Title Berry anthocyanin intake and cardiovascular health

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Abstract

Over half of all cardiovascular (CV) events could be prevented by improved diet. This is reflected in government targets for fruit/vegetable intake, yet these are variable across the world (UK: 5-a-day; USA: 9-a-day), do not identify specific fruits/vegetables, and prove hard to achieve. Mounting evidence from prospective studies, supported by recent randomised controlled trials suggest that the benefits of fruits/vegetables may be due to bioactive substances called flavonoids. Specifically one sub-class of flavonoids, the anthocyanins, responsible for the red/blue hue, are receiving growing attention. Although promising data is emerging from cohort studies, and cell/animal studies, proof of efficacy from longer-term randomised controlled trials, and an understanding of the importance of differential metabolism in relation to clinical efficacy are distinctly lacking. Diet related ill-health are among the leading priorities of our time and simple dietary change, including incorporating a few portions of anthocyanin-rich fruit into our diet could have a significant impact at a public health level.

Background

In an era where preventive medicine is becoming increasingly important, due to an expanding ageing population and increasing prevalence of obesity, an optimised diet is central for improving CV health. A sub-optimal diet is currently the leading risk factor for both disability and death worldwide (Lim et al. 2012) . Worldwide, chronic diseases have been projected to costs $17 trillion of cumulative economic loss from 2011-2030 including healthcare costs and reduced productivity (Bloom et al. 2011). In the UK, the largest economic burden to the National Health Service (NHS) relates to a poor diet, with food-related ill-health costing the NHS £5.8 million per year (Scarborough et al. 2011). Although improved treatments have resulted in significant declines in incidence and mortality rates, cardiovascular disease (CVD) remains a considerable burden, in terms of ill-health, mortality and associated costs. In 2012-13 alone the NHS in England spent £6.8 billion on CVD, predominantly in secondary care and costs are set to rise further (Bhatnagar et al. 2015). Unless there are continued improvements in prevention past gains will not be sustained. Although >50% of contemporary public health problems could be prevented through dietary change (Ezzati and Riboli 2013) it is still unclear what constitutes a healthy diet for different individuals: what are the key constituents in fruits/vegetables for optimal health, what are their physiological and molecular mechanisms of action, what is their metabolic fate, how extensive is inter-individual variability in metabolism and does this variability impact on CV health?

Fruit and CV health

Data suggest that diets rich in fruits are the third most important modifiable factor for reducing global rates of non-communicable diseases (Ezzati and Riboli 2013). In a recent prospective study of over half a million Chinese adults, daily fruit intake was associated with 4 mmHg lower systolic blood pressure (BP), 0.5 mmol/L lower blood glucose levels and a 34% and 40% lower risk of incident major coronary events and CV mortality respectively (Du et al. 2016). If we assume that there is a causal

association, the authors calculate that 16% of deaths from CV could be attributed to low fruit intake and >560,000 deaths from CV each year (including 200,000 before age 70), could be prevented if fruit was consumed daily (Du et al. 2016). There was evidence of a dose-response relationship (Du et al. 2016) and the inverse associations could be causal given that fruit is a rich source of a number of bioactive constituents including flavonoids (Hartley et al. 2013; Hooper et al. 2008; Liu 2003). Growing evidence highlights the beneficial effect of flavonoids such as anthocyanins as likely key constituents in lowering CVD risk and the focus of this review relates only to the anthocyanin sub-class.

Dietary flavonoids and the anthocyanin sub-class

Dietary flavonoids represent a diverse range of polyphenolic compounds that occur naturally in plant foods. Their structural complexity has led to their sub-classification as flavonols, flavones, flavanones, flavan-3-ols (and their oligomers, proanthocyanidins), isoflavones, and anthocyanins (Hooper et al. 2008). They are present in significant amounts in many commonly consumed fruits, vegetables, and beverages.

Anthocyanins are water-soluble plant pigments that are responsible for the red/blue colouration in plants, flowers, seeds and fruits (Smeriglio et al. 2016) and are predominantly found in the skin of fruit, except for berries where they are present in both the skin and flesh (Manach et al. 2004). They are present in a number of foods commonly consumed in the habitual diet with red, blue or purple fruits and vegetables containing concentrations ranging from 0.1% to up to 1.0% of dry weight (Pojer et al. 2013). Fruits such as berries, blackcurrants, red grapes, plums and cherries are rich dietary sources, as are fruit-derived products like red wine and juices; they are also present to a more limited extent in some vegetables such as radishes (Table 1, USDA 2014, (Perez-Jimenez et al. 2010). Although there is wide variability in levels depending on growing and storage conditions, two servings of fresh blueberries contain, on average, 240mg, and two glasses of red wine 56 mg (Table 1).

