Dietary nitrate, aging and brain health: the latest evidence

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Purpose of review
With an increasing population age, cognitive decline and age-associated neurodegenerative diseases are becoming increasingly prevalent and burdensome in society. Dietary supplementation with inorganic nitrate, which serves as a nitric oxide precursor, has been suggested as a potential nutritional strategy to improve brain health in older adults. In this review, we discuss recent findings in this area.

Recent findings
A number of studies have emerged in the past 12–18 months exploring the effects of dietary nitrate supplementation on cognitive function, with typically (although not exclusively) null findings emerging. This research is characterized by small, acute/short-term studies, although observational studies and longer-duration randomised controlled trials are beginning to emerge. From the limited research reporting benefits of nitrate supplementation on cognitive function, one important discovery has been the identification of a potential pathway through which nitrate could impact cognitive health, involving modulation of the oral microbiome, which warrants further investigation.

Summary
Despite some promising early findings, there is currently insufficient evidence to recommend increased dietary nitrate intake for the purpose of improving brain health. However, longer-term, larger-scale trials in potentially responsive groups are warranted to provide definitive evidence in this area.

Keywords
ageing, beetroot juice, brain health, cognitive function, dietary nitrate

INTRODUCTION
As the worldwide population is becoming older, age-related cognitive disorders, such as Alzheimer's disease and other dementias, are becoming increasingly prevalent and burdensome in society [1,2]. There is therefore a need to identify effective strategies which help facilitate healthy brain ageing and minimize dementia risk. Dietary strategies including consumption of bioactive compounds (e.g., n-3 fatty acids and b vitamins), foods (e.g., blueberries and green leafy vegetables) or healthy dietary patterns [e.g., Mediterranean diet or MIND diet (a hybrid between the Mediterranean diet and dietary approach to stop hypertension)] may play a role in this regard [3–6].

One strategy which has attracted recent attention for its potentially beneficial effects on brain health is dietary supplementation with inorganic nitrate - a compound found in foods such as beetroot, spinach, and rhubarb [7]. We previously conducted a systematic review exploring the impact of dietary nitrate on cognitive function and cerebral blood flow [8], which incorporated all studies published up to May 2017. Although we identified some studies suggesting beneficial effects of nitrate, the pooled estimate of treatment effects suggested that there were no overall effects of this inorganic anion on cognitive function or cerebral blood flow. Nevertheless, this area has evolved over the past 5 years, with numerous new studies emerging, such that there is a need for an updated account on the current state of the knowledge around dietary nitrate and brain health.

In this narrative review, we outline the rationale for dietary nitrate supplementation for brain health and provide a brief outline of seminal studies in this area. We then focus our attention on recent
Nitric oxide is produced in the body by two key pathways (Fig. 1). Firstly, nitric oxide can be produced via the oxidation of L-arginine – a semi-essential amino acid – into equimolar amounts of L-citrulline and nitric oxide, in a reaction catalyzed by the nitric oxide synthase (NOS) enzymes [14,15]. Nitric oxide can also be produced by a nonenzymatic pathway, in which the inorganic anion nitrate is reduced by oral bacteria or (more slowly) mammalian nitrate reductases into nitrite, which is then further reduced to nitric oxide via a range of enzymatic and nonenzymatic catalysts [14,15].

Ageing is associated with a decrease in nitric oxide bioavailability, which is magnified by a poor diet and inactivity [16]. This has primarily been attributed to a drop in nitric oxide production via the L-arginine NOS-dependent pathway, which could be due to a decrease in expression of endothelial NOS (eNOS) with advancing age [17]. Alternatively, ageing has been associated with a decreased activity of eNOS, which may be caused by an increased degradation of L-arginine by arginase with advancing age, thus limiting the availability of this substrate for NOS-dependent nitric oxide production, or an age-related increase in asymmetric dimethylarginine (ADMA) – an endogenous eNOS inhibitor [17]. Additionally, ageing is associated with increased oxidation of tetrahydrobiopterin (BH4) – a critical cofactor for NOS-dependent nitric oxide generation – into its inactive form, dihydrobiopterin (BH2), which can lead to eNOS ‘uncoupling’ [17]. Here, instead of producing nitric oxide, superoxide is generated by eNOS. This has the dual effect of reducing nitric oxide production and increasing nitric oxide scavenging (superoxide reacts with nitric oxide to produce peroxynitrite) to further reduce nitric oxide bioavailability [17].

