Heart Foundation

Summary of evidence

Antioxidants in food, drinks and supplements for cardiovascular health

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Contents

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Recommendations

To reduce the risk of cardiovascular disease (CVD) and maintain cardiovascular health (CVH), the Heart Foundation recommends that all Australian adults do the following.

1. Consume at least two serves of fruit and five serves of vegetables every day.

2. As part of a healthy balanced diet, drink:[*]
   - black or green tea[†]
   - cocoa made from raw cocoa powder.[‡]

The Heart Foundation **does not** recommend the following.

1. Consuming milk or dark chocolate for the prevention or treatment of CVD. Due to processing to remove the bitter taste, most chocolate is a poor source of antioxidants, and contains saturated and trans fats.

2. Drinking coffee for the prevention or treatment of CVD. If consuming coffee, drink only paper-filtered, percolated, café-style (espresso) or instant (regular and decaffeinated), in preference to boiled (such as Turkish-style) or plunger coffee. Consume less than five cups per day.[§]

3. Drinking red wine or other types of alcoholic drinks for the prevention or treatment of CVD. The Heart Foundation supports the National Health and Medical Research Council (NHMRC) recommendation for healthy Australians who already drink to have no more than two standard drinks per day for men and women.[1]

4. Using antioxidant supplements, such as vitamins E and C, carotenoids and other antioxidants or combinations, for the prevention or treatment of CVD. There is some concern that high doses (> 800 IU/day) of supplemental vitamin E may increase the risk of CVD.

   The Heart Foundation supports the *Nutrient Reference Values for Australia and New Zealand*,[2] which recommends that people consume a diet that would provide these nutrients at levels currently equating to the 90th centile of intake in the population.

[*]Adding milk and sugar to drinks may contribute substantially to energy intake, depending on the number of cups consumed. Use reduced, low or no fat milk where possible.
[†]This does not include iced tea. Caffeine consumed in large amounts may cause restlessness and disturb sleep in some people.
[‡]Raw cocoa powder contains high levels of polyphenols. This does not include drinking chocolate/milk modifiers.
[§]Caffeine consumed in large amounts may cause restlessness and disturb sleep in some people.

Summary of evidence

Evidence	Level of evidence
Fruit and vegetables	
Consuming a diet rich in fruit and vegetables causes a modest fall in systolic blood pressure in normotensive and hypertensive individuals.[3–5]	II
Increasing fruit and vegetable consumption is associated with: • a reduction in CVD mortality • a reduced risk of stroke and • a lower risk of coronary heart disease (CHD).[6–16]	III-2
Tea	
Drinking tea or consuming tea flavonoids improves endothelial function.[17–26]	II
There is limited evidence that drinking green tea or consuming tea flavonoids reduces visceral fat.[27–31]	II
Regular tea drinking is associated with a reduced risk of CVD.[32–37]	III-2
There is conflicting evidence regarding the effect of regular tea drinking on blood pressure.[23,38,39–45]	n/a**
There is little evidence that drinking tea improves the lipid profile.	n/a
Cocoa	
Acute intake of high polyphenol cocoa and/or chocolate increases endothelial function.[46,47]	I
Consuming high polyphenol (= 500 mg) cocoa and/or up to 100 g/day of high polyphenol (= 500 mg) chocolate can modestly reduce systolic blood pressure.[45,46,48,49]	II
Cocoa and/or chocolate intake reduces platelet reactivity.[50–54]	II

**Where there is insufficient or inconclusive evidence, the level of evidence is categorised as not applicable (n/a).

Evidence	Level of evidence
Coffee	
Consuming approximately five cups per day of coffee causes a small elevation in systolic blood pressure.[55,56]	I
Boiled coffee increases low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) levels. Filtered and instant coffee have very little effect on LDL-C and TC levels.[57–60]	I
Coffee consumption has little impact on the risk of CHD.[61–65]	III-2
Coffee consumption is not associated with increased rates of heart failure hospitalisation or mortality, or cardiovascular mortality.[66–68]	III-2
The role of coffee intake in the development of hypertension is unclear from epidemiological studies (level of evidence: III-2).[69]	III-2
Regular coffee consumption is associated with a lower risk of type 2 diabetes.[70]	III-2
Red wine	
Conflicting and insufficient evidence exists regarding the CVH benefits of polyphenols in red wine.	n/a
Vitamin supplements	
Consuming vitamin E supplements does not decrease all-cause mortality or cardiovascular mortality, or prevent cardiovascular events.[71–74]	I
Consuming β-carotene supplements has a small effect on increasing cardiovascular mortality and all-cause mortality in smokers.[73]	II
There is no evidence for the effectiveness of combination antioxidant supplements for the prevention of CVD.[71,72,74]	II
There is conflicting evidence regarding the effect of supplemental vitamin C intake and the risk of CHD.[75,76]	III-2

Levels of evidence for clinical interventions

Where there is insufficient or inconclusive evidence, the level of evidence is categorised as n/a.

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials (RCT).
II	Evidence obtained from at least one properly designed RCT.
III-1	Evidence obtained from well-designed, pseudo RCTs (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation, not randomised cohort studies, case-control studies or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Source:[77]

Rationale and objectives

Regional variations in the incidence of CHD are incompletely explained by established risk factors, such as hypercholesterolaemia.[78] Some of these variations may be explained by differences in the dietary intake of saturated fat and antioxidants. Fruit and vegetables have been shown to protect against chronic disease,[79] but other foods, such as dark chocolate, and drinks, such as tea, coffee and wine, can be rich in antioxidants, particularly flavonoids, and may also be protective. In addition, supplements of individual antioxidants have been proposed to protect against CHD.[80,81]

There has been considerable research into how antioxidants exert their health benefits. For many years, the beneficial role of antioxidants was thought to be related to it reducing the unwanted and uncontrolled production of reactive oxygen species, which would otherwise lead to oxidative stress. Antioxidants include antioxidation agents that ameliorate oxidative damage by directly reacting with, or scavenging, oxidants that otherwise react with biological molecules, including lipids and proteins. As such, these antioxidants counteract oxidative stress, defined as an imbalance between the production and the removal of oxidants in favour of the former.

Oxidative damage has the potential to contribute to various processes leading to atherosclerosis. For example, oxidants can interfere with the normal function of endothelial cells, they can initiate lipoprotein and cell lipid peroxidation, and they can regulate the activity of enzymes involved in tissue remodelling, including that leading to plaque rupture. Importantly, however, a major unresolved issue is which of the various atherosclerotic processes leading to oxidative damage represents a cause rather than a consequence of the disease.

Current thinking increasingly recognises that the *in vivo* action of dietary antioxidants may be more complex and include processes in addition to direct oxidant scavenging, such as the induction of protective enzymes and processes.

