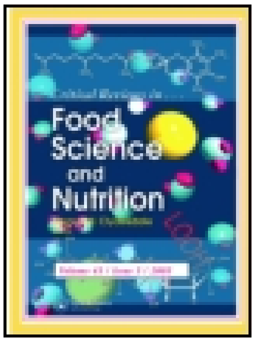

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REVIEW

The benefits and risks of beetroot juice consumption: a systematic review

H. Zamani*, M. E. J. R. de Joode*, I. J. Hossein*, N. F. T. Henckens*, M. A. Guggeis*, J. E. Berends*, T. M. C. M. de Kok, and S. G. J. van Breda

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ABSTRACT
Beetroot juice (BRJ) has become increasingly popular amongst athletes aiming to improve sport performances. BRJ contains high concentrations of nitrate, which can be converted into nitric oxide (NO) after consumption. NO has various functions in the human body, including a vasodilatory effect, which reduces blood pressure and increases oxygen- and nutrient delivery to various organs. These effects indicate that BRJ may have relevant applications in prevention and treatment of cardiovascular disease. Furthermore, the consumption of BRJ also has an impact on oxygen delivery to skeletal muscles, muscle efficiency, tolerance and endurance and may thus have a positive impact on sports performances. Aside from the beneficial aspects of BRJ consumption, there may also be potential health risks. Drinking BRJ may easily increase nitrate intake above the acceptable daily intake, which is known to stimulate the endogenous formation of *N*-nitroso compounds (NOC's), a class of compounds that is known to be carcinogenic and that may also induce several other adverse effects. Compared to studies on the beneficial effects, the amount of data and literature on the negative effects of BRJ is rather limited, and should be increased in order to perform a balanced risk assessment.

KEYWORDS
Beetroot juice; nitrate; nitrite; N-nitroso compounds; risk-benefit; endogenous nitrosation

Introduction

Beetroot juice (BRJ) contains a high concentration of nitrate (up to 11.4 g/L) as compared to drinking water (<45 mg/L in European countries) or other foods and beverages (Drinks 2019; Vermeer & van Maanen, 2001; Wruss et al. 2015). As nitrate intake may enhance sports performances, the use of BRJ by athletes has been increasing over the years, especially in endurance sports (Arciero, Miller, and Ward 2015). A five percent growth each year in the global beetroot juice market has been reported, and this rise will probably continue during the upcoming years (Growing Popularity of Beetroot Juice to Fuel the Global Market for Beetroot Powder During 2017 – 2027 2017). Nitrate in BRJ is converted in the human body to nitrite and subsequently to nitric oxide (NO), a compound that is known to have a vasodilatory effect, resulting in reduced blood pressure and increased oxygen- and nutrient delivery to the active muscle (Jones, Bailey, and Vanhatalo 2012).

Numerous studies have been performed to establish the effect of BRJ consumption on blood pressure and sports performance. Besides the beneficial effects of BRJ consumption, some health risks may also be associated with its consumption. Nitrate intake contributes to the endogenous formation of *N*-nitroso compounds (NOCs), a class of chemical carcinogens. Once ingested, about 20% of the nitrate is converted to nitrite by bacteria that are present in the oral cavity. Nitrous acid (HNO_2) is formed when nitrite is transformed in the acidic environment of the stomach. N_2O_3 and water are released from the reaction of two molecules of HNO_2, and the formed N_2O_3 reacts with amines to nitrosamines, a specific subgroup of NOCs. Protonation of HNO_2 followed by a reaction with amides can also lead to the formation of nitrosamides (Figure 1). Reactive intermediates, formed by these NOC's, can bind to DNA. If these DNA lesions are not repaired, mutations can occur which are potentially involved in the process of cancer development (Vermeer & van Maanen, 2001). Consequently, ingestion of a high concentration of nitrate may increase the amount of endogenous NOCs being formed (Berends et al. 2019). However, the current body of literature on the possible negative effects is rather limited as compared to the beneficial health effects of BRJ consumption.

Previous systematic reviews about the effects of BRJ have mainly focused on specific populations and outcome measures, and only included a limited amount of studies. Most

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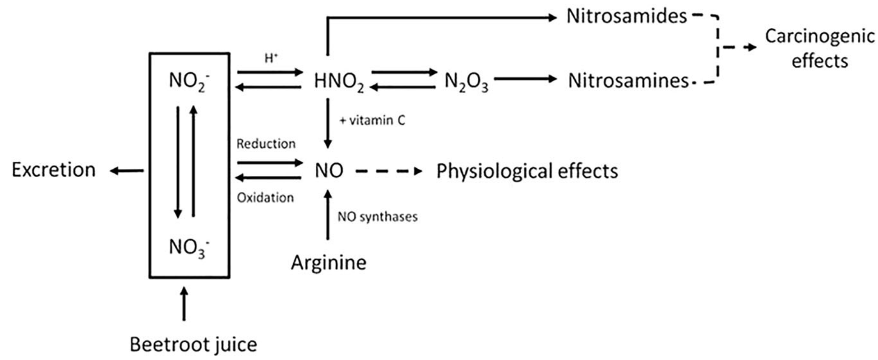

Figure 1. Metabolic pathway of nitrate (NO_3-), nitrite (NO_2-), nitric oxide (NO), nitrosamines and the effect of vitamin C. Nitric oxide (NO) is mainly responsible for the physiological effects of BRJ. The body uses arginine as a source to form NO, and for this reaction oxygen is needed. However, NO can also be formed after intake of nitrate-rich products such as BRJ. Ingested nitrate (NO_3-) will be partly reduced to nitrite (NO_2-) by microflora in the oral cavity. In oxygen-poor environments nitrate and nitrite can be reduced into NO. NO can also be oxidized back into nitrate and nitrite which are water soluble and can therefore be excreted in urine. Under acidic conditions, such as in the human stomach, nitrite will react with the H + and will form HNO_2 (nitrous acid). Also in the stomach, two molecules HNO_2 can form N_2O_3 (dinitrogen trioxide), by proton catalysis. N_2O_3 plays a role in the *N*-nitrosation rate. Increasing the amount of nitrate will therefore lead to an increase in the *N*-nitrosation rate. Subsequently, HNO_2 can react with amides to form nitrosamides, and N_2O_3 can react with amines to form nitrosamines. Both nitrosamides and nitrosamines are *N*-nitroso compounds and potentially carcinogenic. Vitamin C can inhibit the nitrosation process, because it reacts faster than the amine with N_2O_3. Vitamin C reduces $2HNO_2$ to NO, and is itself oxidized to dehydroascorbic acid. This will reduce the amount of *N*-nitroso compounds that can be formed (Figure from Berends et al. (2019) (Berends et al. 2019) with permission).

systematic reviews have investigated the effects on blood pressure. Remington and Winters (2019), for example, analyzed the effect of BRJ on the blood pressure of hypertensive patient populations including twelve studies in which the subjects had a BP of above 120/80 mmHg (Remington and Winters 2019). Another systematic review and meta-analysis was conducted by Bahadoran et al. (2017) including 22 studies on the impact of BRJ on blood pressure, but excluding studies assessing the acute effects on BP (Bahadoran et al. 2017). A few recent systematic reviews have looked at effects of BRJ besides that on blood pressure. Stanaway et al. (2017) reviewed the effects of BRJ specifically on older adults, including twelve studies in his analysis in which the subjects were 50+ years old or in which younger adults were compared to older adults. Outcomes analyzed included for example physical and cognitive performance, and cardiovascular health (Stanaway et al. 2017). Another systematic review focused on subjects who were endurance athletes, and included 23 studies to examine the effect of BRJ (and BRJ in combination with other supplements) on cardiorespiratory endurance (Dominguez et al. 2017). The most recent systematic review on the effect of nitrate supplementation on performance in general that came out of our literature search was by Hoon et al. (2013) dating from 2013, including 17 studies using BRJ supplementation but also other forms of nitrate supplementation (Hoon et al. 2013). It therefore lacks a large amount of recent studies performed in this rapidly growing field of research. Reviews analyzing the effect of BRJ on broader subject populations were not systematic reviews and again mostly only included a specific outcome, such as the effect on training physiology and performance (Olsson et al. 2019), or the properties of BRJ in relation to cardiometabolic disorders (Mirmiran et al. 2020). Other reviews again focus on the effect of BRJ on specific populations, such as the effect on women (Wickham and Spriet 2019), or the effect on exercise performance in heart failure with reduced ejection fraction (Mulkareddy et al. 2019). Only a very limited amount of reviews addressed the potential negative effects of BRJ.

Therefore, the goal of this systematic review is to provide a complete overview of all reported benefits and risks regarding the consumption of nitrate-rich BRJ on healthy subjects based on published literature. Beneficial effects are described for effects on skeletal muscles and oxygen consumption, for cardiovascular function, cardiac output and heart rate, blood pressure, sports performance and for a number of miscellaneous effects. The last paragraph provides an overview of the possible negative health effects which could be associated with intake of BRJ, including studies that investigate the possible health risks of BRJ. Finally, in the conclusion, gaps in knowledge are identified and suggestions for further research are given.

Methods

Search strategy

Only studies on healthy humans or animals were included. No previous reviews or meta-analyses were used. Only studies written in English were included. The search strategy used for this review was split up between the risks and the benefits of BRJ ingestion. For the benefits, the words ‘Blood Pressure’, ‘Performance’, ‘Endurance’, ‘Oxygen’, ‘Nitric Oxide’, ‘Advantage’ and ‘Benefit’ were coupled to ‘Beetroot Juice’. For the risks, the words ‘Nitroso Compounds’, ‘Cancer’, ‘Risk’, ‘Health Risk’ and ‘NDEA’ were coupled to ‘Beetroot Juice’. Additionally, the words ‘Nitrate Rich Food’ or ‘Nitrate Rich Beverage’ were coupled to ‘Nitroso Compounds’, and the words ‘Nitrate Rich Food’ and ‘Nitrate Rich Beverage’ were coupled to ‘Risk’ or ‘Cancer’. The MeSH terms corresponding to the free terms were added and used. The search was conducted using the PubMed database (Supplementary material 1) (last day assessed June, 2019).

Data extraction

The content of each article was summarized and information regarding study population, study design, treatment effect, whether or not a placebo had been used, and possible limitations of the study was collected.

Eligible studies

The search strategy for investigating the benefits of BRJ yielded 258 articles, of which 117 were excluded from the review: 59 articles were excluded because they did not use healthy subjects in their study, 29 articles were reviews or meta-analyses, and 29 articles were not relevant for this review because they described effects of other substances. One-hundred forty-one articles remained eligible for further analysis. Studies were classified by subtopics, which are described in more detail in this review. The search strategy for examining the risks of BRJ and nitrate rich foods identified 86 articles. Only one of these 86 articles was directly about BRJ supplementation. To provide insight into the possible health risks associated with BRJ supplementation, a short summary was made concerning the risks associated with intake of nitrate-rich foods. All studies were read in full and independently analyzed by two reviewers.

Critical appraisal of eligible studies

Methodological quality assessment of the eligible studies was evaluated using the modified Jadad scale (Chalmers et al. 1981; Jadad et al. 1996). The process of randomization, blinding and patient attrition was scored by means of several questions. The scale included eight items: randomization, blinding, withdrawals, dropouts, inclusion/exclusion criteria, adverse effects and statistical analysis (Supplementary material 2). The total score for each article ranged from 0 to 8 and was computed by summing the score of each item. All studies were read in full and independently analyzed by two reviewers. Articles were categorized by in either poor (Jadad score <3), decent (Jadad score 3–6) or good quality (Jadad score ≥ 7). Nine articles could not be analyzed by the Jadad criteria because they were not randomized controlled trials.

In Supplementary data Table 1, an overview is given of the studies used in this review. For each study, the reference details are provided, the characteristics of the study participants, the study design, its main outcome, and the modified jaded score.

General effects of BRJ on skeletal muscles and oxygen consumption

In the following section, the effects of BRJ on oxygen consumption, muscle power and force, and metabolism are discussed.

Studies have analyzed the effect of BRJ on skeletal muscle and oxygen consumption, and have found several parameters that are influenced by acute or short-term supplementation. Physiologically, an increased ATP turnover during muscle contractions leads to a higher oxygen consumption (VO_2). To compensate for this increased demand, NO-mediated vasodilation occurs (Ferguson et al. 2015). BRJ has an effect on both these parameters, by increasing vasodilation and by influencing VO_2.

In several studies, ingestion of BRJ was found to significantly decrease VO_2, regardless of the duration of BRJ consumption and type of intervention (Cermak, Gibala, et al. 2012; Kelly et al. 2014; Kuennen et al. 2015; Lansley, Winyard, Fulford, et al. 2011; Masschelein et al. 2012; Muggeridge et al. 2013, 2014; Rienks et al. 2015; Shannon, Duckworth, et al. 2017; Tan et al. 2018; Thompson et al. 2017; Vanhatalo et al. 2010; Whitfield et al. 2016; Wylie, Kelly, Fulford, et al. 2013). Tan et al. (2018) found that a 3-day supplementation of BRJ before, and ingestion of BRJ during moderate-intensity exercise attenuated the increase in VO_2 that normally accompanies sportive performance, compared to placebo (Tan et al. 2018). Additionally, this study reports that BRJ reduced the amount of glycogen depletion during exercise by 16% as compared to the placebo, which indicates that the metabolic demand of the muscle is decreased. Both the lower VO_2 and the reduced glycogen depletion could be caused by either an improvement in mitochondrial efficiency or in contractile efficiency of skeletal muscle (Tan et al. 2018). However, there is no consensus on the precise mechanism. While an increase in mitochondrial efficiency following nitrate supplementation was indeed found by Larsen et al. (2011) in an ex vivo study (Larsen et al. 2011), most studies that tried to confirm this result with BRJ have failed to show an improvement in mitochondrial function (Lansley, Winyard, Fulford, et al. 2011; Whitfield et al. 2016). Only one in vitro study by Vaughan et al. (2015) found that BRJ induced mitochondrial biogenesis in myocytes and increased oxidative metabolism (Vaughan, Gannon, & Carriker, Mermier, et al. 2016).