Anthocyanins are glycosides of anthocyanidins and it is currently thought that only the following six are of relevance to the human diet (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin). In plants they play a key role in pollination and by absorbing light, protect plants from ultra-violet (UV)-induced damage(Castañeda-Ovando et al. 2009). Habitual dietary intake of anthocyanins is variable and in the US estimated daily intake was on average 12.5 mg/day (Wu et al. 2006), while in Europe mean intakes for men ranged from 19.8 (the Netherlands) to 64.9 mg/ day (Italy), and for women, from 18.4 (Spain) to 44.1 mg/day (Italy) (Zamora-Ros et al. 2011). Fruits are the most common dietary source, and in the EU were responsible for up 61% of habitual intake, predominantly from apples, pears, berries, stone fruit and grapes. Wine contributed 14.4-24.5% of intake across Europe (contributing 24.5% in both Southern and Northern regions) (Zamora-Ros et al. 2011). In the US the main dietary sources are strawberries and blueberries (Cassidy et al. 2011). Although intakes are variable, given their presence in commonly consumed fruits the potential to increase intake is readily achievable. Just consuming 1-2 portions of either strawberries, raspberries or blueberries would significantly increase intakes of anthocyanins to levels that have been reported to be associated with a reduction in risk of CVD (Bhagwat et al. 2013; Cassidy et al. 2013; Cassidy et al. 2011; Jennings et al. 2012; McCullough et al. 2012).

Population-based studies

A number of prospective cohort studies and cross-sectional studies have examined the associations between habitual anthocyanin intakes and cardiovascular disease (CVD) outcomes or biomarkers of CVD risk, predominantly based in US populations (Tables 2). Coronary heart disease (CHD) and non-fatal myocardial infarction (MI) were examined in five studies, with evidence in four to suggest that increased habitual anthocyanin intake is significantly associated with a reduction in risk of CHD by 12-32% in multivariate analyses (Cassidy et al. 2016; Cassidy et al. 2013; McCullough et al. 2012; Mink et al. 2007) (Table 2). The magnitude of the protective effect of increased anthocyanin intake was smaller in the older women and men (12-21%) compared to a study which focused on younger and middle-aged women where a 32% reduction in risk was observed comparing extremes of anthocyanin intake. Median intakes were 12 mg per day in these women, and when extreme deciles of intake were compared those in the top decile had a 47% reduction in risk of MI, suggesting a continual dose-response at higher levels of intake (Cassidy et al. 2013); for every 15 mg increase in anthocyanin intake, the relative risk of MI decreased by 17% in the multivariate model (Cassidy et al. 2013). The relationship between anthocyanin intake and CVD mortality was also examined in several studies, with one study showing no association (Mursu et al. 2008), while two others observed 9-14% reductions in risk comparing higher with lower intake (McCullough et al. 2012; Mink et al. 2007).The impact of increased anthocyanin intake on stroke has to date been examined in five studies, and although there was long-term follow-up, there is currently no evidence for a protective effect (Cassidy et al. 2016; Cassidy et al. 2012; McCullough et al. 2012; Mink et al. 2007; Mursu et al. 2008) (Table 2).

In relation to CV risk biomarkers, prospective studies and cross-sectional data provide mechanistic support for the observed decrease in CHD risk with increased anthocyanin intakes, with evidence that higher intakes improve arterial stiffness (assessed by pulse wave velocity) and blood pressure (Cassidy et al. 2011; Jennings et al. 2012).The magnitude of the associations observed for systolic blood pressure (-4 mmHg decrease with higher intake) were similar to those previously reported for stopping smoking and 2 fold higher than that observed following a small (1.4 portion) increase in fruit/vegetable intake (Jennings et al. 2012). The available data on the effects on inflammatory biomarkers are equivocal (Table 2, (Chun et al. 2008; Jennings et al. 2014; Landberg et al. 2011) although more recent work, using a combined inflammatory score suggests that reduced inflammation may be a key pathway (Cassidy et al. 2015); recent prospective data also support the importance of weight maintenance (Bertoia et al. 2016). Interestingly the greatest reduction in hypertension was observed in the younger/ middle-aged women, supportive evidence for the observed reduction in risk of MI in this age group (Cassidy et al. 2013; Cassidy et al. 2011). Higher habitual anthocyanin intakes (35mg, half a portion of berries), resulted in a 0.7 mIU/L reduction in insulin levels (Jennings et al. 2014) similar to the effects of a low-fat diet (Shikany et al. 2011) or 1hr/day walking (Fung et al. 2000). The magnitude of associations are clinically relevant and of significant public health importance. However, future research should focus on identifying and validating panels of anthocyanin metabolites that reflect intake and subsequent metabolism so that associations of bioavailable anthocyanins (and inter-individual variability) can be assessed in future prospective cohort studies.