Many studies have carried out assays of food items to determine their total antioxidant capacity (TAC), but there are problems with trying to correlate the numbers obtained from these assays with nutritional value.[82] Uptake in the gastrointestinal tract, metabolism and excretion, and biokinetics modify the impact of food items, which may have health effects independent of the antioxidant component. Even if the compound is active *in vitro*, it may not be taken up in the gastrointestinal tract or metabolised before or after uptake to products which are not redox (reduction and oxidation) active, therefore those *in vitro* data do not apply. Whether pro-oxidant, antioxidant or any other biological effects potentially exerted by polyphenols account for the health benefits of certain food and drinks is uncertain.[83]

The dietary antioxidants thought to play a role in CVH are vitamins C and E, coenzyme Q_{10}, and flavonoids. The term ‘vitamin E’ includes four isomers of tocopherols and tocotrienols, of which α-tocopherol has received the most attention. α-tocopherol itself can occur in eight different (stereoisomer) forms. In nature, α-tocopherol is present only as *RRR*-α-tocopherol (also referred to as natural or d-α-tocopherol), whereas chemically synthesised α-tocopherol (vitamin E) is known as all rac-α-tocopherol. Vitamin E supplements are labelled commonly as d-alpha for natural, and dl-alpha for synthetic. Natural and synthetic vitamin E differ in their biological activity. To calculate the amount of vitamin E in supplements, multiply IU x

0.67 and 0.45 for *RRR*-α-tocopherol and all rac-α-tocopherol, respectively; that is, 100 IU of natural vitamin E equals 67 mg of natural vitamin E, and 100 IU of synthetic vitamin E equals 45 mg of natural vitamin E. The major classes of flavonoids include flavanols, flavones, flavanones, flavanols, anthocyanins and isoflavones. There are > 4,000 naturally occurring antioxidants which provide the colour, texture and taste of plant foods.

Aim

To determine if antioxidants in food, drinks and supplements are effective in maintaining CVH and reducing the risk of CVD.

Scope

Given that we consume food and not nutrients, and the wide range of antioxidants that exist, it was decided to conduct this review by antioxidant-rich food and drinks, and antioxidant supplement sources, where possible. In particular, the review examined the effect of:

- fruit and vegetables
- tea
- cocoa and chocolate
- coffee
- red wine.

In addition, the paper reviews new evidence on antioxidant supplementation to update the Heart Foundation's existing review.[84]

We acknowledge that there are other antioxidant-rich, whole foods that contribute to daily intake that are not included in this review.

This paper looks at the effectiveness of antioxidant intake on the following outcomes:

- cardiovascular events and mortality
- cardiovascular risk factors, such as high blood pressure, diabetes, overweight and abnormal lipid profile
- other clinical outcomes related to the risk of CVD, such as endothelial function, platelet function and inflammation.

Methodology

To ensure that the Heart Foundation recommendations were based on the best available evidence, this paper sought to collect and analyse the highest-quality international studies, reviews and reports relating to antioxidant-rich food and drinks and antioxidant supplements. Studies were identified by searching PubMed for all years of the database, except for studies relating to supplementation, which were searched from 2003. In addition, evidence was identified by recommendations from members of the working group and by checking the citations of key reviews, journal articles and articles related to the topic. The year range covered was determined by the date of the last Heart Foundation review.

The NHMRC levels of evidence were attributed to the recommendations, where appropriate, and the associated studies were listed. Where there is insufficient or inconclusive evidence, the level of evidence is categorised as n/a.

Australian intakes and recommendations

The NHMRC Nutrient Reference Values for Australia and New Zealand recommend that people consume a diet (rather than supplements) which would provide nutrients at levels currently equating to the 90th centile of intake in the population.[2] The 90th centile intake for vitamin C is about 220 mg per day for adult males and 190 mg per day for adult females. For vitamin E, the 90th centile intake is about 19 mg for men and 14 mg for women, and for β-carotene, the 90th centile is 5,800 μg per day for men and 5,000 μg per day for women.

Data from the 1995 National Nutrition Survey was analysed to identify major sources of flavanols in the Australian diet.[85] Black and green teas were the main sources of flavanols kaempferol, myricetin and quercetin (the major flavanol in the Western diet). Other significant sources were onions, beans, broccoli, apples, grapes and coffee. Black and green teas were also major sources of flavan-3-ols, with contributions from wine, apples and pears. The major sources of flavanones were oranges, lemons, mandarins and grapefruit. Parsley, celery and English spinach were the major flavone sources. Wine was the major anthocyanidin source, with smaller amounts from cherries and blueberries. For young people, apple consumption was an important source of flavonoids, while citrus fruit were important sources of hesperitin and naringenin.[86]

Part 1: Food and drinks

Fruit and vegetables

Regular consumption of fruit and vegetables has been shown to protect against CVD. Research has sought the components or compounds responsible for this apparent health benefit. Much of that research currently focuses on antioxidants, including carotenoids, vitamins C and E, and flavonoids,[87] but questions remain as to whether other nutrients are protective.[88] A diet rich in fruit and vegetables may be healthier for numerous reasons, including their displacement of other foods; therefore, those diets may be lower in saturated fat, lower in sodium and higher in potassium. The increase in dietary fibre from fruit and vegetable intake may also lower blood cholesterol and improve glucose tolerance, both of which are important risk factors for CVD.

Epidemiological studies have compared populations with a higher intake of fruit and vegetables with populations with the lowest consumption. They have also compared vegetarian groups with non-vegetarian groups. Risk factors, such as blood pressure, blood cholesterol and changes in markers for CVD, such as plasma C-reactive protein, have also been measured.

The positive health effects of fruit and vegetable consumption have prompted an Australia-wide social marketing campaign encouraging adult Australians to consume two serves of fruit and five serves of vegetables every day.[89] While most Australians are not consuming the recommended amount, there are some specific fruit and vegetables that are proving more popular than others, including pears, apples, bananas, pineapples, potatoes, carrots, tomatoes, lettuces, onions, leeks, peas and cabbage.[79]

Cooked vegetables are often associated with reduced nutritional quality. Heating can result in oxidation, thermal degradation, leaching and other events that lead to lower levels of antioxidants and other components. However, a study by Pellegrini and colleagues[90] observed that cooking is not always detrimental to the total antioxidant capacity (TAC). Most boiled vegetables tested increased their TAC value, with the highest increase for artichokes (500%). Negative changes were observed only for spinach, turnips, zucchinis and asparagus. Pan frying had a negative effect on the TAC of most vegetables, with mushrooms being the most affected. Potatoes and aubergines were the only vegetables with an increase in the TAC.

Population studies: CVD and CHD

CVD

A prospective cohort study of middle-aged men suggested that a high consumption of fruit, including berries, and vegetables is associated with a reduced risk of CVD-related, non-CVD related and overall mortality.[6] The men in the highest quintile of intake had greater intakes of vitamin C, lycopene and vitamin E, and these intake levels explained 36% of the protective effect against cardiovascular mortality.

A large prospective cohort study in Japan observed a significant trend between vegetable intake and CVD mortality in women, but not in men.[7] Women who consumed the highest amounts of vegetables were at lower risk of cardiovascular mortality than women who consumed the lowest amount. The inverse association between fruit and cardiovascular

mortality was not significant for women. In men, neither fruit nor vegetable consumption was associated with cardiovascular mortality.

