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The effect of berry-based food interventions on markers of cardiovascular and metabolic health: a systematic review of randomised controlled trials.

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Key words: Berries, cardiovascular risk, dietary intervention, randomised controlled trial, review

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Abbreviations:

AIx, Augmentation index; **BP**, blood pressure; **CI**, Confidence interval; **CVD**, Cardiovascular disease; **FMD**, Flow mediated dilation**; HOMA-IR,** Homeostatic model of assessment of insulin resistance; **ICAM-1**, Intercellular adhesion molecule-1; **IWHS**, Iowa Women's Health Study; **KIHD**, Kuopio Ischemic Heart Disease Risk Factor study; **MeSH**, Medical Subject Headings; **oxLDL**, Oxidised LDL; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-analyses; **PWV**, Pulse wave velocity; **RCTs**, Randomised controlled trials; **RR**, Risk ratio; **SD**, standard deviation, **TAG**, triglycerides; **VCAM-1**, Vascular cellular adhesion molecule-1

Abstract

Scope: Epidemiological evidence, animal and *in vitro* studies suggest that berry consumption may ameliorate markers of cardiovascular disease (CVD). The aim of this systematic review was to evaluate findings from berry-based randomised controlled trials (RCTs) to establish the effects of berry consumption on markers of cardiovascular and metabolic health.

Methods and results: PubMed and Web of Science were searched for RCTs investigating berry consumption on CVD risk outcomes in adults. A total of 23 studies (which includes 1,168 participants) out of 1,384 records met the inclusion criteria. Of these 23 studies, 17 RCTs were of high quality, where 12 RCTs (71%), reported beneficial effects of berry consumption on CVD risk markers. There were 4/11 RCTs that observed a reduction in systolic and/or diastolic blood pressure (BP); 3/7 RCTs reported favourable effects on endothelial function, 2/3 RCTs reported improvements in arterial stiffness, 7/17 studies observed benefits in blood lipids and 3/6 studies reported improvements in glycemic profile.

Conclusion: Our evaluation of the literature indicates that more than two-thirds of high-quality trials have reported beneficial effects of berry consumption on markers of CVD risk. This systematic review contributes moderate to strong evidence for the inclusion of berries into a cardio-protective diet.

1. Introduction

Cardiovascular disease (CVD) is the number one cause of mortality, accounting for 31% of all deaths worldwide [1]. Substantial personal and societal burden on the healthcare economy make CVD reduction a public health priority [2]. Diet is a cornerstone for the primary prevention of CVD [3]. Global dietary recommendations emphasise consumption of a diet rich in cardio-protective foods such as whole grains, fruit and vegetables, nuts and fish. Berries have gained strong recognition in recent times for their putative health benefits which has led to a 21% global increase in berry production [4, 5]. Berries are a rich source of micronutrients and also contain bioactive components such as polyphenols, including anthocyanins, ellagitannins and flavonols [6].

In the prospective Kuopio Ischemic Heart Disease Risk Factor study which consisted of 1,950 men with no prior history of CVD events, men with the highest daily consumption of berries had a significantly lower risk of all-cause, CVD-related and non-CVD related mortality [risk ratio (RR) 0.66 [95% confidence interval (CI) 0.50–0.88]] [7]. In the Iowa Women's Health Study (IWHS), (*n*=34,489, postmenopausal women), strawberries were identified as one of the individual flavonoid-rich foods associated with significant reductions in CVD-related mortality [8]. Data from animal [9] and *in vitro* [10] models also suggest that berry-derived polyphenols may exert beneficial effects through their anti-oxidant, anti-inflammatory, anti-hypertensive and anti-lipidaemic activities which may prevent or attenuate atherosclerosis [11]. However, for these findings to be of clinical significance, they must be translated to well-designed randomised controlled trials (RCTs) in humans which clearly demonstrate cause and effect relationships.

A recent meta-analysis reported that berry-based foods and berry-derived anthocyanin extracts were significantly associated with reductions in LDL-cholesterol, systolic blood pressure (BP), fasting glucose, body mass index, haemoglobin A1c and tumour necrosis factor-α [12]. However, the systematic review and meta-analysis by Huang et al., 2016, did not include endothelial function and arterial stiffness as outcomes which are emerging as important biomarkers of CVD risk [13, 14].

Berries are not only a good source of anthocyanins but also contain other polyphenols such as ellagitannins which may exhibit independently or synergistically beneficial effects on markers of cardiovascular health [15, 16]. In addition, berries are sustainable, they can be easily grown, are pleasant tasting, and therefore, are recognised as a valuable fruit source which can be readily incorporated into the diet.

The objective of this systematic narrative review was to investigate outcomes from RCTs using whole berry fruits or berry-based food products on markers of cardio-metabolic health. Our primary outcomes included the effects of berry fruit consumption on blood pressure, endothelial function and arterial stiffness; while effects on blood lipids (to include oxLDL) and glucose concentrations were secondary outcomes.

2. Materials and Methods

2.1 RCT eligibility criteria

The review protocol was in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [17]. Full publications were included for evaluation subject to meeting the protocol criteria established *a priori*. The primary outcomes of this review were blood pressure, endothelial function and arterial stiffness while the secondary outcomes were blood lipids and glucose homeostasis.