Randomised controlled trials (RCTs)

To date, very few RCTs have examined the impact of anthocyanins on cardiovascular health relative to other sub-classes such as the flavan-3-ols present in tea and cocoa (Hooper et al. 2012) . In several short term interventions (< 2mth duration), anthocyanin rich food intake (predominantly blueberries) resulted in a 5-6% decrease in both systolic and diastolic BP (Basu et al. 2010; Erlund et al. 2008; Johnson et al. 2015) and favourable changes in arterial stiffness (Dohadwala et al. 2011; Johnson et al. 2015). A recent 3-month dose-response study (strawberries, 78 and 155 mg/d anthocyanins) demonstrated beneficial effects on total and LDL-cholesterol levels following high intake (Basu et al. 2010), and the effect was mediated by improvements in cholesterol efflux capacity (Zhu et al. 2014). In a 6-month study, inflammatory biomarkers were reduced following anthocyanins (320 mg/d) in hypercholesterolemia patients (Zhu et al. 2013), while acute intake of strawberries (39mg anthocyanins) attenuated the 6hr postprandial inflammatory response (Edirisinghe et al. 2011). These preliminary RCT findings are supported by animal and *in vitro* data. Anthocyanins inhibit atherosclerosis development, alter cell signalling pathways involved in vascular inflammation, and reduce infarct size following coronary occlusion and perfusion (Lamy et al. 2008; Toufektsian et al. 2008). Mechanistic studies also suggest an impact on whole body insulin action (DeFuria et al. 2009; Inaguma, Han, and Isoda 2011; Stull et al. 2010). However, to date, very few carefully controlled human trials have examined the effects of anthocyanins on insulin resistance (IR) (Stull et al. 2010). Therefore, although promising data is emerging from cohort studies, and cell/animal studies, proof of efficacy from longer-term RCTs and an understanding of the importance of metabolism in relation to clinical efficacy are distinctly lacking.

Bioavailability, metabolism and potential importance of the microbiome

Following ingestion, anthocyanins undergo extensive metabolism; microbiota likely play a key metabolic role, catabolising unabsorbed flavonoids into smaller molecules such as phenolic and aromatic acids, which are also absorbed (Manach et al. 2005; Williamson and Clifford 2010). For anthocyanins consumed in the diet, the parent compounds may not be responsible for bioactivity; instead this may be mediated by metabolites present in the systemic circulation (Czank et al. 2013; Williamson and Clifford 2010). Data from the limited available trials show that following ingestion there is extensive variability in metabolite levels.

This wide inter-individual variability in metabolism (15-99% of the ingested intake recovered as a wide range of urinary metabolites (Czank et al. 2013; Manach et al. 2005; Cassidy and Minihane 2017) suggest that metabolism may be critical in explaining the differential responses in CV risk biomarkers observed in clinical trials (responders v non-responders). This heterogeneity in responsiveness to anthocyanin intake may relate to a number of factors, including post-absorptive variability in Phase I and II metabolism (including reduction, hydrolysis, glucuronidation, sulphation), but the microbiome is likely to be critical as it plays a key role in anthocyanin metabolism (Cassidy and Minihane 2017; Czank et al. 2013; Williamson and Clifford 2010). Furthermore, it is likely that intake alters the composition and function of the gut microbiome (Anhe et al. 2015; Roopchand et al. 2015) and conversely, that the microbiota enhance the metabolism of anthocyanins, but this bidirectional relationship has not yet been addressed. To understand the importance of metabolism, particularly microbiome-mediated biotransformation, in explaining the

CV health effects of flavonoids a combination of epidemiological studies and dietary intervention trials (acute and chronic) are needed.

Is metabolism key to clinical efficacy of anthocyanins and do the microbiota play a role?