A meta-analysis of eight studies (nine individual cohorts, 257,551 individuals) showed that increased fruit and vegetable intake is associated with a reduced risk of stroke.[8] Compared with individuals who consumed fewer than three servings of fruit and vegetables per day, people who consumed three to five serves per day had an 11% reduction in the risk of stroke, and people with more than five serves per day had a reduction of 26%.

Law and Morris[9] estimated that a population increase in fruit and vegetable consumption, moving from the 10th percentile to the 90th percentile, is associated with a decrease in the risk of developing CHD of about 15% (range: 12–19%). This is equivalent to a reduction in CHD mortality of about 10% if everybody below the 90th percentile increased their consumption to the 90th percentile. The authors recommended consumption of eight servings of fruit and vegetables every day, one serve more than currently recommended by the Australian government.

Conclusion
Increasing fruit and vegetable consumption is associated with:

- a reduction in cardiovascular mortality (level of evidence for effect: III-2)
- a reduced risk of stroke (level of evidence for effect: III-2).

CHD
He and colleagues[12] performed a meta-analysis using the results of 12 studies (13 independent cohorts, 278,459 individuals) to quantitatively assess the relationship between fruit and vegetable intake and the risk of CHD. The study showed that an increased consumption of fruit and vegetables is related to a reduced risk of CHD. Those consuming more than five servings per day had a 17% reduction in CHD risk compared to those consuming fewer than three servings per day.

A meta-analysis of nine cohort studies[13] examined the relationship between fruit and vegetable intake and CHD. This study reported an inverse association between both fruit and vegetable intake and CHD, with the risk decreasing by 4% for each additional serving of fruit and vegetables, and by 7% for each additional serving of fruit.

A prospective cohort study involving participants from the Nurse's Health Study and the Health Professionals Follow-Up Study evaluated the association between fruit and vegetable consumption and the risk of CHD.[14] The results suggested an inverse relationship between intake and risk of CHD in men and women. Each additional serving of fruit or vegetables was associated with a 4% lower risk for CHD. Green leafy vegetables and vitamin C-rich fruit and vegetables contributed most to the protective effect of fruit and vegetables.

Apples, pears and onions are good sources of flavonoids in the Australian diet,[85,86] and several studies have measured the effect of their consumption on CHD. The results of the Zutphen Elderly Study showed that intakes of flavonoids from apples and onions (and tea) predicted lower CHD mortality.[15] A Finnish study examining flavonoid intake and coronary mortality found that apple and onion intake was inversely associated with coronary mortality, especially in women.[10] Data from the same study also showed a specific cardioprotective role of quercetin (~ 95% of the total flavonoid intake), which comes mostly from apples and onions in the Finnish diet. In a US study examining the effect of catechins on CHD mortality, apples were found to be inversely associated with CHD mortality in post-menopausal

women (particularly non-smokers free of diabetes mellitus and CVD).[16] Another study of post-menopausal women showed that the flavanols in apples and pears decreased the risk of CHD and CVD mortality.[11]

A systematic review and meta-analysis by Hamer and Chida[91] examined the association between fruit and vegetable intake and the risk of type 2 diabetes. Five cohorts were identified incorporating 167,128 participants with type 2 diabetes. The results suggested that fruit and vegetable consumption is not associated with a substantial reduction in the risk of type 2 diabetes. A second analysis of nine cohort studies and 139,793 participants over 13 years demonstrated that antioxidant intake, mainly vitamin E and carotenoids, was associated with a 13% reduction in risk.

Conclusion
Each additional serve of fruit or vegetables per day is associated with a 4% lower risk of CHD (level of evidence for effect: III-2).

The findings from international studies recommend consumption of more than five serves of fruit and vegetables per day, with an emphasis on onions, green leafy vegetables, apples, pears, berries and other vitamin C-rich fruit and vegetables.

Vegetarians
Vegetarians generally have a higher intake of cereals, nuts, vegetable oils, carrots, green vegetables and fruit. Such a diet is rich in vitamins E, C and A. Epidemiological studies of vegetarians do not provide conclusive evidence of the benefits of fruit and vegetables because it is difficult to determine which aspect of the diet is offering the health benefit. However, the findings from The EPIC-Oxford Study[92], UK Vegetarian Society Study[93] and other vegetarian studies[94,95] show a reduction in mortality from ischemic heart disease.

Conclusion
Further good-quality studies are needed to determine the benefits of a vegetarian diet against CVD and the role, if any, antioxidants play in this.

Fruit and vegetables and CVH risk factors: RCTs
There have been a number of small, short-term RCTs measuring the effect of fruit and vegetable intake on plasma lipids. Increased consumption of fruit and vegetables in people who normally have a low intake have been shown to lower LDL-C (through the consumption of vegetable proteins),[96] increase total carotenoid concentrations in plasma,[97–99] and reduce C-reactive protein.[97]

The Dietary Approaches to Stop Hypertension (DASH) trial demonstrated that a diet rich in fruit and vegetables could help lower systolic blood pressure substantially in normotensive and hypertensive individuals.[3] Due to the strong positive results, the DASH diet is now recommended in US national guidelines for risk factor reduction of CVD.[5] When compared with the control diet, the DASH diet was higher in flavanols, flavanones, flavan-3-ols, ß-carotene, ß-cryptoxanthin, lycopene, lutein and zeaxanthin and phytosterols.[4] The fruit and vegetable diet yielded reductions in systolic blood pressure of 2.8 mmHg ($P< 0.001$) compared to the control diet (typical US diet).[3] While it is attractive to speculate that these antioxidant compounds from fruit and vegetables may in part explain the beneficial effects of the DASH diet, we are not yet in a position to draw this conclusion because of the multiple components of the diet.

Conclusion
A diet rich in fruit and vegetables can result in a fall in systolic blood pressure in normotensive and hypertensive individuals (level of evidence: I).

Conclusions
While many of the studies in this review were not set in Australia, the findings can be applied to the Australian population, based on the types of fruit and vegetables consumed in the studies, the quantities of intake and the Western diet and lifestyle of the majority of participants.

Further research is needed to determine which particular component of fruit and vegetables is responsible for health benefits and its role in CVH. Large RCTs with a focus on diets rich in fruit and vegetables, rather than focused on individual nutrients, are needed to measure CVD outcomes, and ultimately improve our understanding of the beneficial effects of fruit and vegetables.

Tea

After water, tea (green or black tea) is the most widely consumed drink in the world. Every year, Australians drink 8,030 million cups of tea, including green tea (2,000 tonnes per year) and black tea (14,060 tonnes per year), most of which is imported. Both green and black teas are rich in polyphenolic compounds, primarily flavonoids. Flavonoids in general have antioxidant activities, when assessed by *in vitro* methods. It is less clear, however, whether dietary flavonoids can significantly reduce oxidative damage *in vivo*. Of potential importance, tea and tea flavonoids have other activities and effects, which may or may not be linked to antioxidant activity that could provide CVH benefits.