The inclusion criteria consisted of a human RCT which tested the effects of consuming either fresh whole berries or a berry-based product (eg. smoothie, juice) with a control group on at least one defined CVD related outcome (e.g. BP, arterial stiffness, blood lipids profile); with a study duration of ≥4 weeks. Studies were excluded if participants were not randomised or if no control treatment was used. Studies were also excluded if they used a berry extract/capsule intervention; if they had a study duration <4 weeks or if the outcome of interest was not CVD-related. No limits were placed on the type of study participants including sex, ethnicity or participants on medications.

2.2 Search strategy

To develop the search strategy, we first defined a research question which assisted in the identification of key search terms. The online databases PubMed, Web of Science and Cochrane Library were utilised to search for articles related to our key terms, from their inception up until December 2016. Within the PubMed database, Medical Subject Headings (MeSH) terms were used where appropriate and a search history of generated records for each key term from each database was created (**Supporting Information S1**). Terms were combined using the Boolean logic "OR" which identified any articles containing one or more of those terms. The search results from each group were then combined using "AND" which generated articles containing berry terms, CVD markers and RCT design to be considered for the review. No limits were applied for language. The final search was run on 31st January 2017.

2.3 Data extraction

Articles generated as a result of the search in each online database were exported into the citation manager EndNote© (2016 Thomson Reuters). Two investigators (CH and JL) independently screened the titles and abstracts that resulted from the search strategy (**Figure 1**). If disagreements arose they were resolved by consensus. References found within retrieved articles were also reviewed for potential relevant literature and one article was harvested in this manner. Data extracted included: the reference, study duration, intervention type, study design, description of study treatments, daily dose of treatment, total polyphenol dose, baseline value(s) for the CVD marker and significant findings. For articles with multiple interventions arms; findings relating to the comparison of the highest dose with the control arm were considered and presented. One article lacked baseline data for the outcome of interest [18] and an attempt to contact the author was unsuccessful; therefore this article was not included.

2.4 Quality assessment

Articles were quality assessed using an adapted bias assessment tool developed by Jacobs and colleagues [19] which is in line with the Cochrane Collaboration's tool for assessing risk of bias [20]. In this review, the tool was adapted to include criteria considered necessary for evaluation of a dietary

intervention study such as the assessment of compliance, background diet and study design [21, 22]. The articles generated were evaluated according to the criteria outlined in **Supporting Information Table S2.** For every criterion a RCT met, it was awarded an "A" score. The total of "A" scores achieved was then calculated to give a reflective representation of the quality of each RCT (**Table 1**).

3. Results

A total of 1,426 articles were identified from the online databases PubMed (*n*=863), Web of Science (*n*=359) and Cochrane Library (*n*=344) (**Figure 1**). After the removal of duplicates, 1,384 articles remained. Titles and abstracts were screened resulting in a total of 60 RCTs considered eligible. After further evaluation, a final total of 23 RCTs were quality assessed and included in the review and are presented in **Tables 2-5**. These selected studies included a total of 1,168 adult participants. Cranberries (*n*=6), strawberries (*n*=5) and blueberries (*n*=5) were the main types of berries studied. Most studies (*n*=17) were conducted in participants at risk of CVD, such as adults with metabolic syndrome (*n*=5), hyperlipidemia (*n*=5) or hypertension (*n*=3), coronary artery disease (*n*=1), type 2 diabetes (*n*=1), insulin resistance (*n*=1), and smokers (*n*=1). The sample size of studies ranged from 18-71; with 11 RCTs having between 20 and 40 participants and one RCT with less than 20 participants [23]. Compliance with treatments were quantified in 6/23 studies and ranged from 68-100% [24-29].

3.2 Characteristics of selected RCTs

The majority of the selected RCTs in this systematic review were conducted in the USA (*n*=11); followed by Finland (*n*=5), Canada (*n*=2), Iran (*n*=2), Scotland (*n*=1), Sweden (*n*=1) and Italy (*n*=1). Of the 23 included RCTs, there were three RCTs [23, 30, 31] that recruited only male participants and two RCTs that included solely females [29, 32]. The selected RCTs had a mixture of sample populations including healthy (*n*=6), dyslipidemic (*n*=4), hypertensive (*n*=3), diabetic (*n*=1) or comprised of participants with coronary artery disease (*n*=1) or the metabolic syndrome (*n*=8). There were four of the selected RCTs each based in the USA that reported on the differentiation of ethnicity

in the sample population [26, 27, 33, 34]. Several of the selected RCTs contained participants that were taking medication during the study duration such as lipid-lowering drugs [35, 36], anti-hypertensive agents [34-37], diabetic medication [38] or antiplatelet therapy [36]. Apart from two RCTs [28, 32], the included RCTs did not discriminate against whether female participants were pre- or postmenopausal. The study inclusion criterion of being a non-smoker was present in a number of RCTs (*n*=18) while other RCTs (*n*=5) incorporated both smokers and non-smokers into their sample population.

3.3 RCT quality

A summary of the RCT quality assessments applied are presented in **Table 1**. Of the 23 RCTs, 17 studies achieved a total of 6 to 8 "A" scores out of a max score of 8. Nine RCTs were either single blinded, did not use a third party to assign randomisation and/or had insufficient allocation concealment [23, 25, 28, 30, 39-43]. In 7 RCTs, a control that was not identical in terms of appearance, taste and texture was used [25, 28, 30, 40-43]. Five studies did not provide information on the characterisation of the study products in terms of nutrient and polyphenol profiles [28, 30, 41, 42, 44].