Some studies show no significant beneficial effects of BRJ on VO_2 or VO_2 kinetics (Arnold et al. 2015; Betteridge et al. 2016; Boorsma, Whitfield, and Spriet 2014; Breese et al. 2013; Breese et al. 2017; Christensen, Nyberg, and Bangsbo 2013; Christensen et al. 2017; MacLeod et al. 2015; Wickham et al. 2019). It should be noted that the majority of the studies which did not establish effects on VO_2 used "well-trained" or "elite" athletes as subjects (Arnold et al. 2015; Boorsma, Whitfield, and Spriet 2014; Christensen, Nyberg, and Bangsbo 2013; MacLeod et al. 2015). In contrast, studies that demonstrate the positive effects were performed with healthy and recreationally active individuals (Breese et al. 2013; Kelly et al. 2014; Lansley, Winyard, Fulford, et al. 2011; Masschelein et al. 2012; Rienks et al. 2015; Shannon, Duckworth, et al. 2017; Tan et al. 2018; Vanhatalo et al. 2010; Whitfield et al. 2016), or "trained", but not "well-trained" subjects (Cermak, Gibala, et al. 2012; Muggeridge et al. 2013, 2014; Thompson et al. 2017). This may be due to the fact that training has a modifying effect on the body, for example by increasing nitric oxide synthase levels, an enzyme that is used to form NO from L-arginine. It was indeed found that trained subjects have a twice as high plasma nitrate and nitrite level as compared to untrained subjects (Christensen, Nyberg, and Bangsbo 2013). This might have an impact on how the body responds to nitrate supplementation, thus providing a possible explanation for the discrepancy in results. When Carriker, Mermier, et al. (2016) performed a direct comparison between low-fit and high-fit males, it was found that the high-fit men had a smaller reduction in VO_2 after BRJ consumption than the low-fit males (Carriker, Vaughan, et al. 2016).

Several studies found that BRJ improves O_2 kinetics in muscles, for example by speeding up the VO_2 mean response time, thus accelerating the transition from non-oxidative to oxidative energy production in the muscle cell at the onset of exercise or during hypoxia (Bailey et al. 2015; Breese et al. 2013; Craig et al., 2018; Kelly, Fulford et al. 2013; Kelly et al. 2014; Vanhatalo et al. 2011; Waldron et al. 2018). Improved O_2 kinetics can decrease metabolic perturbation in muscles caused by the accumulation of metabolites produced during anaerobic respiration (Bailey et al. 2015; Breese et al. 2013; Kelly, Fulford et al. 2013; Kelly et al. 2014; Vanhatalo et al. 2011). In a study on swimmers, Pinna et al. (2014) showed that BRJ reduced aerobic energy cost, thus improving swimming performance (Pinna et al. 2014). Ferguson et al. (2013) found that the fall in oxygen cost/delivery ratio at contraction onset was slowed after BRJ administration in rats, reflecting an improved metabolic control (Ferguson et al. 2013a). Decreased metabolic perturbation measured in lactate concentration was found in other studies as well, in both rats (Ferguson et al. 2013b) and humans (Carriker, Mermier, et al. 2016; C. Thompson et al. 2017). One study specifically tested nitrate supplementations in subjects exposed to a state of hypoxia, and found that BRJ increased tolerance to exercise and oxidative function values to values normally found in normoxia, and decreased metabolic perturbation in hypoxia (Vanhatalo et al. 2011). Furthermore, Fulford et al. (2013) found that muscle efficiency was improved by BRJ as it significantly decreased phosphocreatinine cost per unit of force output without an increase in yield of anaerobic respiration (Fulford et al. 2013).

There is no consensus on whether BRJ affects mainly type I or type II muscle fibers. One study showed that BRJ intake decreased the maximal change in tissue oxygenation during low-intensity exercise in muscles consisting of mainly type I muscle fibers. These muscle fibers rely mainly on oxidative metabolism, suggesting that BRJ improves energy efficiency during aerobic exercise (Bentley et al. 2014). In contrast, Ferguson et al. (2013, 2015) found that in rats, BRJ supplementation preferentially increases microvascular O_2 pressure (PO_2mv) in contracting skeletal muscle comprised of mostly type IIb (highly glycolytic) fibers (Ferguson et al. 2015). This may be due to the more hypoxic environment in fast-twitch fibers, which favors the reduction of NO_2^- to NO (Ferguson et al. 2015).

Since the metabolic perturbations occurring in (mainly type II) muscle fibers may be linked to the fatigue process, BRJ may delay the onset of fatigue by increasing PO_2mv (Ferguson et al. 2015). Indeed, Hoon et al. (2015) found that four-day BRJ supplementation in healthy individuals decreased muscular fatigue in conditions of reduced blood flow during exhaustive exercise (Hoon et al. 2015), and Husmann et al. (2019) found reduced perceived effort and muscle pain after five-day BRJ ingestion (Husmann et al. 2019). Additionally, several studies have found that BRJ improves exercise tolerance or rate of perceived exhaustion in normoxia (Aucouturier et al. 2015; Bailey et al. 2015; Balsalobre-Fernández et al. 2018; Breese et al. 2013; Wylie, Kelly, Fulford, et al. 2013) as well as hypoxia (Kelly et al. 2014; Vanhatalo et al. 2011). Other studies, however, have failed to show such an effect on oxidative stress (Carriker et al. 2018), rate of fatigue or perceived exertion (de Castro, de Assis Manoel, et al. 2019; Lee et al. 2019).

Besides reducing VO_2, BRJ ingestion seems to increase skeletal muscle power or the time required to reach maximal power output (Coggan et al. 2015; Dominguez, Garnacho-Castano, et al., 2017; Jonvik et al. 2018; Lansley, Winyard, Bailey, et al. 2011), as well as electrically evoked muscle force (Haider and Folland 2014; Whitfield et al. 2017). Interestingly, Haider and Folland (2014) found that after 7-day BRJ supplementation, muscle force was increased during electrical stimulation, but not during voluntary contractions of the subjects. This could be explained by the fact that voluntary force production does not purely depend on the muscle's contractile force, and is an unreliable measurement due to its large variation (Haider and Folland 2014; Whitfield et al. 2017).

In conclusion, BRJ can improve sports performance through several mechanisms. These include a reduction in oxygen consumption in skeletal muscle, acceleration in the transition between anaerobic and aerobic respiration which can reduce muscle perturbation, and may delay the onset of fatigue, as well as an increased power output and force.

Effect of BRJ on cardiovascular function

In the following section we discuss the beneficial effects on cardiovascular function, in particular blood flow and endothelial function, cardiac output, heart rate and blood pressure.

Effect on blood flow and endothelial function

Among others, Richards et al. (Richards et al. 2018) showed that BRJ increases muscle blood flow via vasodilation during handgrip exercises in young adults (Bentley et al. 2017; Kent, Dawson, Cox, Abbiss, et al. 2018). An animal study with rats also showed an increase in muscle blood flow, but only using high doses of nitrate (Ferguson et al. 2014). However, Amano et al. (2018) showed that BRJ intake, 140 ml for 3 days, does not affect skin blood flow (Amano et al. 2018).

Some studies revealed an increase in muscle oxygenation during exercise (Papadopoulos et al. 2018; Vanhatalo et al. 2014), and a decrease in tissue oxygenation in inactive muscles after BRJ ingestion (Horiuchi et al. 2017). Moreover, endothelial dysfunction induced by an acute ischemic insult was prevented by supplementation of dietary nitrate. In response to collagen and adenosine diphosphate, BRJ weakened ex vivo platelet aggregation. These results support the idea that BRJ may be used as a potential natural, low cost treatment and prevention for cardiovascular diseases (Webb et al. 2008). Another study showed a decrease in cerebral arterial blood flow velocity during exercise (Curry et al. 2016), the effects of this decrease need further investigation. Furthermore, Wightman et al. (Wightman et al. 2015) showed an initial increase in cerebral blood flow at the start of a task period after receiving 450 ml beetroot juice. This was followed by consistent reductions of cerebral blood flow when performing the least demanding tasks. These tasks consisted of 5 minutes of Rapid Visual Information Processing, 4 minutes of serial subtractions and a mental fatigue visual analog scale (Wightman et al. 2015). The increased blood flow leads to an improved reaction time of response to the cognitive tasks (C. Thompson et al. 2015). All these effects can be explained by the nitric oxide synthase pathway shown in Figure 1.

Dietary nitrate could improve endothelial function via the NO_3^-–NO_2^-–NO (NOS, nitric oxide synthase) pathway. Several studies found that the supplementation of nitrate increases vasodilatation in the skin of heat-stressed humans. However, NOS-dependent vasodilatation was not affected by nitrate supplementation. This suggests that the detected vasodilatation was NOS-independent, but the exact mechanism is not known (Bakker et al. 2015; Keen et al. 2015; Lee et al. 2015; Levitt, Keen, and Wong 2015).

Several factors can affect endothelial function. Ageing reduces the NO-dependent compensatory vasodilator response during hypoxic exercise. This could be another treatment target for supplementation with dietary nitrate. A study investigating this compensatory vasodilator response in older adults found that it indeed improved after BRJ supplementation (Casey et al., 2015). Walker et al. (2019) demonstrated that a dose of dietary nitrate improved the NO bioavailability and therefore enhanced the endothelial function in older men (69 ± 4 years) (Walker et al. 2019). In healthy females, but not in healthy males, a decrease in platelet reactivity in healthy was observed. This study highlights a previously unknown sexual dimorphism in platelet reactivity to NO; males have a greater dependence of the NO-soluble guanylate cyclase pathway in limiting thrombotic potential (Velmurugan et al. 2013). Therefore, dietary nitrate could be an addition to current antiplatelet therapies to prevent atherothrombotic complications (Velmurugan et al. 2013).

All of these different results show there may be a potentially use for dietary nitrate in the therapy of cardiovascular diseases.

Effect of BRJ on cardiac output and heart rate

Several studies investigated the effect of BRJ on cardiac output in men and women. Studies in men indicated that the ingestion of a single bolus of BRJ did not have any effects on heart rate (Cermak, Res, et al. 2012), neither after drinking several shots of BRJ (Keen et al. 2015; Levitt, Keen, and Wong 2015; Oggioni et al. 2018; Wilkerson et al. 2012). These amounts varied in the studies, *e.g.* 3 shots of 70 ml BRJ in three days, 500 ml of BRJ once and two shots of 70 ml BRJ for subsequent 7 days. An intervention in well-trained male runners showed no beneficial effects on time-tail performances. It showed that nitrate supplementation did not affect arterial oxygen saturation, oxygen cost, heart rate or ratings of perceived exertion (Arnold et al. 2015).

However, studies showed that the acute supplementation of a single dose of BRJ decreased VO_2, systolic blood pressure and the heart rate systolic blood pressure (SBP) product at rest and 40%, 60%, and 80% of the predetermined peak VO_2 in physically active women. No effects on respiratory quotient, minute ventilation, heart rate and diastolic blood pressure were measured (Bond et al., 2014; Curry et al. 2016). These results indicate that BRJ can decrease the cardiac afterload and myocardial oxygen demand at rest and at submaximal levels of aerobic exercise (Bond et al., 2014). However one study with African-American females did show a significantly lower heart rate after ingestion of BRJ (Bond, Curry, Adams, Asadi, et al. 2014).

In conclusion, studies in men don't show any effects on cardiac output, in contrast to the study with female participants. However, most of the studies, apart from one, show no effect of BRJ on heart rate.

Effect on blood pressure

Acute effects after supplementation of BRJ

High blood pressure (BP) is a known risk factor for cardiovascular diseases (Raubenheimer et al. 2017). Blood pressure reduction as one of the potential effects of dietary nitrate has been thoroughly investigated. Webb et al. (2008) studied whether consumption of dietary nitrate through BRJ leads to acute BP reduction following bioconversion by oral bacteria to nitrite and subsequently to NO (Webb et al. 2008). NO is known to be a potent vasodilator, and BRJ was indeed shown to cause a BP reduction (Curry et al. 2016; Hobbs et al. 2012; Jonvik et al. 2016; Kapil et al. 2010; McDonagh et al. 2018; Raubenheimer et al. 2017; Webb et al. 2008). This effect is especially significant when concentrated BRJ is compared to non-concentrated BRJ, beetroot-flapjack and BRJ containing soluble beetroot-crystals (McDonagh et al. 2018). However, Kapil et al. (2010) also found a significant systolic BP reduction after non-concentrated BRJ consumption (Kapil et al. 2010). Several of these studies have in common that the largest reduction in systolic BP (SBP) occurs 3 h after BRJ consumption (Breese et al. 2017; Kapil et al. 2010; McDonagh et al. 2018; Raubenheimer et al. 2017). Burleigh et al. (2019) found a peak SBP reduction after a couple of hours of BRJ ingestion, however, this reduction dissipated after 10 h, suggesting that daily doses of nitrate would be needed for a sustained BP reduction (Burleigh et al. 2019). Kukadia et al. (2019) showed that aortic SBP reduction was at its peak in 30 minutes (5.2 ± 3.3 mmHg) after BRJ consumption compared to placebo. This effect ameliorated after 60 minutes, and disappeared after 24 h (Kukadia et al. 2019). Another study also showed a reduced aortic BP after acute BRJ supplementation (Hughes et al. 2016). Webb et al. (2008) found a peak difference in SBP at 2.5 h following BRJ ingestion (10.4 ± 3.0 mmHg) and a peak difference in diastolic blood pressure (DBP) after 3 h (8.1 ± 2.1 mm Hg) (Webb et al. 2008). In contrast to the study by Kukadia et al. (2019), Webb et al. (2008) also showed a significantly reduced SBP at 24 h after BRJ ingestion, however, there were no significant differences in diastolic DBP at 24 h after BRJ consumption. Hobbs et al. (2012) and Sinead et al. (2017) support this finding (Hobbs et al. 2012; McDonagh et al. 2018).

While most studies investigated BP reduction in younger to middle-aged adults, Raubenheimer et al. (2017) also found BP reduction directly after BRJ consumption in healthy elderly people (Raubenheimer et al. 2017). A study by Kim et al. (2019) specifically demonstrated aortic SBP and mean BP reduction, after BRJ consumption, in postmenopausal women. BRJ did not restore aortic wall stiffness in these women (Kim et al. 2019).

