Reviews in Clinical Gerontology 2014 24; 25–40 First published online 20 November 2013
© Cambridge University Press 2013 doi:10.1017/S0959259813000191

Effect of diet on vascular health

CT McEvoy[1], CE Neville[1], NJ Temple[2] and JV Woodside[1]
[1]Centre for Public Health, Queen's University Belfast, Belfast, UK and [2]Centre for Science, Athabasca University, Athabasca, Canada

Summary

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the Western world in older people. Diet and lifestyle change can reduce CVD risk in older people, and this evidence base is reviewed. For example, diets low in trans fats can reduce CVD risk, while for saturated fats the CVD-lowering effect depends on what is substituted for the saturated fat. Diets rich in fish reduce CVD risk, although n-3 supplements have not been shown to have a consistent effect on CVD end-points. Antioxidant and B-group vitamin supplementation are unlikely to reduce CVD risk, but diets rich in these micronutrients (e.g. rich in fruits and vegetables and the Mediterranean diet) are associated with lower CVD risk, while, for the Mediterranean diet, this has been supported by randomized controlled trials. Maintaining a healthy weight and being physically active reduce CVD risk factors and CVD incidence and mortality.

Key words: cardiovascular disease risk, older people, diet.

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the Western world.[1] Well-established risk factors for CVD include age, sex, smoking, blood pressure, total- and high-density lipoprotein (HDL) cholesterol and type 2 diabetes.[1] During the last 50 years, evidence from observational epidemiological studies and controlled clinical trials has accumulated, supporting a role for diet in the prevention and treatment of CVD, both in the general population and in older people. In a systematic review of evidence supporting a causal link between dietary factors and coronary heart disease (CHD) published in 2009, Bradford Hill guidelines were used to derive a causation score for each dietary exposure from cohort studies and then examined for consistency with the findings of randomized interventions.[2] The evidence for Mediterranean diet (MD), a high quality diet, vegetables, nuts, trans fatty acids (TFA), low glycaemic index or load diets, a prudent diet, a western diet and monounsaturated fatty acids (MUFA) was rated as strong. The evidence base has developed since that time, therefore this review will examine the evidence that nutrients and lifestyle factors, such as saturated fatty acids (SFA), TFA, n-3 polyunsaturated fatty acids (n-3 PUFA), alcohol, salt, B vitamins, antioxidant vitamins, vitamin D, obesity and physical activity (PA), and fruit and vegetable (FV)-rich diets affect CVD risk, but will also consider whole diet patterns, including the MD and Dietary Approaches to Stop Hypertension (DASH) dietary patterns and their association with CVD risk. The evidence base examined is based on all ages, but specific considerations for older people are also included.

Address for correspondence: Professor Jayne Woodside, Nutrition and Metabolism Group, Centre for Public Health, Institute of Clinical Science B, Grosvenor Road, Belfast BT12 6BJ, UK
Email: j.woodside@qub.ac.uk

Dietary fats

Over the last four decades, dietary guidelines have recommended consuming a low fat diet (<30% energy intake), with a reduction in SFA and TFA intake to reduce CVD risk. Dietary fatty acids are known to influence the rate of atherosclerosis, largely through modification of blood lipid levels. However, emerging findings from large intervention studies and meta-analyses have challenged dietary recommendations advocating low fat diets and reduced SFA intake for CVD prevention.[3] Furthermore, when SFA/TFA fat is replaced in the diet, other dietary components are also likely to exert an influence on vascular disease risk, possibly mediated by changes in overall lipid fractions and other mechanisms. Therefore, it is important to evaluate what dietary fat changes are currently effective to reduce CVD risk.[4]

Low-fat diets

There is no convincing evidence demonstrating that low-fat diets reduce CVD risk.[4,5] The

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

Women's Health Initiative randomized controlled trial (RCT), involving 48,835 women over a mean 8 years follow-up, reported no significant difference in the incidence of CVD between a low-fat intervention and a control group. Total fat intake decreased by 8.2% with reductions in SFA 2.9%, MUFA 3.3% and PUFA 1.5% in the intervention group. There was a significant reduction in low-density lipoprotein (LDL) in the intervention group but no improvement in HDL or other lipid fractions.[5]

Saturated fatty acids

It is well established that high SFA consumption increases total cholesterol (TC) and LDL levels, which in turn accelerate atherosclerosis and increase CVD risk. Despite wide acceptance of this classical dietary fat hypothesis, a causal link between SFA intake and CVD has not yet been established. A meta-analysis of 21 prospective studies involving >350,000 adults followed over 5–23 years, found no significant association between SFA intake and CHD, stroke or total CVD risk.[6] Moreover, findings from a large systematic review of prospective cohort and randomized intervention studies, found only weak evidence to support a causal relationship between total SFA intake and CHD.[2] Further large-scale intervention studies are required to fully evaluate the relationship between dietary SFA and CVD risk. A recent meta-analysis suggested that reducing SFA intake by reducing and/or modifying dietary fat reduced risk of CVD events by 14% (RR: 0.86; CI: 0.77–0.96) with no effect demonstrated on CVD mortality or overall mortality risk.[4] Subgroup analyses indicated that reduction in CVD events was seen in studies of fat modification (not fat reduction), of at least two years duration, and in studies of men only.[4] Therefore, whilst it remains prudent to advocate a reduced SFA diet, it is unclear as to what type of dietary component should replace SFA to optimally reduce CVD risk.