Two studies did not evaluate compliance with the study treatment [31, 41]. Of those that did evaluate participant compliance, 4 studies included a biomarker of exposure such as plasma quercetin [43], plasma vitamin C [45], plasma ellagic acid [24] and urinary polyphenol metabolites [39]. In terms of attrition, three studies failed to report dropouts [27, 32, 35], while 3 other studies reported a dropout rate > 20% [25, 42, 44].

3.4 Effect of berry consumption on blood pressure

Eleven RCTs investigated BP as an outcome (**Table 2**). Out of these, 4 studies reported significant reductions in BP from baseline [32, 33, 39, 43] for systolic BP. A mixed berry intervention study reported significant reduction in systolic BP in adults with elevated BP (-1%) [43]; while a blueberry beverage intervention reported a more substantial reduction in hypertensive females (-5%) [32] when compared to the control groups. A chokeberry intervention reported a reduction in

ambulatory diastolic day BP readings (-2%) in adults with elevated BP [39], while a blueberry intervention reported a 6% reduction in diastolic BP in hypertensive females [32]. Similarly, a cranberry juice intervention also reported a 6% reduction in diastolic BP in normotensive adults [33]. These findings support that reductions in systolic BP may be linked to a higher baseline systolic BP while diastolic BP reductions appear more likely to be independent of baseline BP measures.

However, two of the RCTs reporting reductions in BP were single-blinded [39, 43]. In the chokeberry intervention, the authors reported a significant increase in urinary excretion of potassium in the treatment group compared with control [39]. In the mixed berry intervention [43], a significantly higher plasma vitamin C concentration was reported in the berry group compared to the control group; the control was a selection of products (sugar water, semolina porridge, rice porridge and marmalade sweets) and did not have a similar micronutrient profile to the treatment therefore, potential for bias must considered.

3.5 Effect of berry consumption on endothelial function and arterial stiffness

Endothelial function was measured by FMD (n=2) while arterial stiffness was measured using pulse wave velocity (PWV) (n=2) and augmentation index (AIx) (n=1) in studies (**Table 3a**). Markers of endothelial dysfunction, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) concentrations were studied in 4 RCTs (**Table 3b**). Of the RCTs investigating FMD as a measurement of endothelial function, one study observed a significant improvement (+19%) in FMD in healthy adults over 6 weeks [45]. In the 2 RCTs that investigated arterial stiffness, a significant reduction in carotid-femoral PWV (-0.5m/s or 6%) was observed by Dohadwala et al. (2011) after a cranberry intervention and a reduction in brachial-ankle PWV (-0.93 or 6%) was reported by Johnson et al. (2015) after a blueberry intervention. There was no effect of consuming a cranberry drink on arterial stiffness as measured by AIx [31]. No significant reductions in ICAM-1 and VCAM-1 concentrations were reported in 3 RCTs following a cranberry (n=2) or a strawberry intervention [24, 33, 35]. However, Basu et al. (2010) observed an 18% reduction in plasma VCAM-1 concentrations post a strawberry beverage intervention with no changes in ICAM-1 when compared with the control group [37].

3.6 Effect of berry consumption and lipid profile

Seventeen studies (**Table 4**) investigated the effect of berry consumption on blood lipids including total cholesterol (*n*=16), HDL cholesterol (*n*=16), LDL cholesterol (*n*=13), triglycerides (TAG) (*n*=14) and oxidised LDL (oxLDL) (*n*=3) were identified. The study populations from the RCTs included in this review consisted of dyslipidaemic, hypertensive, metabolic syndrome, healthy adults and adults with coronary artery disease. Ten RCTs found no significant effects on circulating blood lipids [26-28, 31, 35, 39-42, 46]. In addition, there was a large variation in the mean (SD) ages of the participants which may have further contributed to heterogeneity and variability in study findings.

For total cholesterol, three strawberry intervention studies reported a significant reduction in concentrations of between 7 and 15% [24, 37, 44] however, the strawberry intervention had an attrition rate of 32% [44] which is substantially higher than the 20% attrition threshold associated with bias in clinical trials [47].

Interestingly, two further strawberry intervention studies reported a significant mean reduction in LDL cholesterol after 12 weeks (21%) and 8 weeks (11%) [24, 37]. One study with mixed berries observed a 5% increase in mean circulating HDL after 4 weeks [43]. Of the 3 studies that investigated oxLDL [29, 31, 48], there was a significant 33% reduction in mean plasma oxLDL concentrations after an 8-week cranberry intervention in adults with metabolic syndrome [29]; a 6-week crossover strawberry intervention in hyperlipidemic adults reported a significant mean reduction in postprandial concentrations of oxLDL (-7.7U/L) in response to a high-fat meal, when adjusted for baseline oxLDL [48]; while a 4-week cranberry intervention in healthy adults reported no change in oxLDL concentrations.

3.7 Berry consumption and blood glucose

Six studies out of the twenty-three studies included fasting blood glucose, insulin and/or the homeostatic assessment model of insulin resistance (HOMA-IR) as an outcome (**Table 5**)[24, 25, 27, 30, 33, 39]. Three RCTs observed no significant changes on fasting glucose and insulin

concentrations or HOMA-IR [24, 25, 39]. Two studies involving a cranberry juice intervention observed significant reductions in fasting glucose concentrations in type 2 diabetic patients (-13%) after 12 weeks [30] and in healthy adults (-2%) after 8 weeks [33]. While Stull et al (2010) observed no significant change in glucose or insulin concentrations after a 6-week blueberry intervention, a significant improvement in insulin sensitivity among 67% of participants in the blueberry treatment group compared with a 41% improvement in the placebo group using a hyperinsulinaemic euglycemic clamp was observed.