There are also studies that do not show any BP reduction after nitrate-rich BRJ supplementation (Craig et al., 2018; de Vries and DeLorey 2019; Notay, Incognito, and Millar 2017; Perez et al. 2019). de Vries & DeLorey (2019) found that sympathetic vasoconstrictor responsiveness was not altered, not in rest not after exercise, after a single dose of BRJ consumption compared to placebo (de Vries and DeLorey 2019). Perez et al. (2019) studied the effects of BRJ on VO_2 and BP during submaximal exercise. No significant changes in BP during exercise were found after SBP or DBP after a single shot of BRJ versus placebo. However, the authors state that the BP reading was difficult to perform due to oscillation of the device during exercise, which may have affected accurate BP measurements (Perez et al. 2019). This finding is also not supported by Craig et al. (2018), who did find a mean arterial BP reduction during handgrip exercises after BRJ ingestion compared to placebo (Craig et al., 2018).

Webb et al. (2008) and Sinead et al. (2017) indicate that the changes in BP are related to changes in plasma nitrite concentrations, as a significant inverse correlation between change in plasma nitrite concentrations and SBP were found. When entero-salivary conversion of dietary nitrate to nitrite was interrupted by spitting after BRJ consumption, the rise in plasma nitrite was prevented, which blocked the SBP reduction (Vanhatalo et al. 2010; Webb et al. 2008). No significant correlation between plasma nitrate and SBP were found (Webb et al. 2008). Kapil et al. (2010) also confirmed the correlation between nitrite levels and reduction of BP (Kapil et al. 2010). Furthermore, Hobbs et al. (2012) found that acute consumption of BRJ significantly lowers BP in a near dose-dependent manner (Hobbs et al. 2012). However, the peak SBP reductions in the study of Hobbs et al. were higher than observed in the previous studies (Bentley et al. 2014; Kapil et al. 2010; Webb et al. 2008). The difference in magnitude may have resulted from gender differences and their role in endogenous handling of nitrate (Hobbs et al. 2012). Kapil et al. showed that there is a direct correlation between BP reduction and baseline BP, with a greater reduction occurring in BP in people with a higher baseline BP. They also showed that female subjects have a lower baseline BP (Kapil et al. 2010). Since the subjects in the study of Hobbs et al. were all males, this provides a possible explanation for the large changes in BP. This explanation is supported by the study of Bond et al. (2013) in which only females were involved and BP changes were relatively small, although significant, and in the study of Coles and Clifton (2012), where BRJ consumption resulted in an increase of 4–5 mmHg in SBP 6 h after consumption in male participants, but showed no difference in SBP in female participants (Bond et al., 2013; Coles and Clifton 2012).

Short-term and chronic effects after supplementation of BRJ

In 2010, Vanhatalo et al. studied the acute and short-term effect of BRJ supplementation on BP (Vanhatalo et al. 2010). Both SBP and DBP were reduced by BRJ at several time points between 2.5 h and 15 days. These findings indicate that the effect of dietary nitrate supplementation on BP is maintained for at least 15 days if supplementation is continued, at which point it would be considered as chronic effects (Vanhatalo et al. 2010). Keen et al. (2014) found no effect on SBP, but did find a reduced DBP after short-term BRJ ingestion of three days (Keen et al. 2015). It should be taken into consideration that this study only comprised six participants. Perez et al. (2019) found no significant changes in BP during exercise after a single shot; however, they also found no significant BP change after seven-day BRJ supplementation versus placebo (Perez et al. 2019).

To evaluate if short-time supplementation of BRJ also reduces BP in elderly (60–70 years), Kelly, Fulford, et al. (2013) performed a study using elderly subjects in which significant SBP reductions (−5 mmHg) and DBP reductions (−3 mmHg) were found following ingestion of the nitrate-rich BRJ, relative to placebo following a 2.5 day BRJ supplementation (Kelly, Fulford et al. 2013). Therefore, as reported in younger adults, healthy elders' BP can also be reduced by BRJ. However, the findings of the study are contrasted by the study of Miller et al. (2013) in which dietary nitrate supplementation did not alter SBP in elderly, nor did the plasma nitrate/nitrate concentration differ from the people who had a nitrate-rich diet versus people who had placebo (Miller et al. 2012). Oggioni et al. (2018) did not find a BP reduction in healthy elderly subjects after short-term BRJ ingestion period of 7 days (Oggioni et al. 2018). The reason for the differences in Oggioni et al.'s and Miller et al.'s studies is unclear, but they may be related to the difference in dosage of nitrate supplementation or the number of participants, which were relatively low in both the study of Miller et al. (8 subjects) and Oggioni et al. (20 subjects) (Miller et al. 2012; Oggioni et al. 2018).

In conclusion, BRJ can potentially help to reduce hypertension by lowering SBP (and in some cases DPB), in younger healthy adults. Results from studies in elderly people are inconclusive. To the best of our knowledge, no studies have been conducted to investigate whether this beneficial effect is sustained with long-term BRJ consumption.

The effects of BRJ supplementation on sports performance

In the following section, the effects of a single dose and short-term BRJ supplementation on training performance will be discussed. This is done separately for recreationally active men, well-trained men, and recreationally active and well-trained women.

Effects of a single dose BRJ supplementation in relation to training

After ingestion of a single dose of BRJ in healthy young adults, whose level of exercise is not well defined, an increase in muscular blood flow via vasodilatation during moderate to high intensity hand grip exercises was found (Richards et al. 2018). A different study concluded that in healthy older adults, BRJ consumption resulted in beneficial effects in vasodilator responses to exercise in hypoxic conditions (Casey et al. 2015). Furthermore, in both male and female competitively trained athletes, maximal muscle power was enhanced after consumption of 70 mL BRJ (Rimer et al. 2016). However, no improvement in repeated sprint performance was found in team sport athletes after a single dose BRJ (Martin et al. 2014). Furthermore in healthy trained male and female apnoeists, one single shot of BRJ did not show physiological improvements in heart rate for VO_2 that indicate a beneficial effect of BRJ for free divers (Barlow et al. 2018). Also, no beneficial effects on short distance swimming performance and under water phases in a time trial were found in a study performed in well trained swimmers (Lowings et al. 2017). Effects of the consumption of a single dose of nitrate-rich BRJ on muscular function or training adaptations here seem beneficial; however, this is not applicable for apnoeists and swimmers.

Recreationally active men

After consuming a single dose of BRJ, sprint- and short term endurance exercise performance was enhanced as compared to placebo (Cuenca et al. 2018). After BRJ supplementation, an increase of ~21% in high-intensity exercise tolerance was observed compared to a placebo at a fixed work rate in hypoxic conditions. Also, high-intensity exercise tolerance in hypoxic conditions was restored by nitrate supplementation to the same level as in normoxic conditions (Levitt, Keen, and Wong 2015). However, in a study from Kent et al. (2019), no improvement in repeated sprint performance was found in hypoxia after BRJ consumption (Kent et al. 2019). A study performed by Smith et al. (2019) concluded that BRJ does not improve high-intensity intermittent exercise performance in different temperatures (temperate, hot and humid) (Smith et al. 2019). Isometric mid-thigh pulls peak force was significantly higher after BRJ consumption in adolescent males (Bender et al. 2018). Four other studies found an improvement in the time trial performance (TT) for running and cycling after BRJ supplementation (Lansley, Winyard, Bailey, et al. 2011; Muggeridge et al. 2014; Shannon, Barlow, et al. 2017; Shannon et al. 2016; Wylie, Mohr, et al. 2013). On the other hand, there are also studies which suggest no or an unclear effect on TT performances (Garnacho-Castano et al. 2018; Hoon, Hopkins, et al. 2014; Muggeridge et al. 2013). Additionally, a study from Clifford, Bell, et al. (2016) concluded that a single dose of BRJ supplementation resulted in attenuation of muscle soreness as pain pressure threshold returns quicker to baseline and enhanced recovery in counter-movement jumps (Clifford, Bell, et al. 2016). A study from Lee et al. 2019, found no effects on knee extensor muscle strength or fatigue after a single dose of BRJ (Lee et al. 2019). In conclusion, results are inconclusive; however, most of the studies suggest beneficial effects by the use of BRJ on performance in moderately trained men.

Well-trained men

One dose of nitrate supplementation in the form of BRJ did not significantly improve TT performance in well-trained athletes in normoxic or hypoxic conditions (Arnold et al. 2015; Hoon, Jones, et al. 2014; MacLeod et al. 2015; Wilkerson et al. 2012). Hoon, Hopkins, et al. (2014) demonstrated a non-significant correlation between changes in plasma nitrate concentration and TT completion time (Hoon, Jones, et al. 2014). However, Wilkerson et al. (2012) found a significant correlation between the increased post-beverage plasma nitrite concentration and the reduction in TT completion time (Wilkerson et al. 2012). Two studies found a significantly enhanced TT performance after the intake of BRJ (Cermak, Gibala, et al. 2012; Peeling et al. 2015). Shannon et al. (2016) concluded that the TT performance on running 1,500 m improved significantly, but not on running 10,000 m (Shannon et al. 2016). In well-trained athletes, a high dose of nitrate in the form of BRJ (8.4 mmol nitrate) may improve TT performance compared to a moderate dose of nitrate in BRJ (4.2 mmol nitrate) and nitrate-depleted BRJ (Hoon, Jones, et al. 2014). Besides observing no differences in TT, Arnold et al. (2015) found no practical performance difference in time to exhaustion in the incremental test (Arnold et al. 2015). The combination of intake of BRJ with caffeine likely has additional beneficial effects in performance compared to either caffeine or BRJ alone (Handzlik and Gleeson 2013; Lane et al. 2014).

BRJ is also likely to have positive effects for divers. BRJ consumption resulted in elevated oxygen saturation after a 75-m dynamic apnea performance which indicated a positive effect on maximal apnea performance (Patrician and Schagatay 2017). However, this is in contrast with a study from Barlow et al. (2018), where in healthy trained male and female apnoeists, one single shot of BRJ did not show physiological improvements that indicate a beneficial effect of BRJ for free divers (Barlow et al. 2018).

To conclude, results on the consumption of BRJ in well-trained athletes are inconclusive, and are dependent on field of sport and method of testing.

Recreationally active and well-trained women

Acute supplementation of dietary nitrate in females seems to have no effect on the cadence of endurance performances. However, there was a significant effect of supplementation with nitrate on time performances (Glaister et al. 2015). In the same study, caffeine supplementation combined with BRJ did not show a significant beneficial effect on endurance performance (Glaister et al. 2015). Another study showed that caffeine administered in the form of a caffeinated gum increased cycling TT performance lasting ∼50–60 min by ∼3–4% in both male and female subjects. In this study, co-ingestion of caffeine with BRJ was found to not be of contributing value (Lane et al. 2014). However, this is in contrast with the earlier mentioned study from Handzlik & Gleeson (2013) where was mentioned that the intake of BRJ with caffeine likely has additional beneficial effects on performance (Handzlik and Gleeson 2013). This study however was performed in well-trained men and the other two in women. When BRJ is consumed by itself in female kayak athletes, greater volumes (140 ml; ∼9.6 mmol nitrate) can enhance TT performance (Peeling et al. 2015). To conclude, BRJ supplementation has an effect on time performance, but not on cadence of endurance in recreationally active and well-trained women.

Effects of short-term BRJ supplementation in relation to training

Recreationally active men

Short-term supplementation of BRJ (more than one shot per day or multiple days) improves time to exhaustion in recreationally active men (Aucouturier et al. 2015; Kelly, Vanhatalo, et al. 2013; Thompson et al. 2015). It also shows a significantly improved time to exhaustion at 60%, 70%, and 80% peak power as compared to the placebo. However, this is not found at 100% peak power (Kelly, Vanhatalo, et al. 2013). No enhancement in endurance exercise was found after hypoxic training after low doses of dietary nitrate (0.07 mmol/kg body weight) supplementation (Puype et al. 2015). Also, performance was not significantly improved after short term BRJ supplementation in a 10 km-run (de Castro, Manoel, et al. 2019). Nevertheless, some studies showed that maximal sprint performance and high intensity intermittent performance was enhanced after short-term BRJ consumption (Esen et al. 2019; Thompson et al. 2016; Thompson et al. 2017; Thompson et al. 2015). Wylie et al. found that BRJ consumption resulted in improved performance in 24 repetitions of 6 s all-out sprints interspersed with 24 s of recovery. However, they also showed that no significant improvement was found when seven 30 s all-out sprints were performed with 4 min recovery or 60 s self-paced maximal efforts with 60 s of recovery (Wylie et al. 2016). Furthermore, quicker recovery was observed after consumption of BRJ, which resulted in enhanced recovery in counter-movement jumps, reactive strength index and repeated sprint test. This study also found that no mean differences were observed for fastest sprint time or fatigue index after BRJ consumption (Clifford, Bell, et al. 2016; Clifford, Berntzen, et al. 2016). Some studies have shown a reduction in muscle pain and fatigue associated with exercise induced muscle damage and reduced after with BRJ supplementation (Clifford, Howatson, et al. 2017; Husmann et al. 2019). Furthermore, Clifford, Bell, et al. (2017) published a study which stated that supplementation of nitrate rich BRJ does not negatively influence acute muscular adaptations after eccentric exercise (Clifford, Bell, et al. 2017). A study from Haider and Folland (2014) concluded that after one week of BRJ supplementation, the in vivo contractile properties of human skeletal muscle were enhanced (Haider and Folland 2014). A study from Tillin et al. (2018) confirmed this for fatigued muscle but not for rested muscle (Tillin et al. 2018). In healthy older adults (60–70 years) there was no improvement in walking performance after BRJ consumption (Kelly, Fulford et al. 2013).

Summarizing these findings, short term BRJ supplementation in recreationally active men overall has beneficial effects on performance, such as improvement in time to exhaustion, maximal sprint performance and high intensity intermittent performance. Also recovery has been found to be quicker after shirt term BRJ supplementation. Nevertheless, there is not always an effect observed, such as on endurance performance and sprinting tests with increased recovery time.