The two main types of tea are black and green. Black and green teas are derived from the same plant, *Camellia sinensis*. Black tea is more widely consumed, accounting for more than 75% of world consumption and about 98% of the international tea trade. Green tea remains popular in China and Japan, and is increasing in popularity in many Westernised countries, due mainly to its perceived health benefits. Black tea is produced by promoting the enzymatic oxidation of the flavonoids, primarily the catechins (flavonols). Green tea is produced by inactivating the enzymes responsible for flavonoid oxidation. The main difference between the two types of tea is their content of flavonoids (Table 1).

Table 1: Flavonoid composition of green and black teas

Component	Green tea (% by dry weight)	Black tea (% by dry weight)
Total flavonoids	15–25	15–25
• Total catechins (flavonols)	12–18	2–3
(–) Epicatechin	1–3	< 1
(–) Epicatechin gallate	3–6	< 1
(–) Epigallocatechin	3–6	< 1
(–) Epigallocatechin gallate	9–13	1–2
• Flavanols (quercetin)	2–3	1–2
• Theaflavins	< 1	4
• Other polyphenols (thearubigins)	2–4	7–15

Derived from a number of sources.[46]

Composition of brewed tea

Depending on the presentation of the tea leaf, the temperature of the water and infusion time, approximately 25–50% of flavonoids will be extracted into the hot water when preparing tea. Brewed tea (2 g tea leaves infused in 200 mL hot water) will contain approximately 170 mg total flavonoids. Fewer flavonoids are found in instant preparations and iced and ready-to-drink teas.[100] The addition of milk can reduce the flavonoid concentration, but does not interfere with catechin absorption.[100] A cup of green tea (2 g tea leaves in 200 mL water) may contain 70 mg of epigallocatechin-3-gallate.[101]

Population studies: CVD

Evidence from population studies suggests that tea consumption and a higher flavonoid intake may reduce the risk of CVD. Peters and coworkers[32] performed a meta-analysis of tea (primarily black tea) consumption in relation to CVD, and estimated that the incidence rate of myocardial infarction decreased by 11% with an increase in tea consumption of three cups per day. Epidemiological studies have also investigated the association between green tea consumption and cardiovascular events, as well as other surrogate markers of CVD.

Most of these studies have been conducted among Asian populations (China and Japan) and suggest a cardioprotective effect of green tea consumption.[33–36] Positive results have been found for consumption of up to 10 cups of green tea per day. Caution should be taken in interpreting the results of these studies because of the strong likelihood of publication bias and the presence of geographical heterogeneity in the results. In another meta-analysis of cohort studies, Huxley and Neil[37] assessed the association of dietary flavanol intake from tea and other sources with the subsequent risk of CHD mortality. Seven prospective cohorts of men and women (105,000 individuals; five studies reported tea as a source of flavonoid intake) were identified, including a total of 2,087 fatal CHD events. Individuals in the top third were compared with those in the bottom third of dietary flavanol intake. This comparison yielded a 20% reduction in the combined risk ratio after adjustment for known CHD risk factors and other dietary components.

Conclusion

Regular black or green tea drinking is associated with a reduced risk of CVD (level of evidence: III-2).

Tea and CVH markers: RCTs

The epidemiological evidence on tea and CVH cannot prove causality; well-designed intervention studies with appropriate outcome measures provide stronger evidence for a link between tea and CVH. The effects of tea on primary or secondary prevention of CVD have not been assessed in an RCT. Therefore, we need to rely on data from RCTs assessing CVH markers.

Endothelial function

The endothelium is a complex structure with diverse, important properties affecting vascular tone, thrombosis and inflammation. Endothelial dysfunction, in relation to vascular physiology, is a broad term used commonly in relation to vascular physiology to refer to the diminished bioavailability of nitric oxide. It is considered to be an early biomarker for the development of atherosclerosis[102,103] and cardiovascular events.[103]

There is adequate evidence from intervention trials that consuming tea (black and green) can improve endothelial function, as assessed by flow-mediated dilation (FMD). This has been observed in at least eight RCTs in humans.[17–24] Acute supplementation with tea flavonoids (such as (–) epicatechin and epigallocatechin gallate) improves endothelial function and augments the nitric oxide status.[25,26] Nitric oxide is a key endothelium-derived relaxing factor that plays a pivotal role in the maintenance of vascular tone and reactivity.

Conclusion

The consumption of black and green teas and tea flavonoids improves endothelial function (level of evidence: II).

Blood pressure/Hypertension

Acutely, black tea can increase blood pressure. Flavonoids with caffeine cause a transient increase in systolic blood pressure in individuals who have avoided caffeine for 12 hours or more.[23,38] The relevance of these acute effects to any longer-term effects of regular consumption is uncertain.

The results of population studies suggest that long-term, regular ingestion of tea may lower blood pressure.[39–42] However, it should be considered that tea intake is generally associated with a range of lifestyle factors related to CVD risk. Short-term, regular ingestion of tea for up to eight weeks was not shown to alter blood pressure in largely normotensive individuals.[43,44] A recent meta-analysis showed no overall effect on systolic or diastolic blood pressure,[45] but longer-term exposure may be required to show the effects on blood pressure.

Conclusion

The results of population studies suggest long-term, regular tea drinking may lower blood pressure (level of evidence: III-2), while data from short-term RCTs indicate that there is no effect of black or green tea on blood pressure. RCTs are required to investigate the longer-term effects of regular tea drinking on blood pressure.

Lipid profile

Despite favourable results from animal experiments, the results of RCTs in humans regarding the effects of green tea[104–106] and black tea[107] on plasma lipids are not uniform. The lipid-lowering effects of tea in humans are, for the most part, quite small. The discrepancies between experimental and clinical data may be explained by the fact that most animal studies were performed with high doses of tea and tea components.[33]

Conclusion
There remains little support from RCTs for a favourable impact of tea on lipid profile.

Body weight and body composition
Available data suggest that regular consumption of tea may increase energy expenditure and reduce visceral fat. Excess visceral fat is specifically associated with metabolic activities linked to an increased risk of CVD. Several studies have shown that tea (green and oolong), or preparations containing tea flavonoids with caffeine, significantly increase 24-hour energy expenditure[108–110] and increase fat oxidation during exercise,[111–113] although it is not clear whether this effect is due to caffeine, catechins or both. The magnitude of this increase is between 3 and 7%, (~ 250–600 kJ/day), and this could contribute to longer-term beneficial effects on body weight and composition. If a small increase in energy expenditure (~ 5%) is sustained over months, a significant reduction in fat mass or body weight could result. The results of trials suggest that green tea or tea flavonoids reduce body weight by less than 1% on average (0.5–1 kg) over two to five months, indicating that there may be some compensation in energy intake.[27–30,114,115] That is, there appears to be very little effect on total body weight. However, data from human intervention trials suggest that the regular consumption of tea or tea flavonoids for two to five months will reduce waist circumference or visceral fat by 1 to 2 cm or 5 to 10%.[27-31]

Conclusion
There is some preliminary evidence that green tea and tea flavonoids can reduce visceral fat during medium-term consumption (level of evidence for benefit: II).