The age-related decrease in nitric oxide bioavailability could have negative consequences in the brain, where it has been associated with reduced basal cerebral blood flow and impaired neurovascular coupling [8]. This could contribute towards the age-related decrease in cognitive function, given experimental studies have demonstrated a causal link between decreased neurovascular coupling and cognitive decline [18]. In accordance with the Vascular Hypothesis of Alzheimer’s Disease, such effects could also be linked to Alzheimer’s disease neuropathology via increased amyloid-β deposition, reduced amyloid-β clearance, and decreased supply of substrates necessary to support the metabolic activity of the brain [19]. Interestingly, eNOS deficient mice have altered neurovascular coupling, increased age-related amyloid-β deposition and tau-phosphorylation (which are major hallmarks of Alzheimer’s disease) in the brain, and manifest memory deficits [20]. This suggests that a chronic reduction in endothelial-derived nitric oxide could contribute towards both amyloid-β related pathology and cognitive decline [20]. The age-related increase in ADMA, and consequent decline in endothelial-derived nitric oxide production, could also contribute towards cognitive dysfunction with advancing age. For example, in a

**KEY POINTS**

- Dietary nitrate supplementation increases nitric oxide bioavailability via the recently identified nitrate-nitrite-nitric oxide pathway.
- Early studies suggested that dietary nitrate supplementation can improve cognitive function and modulate cerebral blood flow.
- Most recent research has demonstrated null effects of dietary nitrate supplementation on cognitive function, and no associations have been observed between nitrate intake and cognitive function in observational studies.
- Further research is needed to understand the specific conditions under which nitrate supplementation can enhance cognitive function and cerebral blood flow, given limited and inconsistent results to date.
- There is currently insufficient evidence to recommend increased nitrate intake for the purpose of enhancing cognitive function and/or cerebral blood flow.

developments in this field over the past 12–18 months. Our aim is that this article serves as a primer on the current state of the knowledge and helps guide future research in this area.

**NITRIC OXIDE, BRAIN AGEING AND THE RATIONALE FOR DIETARY NITRATE SUPPLEMENTATION**

Nitric oxide is a diatomic gasotransmitter involved in myriad functions throughout the human body. Although commonly associated with the cardiovascular system, where it acts as a vasodilator and regulator of platelet activation, nitric oxide is also crucial for healthy muscle [9], immune [10], and brain function [11], amongst others. In the brain, nitric oxide plays a key role in neurovascular coupling – the process through which cerebral blood flow is modulated in accordance with local neural activity [12]. Nitric oxide is also an important neurotransmitter, has an established role in mediating synaptic plasticity, and has been implicated in learning and memory [13]. In contrast, over-synthesis of nitric oxide has been proposed to have cytotoxic effects on neurons and endothelial cells [13].

Nitric oxide is produced in the body by two key pathways (Fig. 1). Firstly, nitric oxide can be produced via the oxidation of L-arginine – a semi-essential amino acid – into equimolar amounts of L-citrulline and nitric oxide, in a reaction catalyzed by the nitric oxide synthase (NOS) enzymes [14,15]. Nitric oxide can also be produced by a nonenzymatic pathway, in
cohort of older participants, raised ADMA concentrations were associated with greater cognitive decline over a 4-year period [21].

Given the role that nitric oxide plays in the brain, and the fact that the bioavailability of nitric oxide decreases with age, this gasotransmitter could represent a potential mechanistic target for interventions seeking to attenuate the age-related decline in cognitive function and reduce dementia risk. In particular, recent research has focused on the effects of dietary nitrate intake to maintain/increase nitric oxide bioavailability in older adults, helping compensate for the reduced nitric oxide production via the L-arginine NOS pathway, and consequently enhancing cerebral blood flow and cognitive function. The findings from these studies will be discussed below.