Our recent human bioavailability trials highlighted extensive inter-individual variability in anthocyanin absorption and metabolism, identified a range of novel downstream metabolites and provided substantial evidence to suggest that the major circulating metabolites are phenolic breakdown products derived from microbial metabolism (Czank et al. 2013; de Ferrars et al. 2014). Microbial metabolites are more bioactive than the parent compounds in *in vitro* models exerting greater vascular and anti-inflammatory activity than the metabolites formed and absorbed in the small intestine (Amin et al. 2015; de Ferrars et al. 2014; di Gesso et al. 2015; Krga et al. 2016). Together, these data provide further evidence that the bioactivity of anthocyanins is highly likely attributed to their microbially-derived metabolites, which are present in the circulation significantly longer and at much higher levels than the parent anthocyanins (Czank et al. 2013; de Ferrars et al. 2014). Colonic metabolism has long been speculated to be a major contributor to overall metabolism (Williamson and Clifford 2010) and our stable isotope study provided the first evidence in humans of the extent of metabolism, suggesting it is key in the production of hippuric acid and a range of phenolic acids, including vanillic and ferulic acid with serum levels reaching >2μM (magnitudes higher than the parent compounds) and remaining in the circulation >48 hrs following intake (Czank et al. 2013; de Ferrars et al. 2014).

Strong interplay: anthocyanins and the microbiome: The large heterogeneity in the bioactivity and bioavailability of anthocyanin metabolites formed following ingestion, including the extensive range of gut metabolites identified, supports strong-interplay. Whether anthocyanins alter the composition and function of the gut microbiome or the microbiota enhances the metabolism of anthocyanins is a key area for future research. In relation to nutrition research, in a cross-sectional study, (n=178 elderly subjects) habitual diet-driven microbiota alterations were associated with measures of frailty and inflammation (Claesson et al. 2012), and a small 2-month intervention study (n=15 women), showed changes in *Gammaproteobacteria* and the Firmicute *Erysipelotrichi* microbial communities (Spencer et al. 2011). In a recent small RCT (n=9) high levels of bifidobacteria were associated with increased levels of flavonoid microbial metabolites following polyphenol-rich wine intake (Boto-Ordonez et al. 2014). In animals, anthocyanin intake resulted in significant effects on gut microbial community structure, including a reduction in the ratio of Firmicutes to Bacteroidetes and an increase in Akkermansia (mucin-degrading Verrucomicrobia) muciniphila; changes that provided protection against a high fat diet, resulting in an improvement in insulin sensitivity and the inflammatory response (Anhe et al. 2015; Roopchand et al. 2015). These data from mice provide the first evidence that either the gut microbiota play a substantial role in mediating the health effects of anthocyanins and/or that anthocyanin intake enhances the health effects of the microbiota. Clinical studies to determine if these effects are also observed in humans are urgently needed. Currently, the identity of the main microbiota phyla and species that modulate anthocyanin metabolism in

humans are unknown, and data from adequately powered acute and long-term RCTs investigating the potential of microbiota diversity to explain associations between anthocyanins and CVD risk are completely lacking.

Future research priorities

There is growing evidence from prospective studies, animal studies and short-term trials of the potential cardiovascular health benefits of anthocyanins. The heterogeneity in the observed effects on CV disease endpoints and biomarkers may obscure the potential health benefits, therefore future research should focus on understanding inter-individual variability in metabolism following intake and the importance of the microbiome. Understanding if a differential capacity to metabolise anthocyanins affects CV health will allow us to develop strategies to enhance and optimise the health benefits. Anthocyanin-rich foods, predominantly from fruit, are readily incorporated into the diet and simple dietary change could have a significant impact in reducing CVD risk.

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Table 1

Common dietary Sources of Anthocyanins

	mg/100g*	serving size	mg/serving
Blueberries	163.3	1/2 cup	120.8
Blackberries	100.6	1/2 cup	70.4
Plums	56.0	1 medium	37.0
Red grapes	48.0	1/2 cup	36.5
Raspberries	48.6	1/2 cup	30.2
Red wine	19.3	5 oz	28.3
Cherries	32.0	1/2 cup	22.4
Strawberries	27.0	1/2 cup	20.5
Radishes	63.1	2 medium	5.7

*mg/100g based on USDA Database for the Flavonoid Content of Selected Foods, Release 3.1 (2014)

Table 2. **Observational studies examining the associations between dietary anthocyanin intakes and cardiovascular disease risk**