Cocoa and chocolate

Cacao (*Theobroma cacao*) is the natural product key to making the processed product of chocolate, whose ingredients include cocoa solids, cocoa butter, vegetable oils, refined sugar and milk powder. Cocoa is potentially one of the richest dietary sources of flavonoids. However, it is important to differentiate between natural cocoa and manufactured cocoa powders and chocolate. Significant amounts of flavonoids are removed or masked during the manufacturing process because they impart a bitter, astringent flavour.[116]

The flavonoids present in high concentrations in cocoa are the flavonols epicatechin and catechin, and procyanidins (polymeric flavonoids).[50] Estimates of the flavonoid content of natural cocoa and cocoa-containing foods, such as chocolate, are presented in Table 2.

Table 2: Flavonoid composition of cocoa and cocoa-containing foods

Flavonoid	Natural cocoa powder (mg/kg)	Cocoa-containing foods (mg/kg)
(–) Epigallocatechin	1500–2500	0–500
(+) Catechin	400–800	0–300
Quercetin	100–150	0–150
Procyanidins	1000–2000	0–400

A comparison of antioxidant activity and the content of commercially available cocoa and chocolate products in the USA found that natural cocoas had the highest levels of antioxidant activities, total polyphenols and procyanidins, followed by baking chocolates, dark chocolates and baking chips, milk chocolate and syrups.[117] Non fat cocoa solids were the primary factor contributing to the level of cocoa antioxidants in the products, while differences in cocoa bean blends and processing were minor factors.

Population studies: CVD

Observational studies in Kuna Indians provide evidence that the consumption of cocoa is responsible for benefits on blood pressure.[118] Traditional Kuna Indians consumed several grams of cocoa daily, and appeared to be protected against CVD and age-dependent increases in blood pressure, often against the background of a high salt diet. In Kuna Indians who moved to the cities and decreased their cocoa intake, age-dependent increases in blood pressure became apparent. Cocoa appears to be the main diet/lifestyle difference between island and mainland Kuna Indians. These observations provided the initial impetus to explore the potential CVH benefits of cocoa and chocolate.

Table 3: Summary of prospective studies on cocoa/chocolate consumption and CVD

Study	Endpoints	Number of participants	Type of intervention	Dose	Finding
Zutphen Elderly Study[48]	CVM ACM	470 elderly men with 15-year follow up	Chocolate and cocoa	Lowest < 0.50 g/d, middle 0.50–2.25 g/d, highest > 2.25 g/d	RR for CVM: lowest 1.00, middle 0.70, highest 0.50; *P* = 0.004 for trend RR for ACM: lowest 1.00, middle 0.73, highest 0.53; *P* < 0.001 for trend
Stockholm Heart Epidemiology Program[119]	CVM ACM	1169 non-diabetic individuals after myocardial infarction	Chocolate (did not differentiate between milk and dark)	50 g portions	HR for CVM: never 1.00, < 1/month 0.73, up to 1/week 0.56, 2 or more/week 0.34; *P* = 0.01 for trend HR for ACM: never 1.00, < 1/month 0.89, up to 1/week 0.96, 2 or more/week 0.94; *P* = 0.96 for trend
Zutphen Elderly Study[48]	BP	470 elderly men with 15-year follow up	Chocolate and cocoa	Lowest < 0.36 g/d, middle 0.36–2.30 g/d, highest > 2.30 g/d	RR for systolic BP: lowest 150.2, middle 149.0, highest 146.5

ACM, all-cause mortality; BP, blood pressure; CVM, cardiovascular mortality; HR, hazard ratio; RR, relative risk.

Epidemiological data linking chocolate and cocoa intake with CVD risk remains limited. A subset of the Zutphen Elderly Study (Table 3) reported that cocoa and chocolate product intake was inversely related to cardiovascular mortality.[48] Compared with the lowest tertile

of cocoa intake, the adjusted relative risk for men in the highest tertile was 0.50 (95% confidence interval (CI): 0.32–0.78; *P* = 0.004 for trend) for cardiovascular mortality and 0.53 (95% CI: 0.39–0.72; *P* < 0.001) for all-cause mortality. A recent cohort study of patients hospitalised after their first myocardial infarction (Table 3) found that chocolate consumption had a strong inverse association with cardiovascular mortality.[119]

Cocoa and CVH markers: RCTs

Vascular function: vasodilation and platelet aggregation

Vasodilation
Several trials have investigated the effects of high flavonoid cocoa or chocolate on endothelial function. Chronic intake is defined as intake over two or more weeks, and acute is defined as intake within six hours. A meta-analysis of six acute intake studies (140 participants) showed chocolate or cocoa consumption increased FMD after acute intake (3.99%; 95% CI: 2.86, 5.12; six studies), with the peak effect at around two hours.[46] While an analysis in chronic intake studies was performed on two studies, more data is needed to confirm a clinically significant effect. Some of the studies may have received industry funding (specific studies not identified). Corti et al[47] identified a number of small intervention studies that used cocoa, a flavonol-rich drink or dark chocolate and improved/increased FMD of healthy individuals, as well as patients with cardiovascular risk factors.

Platelet aggregation
Increased platelet reactivity and aggregation, as well as endothelial dysfunction, can lead to thrombosis and progress atherosclerosis.

A number of smaller studies have demonstrated a suppressive effect on platelet reactivity and platelet-related primary hemostasis from as little as a single dose of flavonoid-rich chocolate or cocoa.[50,52] In addition, some studies have provided support for the anti-aggregatory effects of cocoa flavonols.[51,53,54]

Conclusion
High polyphenol cocoa and/or chocolate consumption increases endothelial function approximately two hours after consumption (level of evidence for effect: I), and may reduce platelet reactivity (level of evidence for effect: II).

Blood pressure/Hypertension
Two small meta-analyses were conducted to determine the effect of cocoa and chocolate products on blood pressure. These have been analysed as RCTs because of the heterogeneity between trials.

A meta-analysis by Hooper et al[46] found that chocolate and cocoa intake reduced systolic blood pressure by 5.88 mmHg (95% CI: 9.55–2.21; five studies).

Taubert et al[45] also examined the effect of cocoa on blood pressure in five studies (mean duration: two weeks, a total of 173 adults). Patients consumed an average of 100 g per day of high flavonoid chocolate and a control chocolate. Subjects consuming the high flavonoid chocolate had a significant further reduction in systolic blood pressure of 4.7 mmHg (95% CI, 4.8 to 0.8; p = 0.006) compared to the control group.[43] A further RCT of 44 hypertensive patients tested 6.3 g per day of dark chocolate containing 30 g of polyphenols against

polyphenol-free white chocolate over 18 weeks. Those who ate dark chocolate had a reduction in systolic blood pressure of 2.9±1.6 mmHg ($P < 0.001$).[49]

Supportive evidence comes from a cross-sectional analysis of the Dutch Zutphen Study[48] of 470 men that showed that cocoa intake was inversely related to blood pressure (Table 3). Systolic blood pressure was 3.7 mmHg lower (95% CI: –7.1 to –0.3; $P = 0.03$ for trend) in the highest tertile compared to the lowest tertile.

