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

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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<sub>2</sub>) is formed when nitrite is transformed in the acidic environment of the stomach. N<sub>2</sub>O<sub>3</sub> and water are released from the reaction of two molecules of HNO<sub>2</sub>, and the formed N<sub>2</sub>O<sub>3</sub> reacts with amines to nitrosamines, a specific subgroup of NOCs. Protonation of HNO<sub>2</sub> 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

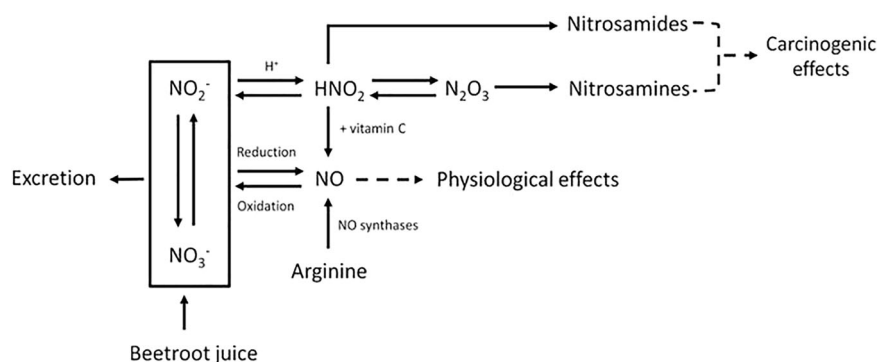
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**Figure 1.** Metabolic pathway of nitrate ( $\text{NO}_3^-$ ), nitrite ( $\text{NO}_2^-$ ), nitric oxide (NO), nitrosamines and the effect of vitamin C. Nitric oxide (NO) is mainly responsible for the physiological effects of BRJ. The body uses arginine 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 ( $\text{NO}_3^-$ ) will be partly reduced to nitrite ( $\text{NO}_2^-$ ) 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  $\text{H}^+$  and will form  $\text{HNO}_2$  (nitrous acid). Also in the stomach, two molecules  $\text{HNO}_2$  can form  $\text{N}_2\text{O}_3$  (dinitrogen trioxide), by proton catalysis.  $\text{N}_2\text{O}_3$  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,  $\text{HNO}_2$  can react with amides to form nitrosamides, and  $\text{N}_2\text{O}_3$  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  $\text{N}_2\text{O}_3$ . Vitamin C reduces  $2\text{HNO}_2$  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 cardio-respiratory 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 jadad 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 ( $\text{VO}_2$ ). 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  $\text{VO}_2$ .

In several studies, ingestion of BRJ was found to significantly decrease  $\text{VO}_2$ , 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  $\text{VO}_2$  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  $\text{VO}_2$  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  $\text{VO}_2$  or  $\text{VO}_2$  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  $\text{VO}_2$  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  $\text{VO}_2$  after BRJ consumption than the low-fit males (Carriker, Vaughan, et al. 2016).

Several studies found that BRJ improves  $\text{O}_2$  kinetics in muscles, for example by speeding up the  $\text{VO}_2$  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  $\text{O}_2$  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  $\text{O}_2$  pressure ( $\text{PO}_{2mv}$ ) 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  $\text{NO}_2^-$  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  $\text{PO}_{2mv}$  (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  $\text{VO}_2$ , 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  $\text{NO}_3^-$ – $\text{NO}_2^-$ –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 ( $69 \pm 4$  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  $\text{VO}_2$ , systolic blood pressure and the heart rate systolic blood pressure (SBP) product at rest and 40%, 60%, and 80% of the predetermined peak  $\text{VO}_2$  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 ( $5.2 \pm 3.3$  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 ( $10.4 \pm 3.0$  mmHg) and a peak difference in diastolic blood pressure (DBP) after 3 h ( $8.1 \pm 2.1$  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  $\text{VO}_2$  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/nitrite 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  $\text{VO}_2$  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 short 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,  $\text{VO}_{2\text{max}}$  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  $\text{VO}_2$  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  $\text{H}^+$  and form  $\text{HNO}_2$  (nitrous acid). Also in the stomach, two molecules  $\text{HNO}_2$  can form  $\text{N}_2\text{O}_3$  (dinitrogen trioxide), by proton catalysis. As  $\text{N}_2\text{O}_3$  plays a role in the *N*-nitrosation rate, increased intake of nitrate can lead to an increase of the *N*-nitrosation rate.  $\text{HNO}_2$  can react with amides to form nitrosamides and  $\text{N}_2\text{O}_3$  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  $\alpha$ -hydroxylation by cytochrome P450 enzymes. Then,  $\alpha$ -hydroxynitrosamines spontaneously become monoalkylnitrosamines, alkyl diazo-hydroxides and alkyl diazonium 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 2A) (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; Hebel 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  $2\text{HNO}_2$  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,  $\text{VO}_2$ , 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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