Investigating dietary recommendations, particularly tart cherries, in gout and cardiovascular disease management

Kirstie Louise Lamb

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Name	*Kirstie Louise Lamb*
Award	*PhD*
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Faculty	*Social and Economic Research Institute, Service Sector Management*
Director(s) of Studies	*Dr Tony Lynn*

Abstract

Gout is a painful form of inflammatory arthritis that affects approximately 3% of adults in the United Kingdom (UK). It is associated with several comorbidities including cardiovascular disease (CVD). Diet can contribute to the prevention and management of gout and several evidence-based dietary guidelines for gout have consequently been published. Nevertheless, gout patients may use alternative sources for dietary recommendations, for example YouTube® videos. One dietary recommendation that has received considerable attention in the prevention and management of gout is the consumption of cherries, but evidence supporting this is limited to observational research and studies without appropriate controls. Therefore, over three studies, this thesis aimed to explore the role of dietary modification in the prevention and management of gout and CVD, with a particular focus on tart cherries.

In Study 1, the accuracy, reliability, quality, and understandability of dietary information for gout provided on the YouTube® platform was assessed. This study highlighted that dietary recommendations for gout on YouTube® often fail to align with evidence-based guidelines in the UK, are inconsistent, and are not always suitable for patients. Almost 30% of videos analysed included advice to consume cherries. Study 2 compared the acute effects of tart cherry juice with a neutral water control on uric acid levels, inflammation, and CVD risk markers in healthy individuals. A single serving of juice was not found to exert any acute health benefits. However, diurnal fluctuations in markers were detected. The effects of 12 months of daily tart cherry supplementation on gout flares, uric acid levels, inflammation, and CVD risk in gout patients were evaluated in Study 3. Compared with a placebo drink, long-term tart cherry supplementation did not present any health-promoting benefits for gout or CVD. This study was limited by low sample size. Nevertheless, long-term cherry juice supplementation was shown to be feasible and accepted by individuals with gout.

Overall, this thesis is unable to support a direct role of tart cherry juice in the prevention and management of gout and CVD, despite the prevalence of this recommendation. However, it appears to be an appropriate alternative to drinks that are known to exacerbate risk marker of gout and CVD. Placebo-controlled studies with larger sample sizes are required to confirm these findings.

Contents

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Abbreviations

ACE – angiotensin-converting enzyme
ACR - American College of Rheumatology
ADA – adenosine deaminase
AE – adverse events
AIx – augmentation index
AMP – adenosine monophosphate
ANCOVA - Analysis of covariance
ANOVA - analyses of variance
APRT - adenine phosphoribosyltransferase
ARA - American Rheumatism Association
ATP – adenosine triphosphate
BMI – body mass index
BP – blood pressure
BSR - British Society for Rheumatology
CI – confidence interval
CRP – c-reactive protein
CVD – cardiovascular disease
COX - cyclooxygenase
DASH - Dietary Approaches to Stop Hypertension
DBP – diastolic blood pressure
DMSO - dimethyl sulfoxide
DNA – deoxyribonucleic acid
EIMD - exercise-induced muscle damage
ESR - erythrocyte sedimentation rate
EULAR - European League Against Rheumatism
FDA – Food and Drug Administration
FEUA – fractional excretion of uric acid
FRAP - ferric-reducing antioxidant power
F_2-IsoP - F_2-isoprostane
GAE - Gallic acid equivalents
GLUT9 - glucose transporter 9
GQS - Global Quality Score Five Point Scale
HAQ – health assessment questionnaire
HDL - high-density lipoprotein
HPRT - hypoxanthine-guanine phosphoribosyltransferase
HR – heart rate
IL-1β - interleukin 1β
IL-6 - interleukin 6
IL-8 - interleukin 8
IL-18 - interleukin 18

IMP - inosine monophosphate
IQR – interquartile range
LDL - low-density lipoprotein
mRNA - messenger ribonucleic acid
MSU – monosodium urate
NALP3 - nacht domain-, leucine-rich repeat-, and PYD-containing protein 3
Nd – no data available
NHS – National Health Service
NICE - National Institute of Clinical Excellence
NK - natural killer
NLRP3 - nucleotide-binding domain-like receptor protein 3
NO – nitric oxide
NPT1 - Nicotinate phosphoribosyltransferase
OR – odds ratio
PA – physical activity
PBS - phosphate buffer saline
PEMAT - Patient Education Materials Assessment Tool for Audio-Visual Materials
PIC - Participant Identification Centre
PIS – participant information sheet
PNP - purine nucleoside phosphorylase
PRPP - phosphoribosyl pyrophosphate
PWV – pulse wave velocity
ROS – reactive oxygen species
RR – relative risk
SBP – systolic blood pressure
SD – standard deviation
SHU – Sheffield Hallam University
SHURDA - Sheffield Hallam University's Research Data Archive
SLC - solute carrier family
SST - serum separator tubes
sUA – serum uric acid
TAS - total antioxidant status
TC – total cholesterol
TEAC - Trolox equivalent antioxidant capacity
TG - triacylglycerides
TNF-α - tumour necrosis factor alpha
T1D – type 1 diabetes mellitus
T2D – type 2 diabete mellitus
UK – United Kingdom
ULT – urate lowering therapy
URAT1 – urate transporter 1

UU – urinary urate
VPI – Video Power Index
XDH - xanthine dehydrogenase
XO - xanthine oxidase
XOR - xanthine oxidoreductase
5′n - 5′nucleotidase

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Philippians 4:13 "I can do all this through him who gives me strength."

Lastly, I would like to dedicate this work to my Grandad. I wish that you could have been here to see me finish this, but I hope that I've made you proud.

1.0. Introduction, aim, and objectives

1.1. Introduction

Gout is a painful and prevalent form of inflammatory arthritis which is caused by the deposition of monosodium urate (MSU) crystals in joints (Choi, Mount, et al., 2005; Zamudio-Cuevas et al., 2015). Acute recurrent attacks of arthritis, also known as gout flares, are a defining feature of gout and are characterised by acute pain, swelling, and inflammation in affected joints (Cavalcanti et al., 2016; Dalbeth et al., 2016). The proportion of people afflicted with gout in the United Kingdom (UK) is substantial; 3.2% of adults aged 20 years or more were affected in 2012, representing approximately 1.9 million people (Kuo, Grainge, Mallen et al., 2015). Chronic elevation of serum uric acid (sUA), or hyperuricaemia, is recognised as the most important risk factor for gout (Terkeltaub et al., 2006). Both hyperuricaemia and gout exert a significant health burden and have been associated with increased risk of several conditions including obesity, hypertension, dyslipidaemia, and cardiovascular disease (CVD) (Cea Soriano et al., 2011; Hui et al., 2017; Kuo et al., 2016; Roddy & Choi, 2014; Rothenbacher et al., 2011), as well as a reduced quality of life (Singh, 2014). It is therefore important that uric acid levels are kept within healthy limits in the general population and that hyperuricaemia and gout are effectively managed.

In spite of the rising prevalence of hyperuricaemia and gout in the UK, pharmacological options to reduce uric acid levels often have poor adherence or acceptance and therefore non-pharmacological options are necessary (Kuo, Grainge, Mallen et al., 2015). Many dietary recommendations have been published for the management of gout, but this advice can be inaccurate and conflicting depending on its source. Evidence-based dietary guidelines are available to the British public (Hui et al., 2017; NICE, 2018; Richette et al., 2017), yet patients may choose to use alternative sources of information, such as newspapers and online videos (Derksen et al., 2017; Duyck et al., 2016; Vaccher et al., 2016). The information provided by these sources may not align with evidence-based guidelines and may be of poor quality. Whilst analyses of written and pictorial health advice for the management of gout have been undertaken previously (Jimenez-Liñan et al., 2017; Johnston et al., 2015; Robinson &

Schumacher, 2013), the quality and accuracy of online videos specifically providing dietary recommendations for gout has yet to be explored.

One contested dietary recommendation for the prevention and management of hyperuricaemia and gout is the consumption of cherries. Cherries, particularly tart cherries, are high in phenolic compounds which are purported to possess anti-inflammatory, anti-oxidative, and pain-reducing properties (McCune et al., 2010). Leading medical societies and charities in the UK endorse cherry consumption as a therapeutic aid for gout (Arthritis Research UK, 2016; Hui et al., 2017; NICE, 2018; Richette et al., 2017; UK Gout Society, n.d.). In contrast, the Food and Drug Administration (FDA) in the United States of America has warned cherry juice growers and processers against making preventive disease claims (U.S. Food and Drug Administration, 2005), whilst the UK's National Health Service (NHS) health information website previously dismissed newspaper claims that advocated cherry consumption for gout (NHS Choices, 2014).

Despite extensive research into the effects of cherries on several health outcomes (Kelley et al., 2018) and their role in exercise performance enhancement and recovery (Bell et al., 2015; Bell et al., 2016; Bell, Walshe, et al., 2014; Dimitriou et al., 2015; Howatson et al., 2009; Levers et al., 2016), current evidence supporting the use of cherries in the prevention and management of gout is limited and inconsistent. Reductions in inflammatory biomarkers and pain have been observed in arthritic patients following the consumption of cherry products (Kuehl et al., 2012; Schumacher et al., 2013), while in healthy individuals, cherries and cherry products have also been demonstrated to reduce uric acid levels, thereby reducing the risk of hyperuricaemia (Bell, Gaze, et al., 2014; Hillman & Uhranowsky, 2021; Jacob et al., 2003). Should these effects transfer across to those with raised uric acid levels, cherries could also benefit individuals already afflicted with gout. Preliminary evidence from observational and feasibility studies supports this, with reductions in the occurrence of gout flares linked to the consumption of cherries (Schlesinger et al., 2012; Singh, Willig, et al., 2020; Zhang, Neogi, et al., 2012). Hyperuricaemia and gout have also been associated with increased risk of CVD and dyslipidaemia (Singh & Gaffo, 2020; Singh, Wong, et al., 2020). Some evidence indicates a beneficial role of cherries in improving blood lipid profile

(Martin et al., 2011) and vascular health (Ataie-Jafari et al., 2008; Keane, Haskell-Ramsay, et al., 2016; Kent et al., 2016) and this has been attributed to their high phenolic content. Nevertheless, many of the aforementioned studies lack appropriate dietary controls, for example neutral control drinks, and there is a shortage of long-term controlled trials, particularly those involving individuals with gout. This warrants further investigation into the role of tart cherries in the prevention and management of gout.

1.2. Aim and objectives

The overall aim of this thesis is to explore the role of dietary modification in the prevention and management of gout and CVD, with a particular focus on the use of tart cherries. This research has three main objectives:

(1) to assess the accuracy, reliability, quality, and understandability of dietary information for gout provided to the public on the YouTube® platform

(2) to compare the acute effects of tart cherry juice with a neutral water control on uric acid levels, inflammation, and CVD risk markers in healthy individuals

(3) to evaluate the effect of long-term daily tart cherry consumption on uric acid levels, gout flare frequency and intensity, inflammation, and CVD risk in gout patients

These objectives will be addressed across three experimental chapters following on from the subsequent literature review.

2.0. Literature review

This review will analyse literature relating to the pathogenesis, risk factors, and comorbidities of gout, recommended pharmacological and non-pharmacological management of the condition with a particular focus on UK dietary recommendations, and the effects of cherry supplementation on gout and CVD risk markers.

2.1. Gout

2.1.1. Definition

Gout is a painful and frequently debilitating form of arthritis caused by the deposition of MSU crystals in joints (Choi, Mount & Reginato, 2005; Zamudio-Cuevas et al., 2016). The intra-articular deposition of urate triggers a cellular inflammatory response, referred to as an acute gout attack or flare, which is characterised by acute pain, redness, and/or swelling at the affected joint (Cavalcanti et al., 2016; Dalbeth et al., 2016). These flares can last from several hours up to several weeks, depending on the use of treatment (Roddy & Doherty, 2010). Oxidative stress, triggered by the production of reactive oxygen species (ROS) and pro-inflammatory cytokines, may also be involved in the manifestation of gout (Zamudio-Cuevas et al., 2015).

2.1.2. Prevalence and epidemiology

Gout is the primary type of inflammatory arthritis globally and is rising in prevalence (Hui et al., 2017; Kuo, Grainge, Zhang, et al., 2015). In 2017, 7.44 million new cases of gout were estimated globally, with a total prevalence of 41.22 million cases (Mattiuzzi & Lippi, 2020). In the UK, 3.2% of adults aged 20 years and over are reported to be afflicted with the condition (Annemans et al., 2008; Kuo, Grainge, Mallen, et al., 2015), similar to rates reported in Spain, Germany, and New Zealand (Annemans et al., 2008; Sicras-Mainar et al., 2013; Winnard et al., 2013). Between 1997 and 2012, the incidence of gout in the UK rose by 29.6%, representing a standardised incidence of 1.77 per 1000 person years (Kuo, Grainge, Mallen, et al., 2015). More up-to-date data for the UK is currently unavailable. Gout prevalence in men is higher than in women across all age groups in the UK; in 2012, prevalence was recorded at 3.97% in men and 1.05% in women, with the difference between sexes peaking at 35-39 years old (Kuo, Grainge, Mallen, et al., 2015). A fall in oestrogen levels following the menopause

is often accompanied by a rise in sUA levels in women (Hak & Choi, 2008; Ragab et al., 2017). This corresponds with an increase in gout risk, bringing the prevalence of gout for post-menopausal women closer to that of men of a similar age (Cea Soriano et al., 2011; Hak et al., 2010).

Higher prevalence of gout has been reported in America and Canada, and in Māori and Pacific Islanders, at 3.9% (Zhu et al., 2011), 3.8% (Rai, Aviña-Zubieta, et al., 2017), 7.7% and 8.6%, respectively (Winnard et al., 2013). Prevalence is especially high in men within Mauri and Pacific Islanders, with reports of more than 30% of Māori and Pacific males aged ≥ 65 years with gout (Jackson et al., 2012; Winnard et al., 2012). Genetic factors, discussed in section 2.1.5., may be responsible for this high prevalence. In contrast, France (Bardin et al., 2016), Western Sweden (Dehlin et al., 2016), Italy (Trifirò et al., 2013), Bangladesh, India, Pakistan, Japan, South Korea, Iran, Malaysia, Philippines, Vietnam, Thailand, and some African countries (Kuo, Grainge, Zhang, et al., 2015) have all reported low prevalence of gout (< 1%). Geographical discrepancies may be explained by differences in socio-demographic index (SDI) (Kuo, Grainge, Zhang, et al., 2015). For example, the incident risk of gout is > 3-fold higher in high socio-demographic index (SDI) regions than low SDI regions (odds ratio (OR) 3.47, $p < 0.001$) and these areas also often have a higher intake of dietary risk factors for gout, such as red meat, seafood, and sugar-sweetened beverages (Afshin et al., 2019; Mattiuzzi & Lippi, 2020). Nevertheless, America, Canada, France, Italy, and Sweden are all considered high SDI regions and so their contrasting gout prevalence rates could instead be explained by other environmental factors, such as differing dietary behaviours (Kuo, Grainge, Zhang, et al., 2015). For example, it has been reported that the intake of sugar-sweetened beverages, a recognised dietary risk factor for gout (see section 2.1.5.), is considerably higher in North America than in European regions (Afshin et al., 2019) and lower consumption of meat has been reported in Sweden compared with many other European countries (Cocking et al., 2020). Despite between-country differences, figures appear to be on the rise globally, with projections suggesting a 55% increase in gout mortality by 2060 (Mattiuzzi & Lippi, 2020). It is therefore vital that effective preventative and management options are available.

2.1.3. Pathogenesis of gout

Uric acid is generated from the metabolism of purine and is implicated in the pathogenesis of gout (Choi, Mount, & Reginato, 2005). Unlike humans, most animals possess the enzyme uricase which enables them to degrade uric acid into the soluble compound allantoin. A mutation in the uricase gene has resulted in the absence of uricase in humans, meaning that circulating uric acid levels are considerably higher than most animals (Hediger, 2005; Johnson & Andrews, 2010). The quantity of urate present in the body is influenced by a balance between urate synthesis, dietary intake of purines, and the rate of urate excretion. Approximately one-third of the elimination of urate takes place in the gastrointestinal tract, a process known as intestinal uricolysis, with the remaining two-thirds excreted by the kidneys in urine (Terkeltaub et al., 2006). It is proposed that urate may offer several benefits to health, including acting as an antioxidant, maintaining blood pressure (BP) during low salt conditions, and even halting the progression of multiple sclerosis (Hediger, 2005). However, uric acid may exert negative effects at both low and high concentrations. Low levels of uric acid have been prospectively associated with the increased risk of several conditions including infectious mononucleosis (Zhang et al., 2017) and Parkinson disease (De Lau et al., 2005). Also, a rapid reduction in serum urate levels can trigger gout flares in some sufferers (Aung et al., 2017). Elevated levels of uric acid can also have a detrimental impact on health, increasing the risk of multiple health conditions, for example hypertension, cardiovascular disease, kidney disease, and gout (Sandoval-Plata et al., 2020; Wang et al., 2018).

Sustained hyperuricaemia is arguably the most important risk factor for the development of gout (Terkeltaub et al., 2006). Hyperuricaemia occurs as a result of an alteration in the metabolism of urate. This can be caused by excessive hepatic production of uric acid, a reduction in fractional excretion of uric acid (FEUA) due to impaired renal uric acid excretion, or a combination of both (Terkeltaub et al., 2006). A study of 65 hyperuricaemic patients found that 80% were under-excreting uric acid, whilst the remaining patients were either over-producing uric acid (9.2%) or were both under-excreting and over-producing (10.8%) (Oka et al., 2014). In addition to uric acid levels, it is acknowledged that increased solubility of urate contributes to a greater risk of gout and subsequent

flares (Choi, Mount, & Reginato, 2005). Several factors have been identified as influencing urate solubility, including temperature, acidity, salt concentration and hydration status (Dalbeth et al., 2016). As such, high plasma urate levels do not always lead to the occurrence of gout, yet hyperuricaemia is considered a prerequisite of the condition.

There are four main pathophysiological stages of gout: 1) asymptomatic hyperuricaemia without MSU crystal deposition; 2) asymptomatic hyperuricaemia with crystal deposition; 3) hyperuricaemia with crystal deposition and acute gout flares; and 4) advanced chronic gout, which is often characterised by visible tophi and bone erosion (Dalbeth et al., 2016). Typically, acute gout first occurs in one joint, primarily those of the extremities. Temperatures in these joints are generally lower, allowing urate in plasma to be deposited and crystallise in the joints (Dalbeth et al., 2016; Loeb, 1972). Most commonly, the first metatarsophalangeal joint is affected by gout, a condition referred to specifically as podagra (Roddy, 2011). The preference for gout to target this joint is believed to be multi-factorial, including the increased susceptibility of the metatarsophalangeal joint to develop osteoarthritis, the lower temperature of this extremity, and physical stresses caused by trauma and/or overuse (Roddy, 2011).

One of the pathways through which increased production of urate occurs is the degradation of adenosine triphosphate (ATP) (Figure 1). This results in the production of adenosine monophosphate (AMP), a precursor of uric acid (Choi et al., 2010; Choi, Mount, & Reginato, 2005). Amplified levels of AMP stimulate increased uric acid production via the activation of a series of catabolic pathways (Choi et al., 2010). Ethanol, excessive fructose intake or intolerance, and glycogen storage diseases can all stimulate this pathway (Torralba et al., 2012). Alternatively, high levels of purine conversion may result in elevated urate production; this may be in response to a prolonged high-purine diet, or as result of a disorder. Whilst genetic disorders resulting in enhanced de novo synthesis of purines and urate can contribute to raised uric acid levels, these conditions are rare (Choi, Mount, & Reginato, 2005). For example, Lesch-Nyhan syndrome, which is caused by mutations in the gene encoding the enzyme hypoxanthine-guanine phosphoribosyl transferase and characterised by the excessive production of uric acid, has a reported prevalence of 1 in 2 million people in the

UK (Mccarthy et al., 2011). Other disorders, such as myeloproliferative disorders, psoriasis, and anaemia may increase the production of purines through increased breakdown of nucleic acids in tissues (Choi, Mount, & Reginato, 2005).

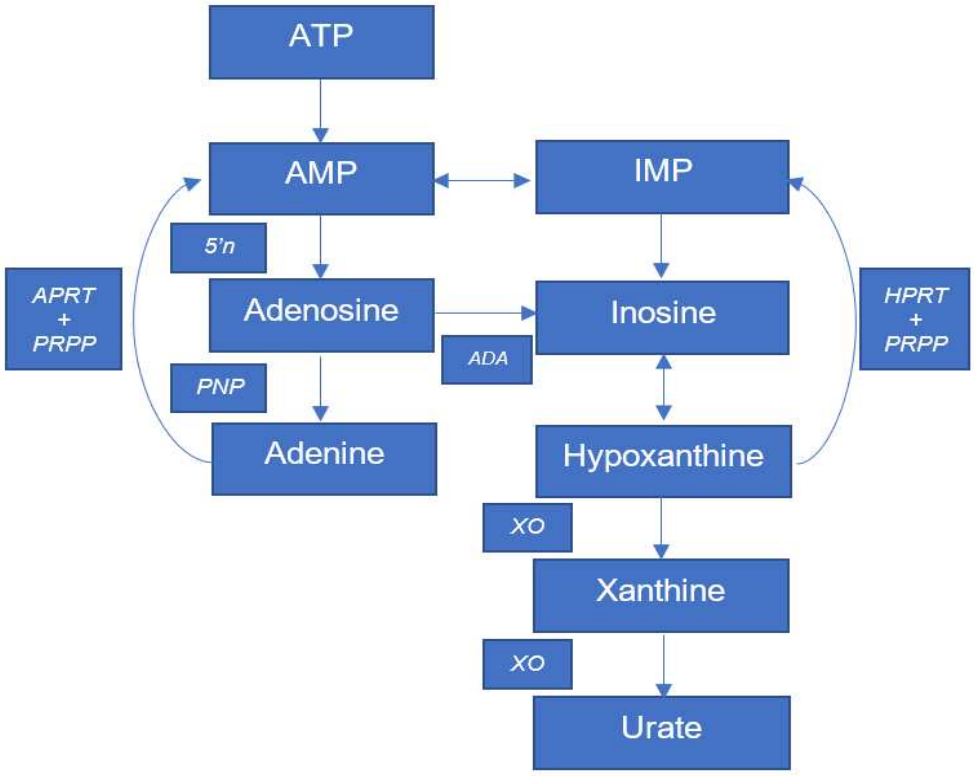

Figure 1. Adapted from Torralba et al. (2012). Synthesis of urate from ATP degradation. ADA, adenosine deaminase; AMP, adenosine monophosphate; APRT, adenine phosphoribosyltransferase; ATP, adenosine triphosphate; HPRT, hypoxanthine-guanine phosphoribosyltransferase; IMP, inosine monophosphate; PNP, purine nucleoside phosphorylase; PRPP, phosphoribosyl pyrophosphate; XO, xanthine oxidase; 5′n, 5′nucleotidase.

Impaired renal urate excretion is arguably the larger contributing factor to the development of hyperuricaemia; many patients with gout display poor renal function (Terkeltaub et al., 2006). Disruption of several renal processes may contribute to impaired urate excretion by the kidneys and the development of hyperuricaemia, including reduced renal blood flow and increased renal and systemic vascular resistance. The secretion and reabsorption of urate is regulated by several pumps and transporters in the kidney (Dalbeth et al., 2016).

These include the urate transporter 1 (URAT1), encoded by the solute carrier family [SLC]22A12 gene and responsible for luminal urate reabsorption, the glucose transporter 9 (GLUT9), which mediates the reabsorption of urate into the blood and is encoded by SLC2A9, and nicotinate phosphoribosyltransferase 1 (NPT1), a sodium-phosphate transporter which facilitates the reabsorption of urate from the proximal tubule and is encoded by SLC17A1 (Chung & Kim, 2021). As such, disruption to the function of these transporters can result in impaired urate excretion. Numerous genes that code for urate transporters have been identified, yet variants in these genes may only account for < 5% of the variation in serum urate; other factors are likely to contribute to hyperuricaemia to a greater degree (Wright et al., 2010). Furthermore, cases of idiopathic hyperuricaemia are recognised (Dalbeth et al., 2016).

Over time, persistently high sUA levels can result in the accumulation of crystals within joints (Abhishek & Doherty, 2018). Gout is considered an auto-inflammatory disease; the intra-articular deposition of MSU crystals can trigger a cellular inflammatory response, referred to as an acute gout attack, typically resulting in redness, swelling, warmth and pain at the joint (Cavalcanti et al., 2016; Dalbeth et al., 2016). It is suggested that the deposition of crystals in gout differs from other types of arthritis in that large and needle-shaped crystals accumulate within the synovial fluid of joints. MSU crystals may be taken up by phagocytic cells such as macrophages and monocytes, activating an inflammasome known as nucleotide-binding domain-like receptor protein 3 (NLRP3) or Nacht Domain-, Leucine-Rich Repeat-, and PYD-Containing Protein 3 (NALP3) (Figure 2) (Dalbeth et al., 2016; Pétrilli & Martinon, 2007). This leads to the activation of caspase-1, an inflammatory cysteine protease which catalyses the processing and activation of inflammatory cytokines interleukin 1β (IL-1β) and interleukin 18 (IL-18) (Busso & So, 2010; Cavalcanti et al., 2016; Dalbeth et al., 2016; Pétrilli & Martinon, 2007). IL-1β is believed to contribute to gouty inflammation through lymphocyte activation and proliferation, enhanced endothelial adhesion, and increased expression of acute-phase proteins such as c-reactive protein (CRP) (Busso & So, 2010; Pétrilli & Martinon, 2007). IL-18

induces inflammation by inducing the production of pro-inflammatory cytokines and the activation of natural killer cells (Pétrilli & Martinon, 2007).

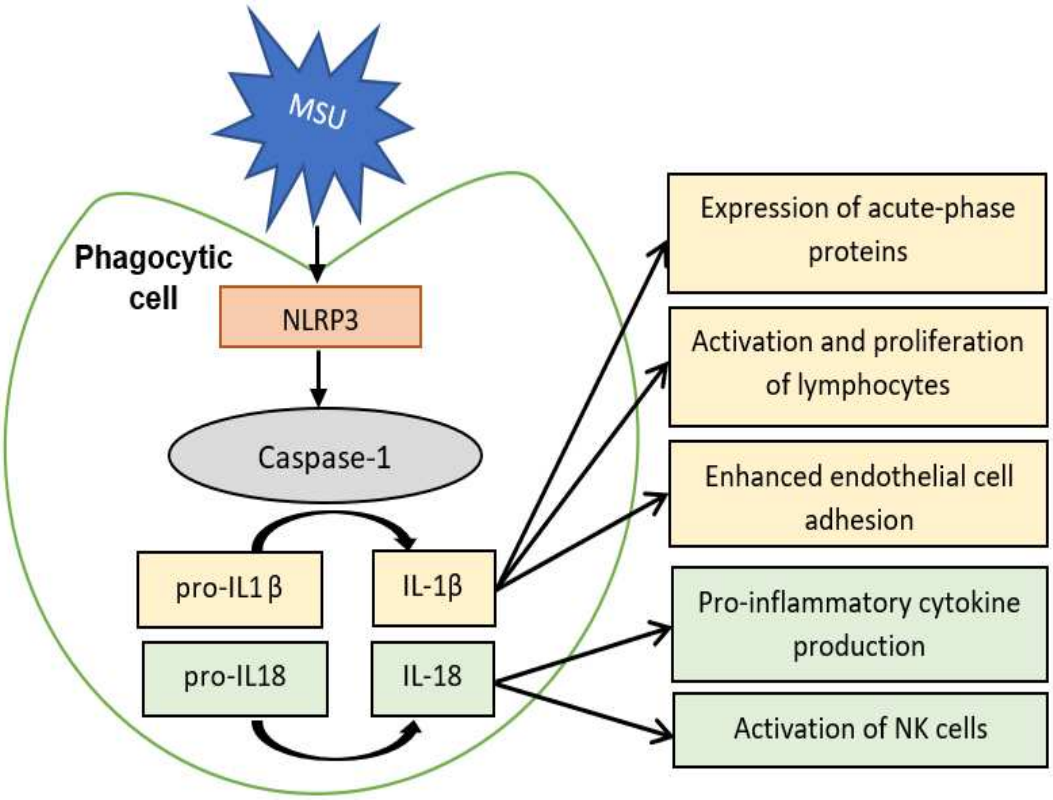

Figure 2. Adapted from Busso & So (2010), Cavalcanti et al. (2016), Dalbeth et al. (2016), and Pétrilli & Martinon (2007). Monosodium urate (MSU) crystal activation of caspase-1, IL-1β, and IL-18. IL-18, interleukin 18; IL-1β, interleukin 1β; MSU, monosodium urate; NK, natural killer; NLRP3, nucleotide-binding domain-like receptor protein 3.

In addition to macrophages and monocytes, mast cells and neutrophils may also be involved in this inflammatory response, stimulating the secretion of several pro-inflammatory factors including cytokines and ROS (Choi, Mount, & Reginato, 2005; Dalbeth et al., 2016). Neutrophils are attracted to the site of inflammation by cytokines, other chemotactic factors such as granulocyte colony-stimulating factor, and the recruitment of mast cells (Busso & So, 2010). Other cytokines that are upregulated as a result of crystal accumulation and subsequently involved in the inflammatory response include: interleukin 6 (IL-6), which amplifies the inflammatory process; interleukin 8 (IL-8), involved in neutrophil recruitment; and tumour necrosis factor alpha (TNF-α), which reportedly contributes to pro-

inflammatory activation and amplified macrophage maturation (Busso & So, 2010; Cavalcanti et al., 2016). Anti-inflammatory cytokines are then recruited to resolve the acute attack of gout that occurs. Additionally, the expression of CRP, a common marker of a systemic inflammatory response, may be directly induced by elevated uric acid levels (Kang et al., 2005). Elevated circulating CRP concentration has been associated with hyperuricaemia (Yang et al., 2016) and gout (Cavalcanti et al., 2016), particularly during an acute gout attack (Jiang et al., 2014).

An acute attack of gout typically reaches peak intensity within 24 hours of symptom onset but may last hours to weeks depending on the severity of the flare (Roddy, 2011). Most flares usually resolve within 14 days, although the use of treatment can speed this process up and promote the resolution of pain and loss of function within 7 days. In acute gout, these sporadic flares are often interspersed by long, symptom-free periods referred to as the intercritical period (Schlesinger, 2013). However, if hyperuricaemia is left untreated, acute flares can increase in frequency and can also spread to other joints over time (Abhishek & Doherty, 2018). Advanced, chronic gout tends to arise several years after the initial acute flare, most commonly in the absence of, or following poor adherence to, urate lowering therapy (ULT). MSU crystals may accumulate as visible tophi; tophus formation is a chronic inflammatory response to high serum urate levels (Smith et al., 2011). These accumulations of crystals can continue to expand, placing pressure on the surrounding joints. If tophi infiltrate into bone, erosion and irreversible damage of joints can occur, often resulting in chronic pain. As a result, symptoms may be experienced between attacks, whilst the attacks themselves may occur in more than one joint and/or be more frequent and intense in nature (Abhishek & Doherty, 2018).

2.1.4. Gout diagnosis

Although there is no universally agreed definition for hyperuricemia, a target sUA value of below 6.8 mg/dL (~400 µmol/L) has been recommended (Smith et al., 2011). This is in line with the saturation point for plasma MSU, above which MSU crystallisation can occur (Dalbeth et al., 2016). Separate definitions of hyperuricaemia for men and women have also been proposed at > 7.0 mg/dL (> 416 µmol/L) and > 6.0 mg/dL (357 µmol/L) (Hediger, 2005), respectively,

reflecting the higher sUA concentrations typically found in men (Cea Soriano et al., 2011; Kuo, Grainge, Zhang, et al., 2015; Ragab et al., 2017). Meanwhile, to account for a rise in uric acid levels following the menopause (Ragab et al., 2017), hyperuricaemia has been defined as sUA levels exceeding 5.7 mg/dL (339 µmol/l) in premenopausal women and 7.0 mg/dL (416 µmol/L) in postmenopausal women (Desideri et al., 2014). More recently, a target threshold of a sUA level at or below 6.0 mg/dl (357 µmol/L) has been proposed for all individuals, owing to the life-long risk of developing gout at and above this concentration (Bardin & Richette, 2014; Desideri et al., 2014). The British Society for Rheumatology (BSR) recommends an even stricter sUA target of < 300 µmol/L to prevent crystal formation and recurrent flares (Hui et al., 2017). The National Institute of Clinical Excellence (NICE) agree with this, recommending lifestyle advice in conjunction with pharmacological therapy to meet this target (NICE, 2018).

The progression of hyperuricaemia to a clinical diagnosis of gout has been defined as the identification of MSU crystals in synovial fluid by a certified observer (Taylor et al., 2016). This may be identified through aspiration or x-ray of affected joints. In Europe, this is considered the gold standard for diagnosis of gout (Richette et al., 2020). Despite this, most patients are diagnosed from clinical observation and symptoms, such as the rapid onset of severe pain in a joint, rather than aspiration or x-rays and thus there is a potential for misdiagnosis (Roddy et al., 2018). Whilst joint pain has been considered as an important symptom in diagnosing a gout flare, other symptoms such as the presence of heat, swelling, and inflammation and impaired mobility may also be used (Gaffo et al., 2018; Gaffo, Schumacher, et al., 2012; Neogi et al., 2015). In the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) validation study of gout flares, a gout flare was defined as pain at rest > 3 and patient self-reported flare (Gaffo, Schumacher, et al., 2012). More recently, it has been argued that fulfilment of ≥ 3 criteria, namely patient-defined flare, pain at rest score of > 3 on a 0–10 numeric rating scale, at least 1 swollen joint, and/or at least 1 warm joint, provides a more accurate validation of gout flares (Gaffo et al., 2018).

Time since onset of gout symptoms is used to determine whether gout is classed as early or established. Taylor et al. (2016) described early gout as symptoms

experienced for less than 2 years, whilst established gout is defined as onset of symptoms of greater than 2 years. Early and established gout are described differently to acute and chronic gout in the literature. Acute gout is defined by the sudden onset of an inflammatory response (gout flare) in one or several joints, which typically resolves within 10 days (Grainger et al., 2009). Meanwhile, chronic gout is characterised by recurrent and overlapping attacks of acute gout and clinically visible tophi (Brook et al., 2010).

2.1.5. Risk factors

Several factors are associated with increased risk of hyperuricaemia and gout, including male sex, increasing age, genetics, high body mass index (BMI), and multiple dietary components (Abhishek & Doherty, 2018; Cea Soriano et al., 2011; Hollis-Moffatt et al., 2009; Köttgen et al., 2013; Kuo, Grainge, Zhang, et al., 2015; Maynard et al., 2014; Ragab et al., 2017; Winnard et al., 2012). Other health conditions, such as ischaemic heart disease, renal failure and hypertension, have also been independently associated with an increased risk of a post-diagnosis gout attack (Rothenbacher et al., 2011).

It is well-documented that uric acid levels tend to be higher in men (Cea Soriano et al., 2011; Kuo, Grainge, Zhang, et al., 2015; Ragab et al., 2017). Correspondingly, a higher incidence of gout has been reported in men in the UK at 3.5 (95% CI 3.26 to 3.44) per 1000 person-years compared with 1.25 (95% CI 1.20 to 1.31) per 1000 person-years in women (Kuo, Grange, Mallen, et al., 2015). Being male has also been significantly associated with an increased number of gout flares in patient diagnosed with gout (Rothenbacher et al., 2011). These sex differences are not unique to the UK (Picavet & Hazes, 2003; Winnard et al., 2012). A rise in female oestrogen levels during puberty is reported to be responsible for between-gender differences in sUA levels in adulthood (Cea Soriano et al., 2011). Oestrogen appears to have a uricosuric effect, preventing the rise in sUA levels observed in men (Cea Soriano et al., 2011; Hak & Choi, 2008). Through the downregulation of GLUT9 protein expression on renal cells, oestrogen may enhance the renal tubular excretion of urate (Zeng et al., 2014). However, further research is needed to confirm this mechanism. Reductions in FEUA rates in men during adolescence and adulthood have also been observed, whilst these appear to remain relatively stable in women (Stiburkova & Bleyer,

2012). This may protect against gout development in pre-menopausal women. However, as oestrogen levels drop following the menopause in women, sUA levels typically rise (Hak & Choi, 2008; Ragab et al., 2017), corresponding with an increase in gout risk for post-menopausal women (Cea Soriano et al., 2011; Hak et al., 2010).

Risk of gout has also been demonstrated to increase with age, with the risk plateauing around the age of 80 years (Cea Soriano et al., 2011; Maynard et al., 2014; Ragab et al., 2017; Winnard et al., 2012). Cea Soriano et al. (2011) observed an increase in the incidence rate per 1000 person years of gout with age in both men and women, although only individuals aged 50 years old and above were analysed. This study also reported that the mean age at first diagnosis of gout was 60.1 years (95% CI, 59.9 to 60.4) among men and 67.7 years (95% CI 67.3 to 68.0) among women (Cea Soriano et al., 2011). Similarly, Annemans et al. (2007) reported that the mean age at diagnosis was 61.62 (± 13.86) in their UK population. This indicates an increased prevalence and risk of gout at this age. One contributing factor to this increased risk is an increase in sUA levels, predominantly because of a reduction in renal function (Doherty, 2009). Additionally, increased use of diuretics has been associated with an increased risk of gout, as use of these can cause an increase in sUA levels (Bruderer et al., 2014; Cea Soriano et al., 2011). As the use of diuretics is more common in older adults, it is plausible that this contributes to an increased gout risk in these individuals. Changes in connective tissues related to age can also increase the risk of uric acid crystals forming (Doherty, 2009). Overall, it could be argued that age is an indirect risk factor for gout; diuretics use, reduced renal function and deterioration in connective tissue health may instead be the direct contributors to risk.

Genetics may also contribute to the risk of developing gout. Twenty-eight gene loci have been identified that influence sUA levels (Köttgen et al., 2013). For example, variants to the SLC2A9 gene, which encodes for the GLUT9 transporter responsible for exchanging uric acid with glucose and fructose in the kidney, have been associated with gout (Hollis-Moffatt et al., 2009; Köttgen et al., 2013). Additionally, although rare, several monogenic disorders can result in increased risk of hyperuricemia and gout (Kuo, Grainge, Zhang, et al., 2015). For example,

Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome are associated with net ATP degradation and elevated levels of uric acid (Estiverne et al., 2020). Pacific Islanders and Maori have been shown to be three times more at risk of developing gout than their counterparts of European descent and these populations have some of the highest mean sUA concentrations worldwide (Winnard et al., 2012). There may be a genetic component to this increased risk. Indeed a genetic defect in renal urate handling has been observed in some Polynesian women (Simmonds et al., 1994), but higher purine intake and obesity rates may also contribute (Winnard et al., 2012). Black men and women have also been found to be at increased risk of gout compared to their white counterparts, after adjustment for dietary, clinical, socioeconomic and demographic confounders, supporting the involvement of a non-environmental factor such as genetics (Maynard et al., 2014). However, specific genetic polymorphisms involved in the regulation of urate metabolism that may explain these racial differences have yet to be identified (Gaffo, Jacobs, et al., 2012; Singh, 2013).

An individual's BMI may also contribute to their gout risk, as raised BMI is associated with an increased risk of gout attacks (Abhishek & Doherty, 2018). In a UK cohort study, higher BMI was associated ($p < 0.001$) with a greater number of flares in individuals with diagnosed gout (mean follow-up time 3.8 years) (Rothenbacher et al., 2011). In support of this, the Health Professionals Follow-up study, an ongoing longitudinal study of 51,529 American male health professionals aged between 40 and 75 years at baseline, reported an age-adjusted relative risk (RR) for gout of 2.35 for an overweight BMI of 25-29.9 kg/m^2 versus a reference group of 21-22.9 kg/m^2 (Choi, Athinson, et al., 2005). RR increased to 4.41 for a BMI of > 35 kg/m^2. Nevertheless, limitations in using BMI as a measure of body composition have been recognised; for example, body fat distribution can vary at the same BMI level and high levels of muscle mass may lead to the misclassification of obesity (Buss, 2014). It is also important to recognise that associations between BMI and gout risk have been largely attributed to increased levels of body fat, rather than lean mass. In metabolically obese adults, total fat mass and visceral fat obesity has been associated with gout, even in the absence of a BMI > 25 kg/m^2 (Lee et al., 2015). Furthermore, higher total fat mass and trunk fat mass has been reported in males with gout

compared to age-matched healthy males (Dao, Harun-Or-Rashid, & Sakamoto, 2010). With the prevalence of obesity in the UK on the rise (Office for National Statistics, 2019), gout prevalence may follow the same trend. Consequently, it is important that effective and acceptable treatment options are available to those who are afflicted by this condition.

Several dietary antecedents to raised uric acid and incidence of gout have been identified. These include purine-rich foods, such as seafood, red meat, and organ meat (Choi et al., 2004a; Choi, Liu, et al., 2005; Lockyer & Stanner, 2016; Major et al., 2018; Williams, 2008). Despite this, moderate purine-rich vegetable intake has not been found to be associated with an increased risk of gout (Choi et al., 2004a; Li et al., 2018). Differing types and bioavailability of purines from different dietary sources (Inazawa et al., 2014) and the effect of preparation and/or cooking method on purine content (Zgaga et al., 2012) may be responsible for this contradiction. Increased consumption of fructose-rich foods and drinks, such as sugar-sweetened soft drinks, apples, oranges, and fruit juices, has also been associated with increased hyperuricaemia and gout risk (Choi et al., 2010; Choi & Curhan, 2008; Choi et al., 2008; Major et al., 2018). Other dietary risk factors for the incidence of hyperuricaemia and gout include alcohol intake, particularly beer and spirits (Cea Soriano et al., 2011; Choi & Curhan, 2004; Lyu et al., 2003; Sharpe, 1984), and inadequate hydration (Choi, Athinson, et al., 2005; Ekpenyong, 2019). Meanwhile, increased dairy intake is associated with a reduced risk of gout (Choi et al., 2004a). In addition to influencing the risk of developing gout, diet may also play a role in its management, and this is discussed in section 2.1.8.