Conclusion
Consuming high polyphenol (= 500 mg) cocoa and/or up to 100 g/day of high polyphenol (= 500 mg) chocolate can modestly reduce systolic blood pressure.

Variations in composition
Many confectionary manufacturers remove the flavonols from chocolate due to its bitter taste. Cocoa solids are darkened to give the appearance of dark chocolate, when in fact it contains mostly fat and sugar. Consumers are led to believe that all dark chocolate is better than milk or white chocolate, as manufacturers are not required to provide flavonol content on the label. Adding to that, the processing of chocolate is not uniform across manufacturers, and the variability in flavonoid levels can be extreme.[120]

Conclusions
The flavonoid component of cocoa and chocolate may have beneficial effects on CVH, particularly blood pressure. The evidence to date comes from smaller, short-term trials (not easily translated into long-term effects), which provide the starting point for further investigation from larger, long-term trials.

Coffee

There are two main species of coffee in the world: *Coffea arabica*, also called Arabica, and *Coffea canephora*, also called Robusta. While coffee contains thousands of compounds, a group of compounds comprising three chemicals have attracted particular attention: caffeine, diterpene alcohols, and chlorogenic acid (a polyphenolic acid). Chlorogenic acids are a family of esters formed between *trans*-cinnamic acids and quinic acid. The most common individual chlorogenic acid is formed between caffeic acid and quinic acid. It has been shown that both chlorogenic acid and caffeic acid are strong antioxidants *in vitro*.[38]

Population studies: CVD
Some studies have reported an association between coffee consumption and CHD, while different population groups have shown negative results. This may be because coffee consumption is often associated with other lifestyle factors, such as smoking and physical inactivity, which contribute to an increased risk of CVD, and several early studies failed to adequately take these into account.[61] It has also been suggested that case-control studies have shown an association because of poorer control of confounding, selection bias or recall bias.[63] Sofi et al[61] reported a positive association between habitual coffee consumption and CHD using 13 case-control studies, but several meta-analyses of cohort studies have found no effect of coffee drinking on the risk of CHD.[61–65]

Recent prospective cohort studies have found that coffee intake at the time of myocardial infarction was associated with a lower risk of total and cardiac mortality,[66] and high coffee consumption was not associated with increased rates of heart failure hospitalisation or

mortality.[67] A follow up of the Health Professionals Study and the Nurses Health Study found that regular coffee consumption was not associated with an increased cardiovascular mortality rate in either men or women.[68]

A meta-analysis of nine cohort studies examined the relationship between coffee consumption and the risk of type 2 diabetes (*n* = 193,473 participants).[70] The study found a significant inverse association between coffee consumption and the risk of type 2 diabetes. Individuals who drank four to six cups per day and more than six cups per day had a 28 and 35% lower risk of type 2 diabetes than those who drank no coffee or less than two cups per day. Despite these findings, the mechanisms remain unclear.[121] As decaffeinated coffee is also associated with a decreased risk of type 2 diabetes, it is proposed that substances other than caffeine are responsible for this protective effect. One proposed mechanism is through chlorogenic acid, which decreases the intestinal absorption of glucose by inhibiting the glucose-6-phosphatase system.[121,122]

Conclusion
Cohort studies suggest that coffee has little impact on the risk of CHD (level of evidence for lack of effect: III-2). Coffee consumption is not associated with increased rates of heart failure hospitalisation or mortality, or cardiovascular mortality (level of evidence for no association: III-2). Regular coffee consumption is associated with a lower risk of type 2 diabetes (level of evidence: III-2).

Coffee and CVH markers: RCTs
The effects of coffee on the primary or secondary prevention of CVD have not been assessed in RCTs. Therefore, we need to rely on data from RCTs that have assessed the effects on markers of CVD risk.

Blood pressure/Hypertension
Caffeine is the main active constituent responsible for the rise in blood pressure after acute consumption of coffee in individuals who have avoided caffeine for 12 hours or more.[123] A single dose of caffeine (200–250 mg; two cups of coffee) increases systolic blood pressure by 3–14 mmHg and diastolic blood pressure by 4–13 mmHg in normotensive individuals. This blood pressure response to caffeine seems to be more pronounced in hypertensive individuals and people who do not normally consume caffeine. The long-term effects of caffeine on blood pressure remain less clear.

Meta-analyses have examined the effect of coffee consumption on blood pressure.[55,56] Jee and colleagues[55] included 11 RCTs with a median duration of 56 days and median coffee intake of five cups per day. They found that systolic and diastolic blood pressure increased by 2.4 (range: 1.0–3.7) and 1.2 (range: 0.4–2.1) mmHg, respectively, with coffee, compared with the control. Noordzij et al[56] included 16 RCTs with a median duration of 43 days. Coffee and caffeine intake significantly increased systolic and diastolic blood pressure by 2.0 and 0.7 mmHg, respectively. Blood pressure elevations were two to three times greater for caffeine tablets than for caffeinated coffee, despite equal average doses of caffeine, suggesting the pressure effect of caffeine was low if ingested through coffee.

It is not clear whether the attenuated pressor effects of chronic coffee consumption compared with caffeine tablets are due to other compounds found in coffee. Prospective epidemiological studies do not provide a clear picture on the role of coffee intake in the development of hypertension.[69]

Conclusion
The results of RCTs show that coffee consumption of approximately five cups per day causes a small (2.4 mmHg) elevation in systolic blood pressure (level of evidence: I). The role of coffee intake in the development of hypertension is unclear from epidemiological studies (level of evidence: III-2).

Lipid profile
Population studies have suggested a link between coffee consumption and raised blood cholesterol levels, but the results are inconsistent. The method of brewing has been identified as an important factor for the hypercholesterolaemic effect of coffee.[59] The mechanism by which blood cholesterol is elevated by coffee-derived compounds may be complex, with effects on a range of genes involved in cholesterol and bile acid metabolism.[124]

Christensen and coworkers[125] hypothesised that terpenoid fractions (found in very high amounts in unfiltered coffee), mainly cafestol and kahweol, in coffee oil raise blood cholesterol levels. It has been shown that boiled coffee contains a lipid fraction that can be removed during filtration though paper, and once filtered, does not raise blood cholesterol levels.[57,58] Instant coffee has very low levels of cafestol and kahweol, and is unlikely to raise blood cholesterol levels. Both Robusta and Arabica coffee beans contain kahweol and cafestol.