Well-trained men

Multiple studies found no effect on TT performance after short term BRJ supplementation in well-trained cyclists and runners (Boorsma, Whitfield, and Spriet 2014; Christensen, Nyberg, and Bangsbo 2013; Kent, Dawson, Cox, Burke, et al. 2018; McQuillan et al. 2018; McQuillan et al. 2017a; Mosher et al. 2019). In contrast, Cermak, Gibala, et al. (2012) found that TT performance and power output improved after BRJ supplementation compared to placebo supplementation (7). Also Rokkedal-Lausch et al. (2019) found an increase TT performance in hypoxia and normoxia after BRJ consumption (Rokkedal-Lausch et al. 2019). Additionally, a study from McQuillan et al. (2017) showed beneficial effects on a 4k-TT in well-trained cyclists (McQuillan et al. 2017b). Furthermore, high-intensity intermittent exercise performance was significantly improved after six days of BRJ consumption (Nyakayiru et al. 2017). However, in a study from Pawlak-Chaouch et al. (2019) after 3 days of BRJ supplementation, no improvement was found in supramaximal intermittent intensity exercise in elite track cyclists (Pawlak-Chaouch et al. 2019). Also, time to exhaustion has been shown to significantly improve after 15 days of BRJ supplementation. However, VO_{2max} wasn't improved after the trial (Balsalobre-Fernández et al. 2018). Another benefit from consuming BRJ for a short period in well-trained rowers was that the maximal rowing-ergometer repetitions improved (Bond, Morton, and Braakhuis 2012). After a short term BRJ supplementation, decreased oxygen utilization during submaximal exercise was observed, even though there were no altered indices of mitochondrial coupling/respiratory responses (Whitfield et al. 2016). In conclusion, performance enhancing effects are increased time to exhaustion, high intermittent exercise and maximal rowing repetitions. Also decreased oxygen utilization was observed which is beneficial for performance. However, the results of the studies are inconclusive about the effects of BRJ consumption on TT.

Well-trained women

Only two studies investigated the effect of short-term BRJ supplementation in relation to training in well-trained women. A study from Jonvik et al. (2017) showed that in elite female water polo-players, BRJ does not improve intermittent sprint performance (Jonvik et al. 2017). The other study showed no reduction in submaximal exercise VO_2 or TT performance after short term BRJ consumption (Wickham et al. 2019).

Conclusion

Overall it can be stated that the effects of the consumption of a single dose of nitrate rich BRJ on muscular function or training adaptations are inconclusive. However, most of the studies suggest beneficial effects of the use of BRJ on performance in recreationally active or well-trained women. For well-trained men, results of the consumption of BRJ in well trained athletes are inconclusive and dependent on the field of sport and method of testing.

Also, short-term supplementation of BRJ (more than one shot per day or multiple days) shows beneficial effects on sport performances in recreationally active men. However, more research has to be done for women, as there are, to our knowledge, only two studies about short-term BRJ consumption.

Miscellaneous positive health effects

Various other studies have investigated health effects of BRJ on the human body. It has been shown that changes in body posture cause rapid alterations of nitrite concentration which should be taken into consideration by researchers when measuring this variable (Liddle et al. 2018). The use of BRJ may have beneficial effects on dental (Hohensinn et al. 2016) and oral health (Burleigh et al. 2019), heat exchange (Kuennen et al. 2015), prevention of bronchoconstriction (Kroll et al. 2018), vasodilation of microvasculature (Levitt, Keen, and Wong 2015), and cognitive function (C. Thompson et al. 2015). However, no effect of BRJ was found on acute mountain sickness (Hennis et al. 2016; Rossetti et al. 2017), apnea-hypopnea index (Patrician et al. 2018), executive function in hypoxia (Dobashi et al. 2019; Rossetti et al. 2017), microvascular diffusion, plasma glucose, C-peptide- or incretin concentration (Shepherd et al. 2016) and cognitive performance post fatigue (Thompson et al. 2014). Further details of these studies are left out because of no further relevance.

Risks associated with beetroot juice consumption

Besides formation of NO in the body, it is known that ingestion of high levels of nitrate may stimulate the generation of NOC, which are potentially carcinogenic compounds (Figure 1). However, the impact of BRJ consumption on endogenous formation of NOCs has hardly been investigated. Drinking BRJ may easily increase nitrate intake above the acceptable daily intake (ADI). After intake, part of the nitrate can be reduced to nitrite in the oral cavity by bacteria. In oxygen-poor environments, nitrate and nitrite can be reduced into NO. NO can also be oxidized back into nitrate and nitrite, which are water soluble and can be excreted by urine. Under acidic conditions, such as in the human stomach, nitrite will react with the $H+$and form HNO_2 (nitrous acid). Also in the stomach, two molecules HNO_2 can form N_2O_3 (dinitrogen trioxide), by proton catalysis. As N_2O_3 plays a role in the *N*-nitrosation rate, increased intake of nitrate can lead to an increase of the *N*-nitrosation rate. HNO_2 can react with amides to form nitrosamides and N_2O_3 can react with amines to form nitrosamines. These amines and amides are present in protein rich and fatty foods, such as fish and meat. Both nitrosamides and nitrosamines are NOC's and potentially carcinogenic. Nitrosamides can form reactive intermediates which can bind to DNA. Nitrosamines undergo α-hydroxylation by cytochrome P450 enzymes. Then, α-hydroxynitrosamines spontaneously become monoalkylnitrosamines, alkyldiazohydroxides and alkyldiazonium ions. Nitrosamides do not require enzymatic activation, but spontaneously hydrolyze to monoalkylnitrosamine. The generated ions may alkylate DNA, RNA and proteins, resulting in the formation of DNA adducts such as N7-alkylguanines and O6-alkylguanines. N7-alkylguanine is not a premutagenic adduct, but O6-alkylguanine causes mutations that are involved in initiation of carcinogenesis (Vermeer & Van Maanen, 2001).

No extensive research has been carried out on BRJ consumption in relation to cancer risk. Only one small-scale human dietary intervention study comprising of healthy recreationally active volunteers investigated the effect of drinking BRJ on excretion of NOC in urine. In this randomized, controlled trial, 29 healthy volunteers ingested BRJ containing 400 mg of nitrate per bottle, thereby exceeding the ADI for most people (i.e. 3.7 mg/kg bodyweight per day) with or without additional vitamin C supplements for one week. A significant increase of urinary apparent total *N*-nitroso compounds (ATNC) was found after one dose, and a further increase was found after seven consecutive doses of BRJ. Vitamin C supplementation inhibited ATNC increase after one dose, but not after seven daily doses. This is the only study that investigated the effect of ingestion of high-nitrate levels through BRJ consumption on the formation of potentially carcinogenic NOCs, and its results demonstrated an increase in the excretion of these compounds after already one single dose (Berends et al. 2019).

Although almost no studies have been performed on the possible health risks associated with ingestion of high levels of nitrate through consumption of BRJ, numerous studies investigated the possible health risks associated with consumption of nitrate in general, or related to specific dietary sources of nitrate (e.g. drinking water, red meat, vegetables and fruits, etc.), in particular epidemiological studies. The International Agency for Research on Cancer (IARC) has classified "ingested nitrate" or "nitrite under conditions that result in endogenous nitrosation" as probably carcinogenic to humans (Group 2 A) (World Health Organization & International Agency for Research on Cancer 2010). Epidemiological studies have demonstrated that consumption of nitrate is associated with increased risk of several types of cancer in humans, such as stomach, esophagus and bladder cancer (World Health Organization & International Agency for Research on Cancer 2010). In a recent review on epidemiologic studies investigating the health effects of nitrate in drinking water, it was concluded that the strongest evidence for a relationship between drinking water, nitrate ingestion and adverse health outcomes (besides methemoglobinemia) is for colorectal cancer, thyroid disease, and neural tube defects (Ward et al. 2018). In addition to epidemiological studies, a few human biomonitoring studies have been carried out. In a study from Vermeer et al. (1998), participants consumed nitrate rich drinking water to the level of the maximum acceptable daily intake, combined with an amine-rich fish meal for one week. During this week, participants showed a rising level of nitrate and nitrite in their saliva and a strong increase in urinary nitrate levels. Urinary N-nitrosamine levels were determined and showed a strong increase as well. It was concluded that nitrate intake at acceptable daily intake level combined with an amine rich meal leads to an increase in potential carcinogenic N-nitrosamine excretion in the urine (Vermeer et al. 1998). In a recent study from van Breda et al. (2019), the effect of nitrate from drinking water, and its interaction with the consumption of white and processed red meat, on the endogenous formation of NOCs in healthy volunteers was examined. Healthy subjects consumed either 3.75 g/kg body weight (maximum 300 g per day) processed red meat or unprocessed white meat per day for two weeks. Furthermore, drinking water nitrate levels were kept low during the first week (< 1.5 mg/L), whereas in week 2, nitrate levels in drinking water were adjusted to the acceptable daily intake level of 3.7 mg/kg bodyweight. The ATNC levels in fecal water of the participants significantly increased during the high drinking water nitrate period. The results show that drinking water nitrate can have a significant contribution to the endogenous formation of NOCs (van Breda et al. 2019).

Numerous epidemiological studies investigated the relationship between intake of red or processed meat, which contains high levels of nitrite and nitrate due to the salts that are added as preservatives, and the occurrence of cancer in humans. These conclude that the consumption of red and processed meat results in an intake-dependent endogenous formation of total NOCs. It appears that the amount of NOCs in the feces correlates with red meat intake (Habermeyer et al. 2015; Hebels et al. 2012; Hughes et al. 2001; Linseisen et al., 2006). However, the underlying mechanisms for this are not entirely clear. Therefore, there might be a possible correlation between nitrite intake and NOC formation. Furthermore, prospective cohort studies also suggest an association between red meat intake and an increased risk for colon cancer. No associations are reported for other types of cancer (Cross et al. 2011; Dubrow et al. 2010). Despite the lack of established casualties in human studies, NOCs have been found to be carcinogenic in at least 39 animal studies (Bogovski and Bogovski 1981).

The largest dietary sources of nitrate are vegetables, especially green leafy vegetables, such as spinach and beetroot. It is generally accepted that eating a variety of fruits and vegetables can protect against cancer and other types of chronic diseases, probably due to the high and diverse level of non-nutritive bioactive compounds, called phytochemicals (World Health Organization & International Agency for Research on Cancer, 2003; World Cancer Research Fund/ American Institute for Cancer Research 2018). These phytochemicals may inhibit the development of cancer at different stages of the carcinogenic process (Ferguson and Philpott 2007; Gonzalez-Vallinas et al. 2013; Surh 2003; van Breda & de Kok, 2018). It is thought that for example the vitamin C which is present in the vegetables is able to block the formation of NOCs by reducing $2HNO_2$ to NO, and is itself oxidized to dehydroascorbic acid (World Health Organization & International Agency for Research on Cancer, 2010). However, the acceptable daily intake of nitrate is unlikely to be exceeded by eating vegetables and fruits, unless they are eaten in concentrated and extreme high amounts on a daily basis (Bahadoran et al. 2017).

In conclusion, as BRJ contains high levels of nitrate, BRJ consumption might pose a health risk due to the possible formation of NOCs. More research is needed to investigate the link between NOC formation and BRJ intake for shorter and longer periods of time, and its potential carcinogenic risk. In the meantime, it is important to be cautious with chronic use of BRJ to enhance sports performances.

Conclusion

A wide range of studies report the beneficial health effects of consuming BRJ, which are in particular sport enhancing effects. This outcome is explained by the high levels of nitrate in BRJ which has a beneficial effect on different parameters including NO, VO_2, blood flow, platelet aggregation, heart rate, cardiac output, blood pressure and performance. Especially because of its effects on the cardiovascular system, BRJ consumption could possibly be used as a supplement in different treatments for cardiovascular disease. However, high intake of nitrate can also result in formation of potentially carcinogenic NOCs. Intake of high levels of nitrate via different routes has been shown to cause an increase in the risk of different types of cancer. But, almost no studies have been published which investigate the possible health risks of BRJ consumption. Therefore, more research is necessary for a comprehensive and reliable assessment of the negative effects of BRJ consumption. In particular, more dedicated human studies are needed in order to secure that the amount of BRJ that is currently advised to lower blood pressure and to enhance sports performances does not increase endogenous formation of NOC and associated health effects in order to guarantee that BRJ can be safely used.

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References

Amano, T., D. Okushima, B. C. Breese, S. J. Bailey, S. Koga, and N. Kondo. 2018. Influence of dietary nitrate supplementation on local sweating and cutaneous vascular responses during exercise in a hot environment. *European Journal of Applied Physiology* 118 (8):1579–88. doi: 10.1007/s00421-018-3889-9.

Arciero, P. J., V. J. Miller, and E. Ward. 2015. Performance enhancing diets and the PRISE Protocol to optimize athletic performance. *Journal of Nutrition and Metabolism* 2015:715859. doi: 10.1155/2015/715859.

Arnold, J. T., S. J. Oliver, T. M. Lewis-Jones, L. J. Wylie, and J. H. Macdonald. 2015. Beetroot juice does not enhance altitude running performance in well-trained athletes. *Applied Physiology, Nutrition and Metabolism* 40 (6):590–5. doi: 10.1139/apnm-2014-0470.

Aucouturier, J., J. Boissiere, M. Pawlak-Chaouch, G. Cuvelier, and F. X. Gamelin. 2015. Effect of dietary nitrate supplementation on tolerance to supramaximal intensity intermittent exercise. *Nitric Oxide* 49:16–25. doi: 10.1016/j.niox.2015.05.004.

Bahadoran, Z., P. Mirmiran, A. Kabir, F. Azizi, and A. Ghasemi. 2017. The nitrate-independent blood pressure-lowering effect of beetroot juice: A systematic review and meta-analysis. *Advances in Nutrition* 8 (6):830–8. doi: 10.3945/an.117.016717.

Bailey, S. J., R. L. Varnham, F. J. DiMenna, B. C. Breese, L. J. Wylie, and A. M. Jones. 2015. Inorganic nitrate supplementation improves muscle oxygenation, O(2) uptake kinetics, and exercise tolerance at high but not low pedal rates. *Journal of Applied Physiology (1985)* 118 (11):1396–405. doi: 10.1152/japplphysiol.01141.2014.

Bakker, E., H. Engan, A. Patrician, E. Schagatay, T. Karlsen, U. Wisloff, and S. E. Gaustad. 2015. Acute dietary nitrate supplementation improves arterial endothelial function at high altitude: A double-blinded randomized controlled cross over study. *Nitric Oxide* 50:58–64. doi: 10.1016/j.niox.2015.08.006.

Balsalobre-Fernández, C., B. Romero-Moraleda, R. Cupeiro, A. B. Peinado, J. Butragueño, and P. J. Benito. 2018. The effects of beetroot juice supplementation on exercise economy, rating of perceived exertion and running mechanics in elite distance runners: A double-blinded, randomized study. *PloS One* 13 (7):e0200517. doi: 10.1371/journal.pone.0200517.