2.1.6. Associated comorbidities

As the primary type of inflammatory arthritis globally, gout exerts an extensive health burden (Hui et al., 2017). The presence of gout has been associated with increased risk of total mortality (Stack et al., 2013). The severity of gout may also increase the risk of mortality, as presence of tophi, higher sUA levels and increased frequency of flares have all been positively associated with mortality risk (Perez-Ruiz et al., 2014; Stack et al., 2013). In addition to the mortality risk attributed directly to gout, hyperuricaemia and gout are associated with several comorbidities including, but not limited to, CVD (discussed in section 2.1.6.1.),

hypertension, dyslipidaemia, type 2 diabetes mellitus (T2D), renal disease, and dementia (Callear et al., 2017; Cea Soriano et al., 2011; Kuo et al., 2016; Rothenbacher et al., 2011; Sandoval-Plata et al., 2020). Hyperuricaemia and gout have also been associated with obesity (Aune et al., 2014; Rothenbacher et al., 2011). The percentage of gout patients with obesity has been found to increase with increasing sUA levels (Annemans et al., 2008) and studies evaluating the prevalence of obesity in UK gout patients have presented figures of 27.7% (Annemans et al., 2008) and 29.1% (Rothenbacher et al., 2011). Psychological co-morbidities of gout, such as depression, are less well understood but are also likely to be common (Kuo et al., 2016). Furthermore, gout has been shown to adversely affect a sufferer's quality of life as a result of these associated comorbidities and through gouty pain, an increased dependency on others, and reductions in mobility, productivity, and function (Singh, 2014).

More recently, rheumatic disease such as gout has been shown to be a significant risk factor for COVID-19 related deaths (Strangfeld et al., 2021; Topless et al., 2022). It has also been suggested that individuals with gout are likely to experience poor outcomes after COVID-19 infection and this is attributed to the common presence of cardiovascular and renal disease comorbidities and other risk factors such as more likely being overweight and older in age (Dalbeth & Robinson, 2021; Strangfeld et al., 2021; Tai et al., 2022).

These factors all highlight the importance for gout sufferers to be able to effectively manage their condition.

2.1.6.1. Cardiovascular disease (CVD)

Arguably, one of the most common comorbidities of gout is CVD (Bardin & Richette, 2007). In epidemiological studies, gout has repeatedly been demonstrated as an independent risk factor for CVD (Abbott et al., 1988; Choi & Curnham, 2007; Krishnan, 2012; Teng et al., 2012; Seminog & Goldacre, 2013), although it is currently unknown if treating gout would provide any cardiovascular benefits, or vice versa (Abels & Pillinger, 2019). Annual screening for cardiovascular risk factors is specifically recommended in the 2017 BSR Guideline for the Management of Gout (Hui et al., 2017). Additionally, hyperuricaemia, gout, and CVD share common risk factors such as hypertension,

obesity, and hypercholesterolaemia (Pillinger et al., 2017). These conditions also share several dietary recommendations for their prevention and management, such as restricting the intake of high fat foods, sugar-sweetened beverages, and alcohol, and encouraging consumption of fruit, vegetables, and fibre (Hui et al., 2017; NICE, 2018; Richette et al., 2017; Verschuren et al., 2022; Yu et al., 2018). Consequently, CVD has been chosen as a focus of this research alongside gout.

A study of 24,768 gout patients in the UK aged 20–89 years observed a history of ischaemic heart disease in 19.9% of the population analysed, compared with 13.4% of 50,000 age-matched individuals without gout (Cea Soriano et al., 2011). Gout has also been associated with a 71% increased risk of stroke and an 82% increased risk of myocardial infarction in English patients (Seminog & Goldacre, 2013). Proposed prevalence rates of hypertension in gout patients in the UK range from 17.5% (Annemans et al., 2008) to 51.6% (Rothenbacher et al., 2011), with prevalence shown to rise with increasing sUA levels (Annemans et al., 2008). A recent longitudinal study of 129,972 patients with gout in the UK reported a prevalence of hypertension at diagnosis of 47.6% (Russell et al., 2022). In comparison, a prevalence of 26.4% has been identified for adults in the general population in the UK (WHO, n.d.). It is proposed that the presence of elevated sUA levels is primarily responsible for an increased CVD risk, as high sUA concentration, irrespective of a gout diagnosis, has been correlated with increased risk of total mortality and cardiovascular mortality (Niskanen et al., 2004). CVD mortality has also been independently predicted by the failure to meet a uric acid target of 360 µmol/L (Pérez Ruiz et al., 2019).

Hyperuricaemia may induce endothelial dysfunction, which is associated with many CVD risk factors (Maruhashi et al., 2018). One proposed mechanism is through the activity of XO, an enzyme involved in the metabolism of purines (Maruhashi et al., 2018; Price, 2006). When XO activity is enhanced, both uric acid and ROS are produced. If an excessive production of ROS reacts with nitric oxide (NO), a reduction in the bioavailability of NO is observed, resulting in the formation of peroxynitrite, a strong oxidant capable of inducing cell death and deoxyribonucleic acid (DNA) damage. Furthermore, as NO plays a critical role in maintaining the dilation of blood vessels and moderating the proliferation of vascular smooth muscle cells, a reduction in NO prevents these important

endothelial functions from occurring (Bauer & Sotníková, 2010). Uric acid is also postulated to reduce NO production in endothelial cells by impairing the activity of endothelial NO synthase (Feig et al., 2006). Another suggested mechanism for the role of uric acid in endothelial dysfunction involves the activation of uric acid transporters within endothelial cells (Price, 2006). Uric acid transporters are primarily expressed in renal tubular cells to aid reabsorption of uric acid but can also be expressed in vascular endothelial cells. Absorption of uric acid into these cells may result in intra-cellular inflammation, oxidative stress and dephosphorylation of endothelial NO synthase, all of which can contribute to endothelial dysfunction and ultimately the development of CVD. It is therefore important that uric acid levels are effectively managed.

2.1.7. Pharmacological management of gout

ULT is often prescribed to treat gout. Allopurinol is the recommended first line of treatment in the UK, although febuxostat may be prescribed to patients who cannot tolerate allopurinol (Hui et al., 2017). Both drugs are competitive inhibitors of XO, the enzyme involved in the synthesis of both uric acid and ROS (see 2.1.6.1.) (Hui et al., 2017). The active metabolite of allopurinol, oxypurinol, inhibits XO, thereby reducing purine production and subsequently the end-product of purine metabolism, uric acid. Despite its effectiveness, patient adherence to ULT is often poor; in 2012, adherence to ULT in UK gout patients was reported at 39.7% (Kuo, Grainge, Mallen, et al., 2015). Side effects from ULT (Harrold et al., 2010), continuation or increase in gout flares upon initiation of ULT, and ineffective ULT dosing (Annemans et al., 2008; Ragab et al., 2017) all contribute to poor adherence.

An initial allopurinol prescription of 50-100 mg per day followed by 100 mg increments every 4 weeks, up to a maximum dose of 900 mg, is currently recommended in the UK (Hui et al., 2017). However, a dosage of ≤300 mg per day, which is a commonly prescribed fixed dose, may be insufficient to meet UK sUA targets (Rees et al., 2013). Indeed, it has been suggested that full dosage of 900 mg per day may be needed in some individuals in order to be effective (Hui et al., 2017). Despite this, only 2.1% of UK gout patients were reportedly prescribed doses of above 300 mg per day between 2000-2005, whilst 63.3% were prescribed between 200 and 300 mg per day (Annemans et al., 2008).

Although up-to-date figures are currently unavailable, should prescription figures be similar today, this may be a contributing factor to the high prevalence of poorly managed gout observed in the UK.

In addition to inadequate prescription, poor adherence to ULT has frequently been reported. Kuo, Grainge, Mallen, et al. (2015) described ULT adherence rates in a UK population of 39.66% (95% CI 39.11 to 40.22 %) in 2012. Similarly, a study of Irish gout patients reported persistence with ULT of 45.8% at 6 months and 22.6% at 12 months (McGowan et al., 2016). Increasing age was associated with increased likelihood of persisting with ULT. Greater adherence to medication with age could reflect more frequent episodes of gout, because it has been suggested that less active gout may be related to poorer adherence (Harrold et al., 2010). Thus, younger individuals experiencing infrequent flares may be less motivated to adhere to a daily medication regime than an individual experiencing regular attacks of gout. Possible side effects of ULT, such as the potential for allopurinol to initially trigger gout attacks, may also contribute to lower adherence rates, either through fear of these adverse reactions, or previous bad experiences (Harrold et al., 2010). In addition to adverse events with medication, Keenan (2017) highlighted several other barriers to treatment success in gout patients. These include a lack of education and/or understanding of ULT, lack of self-motivation to regularly take medication, belief that ULT is ineffective, and concerns with contraindications of medications (Keenan, 2017). These factors all highlight the need for effective and acceptable non-pharmacological alternatives.

2.1.8. Non-pharmacological management – dietary recommendations

In addition to being a risk factor for gout, diet can contribute to its management (Shulten et al., 2009; Zhang et al., 2019; Zhang, Chen, et al., 2012; Zhang, Neogi, et al., 2012). Findings from a cross-sectional internet-based survey suggest that many gout patients prefer non-pharmacological interventions, including dietary modification, to using ULT for the long-term management of gout (Singh et al., 2016). Current dietary recommendations for UK gout patients include restricting purine- and fructose-rich foods and drinks, limiting alcohol consumption, particularly beer and spirits, remaining hydrated, eating sufficient dairy, and encouraging the consumption of fruit, particularly cherries (Hui et al., 2017; NICE, 2018). This section will first outline the potential sources of dietary information

accessed by patients with gout. The evidence underlying dietary recommendations for gout will then be discussed.

2.1.8.1. Sources of dietary recommendations

It has been suggested that early dietary and lifestyle intervention can reduce the number of gout flares and the risk of CVD (Callear et al., 2017). Consequently, evidence-based guidelines for the management of gout often include dietary recommendations. These include those targeted at the UK population produced by the BSR, EULAR, and NICE (Hui et al., 2017; NICE, 2018; Richette et al., 2017). As these have been developed as acceptable guidelines to be used within the NHS, dietary recommendations for gout patients received in UK primary care should be consistent with these guidelines. Despite this, audits of UK primary care medical practices have demonstrated that the provision of lifestyle advice, including dietary recommendations, is often inadequate (Cottrell et al., 2013; Pal et al., 2000; Roddy et al., 2007). For example, in a practice in North Staffordshire the discussion of diet was recorded with only 14% of patients with gout (Cottrell et al., 2013).

Consequently, patients may choose alternative sources of information to obtain dietary advice, such as alternative health practitioners, newspapers, and online resources (Chan et al., 2014; Derksen et al., 2017; Duyck et al., 2016; Vaccher et al., 2016). In a survey of 276 patients with gout, albeit from New Zealand, Chan et al. (2014) reported that 23.9% of patients with gout used complementary and alternative medicine for their condition. Similarly, a survey of 142 UK-based herbalists observed that 63% of respondents had treated patients with gout (Corp & Pendry, 2013). Meanwhile, an analysis of Internet searches for information on gout observed that the term ‘gout’ is commonly combined with search terms relating to food and diet (Jordan et al., 2019). Online dietary advice may be provided in the form of written, pictorial, and/or audio-visual resources. Analyses of written (Jimenez-Liñan et al., 2017; Johnston et al., 2015; Robinson & Schumacher, 2013) and pictorial (Krasnoryadtseva et al., 2020) health advice for the management of gout have frequently reported that resources lack accuracy, provide inadequate information, and/or use complicated language which is unsuitable for their intended audience.

2.1.8.1.1. Online videos as a source of dietary recommendations

Online videos offer an attractive alternative medium through which dietary advice can be obtained. YouTube® (www.youtube.co.uk) is an accessible and popular video-sharing website which may be used for this purpose (Soukup, 2014). According to the YouTube® press office, more than 2 billion logged-in users visit YouTube® each month, resulting in an accumulation of over 1 billion hours of watched content every day (YouTube®, 2020). Despite the popularity of the website, no mandatory editorial or review processes are undertaken during the upload of videos to YouTube® and therefore the information provided to users may be inaccurate, unreliable, and of poor quality. Indeed, studies of YouTube® videos providing educational information on medical conditions and diseases, including renal disease, rheumatoid arthritis, hypertension, irritable bowel syndrome, kyphosis, and severe acute respiratory syndrome (SARS)-CoV-2, have reported that a large proportion of videos are inaccurate and/or of poor quality (Erdem & Karaca, 2018; Kumar et al., 2014; Lambert et al., 2017; Mukewar et al., 2013; Rubel et al., 2020; Singh et al., 2012; Sood et al., 2011; Szmuda et al., 2020). Whilst a recent study assessing videos providing general health information on gout observed the provision of a high proportion of scientifically accurate information (Onder & Zengin, 2021), no studies have reported on the quality and accuracy of YouTube® videos specifically providing dietary recommendations for gout. Irrespective of the medium, the information provided by online resources should be easy to understand and consistent with advice from evidence-based sources to contribute positively to the self-management of gout (Becker & Chohan, 2008; Johnston et al., 2015; Liddle et al., 2021; Roddy et al., 2007). Where dietary information obtained by patients conflicts with that provided by their healthcare team, this may increase the risk of inadequate self-management of their condition (Gobeil-Lavoie et al., 2019; Liddle et al., 2021).

Some of the main dietary recommendations proposed by UK evidence-based dietary guidelines will now be discussed.

2.1.8.2. Purine-rich foods

When dietary purines are consumed, they are metabolised to produce urate which contributes to the body's total uric acid pool and consequently, sUA levels

(Lockyer & Stanner, 2016). High consumption of purines may therefore contribute to hyperuricaemia and/or trigger gout flares in some individuals. As such, the restriction of purine-rich foods, particularly red meats, organ meats, and seafood, has been advised for patients with or at risk of gout.

In an online case-crossover study of 633 individuals with gout, the OR of recurrent gout flares increased with each increasing quintile of purine intake in the two days prior to a flare (OR 4.76 for highest quintile, $p < 0.001$ for trend) (Zhang, Chen, et al., 2012). It is important to note that this was based on dietary recall over a 2-day period and so the effects of chronic consumption were not assessed. In contrast, data collected from 47,150 men in the Health Professionals Follow-up Study did not show an association between total protein intake and risk of gout over its 12-year follow-up period (Choi et al., 2004a). Similarly, using data from the Third National Health and Nutrition Examination Survey, a cross-sectional study of 14,809 men and women aged 20 years and older observed no association between total protein intake and sUA concentration (Choi, Liu, et al., 2005). These findings may be explained by the varying impact of different protein sources of purines and their bioavailability following preparation. Within the Health Professionals Follow-up Study, increased meat (RR 1.21 per additional daily serving, $p = 0.02$ for trend) and seafood (RR 1.07 per additional daily serving, $p = 0.02$ for trend) intake were associated with an increased risk of gout (Choi et al., 2004a). Red meats, namely beef, lamb, and pork, were found to be primarily responsible for this association (RR 1.50 for ≥2 portions/week, $p = 0.01$ for trend). Furthermore, both red meat and seafood consumption were reported as triggers of acute gout attacks in a cross-sectional survey of 550 individuals with gout (Abhishek, Valdes, et al., 2017). Using data from the Third National Health and Nutrition Examination Survey, Choi, Liu, et al. (2005) found sUA levels to be 0.48 mg/dl (28.55 μmol/L) higher in the highest quintile group of total meat intake than the lowest ($p < 0.001$ for trend) and 0.15 mg/dl (8.92 μmol/L) higher in the highest quintile group of seafood intake than in the lowest ($p < 0.005$ for trend). Similarly, a correlation between increased seafood intake and an increased prevalence of hyperuricaemia (OR 1.56 for highest quintile, $p = 0.01$ for trend) was reported in a cross-sectional study of 3978 Chinese men aged 40-74 years (Villegas et al., 2012).

In contrast, no association between intake of purine-rich vegetables and risk of gout was identified in the 47,150 participants of the Health Professional Follow-up Study (Choi et al., 2004a). This is supported by the absence of association between purine-rich vegetables and plasma urate levels in a case-control study involving 2076 healthy Scottish adults (Zgaga et al., 2012) and between vegetables and sUA levels in cross-sectional surveys of 9734 Australian and 3031 Norwegian adults (Zykova et al., 2015). Villegas et al. (2012) also observed no association between consumption of purine-rich vegetables and prevalence of hyperuricaemia in their cross-sectional study of middle-aged Chinese men. The consumption of vegetables may be beneficial for gout sufferers, as plant-derived foods could contribute to the reduced risk of associated comorbidities, such as CVD (Alissa & Ferns, 2017) and T2D (Carter et al., 2010). As such, current dietary guidelines for gout actively promote the consumption of vegetable sources of protein.

Despite many observational studies, there is a paucity of randomised controlled trials (RCT). However, in a parallel RCT of 55 hypertensive and hyperuricaemia adults, adherence to a low purine diet for 12 weeks was found to be as effective as allopurinol in reducing sUA concentration (Peixoto et al., 2001). Similarly, 2 weeks of a low-purine diet reduced sUA by 0.57 mg/dL (33.9 μmol/L) ($p = 0.01$) in a pilot study of 64 men with gout, although no control group was included in this study (Cardona et al., 2005). In a small study of ten healthy males, a significant reduction in urinary uric acid excretion was observed following the consumption of either an ovo-lacto vegetarian diet or balanced omnivorous diet for 5 days relative to a Western diet (both $p < 0.05$) (Siener & Hesse, 2003). A reduction in animal sources of purines may therefore be beneficial for individuals with gout. However, further RCTs are needed to confirm this.

2.1.8.3. Alcohol

A reduction in the quantity of alcohol consumed is also recommended in UK dietary guidelines for gout. Alcohol has been implicated in the pathogenesis of the condition, as its consumption can result in increased uric acid levels (Torralba et al., 2012). Alcohol can increase synthesis of uric acid through increased degradation of ATP to AMP, a precursor of uric acid (see 2.1.3, Figure 1.), and may inhibit the urinary excretion of uric acid through the production of lactate

(Torralba et al., 2012). In addition, the high purine content of some alcoholic beverages may contribute to an increased risk of gout and gout attacks (see 2.1.8.2.) (Choi & Curhan, 2004).

Observational evidence supports a role of limiting alcohol intake in the management of gout. Abhishek et al. (2017) reported alcohol intake as the most frequently self-reported trigger for gout flares (14.18% of participants) in a cross-sectional survey of 550 individuals with gout. In an internet-based case-crossover study of 179 participants with gout, alcohol consumption was also associated with increased risk of recurrent gout attacks when consumed in the previous 48 hours (OR 2.5 for highest quintile, $p < 0.005$ for trend) (Zhang et al., 2006). Furthermore, a prospective internet-based case-crossover study in 724 patients with gout observed a significant dose-response relationship between increased alcohol consumption and risk of gout attacks ($p < 0.001$ for trend) (Neogi et al., 2014).

In addition to quantity, the type of alcohol consumed may affect the risk of gout flares occurring. Consumption of beer, which has a high purine content and generates increased plasma hypoxanthine, xanthine, and uric acid concentrations (Gaffo et al., 2010; Yamamoto et al., 2004), has been associated with increased gout risk in 47,150 healthy men over a 12-year follow-up period (RR per serving per day 1.49) (Choi et al., 2004b). Increased risk was also noted with the consumption of spirits (RR per serving per day 1·15) and this has been attributed to their high alcohol content per serving (Choi et al., 2004b). Meanwhile, moderate wine consumption may be acceptable for gout sufferers, as no association between wine consumption and sUA concentration was reported in either a cross-sectional study of 14,809 healthy adults (Choi & Curhan, 2004) or a prospective study of 3123 American adults (Gaffo et al., 2010). Correspondingly, wine consumption was not associated with gout in a 12-year prospective study of 47,150 men (Choi et al., 2004b). It is proposed that phytonutrients found in wine, such as phenolic compounds (see section 2.2.1.), may offer some protection against the impact of the alcohol on sUA levels (Choi & Curhan, 2004).

Whilst these findings from observational studies support the restriction of alcohol, particularly beers and spirits, for individuals with gout, this needs to be confirmed with RCTs.

2.1.8.4. Dairy

Another common recommendation in UK guidelines for the management of gout is the consumption of dairy products, particularly of the low-fat variety. Consumption of these products has been associated with lower sUA levels (Choi, Liu, et al., 2005). Whilst the exact mechanism is not yet known, proteins found in dairy, namely casein and lactalbumin, are believed to be responsible for this uricosuric effect (Choi, Liu, et al., 2005). Additionally, increased xanthine excretion following the consumption of dairy products may contribute to urate-lowering effects, as this reduces the availability of substrates to produce urate (Dalbeth, Wong, et al., 2010). Calcium has also been proposed as a possible urate-lowering compound (Dalbeth & Palmano, 2011). Another way in which dairy products could be beneficial to gout sufferers is via the ability of dairy fractions to modulate the inflammatory response to MSU crystals, as has been seen *in vitro* (Dalbeth, Gracey, et al., 2010). This may help to reduce the pain and inflammation associated with gout flares.

Observational data supports a role of dairy products in gout management. A study of data from 14,809 American adults in the Third National Health and Nutrition Examination Survey showed an inverse association between total dairy intake and sUA level ($p = 0.02$ for trend), with a difference of -0.21 mg/dl (-12.49 μmol/L) between the highest and lowest quintiles of intake (Choi, Liu, et al., 2005). Additionally, significantly lower sUA levels were observed with the consumption of milk (-0.25 mg/dL [-14.87 μmol/L] for highest quintile) and yoghurt (-0.26 mg/dL [15.46 μmol/L] for highest quintile) at least once a day when compared to abstainers (both $p < 0.001$ for trend). Dairy (-3.9 mmol/dL per serving, $p = 0.008$), calcium (-0.02 mmol/dL per 1 mg, $p = 0.003$), and lactose (-0.5 mmol/dL per 1 g, $p < 0.001$) intakes were also all inversely associated with sUA concentration in a case-control study in 2076 healthy Scottish adults (Zgaga et al., 2012). In support of these findings, a cross-sectional analysis of 1693 adults from the UK identified that individuals consuming a vegan diet, a diet free of dairy products, had the

highest sUA concentrations compared to meat eaters, fish eaters, and vegetarians ($p < 0.001$) (Schmidt et al., 2013).

Evidence from RCTs is less consistent and further research is needed to confirm mechanisms of effect. In support of the observational data indicating higher sUA levels in vegans, a 7.8 μmol/L increase in sUA level ($p = 0.03$) was observed 4 weeks after the adoption of a dairy-free diet in 158 Roman Catholic nuns (Ghadirian et al., 1995). No significant change to sUA was observed following the daily consumption of 30 g of dairy protein. Uricosuric effects of dairy have also been observed in experimental studies. In 10 healthy adults, sUA concentrations were significantly reduced at 3 hours following the consumption of 80 g casein (-29 μmol/L, $p < 0.01$) and 80 g lactalbumin proteins (-34 μmol/L, $p < 0.01$) (Garrel et al., 1991). Additionally, significantly acute reductions in sUA concentration were observed following the consumption of skimmed milk in a cross-over RCT, when compared with a soy control (treatment by time, $p < 0.001$) (Dalbeth, Wong, et al., 2010). In this short-term study, 16 healthy male participants consumed 800 mL of 3 types of skimmed milk (early season, late season, and ultra-filtered) and a soy control and had blood samples collected over 3 hours following each drink. However, the absence of a neutral control could be seen as a limitation of this study, as consumption of the soy control induced a 10% increase in sUA within 2 hours of consumption. In a 3-month double-blinded RCT, the consumption of 15 g skimmed milk powder enriched with glycomacropeptide and G600 milk fat extract over 3 months, administered daily as a 250 mL vanilla flavoured shake, was found to not only significantly increase FEUA by approximately 0.7% ($p < 0.0002$ versus control), but also reduced the frequency ($p = 0.044$ versus control) and pain ($p = 0.047$ versus control) of gout flares in patients with recurrent gout flares (Dalbeth et al., 2012). However, no significant changes in sUA were observed, nor did 15 g skimmed milk powder alone exhibit any urate-lowering effects. It was suggested that the dose used was insufficient to induce these effects. It is evident that further RCTs, particularly those involving individuals with hyperuricaemia and gout, are required to confirm observational findings.

2.1.8.5. Hydration

Prolonged dehydration can result in decreased glomerular filtration rate and reduced urate clearance (Choi, Mount, & Reginato, 2005). Additionally, the

solubility of urate in the body is influenced by hydration status, with dehydration promoting less soluble urate. As these factors can contribute to elevated sUA levels and recurrent gout flares, individuals with gout are thus encouraged to consume sufficient fluids to remain hydrated (Schlesinger, 2005). There are however exceptions to this, namely alcoholic (see 2.2.9.3.) and fructose-rich beverages (see 2.1.8.6.).

In a cross-sectional study of 159 hyperuricaemic and normouricaemic individuals, those who were considered dehydrated were significantly more likely to have hyperuricaemia than their euhydrated counterparts (OR 2.35, p = 0.003) (Ekpenyong, 2019). Hyperuricaemia is also induced by acute diarrheal dehydration in children. In a study of 133 dehydrated patients, 80% were found to have elevated sUA levels and these returned towards normal following rehydration (Adler et al., 1982).

Experimental research is limited, however a 19 µmol/L increase (p < 0.05) in plasma uric acid concentration was observed following 2 x 10 minutes of sauna bathing at 90 °C in 5 healthy males (Yamamoto et al., 2004). This was attributed to the loss of body fluid also observed during this time. Hydration status therefore appears to be important in the management of hyperuricaemia.

2.1.8.6. Fructose

Reducing or limiting the consumption of fructose-rich foods and drinks is also recommended to gout patients. Fructose metabolism can stimulate the production of uric acid due to ATP depletion, an increased rate of purine degradation, and reduced urinary uric acid excretion (Caliceti et al., 2017; Johnson et al., 2007). Furthermore, there is evidence that fructose-induced uric acid production may also contribute to cardiac, kidney, and metabolic disorders, many of which are comorbidities of gout (Jia et al., 2014).

The Health Professionals Follow-up study of 51,529 men found a multivariate RR for gout of 2.02 (95% CI 1.49 to 2.75) for the highest quintile versus lowest quintile for consumption of fructose (p < 0.001 for trend) (Choi & Curhan, 2008). Fructose consumption has also been positively associated with an increase in the risk of gout in women. In the Nurses' Health Study of 78 906 women, compared with the lowest quintile, multivariate RR for gout was 1.62 (95% CI 1.20 to 2.19) for the

highest quintile of intake (p = 0.004 for trend) (Choi et al., 2010). However, the impact of fructose on gout flare occurrence has not yet been investigated.

Despite an absence of experimental studies involving patients with gout, a 0.42 mg/dL (24.98 µmol/L) elevation in 24-hour sUA profile was observed in older overweight and obese individuals (n = 16) following 10 weeks of fructose-sweetened drink consumption (p < 0.001) (Cox et al., 2012). This was not observed in those who consumed a glucose-sweetened drink for the same length of time (n = 15), indicating that urate-raising properties are unique to this monosaccharide. A role of fructose in raising uric acid levels is also supported by the findings of an animal study. Compared with rats fed a control diet, elevated sUA levels were observed in rats fed a 60% fructose diet for a period of 4 weeks (2.4 vs 1.3 mg/dL [142.8 vs 77.3 µmol/L], p < 0.01) (Nakagawa et al., 2006). Increased hepatic urate production and decreased urinary excretion of uric acid were also observed after an additional 6 weeks of the high-fructose diet, highlighting potential mechanisms by which high fructose consumption may contribute to hyperuricemia.

2.1.8.7. Fruits

Despite the recommendation to restrict fructose-rich foods, UK guidelines for gout management still promote the inclusion of fructose-containing fruits in the diet, particularly cherries (Hui et al., 2017; NICE, 2018). This conflicting advice could be explained by the location of the fructose within foods. Many fructose-rich foods, such as sugar-sweetened beverages, contain large amounts of extrinsic sugars, defined as sugars which are not found within the cellular structure of food and are often added during processing (Ruxton, 2003; Scapin et al., 2017). In contrast, fruits contain intrinsic sugars, which are sugars that are naturally incorporated into the cellular structure of foods. Due to their location, intrinsic sugars found in fruits may take longer to be digested and absorbed than extrinsic sugars in other fructose-rich foods and thus have a less detrimental effect on gout flare risk (Englyst & Englyst, 2005). Additionally, the rate of digestion and absorption may also be slowed by the presence of fibre in whole fruits (Nakagawa et al., 2019).

Nevertheless, the effects of fruit and fruit juice consumption on uric acid levels and their potential roles in preventing gout flares are complex. It is widely accepted that there are positive health effects of adequate whole fruit intake, including on CVD and T2D (Dreher, 2018). However, a review of clinical studies has indicated that some specific fruits and/or their juices induce a rise in sUA levels, whilst others may be beneficial for gout sufferers (Nakagawa et al., 2019).

A greater consumption of fruit was associated with a reduced risk of self-reported gout (RR: 0.73 per pieces/day; $p < 0.0001$ for trend) in the National Runners' Health survey of 5291 American men (Williams, 2008). The risk of gout was also 50% lower in men consuming >2 pieces of fruit/day than in men consuming <0.5 pieces/day ($p < 0.01$). Additionally, in a case-control study of Taiwanese men, individuals with gout ($n = 92$) were shown to have a significantly lower monthly frequency of fruit intake (difference of 3.28 portions per month, $p = 0.04$) than healthy controls ($n = 92$) (Chiu et al., 2019). Despite these findings, comparing a diet including 400 g fresh fruit, 100 g orange juice, and 300 g vegetables daily with a diet devoid of fruit and vegetables for 2 weeks found no significant effect on absolute urinary uric acid excretion or uric acid relative saturation in 12 healthy individuals (Meschi et al., 2004). The short duration, relatively small sample size, and use of healthy normouricaemic could explain the null findings and limits the generalisation to gout patients. When the same diet was followed for 1 month by 26 individuals with calcium oxalate stones, significantly lower uric acid relative saturation (-1.66, $p = 0.003$) and urinary uric acid excretion (-1.08 mmol/L, $p < 0.001$) were observed, compared to their usual fruit and vegetable free diet (Meschi et al., 2004).

Analyses of specific fruits and fruit juices have produced conflicting results as effects seem to depend on the type of fruit, nutritional composition, and the form in which they are consumed (Nakagawa et al., 2019). The Health Professionals Follow-up study of 46,393 men found that total fruit juice intake was positively associated with risk of gout (RR 1.81 for highest quintile, $p = 0.01$ for trend) (Choi & Curhan, 2008). In particular, the consumption of 2 or more glasses of apple or orange juice per day was associated with a RR of incident gout of 1.82 (95% CI 1.11 to 3.00, $p = 0.05$ for trend) compared with <1 glass per month. Whole apple or orange consumption was also associated with increased risk of gout (RR 1.64

for highest quintile, $p = 0.006$ for trend). A significant association with risk of gout has also been reported with orange juice intake in women in the Nurses' Health Study (RR 2.42 for highest quintile, $p = 0.02$ for trend), however other fruit juices, apples, or oranges were not found to be significantly associated with gout in this study (Choi et al., 2010).

In agreement with this observational data, servings of apples (205 g and 410 g) or apple juice (170 mL and 340 mL) led to elevated sUA levels in the 60 minutes following consumption in a parallel study of 61 healthy individuals (White et al., 2018). A mean increase of 19 μmol/L (95% CI 8 to 30 μmol/L) was observed for the large serving of apples and an increase of 17 μmol/L (95% CI 9 to 24 μmol/L) was observed for the large serving of apple juice. The effects on sUA were attributed to the fructose content of the fruit, as the observed sUA response did not differ from that of the 26.7 g fructose control used in the study. Some other fruit juices may also be detrimental to gout patients. For example, following the consumption of 330 mL of cranberry juice by 12 healthy males, a significant 0.32 increase in the relative supersaturation for uric acid was observed ($p < 0.05$) (Kessler et al., 2002). However, there was no significant change in urinary urate (UU) excretion. Additionally, in a pilot study exploring fructose-rich beverages and uric acid levels, a single serving of blueberry juice was shown to induce an acute increment in sUA of 15 and 10 μmol/L in T2D and chronic kidney disease patients, respectively (Olofsson et al., 2019). This finding was not replicated in healthy individuals.

In contrast, some whole fruits and fruit products have demonstrated urate-lowering abilities. For example, daily consumption of 35 g of blueberry powder over 3 months has been shown to lower sUA concentrations in 88 older adults with mild cognitive decline (Cheatham et al., 2016). However, 5.83 g or 12.5 g of freeze-dried blueberry powder did not produce any significant acute changes in the sUA levels of 14 healthy individuals (Blacker et al., 2013). Similarly, daily consumption of 50 g whole blueberries for 6 weeks had no effect on the sUA of 27 patients who were obese (Istek & Gurbuz, 2017). Jacob et al. (2003) reported the plasma urate concentrations of healthy women following the acute consumption of 280 g depitted sweet Bing cherries, 280 g red grapes, 300 g strawberries and 300 g kiwifruit. Of the four fruits, only cherries were shown to

significantly reduce plasma urate levels, with a maximum reduction of 31 μmol/L at 5 hours post-consumption. There has been substantial interest in the use of cherries in the management of gout, with evidence suggesting that, in addition to urate-lowering traits, they possess anti-inflammatory, anti-oxidative, and pain-reducing qualities which would be beneficial to this condition (McCune et al., 2010). The remaining sections of this review will therefore focus on discussing the role that cherries may play in the management of gout. As CVD is associated with gout (see 2.1.6.), the effect of cherries on CVD risk markers will also be discussed.

2.2. Cherries

Botanically, cherries are classified as a drupe fruit as they contain a pit (Cásedas et al., 2016). Cherries are typically divided into two broad types, *Prunus cerasus* ('sour' or 'tart' cherries) and *Prunus avium* ('sweet' cherries). Despite being relatively low in calories they are considered a nutritionally dense food, being a good source of fibre, potassium, β-carotene, and vitamin C (see Table 1.) (Blando & Oomah, 2019; Ferretti et al., 2010; McCune et al., 2010). They are also rich in phytochemicals, most notably phenolic compounds. Phenolic compounds demonstrate antioxidant and anti-inflammatory properties (Ozcan et al., 2014). This has prompted research into the role that cherries may play in the prevention and management of several conditions and diseases, including hyperuricaemia, gout, and CVD (Kelley et al., 2018; McCune et al., 2010). Tart cherries have been identified as having a higher phenolic content than sweet cherries (see 2.2.1) (Chaovanalikit & Wrolstad, 2004a; Ferretti et al., 2010). As such, tart cherry cultivars, such as Montmorency and Balaton, may offer greater potential antioxidative and anti-inflammatory benefits than sweet cherries.

Table 1. Mean nutritional composition of tart and sweet cherries (per 100 g fresh weight). Adapted from McCune et al. (2011), Blando and Oomah (2019), and Ferretti et al. (2010).

Nutritional component	Tart cherries	Sweet cherries
Energy (kcal/100g)	50	63
Fibre (g/100g)	1.6	2.1
Total sugars (g/100g)	8.5	12.8
Sucrose (g/100g)	0.8	0.2
Glucose (g/100g)	4.2	6.6
Fructose (g/100g)	3.5	5.3
Vitamin A (IU/100g)	1283	64
Vitamin C (mg/100g)	10	7
Potassium (mg/100g)	173	222
β-carotene (µg/100g)	770	38
Total phenolic content (mg GAE/100g)	241.5*	142.4*
Total anthocyanin content (mg/100g)	54.5	171.4
Flavonols (mg/100g):	Nd.	2.6
Flavanols (mg/100g):	Nd.	15.1
Hydroxycinnamic acids (mg/100g):	42.4	87.8

GAE, Gallic acid equivalents; Nd, no data available.
* Mean of total phenolic content values reported in Blando and Oomah (2019) and Ferretti et al. (2010).

2.2.1. Phenolic compounds

Phenolic compounds, a group of secondary plant metabolites, are abundant in cherries (Damar & Ekşi, 2012; Kirakosyan et al., 2009; Manach et al., 2004). They are characterised by the presence of at least one aromatic ring with one hydroxyl group attached. There are around 8000 phenolic compounds which are classified into two broad groups: flavonoids, the more bioactive and abundant in plants of the two, and non-flavonoids (de la Rosa et al., 2018). Flavonoids can be divided into 6 sub-groups: flavones (e.g. luteolin and apigenin), isoflavones (e.g. glycitein and glycitin), flavonols (e.g. quercetin and kaempferol), flavanones (e.g.

naringenin and hesperetin), flavanols (split into two further sub-groups, catechins and proanthocyanidins), and anthocyanidins (e.g. cyanidin) (Manach et al., 2004). Non-flavonoids include stilbenes (e.g. resveratol), lignans (e.g. matairesinol), and phenolic acids (hydroxybenzoic acids and hydroxycinnamic acids). Phenolic compounds have been shown to possess several health-enhancing characteristics, including anti-inflammatory, antioxidant, neuroprotective, and anti-viral properties (Ozcan et al., 2014). Consequently, there is growing interest in the use of phenolic-rich foods to optimise health (Cory et al., 2018).

Cherries, particularly of the tart variety, have a high content of phenolic compounds, of which anthocyanidins make a large contribution (see 2.2.1.1.) (Chaovanalikit & Wrolstad, 2004a; Kirakosyan et al., 2009). Of four different cultivars of cherries, namely Bing, Rainier, Royal Ann, and Montmorency, Montmorency tart cherries were found to contain the highest total phenolics at 4.07 mg Gallic acid equivalents (GAE)/g (± 0.18), whereas Rainier and Bing, both sweet cherry cultivars, contained the lowest at 0.75 mg GAE/g (± 0.02) and 1.85 mg GAE/g (± 0.13), respectively (Chaovanalikit & Wrolstad, 2004a). This is consistent with the work of Bonerz and colleagues, who observed total phenolic contents of between 2704 and 4998 mg/L in different tart cherry varieties (Bonerz et al., 2007). Table 2 displays the content of phenolic compounds that have been identified in two tart (Montmorency and Balaton) and two sweet (Ranier and Bing) varieties of cherry which are commonly studied.

Table 2. Phenolic compounds identified in edible portions of tart (Montmorency and Balaton) and sweet (Ranier and Bing) cherry varieties. Adapted from: Blando & Oomah, 2019; Chaovanalikit & Wrolstad, 2004a; Chockchaisawasdee et al., 2016; Gao & Mazza, 1995; Kirakosyan et al., 2009; Liu et al., 2011; Mulabagal et al., 2009; Seeram et al., 2001; Serradilla et al., 2015.

Phenolic compound content	Tart cherry varieties		Sweet cherry varieties	
	Montmorency	Balaton	Ranier	Bing
Total phenolic content (mg GAE/100 g)	407.0	254.1	75.0	76.6 – 194
Total anthocyanin content (mg/100 g fresh weight)	8.7 - 36.5	45.0	0.5 - 20.9	26.0 - 224.7
Flavonols (mg/100 g fresh weight):				
Rutin	11.2	nd	0.9 – 1.2	2.8 - 4.1
Isorhamnetin rutinoside	328.9 *	250.2 *	Nd	nd
Kaempferol	13.1 *	3.8 *	Nd	nd
Quercetin	8.5 *	5.9 *	Nd	nd
Flavanols (mg/100 g fresh weight):				
Epicatechin	19.6 - 49.5	nd	2.37 – 7.2	8.3 - 12.8
Anthocyanidins (mg/100 g fresh weight):				
Cyanidin 3-sophoroside	0.97	19.3 *	1.2	nd
Cyanidin 3-glucosylrutinoside	11.0 - 63.0	21.0	4.0	nd
Cyanidin 3-glucoside	1.7	49.1 *	0.1 – 2.5	8.0 - 36.7
Cyanidin 3-rutinoside	5.0 - 28.7	16.5	2.6 – 93.6	8.1 - 180.6
Pelargonidin-3-glucoside	0.9	nd	Nd	0.3 - 0.6
Pelargonidin-3-rutinoside	Nd	nd	1.76	0.3 - 3.1
Peodinin-3-glucoside	48.6 *	141.5 *	Nd	9.2
Peonidin—3-rutinoside	4.9	Nd	0.9 – 1.8	9.2
Hydroxycinnamic acids (mg/100 g fresh weight):				
Neochlorogenic	Nd	Nd	64.1	128.2 - 146.6
Chlorogenic	58.2	Nd	3.9 – 30.0	4.4 - 56.8
p-**Coumaroyl-quinic**	Nd	Nd	Nd	37.0 - 42.7

GAE, Gallic acid equivalents; Nd, no data available. ***** mg/100 g dry weight

2.2.1.1. Anthocyanidins

Anthocyanidins, a flavonoid subgroup, are the principal compounds responsible for the red pigmentation of cherries (Serradilla et al., 2015). They are typically found in plants as anthocyanins, the glycoside form (Tsao, 2010). There is increasing interest in the role that anthocyanins could play in health promotion and disease prevention, and this has been attributed to their antioxidant and anti-inflammatory properties (Pojer et al., 2013; Reis et al., 2016).

Cherries have been found to contain 70-900 mg of anthocyanins per 200 g serving (Manach et al., 2004), with tart cherries reported to contain particularly high quantities of cyanidin (e.g. cyanidin 3-glucosylrutinoside and cyanidin 3-rutinoside) and peonidin (e.g. peonidin 3-rutinoside) derivatives (Kirakosyan et al., 2009; Ou et al., 2012). Many of the reported health benefits of tart cherries, including cardio-protective properties and a role in the management of gout, have been attributed, at least in part, to these anthocyanins (Blando et al., 2004; Kelley et al., 2018).

2.3. Cherries and gout

The first report of using cherries in gout management was by Doctor Ludwig Blau in 1950 (Blau, 1950). Doctor Blau reported that the consumption of about 0.5 lb of fresh or canned cherries daily lowered sUA levels of 12 patients with gout to normal, although only 3 patient cases were described in his published report. Since this time, cherries have received specific attention in gout management (Collins et al., 2019). They are proposed to be efficacious for gout prophylaxis owing to their high content of anti-inflammatory and antioxidative phenolic compounds (Ferretti et al., 2010). Nevertheless, many berries, such as blueberries and chokeberries (Mattila et al., 2006), are similarly high in these compounds and yet are not promoted for the treatment of gout. It is not clear why this is the case. Public attention to the therapeutic role of cherries for gout is substantial and many gout patients report consuming cherries and/or cherry products for their condition (Harrold et al., 2010; Singh et al., 2015; Zhang, Neogi, et al., 2012). Numerous gout information websites, such as Arthritis UK and the UK Gout Society, as well as several recent evidence-based guidelines for gout management, including those published by the EULAR, the BSR, and NICE, endorse consuming cherries (Hui et al., 2017; NICE, 2018; Richette et al., 2017).

However, not all health policy bodies concur with this recommendation; the FDA in the United States have warned cherry juice growers and processers against making preventative disease claims (U.S. Food and Drug Administration, 2005), whilst the National Health Service (NHS) health information website criticised newspaper claims of the benefits of cherry supplementation for gout (NHS Choices, 2014). Greater clinical research is therefore required for claims to be advocated or disregarded. The next five sections of this review aim to critically examine studies investigating the effects of cherries on markers and symptoms of gout, namely gout flares, uric acid level, oxidative stress, inflammation, and pain.