A comparison of diterpenes in various coffee brews found that Turkish/Greek-style coffee contains the highest cafestol levels per cup (mean: 3.9±3.2 mg), while plunger/cafetiere-style coffee contained 3.5±1.2 mg.[59] Five cups per day of either of these styles of coffee would raise serum cholesterol by about 8–10 mg/dL or 0.2–0.25 mmol/L. The cafestol concentrations for espresso-style coffee were highest, but due to the small servings, the cafestol content per cup was 1–2 mg. Five cups of espresso coffee per day raises serum cholesterol by an average of 2.5 mg/dL, not a clinically significant effect on CHD risk. Percolated coffee contained very low levels of cafestol, while drip coffee (with a paper filter) and instant coffee (decaffeinated and regular) contained minimal cafestol.

A meta-analysis of 14 RCTs found that the consumption of boiled coffee dose dependently increased LDL-C and TC levels, while the consumption of filtered coffee resulted in very little change.[60]

Conclusion
RCTs have shown that boiled coffee increases LDL-C and TC levels, but filtered and instant coffee has very little effect (level of evidence: I).

Red wine

Wine was first thought to be beneficial for health when it was observed that people in the Burgundy area of France experienced lower rates of CHD than people in other cultures who did not consume wine as the major alcoholic drink. Along with wine, the diet consisted of foods that were rich in saturated fat, and the lower incidence of CHD became known as the 'French paradox'.[126] It was subsequently suggested that this benefit associated with wine consumption is related to the antioxidants contained in red wine.[127] However, the evidence for this is at best circumstantial; the epidemiological effects of wine may come from variables other than antioxidant contents, such as drinkers having better eating patterns[128] and

healthy behaviours.[129] A recent study on the Danish population found that wine drinking was associated with a healthy diet, defined as mainly comprising fruit and vegetables, fish, salads and olive oil.[130] Such a study has not been conducted within the Australian population.

Red wine can be a rich source of polyphenols, such as anthocyanosides, catechins, proanthocyanosides, stilbenes and other phenolics dependent on the grape variety, area of cultivation and vinification methods.[131] The polyphenol resveratrol is found in the skin of red grapes, and is a constituent of red wine that has attracted considerable study as a compound that may have cardiovascular-protective effects.

Population studies: CVD

Population studies of alcohol, including wine and red wine components, have shown CVD benefits.[132–139]

A study of 36,250 healthy, middle-aged French men reported that moderate wine and beer consumption was associated with a lower relative risk of CVD.[135] Further, the reduction in risk was more significant for wine. Moderate daily wine consumption (22–32 g of alcohol per day; higher than NHMRC recommendations) was significantly associated with a 33% lower relative risk of all-cause mortality compared with abstainers. Heavy drinking of beer and/or wine was associated with a significantly increased risk of death. Moderate wine consumption (< 60 g alcohol per day) was also associated with a lower risk of mortality from all causes in individuals with hypertension, compared with abstainers.[134]

The Copenhagen City Heart Study[136] followed a population of 13,285 participants for 10 to 12 years. They found that the risk of cardiovascular mortality steadily decreased with an increase in wine consumption, reaching a 49% reduction for those drinking three to five drinks per day compared to those who never drank wine. The same study[137] examined 13,329 participants over 16 years and found weekly wine consumption to be significantly associated with a reduced risk of stroke (monthly, relative risk: 0.83; 95% CI: 0.69–0.98; weekly, relative risk: 0.59; 95% CI: 0.45–0.77; daily, relative risk: 0.70; 95% CI: 0.46–1.00) compared with individuals who never/hardly ever drank wine. The study did not differentiate between red and white wine.

Di Castelnuovo et al[139] performed a meta-analysis to determine the relationship between wine and beer consumption and vascular risk. From 13 studies involving 209,418 people, an average significant reduction of 32% of overall vascular risk was associated with wine intake compared to non-drinkers. A J-shaped relationship between wine intake and vascular risk was established, suggesting that light-to-moderate wine drinkers have lower vascular risk than heavier drinkers or abstainers.[139]

The findings from prospective studies that light-to-moderate consumption of alcohol is protective against CVD compared with abstinence has been questioned.[129,140] It has been suggested that a systematic misclassification error is present in most of these prospective studies, because individuals who had stopped drinking or decreased their alcohol consumption to very occasional drinking had been classified in the abstainer category for the analysis. This had biased the findings, making drinkers appear to be less vulnerable to CHD, and abstainers more vulnerable. Individuals may decrease their alcohol consumption as they age, become ill and frail, and/or because of their increased use of medicines.

A meta-analysis of the few studies without these errors show abstainers and light and moderate drinkers to be at equal risk for all-cause and cardiovascular mortality.[129] In addition, the studies mentioned earlier were limited in their measurement, and most used absolute volume of drinking, thereby using imprecise measurements and introducing errors.

The use of the term 'moderate' needs to be considered carefully, because the meaning varies across cultures and time, and because the definitions in studies also vary.[129] In addition, evidence exists that encouraging moderate drinking raises the average alcohol consumption within a country.[141]

Red wine and CVH markers: RCTs

The interaction between red wine polyphenolic compounds and the progression of atherosclerosis has been extensively investigated in animal models and humans. They are thought to exert numerous effects, including antioxidant and free radical properties, anti-aggregatory platelet and antithrombotic activities.[142] Moreover, red wine polyphenolic compounds are thought to be vasodilators and contribute to the preservation of the integrity of the endothelium and the inhibition of smooth muscle cell proliferation and vascular hyperplasia.[142]

There are over 8,000 polyphenolic compounds, and it is still unclear which of these is responsible for the beneficial effects listed earlier. Caffeic acid and protocatechuic acid seem to have the most potent antioxidant effects; resveratrol and quercetin have the highest activity in platelet adhesiveness modulation; and resveratrol may have the strongest antiproliferative potential.[142] Additional research is needed to determine the compounds, doses and possible synergistic effects that would provide optimal CVH benefits.

Red wine and risks associated with increased alcohol consumption

In Australia, the NHMRC recommendations state "for healthy men and women, drinking no more than two standard drinks on any day reduces the lifetime risk of harm from alcohol-related disease or injury".[143] The notion of a standard drink is used widely internationally, but the definition varies from country to country. These guidelines use the Australian standard drink, which is defined as containing 10 g of alcohol (equivalent to 12.5 mL pure alcohol). The studies reviewed were conducted in Organisation for Economic Cooperation and Development countries, where standard drinks are defined in grams of ethanol.

Conclusions

There is no compelling evidence that would justify the Heart Foundation varying from NHMRC advice around the adult intake of no more than two standard drinks on any day. While polyphenols in red wine have been examined for effects on CVH markers, little has been shown in longitudinal RCTs of humans to date.

As wine drinking proves to be associated with a healthier lifestyle profile than the consumption of beer and liquor, this may have a substantial influence on the positive outcome of epidemiological studies. Prospective randomised trials of humans are needed, but due to ethical considerations, they cannot be conducted.