3.8 Reported adverse Effects

Aside from two RCTs that advised participants to record any potential adverse effects in a food diary [27, 39], it appears that in general, adverse effects were not considered or reported systematically in accordance with good clinical practice. In a blackcurrant RCT, Khan and colleagues reported the loss of a study participant due to diarrhea and a further six participants that completed this blackcurrant juice intervention reported indigestion, loose bowel movements and increased urinary frequency [45]. Similarly, gastrointestinal discomfort was reported as the main reason for non-compliance in a blueberry RCT in hypertensive females [32]. In a separate cranberry juice intervention, two participants withdrew from a due to dyspepsia [26].

4. Discussion

The evidence from the RCTs described in this systematic narrative review is largely supportive of the hypothesis that the consumption of berries has the potential to have an effect on multiple cardiovascular outcomes including BP, blood lipid profiles, vascular endothelial function and glycemic profile. This systematic review differs from the previous meta-analysis by Huang et al. (2016)[12]in that it has exclusively focused on RCTs which have used whole berries or berry-based food products as an intervention on markers of cardio-metabolic health, with an objective to evaluate whether the consumption of berries or berry-based food products should be encouraged in the diet to improve cardio-metabolic health. The cardiovascular outcomes: Endothelial function and Arterial stiffness have also been included within the scope of this review.

Of the 17 studies that were considered high quality (achieving between 6 and 8 "A" scores in the quality evaluation), 13 reported a positive effect on at least one marker of cardiovascular risk. Dietary intervention studies are frequently faced with challenges in relation to aspects of their study design e.g. background diet, matched control, assessment of compliance, this was apparent in the current review and further contributes to the large inter-individual variation and the heterogeneity in study findings that is being increasingly reported in polyphenol-based dietary intervention studies. In addition, it is concerning that participant safety and the reporting of adverse events were prioritised in only two of the 23 studies.

Hypertension is defined as a BP reading ≥140 systolic mmHg and ≥90 diastolic mmHg [49]. The findings of the current chapter show reductions in BP in four studies, which are promising. However, our findings do not support a specific berry type or study duration that is more advantageous at lowering BP. Findings from *in vitro* studies indicate that berries may reduce BP through the inhibition of the potent vasoconstrictor, angiotensin converting enzyme [50]. In a subgroup analysis by Erlund et al. (2008), the greatest reductions in BP were observed in those with the highest baseline BP and therefore small BP lowering margins in normotensive populations may explain the null findings in studies conducted in normotensive populations [43]. In the current review as the mean baseline BP was normotensive in three RCTs, reductions were not statistically or clinically significant [23, 28, 40]. Also, a recent Cochrane meta-analysis of cocoa polyphenols and BP reported a trend that BP reduction may not be as efficient in older adults [51]. In the current chapter, there is insufficient evidence to indicate a dose-response relationship between berry-based polyphenol intakes and BP as neither systolic BP or diastolic BP were further reduced with increasing polyphenol intakes. Future studies investigating associations between berry consumption and BP should be inclusive of adults with elevated BP and hypertensive populations.

Endothelial dysfunction is a major hallmark of atherosclerosis [52] as arterial walls become injured due to high BP or oxidative stress [35]. FMD is currently the gold standard method for the measurement of endothelial function [53]. Vascular ageing is linked to endothelial dysfunction [13] and arterial stiffness can be determined through the measurement of PWV and AIx [54]. Several

polyphenol based interventions, as summarised in a meta-analysis conducted by Hooper et al. (2012) and a recent systematic review [55] support positive effects of polyphenol consumption on endothelial function however, outcomes measures of endothelial function have been less studied in berry interventions to date [56]. In the current chapter, six RCTs investigated endothelial function [34, 37, 45] and three RCTs included arterial stiffness as study outcomes. Of these, one study reported positive significant effects of berry consumption on endothelial function, where FMD increased by 19% [45]. Two studies reported positive benefits to arterial stiffness with reductions of 6% in PWV [26, 32]. As there are promising results from polyphenol-based RCTs, endothelial function and arterial stiffness are outcomes that should be considered for investigation in future berry intervention studies.

In berry-based RCTs to date, blood lipid profiles have been frequently included as a primary outcome [57]. Berries may have favourable effects on blood lipids due to putative mechanisms such as their ability to increase HDL and reduce LDL cholesterol through the inhibition of cholesteryl ester transfer protein, a protein which transfers cholesteryl esters from HDL to proatherogenic apolipoprotein B lipoproteins by berry-derived polyphenols such as anthocyanins [58]. Of the 17 RCTs in this review which measured blood lipids as an outcome, only one RCT [43] reported a significant increase in HDL cholesterol concentrations which is in agreement with the findings of the meta-analysis by Huang et al. (2016).

In the current review, six out of 17 RCTs observed significant reductions in total cholesterol, LDL cholesterol, triglycerides and oxidised LDL concentrations. Interestingly, out of a total of five strawberry interventions, four observed clinically significant reductions in circulating total cholesterol, LDL cholesterol, triglyceride and oxidised LDL concentrations [24, 37, 44, 48]. It should be noted that these strawberry interventions were well-designed RCTs on the basis of achieving at least 7 “A” scores out of a total of 8 quality scores. Interestingly, one study did not find a significant effect on blood lipid profile when fresh strawberries (450g/d) were used instead of processed strawberry treatments [28]. This highlights that the berry type and food matrix in which the berries are ingested may impact their physiological efficacy *in vivo*. These findings indicate that the beneficial effects of strawberry consumption on CVD risk may be partially attributable to their lipid-lowering

abilities and indicates a clear requirement for future trials which will impart knowledge on choice of study sample, dose response, study duration, the design of study treatments and potential mechanisms of action.