2.3.1. Cherries and gout flares

The consumption of cherries may help to reduce the frequency of gout flares in gout sufferers. In a case-crossover internet-based trial involving 633 American adults with diagnosed gout, cherry intake on two days prior to an attack was associated with a 35% lower risk of gout attacks compared to no intake (see Table 3) (Zhang, Neogi, et al., 2012). Similarly, in a pilot retrospective study of 24 American patients with gout who self-reported consuming 1 tablespoon of tart cherry concentrate twice daily for ≥4 months ('Study 2'), a significant reduction in the number of gout flares, from 6.9 to 2.0 flares per year (p = 0.0001), was observed (Schlesinger et al., 2012). However, as cherry intake was self-reported in these studies, reporting biases cannot be ruled out. RCTs are required to validate these results, as causality cannot be assumed from observational studies. In another pilot study (n = 14) by Schlesinger et al. (2012) ('Study 1'), the provision of 120 days of twice-daily supplementation of 1 tablespoon of cherry concentrate, but not pomegranate juice, significantly reduced gout flare frequency in patients from 4.99 to 1.56 per 4 months (p < 0.05). Furthermore, over half of the cherry group were flare free within 4 months compared with less than 20% of the pomegranate group. Pomegranate juice has been found to be richer in total phenolics than cherry juice, suggesting that the profile of bioactive compounds responsible for this is specific to cherry (Les et al., 2015). For example, an analysis of the polyphenol composition of commercial pomegranate and tart cherry juices observed that pomegranate was richer in punicalagins, ellagic acids, and gallic acids, whereas derivatives of cyanidin (an anthocyanidin)

and caffeoylquinic acids (a phenolic acid), such as chlorogenic and neochlorogenic acids, were more abundant in tart cherry juice (Carpéné et al., 2019).

Table 3. Studies investigating the effect of cherry intake on the risk or frequency of gout flares in adults with gout.

Author	Study design	Study population	Gout criteria used	Type of cherry product	Comparative product or placebo	Concentration or dose of cherry product and dosing regime	Effect of cherry on gout flares
Zhang, Neogi et al., 2012	Case-crossover Internet-based trial	633 American adults with gout (median age 54 years, 78% male)	ACR preliminary criteria for classification of gout	Not specified	No cherry intake on two days (participants acted as own controls)	Dose not specified. Cherry intake on two days prior to an attack	35% reduced risk of flares compared with no intake (OR 0.65, 95% CI 0.50-0.85)
Schlesinger et al., 2012 (study 1)	Pilot retrospective trial	24 American adults with gout (age and sex distribution not provided)	Primary or secondary diagnosis of gouty arthropathy/gout	Cherry concentrate (cultivar not specified)	n/a	1 tablespoon, twice daily for ≥120 days	Significant reduction in the number of flares, from 6.9 to 2.0 flares per year (p = 0.0001)
Schlesinger et al., 2012 (study 2)	Pilot parallel RCT	14 American adults with gout (mean age 56 years, sex distribution not provided)	MSU crystal-proven gout	Tart cherry concentrate (cultivar not specified)	1 tablespoon pomegranate juice concentrate	1 tablespoon, twice daily for 120 days	Significant reduction in flare frequency from 4.99 to 1.56 per 4 months (p < 0.05)
Singh, Willig et al., 2020	Pilot feasibility Internet parallel RCT	84 American adults with gout (mean age 56 years, 72% male)	ACR preliminary criteria for classification of gout	Tart cherry extract (cultivar not specified)	Individualised diet modification (supported by dietician)	1200 mg extract per capsule, 3 capsules per day (3600 mg extract/day) for 9 months	Significant reduction in flare frequency of 39% (p = 0.049)
Stamp et al., 2020	Parallel RCT	50 New Zealand adults with gout (mean age not provided, 90% men)	ARA preliminary classification criteria for gout	Tart cherry concentrate (Montmorency)	n/a	7.5 mL, 15 mL, 22.5 mL, or 30 mL, twice daily for 28 days	No effect on flare frequency (p = 0.76)

ACR, American College of Rheumatology; ARA, American Rheumatism Association; CI, confidence interval; MSU, monosodium urate; n/a, not applicable; OR, odds ratio; RCT, randomised controlled trial.

In support of these findings, an American feasibility pilot study in which 84 individuals with gout were randomised to receive cherry extract (3 capsules daily) or a general diet modification for 9 months observed a significant 39% reduction (0.22 vs. 0.36 flares per month, $p = 0.049$) in gout flare frequency following cherry supplementation (Singh, Willig, et al., 2020). However, gout flare frequency was not considered a primary outcome of this study and neither adherence to supplementation nor ULT were assessed. In contrast, compared with a placebo drink, 7.5 mL, 15 mL, 22.5 mL, or 30 mL of tart cherry concentrate twice daily for 28 days was not found to have any effect on frequency of gout flares in a parallel study of 50 individuals with gout (Stamp et al., 2020). This study was not however designed to detect changes in gout flares and was limited by its short duration of 28 days.

It is also acknowledged that many of these studies differed in their criteria of gout when recruiting participants, which may limit the comparability of findings between studies (Table 3). Whilst both Zhang, Neogi et al. (2012) and Singh, Willig et al. (2020) used preliminary criteria for the classification of gout from the American College of Rheumatology (ACR), Stamp et al. (2020) utilised the American Rheumatism Association (ARA) classification criteria for gout. Schlesinger et al. (2012) only required participants to have had a MSU crystal-proven diagnosis. Being male has been significantly associated with an increased number of gout flares in patients with gout (Rothenbacher et al., 2011; see section 2.1.5). However, only Zhang, Neogi et al. (2012) considered sex as a potential confounding factor during analysis; in this study, the inverse association between cherry intake and gout attack risk remained when sex was accounted for (OR 0.68, 95% CI 0.51-0.91 for men and 0.48, 95% CI 0.27-0.83 for women). Age was not considered as a confounder in any of these studies.

Further research on the effect of cherries on gout flare frequency is required to confirm preliminary findings. Furthermore, observational data from UK patients indicates that gout attacks are less frequent in this population than has been reported in intervention studies of American and Australian patients, with 4 flares experienced per year on average (Abhishek, Jenkins, et al., 2017). With the intermittent and unpredictable nature of gout flares, intervention studies of a

longer duration may be required to accurately capture changes in flare frequency in UK populations.

2.3.2. Cherries and uric acid

Cherry consumption may reduce gout flare frequency and other detrimental effects of hyperuricaemia through lowering urate levels (Collins et al., 2019). Two main mechanisms of action have been proposed. Firstly, cherries may increase glomerular filtration of urate whilst reducing renal tubular reabsorption, resulting in an increase in UU and a reduction in sUA levels (Jacob et al., 2003; Zhang, Neogi, et al., 2012). Decreased sUA levels enable the body to break down accumulations of urate crystals in joints, subsequently reducing the risk of gout attacks and joint damage. The second proposed mechanism of action is a reduction in the hepatic activity of xanthine dehydrogenase (XDH) and XO, which are components of the enzyme xanthine oxidoreductase (XOR), responsible for the formation of superoxide anions, hydrogen peroxide, and uric acid (Haidari et al., 2009; Kirakosyan et al., 2018). Cherry phenolic compounds may bind to the active site of XOR, inhibiting its activity (Kirakosyan et al., 2009; Lin et al., 2002). By inhibiting XOR, cherries would decrease uric acid production, consequently reducing hyperuricaemia. Whilst this theory has yet to be investigated in humans, tart cherry juice has been shown to inhibit the mean activity of XO and XDH and reduce the experimentally-induced rise in sUA levels in hyperuricaemic rats (Haidari et al., 2009).

Although these proposed mechanisms have not been tested in gout patients, several intervention studies with healthy subjects have demonstrated improvements in uric acid levels following cherry consumption (see Table 4). For example, in an acute RCT of 10 healthy women, plasma urate decreased from 214 μmol/L to 183 μmol/L over 5 hours following a 280 g serving of Bing sweet cherries (Jacob et al., 2003). No significant changes in urate were observed with similar quantities of other fruits, namely red grapes (280 g), strawberries (300 g), or kiwifruit (300 g). In an acute crossover study in 12 healthy individuals, 30 mL and 60 mL doses of tart cherry concentrate produced even greater reductions in sUA levels than observed in the aforementioned study (36% vs 15%) (Bell, Gaze, et al., 2014). However, neutral placebos were not utilised in either study and so it cannot be concluded that the cherry consumption was solely responsible for the

improvements observed. For example, reductions in sUA may be attributed to diurnal variations, as sUA levels typically peak in the morning (Devgun & Dhillon, 1992; Sennels et al., 2012). A placebo-controlled, cross-over study is required to account for the possible effect of diurnal variation in sUA. In contrast to these findings, a recent placebo-controlled parallel study involving 48 healthy participants failed to observe acute reductions in sUA levels following the ingestion of one or two 240 mL bottles of tart cherry juice but did report reductions of ~1 mg/dL (~59 µmol/L) over 24 hours following 480 mg freeze-dried tart cherry powder (Hillman & Uhranowsky, 2021).

Additionally, as these studies were all undertaken in healthy participants, these results cannot be generalised to individuals with or at risk of gout. A crossover RCT in 26 overweight individuals (BMI ≥25.0 $kg.m^{-2}$), of which 46% were hyperuricaemic, reported a significant 19.2% reduction in plasma urate following 4 weeks of daily supplementation with 240 mL tart cherry juice (40 mL tart cherry concentrate and 200 mL water) when compared to a cherry-flavoured placebo drink (Martin & Coles, 2019). In contrast, sUA was unaffected by the consumption of 8 fl oz tart cherry juice blend twice-daily for 6 weeks in 58 patients with knee osteoarthritis, including some hyperuricaemic patients (Schumacher et al., 2013). Surprisingly, the reported total daily intake of anthocyanins from the cherry juice blend provided to osteoarthritic patients was double that of the tart cherry juice provided to overweight individuals by (15.6 mg vs. 60 mg), although similar total phenolic intake of around 900 mg/day were reported (Martin & Coles, 2019; Schumacher et al., 2013). Nevertheless, the cherry juice blend also contained apple juice, which has been previously shown to raise uric acid levels (White et al., 2018). This may have negated any urate-lowering potential of tart cherry juice. Improvements in sUA levels were also not observed following supplementation with tart cherry extract supplementation (3600 mg/day) for 9 months in 84 individuals with gout (Singh, Willig et al., 2020). However, this study was not sufficiently powered to measure changes in sUA, as the primary objective was feasibility of an internet study. It is also plausible that the form and/or dose in which tart cherry is administered is important; other tart cherry products may not be as efficacious in reducing sUA levels as tart cherry concentrate. As the total phenolic and anthocyanin content of the tart cherry extract used in this study was

not provided, it is not possible to determine whether this may be responsible for null findings reported (Singh, Willig, et al., 2020).

Overall, the current evidence base addressing the relationship between cherry consumption, sUA levels, and gout flares is limited; most existing studies are short-term, have small sample sizes, utilise predominantly healthy participants and/or fail to assess both sUA levels and gout flares. It is also presently unknown if a cherry-induced reduction in sUA levels would translate to improvements in other gout symptoms.

Table 4. Studies investigating the effect of cherry intake on serum or plasma urate concentration in adults.

Author	Study design	Study population	Type of cherry product	Comparative product/placebo	Concentration or dose of cherry product and dosing regime	Effect of cherry product on uric acid levels
Jacob et al., 2003	Acute, single-blind, crossover RCT	10 healthy American women (mean age 40 years, 0% male)	Bing sweet cherries (whole fruit)	Red grapes (280 g), strawberries (300 g), kiwifruit (300 g)	Single 280 g serving; followed up for 5 hours post-consumption	Plasma urate decreased from 214 μmol/L to 183 μmol/L over 5 hours (p < 0.05). No significant changes with other fruits.
Bell, Gaze et al., 2014	Acute, single-blind, crossover RCT	12 healthy UK adults (mean age 26 years, 92% male)	Tart cherry concentrate (Montmorency), served as juice	n/a	Single 30 mL or 60 mL dose diluted with 100 mL water; followed up for 48 hours post-consumption	Significant reduction in sUA over time (p < 0.001). Peak reduction of 178 μmol/L (36%) at 8 hours.
Hillman & Uhranowsky, 2021	Acute parallel RCT	48 healthy American adults (mean age not provided, 44% male)	Tart cherry concentrate (Montmorency), served as juice, and freeze-dried tart cherry powder in capsules	Cherry-flavoured placebo fruit drink and powdered placebo capsule/s	One or two 240 mL servings of juice or one or two tart cherry powder capsules (480 mg per capsule)	Group by time interaction for sUA (p = 0.02), with a steady decline up to 8 hours following a single tart cherry capsule and two tart cherry capsules.
Martin & Coles, 2019	4-week crossover RCT	26 overweight (BMI ≥25.0 kg/m^2) American adults (mean age 41 years, 31% male)	Tart cherry concentrate (cultivar not specified), served as juice	Cherry-flavoured placebo drink (240 mL serving)	240 mL tart cherry juice (40 mL tart cherry concentrate and 200 mL water), daily for 4 weeks	Significant 19.2% reduction in plasma urate with tart cherry juice from 378.3 to 320.8 μM (p < 0.05). Plasma urate increased non-significantly following the placebo drink.

Schumacher et al., 2013	6-week crossover RCT	58 American adults with knee osteoarthritis (mean age 57 years, 76% male)	Tart cherry juice blend (Montmorency tart cherry juice and apple juice)	Cherry-flavoured placebo drink (8 fl. oz serving)	8 fl. oz tart cherry juice blend, twice-daily for 6 weeks	No significant change in sUA (p = 0.5).
Singh, Willig et al., 2020	Pilot feasibility parallel RCT	84 American adults with gout (mean age 56 years, 72% male)	Tart cherry extract (cultivar not specified)	Individualised diet modification (supported by dietician)	1200 mg extract per capsule, 3 capsules per day (3600 mg extract/day) for 9 months	No significant change in sUA (p = 0.77).

Na, not applicable; RCT, randomised controlled trial; sUA, serum uric acid.

2.3.3. Cherries and oxidative stress

Many deleterious effects of gout are proposed to result from increased oxidative stress, triggered by the production of pro-inflammatory cytokines and ROS (Zamudio-Cuevas et al., 2015). Increased XO activity plays a role in oxidative stress because free radicals are produced when it catalyses the conversion of hypoxanthine to uric acid (Haidari et al., 2009; Kirakosyan et al., 2018). Cherries may protect against oxidative stress in gout via both direct and indirect antioxidant actions. Through inhibiting XO, cherries may exert an indirect antioxidant effect. Kirakosyan et al. (2018) found that in an *in vitro* assay, tart cherry extract inhibited XO activity by 26%. As discussed in section 2.2., cherries are also reportedly high in antioxidant phytochemicals which may have direct antioxidant effects (McCune et al., 2010; Wang, Nair, Strasburg, Booren, et al., 1999). Supporting this, Virgen Gen et al. (2020) observed a protective effect of cherry extract against oxidative stress, measured by ROS production, in THP-1 cells exposed to MSU crystals.

Tart cherries possess a high antioxidant capacity and contain phytochemical compounds that possess the ability to reduce ROS activity, including anthocyanidins and flavonols (Chaovanalikit & Wrolstad, 2004b). Using the same XO inhibition assay as before, this time with individual phytochemical compounds found in tart cherries, Kirakosyan et al. (2018) reported that kaempferol and cyanidin 3-rutinoside displayed the highest inhibitory activity on XO (23.4% and 21.6%, respectively), followed by isorhamnetin 3-rutinoside (20.7%) and cyanidin 3-glucoside (19.9%). Furthermore, even greater XO inhibitory activity was displayed when some cherry phytochemicals were combined, particularly isorhamnetin 3-rutinoside and kaempferol, indicating that antagonistic, additive, and/or synergistic interactions between phytochemicals may be responsible for the biological effectiveness of cherries. However, these values may not necessarily translate to *in vivo* effects. The stability of bioactive phytochemicals in humans following consumption and their conversion into other secondary metabolites during digestion may not result in the same effects as seen in studies performed *in vitro* (Karaś et al., 2017; Kay et al., 2009). Furthermore, large inter-individual variation in the bioavailability of cherry phytochemicals, due to gut microbiota profile, metabolism, and interactions between food matrix compounds

(Karaś et al., 2017; Selma et al., 2009), may generate inconsistent antioxidative effects between individuals (Keane, Bell, et al., 2016).

Nevertheless, several human studies have explored the use of cherries in improving antioxidant status. There is some evidence to suggest that cherry supplementation can improve antioxidant capacity (Lynn et al., 2014; Seymour et al., 2014). In an acute crossover study of 12 healthy adults, increased plasma antioxidant capacity was demonstrated following the consumption of 45 and 90 whole tart cherries (Seymour et al., 2014). Antioxidant capacity was determined using the Trolox equivalent antioxidant capacity (TEAC) assay, an indirect method of measurement. However, it has been argued that the TEAC value produced by this assay does not correlate accurately with antioxidant activity, as it may include the antioxidant capacity of both the parent compound and reaction products (Arts et al., 2004). Lynn et al. (2014) reported improved plasma antioxidant capacity of healthy adults who consumed 30 mL tart cherry concentrate diluted with 220 mL water (n = 25) or 250 mL lemonade (n = 21) daily for 6 weeks (adjusted difference 173.58 μM, 95% CI 40.00, 307.16), although this was attributed in part to the reduced antioxidant capacity in the lemonade group. Plasma antioxidant capacity was determined by use of the ferric-reducing antioxidant power (FRAP) assay. FRAP is also considered an indirect method for assessing antioxidant status, as it tests the ability of antioxidants to reduce Fe^{3+} to Fe^{2+} rather than true antioxidant activity (Amorati & Valgimigli, 2015). Limitations of this test have also been recognised. For example, FRAP may exclude several important antioxidants whilst including some reductants that are not considered antioxidants (Pinchuk et al., 2012). Despite these findings of improved antioxidant capacity, Jacob et al. (2003) reported a 51 μmol/L reduction in plasma FRAP in the 5 hours following the consumption of 280 g sweet cherries by 10 healthy women. However, this may be explained by the significant reduction in urate that was also observed following consumption of the cherries, as urate is considered one of the main determinants of FRAP (Nälsén et al., 2006).

Improved resistance to oxidative damage has also been observed following the consumption of cherries (Bialasiewicz et al., 2018; Chai et al., 2019; Traustadottir et al., 2009). In a crossover study of 12 healthy adults, the consumption of 240

mL tart cherry juice for 2 weeks was demonstrated to increase capacity to resist oxidative damage compared with a placebo drink (Traustadottir et al., 2009). This capacity was assessed by measuring changes in plasma levels of the oxidative stress marker F_2-isoprostane (F_2-IsoP) in response to ischemia-reperfusion-induced ROS production, before and after the supplementation period. Furthermore, 12 weeks of tart cherry juice supplementation have been shown to significantly increase plasma levels of DNA repair activity of 8-oxoguanine glycosylase from 298.7 to 314.7 ng/nL in a parallel RCT of 37 healthy adults (Chai et al., 2019). Bialasiewicz et al. (2018) also observed the suppression of luminol-enhanced whole blood chemiluminescence, a marker of ROS production, when regular diets of 34 healthy adults were supplemented with 500 g whole tart cherries daily for 30 days. No changes were detected in participants who had their diets supplemented with apples (n = 29) or the control group who were advised to eat their regular diet (n = 24).

Tart cherry supplementation has also been shown to significantly attenuate oxidative stress response, assessed by measurement of aqueous phase lipid hydroperoxides, following prolonged high-intensity stochastic cycling (Bell, Walshe, et al., 2014) and to improve antioxidant activity, determined by improved total antioxidant status (TAS), following marathon running (Howatson et al., 2009). Despite this, improvements in TAS were not observed following high-intensity strength exercises with tart cherry supplementation (Bowtell et al., 2011; Levers et al., 2015) and there were also no effects of supplementation on F2-IsoP following water polo activity (McCormick et al., 2016). This could suggest that protection from tart cherries depends on the type of exercise undertaken.

It has been recognised that, when assayed by different methods, values for oxidative stress often do not correlate with one another (Pinchuk et al., 2012). Therefore, the lack of consistency in methodology used to assess antioxidant capacity and resistance to oxidative damage makes it difficult to compare findings between studies. Furthermore, despite a plethora of studies in healthy populations, studies in those with raised baseline levels of oxidative stress are lacking.

2.3.4. Cherries and inflammation

Gout is also associated with increased levels of inflammation (Cavalcanti et al., 2016; Cronstein & Sunkureddi, 2013). The intra-articular deposition of uric acid crystals initiates an inflammatory response, evidenced by reddened, hot, and/or swollen joints (see 2.1.3.) (Busso & So, 2010; Ragab et al., 2017). High sUA levels are associated with elevated levels of inflammatory markers, including CRP, IL-6, and TNF-α (Lyngdoh et al., 2011; Ruggiero et al., 2006, 2007). Consequently, anti-inflammatory medications, such as colchicine and naproxen, are frequently prescribe in the management of gout (Terkeltaub, 2010). Cherries contain phytochemical compounds with purported anti-inflammatory properties, so they have been investigated as prophylaxis for the inflammation induced by several medical conditions and exercise-induced muscle damage (EIMD).

Anti-inflammatory effects of cherry extracts have been demonstrated *in vitro*, including reduced production of IL-1β following cell exposure to MSU crystals (Vírgen Gen et al., 2020) and decreased expression of IL-6 messenger ribonucleic acid (mRNA) levels in lipopolysaccharide stimulated adipocytes (Jayarathne et al., 2018). Whilst the exact mechanisms behind these effects have not been determined, it is suggested that phenolic compounds in cherries, particularly anthocyanins, can inhibit the activity of cyclooxygenase (COX) enzymes, which play a key role in the generation of inflammation and pain (Mulabagal et al., 2009).

Several studies have reported reductions in markers of inflammation in healthy and patient populations after supplementation with tart cherry. In healthy individuals, RCTs have revealed reductions in inflammatory markers, particularly CRP, following consumption of tart cherry concentrate (Bell, Gaze, et al., 2014; Chai et al., 2019). Chai et al. (2019) reported a 25% fall in CRP in older healthy adults who consumed 68 mL of tart cherry concentrate, diluted to 480 mL with water, daily for 12 weeks. Similarly, a peak decrement in CRP of 29% was reported at 5 hours following the consumption of a 30 mL or 60 mL dose of tart cherry concentrate by 12 healthy adults (Bell, Gaze, et al., 2014). However, despite both studies utilising healthy individuals, baseline CRP levels of participants receiving the cherry intervention were elevated, particularly within the study of Bell, Gaze and colleagues (2014), and so this may have facilitated the

observed reductions in CRP. Significantly attenuated post-exercise increments in inflammatory markers have also been found with cherry products following high-intensity intermittent exercise, high intensity cycling, and long-distance running (Bell et al., 2015; Bell et al., 2016; Bell, Walshe, et al., 2014; Dimitriou et al., 2015; Howatson et al., 2009; Levers et al., 2016).

Whilst the anti-inflammatory effects of cherries have yet to be investigated in gout patients, studies involving patients with osteoarthritis and obesity have reported improvements to inflammatory markers following tart cherry supplementation (Kuehl et al., 2012; Martin et al., 2018; Schumacher et al., 2013). In a study involving patients with knee osteoarthritis, CRP reduced by 23% following 6 weeks of daily tart cherry juice blend supplementation, but unexpectedly increased by 51% with the fruit-flavoured placebo drink (Schumacher et al., 2013). Similarly, Khuel et al. (2012) reported a 3.42 mg/L reduction in the CRP of patients with osteoarthritis (n = 20) when two 10.5 oz bottles of tart cherry juice were consumed daily for 21 days. However, no changes to other inflammatory biomarkers, namely IL-6, IL-10, or TNF-α, were identified. A significant between-group difference of 25% in erythrocyte sedimentation rate (ESR), a marker of chronic inflammation, was detected in overweight/obese individuals following four weeks of tart cherry juice supplementation compared with a placebo drink (Martin et al., 2018). However, this difference was primarily exerted by a rise in ESR in the placebo group rather than a marked suppression in the cherry group. In both studies, a high-fructose placebo drink was used. Fructose has been shown to activate inflammatory pathways in animal models and so may have contributed to the observed increments in CRP and ESR (Miller & Adeli, 2008; Roglans et al., 2007). It is therefore important that future studies utilise low-fructose or fructose-free placebos.

In contrast, other studies have failed to observe anti-inflammatory benefits of sweet or tart cherries in healthy individuals (Hillman & Chrismas, 2021; Hillman & Uhranowsky, 2021; Jacob et al., 2003; Lear et al., 2019; Lynn et al., 2014). There was no significant change in plasma inflammatory biomarkers TNF-α, NO, and CRP following the consumption 280 g of sweet cherries by 10 healthy women (Jacob et al., 2003). However, this study was limited by the absence of a control group. In a cross-over study involving 28 healthy middle-aged men and women,

plasma CRP and IL-6 were also unaffected by daily consumption of 30 mL tart cherry concentrate or placebo for 4 weeks (Lear et al., 2019). Similarly, Lynn et al. (2014) reported no effect of 6-weeks of daily 30 mL tart cherry concentrate supplementation on CRP in healthy adults aged 30-50 years, compared with a placebo group (n = 47). In a parallel study of 58 healthy individuals, no significant reductions in CRP or ESR were observed following 30 days of tart cherry consumption in either a 500 mg/d freeze-dried or ~30 mL concentrate form, when compared with placebos (Hillman & Chrismas, 2021). Hillman and Uhranowsky (2021) also reported no acute effect of tart cherry in either freeze-dried (1 or 2 x 480 mg capsules) or juice (1 or 2 x 240 mL bottles) forms on the CRP concentration of healthy individuals.

Other studies utilising resistance exercise (Bowtell et al., 2011; Jackman et al., 2018; Levers et al., 2015), repeated-sprint (Brown et al., 2019) and water-polo (McCormick et al., 2016) EIMD protocols have also found no effect of tart cherries on inflammatory markers. However, in 4/5 of these EIMD studies, circulating CRP did not significantly increase post-exercise, suggesting that these protocols failed to induce inflammation (Bowtell et al., 2011; Brown et al., 2019; Jackman et al., 2018; McCormick et al., 2016). Raised levels of baseline inflammatory markers, which may not be observed in healthy individuals, could be required to detect clinically significant reductions and may therefore explain the inconsistencies between studies. Nevertheless, whilst Martin and colleagues (2018) observed a significant reduction in ESR in overweight individuals with four weeks of daily tart cherry juice supplementation, CRP, IL-6, IL-10, and TNF-α levels remained unaffected, despite the evidence of elevated inflammation at baseline. Similarly, whilst a 19.4% reduction in CRP was observed following the consumption of 240 mL/day tart cherry juice for 4 weeks by overweight individuals, this did not reach significance (p = 0.09) (Martin & Coles, 2019). Participants in this study also demonstrated raised levels of inflammation at baseline.

Another plausible reason for the inconsistencies between studies could be inter-batch variation in phenolic compounds of cherry products. For example, in a 4-week pilot study in overweight men, during which improvements in markers of inflammation were not observed, a large inter-batch variation in anthocyanin content of the sweet cherries used during the intervention was reported (Vargas

et al., 2014). However, the inconsistent measurement and reporting of phenolic content of cherry products in existing RCTs means that it is difficult to ascertain whether this is responsible for conflicting findings. It is important for future studies of cherry products to perform their own analyses and clearly report this information.

Despite the abundance of research, the effect of cherries on inflammation remains equivocal. To clarify the effect of cherries, future studies need to involve individuals with raised inflammatory biomarkers, such as those with gout, investigate the effects of longer-term cherry supplementation, and include low-fructose or fructose-free placebos.

2.3.5. Cherries and pain

A defining symptom of gout and the inflammatory response induced during a flare is intense and debilitating pain (Gaffo et al., 2018; Vanitallie, 2010). In chronic gout, this pain may continue between flares. Anti-inflammatories and antioxidants may attenuate soreness and pain, and thus may be useful for gout sufferers during flares (Terkeltaub, 2010). Cherries and cherry products are also proposed to possess both these properties because of their high content of phenolic compounds (see 2.3.3 and 2.3.4). In support of this, tart cherry anthocyanins have been shown to dose-dependently reduce inflammation-induced pain in rats (Tall et al., 2004). Consequently, there has been interest in the potential of cherries to reduce or alleviate pain induced by EIMD and various medical conditions.

Reported changes in pain induced by EIMD with consumption of cherry products are inconsistent, with some studies reporting reductions in pain scores (Bell et al., 2016; Connolly et al., 2006; Kuehl & Perrier, 2010; Levers et al., 2015) and others not (Beals et al., 2017; Bell et al., 2015b; Bowtell et al., 2011; Brown et al., 2019; Howatson et al., 2009; Lamb et al., 2019; McCormick et al., 2016). Differing modes of exercise and/or training status of individuals may explain these discrepancies. Research into the use of cherries for medical conditions has also produced conflicting pain results. Improved pain scores in patients with fibromyalgia and osteoarthritis have been reported following consumption of tart cherry juice and cherry juice blends (Elliot et al., 2010; Schumacher et al., 2013).

Conversely, a pilot study of 60 chronic pain sufferers attending a tertiary pain clinic reported no effect of 6 weeks of daily cherry juice supplementation on pain scores (Brain et al., 2019). Participants were provided with 42 bottles of pre-diluted juice to store and so anthocyanin degradation may have occurred during this prolonged storage (Bonerz et al., 2007). Despite claims that cherries are effective in reducing gout-induced pain (Zhang, Neogi, et al., 2012), research involving gout patients is scarce. In a pilot feasibility study, within-group reductions in pain were detected following 6 months of daily consumption of powdered cherry extract (Singh, Willig, et al., 2020). However, these were not found to be significantly different from the comparison group who received individualised diet recommendations. The lack of control group and feasibility design makes it difficult to draw conclusions regarding the effectiveness of cherry extract. The absence of placebo-controlled studies for gout pain, alongside inconsistencies in the findings of other studies, indicate the need for further studies to clarify the analgesic effects of cherries.

2.4. Cherries and CVD

As discussed in section 2.1.6., hyperuricaemia and gout are both associated with increased CVD risk (Kuo et al., 2016). Uric acid-induced inflammation and oxidative stress may contribute to endothelial dysfunction and ultimately the development of CVD (Kanbay et al., 2013; Price, 2006). Given their proposed anti-inflammatory and antioxidant properties, cherries may also exert cardio-protective effects (Kelley et al., 2018; Kirakosyan et al., 2013). Consequently, the effect of cherries on other CVD risk markers, namely brachial and central BP, arterial stiffness, and blood lipid profile, have also been investigated and will be discussed in the final sections of this review.

2.4.1. Cherries and blood pressure (BP)

Hypertension is considered a significant risk factor for CVD (Fuchs & Whelton, 2020), and a higher prevalence of hyperuricaemia and gout has been observed in those with uncontrolled BP (Juraschek et al., 2013). The consumption of phenolic-rich cherries has been proposed to reduce BP by altering the synthesis and activity of vasodilators and vasoconstrictors (Kelley et al., 2018; Kelley et al., 2013). Angiotensin-converting enzyme (ACE) is involved in the regulation of BP through activation of vasoconstrictors and inactivation of bradykinin, a vasodilator

substance (Erdös, 1990; Kirakosyan et al., 2018). Strong ACE inhibition of 88.7% (± 0.08) has been demonstrated *in vitro* with tart cherry extract (Kirakosyan et al., 2018). NO has an important role in maintaining blood vessel dilation (see section 2.1.6.1.) and increased endothelial NO synthase levels have been observed in T2D rats following 2 months of sweet cherry supplementation (Van der Werf et al., 2018). Although these findings suggest that cherry may be beneficial in the management and/or prevention of hypertension, evidence in humans is inconsistent.

In a pilot crossover study involving 13 healthy participants, a single 300 mL serving of Bing sweet cherry juice resulted in significant reductions in brachial systolic BP (SBP), brachial diastolic BP (DBP) and heart rate (HR) at 2 hours post-consumption (Kent et al., 2016). However, this study failed to include a control group. In contrast, when examining acute vascular effects of tart cherry concentrate in trained normotensive cyclists, only reductions in SBP were demonstrated with a single 60 mL dose; other measures including DBP remained unaffected by this dose (Keane et al., 2018). Furthermore, consumption of 60 mL/day tart cherry juice for 20 days and 30 mL/day for 6 weeks have failed to induce any significant improvements to BP measures of healthy normotensive adults (Lynn et al., 2014; Sinclair et al., 2022). It is possible that the use of healthy and/or normotensive participants in the null studies may have limited or masked the potential hypotensive effects of cherries.

Significant reductions in both SBP and DBP were displayed when 40 ml of tart cherry concentrate was consumed daily for 6 weeks by diabetic women (Ataie-Jafari et al., 2008). Improvements in SBP have also been reported in middle-aged adults with moderately elevated SBP and early hypertensive men following a single 60 mL dose of tart cherry concentrate (Keane, George, et al., 2016; Keane, Haskell-Ramsay, et al., 2016) and in adults with mild-to-moderate dementia following 12 weeks of daily Bing sweet cherry juice supplementation (Kent et al., 2017), although no significant improvements in DBP were induced in these studies. Similarly, in a 12-week parallel RCT, the consumption of 68 mL/day of tart cherry concentrate resulted in a significant reduction in SBP, but not DBP, in adults aged 65-80 years; this cohort included adults with elevated BP (Chai et al. 2018). However, SBP increased in response to the black cherry flavoured Kool-

Aid placebo drink, which may have contributed to the statistically significant between-group difference observed. Despite these findings, in a recent crossover trial in individuals with metabolic syndrome, no significant improvements in SBP or DBP were observed following 7 days of daily tart cherry juice (30 mL tart cherry concentrate and 100 mL water) consumption (Desai et al., 2021). However, improvements in mean 24-hour ambulatory SBP and DBP were reported. Whilst it has been suggested that ambulatory BP measurements, the monitoring of BP over 24 hours under normal daily-living conditions, provides a more accurate representation of BP than acute measurements (Hodgkinson et al., 2011), others have questioned its reproducibility (Keren et al., 2015).

Systolic pressure is typically higher in the brachial artery (brachial BP) compared with the aorta (central BP) (McEniery et al., 2014). It is suggested that central BP may be a more accurate predictor of CVD risk, as major arteries and organs, including the heart, are exposed to this pressure rather than brachial pressure (McEniery et al., 2014). Higher anthocyanin intake has been associated with lower central BP in women (Jennings et al., 2012) and so tart cherries, which are considered rich in anthocyanins, may also induce similar BP improvements. Despite this, few studies have investigated the effect of cherries and cherry products on central BP. A recent pilot study by Desai and colleagues compared the effects of acute tart cherry supplementation in juice and powdered form on CVD risk markers in patients with metabolic syndrome (Desai et al., 2019). Brachial SBP was significantly lower with cherry juice compared with placebo at 2 hours post-consumption, corresponding with the pharmacokinetics of active phenolic compounds, but no effect was observed for central SBP or DBP or pulse pressure. Whilst it could be argued that a longer supplementation period is required, neither 6 nor 12 weeks of daily tart cherry juice supplementation led to improvements in central SBP or DBP in adults with metabolic syndrome (Johnson et al., 2020). Despite patients in both studies meeting three or more of the metabolic syndrome diagnostic criteria, many participants presented cardio-metabolic markers, including BP, within ‘normal’ ranges at baseline. Thus, cherry juice may only offer cardio-metabolic benefits to those with raised risk markers. Further investigation is warranted.

2.4.2. Cherries and arterial stiffness

Increased arterial stiffness is another, albeit less commonly used, marker of CVD risk (Abdullah Said et al., 2018). Arterial stiffening occurs when haemodynamic forces and extrinsic factors such as salt and glucose regulation induce alterations to the structural and cellular components of the blood vessel wall (Zieman et al., 2005). Alterations to structural components include the dysregulation of balance between the degradation and production of collagen and elastin proteins and the formation of cross-links between these proteins by advanced glycation end products. The modification of vascular smooth muscle cell tone, induced by changes in calcium signalling, oxidant stress, and NO expression, is an example of a cellular component alteration. These changes all contribute to reduced elasticity of vessel walls and vessels are consequently exposed to increased pulsatile pressure and stress. This also augments endothelial dysfunction which is implicated in the development of atherosclerosis (McEniery et al., 2006; Zieman et al., 2005). Pulse wave velocity (PWV) and augmentation index (AIx), alongside central BP, are used to evaluate arterial stiffness. Higher anthocyanin intake has been associated with reduced arterial stiffness values in women (Jennings et al., 2012). As cherry is considered an anthocyanin-abundant fruit, it has been hypothesised that its consumption could help improve endothelial function, thereby reducing arterial stiffness, and consequently lower the risk of CVD (Bell & Gochenaur, 2006; Lynn et al., 2014).

However, current clinical evidence does not appear to support this claim as many studies have failed to produce any marked improvements in measures of arterial stiffness with cherry products. For example, the acute supplementation of tart cherries in juice (30 mL concentrate and 100 mL water) and capsule (10 x 435 mg freeze-dried tart cherry powder) forms by 11 adults with metabolic syndrome had no significant effect on AIx, compared with the placebo, during the 5 hours post-consumption (Desai et al., 2019). Similarly, no improvements in carotid-femoral PWV or AIx were reported in men with early hypertension over 8 hours following a single 60 mL dose of tart cherry concentrate (Keane, George, et al., 2016). Longer supplementation periods have also failed to induce improvements in arterial stiffness. Daily consumption of tart cherry juice (30 mL tart cherry concentrate with 220 mL water) for six weeks was not found to affect brachial-

knee PWV in healthy adults (Lynn et al., 2014). More recently, Kimble and colleagues reported no significant changes in carotid-femoral PWV following the consumption of tart cherry juice (30 mL tart cherry concentrate with 100 mL water) daily for 28 days in young normotensive individuals (Kimble et al., 2021). A lack of improvement in carotid-femoral PWV, brachial-ankle PWV, and AIx measurements have also been observed in adults with metabolic syndrome with one-week (Desai et al., 2021) and 12-week (Johnson et al., 2020) tart cherry juice supplementation regimes.

Patients with gout have been reported to have significantly higher PWV and central BP than healthy age- and sex-matched individuals (Yilmaz et al., 2013), yet the effect of cherry juice on arterial stiffness has yet to be assessed in this population. Furthermore, longer-term research in populations with raised vascular markers is needed.

2.4.3. Cherries and blood lipid profile

Another risk factor for CVD is dyslipidemia, which includes raised total cholesterol (TC), triacylglycerides (TG) and low-density lipoprotein (LDL) levels and low levels of high-density lipoproteins (HDL). Dyslipidemia is also associated with an increased risk of gout (Yu et al., 2021). Cherry consumption may improve blood lipid profile through the binding of phenolic compounds to bile acids (Chai et al., 2018).

Indeed, reductions in LDL and TC levels have been observed in 17 healthy older adults following 12 weeks' daily tart cherry juice supplementation (68 mL tart cherry concentrate diluted with 412 mL water per day) (Chai et al., 2018) and in 19 diabetic women with hyperlipidaemia after 6 weeks of concentrated tart cherry juice (40 g/day) consumption (Ataie-Jafari et al., 2008). However, these studies are limited by a lack of appropriate dietary controls. Chai et al. (2018) used a high-fructose drink as a control which may have unintentionally raised LDL levels in the control group (Chai et al., 2018), whilst no control group was included in Ataie-Jafari and colleagues' pilot study (Ataie-Jafari et al., 2008).

In contrast to these findings, 28 days of sweet cherries consumption and varying lengths of tart cherry concentrate supplementation (20 days, 4 weeks, 6 weeks, and 3 months) have all failed to significantly improve the blood lipid profiles of

participants (Desai, Bottoms, and Roberts et al., 2018; Johnson et al., 2020; Kelley et al., 2006; Lynn et al., 2014; Martin & Coles, 2019; Sinclair et al., 2022). Whilst the lack of effect in four of these studies could be explained by the use of healthy adults without dyslipidaemia (Desai, Bottoms, & Roberts, 2018; Kelley et al., 2006; Lynn et al., 2014; Sinclair et al., 2022), the remaining studies recruited overweight adults displaying some elevated blood lipids at baseline (Martin & Coles, 2019), individuals with metabolic syndrome (Desai et al., 2019; Johnson et al., 2020), and middle-aged participants with CVD risk factors (Kimble et al., 2021).

Overall, the inconsistencies and limitations of existing studies mean that it remains unclear if tart cherry juice offer cardio-protective effects to individuals with or at risk of CVD or gout. Additional appropriately controlled RCTs, particularly long-term RCTs involving patients with gout, are thus required.

2.5. Conclusion

There is a plethora of recommendations for gout sufferers in the UK regarding the most appropriate diet to adhere to, including several evidence-based dietary guidelines. However, patients often refer to other sources of information. YouTube® is a popular and accessible source, but the quality and accuracy of dietary recommendations provided on this platform is currently unknown. Frequently included within recommendations for the management of gout is the guidance to consume cherries. However, as discussed in this review, there is a limited and inconsistent evidence base to support this recommendation from expert bodies. Thus, there is need for further long-term, placebo-controlled studies to clarify the effect of tart cherry consumption as an adjuvant therapy for gout patients.

Overall, this thesis aims to explore the role of dietary modification in the prevention and management of gout and CVD, with a particular focus on tart cherries. To achieve this, the subsequent three experimental chapters will address the following objectives:

1) To assess the accuracy, reliability, quality, and understandability of dietary information for gout provided to the public on the YouTube® platform.

2) To compare the acute effects of tart cherry juice with a neutral water control on uric acid levels, inflammation, and CVD risk markers in healthy individuals.
3) To evaluate the effect of long-term daily tart cherry consumption on uric acid levels, gout flare frequency and intensity, inflammation, and CVD risk in gout patients.

3.0. Study 1: A content analysis of YouTube® videos containing dietary recommendations for UK gout patients.

3.1. Introduction

Gout is a painful and debilitating form of inflammatory arthritis with an increasing global prevalence and burden of disease (Hui et al., 2017; Singh & Gaffo, 2020). In the UK, 3.2% of adults over 20 years old were afflicted with gout in 2012, a 64% increase in prevalence since 1997 (Kuo, Grainge, Mallen, et al., 2015). Gout is associated with numerous co-morbidities, including diabetes, CVD, and hypertension, so effective management is crucial (Kuo, Grainge, Zhang, et al., 2016; Sandoval-Plata et al., 2020; Singh & Gaffo, 2020; Stack et al., 2013).