Modified low-SFA diets

It has been suggested that SFA replacement by n-6 PUFA may be associated with greatest CHD risk reduction.[7,8] However, the most recent meta-analysis has indicated an adverse effect of replacement with n-6 PUFA on CVD events and mortality, but a significantly reduced CVD risk when SFA was replaced by a combination of both n-3 and n-6 PUFA.[9] As with any meta-analysis, differences in the results observed may be partly explained by heterogeneity in study designs, dietary intake analysis, uncontrolled confounding factors and differences between study end-points.

Replacing SFA with carbohydrate has been shown to increase triglyceride (TG) concentrations,[10] which may adversely affect vascular health, but this will depend on the type of carbohydrate consumed. It has been argued that there is little evidence to suggest that replacement of SFA by MUFA has any benefit for vascular health.[11] However, Mente *et al.*[2] reported strong evidence of an inverse causal link between MUFA and CHD. Furthermore, the MD characterized by increased MUFA is thought to offer greatest protection against CHD[2] (see discussion on MD).

Trans fatty acids

Ratio of TC to HDL (TC:HDL) appears to be the strongest predictor for ischaemic heart disease (IHD) mortality (twice as informative as TC alone).[12] Dietary TFA have greater TC-raising effects and HDL-lowering effects than dietary SFA. A meta-analysis evaluating dietary fatty acids and carbohydrates on blood lipids in 60 controlled trials, reported that TFA increased TC:HDL to almost twice that of SFA at comparable doses.[10] Further small RCTs, investigating blood lipid level responses to changes in TFA intakes, have reported significant reductions in HDL levels and significant increases in TC:HDL ratio, in response to high TFA (6.7–9% total energy intake) diet interventions.[13,14] Overall, the evidence suggests a strong, positive association between dietary TFA intake and CHD risk.[2] Therefore, dietary advice should continue to advocate low TFA intake for CVD risk reduction.

n-3 PUFA intake

In contrast to other fatty acids such as SFA and TFA, n-3 PUFA are essential long-chain fatty acids found in oily fish (eicosapentaenioc acid and docosahexaenoic acid) and vegetable oils (α-linolenic acid). n-3 PUFA significantly reduces TG level in a

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

dose-dependent manner and may increase LDL and HDL levels.[15] Mechanistic effects of n-3 PUFA are also believed to include reductions in thrombotic tendency, inflammation, arrhythmias and overall improvement in endothelial function.

Epidemiological studies provide evidence of an inverse association between fish intake and CHD death in both men and women.[16,17] Consumption of fish appears to provide cardioprotection in a dose–response manner in adults, with or without pre-existing coronary disease, although the cardioprotective benefits of fish may be greater in populations with low habitual fish consumption and those at greater risk of developing CHD. Fish consumption has also been inversely related to stroke risk in adults in a dose-dependent manner. In a meta-analysis of 26 prospective cohort studies, comparing categories of fish intake, the pooled RR for cerebrovascular disease for 2–4 servings/week *versus* ≤1 serving/week was 0.94 (95% CI: 0.90–0.98) and for ≥5 servings/week *versus* 1 serving/week was 0.88 (95% CI: 0.81–0.96).[18]

In the past decade, several large-scale intervention studies and meta-analyses have evaluated the effect of n-3 fish oil supplements in primary and secondary CVD prevention. A recent meta-analysis of 20 RCTs of 68,680 adults (including those with or without existing CVD) found no effect of n-3 PUFA on all-cause mortality, cardiac death, sudden death, myocardial infarction (MI) or stroke.[19] In a further pooled analysis of 14 randomized, double-blind, placebo-controlled trials involving 20,485 patients with existing CVD, n-3 supplementation did not reduce the risk of overall CVD events (RR: 0.99; CI: 0.89–1.09), all-cause mortality, sudden cardiac death, MI, congestive heart failure, or transient ischaemic attack and stroke.[20] Therefore, the current evidence does not support routine n-3 fish oil supplementation for primary or secondary prevention of CVD.

Phytosterols

Phytosterols include β-sitosterol, campesterol and stigmasterol, and are structurally similar to cholesterol. Plant stanols are simply the 'saturated' derivative of the sterol, the most common being sitostanol.[15] Esterifying plant stanols – typically adding oleic acid – makes it easier to incorporate this ingredient into everyday foods.