Among diabetic patients, cardiovascular disease is the main cause of mortality, accounting for 70% of deaths [59]. Incidences of type 2 diabetes are concomitantly on the rise with the increasing rates of global obesity [60]. In the current chapter, out of a total of 6 RCTs, 1 trial investigated glucose and insulin homeostasis as a primary outcome [27]. Cranberry juice and blueberry interventions demonstrated favourable effects on glycemic profile in three well-controlled studies [27, 30, 33], which supports the hypothesis that berry consumption may reduce blood glucose concentrations, particularly in diabetic individuals and substantially improve insulin sensitivity in insulin resistant adults. Future studies should explore the potential effects of berries in glucose and insulin homeostasis as a primary outcome in populations with diabetes or impaired glucose tolerance.

In terms of assessing the quality of these berry-based dietary interventions, the lack of a placebo control and insufficient concealment of treatment allocation were the main criteria most frequently not achieved in our analysis. The creation of a true placebo, free of polyphenols but matched in terms of colour, taste and appearance is a persistent obstacle for the designing of berry-based RCTs [56]. It is also worth noting that the health benefits demonstrated in berry-based RCTs may not be solely attributable to polyphenols but other berry components such as nutrients. Therefore, it is important that potential confounding influences such as intrinsic nutrients including fibre, potassium and vitamin C are considered and addressed through the use of a matched placebo [56].

As polyphenols are present in a variety of foods within the diet, the potential effects of background diet must also be accounted for [61]. Background diet can be controlled to an extent in free-living individuals through the creation of a restricted foods list or can be quantified through food diaries or food frequency questionnaires [62]. In addition to assessing adherence to a restricted foods list, it is also necessary to assess compliance to the prescribed intervention. Most of the RCTs included in this review included an assessment of compliance within their study protocol. Examples

of compliance assessments included counting of unused bottles/sachets, analysis of food diaries and face to face or telephone interviews. However, to fully ensure accurate and valid assessment of compliance with the consumption of study treatments, an appropriate biomarker of exposure is recommended. Three of the included RCTs used a biomarker of exposure such as plasma concentrations of vitamin C [45], urinary polyphenol metabolites [39] and plasma concentrations of polyphenols such as quercetin [43]. To date, the measurement of polyphenols such as flavonoids, which are present in abundance in berries, has proved challenging due to their short half-life in circulation (<6-8 hours) [63]. Ideally, instead of using one biomarker of exposure in a polyphenol-based RCT, a metabolomic profile of the treatment, containing data relating to the metabolites and their corresponding polyphenol precursors should be considered [64, 65]. The identification of this metabolic profile in plasma or urine samples collected in the study may be more specific to the treatment and thus, a more robust biomarker of exposure.

This comprehensive review has provided a clear evaluation of the effects of berry-based interventions on markers of CVD risk, has included a rigorous assessment of bias for the determination of study quality, and has focused on defined cardiovascular outcomes. However, the design of the search strategy that was applied in this systematic review may have excluded potential important markers of cardio-metabolic risk such as inflammatory markers. To date there have been a limited number of berry-based interventions conducted and therefore no limitations were applied as regards the type of study population and may not be applicable to either the general population or a individuals with a particular condition (e.g diabetes) and therefore a possible limitation of this systematic review.

We did not reveal an optimal treatment duration, as positive effects were observed in studies of both 4 and 12 weeks duration for all outcomes. In addition, while there was an absence of dose response trials in the current review, higher polyphenol and anthocyanin intakes did not appear to provide an additive beneficial effect on health outcomes. Optimal dosing, effective methods of administration, use of whole food versus extracts/supplements and the profiling of berry polyphenols to specific health outcomes remain to be investigated [65, 66].

Future studies should endeavor to elucidate the potential effects of berry consumption on surrogate markers of CVD, including endothelial function and arterial stiffness as outcomes, as well as emerging markers of cardio-metabolic health such as inflammatory markers and markers of oxidative stress and glucose using appropriate study designs that have considered the identified knowledge gaps to advance research and elucidate the potential cardio-protective effects of berries [67]. In addition, the safety of berry interventions should be addressed through a systematic approach of reporting potential adverse events according to good clinical practice. A recently developed, freely available toolkit providing guidance for the design and execution of dietary intervention studies could prove a practical resource for the development of future berry-based food interventions [21]. This review has presented a considerable amount of evidence to support the consumption of berries for cardio-protective effects on endothelial function, arterial stiffness, LDL cholesterol and oxidised LDL. High rates of compliance (68-100%) with the berry treatments were reported across RCTs which indicates that the addition of berries to the diet is well accepted with few reported adverse effects. Taking these findings into consideration, the consumption of berries should be extensively encouraged as part of a cardio-protective diet.

Author contributions

AL & MK designed the study. CH created the search strategy under the supervision of JL. CH and JL conducted the literatures searches and evaluated articles. AL and MK interpreted the data, reviewed and revised the article.

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Conflict of interest

The authors have no conflict of interest to declare.