Barlow, M. J., A. Elia, O. M. Shannon, A. Zacharogianni, and A. Lodin-Sundstrom. 2018. The Effect of a Dietary Nitrate Supplementation in the Form of a Single Shot of Beetroot Juice on Static and Dynamic Apnea Performance. *International Journal of Sport Nutrition and Exercise Metabolism* 28:1–5. doi: 10.1123/ijsnem.2017-0300.

Bender, D., J. R. Townsend, W. Vantrease, A. C. Marshall, R. N. Henry, S. Heffington, and K. D. Johnson. 2018. Acute beetroot juice administration improves peak isometric force production in adolescent males. *Applied Physiology, Nutrition and Metabolism* 43 (8):816–21. doi: 10.1139/apnm-2018-0050.

Bentley, R., S. R. Gray, C. Schwarzbauer, D. Dawson, M. Frenneaux, and J. He. 2014. Dietary nitrate reduces skeletal muscle oxygenation response to physical exercise: A quantitative muscle functional MRI study. *Physiological Reports* 2 (7):e12089. doi: 10.14814/phy2.12089.

Bentley, R. F., J. J. Walsh, P. J. Drouin, A. Velickovic, S. J. Kitner, A. M. Fenuta, and M. E. Tschakovsky. 2017. Dietary nitrate restores compensatory vasodilation and exercise capacity in response to a compromise in oxygen delivery in the noncompensator phenotype. *Journal of Applied Physiology (1985)* 123 (3):594–605. doi: 10.1152/japplphysiol.00953.2016.

Berends, J. E., L. M. M. van den Berg, M. A. Guggeis, N. F. T. Henckens, I. J. Hossein, M. E. J. R. de Joode, H. Zamani, K. A. A. J. van Pelt, N. A. Beelen, G. G. Kuhnle, et al. 2019. Consumption of nitrate-rich beetroot juice with or without vitamin c supplementation increases the excretion of urinary nitrate, nitrite, and n-nitroso compounds in humans. *International Journal of Molecular Sciences* 20 (9):2277–92. doi: 10.3390/ijms20092277.

Betteridge, S., R. Bescos, M. Martorell, A. Pons, A. P. Garnham, C. C. Stathis, and G. K. McConell. 2016. No effect of acute beetroot juice ingestion on oxygen consumption, glucose kinetics, or skeletal muscle metabolism during submaximal exercise in males. *Journal of Applied Physiology (1985)* 120 (4):391–8. doi: 10.1152/japplphysiol.00658.2015.

Bogovski, P., and S. Bogovski. 1981. Animal species in which N-nitroso compounds induce cancer. *International Journal of Cancer* 27 (4):471–4. doi: 10.1002/ijc.2910270408.

Bond, V., Jr., B. H. Curry, R. G. Adams, M. S. Asadi, R. M. Millis, and G. E. Haddad. 2013. Effects of dietary nitrates on systemic and cerebrovascular hemodynamics. *Cardiology Research and Practice* 2013:435629. doi: 10.1155/2013/435629.

Bond, V., B. H. Curry, R. G. Adams, M. S. Asadi, K. A. Stancil, R. M. Millis, and G. E. Haddad. 2014. Effects of nitrate supplementation on cardiovascular and autonomic reactivity in african-american females. *ISRN Physiology* 2014:1–7. doi: 10.1155/2014/676235.

Bond, V., Jr., B. H. Curry, R. G. Adams, R. M. Millis, and G. E. Haddad. 2014. Cardiorespiratory function associated with dietary nitrate supplementation. *Applied Physiology, Nutrition and Metabolism* 39 (2):168–72. doi: 10.1139/apnm-2013-0263.

Bond, H., L. Morton, and A. J. Braakhuis. 2012. Dietary nitrate supplementation improves rowing performance in well-trained rowers. *International Journal of Sport Nutrition and Exercise Metabolism* 22 (4):251–6. doi: 10.1123/ijsnem.22.4.251.

Boorsma, R. K., J. Whitfield, and L. L. Spriet. 2014. Beetroot juice supplementation does not improve performance of elite 1500-m runners. *Medicine & Science in Sports & Exercise* 46 (12):2326–34. doi: 10.1249/mss.0000000000000364.

Breese, B. C., M. A. McNarry, S. Marwood, J. R. Blackwell, S. J. Bailey, and A. M. Jones. 2013. Beetroot juice supplementation speeds O_2 uptake kinetics and improves exercise tolerance during severe-intensity exercise initiated from an elevated metabolic rate. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 305 (12):R1441–1450. doi: 10.1152/ajpregu.00295.2013.

Breese, B. C., D. C. Poole, D. Okushima, S. J. Bailey, A. M. Jones, N. Kondo, T. Amano, and S. Koga. 2017. The effect of dietary nitrate supplementation on the spatial heterogeneity of quadriceps deoxygenation during heavy-intensity cycling. *Physiological Reports* 5 (14):e13340. doi: 10.14814/phy2.13340.

Burleigh, M., L. Liddle, D. J. Muggeridge, C. Monaghan, N. Sculthorpe, J. Butcher, F. Henriquez, and C. Easton. 2019. Dietary nitrate supplementation alters the oral microbiome but does not improve the vascular responses to an acute nitrate dose. *Nitric Oxide* 89:54–63. doi: 10.1016/j.niox.2019.04.010.

Carriker, C. R., C. M. Mermier, T. A. Van Dusseldorp, K. E. Johnson, N. M. Beltz, R. A. Vaughan, J. J. McCormick, N. H. Cole, C. C. Witt, and A. L. Gibson. 2016. Effect of acute dietary nitrate consumption on oxygen consumption during submaximal exercise in hypobaric hypoxia. *International Journal of Sport Nutrition and Exercise Metabolism* 26 (4):315–22. doi: 10.1123/ijsnem.2015-0144.

Carriker, C. R., P. Rombach, B. M. Stevens, R. A. Vaughan, and A. L. Gibson. 2018. Acute dietary nitrate supplementation does not attenuate oxidative stress or the hemodynamic response during submaximal exercise in hypobaric hypoxia. *Applied Physiology, Nutrition and Metabolism* 43 (12):1268–74. doi: 10.1139/apnm-2017-0813.

Carriker, C. R., R. A. Vaughan, T. A. VanDusseldorp, K. E. Johnson, N. M. Beltz, J. J. McCormick, N. H. Cole, and A. L. Gibson. 2016. Nitrate-containing beetroot juice reduces oxygen consumption during submaximal exercise in low but not high aerobically fit male runners. *Journal of Exercise Nutrition & Biochemistry* 20 (4):27–34. doi: 10.20463/jenb.2016.0029.

Casey, D. P., Treichler, D. P. Ganger, C. T. Th, Schneider, A. C. Ueda. and K. 2015. Acute dietary nitrate supplementation enhances compensatory vasodilation during hypoxic exercise in older adults. *Journal of Applied Physiology (1985)* 118 (2):178–86. doi: 10.1152/japplphysiol.00662.2014.

Cermak, N. M., M. J. Gibala, and L. J. van Loon. 2012. Nitrate supplementation's improvement of 10-km time-trial performance in trained cyclists. *International Journal of Sport Nutrition and Exercise Metabolism* 22 (1):64–71. doi: 10.1123/ijsnem.22.1.64.

Cermak, N. M., P. Res, R. Stinkens, J. O. Lundberg, M. J. Gibala, and L. J. van Loon. 2012. No improvement in endurance performance after a single dose of beetroot juice. *International Journal of Sport Nutrition and Exercise Metabolism* 22 (6):470–8. doi: 10.1123/ijsnem.22.6.470.

Chalmers, T. C., H. Smith, Jr., B. Blackburn, B. Silverman, B. Schroeder, D. Reitman, and A. Ambroz. 1981. A method for assessing the quality of a randomized control trial. *Controlled Clinical Trials* 2 (1):31–49. doi: 10.1016/0197-2456(81)90056-8.

Christensen, P. M., M. Nyberg, and J. Bangsbo. 2013. Influence of nitrate supplementation on VO(2) kinetics and endurance of elite cyclists. *Scandinavian Journal of Medicine & Science in Sports* 23 (1):e21–31. doi: 10.1111/sms.12005.

Christensen, P. M., N. K. Petersen, S. N. Friis, E. Weitzberg, and L. Nybo. 2017. Effects of nitrate supplementation in trained and untrained muscle are modest with initial high plasma nitrite levels. *Scandinavian Journal of Medicine & Science in Sports* 27 (12):1616–26. doi: 10.1111/sms.12848.

Clifford, T., O. Bell, D. J. West, G. Howatson, and E. J. Stevenson. 2016. The effects of beetroot juice supplementation on indices of muscle damage following eccentric exercise. *European Journal of Applied Physiology* 116 (2):353–62. doi: 10.1007/s00421-015-3290-x.

Clifford, T., O. Bell, D. J. West, G. Howatson, and E. J. Stevenson. 2017. Antioxidant-rich beetroot juice does not adversely affect acute neuromuscular adaptation following eccentric exercise. *Journal of Sports Sciences* 35 (8):812–9. doi: 10.1080/02640414.2016.1192670.

Clifford, T., B. Berntzen, G. W. Davison, D. J. West, G. Howatson, and E. J. Stevenson. 2016. Effects of Beetroot Juice on Recovery of Muscle Function and Performance between Bouts of Repeated Sprint Exercise. *Nutrients* 8 (8). doi: 10.3390/nu8080:.506.

Clifford, T., G. Howatson, D. J. West, and E. J. Stevenson. 2017. Beetroot juice is more beneficial than sodium nitrate for attenuating muscle pain after strenuous eccentric-bias exercise. *Applied Physiology, Nutrition and Metabolism* 42 (11):1185–91. doi: 10.1139/apnm-2017-0238.

Coggan, A. R., J. L. Leibowitz, A. Kadkhodayan, D. P. Thomas, S. Ramamurthy, C. A. Spearie, S. Waller, M. Farmer, and L. R. Peterson. 2015. Effect of acute dietary nitrate intake on maximal knee extensor speed and power in healthy men and women. *Nitric Oxide* 48:16–21. doi: 10.1016/j.niox.2014.08.014.

Coles, L. T., and P. M. Clifton. 2012. Effect of beetroot juice on lowering blood pressure in free-living, disease-free adults: A randomized, placebo-controlled trial. *Nutrition Journal* 11:106. doi: 10.1186/1475-2891-11-106.

Craig, J. C., R. M. Broxterman, J. R. Smith, J. D. Allen, and T. J. Barstow. 2018. Effect of dietary nitrate supplementation on conduit artery blood flow, muscle oxygenation, and metabolic rate during handgrip exercise. *Journal of Applied Physiology (1985)* 125:254–62. doi: 10.1152/japplphysiol.00772.2017.

Craig, J. C., R. M. Broxterman, J. R. Smith, J. D. Allen, and T. J. Barstow. 2018. Effect of dietary nitrate supplementation on conduit artery blood flow, muscle oxygenation, and metabolic rate during handgrip exercise. *Journal of Applied Physiology* 125 (2):254–62. doi: 10.1152/japplphysiol.00772.2017.

Cross, A. J., Freedman, N. D. Ren, Jiansong, Ward, M. H. Hollenbeck, A. R. Schatzkin, Arthur, Sinha, R. Abnet. and C. C. 2011. Meat consumption and risk of esophageal and gastric cancer in a large prospective study. *The American Journal of Gastroenterology* 106 (3):432–42.

Cuenca, E., P. Jodra, A. Perez-Lopez, L. G. Gonzalez-Rodriguez, S. Fernandes da Silva, P. Veiga-Herreros, and R. Dominguez. 2018. Effects of beetroot juice supplementation on performance and fatigue in a 30-s all-out sprint exercise: A randomized, double-blind cross-over study. *Nutrients* 10 (9):1222. doi: 10.3390/nu10091222.

Curry, B. H., V. Bond, S. Pemminati, V. R. Gorantla, Y. A. Volkova, K. Kadur, and R. M. Millis. 2016. Effects of a dietary beetroot juice treatment on systemic and cerebral haemodynamics- A pilot study. *Journal of Clinical and Diagnostic Research* 10 (7):Cc01–05. doi: 10.7860/jcdr/2016/20049.8113.

de Castro, T. F., F. de Assis Manoel, D. H. Figueiredo, D. H. Figueiredo, and F. A. Machado. 2019. Effects of chronic beetroot juice supplementation on maximum oxygen uptake, velocity associated with maximum oxygen uptake, and peak velocity in recreational runners: A double-blinded, randomized and crossover study. *European Journal of Applied Physiology* 119 (5):1043–11. doi: 10.1007/s00421-019-04094-w.

de Castro, T. F., F. A. Manoel, D. H. Figueiredo, D. H. Figueiredo, and F. A. Machado. 2019. Effect of beetroot juice supplementation on 10-km performance in recreational runners. *Applied Physiology, Nutrition and Metabolism* 44 (1):90–4. doi: 10.1139/apnm-2018-0277.

de Vries, C. J., and D. S. DeLorey. 2019. Effect of acute dietary nitrate supplementation on sympathetic vasoconstriction at rest and during exercise. *Journal of Applied Physiology (1985)* 127 (1):81–8. doi: 10.1152/japplphysiol.01053.2018.

Dobashi, S., K. Koyama, J. Endo, M. Kiuchi, and M. Horiuchi. 2019. Impact of dietary nitrate supplementation on executive function during hypoxic exercise. *Search Results* 20 (2):187–91. doi: 10.1089/ham.2018.0114.

Dominguez, R., E. Cuenca, J. L. Mate-Munoz, P. Garcia-Fernandez, N. Serra-Paya, M. C. Estevan, P. V. Herreros, and M. V. Garnacho-Castano. 2017. Effects of beetroot juice supplementation on cardiorespiratory endurance in athletes. *Nutrients* 9 (1):43. doi: 10.3390/nu9010043.

Domínguez, R., M. Garnacho-Castaño, E. Cuenca, P. García-Fernández, A. Muñoz-González, F. de Jesús, M. Lozano-Estevan, S. Fernandes da Silva, P. Veiga-Herreros, and J. Maté-Muñoz. 2017. Effects of beetroot juice supplementation on a 30-s high-intensity inertial cycle ergometer test. *Nutrients* 9 (12):1360. doi: 10.3390/nu9121360.