Both esterified and non-esterified plant sterols and stanols lower TC and LDL in both normocholesterolaemic and hypercholesterolaemic adults.[21–25] Meta-analyses evaluating cholesterol-lowering effects of phytosterols/stanols suggest an average 10% reduction in LDL when 2 g of plant stanol is included in the diet.[26,27] Additive benefits in reducing LDL concentrations are observed when phytosterols/stanols are incorporated into low-fat diets.[23,25] Importantly, further significant benefits in cholesterol lowering have been demonstrated in patients taking statin drug treatments in combination with phytosterols/stanols, with an average net benefit of a further 10% reduction in LDL concentration when 2–3 g/day sitostanol is consumed.[22,28] However, as yet, there are no clinical trials of phytosterols with hard clinical end-points.[29]

Glycaemic index and glycaemic load

It is accepted that carbohydrate-containing foods elicit different postprandial glucose responses. This has been quantified as the 'glycaemic index' (GI), defined as the relative area under the curve for blood glucose concentrations during a 2-hour period after consuming a test food compared with a standard food (glucose or white bread) containing the same amount of digestible carbohydrate (50 g).[30] A second concept, that of glycaemic load (GL), is calculated by adjusting the GI value of the food to the serving size as quantified by carbohydrate content.[31] Such a classification system has been suggested as useful in guiding food choices to reduce chronic disease risk. However, whilst there is some evidence, mainly from observational studies, that low GI and GL diets are associated with reduced risk of CVD, recent meta-analyses have not been consistent regarding whether both GI and GL are important, whether the association persists in both genders and whether the association is equally strong for both CHD and stroke.[32–34] There is some suggestion that the association may depend on initial BMI,[32] while a meta-analysis of intervention studies altering GI/GL suggests inconsistent effects on CVD risk factors.[31]

Alcohol

Many epidemiological studies have shown that alcohol consumed in light to moderate amounts reduces mortality from vascular events[35] and

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

reduces CHD risk by 20–40%.[36–38] While a moderate consumption of alcohol is protective against CHD, alcohol manifests a more complex relationship with other types of CVD. There appears to be a J-shaped relationship between alcohol intake and hypertension: the lowest risk is seen among light and moderate drinkers,[39] while those who consume relatively large amounts of alcohol (>4 drinks/day) frequently have elevated blood pressure.[40,41] A similar pattern is seen with risk of stroke. While the findings from large epidemiological studies are inconsistent, it appears that moderate drinkers experience a reduced risk of stroke while the risk rapidly escalates in heavy drinkers.[38,41] The protective effect of moderate consumption of alcohol is seen only for ischaemic stroke, but not for haemorrhagic stroke.[38] A similar J-shaped relationship has been observed between alcohol consumption and several other conditions.[42]

The cardioprotective effect of alcohol may also depend on the type of alcoholic beverage consumed. While it has consistently been shown that wine confers a cardioprotective effect,[43] there is also recent epidemiological evidence that shows a J-shaped relationship between beer consumption and vascular risk, but no association with spirit consumption.[44]

The mechanistic effect of alcohol is thought to be related to increased HDL concentrations. Alcohol may also prolong blood clot formation by lowering levels of fibrinogen and plasminogen activator, reducing HbA1c and increasing adiponectin, although an increase in TG has also been noted.[36]

There are currently no guidelines regarding alcohol intake for older adults.[35] A sensible policy would appear to be one that informs people that alcohol in moderation will probably have several health benefits for people in middle age and above, but also stresses that binge drinking should be avoided, and stresses the problems of abuse.

Salt

The estimated daily requirement for dietary sodium in the UK is 1500 mg up to age 50, and 1300 mg between ages 50 and 70 (equivalent to a salt intake of 3.8 and 3.3 g, respectively). However, the intake in most countries is far higher, around 3500 mg/day.[45]

Excess sodium intake is believed to play an important role in the aetiology of hypertension.[46] A recent meta-analysis involving 34 RCTs revealed that a decrease in sodium intake of 1700 mg/day (4.4 g of salt) lowered blood pressure by 5.4/2.8 mmHg (systolic/diastolic) in subjects with hypertension and by 2.4/1.0 mmHg in those who were normotensive.[47] They also reported that a greater reduction in sodium intake leads to a larger decrease in blood pressure and that, ideally, sodium intake should be reduced to 1180 mg/day (3 g of salt).

As hypertension is a major risk factor for CHD (and other forms of CVD), it can be predicted that sodium intake will be associated with risk of CHD. Supporting evidence for this comes from another systematic review and meta-analysis by Aburto *et al.*,[48] who reported that a higher sodium intake was significantly associated with increased risk of CHD mortality, stroke and stroke mortality. A separate analysis concluded that a population-wide reduction in dietary sodium of 1200 mg/day (3 g of salt) would prevent between 44,000 and 92,000 deaths/year in the USA.[49] It would also be expected to decrease the annual incidence of CHD cases by between 60,000 and 120,000 and stroke cases by between 32,000 and 66,000.