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Table 1. Quality assessment of included RCTs

Reference	Treatment blinding	Allocation concealment	Baseline Comparability	Sample Number	Drop outs	Results presentation	Compliance	Intervention dose	Number of A scores (out of 8)
Novotny et al. 2015	A	A	A	A	A	A	A	A	8
Stull et al. 2015	A	A	A	A	A	A	A	A	8
Basu et al. 2014	A	A	A	A	A	A	A	A	8
Khan et al.2014	A	A	A	A	A	A	A	A	8
Larmo et al. 2009	A	A	A	A	A	A	A	A	8
Dohadwala et al. 2011	A	A	A	A	A	A	A	A	8
Johnson et al. 2015	A	A	A	A	B	A	A	A	7
Basu et al. 2011	A	A	A	B	A	A	A	A	7
Basu et al. 2010C	A	A	A	B	A	A	A	A	7
Burton-Freeman et al. 2010	A	A	A	B	A	A	A	A	7
Stull et al. 2010	A	A	A	B	A	A	A	A	7
Aghababaee et al. 2015	C	C	A	A	A	A	A	A	6
Flammer et al. 2013	A	A	C	A	B	A	A	A	6
Riso et al.2013	A	B	A	C	A	A	A	A	6
Shidfar et al. 2012	B	A	A	A	A	A	A	C	6
Erlund et al. 2008	B	C	A	A	A	A	A	A	6
Ruel et al. 2013	A	A	A	B	A	A	C	A	6
Loo et al. 2016	B	B	A	B	A	A	A	A	5
Zunino et al. 2012	A	A	A	B	C	A	A	C	5
Kolehmainen et al. 2012	C	C	A	B	C	A	A	A	4
Jenkins et al.2008	B	C	A	B	A	A	A	B	4
Nyberg et al. 2013	C	C	A	B	A	A	C	C	3
Puuponen-pimia et al. 2013	C	C	A	B	C	A	A	B	3

Treatment blinding: Was study single or double-blinded? Allocation concealment: Was the treatment and control matched in appearance, taste and texture? Baseline comparability: Were the comparison groups matched in terms of gender, ethnicity, smokers and medication users? Sample number: Was the sample size ≤20, 20-40 or ≥40? Drop outs: Was the attrition rate <20%, unreported or <20%? Results presentation: Are results presented in a clear manner and the authors have made appropriate conclusions based on the findings? Compliance: Was there an assessment of compliance in the study? Intervention dose: Are the treatment and controls appropriately characterised?

Table 2 Randomised controlled trials investigating berry consumption and blood pressure as an outcome

Reference	Year	RCT participants (*n*)	Mean Age Years (SD)	Duration (weeks)	Study Design	Intervention	Control	Daily dose	Total phenol dose (mg)/day	Baseline SBP[c]/DBP[d] (mmHg)	Significant BP Findings (mmHg)
Loo	2016	Elevated BP adults (37)	55 (NR)	8	C[a]	Chokeberry juice	Placebo	300ml	2194 ACNs[e]: 1024	Resting: 133/83 24-h Ambulatory: 129/85 Day: 135/89 Night: 115/76	↓Day DBP (2%)[i]
Aghababaee	2015	Dyslipidemic adults (72)	45(8)	8	P[b]	Blackberry drink	Usual diet	300ml	948	122/81	No change
Stull	2015	Metabolic syndrome adults (44)	55(2)	6	P	Blueberry smoothie	Placebo	680g	773 ACNs: 290	Resting: 126/83 24-h Ambulatory: 123/79	No change[j]
Johnson	2015	Hypertensive females (48)	60(5)	8	P	Blueberry beverage	Placebo	480ml	845 ACNs:469	138/80	↓SBP (5.1%)[i] ↓DBP (6.3%)
Novotny	2015	Healthy adults (60)	50(11)	8	P	Cranberry juice	Placebo	480ml	346 ACNs:21	122/74	↓DBP (6%)
Basu	2014	Hyperlipidemic adults (60)	49(10)	12	P	Strawberry beverage	Placebo	474ml	HD[f]: 2005 LD[g]: 1001	HD (136/86) LD (128/83)	No change
Khan	2014	Healthy adults (66)	Low dose 55 (10) High dose 51 (11)	6	P	Blackcurrant juice	Placebo	1L (250mlx4)	HD: 820 LD: 270	HD (127/79) LD (130/82)	No change[j]
Riso	2012	Male smokers (18)	48(8)	6	C	Blueberry beverage	Placebo	250ml	ACNs: 375	121/79	No change[j]
Dohadwala	2011	Coronary artery disease adults (44)	62(10)	4	C	Cranberry juice	Placebo	250ml	835 ACNs: 94	131/77	No change[j]
Erlund	2008	Elevated BP adults (71)	58(6)	4	P	Mixed berries, purée, juice	Placebo	Fresh(100g) Puree(100g) Juice (70ml)	837	128/80	↓SBP (1%)
Jenkins	2008	Hyperlipidemic adults (30)	62(1)	4	C	Fresh strawberries	Oat bran bread	454g	NR[h]	111/68	No BP change[j]

a) Crossover, b) Parallel, c) Systolic blood pressure, d) Diastolic blood pressure, e) Anthocyanins, f) High dose, g) Low dose , h) Not reported, i) Primary outcome, j) Secondary outcome

Table 3 (a) Randomised controlled trials investigating berry consumption on endothelial function and arterial stiffness as an outcome