**DIETARY NITRATE, CEREBRAL BLOOD FLOW AND COGNITIVE FUNCTION**

The effects of dietary nitrate supplementation on cerebral blood flow and cognitive function have received considerable attention in the past 10 years. Early studies produced promising findings which catalyzed interest into this area. Notably, Presley and colleagues [22] explored the effects of dietary nitrate on cerebral perfusion using arterial spin labelling in a randomised cross-over trial involving...
14 older adults aged ≥70 years. Although consumption of a high nitrate diet (12.6 mmol/d) for 2 days had no effect on global perfusion, voxel wise analysis revealed significant increases in cerebral blood flow within the subcortical and deep white matter of the frontal lobe compared with a low nitrate diet (<1 mmol/d). Interestingly, these areas are known to be at risk for chronic ischemia in the elderly and play an important role in cognitive function. This raises the intriguing possibility that nitrate could help divert blood to the specific parts of the brain where it is most likely to be needed, which could be related to an increased reduction of nitrite into nitric oxide (and therefore nitric oxide-dependent vasodilatory signaling) under hypoxic conditions. A number of subsequent studies went on to demonstrate beneficial effects of nitrate on other measures of cerebral blood flow/oxygenation [e.g., via use of near-infrared spectrometry (NIRS)], a noninvasive spectroscopic method that uses near-infrared light to monitor concentration changes in oxy- and deoxyhemoglobin to determine oxygenation and blood flow/volume in tissue, including the brain [23,24] and showed improvements in certain measures of cognitive function, including simple reaction time, response time during a Stroop test, and serial 3’s subtraction task performance (for review, see ref. [8]). Nevertheless, the beneficial effects of nitrate were not universally observed, and when we summarized the available literature on this topic up to May 2017 in a systematic review and meta-analysis [8], the pooled estimate of treatment effects suggested no overall effects of nitrate on cerebral blood flow or cognitive function. However, due to the limited number of investigations and substantial heterogeneity in study designs, our interpretation of the literature at that stage was that there was ‘insufficient evidence to know whether supplemental inorganic nitrate or nitrite could improve cognitive function or enhance cerebral blood flow’ [8]. Since the publication of this article, several studies have been published exploring the impact of dietary nitrate on cerebral blood flow/cognitive function, the majority of which have emerged in the past 12–18 months (we identified 7 studies published in the past 18 months during the writing of this article, Table 1). The findings from this most recent body of literature (i.e., the past 18 months) will be discussed below.

**RECENT INVESTIGATIONS AND THE CURRENT STATE OF THE EVIDENCE**

**Short-term randomised controlled trials**

Several studies have emerged in the past 18 months exploring the effects of acute/short-term dietary nitrate supplementation on cognitive function. Three of these studies [25,26,27] involved young, athletic participants and assessed cognitive function via performance on the Stroop test. This is a common cognitive test, used to measure certain aspects of executive function, selective attention and reaction time, in which participants are presented with the names of colors such as ‘red’, ‘green’, ‘blue’ and ‘yellow’. Depending upon the specific condition, participants are required to identify the name of word written (e.g., if the word ‘red’ is written in green ink, the correct answer is ‘red’), or the color in which the word is written (e.g., if the word ‘red’ is written in green ink, this time the correct answer would be ‘green’) with a mix of congruent (i.e., the word and it’s color match) and incongruent (i.e., the word and it’s color differ) stimuli presented. Outcomes of the test are accuracy and reaction time, with some papers presenting data from all conditions and some only on the word-color congruency task [28]. In the identified studies, the Stroop test was administered alongside a wider battery of measurements including assessments of exercise performance [25,26,27]. Specifically, Haynes et al. [25] observed no effect of 7-days red spinach extract consumption (~3 mmol/d nitrate) on Stroop test performance in healthy, resistance-trained men (~20–25 years). Similarly, Berjisian et al. [26] reported no effects of acute beetroot juice supplementation (~6.4 mmol nitrate, plus 500 mg L-arginine and L-Orrnithine) alone, or when combined with caffeine (5 mg/kg body mass), on Stroop test performance in semi-professional male soccer players (~20 years). In contrast, Miraftabi et al. [27] reported improvements in Stroop test performance with lower (~6.5 mmol), but not higher (~13 mmol), dose acute nitrate supplementation compared with control in young taekwondo athletes (~20 years). However, it is noteworthy that Stroop performance (which was measured presupplementation, postsupplementation, and following an exercise task) was noticeably raised in the lower nitrate condition even before supplements had been consumed and postsupplementation performance was broadly consistent with other treatment conditions. This could highlight a potential learning/order effect or be a consequence of poor randomization in a comparatively small sample size (n = 8). It is also unclear why the lower but not higher dose of nitrate improved cognitive performance, when previous studies have tended to show dose-dependent effects of nitrate on other physiological/health parameters [29–31]. Regardless, the findings from these recent acute/short-term randomized controlled trials (RCTs) provide limited evidence for nitrate improving cognitive function, and the generalizability to older adults is likely to be limited.
Table 1. Summary of recent studies published in the past 18 months exploring the impact of dietary nitrate supplementation on cognitive function

