this level of heterogeneity was unavoidable. Additionally, the studies included in our study did not consider the baseline dietary NO3 intake from participants' regular diets, apart from the supplemental NO3 interventions. This may have introduced unmeasured variability in the overall NO3 intake.

While the primary outcomes of this study were of acceptable certainty, the CoE for some outcomes was rated as low or very low. This indicates that future studies may influence the findings, meaning the observed effects could differ from the actual effects. The main factors contributing to the downgrading of evidence included high heterogeneity, publication bias, and a limited number of studies. Future research should focus on specific age and population groups to address these issues to reduce heterogeneity. Additionally, as the number of studies increases, the risk of publication bias is expected to decrease, leading to a more robust evidence base across different outcomes. Notably, elderly individuals who have a higher prevalence of atherosclerosis and those with chronic conditions such as cardiovascular disease and HTN may benefit more from dietary NO3 supplementation. Also, among the sources of heterogeneity, the dose of NO3 used is a key factor. Intervention effectiveness depends on potency (the amount of active ingredients present) and purity (the absence of contaminants). Future studies should ensure appropriate doses of NO3 sources, accounting for NO3 equivalents and other bioactive compounds, to enhance the reliability and applicability of findings.

Further studies could investigate how dietary NO3s may synergistically impact when combined with the DASH or Mediterranean diets. It is important to study the long-term safety of dietary NO3, and future studies should carefully monitor NO3 intake from different sources, especially in control groups.

Conclusions

In conclusion, dose-dependent effects have been established between dietary NO3 and plasma NO3 and NO2 levels, BP, and vascular health markers. Due to the high NO3 content and other active ingredients in dietary NO3 sources, they may effectively regulate BP and enhance arterial stiffness and endothelial function. Moreover, individuals with HTN may derive greater benefits from these sources. The observed effects are at times on par with or comparable to existing treatments, including dietary and pharmaceutical interventions. Before clinical application, further research is required to validate the long-term safety and adherence to dietary NO3 supplementation.

Supplementary Information

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Supplementary Material 1

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Author contributions

MHR: Conceptualization, Methodology, Investigation, Validation, Writing - Review & Editing (Equal contribution) MN: Conceptualization, Methodology, Investigation, Validation, Writing - Review & Editing (Equal contribution) SGH: Writing - Original Draft, Data Curation AMH: Writing - Original Draft, Data Curation NS: Writing - Original Draft HH: Writing - Review & Editing, Visualization, Validation SM: Writing - Review & Editing, Visualization, Validation FS: Writing - Review & Editing, Visualization HF: Writing - Review & Editing, Visualization FT: Writing - Review & Editing, Supervision MKH: Writing - Review & Editing, Supervision PM: Supervision. All authors read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study followed the Declaration of Helsinki and received approval from the Ethics Committee of the Iran University of Medical Sciences (IR.IUMS.REC.1403.406).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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