Persistently elevated serum urate is a well-recognised risk factor for the development of gout and the reoccurrence of gout flares, because it can contribute to a build-up of MSU crystals within joints (Abhishek & Doherty, 2018; Dalbeth et al., 2016; Roddy, 2011; Terkeltaub et al., 2006). Associations have been observed between the consumption of purine- or fructose-rich food and drink, including red meat, beer, and sugar-sweetened beverages, and increased uric acid levels and incidence of gout (Choi et al., 2004a; Choi et al., 2008; Major et al., 2018; Nguyen et al., 2009; Wang et al., 2012; Wang et al., 2013; White et al., 2018). In addition to being a risk factor for gout, diet can contribute to its management (Shulten et al., 2009; Zhang et al., 2019; Zhang, Chen, et al., 2012; Zhang, Neogi, et al., 2012). Consequently, guidelines for the management of gout often include dietary recommendations. These include those targeted at the UK population produced by the BSR, EULAR, and NICE (Hui et al., 2017; NICE, 2018; Richette et al., 2017). Dietary recommendations for gout in these guidelines include restricting most purine- and fructose-rich foods and drinks, limiting alcohol consumption, particularly beer and spirits, remaining hydrated, eating sufficient dairy, and encouraging the consumption of vegetables and fruit, with a specific recommendation to consume cherries.

Despite the availability of evidence-based guidelines, patients may choose alternative sources of information to obtain dietary advice, such as newspapers and online resources (Derksen et al., 2017; Duyck et al., 2016; Vaccher et al.,

2016). Indeed, an analysis of Internet searches for information on gout reported that the term ‘gout’ is commonly combined with search terms relating to food and diet (Jordan et al., 2019). Online dietary advice may be provided in the form of written, pictorial, and/or audio-visual resources. Irrespective of the medium, the information provided by these resources should be easy to understand and consistent with advice from evidence-based sources in order to contribute positively to the self-management of gout (Becker & Chohan, 2008; Johnston et al., 2015; Liddle et al., 2021; Roddy et al., 2007). To our knowledge, no studies have assessed the quality of internet resources providing dietary recommendations for gout, but analyses of written (Jimenez-Liñan et al., 2017; Johnston et al., 2015; Robinson & Schumacher, 2013) and pictorial (Krasnoryadtseva et al., 2020) health advice for the management of gout have frequently reported that resources lack accuracy, provide inadequate information, and/or use complicated language which is unsuitable for their intended audience.

Online videos offer an attractive alternative medium through which dietary advice can be obtained. YouTube® (www.youtube.co.uk) is an accessible and popular video-sharing website which may be used for this purpose (Soukup, 2014). According to the YouTube® press office, more than 2 billion logged-in users visit YouTube® each month, resulting in an accumulation of over 1 billion hours of watched content every day (YouTube®, 2020). Gout is most common in older individuals, with a mean age at first diagnosis of gout of 60.1 years among men and 67.7 years among women (Cea-Soriano et al., 2011). It has been reported that the fastest growing user-group on YouTube® are users over 55 years old (Lee et al., 2022). Furthermore, in a study assessing the demographics of users accessing health-related videos on YouTube®, the highest percentage (30%) of participants were aged between 50 and 64 years old (Langford & Loeb, 2019). Therefore, it is argued that YouTube® is likely to be accessed by individuals with gout for dietary guidance and information.

Despite the popularity of the website, no mandatory editorial or review processes are undertaken during the upload of videos to YouTube® and therefore the information provided to users may be inaccurate, unreliable, and of poor quality. Indeed, studies of YouTube® videos providing educational information on medical

conditions and diseases, including renal disease, rheumatoid arthritis, hypertension, irritable bowel syndrome, kyphosis, and severe acute respiratory syndrome-CoV-2, have reported that a large proportion of videos are inaccurate and/or of poor quality (Erdem & Karaca, 2018; Kumar et al., 2014; Lambert et al., 2017; Mukewar et al., 2013; Rubel et al., 2020; Singh et al., 2012; Sood et al., 2011; Szmuda et al., 2020). A recent study assessed videos providing general health information on gout (Onder & Zengin, 2021). Whilst the percentage of videos containing information on 'gout diet' was recorded, this study did not report the accuracy or reliability of these dietary recommendations. Furthermore, this study did not evaluate the understandability or actionability of videos. To our knowledge, no studies have reported on the quality and accuracy of YouTube® videos specifically providing dietary recommendations for gout.

Therefore, delivering the first objective of this thesis, a content analysis was conducted to assess the alignment of videos on YouTube® providing dietary recommendations for gout with evidence-based guidelines. This study also aimed to evaluate the educational quality, understandability and actionability of these videos and the degree of audience engagement. Additionally, in line with the focus of this thesis, this study sought to highlight the characteristics of videos containing the recommendation to consume cherries.

3.2. Methodology

This study was approved by a Sheffield Hallam University (SHU) ethics committee (ER24922220) (Appendix 1).

3.2.1. Selection of videos

YouTube® (www.youtube.co.uk) was searched in May 2020 for relevant videos using the following search terms: 'gout diet', 'gout food', 'gout nutrition', 'gout healthy diet' and 'gout dietary recommendations'. Additional search terms were considered, for example 'foods to eat for gout', however these generated no new videos. Videos were arranged by relevance and the first 100 videos for each search term were assessed for eligibility. Videos were excluded if they were not focused on gout. For example, videos that only referred to hyperuricaemia and/or high uric acid levels were excluded, because elevated levels of uric acid can be a risk factor for other diseases, such as CVD and kidney disease (Wang et al., 2018). In the context of these other diseases, any dietary advice provided would

not be expected to align with dietary recommendations for gout. Videos were also excluded if they were not focused on humans, did not provide dietary recommendations for gout, or had prohibited access. Additionally, videos greater than 20 minutes in length were excluded, as longer videos may not be viewed in their entirety (Robitza et al., 2020). Videos were not limited to those produced or published by UK sources, but videos were excluded if they were not in English. Where videos were duplicated, the first video was used for analysis and subsequent videos excluded.

3.2.2. Video characteristics and audience engagement

The source that uploaded each YouTube® video was identified as follows: 'health professional or organisation', which included videos produced by certified dieticians or nutritionists, medical doctors, medical facilities, non-profit healthcare organisations (for example, the Gout Education Society), and research centres (for example, Arthritis Research Canada); 'naturopath'; 'non-medical patient support channel or organisation'; 'generic health or diet information channel' with no medical credentials; 'patient testimonials'; 'media'; and 'other', including non-health/diet channels and independent users with no health or medical credentials. The source's country of origin was also recorded. The date of upload was noted and used to calculate the number of days since upload. Other descriptive data recorded were the total duration of the video and duration spent discussing dietary recommendations, which were used to calculate the percentage of time spent discussing dietary recommendations. Audience engagement statistics were recorded on 28th May 2020 and included the number of views, 'likes' and 'dislikes' for a video. The number of views were used alongside the number of days since upload to calculate the view ratio (number of views/number of days since upload). The number of 'likes' and 'dislikes' were used to calculate the 'like ratio' [(number of likes x 100)/(number of likes + number of dislikes)]. This ratio was used along with view ratio to calculate the Video Power Index [VPI; (like ratio x view ratio)/100] (Erdem & Karaca, 2018). The number of comments was not recorded, because many comments were found to be unrelated to the corresponding video's content, for example they contained advertisements for products or websites.

Videos were also classified into one of six topic categories: ‘general diet’ (video covered two or more dietary components and included both foods to avoid and foods to eat), ‘specific diet’ (video focused on only one specific dietary approach, for example ketogenic, Mediterranean, or carnivore diets), ‘specific food or nutrient’ (video focused on only one food, food group, or nutrient to eat or avoid), ‘foods to eat’ (video focused on two or more foods that should be eaten), ‘foods to avoid’ (video focused on two or more foods that should be avoided), and ‘practical guidance’ (video was designed to provide practical recommendations, for example recipes and meal plans).

3.2.3. Compliance of videos with guideline recommendations

To evaluate accuracy and comprehensiveness of dietary information for gout, eligible videos were scored against key items of information identified from three evidence-based dietary guidelines for gout to produce a compliance score (Appendix 2). These guidelines, all targeted at the UK population, were the 2016 updated EULAR Recommendations for the Management of Gout (Richette et al., 2017), 2017 BSR Guideline for the Management of Gout (Hui et al., 2017), and NICE Gout Diagnosis and Management Guideline (NICE, 2018). Videos addressing multiple dietary components (those with topics identified as ‘general diet’ and ‘specific diet’) were scored against the full 30 items; 1 point was awarded for complete alignment with a guideline item, 0.5 for partial alignment, 0 for not mentioned or discussed, and -1 for disagreement with or contradiction to an item. Videos with the topic identified as ‘foods to eat’ were scored against 17 relevant guideline items only, whilst ‘foods to avoid’ videos were scored against 10 relevant guideline items only (Appendix 2). To enable all videos to be analysed collectively, compliance scores were subsequently converted to percentages and videos were given a compliance rating of low (<33%), moderate (33-66%), or high (>66%). Videos with ‘specific food or nutrient’ and ‘practical guidance’ topics were excluded from this analysis because these videos had been designed to have a narrow focus. If videos contained advice that was not covered by guideline recommendations, this was recorded as ‘non-guideline advice’.

3.2.4. Quality, reliability, understandability, and actionability of videos

The Global Quality Score Five Point Scale (GQS) was used to rate videos on their overall educational quality and flow of information (Singh et al., 2012).

Videos were rated as ‘poor’, ‘generally poor’, ‘moderate’, ‘good’, or ‘excellent’ quality according to set definitions (Appendix 3). The reliability of videos was assessed using the adapted-DISCERN tool (Singh et al., 2012). The DISCERN tool has demonstrated good reliability (κ = 0.53, 95% CI κ = 0.48 to κ = 0.59; acceptable level of agreement was set at κ >0.40) and is stated to have good content validity (Charnock et al., 1999). Videos were scored on their alignment with five reliability criteria, with 1 point allocated for ‘yes’ and 0 points allocated for ‘no’ or ‘unclear’ to produce an overall DISCERN score between 0 and 5 (Appendix 4). Videos were categorised as having ‘poor’ (score 0-2), ‘fair’ (score 3) or ‘good’ reliability (score 4-5).

The Patient Education Materials Assessment Tool for Audio-Visual Materials (PEMAT-A/V; https://www.ahrq.gov/ncepcr/tools/self-mgmt/pemat.html) was used to assess the understandability and actionability of the dietary information for gout (Shoemaker et al., 2014; Appendix 5). This tool exhibited strong reliability (average κ = 0.57) and internal consistency (α = 0.71; average item-total correlation = 0.62) during validation (Shoemaker et al., 2014). Patient education materials are considered to have high understandability when the key points of information can be processed and explained by an audience of diverse health literacy levels and backgrounds. Materials have high actionability when the audience can recognise the steps that they can take based on the information presented. A score of less than 70% is suggested to indicate poor understandability or actionability.

3.2.5. Analysis of studies recommending the consumption of cherries

Video characteristics, engagement statistics, and the quality, reliability, understandability, and actionability of videos recommending the consumption of cherries were analysed as a subgroup.

3.2.6. Statistical analysis

Kolmogorov-Smirnov tests were used to assess the normality of continuous data. Differences between video source and continuous variables were assessed using one-way Kruskal-Wallis H tests. When a statistically significant difference was found this was followed by a Dunn test with a Bonferroni correction. For categorical variables, associations with video source were investigated using Fisher-Freeman-Halton tests. Statistically significant effects were followed-up

with post hoc pairwise z-tests with Bonferroni adjustment. Continuous data are reported as medians and interquartile ranges (IQR) and categorical data as percentages or proportions. The degree of agreement between two authors who assessed the compliance of videos with guideline recommendations was determined using the Cohen's kappa (inter-rater agreement) coefficient of agreement. The intra-rater agreement for compliance scoring by the primary author was also determined using Cohen's kappa coefficient. All analyses were conducted using IBM SPSS Statistics, version 24 (SPSS Inc., Chicago, IL, US). The critical value for statistical significance was set at $p \leq 0.05$.

3.3. Results

3.3.1. Video identification

In total, 131 eligible videos were identified from a total pool of 500 videos (first 100 videos for each of the search terms used). The process of video identification is displayed in Figure 3.

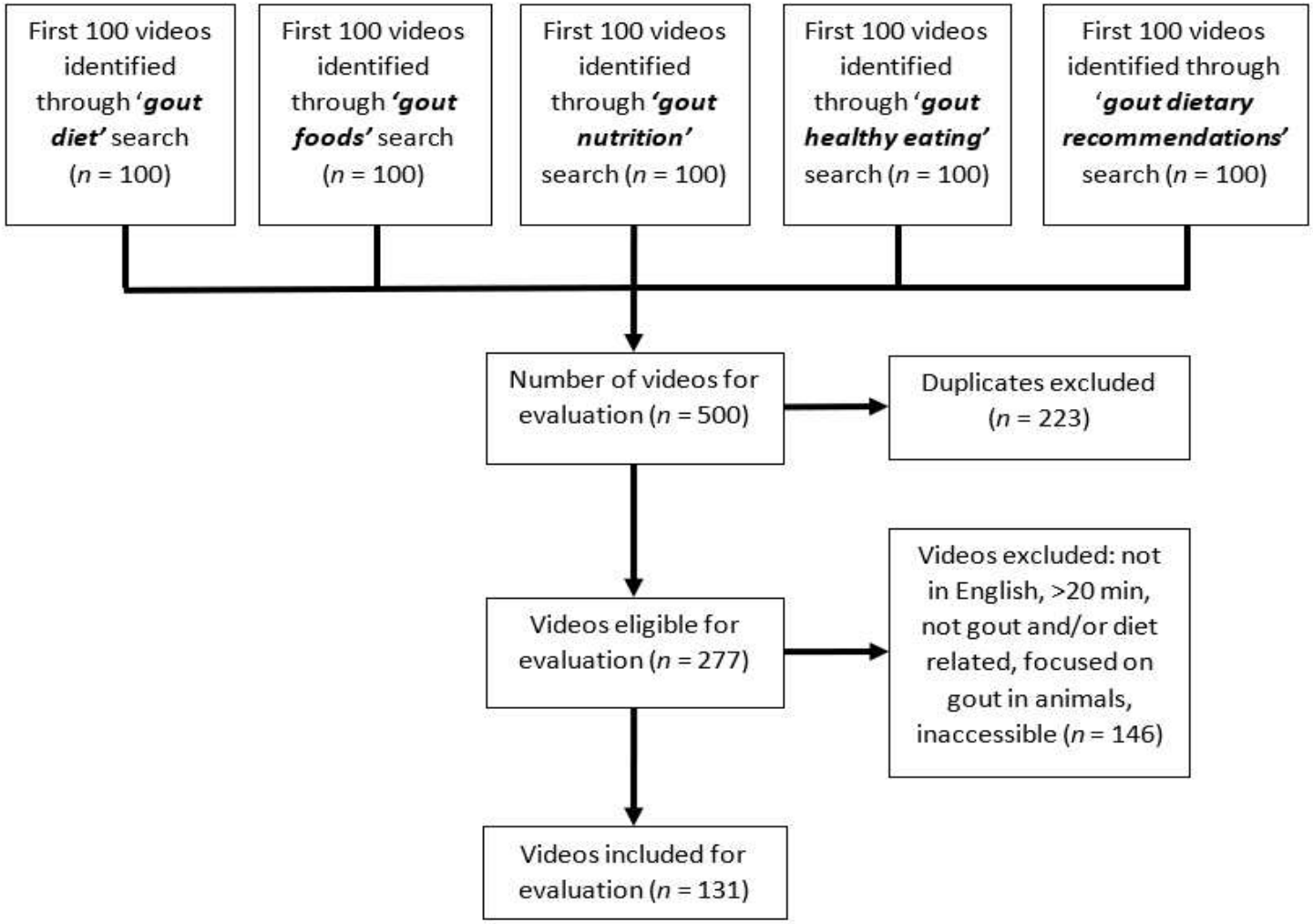

Figure 3. Flowchart of video selection process, including reasons for exclusion of videos.

3.3.2. Video characteristics and audience engagement

Sixty-three percent (*n* = 82) of the videos discussed multiple dietary components. Specific diets or dietary approaches were the focus of 12% (*n* = 10) of these, equivalent to 8% of all videos analysed, and included low carbohydrate, ketogenic, Mediterranean, vegetarian, and carnivore diets. Meanwhile, 19% of videos (*n* = 25) concentrated on a specific food, food group, or nutrient, whilst 16% (*n* = 21) focused on either food to avoid or food to eat. Only 2% of videos (*n* = 3) were designed to solely provide practical guidance or advice such as meal plans and recipes. Fifty-six percent (*n* = 74) of videos were uploaded by sources from the USA, followed by Canada at 13% (*n* = 17). Only 5% (*n* = 7) of videos were produced by UK-based sources. The remaining videos were uploaded by sources from India (5%, *n* = 7), the Philippines (2%, *n* = 2), Australia, Malaysia, Montenegro, Spain, Indonesia, United Arab Emirates, Singapore, Pakistan, and Mexico (all 1%, *n* = 1). Eleven percent (*n* = 15) of videos were uploaded by sources of unknown origin.

The characteristics and audience engagement metrics of videos are displayed in Table 5. The main source of videos was 'health professional' (*n* = 42/131), followed closely by 'generic diet and health information channels' (*n* = 36/131). Median number of days since upload was 947 and median duration of videos was 3 min 34 s (*n* = 131). Videos had a median of 9 views per day since upload, 60 likes, and 4 dislikes. On average, dietary recommendations were discussed for 70% of the total video time.

There were statistically significant differences in days since upload ($p = 0.022$) and duration ($p = 0.021$) between video source categories. All video source categories had like ratios greater than 90% and there were no statistically significant differences across categories.

The amount of time spent discussing dietary recommendations differed by video source ($p < 0.001$). At 97% (94-97%), non-medical patient support channel or organisation ('patient support') videos spent the greatest percentage of time discussing dietary recommendations and this was significantly greater than 'heath professional' ($p < 0.001$), 'naturopath' ($p = 0.007$), 'generic diet and health information channels' ($p = 0.006$) and 'other' ($p = 0.001$) videos.

There were statistically significant differences in view ratio according to video source category (p = 0.001). View ratio was highest in the ‘patient testimony’ category, but there were only two videos in this group. ‘Generic diet and health information channel’ and ‘other’ categories were shown to have significantly higher view ratios than the ‘patient support’ category (p = 0.008 and p = 0.027, respectively).

VPI differed significantly by video source (p < 0.001) and was also highest for the ‘patient testimony’ category. The ‘generic diet and health information channel’ category, which had the second highest VPI at 15.0 (3.5-118.8), was significantly higher than the ‘media’ (p = 0.017) and ‘patient support’ categories (p = 0.001). The ‘other’ video source category also had a significantly higher VPI score than the ‘patient support’ category (p = 0.018).

Table 5. Characteristics and audience engagement metrics of videos providing dietary recommendations for gout, by video upload source.

	Overall (*n* = 131)	Health professional (*n* = 42)	Naturopath (*n* = 16)	Patient support (*n* = 16)	Generic diet/health information channel (*n* = 36)	Media (*n* = 4)	Patient testimony (*n* = 2)	Other (*n* = 15)
Days since upload (IQR)*	947 (470-1834)	1287 (598-2560) [1]	787 (377-1800) [1 2]	388 (229-527) [2]	930 (511-1230) [1 2]	1098 (888-1389) [1 2]	1176 (1160-1191) [1 2]	947 (821-2887) [1 2]
Duration (s, IQR) *[a]	214 (134-345)	194 (112-373)	273 (170-554)	189 (125-204)	261 (162-363)	110 (67-275)	232 (185-277)	219 (187-335)
Video time specifically discussing diet recommendations (%, IQR) *	70 (52-86)	54 (24-71) [1]	67 (60-77) [1]	97 (94-97) [2]	76 (59-86) [1]	75 (61-80) [1 2]	81 (74-87) [1 2]	63 (48-79) [1]
View ratio (views/day, IQR) *	9.1 (1.3-64.8)	16.3 (1.5-60.5) [1 2]	18.8 (3.0-112.4) [1 2]	2.1 (0.7-3.3) [1]	17.0 (3.9-126.6) [2]	0.5 (0.4-0.6) [1 2]	66.8 (35.8-97.7) [1 2]	14.8 (3.8-546.9) [2]
Like ratio (%, IQR)	93 (88-97)	93 (87-98)	95 (92-97)	96 (88-100)	92 (86-96)	95 (85-100)	94 (92-97)	93 (84-95)
VPI (IQR) *	7.1 (1.1-56.4)	10.2 (1.3-50.8) [1 2 3]	14.4 (2.3-65.0) [1 2 3]	1.6 (0.5-2.8) [1]	15.0 (3.5-118.8) [2]	0.4 (0.3-0.6) [1 3]	59.9 (32.4-87.5) [1 2 3]	13.7 (2.8-514.0) [2 3]

Values are displayed as displayed as median (IQR) values.

IQR, interquartile range; VPI, Video Power Index.

*Significantly different ($p < 0.05$) across video sources according to one-way Kruskal-Wallis test. Values with different superscript numbers are significantly different from each other at $p < 0.05$ following post hoc Dunn test with Bonferroni correction.

[a] Post hoc tests revealed no differences between video source categories.

3.3.3. Compliance of videos with guideline recommendations

The distribution of guideline items discussed in the 131 videos is displayed in Table 6. The three most popular items covered were 'avoid excessive meat intake' (70%, 92/131), 'avoid excessive alcohol intake' (57%, 75/131), and 'avoid excessive seafood intake' (55%, 72/131). The three least common items were 'avoid crash dieting/weight loss should be gradual' (3%, 4/131), 'encourage folate intake' (2%, 3/131), and 'fluid/water intake is especially important for those with kidney stones' (2%, 3/131).

Table 6. Guideline items covered across YouTube® videos (*n* = 131). Values displayed as the total number and percentage of sample that covered each item.

Guideline item	***n* videos covering item (% total sample)**
Avoid excessive meat intake	92 (70%)
Avoid excessive alcohol intake/drink alcohol sensibly	75 (57%)
Avoid excessive seafood intake	72 (55%)
Encourage a diet high in vegetables	69 (53%)
Encourage fruit consumption	61 (47%)
Avoid excessive purine intake	59 (45%)
Avoid sugar-sweetened drinks	46 (35%)
Encourage fluid/water intake to prevent dehydration (>2 litres)	45 (34%)
Encourage (low-fat) dairy consumption	44 (34%)
Encourage a diet high in fibre	41 (31%)
Encourage a diet low in added sugar/avoid excessive sugar consumption	39 (30%)
Avoid excessive consumption of beer	39 (30%)
Encourages consumption of cherries	38 (29%)
Consumption of vitamin C may be beneficial	35 (27%)
Taking prescribed gout medication is still important	28 (21%)
Weight loss should be encouraged if appropriate	26 (20%)
Avoid fructose-rich foods	25 (19%)
Coffee consumption may reduce recurrent gout flares	23 (18%)
Encourage diet low in fat	22 (17%)
Encourage skimmed milk consumption	21 (16%)
Encourage regular exercise	17 (13%)
Encourage low-calorie/low-fat yoghurt consumption	16 (12%)
Moderate intake of purine-rich vegetables okay/does not increase risk	16 (12%)
Encourage consumption of soybeans and other vegetable protein sources	15 (12%)
Moderate wine intake (2 glasses/day) acceptable/does not increase risk	10 (8%)
Avoid excessive consumption of spirits	9 (7%)
Reduce orange and apple juice consumption	6 (5%)
Weight loss should be gradual/avoid crash dieting	4 (3%)
Encourage folate intake	3 (2%)
Fluid/water intake is especially important for those with kidney stones	3 (2%)

The dietary advice contained in YouTube® videos typically failed to align with guideline recommendations resulting in a median compliance score of 27% (IQR 17-37%). Almost three-quarters of videos were rated low for their compliance and only 5% of videos were rated high (Table 7). There were no significant differences in the accuracy and comprehensiveness of recommendations across video source categories, as assessed by compliance scores (H (5) = 10.07, p = 0.073) or the distribution of compliance ratings (Fisher's = 13.21, p = 0.128). However, there was a significant difference in the number of videos containing one or more pieces of non-guideline advice across the video source categories (Fisher's = 20.44, p = 0.001), examples of which included the consumption of: apple cider vinegar, dandelions, and tree leaves. The 'health professional' category had the lowest percentage of videos containing non-guideline advice at 31% and this was significantly lower than the 'naturopath' video source category at 81% (p = 0.009). The inter-rater agreement between two reviewers who assessed the compliance of videos with guideline recommendations was 93% with a 'very good' kappa coefficient of 0.789 (p < 0.001). Intra-rater agreement for the primary author was 97% with a 'very good' kappa coefficient of 0.930 (p < 0.001).

Table 7. Alignment of dietary information for gout provided by YouTube® videos with key items from dietary guidelines for gout.

		Overall (*n* = 131)	Health professional (*n* = 42)	Naturopath (*n* = 16)	Patient support (*n* = 16)	Generic diet/health information channel (*n* = 36)	Media (*n* = 4)	Patient testimony (*n* = 2) [a]	Other (*n* = 15)
Presence of non-guideline advice, % category (*n* videos) *		57% (75)	31% (13) [1]	81% (13) [2]	75% (12) [1 2]	61% (22) [1 2]	50% (2) [1 2]	100% (2)	73% (11) [1 2]
Number of videos analysed for compliance score, *n* [b]		103	37	13	9	29	3	0	12
Compliance score, % (IQR) [b]		27 (17-37)	25 (17-33)	23 (18-30)	18 (15-28)	30 (21-60)	18 (16-18)	n/a	32 (16-48)
Compliance rating, % category (*n* videos) [b]	**Low**	71% (73)	76% (28)	92% (12)	89% (8)	55% (16)	100% (3)	n/a	50% (6)
	Mod.	24% (25)	22% (8)	8% (1)	11% (1)	31% (9)	0% (0)	n/a	50% (6)
	High	5% (5)	2% (1)	0% (0)	0% (0)	14% (4)	0% (0)	n/a	0% (0)

IQR, interquartile range; mod., moderate

Values displayed as number and percentage of videos containing non-guideline advice, median compliance score (%), and percentage and number of videos in each compliance rating category.

*Significant difference between number of videos with non-guidance advice and video source category ($p < 0.05$). Values with differing superscript numbers are significantly different from each other at $p < 0.05$ following post hoc comparison.

[a] This category was not used in post hoc comparisons because its column proportions were equal to zero or one.

[b] Compliance score and rating (*n* = 103): 'specific food/nutrient' and 'practical guidance' video scores were excluded; Patient testimony videos did not receive a compliance score or rating, because both videos (*n* = 2) were within the excluded 'specific food/nutrient' topic group.

3.3.4. Reliability, quality, understandability and actionability of videos

Almost 80% of videos were considered poor in terms of their reliability (adapted-DISCERN). Although the 'health professional' source group had the highest percentage of videos rated 'fair' or 'good' for reliability, there were no significant differences between reliability rating categories (Fisher's = 12.43, p = 0.320) or in total reliability scores (H (6) = 6.86, p = 0.334) between video source categories (Table 8). Almost half of the videos were rated poor to generally poor for educational quality (GQS). Only the 'health professional' source group contained a video rated 'excellent' for quality. However, the number of videos in each educational quality rating category (Fisher's = 25.85, p = 0.361) and total educational scores (H (6) = 6.36, p = 0.384) did not differ significantly between video source categories. Only 50% (n = 66) and 22% (n = 29) of the videos had ratings at 70% or above for understandability and actionability (PEMAT), respectively. Whilst understandability did not vary significantly between video source categories, actionability was significantly higher for videos in the 'patient support' category than in the 'health professional' category (p = 0.016). Within the 'health professional' category, five videos were uploaded by dieticians. An exploratory analysis revealed that these five videos had a higher median actionability score when separated from the other 37 'health professional' videos (67% and 33%, respectively). However, this difference was not statistically significant (p = 0.375).

Table 8. Analysis of the reliability, educational quality, understandability and actionability of videos.

	Overall (*n* = 131)	Health professional (*n* = 42)	Naturopath (*n* = 16)	Patient support (*n* = 16)	Generic diet/health information channel (*n* = 36)	Media (*n* = 4)	Patient testimony (*n* = 2)	Other (*n* = 15)
Reliability of information, assessed using the adapted-DISCERN tool, *n* (%)								
Poor	79% (104)	62% (26)	88% (14)	94% (15)	86% (31)	75% (3)	100% (2)	87% (13)
Fair	15% (19)	26% (11)	6% (1)	6% (1)	8% (3)	25% (1)	0% (0)	13% (2)
Good	6% (8)	12% (5)	6% (1)	0% (0)	6% (2)	0% (0)	0% (0)	0% (0)
Educational quality of videos, assessed using the GQS tool, *n* (%)								
Poor	12% (16)	5% (2)	19% (3)	0% (0)	22% (8)	0% (0)	50% (1)	13% (2)
Generally poor	37% (49)	38% (16)	31% (5)	56% (9)	25% (9)	75% (3)	50% (1)	40% (6)
Moderate	37% (49)	36% (15)	50% (8)	44% (7)	36% (13)	25% (1)	0% (0)	33% (5)
Good	12% (16)	19% (8)	0% (0)	0% (0)	17% (6)	0% (0)	0% (0)	13% (2)
Excellent	1% (1)	2% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Understandability and actionability, assessed using the PEMAT tool, % score (IQR)								
Understandability	70 (60-78)	70 (60-80)	67 (58-70)	70 (60-80)	65 (60-72)	50 (49-58)	63 (62-65)	70 (67-78)
Actionability *	67 (33-67)	50 (33-67)[1]	67 (58-100)[1 2]	67 (67-100)[2]	67 (33-67)[1 2]	67 (50-69)[1 2]	83 (75-92)[1 2]	67 (67-67)[1 2]

GQS, Global Quality Score Scale; PEMAT, Patient Education Materials Assessment Tool for Audio-Visual Materials; IQR, interquartile range
GQS and adapted-DISCERN scores are displayed as percentage and number of videos within each score category. PEMAT scores are displayed as median (IQR).
*Significant difference between actionability score and video source category ($p < 0.05$). Values with different superscript letters are significantly different from each other at $p < 0.05$ following post hoc comparison.

3.3.5. Analysis of studies recommending the consumption of cherries

Thirty-eight (29%) of videos encouraged the consumption of cherries. Almost half of these (n = 16) were uploaded by 'generic diet and/or health information channels', followed by 'naturopaths' (n = 8), 'patient support' sources (n = 5), 'other' sources (n = 5), and 'health professional' sources (n = 4). Half of these videos (*n* = 19) were uploaded by sources from the USA, followed jointly by Canada and India at 11% (n = 4) each. Of the 7 videos in this study that had been uploaded by UK sources, three (43%) included a recommendation of cherries for gout management.

Median number of days since upload was 926 and median duration of videos was 4 min 26 s (*n* = 38). Videos had a median of 13 views per day since upload, 122 likes, and 7 dislikes. Median like ratio for these videos was 95%, with a median VPI of 12.3. On average, dietary recommendations were discussed for 69% of the total video time.

Dietary advice in videos recommending the consumption of cherries typically failed to align with guideline recommendations (*n* = 31), resulting in a median compliance score of 30% (IQR 23-50%). Sixty-one percent (*n* = 19) of these videos were rated low for their compliance and only 6% of videos were rated high. Non-guideline recommendations were prevalent in 87% of these videos (*n* = 33/38).

Over 81% (*n* = 31) of these videos were considered poor in terms of their reliability (adapted-DISCERN) and 47% (*n* = 18) were rated poor to generally poor for educational quality (GQS). Only 50% (*n* = 19) and 24% (*n* = 9) of the videos had ratings at 70% or above for understandability and actionability (PEMAT), respectively.

3.4. Discussion

This study found that dietary information provided by the majority of YouTube® videos analysed complied poorly with evidence-based dietary guidelines for gout. A high proportion of videos, including many recommending the consumption of cherries, were also rated poor in terms of their reliability, educational quality,

understandability, and actionability and thus may be deemed unsuitable for UK gout patients to use for nutritional advice.

Almost 60% of the videos analysed provided at least one piece of dietary advice that was considered outside of the three evidence-based guidelines. Examples of this advice included consuming popular traditional remedies such as apple cider vinegar, baking soda, celery extract, and raw garlic, and the avoidance of carbohydrates. Relatively few studies have focused solely on the accuracy of dietary information provided in YouTube® videos. However, in a content analysis of YouTube® videos on diet and renal disease, 82% of videos contained misleading information, compared with our finding of 57% (Lambert et al., 2017). In contrast, studies looking at general health-related information on medical conditions, including rheumatoid arthritis, hypertension, kidney stone disease, and more recently gout, have reported much lower percentages (12 – 33%) of videos containing misleading or inaccurate information (Kumar et al., 2014; Onder & Zengin, 2021; Singh et al., 2012; Sood et al., 2011). The high prevalence of misleading information in videos providing dietary advice may reflect the fact that diet is a controversial area of health management, susceptible to many differing opinions, myths, and misconceptions (Casazza et al., 2013; Dickson-Spillmann & Siegrist, 2011).

In addition to providing dietary recommendations that did not align with guidelines, many videos only discussed a few dietary components. These factors contributed to the low overall compliance score of 27% across all video source categories. The most frequently discussed diet topics were reducing or restricting meat, alcohol, and/or seafood intake. These dietary components have been consistently associated with increased uric acid levels and risk of gout, so it is encouraging that this advice was provided in more than 50% of videos (Choi et al., 2004a, 2004b; Ekpenyong & Daniel, 2015; Major et al., 2018; Shulten et al., 2009; Zhang, Chen, et al., 2012). Nevertheless, several other important dietary factors were rarely addressed. For example, less than 1/3 of videos specifically discouraged excessive beer consumption, yet associations between beer consumption, increased uric acid levels and risk of gout are convincing (Choi &

Curhan, 2004; Gaffo et al., 2010; Williams, 2008; Yu et al., 2008). It has been observed previously that the beer-drinking behaviour of gout patients is frequently inconsistent with evidence-based guidelines, possibly caused by a lack of patient awareness (Shulten et al., 2009). Videos should therefore discuss as many evidence-based dietary factors as possible to equip patients with the knowledge needed to optimise the non-pharmaceutical management of their condition.

Although there were no statistically significant differences in overall compliance scores between video source groups, videos uploaded by naturopaths were found to be the main contributors of 'misleading' videos, with over 80% of these videos containing at least one piece of non-guideline advice. This is a common finding; misleading and/or erroneous information was identified in 78% of internet resources produced by naturopaths on renal diets (Lambert et al., 2017). Furthermore, 92% of videos providing information on rheumatoid arthritis have previously been found to promote unscientific therapies, which included naturopathic therapies (Singh et al., 2012). Naturopathic practitioners favour the use of complementary and alternative medical therapies such as herbs in their practice, but these often have insufficient scientific evidence to support their inclusion in evidence-based guidelines (Tabish, 2008). In contrast, less than one-third of videos within the 'health professional' category provided advice outside of the guidelines. It is encouraging that almost a third of videos were uploaded by health professionals, because this increases the likelihood of patients encountering information that is consistent with guidance provided by their healthcare team.

Video Power Index scores indicated that videos from the 'health professional' category were not favoured over videos from other sources, suggesting that individuals do not actively seek out videos from reliable sources. This is consistent with a content analysis of YouTube® videos providing information on dialysis; engagement was found to be lowest with videos that were identified by two physicians as useful (Garg et al., 2015). Whilst some viewers may be unaware of the inaccuracies and inconsistencies of information provided in YouTube® videos, or the credibility of the source of this information, others may

choose to use complementary and alternative treatments for their condition and actively seek videos containing related information. Indeed, 23.9% of patients with gout have reported using complementary and alternative medicine for their condition (Chan et al., 2014). However, where information obtained by patients conflicts with that provided by their healthcare team, this can increase the risk of inadequate self-management of chronic medical conditions (Gobeil-Lavoie et al., 2019; Liddle et al., 2021). To reduce this risk for individuals with gout, it is vital that patients are guided by their healthcare team towards videos that are consistent with evidence-based guidelines and are educated on the sources of information to avoid.

Irrespective of source, most YouTube® videos analysed displayed poor educational quality and reliability. This finding is consistent with other studies assessing the quality and/or reliability of YouTube® videos providing health information (Erdem & Karaca, 2018; Goobie et al., 2019; Lambert et al., 2017; Szmuda et al., 2020). Median understandability was 70%; this is the lowest possible threshold for being classed as understandable, as defined by Shoemaker et al. (2014), and suggests that the structure and language of many videos could be improved to make them more appropriate for their target audience. Most videos were poorly actionable, further reinforcing the unsuitability of these videos. Actionability was found to be significantly higher in ‘patient support’ videos than ‘health professional’ videos. Additionally, ‘health professional’ videos spent a significantly lower proportion of time discussing dietary recommendations than ‘patient support’ videos. These findings could be explained by differing target audiences and overall purpose of videos; by definition, ‘patient support’ videos are more likely to be targeted explicitly at patients with gout and designed to help them manage their condition, whilst ‘health professional’ videos may be aimed at educating a wider target audience, including other healthcare professionals and those with no prior knowledge of gout. Lambert et al. (2017) also observed that videos uploaded by medical doctors scored poorly for actionability, however those uploaded by dietitians scored higher. In the present study, only five of the 42 health professional videos were uploaded by dieticians and so these were initially combined in the ‘health

professional' category. When separated from the other 37 'health professional' videos, the five videos uploaded by dieticians had a higher median actionability score. However, the difference was not statistically significant and both scores remained below the actionability threshold of 70%.

Despite its inclusion in evidence-based dietary guidelines for gout, the recommendation to consume cherries for the management of gout is currently only supported by observational findings and limited experimental evidence (see sections 2.3.1 and 2.3.2). Nevertheless, this recommendation was present in 29% of videos. These videos had a median of 13 views per day since upload, 4 per day more than the median for all videos analysed in this study, and over two times the number of likes than the overall median (122 versus 60, respectively). Together with a high average VPI, these findings indicate that the recommendation to consume cherries has received considerable exposure on the Internet. This reinforces the need for more robust experimental research on the effects of cherries on gout. Despite the overall prevalence of this recommendation, only 10% of videos uploaded by medical professionals encouraged cherry consumption. Should future research continue to support the use of cherries for gout, the omission of this recommendation by medical professionals would need to be addressed.

Overall, this study has added to a growing body of literature suggesting that health information from videos on YouTube® is often of poor quality and reliability and inconsistent with national and/or international guidelines (Erdem & Karaca, 2018; Lambert et al., 2017; Rubel et al., 2020; Singh et al., 2012; Szmuda et al., 2020). The UK public need to take great care when selecting YouTube® videos containing dietary recommendations for gout, because a large proportion of available information is inconsistent with the evidence-based advice provided by healthcare teams. A screening process to prevent inaccurate or unreliable information from being uploaded on YouTube® should be considered in the future. Since the completion of this study, YouTube® has started to highlight videos that have been identified as 'authoritative sources' for health information, including healthcare providers and public healthcare organisations, by providing

information panels alongside these videos. To identify appropriate sources for UK public, the NHS worked with YouTube® to review published foundational principles (Kington et al., 2021) and create the NHS Standard for Creating Health Content (YouTube®, 2022). Principles include that sources are science-based and accountable (Kington et al., 2021). Currently, only videos uploaded by NHS organisations are eligible to receive information panels in the UK. Additionally, video content uploaded by 'authoritative sources' may not necessarily be understandable or actionable. However, this step indicates that YouTube® acknowledges the importance of credible medical information and may suggest a move towards the screening of all videos in the future. For now, where YouTube® is a preferred source of information for patients, it would be beneficial for healthcare teams to assist in identifying appropriate videos for their patients to watch. There is also a need for health professionals to consider actionability and educational quality when producing evidence-based health information videos for upload onto YouTube®.

The present study has several limitations, including its cross-sectional design. This study was undertaken at the beginning of the COVID-19 pandemic in the UK. As a result of reduced face-to-face contact with health professionals, an increased number of individuals may have accessed online resources, such as YouTube®, for health information during this time (Romão et al., 2020; Smith et al., 2020). As YouTube® video engagement metrics are constantly changing, future research could look at measuring the change in engagement metrics for videos over time. Most videos were uploaded by non-UK sources, with the main countries of upload being the USA and Canada. Thus, content scores for these videos may have differed slightly had they been scored against dietary guidelines for gout from their respective countries. However, whilst there may be small differences in guideline recommendations, the key components of the guidelines used in the present study, such as limiting consumption of high-purine meat, seafood, and alcohol, do not appear to differ substantially across countries (Nielsen et al., 2018). Meanwhile, most of the dietary components classified as 'non-guideline advice' in this study, such as consuming apple cider vinegar, also do not appear in other countries' evidence-based guidelines. Finally, limitations

of content analyses are recognised. For example, content analyses are inherently reductive in nature (Dixon-Woods et al., 2016), whilst issues of validity and subjectivity during sample selection and/or analysis have been highlighted (Kondracki et al., 2002). Furthermore, it has been suggested that it may be inappropriate to generalise conclusions drawn from content analyses (Kondracki et al., 2002).

It is also acknowledged that other media platforms, such as Instagram, Reddit, and TikTok, may be used by the public to access health and/or dietary information (Boulos, Giustini, & Wheeler, 2016; Money et al., 2020; Minadeo & Pope, 2022). Therefore, future research could look at the accuracy and quality of dietary information for gout provided on these platforms.

3.4.1. Conclusion

In conclusion, it is evident that YouTube® videos on diet and gout often fail to provide important information contained in evidence-based dietary guidelines targeted at the UK population. Instead, videos frequently include non-evidence-based information. A substantial number of videos also contained the recommendation to consume cherries, despite the need for more robust experimental research on the effects of cherries on gout. Dietary information provided by these videos is also commonly poor in terms of educational quality, reliability, understandability, and actionability. These factors may result in poor self-management of gout by patients who use YouTube® videos as a source of information. Health care teams should therefore signpost appropriate and evidence-based sources of information to their patients. To aid this, more high-quality, reliable, and comprehensive videos containing clear and consistent dietary guidance are required for gout patients in the UK. Specifically, health professionals should ensure that their own videos are not just evidence-based but are also high in educational quality and actionability.

4.0. Study 2. The acute effects of tart cherry juice on uric acid levels and biomarkers of CVD risk in healthy individuals: a randomised, controlled, crossover trial.

4.1. Introduction

Consistently high sUA concentration, known as hyperuricaemia, has been associated with elevated risk of several medical conditions including CVD, hypertension, and renal disease (Kuo et al., 2016). However, hyperuricaemia is most strongly associated with increased risk of gout (Terkeltaub et al., 2006). Although the definition of hyperuricemia varies between sources, sUA levels above 6 mg/dl (357 μmol/L) are proposed as an appropriate threshold, owing to the increased risk of developing these medical conditions at or above this concentration (Bardin & Richette, 2014). It is therefore vital that uric acid levels are kept below this limit.

Several dietary recommendations have been proposed for the prevention of hyperuricaemia (discussed in section 2.1.8.), including restricting the intake of purine-rich foods, consuming sufficient dairy, and remaining hydrated (Schlesinger, 2005). One dietary recommendation that has received considerable attention is the consumption of cherries (Collins et al., 2019). In the previous chapter of this thesis, this advice was found in 29% of YouTube® videos providing dietary recommendations for gout and these videos were found to have a high number of views and likes (see section 3.3.3.). Meanwhile, other research has reported that over 40% of gout sufferers consume cherries, cherry extract, or cherry juice for their condition (Singh et al., 2015; Zhang et al., 2012).