Reference	Year	RCT participants (*n*)	Mean Age Years (SD)	Duration (weeks)	Study design	Intervention	Control	Daily dose (ml)	Total phenol dose (mg/d)	Baseline PWV[c] (m/s)	Baseline FMD[d] (%)	Baseline RHI[e]	Findings
Stull	2015	Metabolic syndrome adults (44)	55(2)	6	P[a]	Blueberry smoothie	Placebo	680	773 ACNs[f]: 290	NR	NR	1.94	Change in magnitude of RHI response (0.23 vs -0.23)[n]
Johnson	2015	Hypertensive females (48)	60(5)	8	P	Blueberry beverage	Placebo	480	845 ACNs:469	CfPWV:12.3 BaPWV:15.0	NR	NR	No change in CfPWV[g] ↓BaPWV[h] (6%)[n]
Khan	2014	Healthy adults (64)	Low dose 55(10) High dose 51(11)	6	P	Blackcurrant juice drink	Placebo	1000	HD: 820 LD: 270	NR	5.8	NR	↑FMD (19%)[m]
Ruel	2013	Healthy males (35)	45(10)	4	C[b]	Cranberry juice	Placebo	500	400 ACNs :20.8	NR	NR*	NR	No change on AIx [m]
Flammer	2013	CVD risk adults (69)	50(16)	16	P	Cranberry juice	Placebo	460	800 ACNs:69	NR	NR*	NR	No significant effect on FMD
Dohadwala	2011	Coronary artery disease adults (44)	62(10)	4	C	Cranberry juice	Placebo	250	835 ACNs:94	8.3	6.3	NR	No significant effect on FMD ↓PWV (6%)[m]

a) Parallel, b) Crossover, c) Pulse wave velocity, d) Flow mediated dilation, e) Reactive hyperemia index, f) Anthocyanins, g) Carotid-femoral pulse wave velocity, h) Brachial-ankle pulse wave velocity, i) High dose, j) Low dose, k) Augmentation index, l) Not reported , m) Primary outcome, n) Secondary outcome

Table 3 (b) Randomised controlled trials investigating berry consumption on ICAM-1 and VCAM-1 as biomarkers of endothelial dysfunction

Reference	Year	RCT participants (*n*)	Mean Age Years (SD)	Duration (weeks)	Study design	Intervention	Control	Daily dose (ml)	Total phenol dose (mg/d)	Baseline VCAM-1 (ng/ml)	Baseline ICAM-1 (ng/ml)	Findings
Flammer	2013	CVD risk adults (69)	50(16)	16	P[a)]	Cranberry juice	Placebo	460	800 ACNs[d)]: 69	535	189	No significant effect on VCAM-1[b)] / ICAM-1[c)]
Novotny	2015	Healthy adults (60)	50(11)	8	P	Cranberry juice	Placebo	480	346 ACNs: 21	444	263	No significant effect on VCAM-1/ ICAM-1
Basu	2014	Hyperlipidemic adults (60)	49(10)	12	P	Strawberry beverage	Placebo	474	HD: 2005 LD: 1001	HD: 610 LD: 709	HD : 256 LD: 258	No significant effect on VCAM-1 /ICAM-1
Basu	2010	Metabolic syndrome patients (27)	47(3)	8	P	Strawberry beverage	Water	960	2006 ACNs: 154	273	294	No significant effect on ICAM-1 ↓VCAM-1(18%)

a) Parallel b) Vascular cell adhesion molecule-1, c) Intercellular adhesion molecule-1 (ICAM-1), d) Anthocyanins, e) Carotid-femoral pulse wave velocity, f) Brachial-ankle pulse wave velocity, g) High dose, h) Low dose, i) Augmentation index, j) Not reported, k) Primary outcome, l) Secondary outcome

Table 4 Randomised controlled trials investigating berry consumption on blood lipid profile as an outcome

Reference	Year	RCT participants (*n*)	Mean Age Years (SD)	Duration (weeks)	Study design	Intervention	Control	Daily dose	Total phenol dose (mg)	Baseline TCHOL (mmol/L)	Baseline LDL [d](mmol/L)	Baseline HDL[e] (mmol/L)	Baseline TAG[f] (mmol/L)	Baseline oxLDL[g] (U/L)	Findings
Loo	2016	Elevated BP adults (37)	55(NR)	8	C[a]	Chokeberry juice	Placebo	300ml	2194 ACNs[h] : 1024	5.2	NR[k]	1.68	1.09	NR*	No change[l]
Aghababaee	2015	Dyslipidemic adults (72)	45(8)	8	P[b]	Blackberry juice	Usual diet	300ml	964	5.79	3.10	0.99	2.63	NR*	No change
Novotny	2015	Healthy adults (60)	50(11)	8	P	Cranberry juice	Placebo	480ml	346 ACNs: 21	5.00	3.21	1.19	1.28	NR*	↓TAG (10%)
Basu	2014	Hyperlipidemic adults (60)	49(10)	12	P	Strawberry beverage	Placebo	474ml	HD[i]: 2005 LD[j]: 1001	HD: 5.53 LD: 5.20	HD: 3.36 LD: 3.10	HD: 1.27 LD: 1.22	HD: 1.95 LD: 1.73	NR*	↓TCHOL[c] (15%) ↓ LDL (21%)
Nyberg	2013	Healthy adults (26)	28(7)	8	C	Blueberries	Usual diet	150g	NR*	NR*	2.86	1.50	0.94	NR*	No change
Puupponen-Pimia	2013	Metabolic syndrome (32)	NR*	8	P	Mixed fresh and frozen berries	Usual diet	300g	ACNs: 71	5.60	3.70	1.40	NR*	NR*	No change
Ruel	2013	Healthy males (35)	45(10)	4	C	Cranberry juice	Placebo	500ml	400 ACNs: 20.8	5.33	3.51	1.19	1.54	64.3	No change[l]
Flammer	2012	CVD risk adults (69)	50(16)	16	P	Cranberry juice	Placebo	460ml	800 ACNs: 69	4.65	NR*	1.24	2.25	NR*	No change

a) Crossover, b) Parallel, c) Total cholesterol, d) Low density lipoprotein), e) High density lipoprotein, f) Triglycerides, g) Oxidised LDL, h) Anthocyanins, i) High dose), j) Low dose, k) Not reported, l) Secondary outcome