Drinks, J. W. 2019. Nitrate 3000 concentrate. https://www.beet-it.com/buy-now/beet-it-sport-nitrate-3000

Dubrow, R., A. S. Darefsky, Y. Park, S. T. Mayne, S. C. Moore, Kilfoy, C. Briseis, J. Amanda, R. Sinha, A. R. Hollenbeck, and A. Schatzkin. 2010. Dietary components related to N-nitroso compound formation: A prospective study of adult glioma. *Cancer Epidemiology Biomarkers & Prevention* 19 (7):1709–22. doi: 10.1158/1055-9965.EPI-10-0225.

Esen, O., C. Nicholas, M. Morris, and S. J. Bailey. 2019. No effect of beetroot juice supplementation on 100-m and 200-m swimming performance in moderately trained swimmers. *International Journal of Sports Physiology and Performance* 14 (6):706–10. doi: 10.1123/ijspp.2018-0654.

Ferguson, S. K., D. M. Hirai, S. W. Copp, C. T. Holdsworth, J. D. Allen, A. M. Jones, T. I. Musch, and D. C. Poole. 2013a. Effects of nitrate supplementation via beetroot juice on contracting rat skeletal muscle microvascular oxygen pressure dynamics. *Respiratory Physiology & Neurobiology* 187 (3):250–5. doi: 10.1016/j.resp.2013.04.001.

Ferguson, S. K., D. M. Hirai, S. W. Copp, C. T. Holdsworth, J. D. Allen, A. M. Jones, T. I. Musch, and D. C. Poole. 2013b. Impact of dietary nitrate supplementation via beetroot juice on exercising muscle vascular control in rats. *Journal of Physiology* 591 (2):547–57. doi: 10.1113/jphysiol.2012.243121.

Ferguson, S. K., D. M. Hirai, S. W. Copp, C. T. Holdsworth, J. D. Allen, A. M. Jones, T. I. Musch, and D. C. Poole. 2014. Dose dependent effects of nitrate supplementation on cardiovascular control and microvascular oxygenation dynamics in healthy rats. *Nitric Oxide* 39:51–8. doi: 10.1016/j.niox.2014.04.007.

Ferguson, S. K., C. T. Holdsworth, J. L. Wright, A. J. Fees, J. D. Allen, A. M. Jones, T. I. Musch, and D. C. Poole. 2015. Microvascular oxygen pressures in muscles comprised of different fiber types: Impact of dietary nitrate supplementation. *Nitric Oxide* 48:38–43. doi: 10.1016/j.niox.2014.09.157.

Ferguson, L. R., and M. Philpott. 2007. Cancer prevention by dietary bioactive components that target the immune response. *Current Cancer Drug Targets* 7 (5):459–64.

Fulford, J., P. G. Winyard, A. Vanhatalo, S. J. Bailey, J. R. Blackwell, and A. M. Jones. 2013. Influence of dietary nitrate supplementation on human skeletal muscle metabolism and force production during maximum voluntary contractions. *Pflugers Archiv* 465 (4):517–28. doi: 10.1007/s00424-013-1220-5.

Garnacho-Castano, M. V., G. Palau-Salva, E. Cuenca, A. Munoz-Gonzalez, P. Garcia-Fernandez, M. Del Carmen Lozano-Estevan, P. Veiga-Herreros, J. L. Mate-Munoz, and R. Dominguez. 2018. Effects of a single dose of beetroot juice on cycling time trial performance at ventilatory thresholds intensity in male triathletes. *Journal of the International Society of Sports Nutrition* 15 (1):49. doi: 10.1186/s12970-018-0255-6.

Glaister, M., J. R. Pattison, D. Muniz-Pumares, S. D. Patterson, and P. Foley. 2015. Effects of dietary nitrate, caffeine, and their combination on 20-km cycling time trial performance. *The Journal of Strength and Conditioning Research* 29 (1):165–74. doi: 10.1519/jsc.0000000000000596.

Gonzalez-Vallinas, M., M. Gonzalez-Castejon, A. Rodriguez-Casado, and A. Ramirez de Molina. 2013. Dietary phytochemicals in cancer prevention and therapy: A complementary approach with promising perspectives. *Nutrition Reviews* 71 (9):585–99. doi: 10.1111/nure.12051.

Growing Popularity of Beetroot Juice to Fuel the Global Market for Beetroot Powder During 2017–2027. 2017. https://www.futuremarketinsights.com/press-release/beetroot-powder-market-092017

Habermeyer, M., A. Roth, S. Guth, P. Diel, K. -H. Engel, B. Epe, P. Fürst, V. Heinz, H. U. Humpf, andH. G. Joost. 2015. Nitrate and nitrite in the diet: How to assess their benefit and risk for human health. *Molecular Nutrition & Food Research* 59 (1):106–28. doi: 10.1002/mnfr.201400286.

Haider, G., and J. P. Folland. 2014. Nitrate supplementation enhances the contractile properties of human skeletal muscle. *Medicine & Science in Sports & Exercise* 46 (12):2234–43. doi: 10.1249/mss.0000000000000351.

Handzlik, M. K., and M. Gleeson. 2013. Likely additive ergogenic effects of combined preexercise dietary nitrate and caffeine ingestion in trained cyclists. *ISRN Nutrition* 2013:396581. doi: 10.5402/2013/396581.

Hebels, D. G., K. M. Sveje, M. C. de Kok, M. H. M. van Herwijnen, G. G. Kuhnle, L. G. Engels, C. B. Vleugels-Simon, W. G. Mares, M. Pierik, and A. A. Masclee. 2012. Red meat intake-induced increases in fecal water genotoxicity correlate with pro-carcinogenic gene expression changes in the human colon. *Food and Chemical Toxicology* 50 (2):95–103. doi: 10.1016/j.fct.2011.10.038.

Hennis, P. J., K. Mitchell, E. Gilbert-Kawai, V. Bountziouka, A. Wade, M. Feelisch, M. P. Grocott, and D. S. Martin. 2016. Effects of dietary nitrate supplementation on symptoms of acute mountain sickness and basic physiological responses in a group of male adolescents during ascent to Mount Everest Base Camp. *Nitric Oxide* 60:24–31. doi: 10.1016/j.niox.2016.08.007.

Hobbs, D. A., N. Kaffa, T. W. George, L. Methven, and J. A. Lovegrove. 2012. Blood pressure-lowering effects of beetroot juice and novel beetroot-enriched bread products in normotensive male subjects. *British Journal of Nutrition* 108 (11):2066–74. doi: 10.1017/s0007114512000190.

Hohensinn, B., R. Haselgrubler, U. Muller, V. Stadlbauer, P. Lanzerstorfer, G. Lirk, O. Hoglinger, and J. Weghuber. 2016. Sustaining elevated levels of nitrite in the oral cavity through consumption of nitrate-rich beetroot juice in young healthy adults reduces salivary pH. *Nitric Oxide* 60:10–5. doi: 10.1016/j.niox.2016.08.006.

Hoon, M. W., C. Fornusek, P. G. Chapman, and N. A. Johnson. 2015. The effect of nitrate supplementation on muscle contraction in healthy adults. *European Journal of Sport Science* 15 (8):712–9. doi: 10.1080/17461391.2015.1053418.

Hoon, M. W., W. G. Hopkins, A. M. Jones, D. T. Martin, S. L. Halson, N. P. West, N. A. Johnson, and L. M. Burke. 2014. Nitrate supplementation and high-intensity performance in competitive cyclists. *Applied Physiology, Nutrition and Metabolism* 39 (9):1043–9. doi: 10.1139/apnm-2013-0574.

Hoon, M. W., N. A. Johnson, P. G. Chapman, and L. M. Burke. 2013. The effect of nitrate supplementation on exercise performance in healthy individuals: A systematic review and meta-analysis. *International Journal of Sport Nutrition and Exercise Metabolism* 23 (5):522–32. doi: 10.1123/ijsnem.23.5.522.

Hoon, M. W., A. M. Jones, N. A. Johnson, J. R. Blackwell, E. M. Broad, B. Lundy, A. J. Rice, and L. M. Burke. 2014. The effect of variable doses of inorganic nitrate-rich beetroot juice on simulated 2,000-m rowing performance in trained athletes. *International Journal of Sports Physiology and Performance* 9 (4):615–20. doi: 10.1123/ijspp.2013-0207.

Horiuchi, M., J. Endo, S. Dobashi, Y. Handa, M. Kiuchi, and K. Koyama. 2017. Muscle oxygenation profiles between active and inactive muscles with nitrate supplementation under hypoxic exercise. *Physiological Reports* 5 (20):e13475. doi: 10.14814/phy2.13475.

Hughes, R., A. J. Cross, J. R. A. Pollock, and S. Bingham. 2001. Dose-dependent effect of dietary meat on endogenous colonic N-nitrosation. *Carcinogenesis* 22 (1):199–202. doi: 10.1093/oxfordjournals.carcin.a000409.

Hughes, W. E., K. Ueda, D. P. Treichler, and D. P. Casey. 2016. Effects of acute dietary nitrate supplementation on aortic blood pressure and aortic augmentation index in young and older adults. *Nitric Oxide* 59:21–7. doi: 10.1016/j.niox.2016.06.007.

Husmann, F., S. Bruhn, T. Mittlmeier, V. Zschorlich, and M. Behrens. 2019. Dietary nitrate supplementation improves exercise tolerance by reducing muscle fatigue and perceptual responses. *Frontiers in Physiology* 10:1–13. doi: 10.3389/fphys.2019.00404.

Jadad, A. R., R. A. Moore, D. Carroll, C. Jenkinson, D. J. Reynolds, D. J. Gavaghan, and H. J. McQuay. 1996. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials* 17 (1):1–12. doi: 10.1016/0197-2456(95)00134-4.

Jones, A. M., S. J. Bailey, and A. Vanhatalo. 2012. Dietary nitrate and O(2) consumption during exercise. *Medicine and Sport Science* 59:29–35. doi: 10.1159/000342062.

Jonvik, K. L., J. Nyakayiru, P. J. Pinckaers, J. M. Senden, L. J. van Loon, and L. B. Verdijk. 2016. Nitrate-rich vegetables increase plasma nitrate and nitrite concentrations and lower blood pressure in healthy adults. *Journal of Nutrition* 146 (5):986–93. doi: 10.3945/jn.116.229807.

Jonvik, K. L., J. Nyakayiru, J. W. Van Dijk, K. Maase, S. B. Ballak, J. M. G. Senden, L. J. C. Van Loon, and L. B. Verdijk. 2018. Repeated-sprint performance and plasma responses following beetroot juice supplementation do not differ between recreational, competitive and elite sprint athletes. *European Journal of Sport Science* 18 (4):524–33. doi: 10.1080/17461391.2018.1433722.

Jonvik, K. L., J. W. Van Dijk, J. M. G. Senden, L. J. C. Van Loon, and L. B. Verdijk. 2017. The effect of beetroot juice supplementation on dynamic apnea and intermittent sprint performance in elite female water polo players. *International Journal of Sport Nutrition and Exercise Metabolism* 28:1–20. doi: 10.1123/ijsnem.2017-0293.

Kapil, V., A. B. Milsom, M. Okorie, S. Maleki-Toyserkani, F. Akram, F. Rehman, S. Arghandawi, V. Pearl, N. Benjamin, S. Loukogeorgakis, et al. 2010. Inorganic nitrate supplementation lowers blood pressure in humans: Role for nitrite-derived NO. *Hypertension* 56 (2):274–81. doi: 10.1161/hypertensionaha.110.153536.

Keen, J. T., E. L. Levitt, G. J. Hodges, and B. J. Wong. 2015. Short-term dietary nitrate supplementation augments cutaneous vasodilatation and reduces mean arterial pressure in healthy humans. *Microvascular Research* 98:48–53. doi: 10.1016/j.mvr.2014.12.002.

Kelly, J., J. Fulford, A. Vanhatalo, J. R. Blackwell, O. French, S. J. Bailey, M. Gilchrist, P. G. Winyard, and A. M. Jones. 2013. Effects of short-term dietary nitrate supplementation on blood pressure, O2 uptake kinetics, and muscle and cognitive function in older adults. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 304 (2):R73–83. doi: 10.1152/ajpregu.00406.2012.

Kelly, J., A. Vanhatalo, S. J. Bailey, L. J. Wylie, C. Tucker, S. List, P. G. Winyard, and A. M. Jones. 2014. Dietary nitrate supplementation: Effects on plasma nitrite and pulmonary O2 uptake dynamics during exercise in hypoxia and normoxia. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 307 (7):R920–930. doi: 10.1152/ajpregu.00068.2014.

Kelly, J., A. Vanhatalo, D. P. Wilkerson, L. J. Wylie, and A. M. Jones. 2013. Effects of nitrate on the power-duration relationship for severe-intensity exercise. *Medicine & Science in Sports & Exercise* 45 (9):1798–806. doi: 10.1249/MSS.0b013e31828e885c.

Kent, G. L., B. Dawson, G. R. Cox, C. R. Abbiss, K. J. Smith, K. D. Croft, Z. X. Lim, A. Eastwood, L. M. Burke, and P. Peeling. 2018. Effect of dietary nitrate supplementation on thermoregulatory and cardiovascular responses to submaximal cycling in the heat. *European Journal of Applied Physiology* 118 (3):657–68. doi: 10.1007/s00421-018-3809-z.

Kent, G. L., B. Dawson, G. R. Cox, L. M. Burke, A. Eastwood, K. D. Croft, and P. Peeling. 2018. Dietary nitrate supplementation does not improve cycling time-trial performance in the heat. *Journal of Sports Sciences* 36 (11):1204–11. doi: 10.1080/02640414.2017.1364404.

Kent, G. L., B. Dawson, L. R. McNaughton, G. R. Cox, L. M. Burke, and P. Peeling. 2019. The effect of beetroot juice supplementation on repeat-sprint performance in hypoxia. *Journal of Sports Sciences* 37 (3):339–46. doi: 10.1080/02640414.2018.1504369.

Kim, D. J., C. A. Roe, Y. B. Somani, D. J. Moore, M. A. Barrett, M. Flanagan, D. B. Kim-Shapiro, S. Basu, M. D. Muller, and D. N. Proctor. 2019. Effects of acute dietary nitrate supplementation on aortic blood pressures and pulse wave characteristics in post-menopausal women. *Nitric Oxide* 85:10–6. doi: 10.1016/j.niox.2019.01.008.