The overall evidence suggests that a major reduction in the average population intake of salt should be a priority. Approximately 75–80% of dietary salt intake comes from processed foods,[50] therefore intake of these foods should be limited. In the UK, voluntary efforts are already being undertaken by the Food Industry to lower the salt content of processed food. This strategy has achieved some success: between 2001 and 2011 mean sodium intakes of adults in the UK fell by about 15% (from about 3700 to 3200 mg/day).[51] However, in order to achieve country specific sodium targets within a reasonable timespan it will be necessary to adopt a legislative strategy, which could be hugely beneficial for public health.[52]

Sugar-sweetened beverages

There has been speculation for many years that a high sugar intake (i.e. highly processed sugar added to food) may increase the risk of CHD.[53,54] Most attention has focused on sugar-sweetened beverages (SSBs), and recent evidence supports this. The Nurses' Health Study reported that risk is

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

associated with an excessive consumption of SSBs. In this cohort study, the diets of 88,000 nurses were assessed several times over 24 years. The findings revealed that risk of CHD was 35% higher among women who consumed two or more servings per day of SSBs compared with those consuming SSBs less than once a month.[55]

There has also been research into the relationship between consumption of SSBs and risk factors for CHD. Large cohort studies have demonstrated that people who regularly consume SSBs have increased risk of developing hypertension. This was shown in the Nurses' Health Study I and II, where women who consumed four or more servings per day of SSBs had a 44 and 28%, respectively, higher risk of hypertension compared with women who consumed less than 1 serving per day.[56] However, these results were not clear cut, as consumers of diet fizzy drinks also had increased risk of hypertension. The Framingham Offspring Study reported that those who drank at least one serving of SSB per day had a roughly 20% higher risk of hypertension, but this increase was not statistically significant.[57] This study also observed a significantly higher risk of developing both hypertriglyceridaemia and low HDL-cholesterol in regular consumers of SSBs. On the whole, these findings suggest that frequent consumption of SSBs are associated with detrimental changes in risk factors for CHD.

Whole grains and fibre

A strong body of evidence has emerged from cohort studies showing that people who have relatively high intakes of whole grains or cereal fibre have lower risk of CHD.[58,59] As cereal fibre is usually eaten as part of whole grains, studies that show a protective association between intake of cereal fibre and risk of CHD are best interpreted as indicating that whole grains are protective; it is unwarranted to conclude without further evidence that cereal fibre specifically is protective.

There has been some investigation into possible mechanisms by which whole grains prevent CHD. One mechanism with reasonably solid supporting evidence, based on findings from several RCTs, is that whole grains lower LDL-cholesterol.[60] Most of the RCTs that have reported this effect have been carried out using oats.[61] However, this still requires further investigation.

Folic acid and B vitamins

Over the past 20 years, a wealth of observational evidence has linked low concentrations of folate and/or high homocysteine concentrations with increased CVD risk in middle-aged and older adults, and these studies have been subjected to meta-analysis.[62,63] The homocysteine-lowering effect of a combination of B-group vitamins has been demonstrated in a number of studies, and has also been confirmed by meta-analysis.[64,65] However, a number of RCTs have examined the effects of B vitamin supplementation on CVD risk, and meta-analyses have shown that such lowering has not led to a reduction in CVD risk,[66] although an effect on stroke has been suggested in some analyses.[67–70] For stroke, a beneficial effect was notably stronger among trials with longer duration of follow-up, in those showing a greater reduction in total homocysteine (tHcy), in those without a history of stroke, and in geographical areas where grain is not fortified with folic acid.[67,68] However, a comprehensive meta-analysis, which pooled together individual patient data, rather than summary results, showed that folic acid supplementation had no effect on the incidence of cardiovascular events (RR: 1.01; CI: 0.97–1.05) for major vascular events, 1.03 (0.97–1.10) for major coronary events and 0.96 (0.87–1.07) for stroke). There was also no evidence of a beneficial effect among the trials where treatment was continued for >5 years, or in patients presenting with low folate status or high homocysteine levels,[71] and these findings appear conclusive.