Part 2: Supplements

In 2002, the Heart Foundation reviewed RCTs and several large prospective cohort studies involving the clinical use of antioxidant supplements.[78] From the RCTs investigating vitamin E, retinoic acid and β-carotene, the majority of data indicated a neutral effect of supplementation with antioxidants on cardiovascular outcomes. The review concluded that there was insufficient data to recommend the consumption of antioxidant vitamin supplements for the prevention or treatment of CHD. It recommended that emerging evidence on the role of antioxidant supplements be monitored.[78]

In 2004, the American Heart Association conducted a review of the evidence to determine the effects of antioxidant vitamin and mineral supplements on CVD risk.[144] They also found, for the most part, that clinical trials failed to demonstrate a beneficial effect of antioxidant supplements on cardiovascular morbidity and mortality. The authors concluded that the scientific data at that time did not justify the use of antioxidant supplements for CVD risk reduction.

Other reviews and meta-analyses conducted since 2002 are discussed below.

Supplements: systematic reviews and meta-analyses of RCTs

Katsiki and Manes[71] reviewed RCTs of antioxidant supplementation, particularly vitamins E, C and/or A, to examine their role in the prevention of atherosclerosis. The authors identified 22 trials; 10 for a single supplement and 12 for the effect of a combination of antioxidants. Overall, the studies failed to demonstrate a consistent protective effect of any single antioxidant or combination of antioxidants on the incidence of or death from CVD.

A systematic review and meta-analysis by Shekelle et al[72] assessed the efficacy of vitamin E supplementation for the prevention and treatment of CVD. Eighty-four eligible trials were identified. The results did not support any benefit associated with the use of vitamin E, alone or in combination, for the prevention of all-cause mortality or cardiovascular mortality. The analysis did not find an effect for vitamin E supplementation, alone or in combination, on the risk of myocardial infarction, fatal or non-fatal. Intervention with vitamin E in doses ranging from 100 to 1200 IU per day and treatment durations of eight to 24 weeks did not demonstrate a significant effect on serum lipids.

A smaller meta-analysis of RCTs examined the effect of vitamin E and β-carotene on all-cause mortality and cardiovascular mortality.[73] Seven trials of vitamin E treatment (81,788 individuals) and eight trials of β-carotene (138,113 individuals; most people in the secondary prevention group were smokers) were included. Vitamin E did not provide benefits in mortality when compared with the control, nor did it significantly decrease the risk of cardiovascular mortality or cerebrovascular accident. A small, harmful effect of β-carotene was observed, mainly due to the inclusion of patients who were at high risk of lung cancer due to smoking.

In 2004, Eidelman and colleagues[74] examined randomised trials for the effectiveness of vitamin E, alone or in combination, in the treatment and prevention of CVD. Seven large-scale trials were found with data on non-fatal myocardial infarction, non-fatal stroke

and cardiovascular mortality. The analysis did not find a statistically significant or clinically important effect on CVD.

Conclusion
The use of supplemental vitamin E does not decrease the risk of all-cause mortality or cardiovascular mortality, nor does it have any effect on the prevention of cardiovascular events (level of evidence for meta-analysis: I). There are potential concerns about the consumption of large doses of supplemental vitamin E with regards to the possibility of increased all-cause mortality.

The consumption of supplemental β-carotene has a small effect on increasing cardiovascular mortality and all-cause mortality in smokers (level of evidence: II).

There is no evidence for effectiveness from a combination of antioxidants as supplements for the prevention of CVD (level of evidence: II).

Supplements: systematic reviews and meta-analyses of population studies

A meta-analysis by Ye and Song[75] sought to examine the relationship between antioxidant vitamins E and C and β-carotene and CHD risk. Fifteen relevant cohort studies were identified involving a total of 7,415 incident CHD cases and 374,488 participants. Subgroup analyses show that dietary intake of vitamins C and E and using vitamin E supplements had an inverse association with CHD risk; vitamin C had no significant association. In the dose-response analysis, no association was observed between vitamin C intake of 30 mg per day and the risk of CHD (relative risk: 1.01, CI: 0.99–1.02). No association was observed between β-carotene intake of 1 mg per day and the risk of CHD (relative risk: 1.0, CI: 0.88–1.14). An inverse relationship was found between vitamin E intake and the risk of CHD; an increment of 30 IU per day was found to lower CHD risk by 4%.

A pooled analysis of nine cohort studies by Knekt et al[76] involved 4,647 major incident CHD events in 293,172 individuals free of CHD. Over 10 years, higher overall intakes of vitamin C were associated with lower CHD rates. Participants in the highest quintile of intake (median: 756 mg/day) had a 24% lower risk than those in the lowest quintile.

Conclusion
There is conflicting evidence regarding the effect of supplemental vitamin C intake and the risk of CHD (level of evidence: III-2).

Conclusions

The epidemiological evidence on antioxidants in food and drinks shows some positive outcomes for CVH and the prevention of CVD. However, RCTs have not supported such findings for antioxidant supplements and CVH.

Positively, intervention studies have shown that:
- fruit and vegetables lower blood pressure
- regular, warm black and/or green tea drinking improves endothelial function and may reduce the risk of CVD
- the consumption of high polyphenol cocoa and chocolate increases endothelial function
- the consumption of high polyphenol cocoa and chocolate reduces platelet reactivity
- the consumption of high polyphenol cocoa and chocolate reduces systolic blood pressure.

Negatively, intervention studies have shown that:
- five cups of coffee per day can slightly increase systolic blood pressure
- drinking boiled coffee, as opposed to filtered or instant, increases LDL-C and TC levels
- β-carotene supplementation has a small effect on increasing cardiovascular mortality and all-cause mortality in smokers.

There was no evidence of effectiveness for the prevention of CVD from:
- combinations of antioxidant supplements
- supplemental vitamin E.

There was conflicting evidence regarding the effect of supplemental vitamin C intake and the risk of CHD.

The Heart Foundation recommends that fruit and vegetables (including nuts and seeds) and warm black or green tea be incorporated into a healthy, balanced diet. High polyphenol cocoa drinks may be included as a good source of antioxidants, but most commercially available chocolate is high in energy, and processing removes the antioxidants due to their bitter taste. Coffee should not be boiled on the stove top or prepared in a plunger, and we recommend no more than five cups per day.

Based on the available research, the Heart Foundation will continue to encourage safe drinking practices for CVD without specification of the type of drink. The Heart Foundation supports the NHMRC recommendation for healthy Australians to have no more than two standard alcoholic drinks per day. We also advise individuals with hypertension to have no more than two standard drinks per day, people with chronic heart failure who have alcohol-related cardiomyopathy to abstain from alcohol, and other people with chronic heart failure to limit their alcohol intake to no more than 10–20 g (one to two standard drinks) per day.[145]

We do not recommend combination or individual antioxidant supplements for the prevention of CVD.

Abbreviations

ACM	All-cause mortality
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
CVH	Cardiovascular health
CVM	Cardiovascular mortality
DASH	Dietary Approaches to Stop Hypertension
FMD	Flow-mediated dilation
HR	Hazard ratio
LDL-C	Low-density lipoprotein cholesterol
NHMRC	National Health and Medical Research Council
RCT	Randomised controlled trial
RR	Relative risk
TAC	Total antioxidant capacity
TC	Total cholesterol

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