| Authors          | Study sample                                      | Study design | Nitrate supplementation protocol                                                                 | Key findings                                                                 |
|------------------|---------------------------------------------------|--------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Acute or short duration randomised controlled trials    |                                                    |              |                                                                                                   |                                                                               |
| Haynes et al. [25] | 10 healthy, resistance trained men                | Crossover    | 7 days supplementation with red spinach extract (~3 mmol/d nitrate)                              | Stroop test performance was no different between nitrate and placebo conditions |
| Berjisian et al. [26] | 16 semi-professional male soccer players          | Crossover    | Acute supplementation with beetroot juice (~6.4 mmol nitrate, 500 mg L-Arginine, and L-Ornithine) alone or alongside caffeine (5 mg/kg body mass) | Stroop test performance was no different between nitrate alone, nitrate plus caffeine, caffeine alone or placebo conditions |
| Miraftabi et al. [27*] | 8 male trained Taekwondo athletes                 | Crossover    | Acute supplementation with a low (~6.5 mmol nitrate) or high (~13 mmol nitrate) dose of nitrate-rich beetroot juice | Stroop test performance was greater when participants were supplemented with 6.5 mmol nitrate compared with placebo, control (no supplement) and the high nitrate condition |
| Vanhatalo et al. [32**] | 30 cognitively healthy and mildly cognitively impaired older adults (70–80 years) | Crossover    | 10 days supplementation with nitrate-rich beetroot juice (12 mmol/d nitrate)                   | Sustained attention (rapid visual information processing task performance) was significantly improved with nitrate supplementation Nitrate-dependant changes in the oral microbiome were identified as a potential mechanism through which this compound could improve cognitive health |
| Medium duration randomised controlled trials             |                                                    |              |                                                                                                   |                                                                               |
| Babateen et al. [33*] | 62 overweight and obese older adults (60 to 75 years) | Parallel     | 13 weeks supplementation with low (~6.5 mmol nitrate on alternative days), moderate (~6.5 mmol/d nitrate) or high (~13 mmol/d nitrate) doses of nitrate-rich beetroot juice | There were no significant differences in domain-specific or global cognitive function, nor cerebral blood flow parameters, between conditions |
| Observational studies                                   |                                                    |              |                                                                                                   |                                                                               |
| Pereira et al. [36*] | 1015 older adults (60–80 years)                   | Cross-sectional | Urinary nitrate was used as a marker of habitual nitrate intake                                   | There were no significant associations between urinary nitrate concentration and cognitive performance in primary analyses In stratified analyses, higher urinary nitrate concentration was associated with greater risk of poor cognition in participants with high vitamin C intake and low CVD risk |
| McGrattan et al. [37] | 989 participants middle-aged and older adults (>50 years) | Cross-sectional | Urinary nitrate and self-reported nitrate consumption were used as objective and subjective measures of dietary nitrate intake, respectively | There were no significant associations between objective or subjective nitrate intake and cognitive function |
More relevant to the topic of brain ageing is the elegant study by Vanhatalo et al. [32**], who explored the effects of 10 days nitrate-rich beetroot juice (~12 mmol/d nitrate) versus placebo in cognitively healthy and mildly cognitively impaired older adults (70–80 years). Those authors observed a significant increase in sustained attention (rapid visual information processing task performance) in the treatment group versus placebo. However, there were no between-condition differences in short term memory, selective attention or information processing speed, and no differences in key metabolite concentrations (as determined by 1H-MRS brain scans) in the occipito-parietal grey matter or left frontal white matter. The authors then applied an interesting network analysis approach to explore correlations between clusters of co-occurring oral bacterial and cognitive and cardiovascular outcomes. Fascinatingly, their analysis revealed modules of co-occurring bacteria which were sensitive to nitrate supplementation and were correlated with cognitive function, suggesting that nitrate-dependent alterations in the oral microbiome could represent a potential pathway through which this dietary compound positively influences cognitive health. This promising area warrants further study.

**Medium term randomized controlled trials**

One medium term RCT exploring the effects of nitrate on cognitive function has emerged in the past 18 months. Specifically, our group published a study in which 62 older (60–75 years) participants with overweight/obesity were randomized to placebo, low nitrate (~6.5 mmol nitrate on alternative days), moderate nitrate (~6.5 mmol/d nitrate) or high nitrate (~13 mmol/d nitrate) conditions for 13-weeks [33*]. Prior to and following the intervention period, cognitive function was assessed via a comprehensive set of cognitive measures. Nevertheless, there were no between-condition differences in domain-specific or global cognitive function and resting blood pressure in individuals with both low and high sodium intake. However, there were no associations between objectively or subjectively measured nitrate intake (irrespective of sodium intake) and cognitive function (evaluated using the Mini Mental State Examination) and cognitive function (assessed using the Word List Learning, Word List Recall, Animal Fluency and Digit Symbol Substitution tests) [34]. In the primary analyses, we observed no significant associations between urinary nitrate concentrations and cognitive function for any of the cognitive tests. However, we also explored whether associations between urinary nitrate concentrations and cognition were impacted by three factors that have established links with nitric oxide production, nitrate metabolism and risk of cognitive decline (vitamin C, vitamin D, and cardiovascular disease (CVD) risk status). Unexpectedly, we found greater risk of poor cognition (defined as a score in the bottom 20 percentage of the population distribution) with high versus low urinary nitrate concentrations in participants with high vitamin C intake and low CVD risk. There was no clear mechanistic explanation for these findings.