Author	**Intake (mg/d)**	**Outcome measure**	**Country, Gender Age range**	**Population**	**Multivariate-adjusted RR (95% CI), *p*-trend Highest versus lowest category**
PROSPECTIVE STUDIES					
Mink et al 2007[1]	Median (range) 0.2 (0-1040)	CHD mortality	USA, Postmenopausal women 55-69 y	34,489 16 y follow-up Cases = 1329	0.88 (0.78-0.99), p=0.03
McCullough et al 2012	Median (range) 3.8 (0-5.5) Q1 to 22.2 (≥16.7) Q5	CHD mortality	USA, Men (Mean age = 70 y), Postmenopausal women (Mean age = 69 y)	98,469 (38,180 men; 60,289 women) 7 y follow-up Cases = 1286 (803 men, 483 women)	Men & women: 0.79 (0.67-0.94), p=0.06 Men only: 0.81 (0.65-1.00) p=0.2 Women only:0.81 (0.60-1.07) p=0.2
Jacques et al 2015	Median and IQR 9.1 (3.4-17.3) 1991-1995 and 17.8 (8.1-29.2) 2005-2008	CHD (incident)	USA, 2880 men and women, Mean age = 54 y	2880 14.9 y follow-up, 261 CHD events	0.96 (0.85-1.08) p=0.49

Author	Intake (mg/d)	Outcome measure	Country, Gender Age range	Population	Multivariate-adjusted RR (95% CI), *p*-trend Highest versus lowest category
Cassidy et al 2013	Mean (IQR) 12.3 (1.9-35.0)	CHD (incident and fatal)	USA, Premenopausal women 25-42 y	93,600 18 y follow-up Cases = 405	0.68 (0.49-0.96), p=0.047
Cassidy et al 2016	0-613 range, IQR (3.9-15)	CHD (incident and fatal)	USA, men 39-77 y	43,880 24 y follow-up Cases = 4046 MI (2222 non-fatal)	Total MI 0.97 (0.85-1.07) p=0.44 Fatal MI 1.10 (0.94-1.28) p=0.56 Non-fatal MI 0.87 (0.75-1.00) p=0.098
Mink et al 2007[1]	Median (range) 0.2 (0-1040)	Stroke mortality	USA, Postmenopausal women 55-69 y	34,489 16 y follow-up Cases = 469	1.01 (0.83-1.24) p=0.90
McCullough et al 2012	Median (range) 4.3 (0-6.2) Q1 to 20.4 (≥15.0) Q4	Stroke mortality	USA, Men (Mean age = 70 y), Postmenopausal women (Mean age = 69 y)	98,469 (38,180 men, 60,289 women) 7 y follow-up Cases = 573 (281 men, 292 women)	Men & women: 0.95 (0.75-1.20) p=0.7 Men only: 0.84 (0.59-1.20) p=0.2 Women only:1.05 (0.76-1.46) p=0.6

Author	Intake (mg/d)	Outcome measure	Country, Gender Age range	Population	Multivariate-adjusted RR (95% CI), *p*-trend Highest versus lowest category
Mursu et al 2008[1]	Mean 6.2	Ischemic stroke (incident)	Finland, Men 42-60 y	1950 15 y follow-up Cases = 102	0.88 (0.47-1.62) p=0.81
Cassidy et al 2012	Median (range) 8.9 (0-354.9)	Ischemic stroke (incident)	USA, Women 30-55 y	69,622 14 y follow-up Cases = 943	0.89 (0.72-1.11) p=0.59
Cassidy et al 2016	0-613 range, IQR (3.9-15)	Ischemic stroke (incident)	USA, men 39-77 y	43,880 24 y follow-up Cases = 901 ischemic stroke	Ischemic stroke 0.93 (0.75-1.15) p=0.51
Mink et al 2007[1]	Median (range) 0.2 (0-1040)	CVD mortality	USA, Postmenopausal women 55-69 y	34,489 16 y follow-up Cases = 2316	0.91 (0.83-0.99) p=0.03
Mursu et al 2008[1]	Mean 6.2	CVD mortality	Men 42-60 y	1950 15 y follow-up Cases = 153	0.99 (0.62-1.85) p=0.19