Kroll, J. L., C. A. Werchan, D. Rosenfield, and T. Ritz. 2018. Acute ingestion of beetroot juice increases exhaled nitric oxide in healthy individuals. *PLoS One* 13 (1):e0191030. doi: 10.1371/journal.pone.0191030.

Kuennen, M., L. Jansen, T. Gillum, J. Granados, W. Castillo, A. Nabiyar, and K. Christmas. 2015. Dietary nitrate reduces the O2 cost of desert marching but elevates the rise in core temperature. *European Journal of Applied Physiology* 115 (12):2557–69. doi: 10.1007/s00421-015-3255-0.

Kukadia, S., H. M. Dehbi, T. Tillin, E. Coady, N. Chaturvedi, and A. D. Hughes. 2019. A double-blind placebo-controlled crossover study of the effect of beetroot juice containing dietary nitrate on aortic and brachial blood pressure over 24 h. *Frontiers in Physiology* 10:47. doi: 10.3389/fphys.2019.00047.

Lane, S. C., J. A. Hawley, B. Desbrow, A. M. Jones, J. R. Blackwell, M. L. Ross, A. J. Zemski, and L. M. Burke. 2014. Single and combined effects of beetroot juice and caffeine supplementation on cycling time trial performance. *Applied Physiology, Nutrition and Metabolism* 39 (9):1050–7. doi: 10.1139/apnm-2013-0336.

Lansley, K. E., P. G. Winyard, S. J. Bailey, A. Vanhatalo, D. P. Wilkerson, J. R. Blackwell, M. Gilchrist, N. Benjamin, and A. M. Jones. 2011. Acute dietary nitrate supplementation improves cycling time trial performance. *Medicine & Science in Sports & Exercise* 43 (6):1125–31. doi: 10.1249/MSS.0b013e31821597b4.

Lansley, K. E., P. G. Winyard, J. Fulford, A. Vanhatalo, S. J. Bailey, J. R. Blackwell, F. J. DiMenna, M. Gilchrist, N. Benjamin, and A. M. Jones. 2011. Dietary nitrate supplementation reduces the O2 cost of walking and running: A placebo-controlled study. *Journal of Applied Physiology (1985)* 110 (3):591–600. doi: 10.1152/japplphysiol.01070.2010.

Larsen, F. J., T. A. Schiffer, S. Borniquel, K. Sahlin, B. Ekblom, J. O. Lundberg, and E. Weitzberg. 2011. Dietary inorganic nitrate improves mitochondrial efficiency in humans. *Cell Metabolism* 13 (2):149–59. doi: 10.1016/j.cmet.2011.01.004.

Lee, S., M. G. Abel, T. Thomas, T. B. Symons, and J. W. Yates. 2019. Acute beetroot juice supplementation does not attenuate knee extensor exercise muscle fatigue in a healthy young population. *Journal of Exercise Nutrition & Biochemistry* 23 (1):55. doi: 10.20463/jenb.2019.0008.

Lee, J. S., C. L. Stebbins, E. Jung, H. Nho, J. K. Kim, M. J. Chang, and H. M. Choi. 2015. Effects of chronic dietary nitrate supplementation on the hemodynamic response to dynamic exercise. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 309 (5):R459–466. doi: 10.1152/ajpregu.00099.2015.

Levitt, E. L., J. T. Keen, and B. J. Wong. 2015. Augmented reflex cutaneous vasodilatation following short-term dietary nitrate supplementation in humans. *Experimental Physiology* 100 (6):708–18. doi: 10.1113/ep085061.

Liddle, L., C. Monaghan, M. C. Burleigh, L. C. McIlvenna, D. J. Muggeridge, and C. Easton. 2018. Changes in body posture alter plasma nitrite but not nitrate concentration in humans. *Nitric Oxide* 72:59–65. doi: 10.1016/j.niox.2017.11.008.

Linseisen, J., S. Rohrmann, T. Norat, C. A. Gonzalez, M. Dorronsoro Iraeta, P. Morote Gomez, M. D. Chirlaque, B. G. Pozo, E. Ardanaz, I. Mattisson, et al. 2006. Dietary intake of different types and characteristics of processed meat which might be associated with cancer risk–results from the 24-hour diet recalls in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutrition* 9 (4):449–64. doi: 10.1079/phn2005861.

Lowings, S., O. M. Shannon, K. Deighton, J. Matu, and M. J. Barlow. 2017. Effect of dietary nitrate supplementation on swimming performance in trained swimmers. *International Journal of Sport Nutrition and Exercise Metabolism* 27 (4):377–84. doi: 10.1123/ijsnem.2016-0251.

MacLeod, K. E., S. F. Nugent, S. I. Barr, M. S. Koehle, B. C. Sporer, and M. J. MacInnis. 2015. Acute beetroot juice supplementation does not improve cycling performance in normoxia or moderate hypoxia. *International Journal of Sport Nutrition and Exercise Metabolism* 25 (4):359–66. doi: 10.1123/ijsnem.2014-0129.

Martin, K., D. Smee, K. G. Thompson, and B. Rattray. 2014. No improvement of repeated-sprint performance with dietary nitrate. *International Journal of Sports Physiology and Performance* 9 (5):845–50. doi: 10.1123/ijspp.2013-0384.

Masschelein, E., R. Van Thienen, X. Wang, A. Van Schepdael, M. Thomis, and P. Hespel. 2012. Dietary nitrate improves muscle but not cerebral oxygenation status during exercise in hypoxia. *Journal of Applied Physiology (1985)* 113 (5):736–45. doi: 10.1152/japplphysiol.01253.2011.

McDonagh, S. T. J., L. J. Wylie, J. M. A. Webster, A. Vanhatalo, and A. M. Jones. 2018. Influence of dietary nitrate food forms on nitrate metabolism and blood pressure in healthy normotensive adults. *Nitric Oxide* 72:66–74. doi: 10.1016/j.niox.2017.12.001.

McQuillan, J. A., J. R. Casadio, D. K. Dulson, P. B. Laursen, and A. E. Kilding. 2018. The effect of nitrate supplementation on cycling performance in the heat in well-trained cyclists. *International Journal of Sports Physiology and Performance* 13 (1):50–6. doi: 10.1123/ijspp.2016-0793.

McQuillan, J. A., D. K. Dulson, P. B. Laursen, and A. E. Kilding. 2017a. Dietary nitrate fails to improve 1 and 4 km cycling performance in highly trained cyclists. *International Journal of Sport Nutrition and Exercise Metabolism* 27 (3):255–63. doi: 10.1123/ijsnem.2016-0212.

McQuillan, J. A., D. K. Dulson, P. B. Laursen, and A. E. Kilding. 2017b. The effect of dietary nitrate supplementation on physiology and performance in trained cyclists. *International Journal of Sports*

Physiology and Performance 12 (5):684–9. doi: 10.1123/ijspp.2016-0202.

Miller, G. D., A. P. Marsh, R. W. Dove, D. Beavers, T. Presley, C. Helms, E. Bechtold, S. B. King, and D. Kim-Shapiro. 2012. Plasma nitrate and nitrite are increased by a high-nitrate supplement but not by high-nitrate foods in older adults. *Nutrition Research* 32 (3):160–8. doi: 10.1016/j.nutres.2012.02.002.

Mirmiran, P., Z. Houshialsadat, Z. Gaeini, Z. Bahadoran, and F. Azizi. 2020. Functional properties of beetroot (Beta vulgaris) in management of cardio-metabolic diseases. *Nutrition & Metabolism (London)* 17:3. doi: 10.1186/s12986-019-0421-0.

Mosher, S. L., L. A. Gough, S. Deb, B. Saunders, L. R. Mc Naughton, D. R. Brown, and S. A. Sparks. 2019. High dose Nitrate ingestion does not improve 40 km cycling time trial performance in trained cyclists. *Research in Sports Medicine* 28:1–9. doi: 10.1080/15438627.2019.1586707.

Muggeridge, D. J., C. C. Howe, O. Spendiff, C. Pedlar, P. E. James, and C. Easton. 2013. The effects of a single dose of concentrated beetroot juice on performance in trained flatwater kayakers. *International Journal of Sport Nutrition and Exercise Metabolism* 23 (5):498–506. doi: 10.1123/ijsnem.23.5.498.

Muggeridge, D. J., C. C. Howe, O. Spendiff, C. Pedlar, P. E. James, and C. Easton. 2014. A single dose of beetroot juice enhances cycling performance in simulated altitude. *Medicine & Science in Sports & Exercise* 46 (1):143–50. doi: 10.1249/MSS.0b013e3182a1dc51.

Mulkareddy, V., S. B. Racette, A. R. Coggan, and L. R. Peterson. 2019. Dietary nitrate's effects on exercise performance in heart failure with reduced ejection fraction (HFrEF). *Biochimica et Biophysica Acta - Molecular Basis of Disease* 1865 (4):735–40. doi: 10.1016/j.bbadis.2018.09.026.

Notay, K., A. V. Incognito, and P. J. Millar. 2017. Acute beetroot juice supplementation on sympathetic nerve activity: A randomized, double-blind, placebo-controlled proof-of-concept study. *American Journal of Physiology - Heart and Circulatory Physiology* 313 (1):H59–h65. doi: 10.1152/ajpheart.00163.2017.

Nyakayiru, J., K. L. Jonvik, J. Trommelen, P. J. Pinckaers, J. M. Senden, L. J. van Loon, and L. B. Verdijk. 2017. Beetroot juice supplementation improves high-intensity intermittent type exercise performance in trained soccer players. *Nutrients* 9 (3):314. doi: 10.3390/nu9030314.

Oggioni, C., D. G. Jakovljevic, M. Klonizakis, A. W. Ashor, A. Ruddock, M. Ranchordas, E. Williams, and M. Siervo. 2018. Dietary nitrate does not modify blood pressure and cardiac output at rest and during exercise in older adults: A randomised cross-over study. *International Journal of Food Science and Nutrition* 69 (1):74–83. doi: 10.1080/09637486.2017.1328666.

Olsson, H., J. Al-Saadi, D. Oehler, J. Pergolizzi, Jr., and P. Magnusson. 2019. Physiological effects of beetroot in athletes and patients. *Cureus* 11 (12):e6355. doi: 10.7759/cureus.6355.

Papadopoulos, S., K. Dipla, A. Triantafyllou, M. G. Nikolaidis, A. Kyparos, P. Touplikioti, I. S. Vrabas, and A. Zafeiridis. 2018. Beetroot increases muscle performance and oxygenation during sustained isometric exercise, but does not alter muscle oxidative efficiency and microvascular reactivity at rest. *Journal of the American College of Nutrition* 37:1–12. doi: 10.1080/07315724.2017.1401497.

Patrician, A., H. Engan, D. Lundsten, L. Grote, H. Vigetun-Haughey, and E. Schagatay. 2018. The effect of dietary nitrate on nocturnal sleep-disordered breathing and arterial oxygen desaturation at high altitude. *Search Results* 19 (1):21–7. doi: 10.1089/ham.2017.0039.

Patrician, A., and E. Schagatay. 2017. Dietary nitrate enhances arterial oxygen saturation after dynamic apnea. *Scandinavian Journal of Medicine & Science in Sports* 27 (6):622–6. doi: 10.1111/sms.12684.

Pawlak-Chaouch, M., J. Boissiere, D. Munyaneza, F. X. Gamelin, G. Cuvelier, S. Berthoin, and J. Aucouturier. 2019. Beetroot juice does not enhance supramaximal intermittent exercise performance in elite endurance athletes. *Journal of the American College of Nutrition* 38:1–10. doi: 10.1080/07315724.2019.1601601.

Peeling, P., G. R. Cox, N. Bullock, and L. M. Burke. 2015. Beetroot juice improves on-water 500 M time-trial performance, and laboratory-based paddling economy in national and international-level kayak athletes. *International Journal of Sport Nutrition and Exercise Metabolism* 25 (3):278–84. doi: 10.1123/ijsnem.2014-0110.

Perez, J. M., J. L. Dobson, G. A. Ryan, and A. J. Riggs. 2019. The effects of beetroot juice on VO2max and blood pressure during submaximal exercise. *International Journal of Exercise Science* 12 (2):332–42.

Pinna, M., S. Roberto, R. Milia, E. Marongiu, S. Olla, A. Loi, G. M. Migliaccio, J. Padulo, C. Orlandi, F. Tocco, et al. 2014. Effect of beetroot juice supplementation on aerobic response during swimming. *Nutrients* 6 (2):605–15. doi: 10.3390/nu6020605.

Puype, J., M. Ramaekers, R. Van Thienen, L. Deldicque, and P. Hespel. 2015. No effect of dietary nitrate supplementation on endurance training in hypoxia. *Scandinavian Journal of Medicine & Science in Sports* 25 (2):234–41. doi: 10.1111/sms.12199.

Raubenheimer, K., D. Hickey, M. Leveritt, R. Fassett, J. Ortiz de Zevallos Munoz, J. D. Allen, D. Briskey, T. J. Parker, G. Kerr, J. M. Peake, et al. 2017. Acute effects of nitrate-rich beetroot juice on blood pressure, hemostasis and vascular inflammation markers in healthy older adults: A randomized, placebo-controlled crossover study. *Nutrients* 9 (11):1270. doi: 10.3390/nu9111270.

Remington, J., and K. Winters. 2019. Effectiveness of dietary inorganic nitrate for lowering blood pressure in hypertensive adults: A systematic review. *The JBI Database of Systematic Reviews and Implementation Reports* 17 (3):365–89. doi: 10.11124/JBISRIR-2017-003842.

Richards, J. C., M. L. Racine, C. M. Hearon, Jr., M. Kunkel, G. J. Luckasen, D. G. Larson, J. D. Allen, and F. A. Dinenno. 2018. Acute ingestion of dietary nitrate increases muscle blood flow via local vasodilation during handgrip exercise in young adults. *Physiological Reports* 6 (2):e13572. doi: 10.14814/phy2.13572.

Rienks, J. N., A. A. Vanderwoude, E. Maas, Z. M. Blea, and A. W. Subudhi. 2015. Effect of beetroot juice on moderate-intensity exercise at a constant rating of perceived exertion. *International Journal of Exercise Science* 8 (3):277–86.