Antioxidants

Many observational studies have demonstrated an association between vitamin E and β-carotene intake and CVD risk, although the evidence is less consistent for vitamin C.[72] In the past 15 years, a number of RCTs have tested the effect of vitamin E and other antioxidant vitamins or their combinations on clinical CVD end-points. These trials have consistently shown that commonly used antioxidant regimens (vitamins E, C, β-carotene, singly or in combination) do not significantly reduce overall cardiovascular events, and this has been confirmed by meta-analyses.[73,74] The HOPE-TOO study, an extended follow-up of the HOPE study, even suggested an increased risk of heart failure in the vitamin E-supplemented

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

group.[75] Indeed, a meta-analysis of 19 clinical trials involving 135,967 participants found a significant dose-dependent adverse mortality effect of vitamin E when taken at 400 IU daily and above.[76] A beneficial effect of vitamin E supplementation in end-stage renal failure subjects cannot be excluded.[77]

β-Carotene supplementation has also been evaluated in a number of trials examining both cancer and CVD end-points, with no reduction in CVD morbidity or mortality being demonstrated, alongside high-dose β-carotene supplementation increasing the incidence of both lung cancer and all-cause mortality in smokers.[78,79] This lack of effect of β-carotene supplementation on CVD end-points has also been confirmed by meta-analysis.[73]

A Cochrane review and meta-analysis of 68 RCTs including 232,606 participants has shown that supplementing with antioxidant nutrients (vitamins A, E and β-carotene) did not affect all-cause mortality.[80,81] However, when poorer quality trials were omitted, the results from the better quality studies revealed a positive effect of antioxidant supplement use on mortality (RR: 1.05; 95% CI: 1.02–1.08). Significant increases in mortality were also shown for use of vitamins A, E or β-carotene, either singly or in combination.[80,81]

In 2007, the National Institutes of Health State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention concluded that there was insufficient evidence to recommend either for or against the use of multivitamin/mineral supplements to prevent chronic disease.[82] It can be concluded that, for CVD specifically, antioxidant vitamin supplements should not be recommended to reduce primary or secondary CVD risk.

Polyphenols

In recent years, there has been growing interest in the role of polyphenols, such as flavonoids, for CVD prevention. Flavonoids are bioactive, polyphenolic metabolites that are primarily found in FV, nuts, cocoa and beverages such as tea and red wine. The link between flavonoids and CVD first emerged in studies conducted in Asian populations.[83] A number of prospective studies conducted in Western populations have also shown that high intakes of flavonoids are associated with lower CVD incidence and mortality.[84–86] The association between flavonoids and stroke risk or mortality is less clear. While reduced risk of stroke was reported in one study,[85] another study found no association between dietary flavonoids and stroke mortality.[84] The most comprehensive evidence to date comes from the Cancer Prevention Study II Nutrition Cohort. This large prospective study of 38,180 men and 60,289 women showed that those in the highest quintile for total flavonoid intakes had decreased risk of CVD mortality compared with those in the lowest quintile (P for trend = 0.01). The inverse associations between flavonoid intake and CVD mortality were also observed with intermediate intakes of flavonoids, which led them to suggest that even small amounts of flavonoid-rich foods may confer beneficial effects.[86] Although clinical trial evidence has yet to appear to support these findings, a few RCTs have shown beneficial effects of polyphenols found in soy and cocoa on CVD risk factors including blood pressure, flow-mediated dilatation and lipids.[87,88] However, this area is still largely under-investigated and long-term clinical trials are needed to clarify the effect of flavonoids on clinical CVD end-points.

Vitamin D

Vitamin D, which is often deficient in older adults, may be associated with cardiovascular health. Evidence for a role of vitamin D in CVD mainly comes from epidemiological studies that examined the association between 25(OH)D concentrations and subsequent CVD events. The majority, although not all, of these studies have shown that low levels of 25(OH)D are associated with increased cardiovascular incidents and CVD mortality[89–95] and this has also been confirmed by meta-analyses.[96–99] The most recent meta-analysis by Wang and colleagues[96] reported that individuals with low 25(OH)D concentrations had 48% greater risk of total CVD (95% CI: 1.30–1.77), 58% greater risk of CVD mortality (95% CI: 1.19–1.71), 62% greater risk of CHD (95% CI: 1.21–1.57) and 36% greater risk of stroke compared with those in the highest 25(OH)D categories. Moreover, they observed a general linear dose–response association between 25(OH)D (at a range of 20–60 nmol/l) and CVD risk, with a RR of 1.03 (95% CI: 1.00–1.06) per 25 nmol/l decrease in 25(OH)D.[96] Two other

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

meta-analyses also reported a modest association between low levels of 25(OH)D and increased risk of stroke.[100,101] However, despite the abundance of epidemiological evidence, numerous shortcomings in the literature have been identified, including variation in vitamin D status, seasonal variation, differences in CV outcomes and baseline vitamin D status.[102] Furthermore, there is still insufficient clinical trial evidence to support a causal role, and meta-analyses of clinical trials conducted thus far have shown no significant effect of vitamin D supplementation on CVD end-points, including CVD mortality, MI, stroke and cardiovascular risk factors.[103,104] However, it is worth noting that the majority of the studies included in these meta-analyses did not evaluate cardiovascular outcomes as a primary end-point and many were using a combined calcium plus vitamin D supplement. A recent report by the Institute of Medicine[105] concluded that there was still insufficient evidence to demonstrate a protective role of vitamin D against CVD, and highlighted a need for more research to be undertaken. At least one trial is ongoing,[106] and additional large-scale and robustly designed RCTs such as VITAL are needed before vitamin D supplements can be routinely recommended for the prevention and treatment of CVD.