Table 4 *continued* Randomised controlled trials investigating berry consumption and lipid profile as an outcome

Reference	Year	RCT participants (*n*)	Mean Age Years (SD)	Duration (weeks)	Study design	Intervention	Control	Daily dose	Total phenol dose (mg)	Baseline TCHOL[c] (mmol/L)	Baseline LDL[d] (mmol/L)	Baseline HDL[e] (mmol/L)	Baseline TAG[f] (mmol/L)	Baseline oxLDL[g] (U/L)	Findings
Zunino	2012	Healthy adults (27)	F:32(11) M:29(7)	7	C[a]	Strawberry powder	Placebo	320g	NR[h]	4.72	NR	NR	NR	NR	↓TCHOL (7%)[j]
Basu	2011	Metabolic syndrome (36)	52(8)	8	P[b]	Cranberry beverage	Placebo	480ml	458 ACNs[i]): 24.8	5.22	3.54	1.24	1.58	120	↓ oxLDL (33%)
Dohadwala	2011	Coronary artery disease adults (44)	62(10)	4	C	Cranberry juice	Placebo	250ml	835 ACNs: 94	4.08	2.30	1.11	3.36	NR	No change[k]
Basu	2010	Metabolic syndrome patients (27)	47(3)	8	P	Strawberry beverage	Water	960ml	2006 ACNs: 154	5.80	3.50	1.20	1.60	NR	↓TCHOL (10%) ↓LDL (11%)
Burton-Freeman	2010	Hyperlipidemic adults (24)	51(15)	6	C	Strawberry beverage	Placebo	305g	338	5.43	3.67	1.27	2.67	NR	↓TAG (3%) ↓postprandial oxLDL response[j]
Stull	2010	Insulin resistant adults (32)	54(3)	6	P	Blueberry smoothie	Placebo	757g	1462 ACNs:668	5.34	3.28	1.35	1.53	NR	No change[k]
Larmo	2009	Healthy adults (229)	31(7)	12	P	Sea buckthorn purée	Placebo	28g	NR	4.98	2.87	1.57	NR	NR	No change[j]
Erlund	2008	Elevated BP adults (71)	58(6)	4	P	Mixed berries, purée, juice	Placebo	Fresh(100g) puree(100g) juice (70ml)	837	6.30	NR	1.50	1.60	NR	Increase in HDL (5%)
Jenkins	2008	Hyperlipidemic adults (28)	62(1)	4	C	Fresh strawberries	Oat bran bread	450g	NR	5.62	3.61	1.36	1.43	NR	No change[j]

a) Crossover, b) Parallel, c) Total cholesterol, d) Low density lipoprotein e) High density lipoprotein, f) Triglycerides, g) Oxidised LDL, h) Not reported i) Anthocyanins, j) Primary outcome, k) Secondary outcome

Table 5 Randomised controlled trials investigating berry consumption and metabolic profile as an outcome

Reference	Year	RCT participants (*n*)	Mean Age Years (SD)	Duration (weeks)	Study design	Intervention	Control	Daily dose	Total phenol dose (mg)	Baseline Glucose (mmol/L)	Baseline Insulin (pmol/L)	Baseline HOMA-IR[c)]	Findings
Loo	2016	Elevated BP adults (37)	55(NR)	8	C[a)]	Chokeberry juice	Placebo	300ml	2194 ACNs[d)] : 1024	5.25	NR[g)]	NR	No change in glucose concentrations[i)]
Novotny	2015	Healthy adults (60)	50(11)	8	P[b)]	Cranberry juice	Placebo	480ml	346 ACNs: 21	5.42	53.02	1.8	↓ Fasting glucose (2%) ↓HOMA-IR (2%)
Basu	2014	Hyperlipidemic adults (60)	49(10)	12	P	Strawberry beverage	Placebo	474ml	HD[e)]: 2005 LD[f)]: 1001	HD: 5.2 LD: 5.5	HD: 115 LD: 136	HD: 3.8 LD: 4.9	No change in glucose, insulin or HOMA-IR
Kolehmainen	2012	Metabolic syndrome adults (27)	53(6)	8	P	Bilberry puree & Dried Bilberries	Usual diet	240g	ACNs Puree: 524 Dried: 832	6.1	NR	NR	No change in glucose and insulin concentrations
Shidfar	2012	Type 2 diabetic males (58)	55(9)	12	P	Cranberry juice	Placebo	240ml	NR	7.7	NR	NR	↓ Fasting glucose (13%)
Stull	2010	Obese and insulin resistant adults (32)	54(3)	6	P	Blueberry beverage	Placebo	757g	1462 ACNs:668	5.7	132	NR	Increase in insulin sensitivity (22%) No change in glucose and insulin concentrations[h)]

a)Crossover, b) Parallel, c) Homeostatic model assessment of insulin resistance, d) Anthocyanins, e) High dose , f) Low dose, g) Not reported, h) Primary outcome, i) Secondary outcome