Cherries are particularly bountiful in phenolic compounds purported to exert urate-lowering effects (Chaovanalikit & Wrolstad, 2004a; Kelley et al., 2018; Kirakosyan et al., 2009). Studies have reported beneficial acute effects of cherries on urate metabolism in healthy individuals (Bell, Gaze, et al., 2014; Jacob et al., 2003). Jacob et al. (2003) reported that a single 280 g serving of sweet cherries reduced serum urate by 31 μmol/L at 5 hours post intake and increased UU excretion by 148 μmol/mmol creatinine at 3 hours post intake in healthy women. Bell, Gaze, et al. (2014) reported that 30 mL and 60 mL of tart

cherry concentrate lowered urate by 36% at 8 hours post-consumption and increased UU by 250% at 2 hours post-consumption in healthy adults (11 male and 1 female), with both doses being equally effective. However, the results of both studies need to be interpreted with caution, because neither contained a placebo control group and sUA has been reported to fall naturally during the day (Devgun & Dhillon, 1992; Sennels et al., 2012). Hillman and Uhranowsky (2021) observed significant reductions in sUA in the 24 hours following consumption of tart cherry in powdered capsule form, yet no improvement occurred when cherry was consumed in juice form. Although appropriate placebos were utilised, the cherry juice used in this study contained apple juice which has been previously shown to elevate sUA levels after ingestion (White et al., 2018). Consequently, this may have masked any beneficial effect of the tart cherry. Therefore, a RCT using 100% tart cherry concentrate and appropriate controls is required to verify the acute effect of tart cherry on sUA and UU excretion.

Hyperuricemia is associated with increased risk of vascular damage, hypertension, and CVD (Annemans et al., 2008; Canepa et al., 2017). Several mechanisms have been proposed to explain the detrimental effects of hyperuricaemia on risk of CVD, including the inhibition of NO synthesis (Zieman et al., 2005), the activation of uric acid transporters in vascular endothelial cells (Price, 2006) and increased oxidative stress and inflammation (Kanbay et al., 2013; Price, 2006). Cherry extract and a number of cherry polyphenols have been shown to improve markers of CVD risk in cell models. For example, reduced production of IL-1β and ROS, indicating attenuated inflammation and oxidative stress, has been demonstrated in cells stimulated with MSU crystals when also exposed to cherry polyphenols (Vírgen Gen et al., 2020). Inhibition of ACE, an enzyme linked to hypertension, has also been shown *in vitro* with tart cherry extract (Kirakosyan et al., 2018). Furthermore, decreased oxidative stress and increased endothelial NO synthase levels have been observed in T2D rats fed sweet cherries daily for 2 months (Van der Werf et al., 2018).

A number of human studies have also reported on the effect of cherry on various markers of CVD risk, including inflammatory markers. Studies in arthritic

populations have observed acute reductions in CRP concentration with tart cherry juice (Kuehl et al., 2012; Schumacher et al., 2013). Several short-term RCTs with healthy participants have also demonstrated acute reductions in inflammatory markers following consumption of both sweet and tart cherries and/or cherry products (Bell, Gaze, et al., 2014; Bell, Walshe, et al., 2014; Kelley et al., 2006, 2013). However, the absence of placebos or use of inappropriate controls in these studies again justifies the need for a placebo-controlled acute trial.

Phenolic compounds found in cherries are purported to improve endothelial function and BP (Wang et al., 1999), yet evidence from human trials is inconsistent. In two separate placebo-controlled crossover trials, one in men with early hypertension (Keane, George, et al., 2016) and the other in healthy middle-aged adults with moderately raised SBP (Keane, Haskell-Ramsay, et al., 2016), a single 60 mL dose of tart cherry concentrate was shown to significantly lower SBP over 3 hours post-consumption. Other vascular variables, including DBP, PWV and AIx, were not altered by the cherry concentrate in either study. Similarly, in a 12-week parallel RCT, the consumption of 68 mL of tart cherry concentrate daily resulted in a significant reduction in SBP, but not DBP, in healthy adults aged 65-80 years when compared to a black cherry flavoured Kool-Aid beverage (Chai et al., 2018). However, it is important to note that SBP increased in response to the placebo, potentially owing to the high fructose content of this drink. In contrast, Lynn et al. (2014) found that a 30 mL daily dose of tart cherry concentrate for 6 weeks had no effect on BP or arterial stiffness in healthy adults aged 30-50 years and Sinclair et al. (2022) also observed no significant improvements in BP in healthy adults following the consumption of 2 x 30 mL tart cherry concentrate doses daily for 20 days. These studies also had limitations, for example neither controlled the dietary intake of participants. Thus, it is currently unclear if a single 30 mL dose of tart cherry concentrate would elicit any acute improvements in endothelial function and/or BP in healthy individuals and so further investigation is warranted.

The aim of this crossover RCT was to investigate the acute effects of a single serving of tart cherry juice on sUA, UU, CRP, BP, and arterial stiffness, when compared to a neutral water control, accomplishing the third objective of this thesis. Findings from this study will provide evidence as to whether the consumption of tart cherry juice can reduce the risk of hyperuricaemia and CVD in an acute context and will highlight possible mechanisms through which it may reduce this risk.

4.2. Methodology

This study was reported following the guidelines provided in the CONSORT 2010 statement (Dwan et al., 2019). All laboratory work in this study, namely the analysis of drinks, the collection, processing, and analysis of blood samples, the processing and analysis of urine samples, anthropometric measurements, and measurements of blood pressure and arterial stiffness, was completed by the author of this thesis (KL).

4.2.1. Trial design

The study was a 2-arm, randomised, open-label, placebo-controlled, cross-over trial, performed on 13 healthy adults aged 18-85 years. To compare the acute effects of a single dose of tart cherry juice with a neutral control, participants consumed 250 mL of tart cherry juice (30 mL tart cherry concentrate and 220 mL water) or 250 mL of water on two separate occasions, separated by a wash-out period of at least 7 days. Blood, urine, and vascular measurements were collected at baseline and at multiple time-points over the 24 hours following consumption of each drink. Each participant was enrolled onto the study for approximately 2 weeks. An overview of the study design (which was undertaken on two occasions per participant) is given in Figure 4.

The study opened recruitment in July 2021 and closed at the end of February 2022. This study was approved by a Sheffield Hallam University (SHU) ethics committee (ER9199256) (Appendix 6). A protocol for monitoring and managing adverse events and a data management plan were produced for this project.

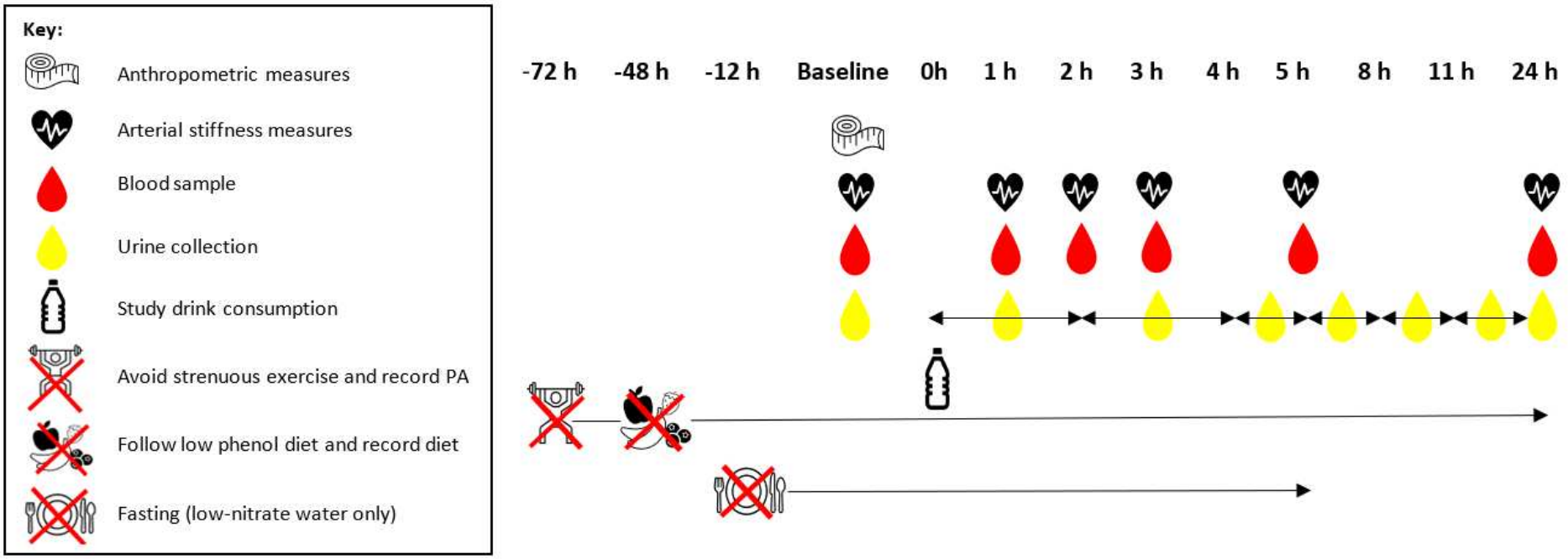

Figure 4. Study 2 protocol. PA; physical activity

4.2.2. Participants

Healthy, non-smoking, adult volunteers aged between 18 and 85 years were recruited through word-of-mouth. Individuals with a history of gout, T2D or type 1 diabetes (T1D), gastrointestinal disorders, CVD, and kidney disease were excluded from participating. Interested individuals were provided with a participant information sheet (PIS) containing further details of the study. Potential participants also received a verbal explanation of the study and were screened for inclusion and exclusion criteria through completion of a personal information sheet which contained questions on medical history and smoking status. Written informed consent was gained from all willing and eligible participants.

4.2.3. Settings and location

Measurements were made at SHU's Food and Nutrition Research Laboratories in Sheffield, United Kingdom.

4.2.4. Dietary interventions

During the active intervention arm of the study, participants consumed 250 mL of tart cherry juice, consisting of 30 mL Montmorency tart cherry 68 brix concentrate (CherryActive®, ActiveEdge™, Hanworth, UK) and 220 mL low-nitrate water (Buxton®, UK). During the control arm, participants consumed 250 mL of low-nitrate water (Buxton®, UK). Water was chosen as the control drink to avoid any intake of bioactive compounds, particularly polyphenols, during the control arm. A low-nitrate brand was selected to avoid any vascular effects of this drink (Hobbs et al., 2013). The two study arms were separated by a wash-out period of at least 7 days. The duration of the wash-out period was chosen based on the known pharmacokinetics of cherry polyphenols (Phillip et al., 2014; Keane, Bell, et al., 2016) and the likely transient nature of any effects on the outcome measures. The order of allocation was randomised; however, it was not possible to blind participants or researcher from this allocation.

Participants were instructed to follow a low-polyphenolic diet, including avoiding fruits, vegetables, wholegrains, and nuts, for 48 hours prior to baseline measurements. Participants were provided with a dietary advice sheet containing

meal recommendations (Appendix 7). The evening prior to the baseline measurements, participants were provided with a low-phenol spaghetti carbonara ready-meal (Sainsbury's PLC, UK), low-phenol dessert (Bonne Maman®, Somerset, UK), and low-nitrate water (Buxton®, UK) to consume. Participants attended the laboratory following an overnight fast of at least 10 hours, although low-nitrate water was permitted.

Participants remained fasted during the first 5 hours post-consumption of their drink; however, 500 mL low-nitrate water (Buxton®, UK) was provided during this time. Participants were advised to drink this when thirsty but to avoid consuming large volumes of this at a single time-point to minimise possible effects on vascular function (Callegaro et al., 2007). A low-phenol lunch consisting of sandwiches made from white bread and ham (Sainsbury's PLC, UK), ready salted crisps (Walkers, UK), and a plain Greek yoghurt (Tesco PLC, UK) were provided immediately following the 5-hour measurements. Participants were also provided with low-phenol snacks, a low-phenol macaroni cheese ready-meal (Tesco PLC, UK), and additional low-nitrate water (Buxton®, UK) to consume over the rest of the day. Participants returned to the laboratory following another overnight fast of at least 10 hours for their 24-hour measurements.

Participants were asked to record their dietary intake throughout the first arm of the study and were instructed to replicate this diet during the second arm.

Participants were also asked to avoid strenuous exercise from 72 hours before each test day until after their 24-hour measurements had been taken.

4.2.5. Tart cherry concentrate analysis

4.2.5.1. Total phenolic content

The total phenolic content of tart cherry concentrate (CherryActive®, ActiveEdge™, Hanworth, UK) was measured using the Folin Ciocalteu method of Singleton and Rossi (Singleton & Rossi, 1965). Samples of tart cherry concentrate from 3 separate bottles were diluted with di.H_20 in a ratio of 1:200 before analysis. Aqueous solutions of gallic acid standards were prepared over the range 0 to 100 mg/L. Each standard and sample (0.5 mL) were added to 2.5

mL of 10% Folin Ciocalteu reagent and vortex mixed for 10 seconds. All standards and samples were prepared in this way in duplicate. Between 30 and 480 seconds after mixing, 2 mL 7.5% sodium carbonate solution was added to each sample and standard solution, and these were vortex mixed for 10 seconds. Solutions were then incubated at 24 ˚C for 2 hours. The absorbance of each sample and standard was read at 765 nm (Jenway 7315 spectrophotometer, Bibby Scientific Ltd, Staffordshire, UK) against a di.H_2O blank. A standard curve was constructed by plotting the absorbance of each gallic acid standard against its concentration. The total phenol content of each tart cherry sample was calculated from the standard curve using linear regression. Values are expressed as mg of GAE per 30 mL serving and reported as the mean and standard deviation (SD) of the three samples.

4.2.5.2. Total anthocyanin content

The total anthocyanin content of 3 samples of tart cherry concentrate was determined in duplicate using the pH differential method (Lee et al., 2005). Two 1:20 dilutions of each tart cherry concentrate sample were made, one in 0.025 M potassium chloride (pH 1.0) and one in 0.4 M sodium acetate (pH 4.5). This was repeated to provide duplicate readings. After 20 minutes, the absorbance of each sample was read at 520 nm and 700 nm against a di.H_2O blank (Jenway 7315 spectrophotometer, Bibby Scientific Ltd, Staffordshire, UK). The following equation was used to calculate total anthocyanins:

Cyanidin-3-glucoside (cyd-3-glu) equivalents (mg/L) =

$$\frac{(A\ x\ molecular\ weight\ (MW)\ x\ dilution factor\ (DF)\ x\ 10^3)}{\varepsilon\ x\ l}$$

A = (A_{520nm} - A_{700nm}) pH 1.0 - (A_{520nm}-A_{700nm}) pH 4.5.

A = absorbance. Absorbance was calculated by subtracting absorption at 700 nm from absorption at 520 nm for each buffer to correct for haze. The absorption at pH 4.5 was then subtracted from the absorption at pH 1.0.

DF = dilution factor. A DF of 16.6 was used.

MW = molecular weight, 449.2 g/mol for cyd-3-glu.

$\boldsymbol{l}$ = pathlength in cm.

$\boldsymbol{\varepsilon}$ = 26 900, the molar extinction coefficient in L x mol^{-1} x cm^{-1} for cyd-3-glu.

$\mathbf{10^3}$ = factor for conversion from g to mg.

The mean and SD of the total anthocyanin content of the three concentrates was expressed as cyd-3-glu equivalents (mg/30 mL serving).

4.2.6. Outcomes

The primary outcome measure was between-treatment difference in the change in sUA levels from baseline to 24 hours post-drink. Secondary outcome measures were between-treatment differences in the change in serum inflammatory marker CRP from baseline to 5 hours post-consumption, and changes in UU excretion and vascular function (resting brachial and central BP and arterial stiffness) from baseline to 24 hours post-consumption. Non-efficacy outcomes included PA and dietary intake measures, for example the consumption of high-phenolic foods.

4.2.6.1. Anthropometric measurements

Anthropometric measures of height and mass were collected upon arrival in the laboratory at baseline and used to calculate BMI (mass (kg)/height $(m)^2$). Height without shoes was measured to the nearest 0.1 cm using a stadiometer (Seca, Hamburg, Germany). Body mass was measured in light clothing to the nearest 0.1 kg using calibrated weighing scales (Seca 899, Hamburg, Germany).

4.2.6.2. Arterial stiffness and blood pressure (BP)

A Vicorder® device (SMT Medical, Germany) was used to measure brachial and central BP, carotid-femoral PWV, and AIx. The Vicorder® has demonstrated high repeatability when used to measure aortic PWV (within-measure coefficient of variation 2.8%) and these measurements were on average highly correlated with those produced by the commonly used SphygmoCor device (between-device mean difference 0.31 ± 1.54 m s^{-1}, $p < 0.001$) (Hickson et al., 2009). Participants were familiarised with the Vicorder® device prior to their first session to reduce anxiety and the effect that this may have on BP and other vascular measures (Franklin et al., 2013). Familiarisation consisted of practice measurements with the carotid (neck), arm, and femoral (leg) cuffs, helping participants to become

accustomed to the sensation of each of these cuffs when inflated. BP, PWV, and AIx were measured at baseline and 1, 2, 3, 5, and 24 hours post-drink consumption. Following the Vicorder® instructions, brachial DBP values were also used as central DBP values. Three of each measurement were taken at each time-point, with 1-minute intervals between replicates. Participants were instructed to rest in a supine position for 15 minutes prior to and during the measurements.

4.2.6.3. Collection and processing of blood samples

Venous blood samples were collected at baseline, 1, and 2 hours into 15 mL serum separator tubes (SST). Finger prick blood samples were collected into 600 µL monovette SSTs at 3, 5, and 24 hours after consumption of the test drinks. Blood samples were inverted at least 5 times and allowed to clot for 20 minutes. Samples were then centrifuged at 2500 x g for 15 minutes at 18 °C to separate the serum (Hermle Z 36 HK, HERMLE Labortechnik GmbH, Germany), which was then stored at -80^{o}C until analysis.

4.2.6.3.1. Analysis of CRP and uric acid in serum samples

CRP concentration was measured in serum samples collected at baseline, 2, and 5 hours using a CRP quantikine ELISA kit (R&D systems, Abingdon, UK). The intra-assay % CV for CRP was 5.5%. Concentrations of sUA were assessed from serum samples collected at baseline, 1, 2, 3, 5, and 24 hours using a uric acid (Amplex® Red, Invitrogen™, UK) assay kit. The intra-assay % CV for serum urate was 3.9%. Both analytes were measured using a microplate reader (BioTek synergy HT, Winooski, USA).

4.2.6.4. Urine samples

Spot urine samples were collected at baseline and at 24 hours post-drink consumption. Urine was also collected between 0-2, 2-4, 4-5, 5-8, 8-11, and 11-24 hours. The total volumes of urine collected within each of these time periods were noted. Samples were centrifuged twice at 2800 x g for 15 minutes to remove unwanted cells (Hermle Z 36 HK, HERMLE Labortechnik GmbH, Germany) and material and were stored at -80 °C until analysis. Urine samples collected at baseline, 0-2, 2-4, 4-5, and at 24 hours were analysed for UU (Amplex® Red,

Invitrogen™, UK) and creatinine (ELISA; R&D systems, Abingdon, UK) concentrations, using a microplate reader (BioTek synergy HT, Winooski, USA). The intra-assay % CV was 2.0% for UU and 2.1% for urinary creatinine. UU (µmol) was corrected for creatinine concentration (µMol) to provide UU to urinary creatinine excretion ratios. Samples collected between 5-8, 8-11, and 11-24 hours were kept in storage for future polyphenolic profiling.

4.2.6.5. Assessment of diet and physical activity (PA) levels

From 48 hours prior to baseline measurements until their 24-hour post-consumption measurements, participants completed a food diary using estimated household measures. Participants also recorded PA in a diary from 72 hours prior to their two main laboratory sessions until their 24-hour post-consumption measurements. These diaries were assessed for compliance to diet and PA guidance.

4.2.7. Sample size

Sample size was calculated using data from White et al. (2018), using the primary outcome of change in sUA level. It was estimated that cherry juice would decrease sUA by 15 µmol/L (Jacob et al., 2003). Thirteen participants were needed to detect this change with 80% power at a significance level of 0.05.

4.2.8. Randomisation

The order of drink allocation for participants was generated by block randomisation (block size 4). Allocation sequence was generated using a computer random number generator by an investigator not involved in data collection. This investigator also assigned participants to their sequence of interventions. Due to the use of a water control, it was not possible to conceal this sequence from participants or the researcher collecting data. Participants were enrolled by the study investigator involved in data collection.

4.2.9. Data management

The collection and storage of data adhered to the standard requirements of the EU General Data Protection Regulation 2016/679. Data was entered onto electronic spreadsheets stored on a secure University server. All data was treated

confidentially and pseudo-anonymised. Hard copies of data and documents were kept in a locked and secure cabinet for the duration of the study. Following completion of the study, data was transferred to Sheffield Hallam University's Research Data Archive (SHURDA), where it will be kept for 10 years. Hard copies will be disposed of confidentially and electronic data deleted after this period.

4.2.10. Statistical methods

The primary outcome of this study was change in serum urate concentration. Change in UU, CRP, central and brachial BP, AIx, and PWV were considered secondary end points. To account for any interindividual differences at baseline between treatment arms, percentage (%) change from baseline was calculated at each timepoint for each variable. The effect of treatment (tart cherry versus water control) on all outcome variables was analysed using two-way repeated measures analyses of variance (ANOVA) with Bonferroni post-hoc tests. Effect sizes for ANOVA were reported using Partial Eta-Squared (ηp^2). Effects were classified as small (0.01 – 0.059), moderate (0.06-0.137), and large (≥ 0.138) (Pallant, 2010). Further exploratory analyses of any between-sex differences on the effect of cherry consumption on serum and urinary urate were undertaken by adding gender as a between-subjects factor in two-way repeated measures ANOVAs. Baseline data is presented as mean and SD or median and IQR. Results are reported as mean % and SD for continuous data. All analyses were conducted using IBM SPSS Statistics v24. The critical value for statistical significance was set at $p < 0.05$.

4.3. Results

4.3.1. Baseline participant characteristics

Thirteen participants were enrolled onto the study, however one participant dropped out following completion of the control treatment arm. Due to time restraints, a final sample size of 12 participants was used for this study. Of the 12 participants who completed the study, 7 were male (58%), average age was 41.1 (± 11.1) years, and average BMI was 26.4 (± 4.3) kg/m^2. Baseline clinical data for participants prior to each arm of the study are displayed in Table 9. This data did not differ significantly between treatment arms ($p > 0.05$ for all).

Table 9. Baseline clinical data of participants prior to the provision of 250 mL tart cherry juice and 250 mL water and normative values for comparison. Data are presented as mean (± SD) or median (IQR).

	Tart cherry juice	Water (control)	Normative value/s
Brachial systolic blood pressure, mmHg, mean (SD)	126.2 (11.0)	123.6 (8.4)	< 130 mmHg [a]
Brachial diastolic blood pressure, mmHg, mean (SD)	65.8 (6.1)	64.9 (6.4)	< 80 mmHg [a]
Central systolic blood pressure, mmHg, mean (SD)	120.3 (11.8)	118.7 (8.6)	Na [b]
Pulse wave velocity, m/s, median (IQR)	8.2 (2.6)	7.3 (2.0)	< 10 m/s [c]
Augmentation index, %, mean (SD)[1]	14.8 (7.3)	18.2 (9.8)	< 25 – 48 [d]
Serum urate, µmol/L, mean (SD)	155.4 (59.2)	168.3 (57.1)	< 357 µmol/l [e]
Urinary urate:urinary creatinine, mmol/mmol, mean (SD)	0.4 (0.1)	0.5 (0.2)	≤ 0.5 [f]
C-reactive protein, mg/L, median (IQR)	0.4 (0.7)	0.6 (1.8)	< 1.2 mg/L [g]

SD, standard deviation; IQR, interquartile range; na, not available.
[1] *n* = 10 for both treatment arms
[a] Williams et al. (2004)
[b] a normative value for central systolic blood pressure is not available.
[c] Van Bortel et al. (2012)
[d] a normative value for augmentation index is not currently available, but threshold values between 24 and 48% have been predicted for an increased risk of CVD (Woodiwiss & Norton, 2012).
[e] Bardin & Richette (2014)
[f] NHS (2014)
[g] Ridker (2003)

4.3.2. Tart cherry concentrate analysis

The average total phenolic content of the three samples of tart cherry concentrate was 407.6 (± 5.4) mg GAE per 30 mL serving. Anthocyanin content was 3.8 (± 0.3) mg cyd-3-gluc/30 mL.

4.3.3. Dietary adherence and avoidance of high-intensity physical activity (PA)

Evaluation of participants' diet diaries indicated that participants complied with the low-phenol dietary guidance in the two days prior to their laboratory sessions. Assessment of PA diaries showed that participants also adhered to instructions to avoid high-intensity PA in the three days prior to their laboratory sessions.

4.3.4. Serum urate

There was a large-sized main effect of time on serum urate following consumption of the drinks ($F_{5,55}$ = 3.529, p = 0.008, ηp^2 = 0.243). On average, there was a 10.4% reduction in serum urate between 1 hour and 5 hours post-consumption (p = 0.034) and an 8.5% increase from 5 hours to 24 hours post-consumption (p = 0.022) (Figure 5 and Table 10). However, no drink type ($F_{1,11}$ = 2.061, p = 0.179, ηp^2 = 0.158) or drink by time interaction ($F_{5,55}$ = 1.222, p = 0.311, ηp^2 = 0.100) effects were found. Furthermore, there were no between-sex differences on the effect of cherry consumption on serum urate ($F_{5,55}$ = 1.151, p = 0.347, ηp^2 = 0.103).

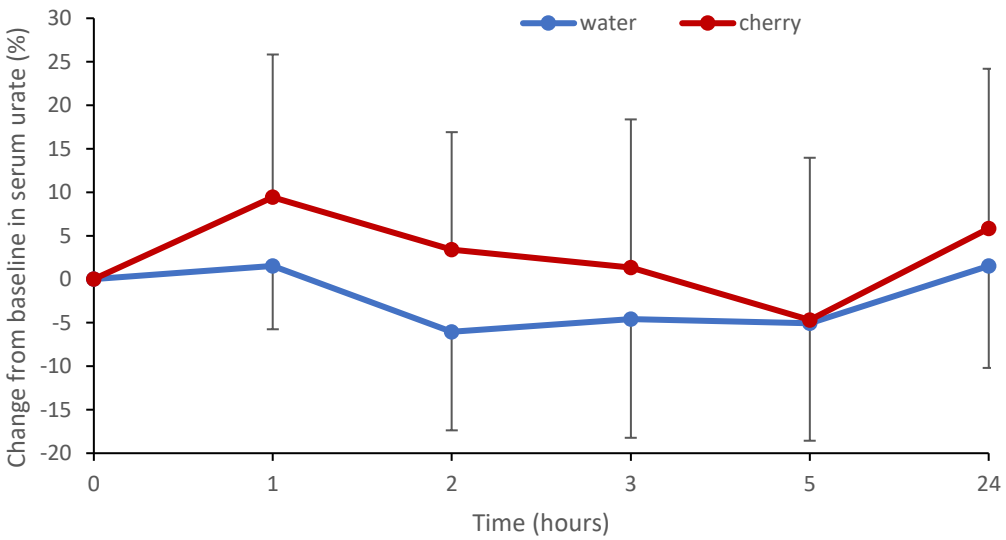

Figure 5. Effects of water and cherry juice on percentage change in serum urate concentration from baseline values. Data are presented as mean (± SD).

Table 10. Percentage change from baseline of clinical measurements following 250 mL tart cherry juice and 250 mL water. Data are presented as mean (± SD).

		Time (Hours)				
Clinical measurement	**Study drink**	**1**	**2**	**3**	**5**	**24**
Brachial systolic blood pressure, % change from baseline, mean (SD) *	Cherry	-0.1 (6.3)	0.0 (3.9)	1.0 (5.7)	1.2 (5.2) [a]	-3.3 (6.1) [a]
	Water (control)	3.4 (7.7)	7.1 (11.1)	4.8 (4.9)	6.6 (8.6) [a]	-0.5 (6.6) [a]
Brachial diastolic blood pressure, % change from baseline, mean (SD) *	Cherry	1.8 (5.2)	2.2 (5.6) [a]	3.0 (6.5) [b]	1.3 (7.4)	-1.8 (7.1) [ab]
	Water (control)	3.2 (4.0)	5.3 (7.0) [a]	5.5 (5.9) [b]	5.7 (10.3)	-1.5 (6.6) [ab]
Central systolic blood pressure, % change from baseline, mean (SD) *	Cherry	0.1 (4.3)	-0.1 (2.8)	0.0 (4.7)	-0.3 (3.9) [a]	-2.4 (4.5) [a]
	Water (control)	2.1 (7.0)	5.3 (9.7)	3.5 (5.3)	4.7 (8.5) [a]	-1.1 (5.5) [a]
Pulse wave velocity, % change from baseline, mean (SD)	Cherry	-6.4 (16.7)	-5.2 (11.7)	-0.3 (14.1)	-3.9 (13.1)	-6.9 (17.2)
	Water (control)	3.5 (10.6)	0.7 (7.9)	-1.2 (10.0)	3.8 (20.3)	-0.4 (12.8)
Augmentation index, % change from baseline, mean (SD)	Cherry	3.7 (26.6)	-2.4 (15.6)	-9.9 (24.7)	-4.3 (25.9)	29.1 (77.8)
	Water (control)	-13.8 (23.9)	-16.7 (30.6)	-18.7 (38.4)	-18.3 (34.3)	-2.5 (22.3)
Serum urate, % change from baseline, mean (SD) *	Cherry	9.4 (16.4) [a]	3.4 (13.5)	1.3 (17.0)	-4.7 (18.6) [ab]	5.8 (18.4) [b]
	Water (control)	1.5 (7.3) [a]	-6.0 (11.3)	-4.6 (13.7)	-5.1 (13.5) [ab]	1.5 (11.7) [b]
C-reactive protein, % change from baseline, mean (SD) *	Cherry	-	0.6 (9.0) [a]	-	-8.8 (14.7) [a]	-
	Water (control)	-	1.5 (15.3) [a]	-	-3.8 (12.0) [a]	-
			0-2	**2-4**	**4-5**	**24**
Urinary urate:urinary creatinine, % change from baseline, mean (SD) *	Cherry		38.9 (23.0)	41.9 (19.3)	16.8 (36.4)	0.0 (26.6)
	Water (control)		25.5 (29.3)	40.2 (53.0)	32.3 (51.4)	6.0 (31.5)

SD, standard deviation.

* Significant main effect of time ($p < 0.05$); corresponding superscript letters display time-points that are significantly different from each other (Nb. There were no significant drink or drink by time effects).

4.3.5. Urinary urate (UU) (mmol/mmol creatinine)

As shown in Figure 6 and Table 10, creatinine-adjusted UU fluctuated significantly over time and this main effect was large ($F_{4,44}$ = 11.656, p < 0.001, ηp^2 = 0.514). The greatest increase in UU above baseline (0 hours) was observed at 2-4 hours (41.0 %; p = 0.001), followed by 0-2 hours (32.2 %; p < 0.001). UU was significantly lower at 24 hours than at 0-2 hours (p < 0.001) and 2-4 hours (p = 0.005). There were no statistically significant main effects of drink type ($F_{1,11}$ = 0.015, p = 0.906, ηp^2 = 0.001) or drink by time interaction ($F_{4,44}$ = 1.084, p = 0.358, ηp^2 = 0.090). There were also no between-sex differences on the effect of cherry consumption on UU ($F_{4,44}$ = 1.397, p = 0.263, ηp^2 = 0.123).

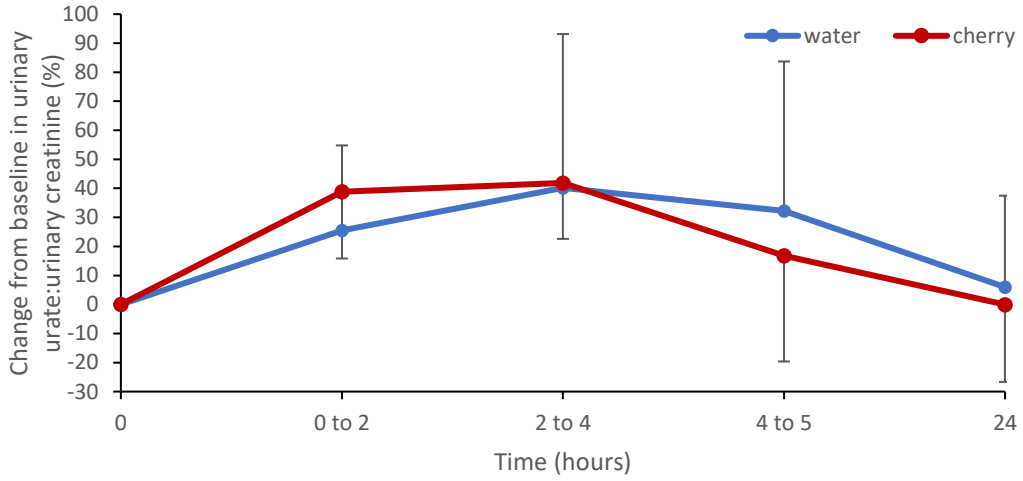

Figure 6. Effects of water and cherry juice on percentage change in urinary urate (UU) to urinary creatinine ratio from baseline values. Data are presented as mean (± SD).

4.3.6. C-reactive protein (CRP)

There was a large-sized main effect of time for percentage change in CRP from baseline ($F_{2,22}$ = 4.488, p = 0.023, ηp^2 = 0.290), with a statistically significant 7.4 % reduction observed between 2 hours and 5 hours (p = 0.020) (Figure 7 and Table 10). Despite this, CRP at 5 hours was not significantly different from baseline (p = 0.202) and no main effect of drink type ($F_{1,11}$ = 0.434, p = 0.524, ηp^2 = 0.038) or drink by time interaction ($F_{2,22}$ = 0.644, p = 0.525, ηp^2 = 0.055) were detected.

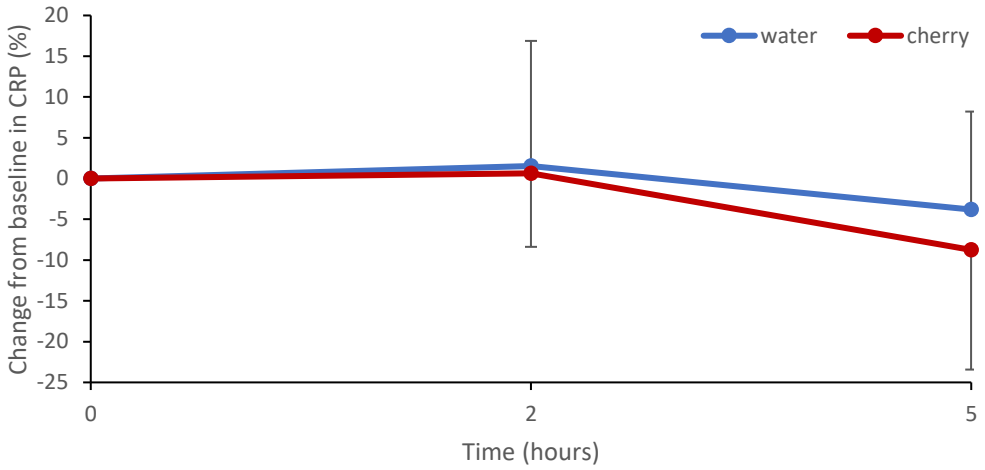

Figure 7. Effects of water and cherry juice on percentage change in c-reactive protein (CRP) concentration from baseline values. Data are presented as mean (± SD).

4.3.7. Blood pressure (BP)

4.3.7.1. Brachial systolic BP (SBP)

A large main effect of time ($F_{5,55}$ = 5.360, p < 0.001, ηp^2 = 0.328) was detected for brachial SBP (Figure 8a and Table 10), with an average reduction of 4.6 % between 5 hours and 24 hours on (p < 0.001). There was a trend towards a statistically significant medium main effect of drink ($F_{1,11}$ = 3.654, p = 0.082, ηp^2 = 0.249); estimated marginal mean for brachial SBP was 3.0 % (95% CI -0.5, 6.5) greater in the water arm of the trial than in the tart cherry juice arm. However, no drink by time interaction effect ($F_{5,55}$ = 1.459, p = 0.218, ηp^2 = 0.117) was observed.

4.3.7.2. Brachial (and central) diastolic BP (DBP)

Brachial DBP values were also used as central DBP values, in accordance with the Vicorder® instructions. There was a large significant main effect of time ($F_{5,55}$ = 5.908, p < 0.001, ηp^2 = 0.349) for DBP (Figure 8b and Table 10). On average, DBP fell by 5.4 % between 2 hours and 24 hours (p = 0.027) and by 5.9 % between 3 hours and 24 hours (p = 0.001). There was no drink by time interaction effect ($F_{5,55}$ = 0.718, p = 0.612, ηp^2 = 0.061) or main effect of drink type ($F_{1,11}$ = 1.782, p = 0.209, ηp^2 = 0.139).

4.3.7.3. Central systolic BP (SBP)

A large main effect of time ($F_{5,55}$ = 3.403, p = 0.009, ηp^2 = 0.236) was detected for central SBP, with a 4.0 % reduction in percentage change observed between 5 hours and 24 hours (p = 0.014) (Figure 8c and Table 10). There was no drink by time interaction effect ($F_{5,55}$ = 1.866, p = 0.154, ηp^2 = 0.145) or main effect of drink type ($F_{1,11}$ = 3.234, p = 0.100, ηp^2 = 0.227).

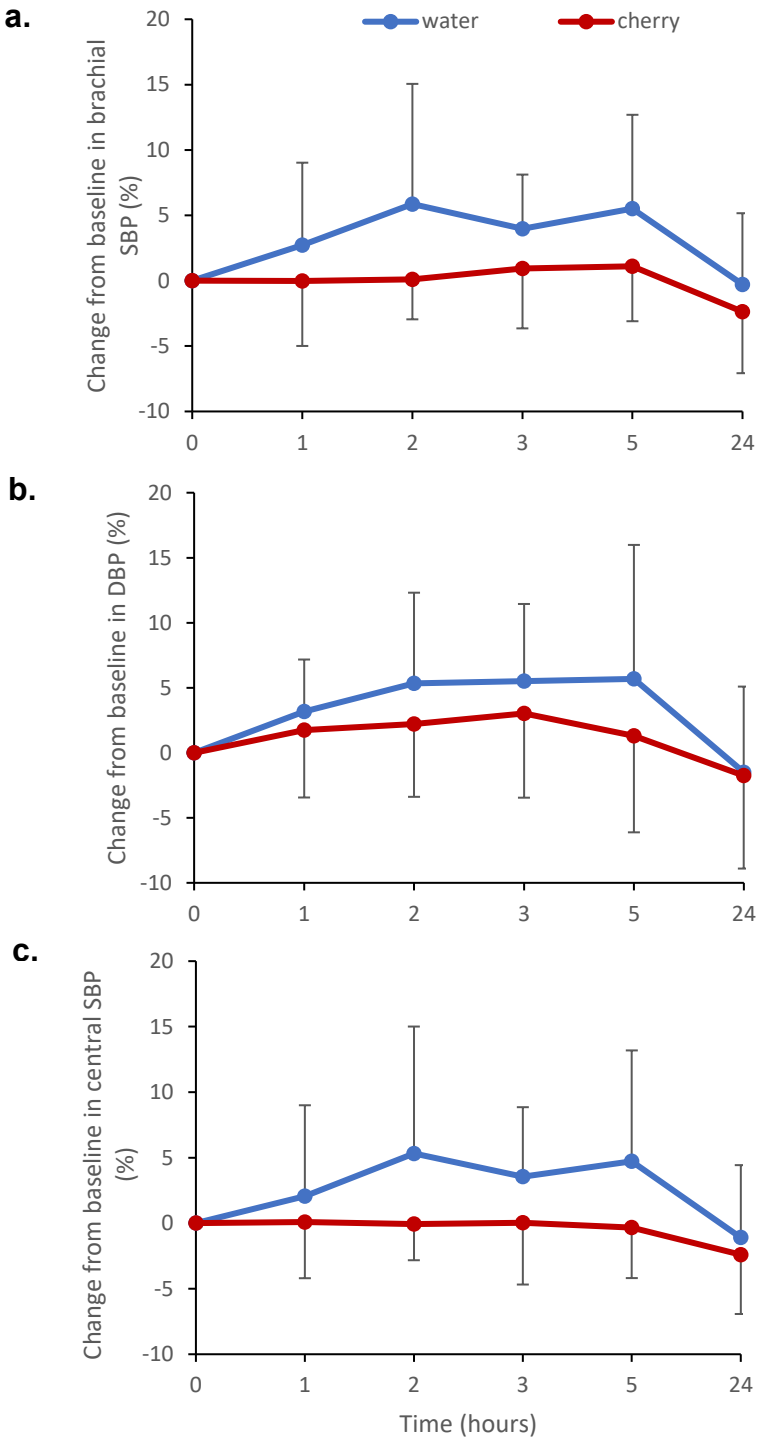

Figure 8. Effects of water and cherry juice on percentage change from baseline values in a) brachial systolic blood pressure (SBP), b) brachial and central diastolic blood pressure (DBP), and c) central systolic blood pressure (SBP). Data are presented as mean (± SD).

4.3.8. Arterial stiffness

4.3.8.1. Pulse wave velocity (PWV)

As shown in Figure 9 and Table 10, carotid-femoral PWV fluctuated over the measurement period with both drinks. However, these fluctuations were not found to be statistically significant (time: $F_{5,50} = 0.493$, $p = 0.667$, $\eta p^2 = 0.047$) and no main effects of drink type ($F_{1,10} = 1.948$, $p = 0.193$, $\eta p^2 = 0.163$) or drink by time interaction ($F_{5,50} = 1.257$, $p = 0.297$, $\eta p^2 = 0.112$) were detected for PWV.