Rimer, E. G., L. R. Peterson, A. R. Coggan, and J. C. Martin. 2016. Increase in maximal cycling power with acute dietary nitrate supplementation. *International Journal of Sports Physiology and Performance* 11 (6):715–20. doi: 10.1123/ijspp.2015-0533.

Rokkedal-Lausch, T., J. Franch, M. K. Poulsen, L. P. Thomsen, E. Weitzberg, E. N. Kamavuako, D. S. Karbing, and R. G. Larsen. 2019. Chronic high-dose beetroot juice supplementation improves time trial performance of well-trained cyclists in normoxia and hypoxia. *Nitric Oxide* 85:44–52. doi: 10.1016/j.niox.2019.01.011.

Rossetti, G. M. K., J. H. Macdonald, L. J. Wylie, S. J. Little, V. Newton, B. Wood, K. A. Hawkins, R. Beddoe, H. E. Davies, and S. J. Oliver. 2017. Dietary nitrate supplementation increases acute mountain sickness severity and sense of effort during hypoxic exercise. *Journal of Applied Physiology (1985)* 123 (4):983–92. doi: 10.1152/japplphysiol.00293.2017.

Shannon, O. M., M. J. Barlow, L. Duckworth, E. Williams, G. Wort, D. Woods, M. Siervo, and J. P. O'Hara. 2017. Dietary nitrate supplementation enhances short but not longer duration running time-trial performance. *European Journal of Applied Physiology* 117 (4):775–85. doi: 10.1007/s00421-017-3580-6.

Shannon, O. M., L. Duckworth, M. J. Barlow, K. Deighton, J. Matu, E. L. Williams, D. Woods, L. Xie, B. C. M. Stephan, M. Siervo, et al. 2017. Effects of dietary nitrate supplementation on physiological responses, cognitive function, and exercise performance at moderate and very-high simulated altitude. *Frontiers in Physiology* 8:401. doi: 10.3389/fphys.2017.00401.

Shannon, O. M., L. Duckworth, M. J. Barlow, D. Woods, J. Lara, M. Siervo, and J. P. O'Hara. 2016. Dietary nitrate supplementation enhances high-intensity running performance in moderate normobaric hypoxia, independent of aerobic fitness. *Nitric Oxide* 59:63–70. doi: 10.1016/j.niox.2016.08.001.

Shepherd, A. I., D. P. Wilkerson, J. Fulford, P. G. Winyard, N. Benjamin, A. C. Shore, and M. Gilchrist. 2016. Effect of nitrate supplementation on hepatic blood flow and glucose homeostasis: A double-blind, placebo-controlled, randomized control trial. *American*

Journal of Physiology: Gastrointestinal and Liver Physiology 311 (3): G356–364. doi: 10.1152/ajpgi.00203.2016.

Smith, K., D. J. Muggeridge, C. Easton, and M. D. Ross. 2019. An acute dose of inorganic dietary nitrate does not improve high-intensity, intermittent exercise performance in temperate or hot and humid conditions. *European Journal of Applied Physiology* 119 (3):723–33. doi: 10.1007/s00421-018-04063-9.

Stanaway, L., K. Rutherfurd-Markwick, R. Page, and A. Ali. 2017. Performance and health benefits of dietary nitrate supplementation in older adults: A systematic review. *Nutrients* 9 (11):1171. doi: 10.3390/nu9111171.

Surh, Y. J. 2003. Cancer chemoprevention with dietary phytochemicals. *Nature Reviews Cancer* 3 (10):768–80. doi: 10.1038/nrc1189.

Tan, R., L. J. Wylie, C. Thompson, J. R. Blackwell, S. J. Bailey, A. Vanhatalo, and A. M. Jones. 2018. Beetroot juice ingestion during prolonged moderate-intensity exercise attenuates progressive rise in O2 uptake. *Journal of Applied Physiology (1985)* 124 (5):1254–63. doi: 10.1152/japplphysiol.01006.2017.

Thompson, K. G., L. Turner, J. Prichard, F. Dodd, D. O. Kennedy, C. Haskell, J. R. Blackwell, and A. M. Jones. 2014. Influence of dietary nitrate supplementation on physiological and cognitive responses to incremental cycle exercise. *Respiratory Physiology & Neurobiology* 193:11–20. doi: 10.1016/j.resp.2013.12.015.

Thompson, C., A. Vanhatalo, H. Jell, J. Fulford, J. Carter, L. Nyman, S. J. Bailey, and A. M. Jones. 2016. Dietary nitrate supplementation improves sprint and high-intensity intermittent running performance. *Nitric Oxide* 61:55–61. doi: 10.1016/j.niox.2016.10.006.

Thompson, C., L. J. Wylie, J. R. Blackwell, J. Fulford, M. I. Black, J. Kelly, S. T. McDonagh, J. Carter, S. J. Bailey, A. Vanhatalo, et al. 2017. Influence of dietary nitrate supplementation on physiological and muscle metabolic adaptations to sprint interval training. *Journal of Applied Physiology (1985)* 122 (3):642–52. doi: 10.1152/japplphysiol.00909.2016.

Thompson, C., L. J. Wylie, J. Fulford, J. Kelly, M. I. Black, S. T. McDonagh, A. E. Jeukendrup, A. Vanhatalo, and A. M. Jones. 2015. Dietary nitrate improves sprint performance and cognitive function during prolonged intermittent exercise. *European Journal of Applied Physiology* 115 (9):1825–34. doi: 10.1007/s00421-015-3166-0.

Tillin, N. A., S. Moudy, K. M. Nourse, and C. J. Tyler. 2018. Nitrate supplement benefits contractile forces in fatigued but not unfatigued muscle. *Medicine & Science in Sports & Exercise* 50:2122–31. doi: 10.1249/mss.0000000000001655.

van Breda, S. G. J. de Kok, Tmcm. 2018. Smart combinations of bioactive compounds in fruits and vegetables may guide new strategies for personalized prevention of chronic diseases. *Molecular Nutrition & Food Research* 62 (1):1700597–609. doi: 10.1002/mnfr.201700597.

van Breda, S. G., K. Mathijs, V. Sagi-Kiss, G. G. Kuhnle, B. van der Veer, R. R. Jones, R. Sinha, M. H. Ward, and T. M. de Kok. 2019. Impact of high drinking water nitrate levels on the endogenous formation of apparent N-nitroso compounds in combination with meat intake in healthy volunteers. *Environ Health* 18 (1):87. doi: 10.1186/s12940-019-0525-z.

Vanhatalo, A., S. J. Bailey, J. R. Blackwell, F. J. DiMenna, T. G. Pavey, D. P. Wilkerson, N. Benjamin, P. G. Winyard, and A. M. Jones. 2010. Acute and chronic effects of dietary nitrate supplementation on blood pressure and the physiological responses to moderate-intensity and incremental exercise. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 299 (4): R1121–1131. doi: 10.1152/ajpregu.00206.2010.

Vanhatalo, A., J. Fulford, S. J. Bailey, J. R. Blackwell, P. G. Winyard, and A. M. Jones. 2011. Dietary nitrate reduces muscle metabolic perturbation and improves exercise tolerance in hypoxia. *Journal of Physiology* 589 (Pt 22):5517–28. doi: 10.1113/jphysiol.2011.216341.

Vanhatalo, A., A. M. Jones, J. R. Blackwell, P. G. Winyard, and J. Fulford. 2014. Dietary nitrate accelerates postexercise muscle metabolic recovery and O2 delivery in hypoxia. *Journal of Applied Physiology (1985)* 117 (12):1460–70. doi: 10.1152/japplphysiol.00096.2014.

Vaughan, R. A., N. P. Gannon, and C. R. Carriker. 2016. Nitrate-containing beetroot enhances myocyte metabolism and mitochondrial content. *Journal of Traditional and Complementary Medicine* 6 (1): 17–22. doi: 10.1016/j.jtcme.2014.11.033.

Velmurugan, S., V. Kapil, S. M. Ghosh, S. Davies, A. McKnight, Z. Aboud, R. S. Khambata, A. J. Webb, A. Poole, and A. Ahluwalia. 2013. Antiplatelet effects of dietary nitrate in healthy volunteers: Involvement of cGMP and influence of sex. *Free Radical Biology & Medicine* 65:1521–32. doi: 10.1016/j.freeradbiomed.2013.06.031.

Vermeer, I. T., D. M. Pachen, J. W. Dallinga, J. C. Kleinjans, and J. M. van Maanen. 1998. Volatile N-nitrosamine formation after intake of nitrate at the ADI level in combination with an amine-rich diet. *Environmental Health Perspectives* 106 (8):459–63. doi: 10.1289/ehp.106-1533225.

Vermeer, I. T., and J. M. van Maanen. 2001. Nitrate exposure and the endogenous formation of carcinogenic nitrosamines in humans. *Reviews on Environmental Health* 16 (2):105–16.

Waldron, M., L. Waldron, C. Lawlor, A. Gray, and J. Highton. 2018. Beetroot supplementation improves the physiological responses to incline walking. *European Journal of Applied Physiology* 118 (6): 1131–41. doi: 10.1007/s00421-018-3843-x.

Walker, M. A., T. G. Bailey, L. McIlvenna, J. D. Allen, D. J. Green, and C. D. Askew. 2019. Acute dietary nitrate supplementation improves flow mediated dilatation of the superficial femoral artery in healthy older males. *Nutrients* 11 (5):954. doi: 10.3390/nu11050954.

Ward, M. H., R. R. Jones, J. D. Brender, T. M. de Kok, P. J. Weyer, B. T. Nolan, C. M. Villanueva, and S. G. van Breda. 2018. Drinking water nitrate and human health: An updated review. *International Journal of Environmental Research and Public Health* 15 (7): 1557–88. doi: 10.3390/ijerph15071557.

Webb, A. J., N. Patel, S. Loukogeorgakis, M. Okorie, Z. Aboud, S. Misra, R. Rashid, P. Miall, J. Deanfield, N. Benjamin, et al. 2008. Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite. *Hypertension* 51 (3):784–90. doi: 10.1161/hypertensionaha.107.103523.

Whitfield, J., D. Gamu, G. J. F. L. J. C. Heigenhauser, V. A. N. Loon, L. L. Spriet, A. R. Tupling, and G. P. Holloway. 2017. Beetroot juice increases human muscle force without changing ca2+-handling proteins. *Medicine & Science in Sports & Exercise* 49 (10):2016–24. doi: 10.1249/mss.0000000000001321.

Whitfield, J., A. Ludzki, G. J. Heigenhauser, J. M. Senden, L. B. Verdijk, L. J. van Loon, L. L. Spriet, and G. P. Holloway. 2016. Beetroot juice supplementation reduces whole body oxygen consumption but does not improve indices of mitochondrial efficiency in human skeletal muscle. *Journal of Physiology* 594 (2):421–35. doi: 10.1113/jp270844.

Wickham, K. A., D. G. McCarthy, J. M. Pereira, D. T. Cervone, L. B. Verdijk, L. J. van Loon, G. A. Power, and L. L. Spriet. 2019. No effect of beetroot juice supplementation on exercise economy and performance in recreationally active females despite increased torque production. *Physiological Reports* 7 (2):e13982. doi: 10.14814/phy2.13982.

Wickham, K. A., and L. L. Spriet. 2019. No longer beeting around the bush: A review of potential sex differences with dietary nitrate supplementation (1). *Applied Physiology, Nutrition and Metabolism* 44 (9):915–24. doi: 10.1139/apnm-2019-0063.

Wightman, E. L., C. F. Haskell-Ramsay, K. G. Thompson, J. R. Blackwell, P. G. Winyard, J. Forster, A. M. Jones, and D. O. Kennedy. 2015. Dietary nitrate modulates cerebral blood flow parameters and cognitive performance in humans: A double-blind, placebo-controlled, crossover investigation. *Physiology & Behavior* 149:149–58. doi: 10.1016/j.physbeh.2015.05.035.

Wilkerson, D. P., G. M. Hayward, S. J. Bailey, A. Vanhatalo, J. R. Blackwell, and A. M. Jones. 2012. Influence of acute dietary nitrate supplementation on 50 mile time trial performance in well-trained cyclists. *European Journal of Applied Physiology* 112 (12):4127–34. doi: 10.1007/s00421-012-2397-6.

World Cancer Research Fund/American Institute for Cancer Research. 2018. Diet, nutrition, physical activity and cancer: a global perspective. Continuous update project expert report 2018.

World Health Organization & International Agency for Research on Cancer. 2003. IARC handbooks of cancer prevention vol. 8: Fruits and Vegetables. Lyon, France.
World Health Organization & International Agency for Research on Cancer. 2010. IARC monographs on the evaluation of carcinogenic risks to humans. vol. 94: Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins. Lyon, France.
Wruss, J., G. Waldenberger, S. Huemer, P. Uygun, P. Lanzerstorfer, U. Müller, O. Höglinger, and J. Weghuber. 2015. Compositional characteristics of commercial beetroot products and beetroot juice prepared from seven beetroot varieties grown in Upper Austria. *Journal of Food Composition and Analysis* 42:46–55. doi: 10.1016/j.jfca.2015.03.005.
Wylie, L. J., S. J. Bailey, J. Kelly, J. R. Blackwell, A. Vanhatalo, and A. M. Jones. 2016. Influence of beetroot juice supplementation on intermittent exercise performance. *European Journal of Applied Physiology* 116 (2):415–25. doi: 10.1007/s00421-015-3296-4.
Wylie, L. J., J. Kelly, S. J. Bailey, J. R. Blackwell, P. F. Skiba, P. G. Winyard, A. E. Jeukendrup, A. Vanhatalo, and A. M. Jones. 2013. Beetroot juice and exercise: Pharmacodynamic and dose-response relationships. *Journal of Applied Physiology (1985)* 115 (3):325–36. doi: 10.1152/japplphysiol.00372.2013.
Wylie, L. J., M. Mohr, P. Krustrup, S. R. Jackman, G. Ermiotadis, J. Kelly, M. I. Black, S. J. Bailey, A. Vanhatalo, and A. M. Jones. 2013. Dietary nitrate supplementation improves team sport-specific intense intermittent exercise performance. *European Journal of Applied Physiology* 113 (7):1673–84. doi: 10.1007/s00421-013-2589-8.