Author	Intake (mg/d)	Outcome measure	Country, Gender Age range	Population	Multivariate-adjusted RR (95% CI), *p*-trend Highest versus lowest category
McCullough et al 2012	Median (range) 3.8 (0-5.5) Q1 to 22.2 (≥16.7) Q5	CVD mortality	Men (Mean age = 70 y), Postmenopausal women (Mean age = 69 y)	98,469 (38,180 men, 60,289 women) 7 y follow-up Cases = 2771 (1589 men)	Men & women: 0.86 (0.76-0.97) p=0.04 Men only: 0.91 (0.77-1.06) p=0.3 Women only:0.82 (0.69-0.99) p=0.06
Jacques et al 2015	Median and IQR 9.1 (3.4-17.3) 1991-1995 and 17.8 (8.1-29.2) 2005-2008	CVD incidence	USA, 2880 men and women mean age 54 y	2880 14.9 y follow-up, 518 CVD events	0.94 (0.86-1.02) p=0.14
Cassidy et al 2011	Mean (IQR) 14.0 (5.4-17.8)	Incident hypertension	USA, Young/middle aged women 26-42 y	87,242 14 y follow-up Cases = 11,402	0.87 (0.81-0.92) p<0.0001
Cassidy et al 2011	Mean (IQR) 12.5 (4.6-15.9)	Incident hypertension	USA, Older women 43-71 y	46,672 14 y follow-up Cases = 17,616	0.93 (0.88-0.98) p=0.02
Cassidy et al 2011	Mean (IQR) 15.2 (5.8-19.3)	Incident hypertension	USA, Men 36-80 y	23,043 14 y follow-up Cases = 5,629	0.99 (0.90-1.09) p=0.82

Author	Intake (mg/d)	Outcome measure	Country, Gender Age range	Population	Multivariate-adjusted RR (95% CI), *p*-trend Highest versus lowest category
CROSS-SECTIONAL STUDIES					
Cassidy et al 2015	0-365 range	Combined inflammation score	USA, middle-aged men and women	2375	Combined inflammation score -0.71 (-1.17, -0.25)
Jennings et al 2014	Mean ± SD (IQR) 17.8 ± 14.3 (8.4-23.8)	CRP	UK, Women 18-76 y	1997	-0.3 mg/L, *p* = 0.04 Q5 vs. Q1
Landberg et al 2011	Median 10	Inflammatory biomarkers	USA, Women 43-70 y	1,087-1,598	No association for CRP, IL6 & other inflammatory biomarkers; higher intakes associated with lower IL-18 levels (*p* = 0.014)
Jennings et al 2012	Mean ± SD (IQR) 17.7 ± 14.9 (8.4-23.6)	Blood pressure Augmentation index (AI)	UK, Women 18-75 y	1,898	Peripheral systolic BP -4.0 mmHg (p=0.009) Central systolic BP -3.0±1.4 mmHg (p=0.017) Central diastolic BP -1.9±1.0 mmHg (p=0.05) MAP -2.3±1.2 mmHg (p=0.037) Q5 vs. Q1 intake PP and AI: no association
Jennings et al	Mean ± SD (IQR)	Pulse wave velocity	UK, Women	728	PWV is 3.9% lower: -0.4 ± 0.22 m/s, *p* = 0.044

Author	Intake (mg/d)	Outcome measure	Country, Gender Age range	Population	Multivariate-adjusted RR (95% CI), *p*-trend Highest versus lowest category
2012	17.7 ± 14.9 (8.4-23.6)	(PWV) Intima media thickness (IMT)	18-75 y		Q5 vs. Q1 IMT: no significant association
Landberg et al 2011	Median 10	Inflammatory biomarkers	USA, Women 43-70 y	1,087-1,598	No association for CRP, IL6 & other inflammatory biomarkers; higher intakes associated with lower IL-18 levels (p = 0.014)
Mursu et al 2007[1]	Mean 7.5	Intima media thickness (IMT)	Finland, Men 42-60 y	1,380	No significant association (p=0.58)
Chun et al 2008	Range (tertile 1 to tertile 3) 0 - >22.6	CRP levels	USA, Men and women 19-70+ y	8,335 (4,225 men, 4,110 women)	-0.18 mg/L decrease tertile 1 vs. tertile 3 of intake (p < 0.05)

[1]Relies on data from earlier version of the USDA database on flavonoid contents in foods 2003 and additional analyses for anthocyanin contents of Finnish berries (Jacques et al. 2015; Mursu et al. 2007).

CHD, coronary heart disease, **CVD,** cardiovascular disease, **MI,** myocardial infarction, **AI**, augmentation index; **BP**, blood pressure; **CRP**, C-reactive protein; **HDL**, high-density lipoprotein; **IL**, interleukin; **IMT**, intima media thickness **MAP**, mean arterial pressure; **PP**, pulse pressure; **PWV**, pulse wave velocity; Q1 quintile 1, Q5 quintile 5