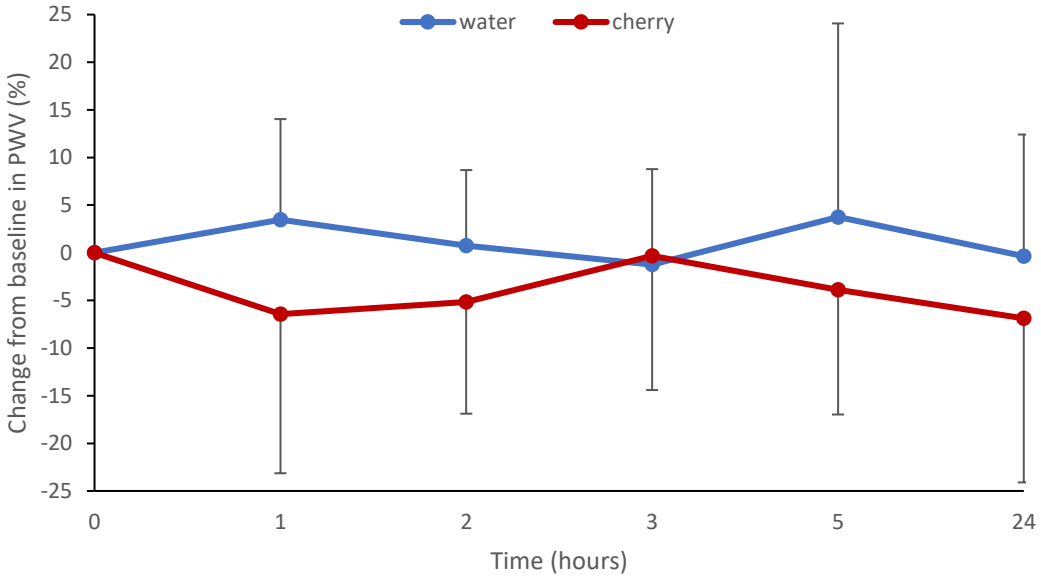

Figure 9. Effects of water and cherry juice on percentage change in pulse wave velocity (PWV) from baseline values. Data are presented as mean (± SD).

4.3.8.2. Augmentation Index (AIx)

As a result of equipment failure, AIx was measured in $n = 10$ participants only. As with PWV, there were no main effects of time ($F_{5,45} = 1.819$, $p = 0.204$, $\eta p^2 = 0.168$), drink type ($F_{1,9} = 2.688$, $p = 0.136$, $\eta p^2 = 0.230$), or drink by time interaction ($F_{5,45} = 1.085$, $p = 0.344$, $\eta p^2 = 0.108$) (Figure 10 and Table 10).

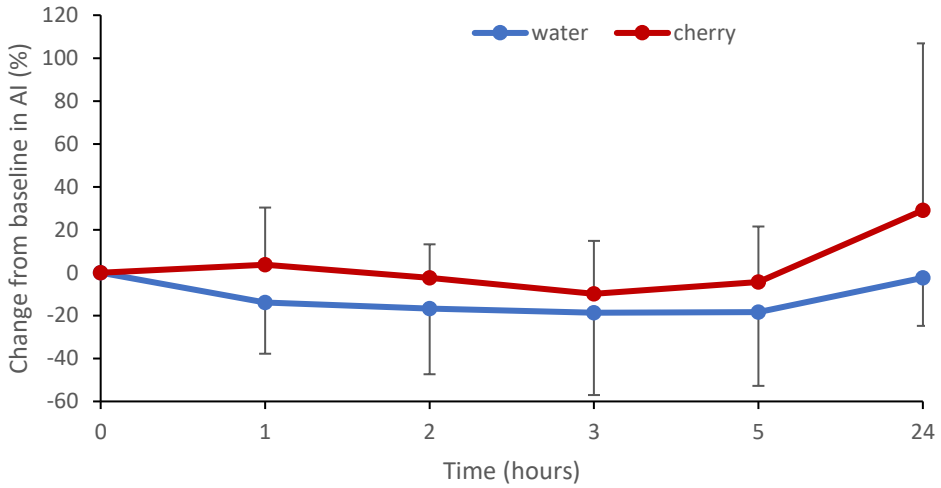

Figure 10. Effects of water and cherry juice on percentage change in augmentation index (AI) from baseline values. Data are presented as mean (± SD).

4.4. Discussion

The present study aimed to investigate the acute effects of a single serving of tart cherry juice on sUA, UU, CRP, BP, and arterial stiffness in healthy adults, when compared to a neutral water control. Tart cherry juice did not appear to influence any of these measurements, but statistically significant fluctuations in serum urate, UU, CRP, brachial and central SBP, and brachial and central DBP were observed over the 24-hour measurement period.

In this study, tart cherry juice had no effect on serum or UU concentrations in comparison to a water control drink. This finding contrasts with the conclusions of previous acute studies by Jacob et al. (2003) and Bell, Gaze, et al. (2014) who reported that sweet and tart cherries altered both sUA and UU over a similar period of time post-consumption. A possible explanation for this discrepancy is that neither of these two studies contained a control group and so they may have simply been reporting diurnal variations in urate. Indeed, in the present study there was evidence of statistically significant diurnal variation in urate over the 24-hour measurement period; UU was highest at 2-4 hours post-consumption and sUA peaked in the morning and then fell throughout the day. In line with this finding, a 24-hour diurnal rhythm in serum urate has been previously

demonstrated, with the highest concentration observed in the early hours of the morning before falling during the day (Sennels et al., 2012). This highlights the importance of studies including an appropriate control group when evaluating changes in urate.

Our findings build on the work of Hillman and Uhranowsky (2021) who failed to observe a significant treatment effect of a tart cherry juice blend on sUA when compared to a placebo drink. It is important to note however, that the juice blend they used contained apple juice which has been shown to elevate sUA levels (White et al., 2018). Target sUA levels of below 357 μmol/l are proposed to reduce the risk of developing gout (Bardin & Richette, 2014; Desideri et al., 2014). In both the present study and that of Hillman and Uhranowsky (2021), mean baseline serum urate concentrations of participants were below 357 μmol/L. Whilst tart cherry juice may not be beneficial to normouricaemic individuals, it could be effective in those with raised urate levels, such as patients with uncontrolled hyperuricaemia and gout. Observational and pilot research involving gout patients indicates that this may be the case (Schlesinger et al., 2012; Singh, Willig, et al., 2020; Zhang, Neogi, et al., 2012), however greater clinical evidence is needed to confirm these findings.

The acute phase protein CRP is a biomarker of whole-body inflammation (Del Giudice & Gangestad, 2018). Processed tart cherry products, whole tart cherry extracts, and anthocyanins found in tart cherries, namely cyanidin-3-glucosylrutinoside and cyanidin-3-rutinoside, have been demonstrated to exert anti-inflammatory effects *in vitro* and so cherry consumption could be expected to reduce the serum concentration of CRP (Ou et al., 2012; Seeram et al., 2001; Wang et al., 1999). Nevertheless, in the present study, a single serving of tart cherry juice did not have any significant effect on CRP, although reductions were observed between 2 and 5 hours after the consumption of both tart cherry juice and water. This finding is consistent with the results of a 6-week tart cherry juice supplementation study of 47 healthy adults (Lynn et al., 2014). In both studies, low baseline CRP concentrations (< 1.2 mg/L) indicate that participants had little underlying inflammation and were at low risk of CVD (Ridker, 2003).

In contrast, significant reductions in serum CRP concentration have been observed across 5 hours in healthy young adults following the consumption of 30 mL and 60 mL tart cherry juice (Bell, Gaze, et al., 2014) and after 14 and 28 days of sweet cherry supplementation in healthy middle-aged men and women (Kelley et al., 2006, 2013). However, these studies lacked a control group and so other confounding factors may have contributed to the observed reductions. Additionally, participants in these studies appeared to have some underlying inflammation, as average baseline CRP concentrations were all > 2 mg/L (Nordestgaard & Zacho, 2009). This was particularly surprising in the study of Bell, Gaze, et al. (2014) given that participants were reported to be healthy with a mean age of 26 years, so would be expected to have a CRP within the normal range.

Cherries have also been shown to attenuate the rise in CRP in healthy individuals following exercise-induced muscle damage (Bell, Walshe, et al., 2014; 2015; 2016; Dimitriou et al., 2015; Howatson et al., 2009; Levers et al., 2016). Collectively, these studies indicate that significant reductions in CRP may only be induced by the consumption of cherries when CRP levels are raised. However, a pilot study of 10 overweight and obese individuals with elevated CRP concentrations did not observe a significant reduction in CRP after consuming tart cherry juice daily for 4 weeks (Martin et al., 2018). Therefore, further well-controlled studies involving a greater number of participants with conditions associated with inflammation, such as obesity, gout, and CVD, are needed to clarify the effect of cherry consumption on inflammation.

We also observed no effect of tart cherry juice on brachial or central BP in healthy individuals. Previous findings on the effects of cherries or cherry products on BP are inconsistent but this may be explained by differences in study design. Neither twice-daily consumption of tart cherry juice (30 mL tart cherry concentrate and 100 mL water) for 20 days nor daily tart cherry juice consumption (30 ml of cherry concentrate diluted with 220 mL water) for 6 weeks were found to reduce BP in apparently healthy young and middle-aged adults (Desai, Bottoms, & Roberts, 2018; Lynn et al., 2014). Similarly, the consumption of 30 mL tart cherry

concentrate twice daily for 12 weeks had no effect on BP in middle-aged adults with ≥1 risk factor for T2D (Kimble et al., 2021) and twice-daily consumption of 240 mL tart cherry juice for the same period of time was also not found to improve BP in adults with metabolic syndrome (Johnson et al., 2020).

In contrast, significant reductions in SBP have been observed in healthy adults and men with early hypertension after a single 60 mL dose of tart cherry concentrate (Keane, George, et al., 2016; Keane, Haskell-Ramsay, et al., 2016), in adults with metabolic syndrome with a single 30 mL serving of tart cherry concentrate diluted with 100 mL of water (Desai et al., 2019), in older adults following 12 weeks of 480 mL daily tart cherry juice supplementation (Chai et al., 2018), and in older adults with mild-to-moderate dementia after consuming 200 mL of sweet cherry juice daily for 12 weeks (Kent et al., 2017). In these latter five studies, average baseline SBP of participants was elevated at >130 mmHg, whereas average SBP values were considered normotensive in the present study and that of Lynn et al. (2014), Desai, Bottoms, and Roberts (2018), and Kimble et al. (2021). As with urate and CRP, reductions in BP may only be observed in those with elevated baseline values; BP may not be responsive to cherry juice when it is within a healthy range at baseline. Indeed, baseline BP has been highlighted as an important determinant of effect in a review of potential factors influencing the effects of anthocyanins on the regulation of BP (Vendrame & Klimis-Zacas, 2019).

Despite this, in a pilot study of healthy adults, acute reductions in both SBP and DBP were reported in the 6 hours following consumption of a single 300 mL dose of sweet cherry juice (Kent et al., 2016). However, when provided as 3 x 100 mL servings at 0, 1 and 2 hours, the cherry juice did not result in significant BP reductions. This indicates that the acute effects of cherry juice on BP may also be dose-dependent, and this is supported by the observation from a cross-sectional study in 1898 women aged 18-75 years that a higher anthocyanin intake is associated with lower central BP (Jennings et al., 2012). Three of the studies reporting significant BP improvements with tart cherry juice provided participants with larger volumes of tart cherry concentrate than the present study (Chai et al.,

2018; Keane, George, et al., 2016; Keane, Haskell-Ramsay, et al., 2016). The total anthocyanin content of our tart cherry juice was found to be low and so may have contributed to the absence of improvements in the present study. However, as 30 mL is the manufacturer's recommended serving size for tart cherry concentrate, it may more closely reflect average consumer intake. Nevertheless, future studies of healthy populations should consider including larger doses of tart cherry concentrate to investigate effects on vascular health and the feasibility of consuming larger doses.

The intake of anthocyanins has also been associated with reduced arterial stiffness in a cross-sectional study of women aged 18-75 years (Jennings et al., 2012). As such, cherries, which are considered an anthocyanin-abundant fruit, might be expected to benefit arterial health (Bell & Gochenaur, 2006). However, no significant differences in carotid-femoral PWV or AIx, both indicators of arterial stiffness, were observed between the tart cherry juice and water control across the 24-hour measurement period of the present study. These findings agree with longer term supplementation studies in healthy normotensive participants (Kimble et al., 2021; Lynn et al., 2014). PWV and AIx measures in the current study were within expected values for healthy populations and so it could be argued that the use of healthy participants is a limiting factor here (Koivistoinen et al., 2007; Mattace-Raso et al., 2010; Mitchell et al., 2004).

However, studies involving patients with impaired vascular health have also reported an absence of improvement in arterial stiffness measures with cherry juice (Desai et al., 2019, 2021; Johnson et al., 2020; Keane, George, et al., 2016; Kimble et al., 2021). It is plausible that the previously reported association between total anthocyanin intake and arterial stiffness was confounded by other healthy lifestyle factors because of the observational nature of this study (Jennings et al., 2012). Alternatively, this association may arise from synergistic effects of different anthocyanin-containing foods consumed as part of the diet, rather than from specific foods consumed in isolation (Vendrame & Klimis-Zacas, 2019).

This study has several strengths. There is evidence to suggest that dietary nitrate may improve BP and endothelial function and so the use of low-nitrate water throughout the study helped to avoid any vascular effects of this drink (Hobbs et al., 2013). Other strengths include the avoidance of food by participants during the 5 hours following the consumption of study drinks, the provision of low-polyphenolic food prior to and during the 24-hour measurement period, and the high participant adherence to a low-polyphenolic diet throughout the study. These all helped minimise the influence of external dietary factors, particularly polyphenols, on measurements.

However, this study also had several limitations. Due to time restraints and the withdrawal of one participant part-way through the study, we did not quite reach the recruitment target of 13 participants calculated to identify change in serum urate with 80% power. Thus, the power to detect this change was reduced slightly. As a result of equipment failure, it was not possible to collect consistent AIx measurements for two participants and so these individuals were excluded from this analysis. Limited resources also meant that CRP was only measured at three time-points. It is possible that measurement of CRP more frequently and over a longer time period may have revealed a treatment effect. Nevertheless, as acute reductions in CRP have previously been reported in the first 5 hours after tart cherry juice consumption and there were no differences between drinks during this time in the present study, this is unlikely to have changed our conclusion (Bell, Gaze, et al., 2014). Finally, only healthy participants were used in the present study and any benefits of tart cherry juice may be more apparent in individuals with raised urate and risk markers for CVD.

4.4.1. Conclusion

To conclude, the consumption of a single serving of tart cherry juice did not alter uric acid, CRP, or markers of vascular function in healthy adults. Statistically significant changes in BP, markers of urate metabolism, and inflammation were observed over the 24-hour measurement period. These diurnal fluctuations must be considered when interpreting the results of previous uncontrolled studies that reported beneficial effects of acute intakes of tart cherry juice or sweet cherries

on urate and CRP. Additional placebo-controlled studies on the acute effects of tart cherry on urate metabolism and inflammation are needed in individuals with raised inflammatory and hyperuricaemia risk markers. Given that hyperuricaemia is strongly associated with an increased risk of gout, these effects also need exploring in individuals with diagnosed gout.

5.0. Study 3. The effect of tart cherry juice on risk of gout attacks: a randomized controlled trial

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5.1. Introduction

Gout is a debilitating and common type of inflammatory arthritis (Hui et al., 2017). The proportion of people afflicted with gout in the UK is substantial; approximately 1.9 million adults were affected in 2012 (Kuo, Grainge, Mallen, et al., 2015). Gout exerts a significant health burden (Kuo, Grainge, Zhang, et al., 2015) and is associated with numerous comorbidities, including hypertension, CVD, and dyslipidaemia (Sandoval-Plata et al., 2020), and a reduced quality of life (Singh, 2014). More recently, gout has been shown to be a risk factor for COVID-19 related deaths (Strangfeld et al., 2021; Topless et al., 2022) and it has been suggested that individuals with gout are likely to experience poor outcomes after COVID-19 infection (Dalbeth & Robinson, 2021; Tai et al., 2022).

Acute recurrent attacks of arthritis, typically lasting from several days to up to several weeks, are a defining feature of gout (Roddy & Doherty, 2010). The underlying cause of these attacks, known as gout flares, is a build-up of MSU crystalline deposits in the joints, causing acute pain, swelling, and inflammation (Dalbeth et al., 2016). Sustained hyperuricaemia, which most commonly occurs secondary to reduced fractional uric acid clearance, is recognised as the most important risk factor for gout and recurrent flares (Abhishek & Doherty, 2018; Terkeltaub et al., 2006). ULT is commonly prescribed to help lower sUA levels, yet poor adherence to medication has been reported (Kuo, Grainge, Mallen, et al., 2015). Furthermore, the use of alternative dietary treatments by gout sufferers is common (Singh et al., 2015).

Early case reports from the 1950s suggested that consumption of cherries had a role to play in alleviating gouty pain and inflammation (Blau, 1950). Whilst cherries and cherry products have previously been shown to acutely lower sUA after consumption in healthy people (Bell, Gaze, et al., 2014; Hillman &

Uhranowsky, 2021; Jacob et al., 2003), data presented in Chapter 4 indicated that these effects might be attributed to diurnal variation. Nevertheless, as individuals in this study were considered normouricaemic, a role of cherries in the management of gout cannot be ruled out from these findings alone.

There are currently very few studies of cherry consumption in gout patients. In a case cross-over study of 633 gout sufferers, cherry consumption was associated with a 35% lower risk of gout flares (Zhang, Neogi, et al., 2012). This study was predicated on an acute temporal relationship between cherry consumption and likelihood of gout flares and did not evaluate the habitual effect of cherry consumption. Furthermore, being observational in design, causality cannot be assumed (Zhang, Neogi, et al., 2012). While there have been two intervention studies that have addressed the potential for cherry to reduce risk of gout, these were both feasibility studies with limited sample size, lack of an appropriate placebo, and within-group statistical comparison (Schlesinger et al., 2012; Singh, Willig, et al., 2020). Further research is therefore required to confirm these findings.

In addition to lowering sUA, cherry consumption may be of benefit in gout prophylaxis because cherries contain a variety of phenolic compounds with anti-inflammatory properties (McCune et al., 2010). These compounds may ameliorate the MSU crystal-induced inflammatory response and associated pain (Bell, McHugh, et al., 2014; Zhang, Neogi, et al., 2012). Indeed, tart cherry juice has been shown to lower a recognised biomarker of inflammation, CRP, when consumed twice daily for 3 weeks by women aged 40 to 70 years with osteoarthritis (Kuehl et al., 2012) and twice daily for 6 weeks by men and women aged over 18 years with knee osteoarthritis (Schumacher et al., 2013). However, observations in healthy individuals are inconsistent. For example, no significant reductions in CRP were observed following 6 weeks of daily tart cherry juice supplementation (Lynn et al., 2014), 4 weeks' consumption of daily tart cherry concentrate (Lear et al., 2019), or 30 days of daily tart cherry consumption, either in 500 mg/d freeze-dried powder or 30 mL concentrate form (Hillman & Chrismas, 2021), in healthy adults. Additionally, no acute effect of tart cherry juice on CRP

was detected in our study presented in the previous chapter. Meanwhile, a 25 % reduction in CRP was reported in older healthy adults who consumed 68 mL of tart cherry concentrate daily for 12 weeks (Chai et al., 2019) and a 29 % reduction reported in healthy adults at 5 hours following the consumption of 30 mL or 60 mL tart cherry concentrate (Bell, Gaze, et al., 2014). It must be recognised however that baseline CRP levels of participants were elevated in both studies.

Gout is also associated with an increased CVD risk (Cea Soriano et al., 2011). As inflammation and oxidative stress are both implicated in the pathogenesis of CVD (Kanbay et al., 2013; Price, 2006) and cherries are proposed to exert anti-inflammatory and antioxidative properties, they may also offer cardioprotective benefits to gout sufferers, such as improvements in BP and reduced arterial stiffness (Bell & Gochenaur, 2006; McCune et al., 2010). Despite a paucity of RCTs in individuals with gout, improvements in SBP and DBP have been observed in women with diabetes, a condition also associated with increased CVD risk, following daily consumption of tart cherry concentrate for 6 weeks (Ataie-Jafari et al., 2008). Nevertheless, consumption of tart cherry concentrate daily for 7 days failed to induce any significant improvements in acute brachial BP measurements in individuals with metabolic syndrome (Desai et al., 2021). Furthermore, no improvements in measures of arterial stiffness were observed in this study (Desai et al., 2021) nor in another study of individuals with metabolic syndrome who consumed tart cherry juice daily for 12 weeks (Johnson et al., 2020). The effect of tart cherry juice consumption on arterial stiffness has yet to be assessed in adults with gout and so further research is warranted.

Despite the limited scientific evidence base, leading medical societies and charities, for example, BSR, EULAR, NICE, Arthritis Research UK, and the UK Gout Society, endorse cherry consumption as a therapeutic aid for gout (Arthritis Research UK, 2016; Hui et al., 2017; NICE, 2018; Richette et al., 2017; UK Gout Society, n.d.), whilst a content analysis of US and UK newspapers reported that 25% of articles discussing dietary management of gout recommended cherry consumption (Duyck et al., 2016). In our own content analysis of YouTube® videos providing dietary recommendations for gout (Study 1), the

recommendation to consume cherries was found to be present in 29% of videos (see section 3.3.3). Despite poor overall educational quality, reliability, understandability and actionability, these videos appeared to be popular, averaging 13 views per day and a 95% like ratio, which indicates considerable public attention to the recommendation to consume cherries for gout. This attention may subsequently influence the dietary choices of patients with gout. Contrastingly, the UK's NHS health information website previously dismissed newspaper claims that advocated cherry consumption for gout (NHS Choices, 2014) and the FDA in the USA has warned cherry juice growers and processers against making preventive disease claims (U.S. Food and Drug Administration, 2005). There is a clear need for definitive evidence from a RCT involving patients with gout.

Therefore, addressing the fourth objective of this thesis, a 12-month RCT was conducted to assess the effect of daily tart cherry juice consumption compared with a fruit-flavoured placebo drink on risk of gout attacks and markers of gout and CVD risk. The primary objective was to explore the effectiveness of consuming tart cherry juice versus a low-phenol placebo drink daily for 12 months as an adjuvant therapy for gout, providing preliminary evidence in this area. The study aimed to elucidate possible mechanisms of effect through the measurement of serum urate, UU excretion, and a biomarker of inflammation. Additionally, as participants were likely to be at increased risk of CVD, the effects of 12-month tart cherry juice consumption on BP, arterial stiffness, and blood lipids were explored. Finally, the trial aimed to determine the feasibility, including compliance, acceptability, and tolerability, of consuming tart cherry juice daily for 12 months.

5.2. Methodology

The study is described below according to the CONSORT 2010 updated guidelines for reporting parallel group randomized trials (Moher et al., 2012). Excluding the analysis of blood samples for urate, creatinine, and blood lipid profile and the analysis of urine samples for urate and creatinine, all other laboratory work in this study, namely the analysis of drinks, the collection and

processing of blood and urine samples, the analysis of serum CRP, anthropometric measurements, and measurements of blood pressure and arterial stiffness, was completed by the author of this thesis (KL).

5.2.1. Trial design

The study was a 12-month, double-blind, two-armed, parallel RCT performed in adults aged 18 to 80 years, with an existing clinical diagnosis of gout who had reported at least one gout flare in the previous 12 months. The intervention group received a daily supplement of tart cherry juice, and the placebo group received a daily supplement of cherry-flavoured drink. Each participant was enrolled onto the study for 12 months; physical and vascular measurements and fasted blood and urine samples were collected at 0, 6 and 12 months. Laboratory visits were postponed for any participant that was experiencing a gout flare until after the flare had resolved. An overview of the study design and timeline is given in Figure 11. During the design of the trial, retired people from a local church group (Christ Church Fulwood, Sheffield, England) were consulted as to their understanding of written participant information and questionnaires. This group also provided feedback on the acceptability of the schedule of visits, study measures and intervention. This group was chosen because it was comprised of individuals with differing educational and occupational backgrounds and included some individuals with arthritis.

The study opened recruitment in June 2019 but recruitment was closed prematurely in March 2020 due to the COVID-19 pandemic. As a result of restrictions imposed because of the pandemic, laboratory-based 6-month measurements were not possible for most participants and three participants chose not to attend their 12-month laboratory sessions. Consequently, the study became a pilot study rather than an appropriately powered full clinical trial.

The trial was approved by Leeds West NHS Research Ethics Committee (18/SW/0262) and the HRA and Health and Care Research Wales (Appendix 8). It was registered at ClinicalTrials.gov (NCT03621215).

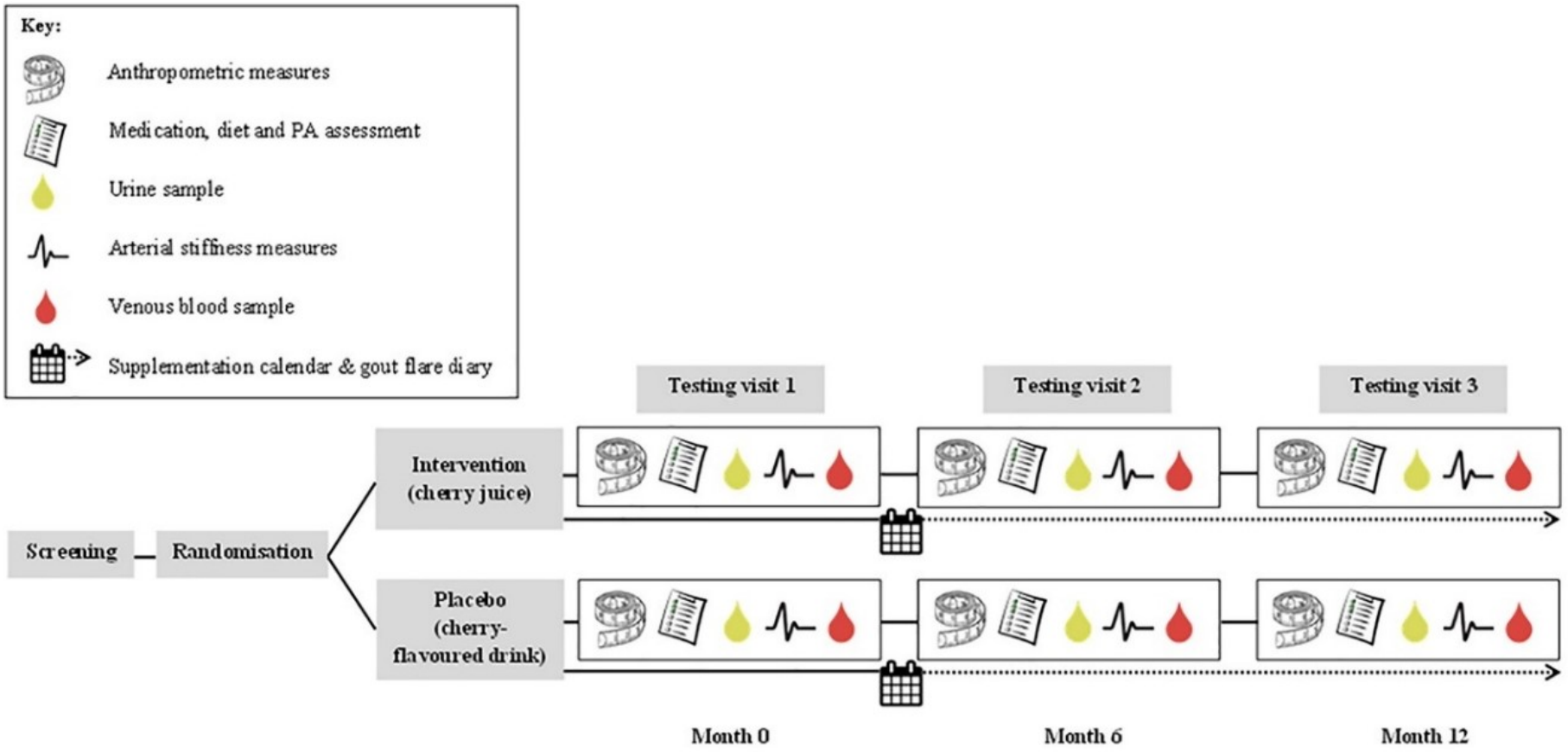

Figure 11. Participant flow through study 3. PA; physical activity

5.2.2. Participants

Inclusion criteria included: aged between 18 and 80 years; clinical diagnosis of gout; at least one self-reported gout flare with a pain score >3 (on a 0-10 numerical rating scale) in the past 12 months; and participant able to give informed consent. Exclusion criteria included the following: cherry allergy; habitual consumption of cherries and/or cherry products (one or more times per week); severe renal impairment (glomerular filtration rate <30 mg/L); T1D or T2D; and recruiting practitioner deemed that the patient was unsuitable to participate (frailty, dementia and terminal medical conditions). Individuals prescribed ULT were not excluded from the study, nor were they required to reduce or stop taking their medication.

Participants were mainly recruited from primary care practices in the city of Sheffield and surrounding areas. The Clinical Research Network of Yorkshire and Humber, which provides localised infrastructure to support delivery of research, selected practices to function as Participant Identification Centres (PIC). At each PIC, computerised patient records were searched to identify eligible individuals that had a clinical diagnosis of gout. Diagnosis is typically based on clinical examination, assessment of reported symptoms and elevated serum urate. A general practitioner screened the list of patients generated from this search for suitability to participate (for example, people who were frail or suffering from dementia were not recruited). People who were eligible were sent an invitation to participate; interested individuals were encouraged to contact the research team for further study information. Such participants were then invited to attend an information, screening, and enrolment meeting at SHU. Recruitment from PICs was augmented by poster advertisements at local primary care practices and across the University campus and via advertising on the UK Gout Society website. The general practitioners of participants not recruited via PICs were contacted to verify the participants' eligibility. Written informed consent was collected from those willing and eligible to take part by the study coordinator. All study measurements were made at SHU's Food and Nutrition Research Laboratories in Sheffield, United Kingdom.

5.2.3. Dietary interventions

Participants were provided monthly with either Montmorency tart cherry 68 Brix concentrate (King Orchards, Michigan, USA) or a low-phenol, cherry-flavoured placebo concentrate. Both drinks were diluted with water by participants before consumption (30 mL of concentrate with 220 mL of water, totalling 250 ml daily). Graduated cups with clear markings indicating required volumes of concentrate and water were provided to participants. Participants were advised to consume their drink with breakfast and to keep the concentrate refrigerated. Consumption was recorded daily on a calendar. Advice was given to maintain usual dietary habits throughout the course of the intervention and to avoid cherry consumption.

The placebo concentrate was constituted to have similar colour, taste, and tartness as the cherry concentrate through the addition of blue and red food colourings, red and black cherry flavourings, and citric acid to a low-fruit cordial (Robinsons Summer Fruits, no-added sugar). Prior to its use in this study, samples of the drink were sent for independent incubation testing (Campden BRI©) to verify microbiological safety over an extended period of time. Fresh batches of placebo drink were made up for participants every month.

Product nutritional information provided by the manufacturer indicated that each daily serving of tart cherry concentrate provided approximately: 80 kcal and 20 g carbohydrate. Each serving of the placebo drink provided: 2.9 kcal and 0.3 g carbohydrate. It was not possible to match the drinks for energy content because the addition of sugars to the placebo drink would have jeopardised its shelf life. Furthermore, the addition of sucrose (comprising 50% fructose) has the potential to raise serum urate (Caliceti et al., 2017).

5.2.4. Analysis of tart cherry concentrate and cherry-flavoured placebo drink

Due to the lengthy nature of the study and COVID-19 storage access restrictions, two different sources of Montmorency tart cherry concentrate were utilised during the study period, split over three separate batches (batch 1: King Orchards, Michigan, USA and batches 2 & 3: CherryActive®, ActiveEdge™, Hanworth, UK).

Laboratory access restrictions during the COVID-19 pandemic meant that it was not possible to analyse the second batch of tart cherry concentrate. Analyses of the total phenolic and anthocyanin contents of the first and third batches of tart cherry concentrate as well as the cherry-flavoured placebo drink were undertaken as follows.

5.2.4.1. Total phenolic content

The total phenolic contents of the two tart cherry concentrate batches and the cherry flavoured placebo concentrate were measured using the Folin Ciocalteu method of Singleton and Rossi (Singleton & Rossi, 1965), as described in section 4.2.. Three separate cherry concentrate samples were diluted with di.$H_2$0 in a ratio of 1:200 before analysis. The placebo concentrate was made up in duplicate as per 5.2.3. and was not diluted prior to analysis. The total phenol content of each tart cherry and cherry-flavoured concentrate sample was calculated from the standard curve using linear regression. Values are expressed as mg of GAE per 30 mL serving and reported as the mean of the samples ± SD.

5.2.4.2. Total anthocyanin content

The total anthocyanin content of 3 samples of tart cherry concentrate and 2 samples of cherry flavoured placebo concentrate was determined in duplicate using the pH differential method (Lee et al., 2005), as described in section 4.2.. Two 1:20 dilutions of each tart cherry concentrate sample and two 1:5 dilutions of each placebo concentrate sample were made, one in 0.025 M potassium chloride (pH 1.0) and one in 0.4 M sodium acetate (pH 4.5). This was repeated to provide duplicate readings. The mean ± SD total anthocyanin content of samples from each batch of tart cherry concentrate and the cherry-flavoured placebo concentrate samples was expressed as cyanidin-3-glucoside equivalents (mg/30 mL serving).

5.2.5. Outcomes

At the start of the study, the primary outcome measure was between-group difference in the frequency of gout flares from baseline to 12 months. However, premature cessation of recruitment because of the COVID pandemic shifted the focus of the study to being a feasibility/pilot study. Therefore, measures of

feasibility, including participant compliance to interventions, participant retention, and tolerability of interventions, were upgraded to additional primary outcomes following this decision. Secondary outcome measures were between-group differences in gout flare pain, serum urate concentration, serum creatinine concentration, blood lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, TG, and TG:HDL ratio), a recognised blood marker of inflammation (CRP), FEUA, 24-hour UU excretion, and vascular function (BP and arterial stiffness). Changes in PA, perceived health, and general pain were also secondary outcomes. Non-efficacy outcomes included dietary intake measures, for example total energy and total sugars.

5.2.5.1. Gout flares

Information on gout flares experienced by participants in the preceding 12 months was collected at baseline. This information covered frequency, duration, location, pain severity (0-10 numerical rating scale) and treatment (pharmacological and non-pharmacological). During the 12-month supplementation period, participants kept a diary to record all instances of gouty pain, again covering duration, location, pain severity, and treatment. A gout flare was logged when self-reported pain at rest was recorded as >3 on the pain severity scale (Gaffo, Schumacher, et al., 2012).

5.2.5.2. Anthropometric measurements

Anthropometric measures of height and mass were used to calculate BMI (mass (kg)/height $(m)^2$) at baseline, 6 and 12 months. Height without shoes was measured to the nearest 0.1 cm using a stadiometer (Seca, Hamburg, Germany). Body mass was measured in light clothing to the nearest 0.1 kg using calibrated weighing scales (Seca 899, Hamburg, Germany).

5.2.5.3. Arterial stiffness and blood pressure (BP)

A Vicorder® device (SMT Medical, Germany) was used to measure brachial BP, central BP, carotid-femoral PWV, AIx, and heart rate at baseline, 6, and 12 months, as previously described in section 4.2.6.2. As with Study 2, participants were familiarised with the Vicorder® device prior to their first session. Familiarisation consisted of practice measurements with the carotid (neck), arm,

and femoral (leg) cuffs. The arm and leg cuffs were fitted by the same individual, on the same limbs, at all laboratory visits.

5.2.5.4. Fasted blood samples

Fasted venous blood samples were collected at baseline, 6, and 12 months into 15 mL SST tubes. Where it was not possible to collect venous blood samples due to poor venous access, finger prick samples were collected into 600 µL monovette SSTs, however these were only used for collecting serum. Blood samples were inverted at least 5 times and allowed to clot for 20 minutes.

5.2.5.4.1. Processing and analysis of serum samples

Whole blood samples collected in SST tubes were centrifuged at 2500 x g for 15 minutes at 18 °C to separate serum (Hermle Z 36 HK, HERMLE Labortechnik GmbH, Germany). Serum was aspirated and samples were stored in 0.5-1.5 mL aliquots at -80 °C until analysis. Serum aliquots were sent to the Clinical Chemistry department at the Royal Hallamshire Hospital, Sheffield, to be analysed for urate, creatinine, and blood lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triacylglycerol). Serum samples were analysed at SHU for the inflammatory marker CRP using a human CRP quantikine ELISA kit (R&D systems, Abingdon, UK) on a microplate reader (BioTek synergy HT, Winooski, USA).

5.2.5.5. Collection, processing, and analysis of urine samples

Immediately prior to each visit at baseline, 6, and 12 months, participants carried out a 24-hour urine collection. Participants were instructed to start this collection after their first urination on the morning before their laboratory visit and to keep the collected urine cool over the 24 hours. A further spot urine sample was collected alongside the fasting blood sample. Total volumes of 24-hour and spot urine samples were noted before smaller samples of each were centrifuged twice at 2800 x g for 15 minutes to remove unwanted cells ((Hermle Z 36 HK, HERMLE Labortechnik GmbH, Germany). Spun samples were stored in 1 mL aliquots at -80 °C until analysis. Spot and 24-hour urine aliquots were sent to the Clinical Chemistry department at the Royal Hallamshire Hospital, Sheffield, to be analysed for urate and creatinine concentrations.

Uric acid and creatinine concentrations of spot urine samples were used alongside sUA and creatinine concentrations to calculate fractional excretion of uric acid as follows: ((urinary uric acid [mg/mL] x serum creatinine [mg/mL]) / (sUA [mg/mL] x urinary creatinine [mg/mL])) x 100. Additionally, spot and 24-hour urine uric acid concentrations were corrected for their corresponding creatinine concentrations to calculate spot and 24-hour UU (μmol/mMol creatinine) values.

5.2.5.6. Medication use and functional status

Medication use (contemporary and historical) was recorded at baseline and monitored closely throughout the study through routine telephone contact. This record included both prescribed and over-the-counter medication. Any changes to medication use, for example dosing changes or new prescriptions, were recorded in the participant's medication log. Dietary supplement use was also recorded at baseline, 6, and 12 months. Assessment of daily functional status covering daily pain from gout and the interference of their condition on daily mobility, daily activities, and daily sleep was collected through interview using questions from a validated health assessment questionnaire (HAQ) (Álvarez-Hernández et al., 2008). At the end of the 12-month trial period, participants were also asked to report the perceived change in their gout since starting the trial. This was assessed on a 7-point Likert scale; 'much worse', 'worse', 'slightly worse', 'no change', 'slightly improved', 'improved', 'much improved'.

5.2.5.7. Assessment of diet and physical activity (PA) levels

At baseline, 6 months, and 12 months, participants completed a 4-day food diary using estimated household measures and recorded PA in a diary over a 4-day period. Participants were advised to select three weekdays and one weekend day that were considered typical of their diet at the time.

5.2.5.8. Measures of feasibility

5.2.5.8.1. Participant compliance

A daily calendar was completed to record adherence to the intervention. Routine monthly telephone contact and face-to-face contact when delivering the drinks was used to encourage compliance. Good compliance to trial interventions was defined as intake ≥ 80% over the 12 months (i.e. participants consumed the daily

prescribed dose of tart cherry juice or placebo drink on 292 days across their 12 month trial duration), following conventions for defining good adherence to chronic disease treatments, including ULT for gout (Dunbar-Jacob & Mortimer-Stephens, 2001; McGowan et al., 2016).

5.2.5.8.2. Retention of participants

Participants were able to withdraw from the study at any time without giving any reason. However, when participants provided a reason for discontinuing the study this was recorded. Participants who decided to discontinue the intervention were invited to return for follow-up visits to assess outcome measures.

5.2.5.8.3. Acceptability of drinks

Acceptability of the drinks was assessed by a participant's response on a 0-10 scale at the end of the trial; the scale ranged from 0, 'I really disliked the drink and would never drink it again', 5, 'I am indifferent to the drink', to 10, 'I really liked the drink and would continue to drink it daily'.

5.2.5.8.4. Tolerability of drinks

Tolerability of supplements was assessed by reported adverse events (AE). All AEs were recorded and reported, where applicable, following Good Clinical Practice and Health Research Authority guidelines. Participants were advised to report all serious or non-serious AEs to the research team; these data were recorded. Additionally, the incidence of adverse events was logged at laboratory visits and via telephone contact.

5.2.5.8.5. Effectiveness of blinding

To assess the effectiveness of blinding, participants were asked at the end of their trial period to speculate whether they had been provided with tart cherry juice or the placebo drink to consume over the past 12 months. Participants were also given the option to state that they were 'unsure'.

5.2.6. Sample size

The original pre-defined primary outcome was change in gout flare frequency. Using UK data on gout flares (Rothenbacher et al., 2011) it was calculated that 94 participants were required to detect a 75% reduction in annual gout flare

recurrence over a 12-month period with a power of 95% and an alpha of 0.05. A 75% reduction was chosen from a previous dietary intervention for gout flares in which a similar reduction in gout flare frequency was predicted (Dalbeth et al., 2012). The aim was to recruit 120 participants to allow for a study attrition rate of 20%.

5.2.7. Randomisation

All consenting participants were block randomised (block size 4) in a 1:1 allocation to either a tart cherry juice group or a placebo cherry-flavoured drink group with stratification by sex and smoking status. Allocation sequence was generated using a computer random number generator (www.random.org) by an investigator not involved in participant enrolment and data collection and concealed from research personnel until the completion of the trial. The study coordinator (KL) was responsible for participant enrolment, distribution of intervention drinks, and data collection.

5.2.8. Blinding

The study coordinator was blinded to treatment allocation until results had been analysed. Drinks were provided to participants in identical bottles and labelled with participant identification number only to ensure that both study coordinator and participants were blinded to drink allocation throughout the study. The placebo drink had a similar colour, taste, and tartness as the cherry concentrate.

5.2.9. Data management

The collection and storage of data adhered to the standard requirements of the EU General Data Protection Regulation 2016/679. Data was entered onto electronic spreadsheets stored on a secure University server. All data was treated confidentially and pseudo-anonymised. Hard copies of data and documents were kept in a locked and secure cabinet for the duration of the study. Following completion of the study, data was transferred to SHURDA, to be kept for 10 years. Hard copies will be disposed of confidentially and electronic data deleted after this period of time.

5.2.10. Statistical analysis

Descriptive analysis of all baseline variables was conducted to compare the two treatment groups (cherry *versus* placebo). Normally distributed continuous data was compared between groups using independent t-tests. Mann-Whitney U tests were used to compare non-normally distributed continuous baseline data. Categorical data were compared between groups with the use of Fisher's exact tests.

A generalised linear mixed model analysis (assuming Poisson distribution) was performed to test for changes in frequency of flares from baseline to 12 months between treatments. Gamma multi-level modelling was used to detect any changes in the duration of flares from baseline to 12 months between treatments. Fisher-Freeman Halton tests were used to identify between-group differences in the distribution of flare locations at baseline and 12 months, and self-reported condition ratings at 12 months. Differences in gout medication use between groups at baseline and 12 months were assessed using Fisher's exact tests. Measures of retention and intervention compliance, tolerability, acceptability, and blinding effectiveness were compared between groups with the use of independent t-tests. Analysis of covariance (ANCOVA) were used to compare all other secondary outcomes at 12 months, with baseline measurements used as the covariate. Baseline ULT use (allopurinol or febuxostat) was also used as a covariate when comparing serum urate concentrations at 12 months.