Obesity

Obesity (BMI $\geq$ 30 kg/m^2) is an independent risk factor for CVD,[107,108] but is also accompanied by a number of CVD risk factors, including hypertension, hyperlipidaemia and insulin resistance.[109–111] BMI is the most widely used index of obesity, but waist circumference and waist-to-hip ratio (WHR) both measure abdominal adiposity, and each of these have been shown to be associated with increased CHD incidence and mortality (as reviewed by van Horn *et al.*[15]). BMI is poorly associated with total and CVD mortality in those older than 65 years,[112,113] but even in those less than 65 years of age, waist circumference and WHR would appear to be better predictors of CVD risk than BMI (as reviewed by van Horn *et al.*[15]). However, whilst cut-points for BMI for overweight and obesity are well-established and accepted, further research is required to determine similar cut-points for WHR and waist circumference in different sex, age and ethnic groups.[15]

Physical activity

One of the factors limiting research into PA and primary and secondary CVD risk is the difficulty in objectively measuring PA.[15] Nevertheless, PA has consistently been associated with a reduction both in CVD risk factors and CVD events in both primary and secondary prevention, and this has been shown in both observational epidemiological studies and in RCTs.[114–119] PA favourably affects blood pressure, lipids, insulin sensitivity, glucose tolerance and body weight.[120] There is some debate over how much activity and what intensity of activity is required to produce a beneficial effect on CVD risk,[121,122] but the main health-promoting bodies worldwide (e.g. American Heart Association, Centers for Disease Control and Prevention, British Heart Foundation and the UK government) all recommend individuals to engage in regular, moderate-intensity PA. A major challenge in this area is to determine what behavioural strategies will motivate individuals to become and remain physically active, as PA rates are declining, for example in the United States.[123,124]

Whole diet/food approaches

While the traditional approach in nutrition epidemiology is to study the effect of individual nutrients, a growing number of studies are using a whole diet/food approach in the study of CVD prevention and therapy.

Fruit and vegetable intake

FV are complex foods that contain a variety of bioactive compounds,[125] and the complex mixture of micronutrients found in a FV-rich diet may be more effective than large supplemental doses of a small number of micronutrients at reducing CVD risk.[126] The evidence to date regarding the association between FV consumption and CVD risk is largely confined to epidemiological studies.[127] These studies have consistently shown a positive association between increased FV consumption and reduced risk of both CHD and stroke, and this has been confirmed by meta-analyses.[128–131] This dose-dependent association has largely been confirmed in more recent prospective cohort studies,[132–135] including an analysis of the large EPIC study (n = 313,074),

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

where a one-portion increment in FV was associated with a 4% lower risk of fatal IHD (95% CI: 0.92–1.00; P for trend = 0.033).[136]

While the epidemiological evidence is strong, no intervention studies with hard clinical end-points have yet been carried out, which show a causal effect of FV on CVD risk. Evidence has tended to focus on intermediate end-points, such as markers of cardiovascular risk. An effect of increased FV intake on blood pressure has been demonstrated in some studies,[137,138] although not all,[139–141] while an effect of increased FV intake on vascular function has also been demonstrated in some,[142] but not all studies.[141] A trend ($P = 0.06$ for between-group change) towards an effect of FV puree-based drinks (200 ml/day for 6 weeks) on endothelium-dependent vasodilatation in healthy volunteers[143] has been demonstrated. However, comparing results from these studies is difficult due to variation in participant characteristics and methods used to assess vascular function.

The DASH diet

The Dietary Approaches to Stop Hypertension (DASH) diet is characterized by high intakes of FV, whole grains, low-fat dairy products and low intakes of meat. Interest in the DASH diet began in 1997 when an RCT by Appel and colleagues[138] demonstrated that the DASH diet had a blood pressure-lowering effect that resulted in a reduction in estimated 10-year CHD risk.[144] This effect was improved further with the accompanying restriction of sodium intake,[145] and the effectiveness of the DASH diet has also been shown in free-living populations.[146,147] Building on this evidence, a number of observational studies have examined the association between the DASH diet and cardiovascular outcomes including fatal and non-fatal CHD[148] and stroke.[148,149] While some of these studies have shown that adherence to the DASH diet is independently associated with fatal and non-fatal CHD[147] and stroke,[148,149] others have shown no association with fatal CVD,[149,150] IHD,[149] CHD[149] or stroke.[150] Consistent with previous findings, a recent study that examined 34,827 women from the Women's Health Study showed that higher DASH dietary scores were associated with reduced CVD and CHD risk, but significance was lost after adjusting for other cardiovascular risk factors.[151]

Mediterranean diet

It has been recognized for some time that there is a lower mortality from CHD in Mediterranean countries compared with Northern European countries.[152] High intakes of FV, bread and other forms of cereals, beans, nuts and seeds are key characteristics of the MD pattern. Olive oil is considered an important fat source of the MD, while dairy products, fish and poultry are consumed in low to moderate amounts; eggs are consumed <4 times/week; and little red meat is consumed. In addition, wine is consumed in low to moderate amounts with meals.