In our second observational study in this area, we explored associations between objective (24-h urinary nitrate) and subjective (self-reported) measures of dietary nitrate and sodium intake on cognitive function and resting blood pressure in ~1000 middle- and older-aged participants (>50 years) from the InCHIANTI cohort [37]. Objectively measured nitrate intake was associated with ~50% lower odds of high blood pressure in individuals with both low and high sodium intake. However, there were no associations between objectively or subjectively measured nitrate intake (irrespective of sodium intake) and cognitive function (evaluated using the Mini Mental State Examination).
Examination (MMSE) and Trail Making Tests A and B). While the Trail Making Tests are appropriate across the cognitive impairment spectrum, it should be noted that the MMSE has limited use in cognitively healthy participants, with known issues including the ceiling effect, and a lack of sensitivity and specificity in identifying those most likely to develop dementia in the future [38].

**CONCLUSION AND FUTURE DIRECTIONS**

Despite several early studies suggesting promising effects of dietary nitrate on cerebral blood flow/cognitive function, most recent investigations have reported null findings. Therefore, consistent with our earlier review in 2017 [8], our current view is that there remains insufficient evidence to recommend increased dietary nitrate intake for the purpose of improving brain health. Nevertheless, it important to acknowledge several limitations which require addressing before firm conclusions can be made.

Most recent RCTs have explored the effects of nitrate on cognitive function in young, healthy volunteers following acute/short-term supplementation and have included relatively simple (e.g., Stroop test) measures of cognition. Larger, longer-term RCTs which are specifically designed to explore the effects of dietary nitrate on cognitive function (including comprehensive neuropsychological test batteries administered in controlled conditions), targeting potentially responsive cohorts (e.g., older adults with nitric oxide insufficiency and poor cardiovascular/cognitive health) are needed to provide definitive evidence. Given nitrate has been shown to alter cerebral blood flow, cognitive domains associated with cerebral blood flow should be particularly considered for inclusion in neuropsychological batteries [such as executive function and attention (Caucasian participants only [39]), psychomotor speed, verbal memory, working memory] [40].

Although the emergence of observational studies in this area should be welcomed for providing complementary insight (alongside RCTs) into the impact of nitrate on brain health, certain methodological issues should be considered when interpreting the findings from the current observational investigations. Notably, the studies by Pereira et al. [36*] and McGrattan et al. [37] were cross-sectional, making them vulnerable to reverse causality. Applying statistical techniques such as propensity scores may increase confidence in conclusions drawn about effects from future observational studies in this field [41]. In addition, as nitrate intake was only measured at a single instance (via self-report/urine samples), it is unclear whether values are a true representation of habitual consumption. Repeated assessments of diet would be advantageous to explore associations between longer-term/habitual nitrate intake and cognitive outcomes. Although somewhat speculative, it is possible that prolonged high nitrate intake may be required to elicit consistent, meaningful cognitive changes (either via indirect benefits through improved cardiovascular health or direct effects on the brain, including changes to neurovascular coupling and cerebral blood flow or structural alterations [12]). While the sample size of the current observational studies is 10–20 x greater than most RCTs, additional investigations which explore the associations between nitrate intake and cognitive function in large prospective cohort studies could be advantageous, especially those with rich genetic and phenotypic data to further explore potential effect moderators/mediators. Observational studies which focus on hard clinical endpoints (e.g., dementia incidence), the assessment of which is often unfeasible in RCTs, would also be a significant advancement to the field, and could be conducted by mapping nitrate intake in cohort studies which include healthcare record linkage [14].

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**Conflicts of interest**

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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This study suggested that low but not high dose nitrate supplementation can improve cognitive function (Stroop test performance). While the findings are of interest, they should be interpreted with some caution, not least because the small sample size and young, healthy cohort limit generalizability to older adults.