Continuous variables are presented as mean and SD, median and IQR, or geometric mean and 95% CI. Categorical data are reported as frequency and percentage of treatment group. Analysis was performed using IBM SPSS Statistics for Windows version 24 (New York, USA). Statistical significance was set at $p < 0.05$.

5.3. Results

5.3.1. Participant flow through the study

Unfortunately, due to the COVID-19 pandemic in the UK, recruitment to this study was closed prematurely. Therefore, only 38 eligible individuals were enrolled onto the study and only 37 attended a baseline session and started their

supplementation period (Figure 12); 17 were randomised into the tart cherry juice group and 20 were randomised into the placebo drink group. The study had an overall completion rate of 86.5%. In the cherry juice group, four participants were lost to follow-up at 6 months, whilst another participant left the study before the 12-month follow-up session. As a result, only 12 participants completed the study in the cherry juice group, representing a 70.6% completion rate in this group. All 20 participants in the placebo group completed the study.

Laboratory closures because of the COVID-19 pandemic resulted in only 5 participants (*n* = 2 in the cherry group and *n* = 3 in the placebo group) attending their 6-month follow-up laboratory session. Clinical data at 6 months was therefore excluded from analysis. Due to COVID-19 related concerns, 3 participants (*n* = 2 in the cherry group and *n* = 1 in the placebo group) chose not to attend the 12-month follow-up laboratory session in person. Whilst self-reported measurements and 24-hour urine samples were collected from these three participants at 12 months, it was not possible to collect any other clinical measurements. As a result of the lower than anticipated sample size, the decision was made to use the data collected during this study to primarily assess the feasibility of long-term tart cherry consumption by gout patients (upgraded from secondary to primary outcome) and to provide preliminary less precise estimates of treatment effects.

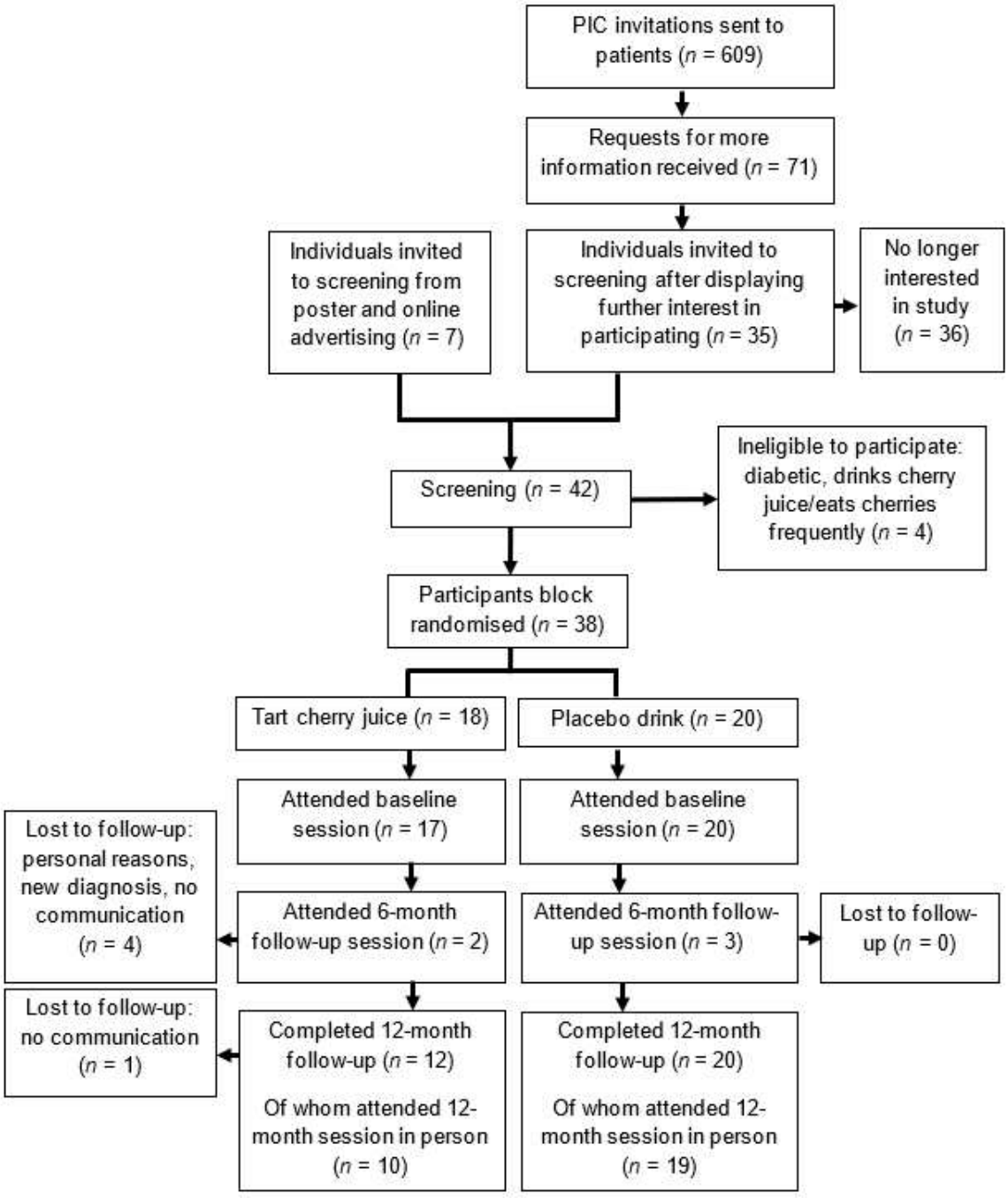

Figure 12. Flow diagram of participant enrolment and analyses in the study. PIC, participant identification centre.

5.3.2. Analysis of tart cherry concentrate and cherry-flavoured placebo drink

Total phenolic and anthocyanin content analysis indicated that each 30 mL daily serving of the first batch of tart cherry concentrate (King Orchard) provided 247.1 (± 15.3) mg phenolics and 2.9 (± 0.3) mg of intact anthocyanins, whilst the third batch (CherryActive®) provided 355.7 (± 1.7) mg phenolics and 2.9 (± 0.008) mg of intact anthocyanins. Each serving of the placebo drink provided 1.6 (± 0.1) mg phenolics and 0.02 (± 0.001) mg anthocyanins.

5.3.3. Baseline characteristics of participants

There were no significant differences in baseline characteristics of participants between the cherry and placebo groups, indicating that patients were well-matched at baseline (Table 11). Participants were predominantly male (*n* = 34, 92%), non-smokers (*n* = 34, 92%), and of Caucasian ethnicity (*n* = 36, 97%), with an average age of 67.0 (IQR 18.0) years and BMI of 31.8 (± 5.4) kg/m^2.

Patients had received their diagnosis of gout a median of 7.0 (IQR 12.5) years prior to their enrolment in the study. At enrolment, participants reported experiencing 2.5 (IQR 3.8) flares in the 12 months preceding this, equating to 0.3 (IQR 0.3) flares per month, with an average pain score of 7.4 (IQR 2.4) out of 10 and a duration of 6 (IQR 6) days. Daily ULT, namely allopurinol or febuxostat, was used by 57% of participants (*n* = 21), whilst drugs to treat acute flares, specifically colchicine or naproxen, were used by 68% of participants during flare episodes (*n* = 25). The presence of tophi was identified in 5 (14%) participants.

Table 11. Baseline characteristics of participants (*n* = 37).

	Cherry (*n* = 17)	**Placebo (*n* = 20)**	**Significance (p-value)**
Age, years, median (IQR)	69 (20)	64 (17)	0.265
Male, *n* (%)	16 (94%)	18 (90%)	0.658
BMI, mean (SD)	31.9 (5.9)	31.8 (5.1)	0.937
Smoker, *n* (%)	1 (6%)	2 (10%)	0.658
Caucasian ethnicity, *n* (%)	16 (94%)	20 (100%)	0.284
Time since diagnosis, years, median (IQR)	5.0 (15.0)	10.5 (12.0)	0.725
Number of self-reported flares in preceding 12 months, median (IQR)	3.5 (7.0)	2.0 (2.8)	0.256
Number of self-reported flares per month in preceding 12 months, median (IQR)	0.3 (0.6)	0.2 (0.2)	0.213
Average pain of self-reported flares in preceding 12 months, median (IQR)	7.0 (3.5)	7.8 (1.9)	0.334
Average duration of self-reported flares in preceding 12 months, days, median (IQR)	4.0 (6.0)	6.5 (8.0)	0.650
Allopurinol or febuxostat use, *n* (%)	10 (59%)	11 (55%)	0.821
Colchicine or naproxen use, *n* (%)	11 (65%)	14 (70%)	0.740
Tophaceous gout presence, *n* (%)	2 (12%)	3 (15%)	0.782

BMI, body mass index.

The most common flare location in the 12 months preceding enrolment was the big toe, with 25 (68%) participants experiencing one or more flares in one or both digits (Table 12). The distribution of reported flare locations was similar between groups (Fisher's = 7.648, p = 0.762).

Table 12. Location of flares in 12 months preceding enrolment, reported as the number of participants having experienced one or more flare in the specified location.

Locations of flares, *n* participants (% group)	**Cherry (*n* = 17)**	**Placebo (*n* = 19)**
Neck	1 (5.9)	0 (0.0)
Elbow/s	1 (5.9)	1 (5.0)
Wrist/s	1 (5.9)	2 (10.0)
Hand/s	1 (5.9)	1 (5.0)
Finger/s	2 (11.8)	1 (5.0)
Hip/s	1 (5.9)	0 (0.0)
Knee/s	1 (5.9)	5 (25.0)
Ankle/s	2 (11.8)	3 (15.0)
Foot/feet	1 (5.9)	1 (5.0)
Big toe/s	13 (76.5)	12 (60.0)
Other toe/s	1 (5.9)	3 (15.0)

The reported frequency of cherry consumption at baseline is displayed in Table 13. There was no difference in the reported frequency between groups (Fisher's = 3.532, p = 0.580). Almost half of participants reported consuming cherries 'a few times per year' (*n* = 17, 46%), followed closely by 'never' (*n* = 14, 38%).

Table 13. Cherry consumption at baseline.

Cherry consumption frequency, *n* (%)	Cherry (*n* = 17)	Placebo (*n* = 20)
Once a week	1 (5.9)	1 (5.0)
Few times a month	1 (5.9)	1 (5.0)
Once a month	0 (0.0)	2 (10.0)
Few times a year	10 (58.8)	7 (35.0)
Never	5 (29.4)	9 (45.0)

Clinical data, including measures of vascular health, inflammation, urate, and blood lipid profile, did not differ significantly between groups at baseline (Table 14). However, brachial and central SBP were trending towards being statistically higher in the cherry group (p = 0.078 for both). For four participants (n = 3 in cherry group, n = 1 in placebo group), only finger-prick blood samples could be collected at the baseline session due to poor venous access, so analyses were restricted to uric acid and CRP only (Table 14).

Table 14. Baseline clinical data of participants (*n* = 37).

	Cherry (*n* = 17)	**Placebo (*n* = 20)**	**Significance (p-value)**
Brachial systolic blood pressure, mmHg, mean (SD)	146 (16)	136 (17)	0.078
Brachial diastolic blood pressure, mmHg, mean (SD)	74 (7)	74 (7)	0.899
Central systolic blood pressure, mmHg, mean (SD)	144 (16)	134 (17)	0.078
Pulse wave velocity, m/s, mean (SD)	9.8 (2.7)	9.2 (2.4)	0.670
Augmentation index, %, mean (SD)	26.9 (6.6)	24.8 (6.8)	0.351
Heart rate, BPM, mean (SD)	63 (11)	68 (14)	0.174
C-reactive protein, mg/L, median (IQR)	1.21 (3.80)	1.99 (6.8)	0.211
Serum urate, µmol/L, mean (SD)	400 (108)	361 (102)	0.270
Spot fractional excretion of uric acid, %, median (IQR)	3.8 (1.4)	3.7 (1.2)	0.884
24 hour fractional excretion of uric acid, %, mean (SD)	4.8 (1.4)	4.0 (1.5)	0.125
Spot urinary urate, µmol/mMol creatinine, mean (SD)	179.9 (50.8)	155.8 (72.3)	0.256
24 hour urinary urate, µmol/mMol creatinine, mean (SD)	206.2 (58.7)	166 (83.7)	0.097
	Cherry (*n* = 14)	**Placebo (*n* = 19)**	**Significance (p-value)**
Total cholesterol, mmol/L, mean (SD)	4.78 (1.22)	4.34 (0.80)	0.217
LDL, mmol/L, mean (SD)	3.20 (1.00)	2.91 (0.75)	0.360
HDL, mmol/L, mean (SD)	1.17 (0.29)	1.12 (0.32)	0.596
Non-HDL, mean (SD)	3.62 (1.20)	3.22 (0.81)	0.260
TG, mmol/L, median (IQR)	1.40 (0.88)	1.40 (0.70)	0.784
Total/HDL, median (IQR)	3.80 (1.60)	3.90 (1.80)	0.985

BPM, beats per minute; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triacylglyceride.

5.3.4. Primary outcome: Change in frequency of self-reported gout flares

One participant in the cherry group failed to complete their flare diary during 4 months of their intervention period, whilst another experienced chronic gout and so was unable to track individual flares during the study. Both participants were subsequently excluded from the analysis of gout flare frequency. As shown in Table 15, mean annual frequency of self-reported gout flares reduced over the 12-month study duration by 1.0 (-39%) in the cherry group and by 0.5 (-11%) in the placebo groups. However, this between-group difference was not found to be statistically significant *(p* = 0.287). When corrected for baseline flare frequency, there was also no significant difference in monthly flare frequency between the groups ($F_{1,26}$ = 0.034, *p* = 0.855, ηp^2 = 0.001). In the cherry group, 40% (*n* = 4) of participants reported no flares during the 12-month intervention period, compared with 15% (*n* = 3) in the placebo group, but the distribution of flares versus no flares during intervention was not significantly different between groups (Fisher's = 2.329, *p* = 0.181).

Table 15. Self-reported flares at baseline and 12 months in the cherry and placebo groups.

	Cherry (*n* = 10)		**Placebo (*n* = 20)**		**Adjusted treatment difference* (95% CI) at 12M**
	0M	**12M**	**0M**	**12M**	
Total number of self-reported flares in 12 months, mean (SD)	2.6 (1.8)	1.6 (2.0)	4.7 (6.6)	4.2 (4.6)	-1.27 (-2.85, 0.32)
Number of self-reported flares per month over 12 months, mean (SD)	0.2 (0.1)	0.1 (0.2)	0.4 (0.6)	0.3 (0.4)	-0.11 (-0.24, 0.02)

0M, 0 months (baseline); 12M, 12 months.
*Adjusted for 0M.

5.3.5. Primary outcomes (upgraded from secondary): retention, tolerability, compliance, acceptability, and effectiveness of blinding

Four participants withdrew from the study within the first 6 months, and a fifth participant dropped out at 7 months; all five participants were in the tart cherry group (Table 16). Reasons given for withdrawing from the study were personal/family circumstances (n = 2) and a re-diagnosis of arthritis instead of gout shortly after beginning the study (n = 1). Two participants were withdrawn by the researcher due to no communication. Aversion to the drink was not reported as a reason for withdrawing by any participant.

A total of 11 adverse events were reported by participants during the intervention period of the study (Table 16). There was no significant difference between the cherry and placebo groups in the total number of adverse events reported (U = 117, p = 0.877) and no association between drink allocation and the reporting of an adverse event ($\chi^2(1) = 0.000$, p = 1.000). Only one participant reported a gastrointestinal adverse event, and this occurred 2 months after commencing the study intervention (cherry juice). Following a reduction in the frequency of drink consumption, no further symptoms were reported after this point. Other adverse events recorded during the study included a sickness bug, migraines, and COVID-19 and these lasted between 1 week and 1 month in duration. Drink allocation was also not significantly associated with admissions to hospital ($\chi^2(1) = 0.055$, p = 0.815). There were 6 reported adverse events which resulted in admission to hospital, including a transient ischaemic attack, a severe gout attack, COVID-19, and a hip replacement operation. None of these events were considered by researchers to be related to the study supplements consumed. No deaths occurred during the study.

There was high overall adherence to the drink supplementation regime during the study (98.6 % of year, IQR 4.0) and this was similar between the two groups (U = 117, p = 0.906); the allocated drink was consumed daily for 98.8 (IQR 7.0) % of the year by the tart cherry group and 98.6 (IQR 4.0) % of the year by the placebo group (Table 16).

As displayed in Table 16, the cherry-flavoured placebo drink recorded slightly higher palatability at 12 months, with a median score of 8/10 given by participants compared with 7/10 for the cherry juice, but this was not significantly different (U = 94, p = 0.303). However, the range of palatability scores reported by the cherry group (IQR = 7.6) was considerably wider than in the placebo group (IQR = 2.8).

Correct drink allocation was identified by only 37.5 % of participants at the end of the trial, indicating appropriate blinding of the drinks (Table 16). There was no statistically significant difference in the distribution of correct and incorrect guesses between groups ($\chi^2(1) = 0.142$, p = 0.706).

Table 16. Measures of compliance, retention, tolerability, acceptability, and blinding effectiveness.

	Cherry (*n* = 12)	**Placebo (*n* = 20)**
Drop-out rate, *n* (% of baseline number[1])	5 (29.4)	0 (0.0)
Total number of reported adverse events, *n*	3	8
Number of patients reporting adverse events, *n* (% group)	3 (25%)	5 (25%)
Adverse events related to hospital admissions, *n* (% group)	2 (17%)	4 (20%)
Drink adherence, % year, median (IQR)	98.8 (7.0)	98.6 (4.0)
Drink palatability /10, median (IQR)	7.0 (7.6)	8.0 (2.8)
Correctly guessed drink allocation, *n* (%)	4 (33.3)	8 (40.0)

[1]at baseline, n = 17 for cherry and n = 20 for placebo

5.3.6. Secondary outcomes: change in self-reported pain, duration, and location of gout flares

As stated in 4.4.3, one participant in the cherry group failed to complete their flare diary during their intervention period and so was excluded from the analysis of gout flare pain and duration (Table 17). One participant from the placebo group did not provide flare duration data in their flare diary and so was excluded from flare duration analysis. Following 12 months of supplementation, flare duration reduced by more than 1/3 in the cherry group and by half in the placebo group, but there was no statistically significant difference between groups ($F_{1,20} = 0.712$, $p = 0.409$, $\eta p^2 = 0.034$). Gout flare pain fell by 45% in the cherry group and 30% in the placebo group, but there was no significant between group difference when corrected for baseline flare pain ($F_{1,27} = 2.503$, $p = 0.125$, $\eta p^2 = 0.085$). When pain scores of participants who reported no flares and an average pain score of 0 during the 12-month intervention period were excluded from analysis, gout flare pain reduced by 7 % and 17 % in the cherry group and placebo group, respectively. There was no significant difference between groups ($F_{1,20} = 2.028$, $p = 0.170$, $\eta p^2 = 0.092$).

Table 17. Self-reported pain and duration of gout flares at baseline and 12 months in the cherry and placebo groups.

	Cherry (*n* = 11)		Placebo (*n* = 20)		
	0M	**12M**	**0M**	**12M**	**Adjusted treatment difference* (95% CI) at 12M**
Average pain of self-reported flares in preceding 12 months, mean (SD)	6.6 (1.9)	3.6 (3.6)	7.7 (1.6)	5.4 (2.9)	-1.89 (-4.44, 0.67)
Average pain of self-reported flares in preceding 12 months, mean (SD)[1]	6.1 (2.2)	5.7 (2.8)	7.7 (1.7)	6.4 (1.9)	-0.33 (-2.41, 1.75)
Average duration of self-reported flares in preceding 12 months, days, geometric mean (95% CI)[2]	8.3 (4.3, 15.9)	5.4 (2.1, 14.0)	6.1 (4.2, 9.0)	3.1 (1.7, 5.6)	0.20 (-0.26, 0.66)

0M, 0 months (baseline); 12M, 12 months.
[1] *n* = 7 for cherry group and *n* = 17 for placebo group. These values exclude pain scores for participants who did not experience any gout flares and recorded an average pain score of 0.0 during the 12-month intervention period.
[2] *n* = 19 in placebo group for duration of self-reported flares.
*Adjusted for 0M.

Over the course of the study, there was a 50% reduction in participants in the cherry group reporting one or more flares in their big toe/s; the number of participants reporting big toe flares stayed relatively consistent in the placebo group (Table 18). However, the distribution of reported flare locations was similar between groups during the 12 months of the study (Fisher's = 4.911, $p = 0.833$).

Table 18. The distribution of flare locations at baseline and 12 months, reported as the number of participants having experienced one or more flare in the specified location.

	Cherry (*n* = 12)		**Placebo (*n* = 20)**	
Locations of flares, *n* (%)	**0M**	**12M**	**0M**	**12M**
Neck	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elbow/s	1 (8.3)	0 (0.0)	1 (5.0)	2 (10.0)
Wrist/s	0 (0.0)	0 (0.0)	2 (10.0)	3 (15.0)
Hand/s	0 (0.0)	1 (8.3)	1 (5.0)	2 (10.0)
Finger/s	2 (16.7)	2 (16.7)	1 (5.0)	2 (10.0)
Hip/s	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Knee/s	1 (8.3)	2 (16.7)	5 (25.0)	3 (15.0)
Ankle/s	2 (16.7)	2 (16.7)	3 (15.0)	5 (25.0)
Foot/feet	1 (8.3)	4 (33.3)	1 (5.0)	5 (25.0)
Big toe/s	10 (83.3)	5 (41.7)	12 (60.0)	13 (65.0)
Other toe/s	1 (8.3)	0 (0.0)	3 (15.0)	3 (15.0)

0M, 0 months (baseline); 12M, 12 months.

5.3.7. Secondary outcomes: change in serum urate and urinary urate (UU)

Serum and UU measurements are displayed in Table 19. At the end of the 12-month intervention there was no statistically significant differences between the tart cherry and placebo groups in serum urate ($F_{(1,26)} = 0.005$, $p = 0.943$, $\eta p^2 = 0.000$). Seven participants were found to have baseline serum urate levels below the 300 µmol/L threshold proposed by the BSR for effective gout management

and a further nine participants were between the 300-357 μmol/L target presented in the EULAR guidelines. An exploratory analysis excluding these participants increased the magnitude of the adjusted mean difference in serum urate at 12 months (-2.25 μmol/L, 95% CI -68.30, 63.80), but this was still not statistically significant for participants with baseline serum urate >300 μmol/L ($F_{(1,19)}$ = 2.070, p = 0.166, ηp^2 = 0.098) or for participants with baseline serum urate >357 μmol/L ($F_{(1,11)}$ = 0.451, p = 0.516, ηp^2 = 0.039). Furthermore, there was still no difference between groups when baseline ULT use was adjusted for ($F_{(1,22)}$ = 2.748, p = 0.112, ηp^2 = 0.111). Daily tart cherry juice consumption also failed to have any benefit relative to placebo for measures of UU excretion, namely spot FEUA ($F_{(1,19)}$ = 0.132, p = 0.720, ηp^2 = 0.007), 24 hour FEUA ($F_{(1,20)}$ = 0.024, p = 0.878, ηp^2 = 0.001), spot UU excretion ($F_{(1,25)}$ = 0.575, p = 0.456, ηp^2 = 0.023), or 24 hour UU excretion ($F_{(1,29)}$ = 1.864, p = 0.183, ηp^2 = 0.060), when adjusted for baseline values.

Table 19. Urate and creatinine measurements at baseline and 12 months in the cherry and placebo groups.

	Cherry (*n* = 10)		Placebo (*n* = 19)		Adjusted treatment difference* (95% CI) at 12M
	0M	12M	0M	12M	
Serum urate, µmol/L, mean (SD)	397 (107)	408 (104)	367 (102)	381 (128)	-1.97 (-57.82, 53.88)
24 hr FEUA, %, mean (SD)	5.3 (1.5)[1]	4.0 (1.3)[1]	3.7 (1.3)[2]	3.7 (1.0)[2]	-0.09 (-1.31, 1.13)
Spot FEUA, %, mean (SD)	5.0 (2.2)[3]	4.2 (1.2)[3]	3.6 (1.2)[2]	3.7 (1.0)[2]	0.20 (-0.97, 1.38)
24 hr urinary urate, µmol/mMol creatinine, mean (SD)	200 (44)[5]	178 (47)[5]	166 (84)[6]	186 (79)[6]	-28.27 (-70.62, 14.07)
Spot urinary urate, µmol/mMol creatinine, mean (SD)	193 (46)[4]	181 (54)[4]	154 (74)	173 (96)	-22.29 (-82.85, 38.27)

FEUA, fractional excretion of uric acid; 0M, 0 months; 12M, 12 months.
*Adjusted for baseline (0M).
[1]*n* = 7, [2]*n* = 16, [3]*n* = 6, [4]*n* = 9, [5]*n* = 12, [6]*n* = 20.

5.3.8. Secondary outcomes: change in blood lipid profile and inflammatory markers

Table 20 displays concentrations of blood lipids and inflammatory markers (CRP) for participants in the cherry and placebo groups at baseline and 12 months. Due to failed venous access, only finger-prick blood samples could be collected at the 12-month follow-up session for six participants (n = 3 in cherry group, n = 3 in placebo group), so analyses of these were restricted to urate and CRP only.

Tart cherry concentrate failed to improve blood lipid measures of participants, relative to the placebo group. A 0.6 mmol/L increase in total cholesterol was observed in the cherry group by the end of the 12 months, however this was not found to differ significantly from the placebo group when adjusted for baseline ($F_{(1,20)}$ = 1.987, p = 0.174, ηp^2 = 0.090). ANCOVA tests revealed that there were also no significant differences between groups in other end of intervention blood lipid profile measurements, namely LDL ($F_{(1,20)}$ = 1.905, p = 0.183 ηp^2 = 0.087), HDL ($F_{(1,20)}$ = 0.181, p = 0.675, ηp^2 = 0.009), non-HDL ($F_{(1,20)}$ = 1.109, p = 0.305, ηp^2 = 0.053), TG ($F_{(1,20)}$ = 0.948, p = 0.342, ηp^2 = 0.045), and total cholesterol/HDL ratio ($F_{(1,20)}$ = 0.861, p = 0.364, ηp^2 = 0.041). CRP increased by 1.3 mg/L from baseline in the tart cherry group but only by 0.1 mg/L in the placebo group. However, when adjusted for baseline, CRP was not found to be significantly different between groups at 12 months ($F_{(1,25)}$ = 0.554, p = 0.464, ηp^2 = 0.022).

Table 20. Blood lipid profile and inflammatory markers at baseline and 12 months in the cherry and placebo groups.

	Cherry (*n* = 7)		Placebo (*n* = 16)		Adjusted treatment difference* (95% CI) at 12M
	0M	12M	0M	12M	
Total cholesterol, mmol/L, geometric mean (95% CI)	4.6 (4.0, 5.4)	5.2 (4.4, 6.1)	4.3 (3.9, 4.7)	4.5 (4.0, 5.0)	0.03 (-0.02, 0.08)
LDL, mmol/L, geometric mean (95% CI)	3.0 (2.5, 3.7)	3.4 (2.8, 4.3)	2.8 (2.5, 3.2)	3.0 (2.5, 3.5)	0.05 (-0.03, 0.13)
HDL, mmol/L, mean (SD)	1.2 (0.3)	1.3 (0.5)	1.1 (0.3)	1.2 (0.3)	0.03 (-0.13, 0.19)
Non-HDL, mmol/L, geometric mean (95% CI)	3.4 (2.8, 4.2)	3.8 (3.0, 4.9)	3.1 (2.8, 3.5)	3.3 (2.8, 3.8)	0.04 (-0.04, 0.11)
TG, mmol/L, geometric mean (95% CI)	1.6 (1.2, 2.3)	1.7 (1.0, 2.8)	1.4 (1.2, 1.7)	1.5 (1.2, 1.8)	-0.05 (-0.16, 0.06)
Total cholesterol/HDL ratio, geometric mean (95% CI)	4.1 (3.4, 4.9)	4.1 (3.0, 5.7)	4.0 (3.4, 4.6)	4.0 (3.4, 4.7)	0.03 (-0.04, 0.09)
CRP, mg/L, geometric mean (95% CI)	0.9 (0.4, 2.0)[1]	2.2 (1.3, 3.8)[1]	1.9 (0.9, 3.6)[2]	2.0 (1.1, 3.7)[2]	-0.14 (-0.51, 0.24)

0M, 0 months; 12M, 12 months; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triacylglyceride; CRP, C-reactive protein.
*Adjusted for baseline (0M).
[1]*n*=10, [2]*n*=19.

5.3.9. Secondary outcomes: change in arterial stiffness and blood pressure (BP) measures

Vascular measures of arterial stiffness and BP are shown in Table 21. PWV fell in both groups over the intervention period but there was no significant between-group difference ($F_{(1,24)}$ = 0.015, p = 0.904, ηp^2 = 0.001). A 3 mmHg increase in brachial SBP and a 4 mmHg increase in central SBP were observed in the placebo group at the end of the intervention, whereas these measures remained consistent in the cherry group. However, these differences were not statistically significant (brachial SBP, $F_{(1,26)}$ = 0.007, p = 0.936, ηp^2 = 0.000; central SBP, $F_{(1,26)}$ = 0.000, p = 0.988, ηp^2 = 0.000). When adjusted for baseline, there were also no significant differences between groups in brachial DBP ($F_{(1,26)}$ = 1.364, p = 0.253, ηp^2 = 0.050), AIx ($F_{(1,26)}$ = 0.017, p = 0.896, ηp^2 = 0.000), or resting HR ($F_{(1,26)}$ = 0.398, p = 0.533, ηp^2 = 0.015).

Table 21. Vascular measurements at rest at baseline and 12 months in the cherry and placebo groups.

	Cherry (*n* = 10)		Placebo (*n* = 19)		Adjusted treatment difference* (95% CI) at 12M
	0M	12M	0M	12M	
Brachial SBP, mmHg, mean (SD)	152 (18)	151 (19)	138 (17)	141 (19)	-0.47 (-12.40, 11.46)
Brachial DBP, mmHg, geometric mean (95% CI)	77 (73, 80)	79 (72, 87)	74 (71, 77)	74 (70, 78)	0.02 (-0.01, 0.05)
Central SBP, mmHg, mean (SD)	149 (18)	149 (17)	135 (17)	139 (18)	0.09 (-11.71, 11.89)
Pulse wave velocity, m/s, mean (SD)	9.5 (2.4)	8.9 (2.4)	9.1 (2.4)	8.6 (2.0)	0.09 (-1.44, 1.62)
Augmentation index, %, mean (SD)	26.0 (6.6)	26.1 (6.3)	25.0 (6.9)	25.6 (4.0)	0.24 (-3.52, 4.01)
Heart rate, BPM, geometric mean (95% CI)	62 (56, 69)	64 (56, 73)	66 (60, 74)	64 (60, 69)	0.01 (-0.03, 0.06)

0M, 0 months; 12M, 12 months; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPM, beats per minute.
*Adjusted for baseline (0M).

5.3.10. Secondary outcomes: change in medication use and perceived functional status

HAQ scores were measured at baseline, 6 months, and 12 months. However, most participants recorded no impediment from their gout in the preceding 6 months on daily pain, activities, mobility, or sleep at each of the time-points.

Table 22 displays the condition rating reported by participants at the end of the 12-month intervention period. In the tart cherry group, 83% of participants believed their condition had improved to some extent by 12 months ('slightly improved', 'improved', or 'much improved'), compared with 60% of the placebo group. Furthermore, 10% of the placebo group stated that their condition had deteriorated to some degree ('slightly worse', 'worse', or 'much worse'), yet deterioration was not reported by any participants in the tart cherry group. Despite this, there was no significant difference in self-reported condition status between groups (Fisher's = 2.764, $p = 0.663$).

Table 22. Self-reported condition rating at the end of the 12-month intervention period.

	Cherry (*n* = 12)	**Placebo (*n* = 20)**
Condition status, *n* (%)		
Much improved	2 (16.7)	1 (5.0)
Improved	5 (41.7)	7 (35.0)
Slightly improved	3 (25.0)	4 (20.0)
Stayed same	2 (16.7)	6 (30.0)
Slightly worse	0 (0.0)	0 (0.0)
Worse	0 (0.0)	2 (10.0)
Much worse	0 (0.0)	0 (0.0)

Both groups reported a reduction in use of gout medication during the intervention, but there was no difference between groups in the magnitude of reduction in use of either ULT (Fisher's = 3.556, p = 0.133) or anti-inflammatory (Fisher's = 2.108, p = 0.414) drugs (Table 23).

Table 23. Use of gout flare prevention and management medication in the cherry and placebo groups at baseline and 12 months.

	Cherry (n = 12)		**Placebo (n = 20)**	
	0M	**12M**	**0M**	**12M**
Allopurinol or febuxostat use, *n* (%)	8 (67)	6 (50)	11 (55)	11 (55)
Colchicine or naproxen use, *n* (%)	8 (67)	5 (42)	14 (70)	9 (45)

0M, 0 months; 12M, 12 months.

5.3.11. Secondary outcomes: change in BMI, diet, and physical activity (PA) levels

There was no significant change in BMI from baseline to 12 months in either group ($F_{(1,27)}$ = 0.044, p = 0.836, ηp^2 = 0.002) and no significant between-group difference ($F_{(1,27)}$ = 0.123, p = 0.795, ηp^2 = 0.003).

Table 24 displays the average daily energy and nutrient composition of participants' diets reported in their four-day food diary at baseline and 12 months. There were insufficient completed food diaries at 6 months and so this data was excluded from analysis. Reported fibre intake was significantly greater in the cherry group at both baseline and 12 months (group, p = 0.001). However, no statistically significant group by time interaction effect was detected for fibre (p = 0.868), or for any other dietary component (Table 24). Reported kcal (time, p = 0.007), carbohydrate (time, p = 0.008), and sugar (time, p = 0.002) consumption significantly reduced from baseline to 12 months in both groups. There were no other significant differences between the two groups in dietary composition over the 12-month intervention.

PA diaries were inadequately completed by many participants, so no analysis was conducted.

Table 24. Average daily energy (kcal) and nutrient intake at baseline and 12 months.

	Cherry (*n* = 12)		Placebo (*n* = 18)		Group*time significance (p-value)
	0M	**12M**	**0M**	**12M**	
Total energy, kcal, mean (SD)	1885 (338)	1677 (340)	1701 (474)	1494 (492)	0.992
Carbohydrates, g, mean (SD)	201 (36)	185 (37)	185 (49)	152 (50)	0.318
Sugars, g, geometric mean (95% CI)	73 (59, 89)	57 (40, 80)	62 (50, 78)	48 (38, 61)	0.693
Protein, g, mean (SD)	88 (21)	78 (21)	74 (20)	69 (17)	0.473
Fat, g, geometric mean (95% CI)	69 (59, 81)	59 (47, 73)	65 (51, 84)	53 (41, 69)	0.931
Saturated fat, g, mean (SD)	25 (8)	24 (9)	25 (12)	25 (12)	0.889
Water, ml, mean (SD)	2600 (699)	2416 (672)	2365 (845)	2116 (853)	0.763
Alcohol, ml, geometric mean (95% CI)	14 (7, 28)	14 (9, 23)	16 (10, 26)	14 (8, 27)	0.992
Fibre, g, mean (SD)	22 (5)	20 (5)	16 (5)	14 (4)	0.868

0M, 0 months; 12M, 12 months.

5.4. Discussion

Previous observational and pilot experimental research has suggested that tart cherry juice may reduce the risk of gout flares. To our knowledge, this placebo-controlled parallel study is the first to evaluate the effects of 12 months of daily tart cherry juice supplementation on the risk of gout flares, other markers of gout, and CVD risk in patients with gout. The original intention of this study was to conduct an RCT with a minimum of 94 participants. However, the COVID-19 pandemic meant that recruitment had to be halted prematurely at 38 participants. Thus, the study transformed largely into a feasibility study. The first part of this discussion will therefore focus on the acceptability of the treatments and outcome measures, retention and compliance, and sample size estimation. The trial had a high overall completion rate and there was high compliance, tolerability, and acceptability of study drinks. The second section of this discussion will discuss the effect of the intervention on primary and secondary outcome markers, with the acknowledgement that the study was only powered to detect a very large treatment effect. In the present study, the consumption of tart cherry juice daily for 12 months was found to have no clinically significant effect on gout flare frequency, serum urate, measures of UU, blood lipid profile, CRP, or vascular measures of arterial stiffness and BP.

The study had an overall completion rate of 86.5% and no between-group difference was observed. This indicates that the study protocol was appropriate and feasible in design. High self-reported adherence to the supplementation regime (98.6% for the placebo and 98.8% for the cherry) further support this. However, whilst the average reported palatability of the tart cherry juice was considered high at 12 months (7.0 out of 10.0), this varied greatly between participants, ranging from 0 to 10 out of 10. This indicates that some individuals could struggle to consume the drink outside of a study setting.

Other fruit juices, such as apple juice, and high-fructose beverages have been demonstrated to elevate serum urate levels (White et al., 2018) and their consumption has been associated with CVD (DeChristopher et al., 2017) and an increased RR of incident gout (Choi et al., 2010; Choi & Curhan, 2008). Daily tart

cherry juice consumption did not appear to have any detrimental impact on markers of gout or CVD risk or BMI when consumed daily for 12 months. This lack of a deleterious effect of cherry juice consumption indicates it may be an appropriate option for individuals with gout who wish to regularly consume fruit juice irrespective of whether it reduces the frequency of gout flares. Furthermore, our findings indicate that daily cherry juice consumption was tolerated by almost all participants, as no study withdrawals were related to the cherry juice and only one participant experienced minor gastrointestinal discomfort that was resolved by reducing consumption frequency from daily to every other day. Overall, the high trial completion rate and high drink compliance, tolerability, and acceptability suggest that this 12-month intervention protocol is safe, feasible, and appropriate, and could therefore be replicated in the future with a larger sample of gout patients.

We previously estimated that 94 participants were required to detect a 75% reduction in annual gout flare frequency. However, based on the 12-month mean gout flare frequency of 4.2 and SD of 4.6 in the placebo group of our study, a sample size of 114 (n = 57 per group) would be required to detect this reduction, assuming a power of 0.95 and an alpha of 0.05. On reflection, our suggested reduction in flare frequency was possibly too large for our target population. Therefore, using the data above, we have calculated that 252 participants (n = 126 per group) would be required to detect a 50% reduction in gout flare frequency, whilst 1000 participants (n = 500 per group) would be required to detect a 25% reduction. Based on experiences from the present single-centre study, a multi-centre study would be more appropriate for recruiting these numbers of participants. Despite limitations with sample size, our aim to over-recruit by 20% appeared to be sufficient to account for dropouts, as an attrition rate of 13.5% was found in this study, even in the context of a pandemic.

In the present study, tart cherry juice failed to cause statistically significant reductions in gout flare frequency, gout flare duration, and gout flare pain relative to the placebo drink. The absence of statistical significance might be partly explained by the lower than planned sample size. The lack of significant effect for

gout flare frequency contrasts with Schlesinger et al. (2012) who reported a significant reduction in gout flare frequency in 14 patients with gout, from 4.99 to 1.56 flares per 4 months, following 30 mL daily supplementation of cherry concentrate over 4 months. However, this study did not include a comparative placebo drink and so the reduction cannot be attributed to the cherry concentrate alone. Furthermore, as acute gout flares are intermittent with lengthy symptom-free, intercritical periods between flares, as was observed in the present study, 4 months may be an insufficient length of time to accurately detect changes in flare frequency (Schlesinger et al., 2012). Positive effects of cherry on the risk of gout flares have also been reported in a case-crossover study involving 633 adults, however causality cannot be confirmed here due to the observational design (Zhang, Neogi, et al., 2012). At present, there is insufficient evidence to support the use of tart cherry juice as an adjuvant treatment for gout flares.

Interestingly, in the present study, 23% more participants in the cherry group reported an improvement in their condition than in the placebo group, although it is important to note that these differences were not statistically significant. Blinding issues were unlikely to be responsible for perceived improvements in the cherry group, as only 38% of participants correctly guessed their treatment allocation and the distribution of correct and incorrect guesses were not significantly different between groups. Further investigation through the completion of a larger, placebo-controlled, 12-month trial is thus warranted.

No improvements in mean sUA concentration were observed at the end of the 12-month cherry juice intervention. Additionally, tart cherry juice had no effect on spot or 24-hour FEUA and UU over this time. Mean baseline sUA levels (397 µmol/L in the cherry group and 367 µmol/L in the placebo group) were above the <300 µmol/L and <357 µmol/L targets proposed by the BSR (Hui et al., 2017) and EULAR (Richette et al., 2017), but 16 (50%) participants had sUA levels below this threshold, indicating appropriate urate management at the time of study enrolment. Nevertheless, removal of these participants from the statistical analysis did not substantially alter the estimate of treatment effect. Baseline allopurinol and febuxostat use by our participants (57%) was also higher than the

30-33% that has been previously reported in UK populations (Kuo, Grainge, Mallen, et al., 2015; Roddy et al., 2007). However, adjustment for ULT use during analysis did not produce a significant between-group difference in sUA concentrations at 12 months.

These findings support the work of Stamp et al. (2020), whereby 28 days of daily cherry juice supplementation had no significant effect on the serum urate or UU excretion of 50 gout patients, and Schlesinger and colleagues (2012), where 120 days of daily tart cherry concentrate consumption failed to produce reductions in sUA in 14 patients with gout. Acute improvements in urate levels have been reported following the consumption of 280 g of depitted sweet cherries (Jacob et al., 2003) and 30 mL and 60 mL of tart cherry concentrate (Bell, Gaze, et al., 2014). However, these studies contained no placebo and urate exhibits diurnal variation (see Chapter 4; Devgun & Dhillon, 1992; Sennels et al., 2012) so their results need to be interpreted cautiously. Indeed, in our study reported in Chapter 4 which contained a placebo group, a 30 mL serving of tart cherry concentrate failed to cause a significant reduction in sUA or increase in UU excretion relative to the placebo group, but diurnal fluctuations in both were observed. Thus, at present, there is limited evidence to indicate that cherries decrease sUA or increase UU excretion.