A recent meta-analysis by Sofi and colleagues[153] examined the association between adherence to the MD and health status. The results were pooled from 18 prospective studies (including non-Mediterranean populations) involving more than 2 million individuals, and showed that a two-unit increment in adherence to the MD was associated with a significant reduction in cardiovascular incidence or mortality (RR: 0.90; 95% CI: 0.87–0.93) over a follow-up period of 4–20 years, and this has been confirmed in more recent analyses.[154–157]

The MD has been rated as the most likely dietary pattern to offer protection against CHD,[2] as, in addition to the observational evidence base, a number of studies have examined the effect of a MD on clinical end-points. The Lyon Diet Heart Study, a secondary prevention trial in MI patients, showed that a MD resulted in a 50–70% reduction of cardiac end-points. de Lorgeril *et al.*[158] reported significant reductions in three composite outcomes (CO): CO1 (cardiac death and non-fatal MI), CO2 (CO1 plus unstable angina, stroke, heart failure, pulmonary or peripheral embolism), and CO3 (CO2 plus minor events requiring hospital admission), with adjusted risk ratios ranging from 0.28 to 0.53.

More recent evidence comes from the primary prevention PREDIMED study.[159] This RCT tested the efficacy of two different types of MD (one supplemented with extra-virgin olive oil and the other with nuts) on the primary prevention of CVD in 7447 older men and women. Both diets were shown to reduce the risk of major cardiovascular events among high-risk individuals by approximately 30% (multivariable adjusted hazard ratio 0.70 (95% CI 0.54–0.92) for MD supplemented with extra-virgin olive oil, 0.72

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

(95% CI 0.54–0.96) for MD supplemented with mixed nuts).

While the evidence from both these studies[158,159] is convincing, more well-designed studies are needed to confirm the effectiveness of the MD in protecting against CVD. Further studies also need to be undertaken in non-Mediterranean populations to determine how best an increase in adherence to the MD can be achieved.

A posteriori dietary patterns

Alongside the research examining *a priori* dietary patterns[160–162] where the level of adherence to a specific diet, for example, the MD or the DASH diet, or an index based on national dietary guidelines, e.g. the Healthy Eating Index is examined,[163] a number of observational studies have used an exploratory approach utilizing statistical techniques such as cluster analysis or principal component analysis/factor analysis to define empirical overall dietary patterns and examine their association with CVD risk. Studies using such *a posteriori* analyses have generally identified two main dietary patterns: the 'Prudent or Healthy' pattern which is characterized by high intakes of FV, legumes, fish and whole grains, and the 'Western' pattern which is characterized by high intakes of processed meat, red meat, refined grains and sweets and desserts. In general, the 'Prudent' pattern has been associated with reduced risk of CHD,[164,165] stroke[166] and CVD mortality,[167] whereas the 'Western' pattern has been associated with increased risk of CHD[164,165] and stroke,[166] and a recent analysis of the EPIC-NL cohort showed similar associations.[168] Overall, dietary pattern analysis has become a complementary approach in the study of diet–disease relationships and has been recommended as a strategy for future cohort studies and RCTs investigating relationships with chronic diseases such as CHD.[2]

Diet and vascular health – specific considerations for older people

The evidence base for an effect of diet on CVD risk has been reviewed for all ages, as most studies of diet for chronic disease prevention, although not conducted exclusively in older adults, have included older adults, and it seems reasonable that the health benefits of the dietary changes reviewed would extend into older adulthood.[169] There are, however, a number of specific considerations when focusing on older people. Changes in body composition, hormonal status and gut function can have an effect on appetite, energy intake and the absorption of and requirements for particular nutrients (e.g. vitamin B12), whilst co-morbidities, concurrent medication use, cognitive decline, vision and hearing loss, loss of taste, change in dentition, pain, isolation, bereavement, decreased mobility and reduced income, which can all occur with ageing, will affect the ability to buy, prepare and consume food, as well as affecting appetite.[170] Such ageing-related changes must be considered when developing dietary recommendations specifically for older people.

Conclusion

Compelling evidence that diet and lifestyle changes can reduce CVD risk in older people exists. Diets low in TFA and SFA and rich in fish, MUFA, high in FV and whole grains and low in refined grains (such as that found in the traditional MD) have been associated with a reduced risk of CVD, whilst it has been demonstrated that simply lowering the percentage of energy from total fat will be unlikely to reduce total- and LDL-cholesterol or reduce CVD incidence. Antioxidant and B-group vitamin supplements do not reduce CVD risk, while the evidence base for vitamin D is only based on observational evidence. Maintaining a healthy body weight and increasing PA is also likely to reduce CVD risk. Therefore public health policies encouraging consumption of a healthy diet (as outlined above), maintenance of a healthy weight, PA and smoking avoidance have the potential to reduce the disease burden of CVD in older people in Western populations.