Twelve months of tart cherry juice supplementation also failed to improve CRP levels in gout patients. In contrast, others have observed significant reductions in serum CRP levels following the consumption of tart cherry products in healthy individuals (Bell, Gaze, et al., 2014; Chai et al., 2019) and in those with osteoarthritis (Kuehl et al., 2012; Schumacher et al., 2013). However, our observation is in agreement with studies involving 58 healthy individuals following 30 days of 60 mL tart cherry juice supplementation (Hillman & Chrismas, 2021) and 10 overweight individuals following the consumption of 240 mL/day tart cherry juice for 4 weeks (Martin et al., 2018). The lack of effect is also supported by a recent meta-analysis involving seven tart cherry RCTs (Han et al., 2020). Previous research has indicated a positive association between raised CRP and uric acid levels (Lyngdoh et al., 2011; Ruggiero et al., 2006, 2007). However,

despite the elevated sUA levels of participants in the present study, median baseline CRP concentrations were relatively low (<2.0 mg/L), which may have limited the ability to detect a treatment effect (Nordestgaard & Zacho, 2009).

The reason for discrepancies in the literature is not clear, however variation in phenolic and anthocyanin content of cherry juices may offer one potential explanation. The phenolic compounds found in tart cherries, particularly anthocyanins, have been proposed to regulate enzymes and cell-signalling pathways involved in the inflammatory process (see section 2.3.4.; Mulabagal et al., 2009). Therefore, tart cherry juice containing lower quantities of phenolic compounds may exhibit weaker anti-inflammatory effects. In the present study, the total phenolic and anthocyanin content of the two batches of tart cherry concentrate was lower than has been previously reported in the literature (Bell, Gaze, et al., 2014; Keane, Bell, et al., 2016; Schumacher et al., 2013).

It is plausible that a loss in active phenolic compounds may have occurred during transportation from suppliers, as these compounds are considered relatively unstable (Bonerz et al., 2007; Ou et al., 2012). Likewise, as this was a free-living study and participants were required to store several bottles of cherry concentrate at a time in their own homes, inappropriate storage conditions may have contributed to further degradation of phenolic compounds (Sanchez et al., 2015). Inter-batch variation in phenolic content may also occur (Poll et al., 2003), yet many studies have relied on manufacturers' values when reporting the phenolic and anthocyanin content of their concentrate. Furthermore, the bioavailability of anthocyanins and other phenolic compounds can vary between batches and between-participant differences in absorption may occur (Manach et al., 2004). It would be useful for future studies to assess the appearance of plasma metabolites of bioactive compounds during the long-term consumption of cherry juice. Researchers should also analyse and report the phenolic composition of the cherry product they are investigating and ensure it is stored appropriately throughout intervention periods.

It has been suggested that cherry consumption may improve blood lipid profile through the binding of its phenolic compounds to bile acids (Chai et al., 2018).

However, no improvement in lipid profile was observed following the 12 months of daily tart cherry juice supplementation in the present study. This is in line with previous findings from studies of cherry juice supplementation of up to 3 months duration with healthy adults (Desai, Bottoms, & Roberts, 2018; Kelley et al., 2006; Lynn et al., 2014; Sinclair et al., 2022) and adults with metabolic syndrome (Johnson et al., 2020). Mean blood lipid measurements were considered within the healthy range at baseline in these studies and in the present study (Heart UK, n.d.). Whilst it could be argued that the absence of dyslipidaemia may mask the potential for cherry juice to improve blood lipid profile, other studies on participants with mildly elevated blood lipid indices and CVD risk ratios at baseline have also identified no changes in these markers following acute or chronic cherry consumption (Desai et al., 2019; Kimble et al., 2021; Martin & Coles, 2019). It is therefore reasonable to suggest that tart cherry juice is unlikely to improve blood lipid profile of individuals with gout without, or with mild, dyslipidaemia.

Twelve months of cherry juice supplementation also failed to improve markers of vascular health, namely brachial and central BP, PWV, AIx, and resting HR. Average brachial DBP was in the healthy range in both groups at baseline which could explain the lack of effect. Indeed, other studies involving individuals with healthy DBP have similarly noted the absence of effect of tart cherry on DBP (Keane et al., 2018; Keane, Haskell-Ramsay, et al., 2016; Lynn et al., 2014; Sinclair et al., 2022). Tart cherry juice also had no effect on brachial or central SBP in our study, despite both groups displaying raised average brachial SBP at baseline (>140 mmHg SBP in cherry group and >130 mmHg in placebo group). Significant reductions in SBP have previously been observed following both the acute ingestion of tart cherry juice (Keane, George, et al., 2016; Keane, Haskell-Ramsay, et al., 2016) and 12 weeks of daily tart cherry juice consumption (Chai et al., 2018) where baseline SBP of participants was above 130 mmHg. However, a recent meta-analysis involving seven RCTs investigating the effects of cherry juice (n = 1 for sweet cherry and n = 6 for tart cherry) on BP, which included studies of both normotensive and hypertensive participants, concluded that cherry consumption had no significant effect on DBP or SBP (Eslami et al., 2022).

Strong inhibition of ACE, an enzyme involved in the activation of vasoconstrictors and inactivation of vasodilators, has been demonstrated *in vitro* with tart cherry extract, with anthocyanins proposed to be primarily responsible for this effect (Kirakosyan et al., 2018). As discussed previously, the anthocyanin content of our cherry concentrate was lower than some previous reports (Keane, Bell, et al., 2016), so this may have contributed to the absence of improvement in SBP in the present study. Furthermore, although mean baseline SBP was above 130 mmHg, not all participants were classified as having hypertension. Future research could consider recruiting solely hypertensive gout patients.

Arterial stiffness measurements of AIx and PWV were also not differentially altered by cherry juice at 12 months when compared to the placebo drink. It has been speculated that anthocyanin intake may be less effective at altering arterial stiffness in healthy individuals (Lynn et al., 2014). At baseline, average PWV and HR in the present study were in line with those previously reported in healthy populations (Koivistoinen et al., 2007; Mitchell et al., 2004) which could explain why cherry juice consumption did not significantly alter these measurements following 12 months of consumption. However, average baseline AIx measurements were similar to those of individuals with metabolic syndrome (Desai et al., 2021; Johnson et al., 2020). In these studies, neither 7 days (Desai et al., 2021) nor 12 weeks (Johnson et al., 2020) of daily tart cherry supplementation resulted in improvements in AIx, suggesting that AIx is not affected by the consumption of tart cherry supplementation. Overall, our findings add to a growing body of literature, including studies involving patients with hypertension, high CVD risk, and metabolic syndrome, reporting an absence or limited effect of cherry juice on measures of vascular health (Desai et al., 2019, 2021; Johnson et al., 2020; Keane, George, et al., 2016; Kimble et al., 2021).

A strength of this study was that the groups appeared well-matched at baseline, with no significant differences identified between group characteristics. Participants were predominantly male, middle-aged or above, overweight or obese, and most likely to experience flares in their big toe/s. This is representative

of the demographics of gout patients in the UK (Cea Soriano et al., 2011; Kuo, Grainge, Mallen, et al., 2015; Rothenbacher et al., 2011; Schlesinger, 2013).

However, there were several limitations of the current study, largely caused by the COVID-19 pandemic. The main limitation was the low final participant sample size because the pandemic prematurely halted recruitment. Additionally, the five participants who dropped out were originally in the cherry group. Despite the use of block randomisation at baseline, this resulted in considerably fewer participants in the cherry group compared with the placebo group at 12 months (n = 12 and n = 20). A larger initial sample size may have helped prevent this unbalance. The pandemic also prevented all but five participants from attending laboratory follow-up sessions at 6 months and three participants at 12 months. Restrictions to laboratory access during this time also meant that phenolics could not be measured in the 2nd batch of cherry juice. Furthermore, larger than preferred batches of cherry concentrate had to be delivered to participants at times to ensure a consistent supplementation regime during COVID-19 lockdowns. As discussed previously, this may have resulted in the inappropriate storage of drinks and possible increased degradation of phenolic compounds. This also reduced opportunities for face-to-face contact with participants. However, this did not appear to negatively influence adherence to the supplementation regime. Regular telephone calls and email reminders appeared to have been effective here.

Due to limited resources and time, there was a reliance on self-reported retrospective recall of gout flares in the 12 months preceding baseline and so there is a potential for recall bias, an issue acknowledged by others utilising retrospective gout flare data (Taylor et al., 2021). This may have contributed to the observed reductions in gout flare frequency and pain in both groups over the 12-month intervention period.

It is also acknowledged that the placebo drink was not matched to the tart cherry juice for protein or carbohydrate content, both of which have been shown to impact serum urate. For example, increased consumption of protein, particularly from plant-based sources, has recently been demonstrated to lower sUA levels

in individuals with elevated BP (Belanger et al., 2021), whilst moderate carbohydrate restriction has been shown to reduce sUA levels of men with gout (Dessein et al., 2000). Fructose is also proposed to increase the synthesis of uric acid whilst reducing its excretion, resulting in increased sUA levels (Caliceti et al., 2017; Johnson et al., 2007). Owing to the duration of drink storage required in this trial, the addition of these macronutrients would have implicated the stability of the placebo drink. Furthermore, sUA did not change significantly from baseline to 12 months in either group, suggesting that the presence or absence of these macronutrients in the intervention drinks had no effect on serum urate levels in the present study.

Garcia-Maturano et al. (2022) reported that gout flares during the COVID-19 pandemic were 9 times more frequent and that patients' urate levels also increased. Similarly, others have suggested that the pandemic had a negative impact on the management of gout by patients (Singh & Edwards, 2020; Tai et al., 2022). Changes in diet and exercise and difficulties in accessing healthcare have been proposed as contributing factors to poorer gout management during the pandemic (Garcia-Maturano et al., 2022; Singh & Edwards, 2020; Tai et al., 2022). Nevertheless, impaired gout management was not observed in our 12-month intervention, despite this taking place during the pandemic. Indeed, the frequency of gout flares decreased in both groups following the intervention. The reduction in flare frequency cannot be attributed to the cherry juice, as no treatment effect was observed.

Whilst the free-living setting of Study 3 could be considered an overall strength of the design, this introduced other limitations. Participants were asked to continue consuming their 'typical' diet throughout the study duration, although cherry consumption was limited. Despite this, the four-day food diaries indicated that there was a significant reduction in calories, carbohydrate, and sugar in both groups at 12 months. The COVID-19 pandemic influenced food availability, health awareness, and eating behaviours, and so participants' diets may have changed because of this (Bennett et al., 2021; Rivington et al., 2021; Snuggs & McGregor, 2021). Nevertheless, a previous feasibility study undertaken prior to

the pandemic also observed reductions in total energy and carbohydrate intake following 6 months of daily tart cherry juice consumption, suggesting broader issues of long-term adherence to dietary guidance (Middleton et al., 2013) and the influence of research participation on behaviour (McCambridge et al., 2014). One or all of these dietary changes may have contributed to the reduction in flares observed in both groups in Study 3. Future research should aim to tackle these limitations through increased reminders of dietary guidance.

Changes in PA levels because of the COVID-19 pandemic have also been reported (Sport England, 2022). If this were the case in the present study, this could have also confounded findings. However, unfortunately, we were unable to ascertain this from the limited PA data provided by participants.

Our study has shown that this 12-month regime was appropriate and achievable for most individuals with gout and so the current study's protocol should be replicated with a larger sample size in a multi-centre study. Additionally, to improve the current protocol, monitoring individuals for 12 months before starting their intervention would likely result in more accurate baseline gout data and overcome potential recall issues associated with retrospective recall of gout flare frequency, pain, and duration. However, 12 months of pre-intervention monitoring would be difficult to implement and could substantially reduce retention of participants.

Low scores for HAQ at baseline indicated that most participants had acute rather than chronic gout, characterised by periods of gouty pain interspersed with periods without pain (Schlesinger, 2013). This is supported by baseline data indicating the presence of tophi in only five participants, flares occurring in just one joint in most participants, and the absence of overlapping flares. Prior research has focused on the role of cherries in managing acute gout and so future research into their use for chronic gout is needed.

Finally, urate levels may be impacted by differences in sex and, for women, the rise in urate levels seen following the menopause (Hak & Choi, 2008; Ragab et al., 2017). In the current study, it was not possible to explore any differences in

the effect of cherry juice on urate levels between sexes or pre- and post-menopause, because only two women participated in the study and these women were both randomised into the placebo arm of the trial. Additionally, menopause status was not collected from female participants during the study. Therefore, future research should aim to explore any differences that may result from these factors.

5.4.1. Conclusion

To conclude, the present study indicates that a 12-month intervention with tart cherry juice in gout patients is feasible given the high retention of participants, their compliance with the protocol, and tolerance of the study procedures. Our study was limited by a small sample size due to COVID-19 leading to the premature cessation of recruitment, however we failed to detect any signal of a possible effect of tart cherry juice on gout flare frequency, uric acid, CRP, measures of vascular health, or blood lipid profile. Future adequately powered RCTs are required to clarify whether tart cherry juice consumption has a role as an adjuvant therapy for the treatment of gout.

6.0. General Discussion, Limitations, and Conclusion

6.1. Synopsis of main findings

There are numerous sources of dietary guidelines available for patients with gout in the UK, yet many recommendations are currently supported by a limited, weak, or fragmented evidence base. As discussed in Chapter 2, cherries have garnered growing public and research interest into their role in the prevention and management of gout. Recently, gout has been shown to be a risk factor for COVID-19 related deaths (Strangfeld et al., 2021; Topless et al., 2022), emphasising the importance of research into the management of gout during the COVID pandemic. Furthermore, hyperuricaemia and gout are associated with increased risk of CVD, and the role of cherries in reducing this risk has also received attention. Preliminary research indicates that the consumption of cherries and/or cherry products may produce improvements in urate levels, inflammation, pain, gout flares, and some vascular measures (see sections 2.3. and 2.4.). However, as highlighted in Chapter 2, existing evidence is limited by study design, such as a lack of appropriate controls, short duration of supplementation, observational methodology, and the use of healthy participants rather than individuals with gout. The three main studies presented in this thesis were designed to overcome these limitations and achieve an overall aim of exploring the role of dietary modification in the prevention of gout and CVD, with a particular focus on tart cherries.

The first objective of this thesis was to assess the accuracy, reliability, quality, and understandability of dietary information for gout provided to the public on the YouTube® platform. Study 1 (see Chapter 3) indicated that dietary recommendations for gout provided by YouTube® videos frequently do not align with national evidence-based dietary guidelines, are often of poor quality, and are not always appropriate for residents in the UK. It was also noted from this study that the inclusion of cherries in the diet was encouraged by all three evidence-based dietary guidelines for the management of gout (Hui et al., 2017; NICE, 2018; Richette et al., 2017). However, the BSR and EULAR both acknowledged that this recommendation was established from epidemiological evidence only. Despite the relatively weak evidence base for this advice, 29% of YouTube®

videos providing dietary recommendations for gout were found to endorse cherry consumption as a therapeutic aid (see section 3.3.3.). This figure is in line with that of a content analysis of UK and US newspapers in which 25% of articles discussing dietary management of gout recommended the consumption of cherries (Duyck et al., 2016). Videos recommending the consumption of cherries for gout in Study 1 often scored poorly for educational quality, reliability, understandability, and actionability and complied poorly with other evidence-based dietary recommendations. Despite this, these videos received considerable attention and were well-liked by viewers overall. It is clear from these observations that the recommendation to consume cherries is publicly recognised, reinforcing the need for well-controlled experimental studies to underpin this guidance.

Studies 2 and 3 were designed to provide evidence to support or dispute this recommendation by identifying the role of tart cherries in the prevention and management of gout and CVD. Study 2 (see Chapter 4) sought to compare the acute effects of tart cherry juice with a neutral water control on uric acid levels, inflammation, and CVD risk markers in healthy individuals. Compared with a water control, tart cherry juice did not induce any significant effects on sUA concentration, UU:creatinine, serum CRP concentration, or markers of vascular health in the 5 hours following its consumption. However, diurnal variations in sUA, UU:creatinine, serum CRP, and BP measurements were identified. Whilst the dietary controls of Study 2 are considered strengths of this study, the clinical applicability of findings to patients with gout is limited by its use of healthy individuals, because gout is typically characterised by raised levels of uric acid and inflammation and is associated with an increased risk of CVD (see sections 2.1.3. and 2.1.6.1.).

Study 3 (see Chapter 5) therefore builds on the findings of Study 2 by evaluating the effect of long-term tart cherry juice consumption on uric acid levels, gout flare frequency and intensity, inflammation, and CVD risk in patients with diagnosed gout. After twelve months of daily consumption, tart cherry juice was not found to have any statistically significant effect on patients' gout attacks, gout medication

use, or self-reported condition status when compared with a low-phenol placebo drink. Furthermore, in line with Study 2, measures of urate, inflammation, and CVD risk were also found to be unaffected by tart cherry juice consumption.

6.2. Discussion of main findings and clinical applications

6.2.1. Dietary recommendations for gout on YouTube®

Previous research has demonstrated that resources containing written (Jimenez-Liñan et al., 2017; Johnston et al., 2015; Robinson & Schumacher, 2013) and pictorial (Krasnoryadtseva et al., 2020) health advice for the management of gout commonly lack accuracy, provide inadequate information, and/or use complicated language which is unsuitable for their intended audience. This is further supported by findings of Study 1 (see Chapter 3) which indicated that dietary recommendations for gout provided by YouTube® videos frequently do not align with national evidence-based dietary guidelines, are often of poor quality, and are not always appropriate for residents in the UK. Clearer and more consistent recommendations across sources are required to ensure effective treatment and management of gout (Gobeil-Lavoie et al., 2019; Liddle et al., 2021), and these guidelines should be based on strong, high-quality evidence.

The recommendation to consume cherries for gout was prevalent across YouTube® videos and these videos appeared to be popular with viewers. As these videos also contained at least one other dietary recommendation for gout, is it not possible to attribute the popularity of these videos directly to their advocacy of cherry consumption for gout. Nevertheless, the prevalence of this recommendation and its potential exposure to viewers reinforces the need for well-controlled studies to underpin this guidance. It is important to note that these findings do not indicate that members of the public who are aware of this recommendation are consuming cherries. Current cherry or cherry product consumption by patients with gout in the UK is unknown, but a figure of 43% has been proposed for patients in the US (Singh et al., 2016). It would be useful for future studies to assess the rates of use of cherries and cherry products as a sole or adjuvant therapy for gout in the UK, particularly in those who are aware of the recommendation to consume cherries.

6.2.2. Hyperuricaemia and gout

Collectively, results from Studies 2 and 3 are unable to support a direct role of tart cherries in the management of hyperuricaemia or gout (see Chapters 4 and 5). Increased glomerular filtration of urate and inhibited hepatic activity of enzymes involved in the production of uric acid have previously been proposed as the main mechanisms by which the risk of gout flares may be reduced by cherry consumption (Haidari et al., 2009; Jacob et al., 2003; Kirakosyan et al., 2018; Zhang, Neogi, et al., 2012). However, no significant improvements in sUA or measures of UU excretion were observed following the consumption of 30 mL tart cherry concentrate (diluted with 220 mL water) in a single dose by healthy individuals (Study 2) or 12 months of daily supplementation in patients with gout (Study 3). This is in line with research showing that tart cherry concentrate had no clinically significant effect on sUA levels or UU excretion of patients with gout when consumed in doses between 7.5 mL to 30 mL twice daily for 4 weeks (Stamp et al., 2020) or 15 mL twice daily for 120 days (Schlesinger et al., 2012). Together, these findings suggest that if tart cherry concentrate were found to reduce risk of gout flares, it is unlikely to be facilitated through either of the mechanisms outlined above.

Whilst observational (Zhang, Neogi, et al., 2012) and pilot experimental (Schlesinger et al., 2012; Singh, Willig, et al., 2020) research has previously indicated a role of cherries in reducing the frequency of gout flares, Study 3 did not demonstrate improvements in the frequency, intensity, or duration of gout flares, self-reported condition rating, or use of gout medication in gout patients with 12 months of daily tart cherry juice consumption when compared with a cherry-flavoured placebo (see Chapter 5). Although originally planned as a large-scale intervention study (n = 94), this was adapted into a smaller feasibility study (n = 37) because of the COVID-19 pandemic.

Prior to this research, intervention studies investigating the effects of tart cherry on gout attack risk in individuals with gout have ranged from 28 days to 9 months in duration (Schlesinger et al., 2012; Singh, Willig, et al., 2020; Stamp et al., 2020). Participants in Study 3 experienced an average of 2.8 flares per year at

baseline. Had a shorter intervention period been utilised for this study, it is likely that no flares would have been recorded for many participants during this period, resulting in inaccurate conclusions regarding the change in flare frequency. Furthermore, seasonal variation in acute gout has been reported (Karmacharya et al., 2016) and Study 3 has accounted for this by encompassing all seasons during the 12-month intervention period. This was not acknowledged by previous studies yet could have contributed to reported reductions in gout flares. Nevertheless, Study 3 is restricted by its limited sample size and so additional long-term studies involving larger samples of patients with gout are needed to confirm the effects of tart cherry juice on gout flares. To assess any short-term changes in urate metabolism, the acute study design of Study 2 should also be replicated in patients with gout.

Levels of inflammation, as indicated by serum CRP concentrations, did not significantly decrease following the consumption of tart cherry juice in either healthy individuals (see Chapter 4) or patients with gout (see Chapter 5). Prior studies of cherries and cherry products have drawn inconsistent conclusions, with some demonstrating anti-inflammatory benefits (Bell, Gaze, et al., 2014; Chai et al., 2019; Kelley et al., 2006, 2013; Kuehl et al., 2012) and others failing to observe statistically significant reductions in CRP (Bowtell et al., 2011; Brown et al., 2019; Jackman et al., 2018; Martin et al., 2018; McCormick et al., 2016; Vargas et al., 2014). The reason for discrepancies between studies is not definitive, but differing baseline CRP levels, inter-batch variation in the phenolic and anthocyanin content of cherry products, and the choice of, or lack of, control groups may be responsible (see sections 4.4. and 5.4). In both intervention studies in this thesis, average baseline CRP concentrations were considered relatively low, indicating minimal levels of inflammation. Whist this was not surprising for the healthy participants in Study 2, elevated CRP levels at baseline were expected in Study 3, as gout is considered an inflammatory condition (see section 2.1.3.).

It has also been acknowledged that levels of cytokines and other inflammatory markers may be lower throughout inter-critical periods between gout flares than

during flares (Cavalcanti et al., 2016). Participants in Study 3 were requested not to attend laboratory sessions during or in the week following an acute gout flare, as decreased sUA concentrations have been observed during these events (Urano et al., 2002). As such, the effect of cherry juice on flare-induced inflammation was not assessed.

6.2.3. CVD

The studies described in Chapters 4 and 5 are also unable to provide evidence to support the use of tart cherry juice in the prevention or management of CVD. In addition to CRP, which has been considered a useful tool for indicating risk of CVD (Backes et al., 2004), tart cherry juice consumption did not improve any measures of vascular function (see Chapters 4 and 5) or blood lipid profile (see Chapter 5) either acutely or following long-term supplementation. This adds to an expanding literature base, including studies in healthy normotensive individuals and those with elevated CVD risk markers, suggesting that cherry juice supplementation has no effect on measures of arterial stiffness (See section 2.4.2.; Desai et al., 2019, 2021; Johnson et al., 2020; Keane, Haskell-Ramsay, et al., 2016; Kimble et al., 2021; Lynn et al., 2014), blood lipid profile (See section 2.4.3.; Desai, Bottoms, et al., 2018, 2019; Johnson et al., 2020; Kelley et al., 2006; Kimble et al., 2021; Lynn et al., 2014; Martin & Coles, 2019; Sinclair et al., 2022), or DBP (See section 2.4.1.; Chai et al., 2018; Desai et al., 2019; Johnson et al., 2020; Keane et al., 2018; Keane, George, et al., 2016; Keane, Haskell-Ramsay, et al., 2016; Kent et al., 2017; Lynn et al., 2014; Sinclair et al., 2022).

In contrast, studies involving participants with raised baseline BP measurements have previously indicated a role of tart cherry juice in improving SBP (See section 2.4.1.; Chai et al., 2018; Desai et al., 2019; Keane, George, et al., 2016; Keane, Haskell-Ramsay, et al., 2016), but this was not observed in our studies. The use of normotensive individuals may explain the absence of an improvement in SBP in Study 2, however participants with gout in Study 3 displayed an average baseline brachial SBP > 130 mmHg and yet no statistically significant reductions were observed. The reason for this disagreement may instead be attributed to the different volumes of cherry juice provided in these studies. In Studies 2 and

3, participants were provided with 30 mL servings of tart cherry concentrate, whereas Chai et al. (2018), Keane, George, et al. (2016) and Keane, Haskell-Ramsey, et al. (2016) provided participants with double this volume of tart cherry concentrate. Additionally, as discussed in sections 4.4. and 5.4., the total phenolic and anthocyanin contents of the tart cherry juice used in Studies 2 and 3 were lower than values previously published for similar servings. As phenolic compounds, particularly anthocyanins, have been considered primarily responsible for the improvements in BP (see section 2.4.1.), insufficient provision of these compounds may have contributed to the absence of reduced BP measurements in the two experimental studies described in this thesis.

6.2.4. Tart cherry juice versus other high fructose beverages

Although no health-promoting benefits of cherry juice were identified in Studies 2 and 3, tart cherry juice did not appear to exert any detrimental effects on any of the gout or CVD health markers measured and may therefore be considered an appropriate drink for individuals with or at risk of gout or CVD (see Chapters 4 and 5). In contrast, some other 100% fruit juices, such as apple juice, blueberry, orange juice, and grape juice, have been shown to impair markers of gout and CVD, or are associated with an increased risk of these conditions (Godycki-Cwirko et al., 2010; Olofsson et al., 2019; Vieira et al., 2012; White et al., 2018). Sugar-sweetened beverages have also been associated with an increased risk of hyperuricaemia, gout, and CVD (see sections 2.1.5. and 2.1.8.6.; Jiang et al., 2021). Indeed, as identified in Study 1 (see Chapter 3), recommendations to avoid sugar-sweetened drinks and reduce orange and apple juice consumption are included in evidence-based dietary guidelines for the management of gout in the UK.

The negative effects of these beverages has been largely attributed to their high fructose content, as the metabolism of fructose can result in impaired urate and lipid metabolism (Aeberli et al., 2011; Caliceti et al., 2017) and the promotion of inflammation (Miller & Adeli, 2008; Roglans et al., 2007). One 30 mL serving of the tart cherry concentrate used contained approximately 7.9 g of fructose (Desai et al., 2021), yet this fructose did not appear to be similarly detrimental to the

health of participants in Studies 2 and 3. The difference between drinks could be explained by individual and/or synergistic effects of bioactive compounds found in tart cherries that may counteract the urate-stimulating mechanisms of fructose (Ayoub-Charette et al., 2021). However, further research is required to confirm this. Nevertheless, the observation from Studies 2 and 3 that tart cherry juice did not impair uric acid concentrations or CVD risk markers may provide gout sufferers with an appropriate alternative to sugar-sweetened beverages and fruit juices that can exacerbate gout risk markers. The high acceptability and tolerability of the cherry juice across Studies 2 and 3 further supports this as a suitable beverage.

The use of appropriate placebo drinks in Studies 2 and 3 can be considered strengths of this research. Control groups have been missing from previous intervention studies reporting positive effects of tart cherries on gout flares (Schlesinger et al., 2012; Singh, Willig, et al., 2020). In addition to the seasonal variation in gout discussed previously, potential observer bias due to a lack of blinding and the influence of research participation on behaviour could have contributed to the reported reductions in gout flares in these studies. The provision of an adequately blinded placebo drink in Study 3 helped to limit these confounding factors. The identification of diurnal variation in Study 2 following the use of a neutral control drink also brings into question the results of uncontrolled studies that have failed to account for these daily fluctuations yet report beneficial acute effects of cherries and cherry juice (Bell, Gaze, et al., 2014; Jacob et al., 2003). Collectively, these observations highlight the importance of including appropriate control groups when evaluating the effects of cherry juice in the future. Long-term prospective studies of cherry juice should also ensure that follow-up measurements are collected at similar times of the day to account for possible diurnal fluctuations.

6.3. Limitations and future research

Despite best efforts to control studies, several limitations have been identified. As previously mentioned, samples of tart cherry concentrate used in Studies 2 and 3 were found to have a lower total phenolic and anthocyanin content than has

been previously reported. This could be explained by inter-batch variation, differences in analytical methodologies, and/or storage and transport conditions (see sections 4.3.2. and 5.3.2.). If phenolic compounds were responsible for beneficial health effects of cherries and cherry products seen in previous studies, then this may explain the absence of improvements to health markers in this thesis. The reporting of bioactive compounds in cherry products has been inconsistent in the literature and so future studies should aim to measure and publish total phenolic content as a minimum to enable comparisons to be made across studies.

Another factor that may explain between-study differences is the inter-individual variability in participants' responses to tart cherry juice. Differences in bioavailability, including intestinal absorption, metabolism, and excretion variances, the bioactivity of polyphenols and their metabolites, and participants' age, sex, and overall health status have all been identified as factors that may contribute to this variability (Eker et al., 2020; Manach et al., 2004; Ruskovska et al., 2020). It would have been useful to have characterised the phenolic metabolites appearing following the consumption of tart cherry juice to help determine the bioavailability of these components, but this was outside of the timescale and funding of this research. Urine samples from Study 2 have however been stored for investigation of metabolites in the future.

Due to limited resources, CRP was the only marker of inflammation measured in studies 2 and 3. Uric acid induced caspase-1 activity results in the increased secretion of many different inflammatory cytokines, including IL-1β, IL-18, IL-8, IL-6, and TNFα (see section 2.1.3). Although CRP concentration has been correlated with IL-6 and IL-18 concentrations in patients with gout, direct high-sensitive measures of cytokines may provide a more accurate indication of inflammatory activity and/or the mechanisms of gout (Cavalcanti et al., 2016). Future analysis of the acute and long-term effects of tart cherry juice on inflammation should consider evaluating a greater range of inflammatory markers.

A major barrier to the work in this thesis was the COVID-19 pandemic in the UK, which was present during much of this research. This unpredictable event made the recruitment and retention of participants particularly difficult and may also have influenced the free-living dietary and PA habits of participants, as discussed in section 5.4. Both intervention studies were limited by sample size because of the COVID-19 pandemic. Study 3 has demonstrated that a long-term intervention is feasible and so this study should be repeated in multi-centre study using a larger sample of patients with gout. Furthermore, to enable greater generalisability of findings, studies should aim to recruit participants from different areas of the UK. It was not possible to measure the anthocyanin and total phenol content of every batch of cherry juice as a result of laboratory closures during the pandemic, yet, as discussed above and in section 5.4, it has been recognised that inter-batch variation can occur. Finally, audience engagement with YouTube® videos in Study 1 may have been skewed by a reduction in face-to-face contact with health care professionals during this time. As discussed in Chapter 3, it would be beneficial to measure the change in engagement metrics for these videos over time, especially as face-to-face contact is re-established. Additionally, as new data on the effect of dietary components on gout is published and dietary guidelines are adapted correspondingly, future research could assess if videos are updated in line with these updates.

6.4. Conclusion

To conclude, this work has demonstrated that readily accessible sources of dietary information for gout often fail to align with evidence-based guidelines for gout and are not always suitable for patients with gout in the UK. Greater consistency across sources is required to support the self-management of gout. The recommendation to consume cherries for gout management has been included in both UK evidence-based dietary guidelines for gout and in many online resources, including YouTube® videos.

This research has demonstrated that long-term tart cherry supplementation is feasible and accepted by patients with gout and does not appear to be detrimental to health. However, no health-promoting benefits for hyperuricaemia, gout, or

CVD, were observed following the consumption of a single dose of tart cherry concentrate in healthy individuals or after 12 months of daily consumption in patients with gout, when compared with placebo beverages.

Studies with larger sample sizes are required to confirm these findings. It would also be useful to assess the metabolism of polyphenolic compounds following the consumption of tart cherry juice, to ascertain whether this may be a limiting factor to potential health benefits of cherries.

Overall, whilst there is insufficient evidence to support a direct role of tart cherry juice in the prevention and management of gout and CVD, it appears to be an appropriate alternative to drinks that are known to exacerbate risk markers of gout and CVD.

7.0. References

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8.0. Appendices

Appendix 1. SHU ethical approval for Study 1

A content analysis of YouTube videos containing dietary recommendations for gout

Ethics Review ID: ER24922220
Workflow Status: Application Approved
Type of Ethics Review Template: No human participants, human tissue or personal data

Primary Researcher / Principal Investigator

Kirstie Lamb
(Sheffield Business School)

Converis Project Application:
Q1. Is this project ii) Doctoral research

Director of Studies

Margo Barker
(Sheffield Business School)

Appendix 2. Dietary recommendation items from British Society for Rheumatology (BSR), European League against Rheumatism (EULAR) and National Institute for Clinical Excellence (NICE) guidelines for the management of gout that YouTube® videos were scored against to produce compliance scores

Full 30 items from guidelines	17 items that 'Foods to eat' videos were scored against	10 items that 'Foods to avoid' videos were scored against
Avoid excessive meat intake		X
Avoid excessive alcohol intake/drink alcohol sensibly		X
Avoid excessive consumption of beer		X
Avoid excessive consumption of spirits		X
Avoid excessive seafood intake		X
Avoid excessive purine intake		X
Avoid fructose-rich foods		X
Avoid sugar-sweetened drinks		X
Reduce orange and apple juice consumption		X
Encourages diet low in sugar/Avoid excessive sugar consumption	X	X
Encourage a diet high in vegetables	X	
Encourage fruit consumption	X	
Encourage fluid/water intake to prevent dehydration (>2 litres)	X	
Encourage (low-fat) dairy consumption	X	
Encourage a diet high in fibre	X	
Encourages consumption of cherries	X	
Consumption of vitamin C may be beneficial	X	
Coffee consumption may reduce recurrent gout flares	X	
Encourage diet low in fat	X	

Encourage skimmed milk consumption	**X**
Encourage regular exercise	
Encourage low-calorie/low-fat yoghurt consumption	**X**
Moderate intake of purine-rich vegetables okay/does not increase risk	**X**
Encourage consumption of soybeans and other vegetable protein sources	**X**
Moderate wine intake (2 glasses/day) acceptable/does not increase risk	**X**
Encourage folate intake	**X**
Fluid/water intake is especially important for those with kidney stones	**X**
Taking prescribed gout medication is still important	
Weight loss should be encouraged if appropriate	
Weight loss should be gradual/avoid crash dieting	

Appendix 3. Global Quality Scale (GQS) definitions

POOR	Poor quality, poor flow of the video, most information missing, not at all useful for patients
GENERALLY POOR	Generally poor quality and poor flow, some information listed but many important topics missing, of very limited use to patients
MODERATE	Moderate quality, suboptimal flow, some important information is adequately discussed but others poorly discussed, somewhat useful for patients
GOOD	Good quality and generally good flow. Most of the relevant information is listed, but some topics not covered, useful for patients
EXCELLENT	Excellent quality and flow, very useful to patients

Appendix 4. Adapted-DISCERN tool criteria

Reliability of information (1 point for Yes, 0 points for No or Unclear)
1. Are the aims clear and achieved?
2. Are reliable sources of information used? (i.e. video includes citations/references, speaker is board-certified rheumatologist or dietician etc.)
3. Is the information presented balanced and unbiased?
4. Are additional sources of information listed for patient reference?
5. Are areas of uncertainty mentioned?

Appendix 5. Patient Education Materials Assessments Tool for Audio-visual Materials

UNDERSTANDABILITY

Item #	Item	Response Options	Rating
Topic: **Content**			
1	The material makes its purpose completely evident.	Disagree=0, Agree=1	
Topic: **Word Choice & Style**			
3	The material uses common, everyday language.	Disagree=0, Agree=1	
4	Medical terms are used only to familiarize audience with the terms. When used, medical terms are defined.	Disagree=0, Agree=1	
5	The material uses the active voice.	Disagree=0, Agree=1	
Topic: **Organization**			
8	The material breaks or "chunks" information into short sections.	Disagree=0, Agree=1, Very short material[1]=N/A	
9	The material's sections have informative headers.	Disagree=0, Agree=1, Very short material[*]=N/A	
10	The material presents information in a logical sequence.	Disagree=0, Agree=1	
11	The material provides a summary.	Disagree=0, Agree=1, Very short material[*]=N/A	
Topic: **Layout & Design**			
12	The material uses visual cues (e.g., arrows, boxes, bullets, bold, larger font, highlighting) to draw attention to key points.	Disagree=0, Agree=1, Video=N/A	
13	Text on the screen is easy to read.	Disagree=0, Agree=1, No text or all text is narrated=N/A	
14	The material allows the user to hear the words clearly (e.g., not too fast, not garbled).	Disagree=0, Agree=1, No narration=N/A	

Item #	Item	Response Options	Rating
Topic: **Use of Visual Aids**			
18	The material uses illustrations and photographs that are clear and uncluttered.	Disagree=0, Agree=1, No visual aids=N/A	
19	The material uses simple tables with short and clear row and column headings.	Disagree=0, Agree=1, No tables=N/A	

Total Points: _____

Total Possible Points: _____

Understandability Score (%): _____

(*Total Points* / *Total Possible Points* × 100)

ACTIONABILITY

Item #	Item	Response Options	Rating
20	The material clearly identifies at least one action the user can take.	Disagree=0, Agree=1	
21	The material addresses the user directly when describing actions.	Disagree=0, Agree=1	
22	The material breaks down any action into manageable, explicit steps.	Disagree=0, Agree=1	
25	The material explains how to use the charts, graphs, tables, or diagrams to take actions.	Disagree=0, Agree=1, No charts, graphs, tables, diagrams=N/A	

***Total Points*:** _____

***Total Possible Points*:** _____

Actionability Score (%): _____
(Total Points / Total Possible Points

Appendix 6. SHU ethical approval for Study 2

A controlled study to evaluate the bioavailability of tart cherry juice and its acute effects on uric acid and other biomarkers of cardiovascular disease risk in healthy individuals

Ethics Review ID: ER9199256
Workflow Status: Application Approved
Type of Ethics Review Template: All other research with human participants

Primary Researcher / Principal Investigator

Kirstie Lamb

(Sheffield Business School)

Converis Project Application:
Q1. Is this project ii) Doctoral research

Director of Studies

Anthony Lynn

(Sheffield Business School)

Appendix 7. Dietary advice sheet containing low-phenol meal recommendations for Study 2

Sheffield Hallam University

Meal suggestions

For **2 days** prior to visits 1 and 3, please choose meals from the suggestions below, if possible. We will provide you with a ready meal dinner to consume the evening before visits 1 and 3. We will also provide a sandwich lunch, pasta dinner, and snacks to consume between main and follow-up sessions (between visits 1 and 2 and between visits 3 and 4). Please avoid any other food/drink during this time.

Breakfast

- White toast with butter/peanut butter
- Scrambled/poached/boiled/fried egg and white toast
- Cooked breakfast (e.g. bacon, egg, cooked mushrooms and white toast)
- Greek yoghurt with coconut

Lunch

- Sandwich (white bread) with the following filling/s: ham, chicken, iceberg lettuce, cheese, tuna/egg mayonnaise, cucumber
- Pitta bread, celery and cucumber with hummus
- Tuna mayonnaise pasta with iceberg lettuce, sweetcorn, cucumber, celery
- Cream of chicken/mushroom soup and white bread

Dinner

Carbohydrate: white rice, pasta, noodle, wraps or bread, Yorkshire puddings

Protein: non-processed meat/poultry (chicken, turkey, pork, lamb, beef), fish and other seafood, egg, chickpeas, Quorn meat alternatives (plain options)

Sauces/condiments: cheese-based (e.g. béchamel), cream-based, Hollandaise, bread-sauce, gravy, mayonnaise

Vegetables: iceberg lettuce, celery, cucumber, mushrooms, sweetcorn (2 tbsp max.), white cabbage (cooked)

- Bacon and mushroom omelette with salad (iceberg lettuce, celery, cucumber)
- Chicken, lettuce and cucumber wraps
- Tuna mayonnaise salad/pasta
- Spaghetti carbonara (spaghetti, bacon, cream, egg, and parmesan cheese)
- Mushroom and bacon risotto with cheese
- Macaroni cheese
- Chicken/beef burger with cheese and salad (iceberg lettuce, celery, cucumber)
- Beef pie with gravy, sweetcorn and white cabbage

Snacks

- Fruits: pineapple, melon (Cantaloupe or honeydew), passionfruit, mandarin/tangerine, coconut
- Crisps
- Rich tea or Nice biscuits (but **not** digestive)
- Yoghurt (plain/Greek/natural/coconut)
- Celery/cucumber with hummus

Drinks

- Water
- Milk
- Low fruit (less than 20% fruit) cordials/squashes
- Fizzy drinks (full sugar or diet alternatives)
- Alcoholic: Spirits

Please use minimal amounts of herbs, spices and oil when cooking

Should you wish to cook/eat a meal not included on the list above, please avoid:

- **Fruits (including juices)**: apple, apricot, banana, all berries (including strawberries, blueberries and raspberries), blackcurrant, oranges (most types), cherries, grapefruit, grapes, nectarine, peach, pear, plum, pomegranate, prunes, quince, rhubarb
- **Vegetables (including juices)**: carrots, all beans, spring-greens and brassicas (including kale, broccoli, cauliflower, red cabbage, Brussels sprouts, pak choi), leeks, chicory, globe artichoke, onions/shallots (red and white), peas, peppers (including chilli peppers), potatoes, squash, spinach, tomato (including passata and ketchup), aubergines, asparagus,
- **Nuts/seeds/grains:** flaxseed, all nuts (e.g. pine nuts, hazelnuts, almond, walnuts, pecan) wholegrain rye or wheat products (including wholegrain flour, bread, rice and pasta), couscous, quinoa, pearl barley, beans (e.g. black, white, kidney, baked)
- **Drinks**: coffee (all types), tea (all types, including de-caffeinated, fruit, mint, black and green), wine (red, rosé and white), cider, beer, energy drinks
- **Other**: dark and milk chocolate, cocoa powder, soy products (e.g. yoghurt/milk/tofu/soybean/flour)

Please record what you eat during this time in the diet diary provided to you. Prior to visits 1,2, 3 and 4, please avoid consuming any food/drink except water after your evening meal (please attend sessions in a fasted state).

Appendix 8. SHU ethical approval and NHS HRA (IRAS) approval for Study 3

The effect of tart cherry juice on gout attack risk: a randomised controlled trial

Ethics Review ID: ER7166682
Workflow Status: Approved with Advisory Comments
Type of Ethics Review Template: IRAS - projects requiring NHS or HMPPS ethics

Primary Researcher / Principal Investigator

Kirstie Lamb
(Sheffield Business School)

Converis Project Application:
Q1. Is this project ii) Doctoral research

Director of Studies

Anthony Lynn
(Sheffield Business School)

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

8 April 2019

Dear Professor Barker

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**The effect of tart cherry juice on the risk of gout attacks: a randomised controlled trial**
IRAS project ID:	**250387**
Protocol number:	**ER7166682**
REC reference:	**18/SW/0262**
Sponsor	**Sheffield Hallam University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.