Conflicts of interest

The authors declare they have no conflicts of interest.

References

1 Mann JI. Diet and risk of coronary heart disease and type 2 diabetes. *Lancet* 2002; **360**: 783–89.

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

2 Mente A, de Koning L, Shannon HS *et al.* A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* 2009; **169**: 659–69.
3 Hoenselaar R. Saturated fat and cardiovascular disease: the discrepancy between the scientific literature and dietary advice. *Nutrition* 2012; **28**: 118–23.
4 Hooper L, Summerbell CD, Thompson R *et al.* Reduced or modified dietary fat for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2012; **5**: CD002137.
5 Howard BV, Van Horn L, Hsia J *et al.* Low-fat dietary pattern and risk of cardiovascular disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006; **295**: 655–66.
6 Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* 2010; **91**: 535–46.
7 Jakobsen MU, O'Reilly EJ, Heitmann BL *et al.* Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr* 2009; **89**: 1425–32.
8 Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* 2010; **7**: e1000252.
9 Ramsden CE, Zamora D, Leelarthaepin B *et al.* Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *BMJ* 2013; **346**: e8707.
10 Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: A meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003; **77**: 1146–55.
11 Astrup A, Dyerberg J, Elwood P *et al.* The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010? *Am J Clin Nutr* 2011; **93**: 684–88.
12 Prospective Studies Collaboration, Lewington S, Whitlock G *et al.* Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007; **370**: 1829–39.
13 Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ. Effects of different forms of dietary hydrogenated fats on serum lipoprotein cholesterol levels. *N Engl J Med* 1999; **340**: 1933–40.
14 de Roos NM, Schouten EG, Scheek LM, van Tol A, Katan MB. Replacement of dietary saturated fat with trans fat reduces serum paraoxonase activity in healthy men and women. *Metabolism* 2002; **51**: 1534–37.
15 Van Horn L, Mc Coin M, Kris-Etherton PM *et al.* The evidence for dietary prevention and treatment of cardiovascular disease. *J Am Diet Assoc* 2008; **108**: 287–331.
16 He K, Song Y, Daviglus ML *et al.* Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation* 2004; **109**: 2705–11.
17 Whelton SP, He J, Whelton PK, Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease. *Am J Cardiol* 2004; **93**: 1119–23.
18 Chowdhury R, Stevens S, Gorman D *et al.* Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. *BMJ* 2012; **345**: e6698.
19 Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA* 2012; **308**: 1024–33.
20 Kwak SM, Myung SK, Lee YJ, Seo HG; Korean Meta-analysis Study Group. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch Intern Med* 2012; **172**: 686–94.
21 Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartiainen E. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med* 1995; **333**: 1308–12.
22 Blair SN, Capuzzi DM, Gottlieb SO, Nguyen T, Morgan JM, Cater NB. Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol estercontaining spread to statin therapy. *Am J Cardiol* 2000; **86**: 46–52.
23 Maki KC, Davidson MH, Umporowicz DM *et al.* Lipid responses to plantsterol-enriched reduced-fat spreads incorporated into a National Cholesterol Education Program Step I diet. *Am J Clin Nutr* 2001; **74**: 33–43.
24 Christiansen LI, Lahteenmaki PL, Mannelin MR, Seppanen-Laakso TE, Hiltunen RV, Yliruusi JK. Cholesterol-lowering effect of spreads enriched

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

with microcrystalline plant sterols in hypercholesterolemic subjects. *Eur J Nutr* 2001; **40**: 66–73.
25 Volpe R, Niittynen L, Korpela R, Sirtori C, Bucci A, Fraone N, Pazzucconi F. Effects of yoghurt enriched with plant sterols on serum lipids in patients with moderate hypercholesterolaemia. *Br J Nutr* 2001; **86**: 233–39.
26 Moruisi KG, Oosthuizen W, Opperman AM. Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. *J Am Coll Nutr* 2006; **25**: 41–48.
27 Law M. Plant sterol and stanol margarines and health. *BMJ* 2000; **320**: 861–64.
28 Gylling H, Radhakrishnan R, Miettinen TA. Reduction of serum cholesterol in postmenopausal women with previous myocardial infarction and cholesterol malabsorption induced by dietary sitostanol ester margarine: women and dietary sitostanol. *Circulation* 1997; **96**: 4226–31.
29 Silbernagel G, Genser B, Nestel P, März W. Plant sterols and atherosclerosis. *Curr Opin Lipidol* 2013; **24**: 12–17.
30 Jenkins DJ, Wolever TM, Taylor RH *et al.* Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* 1981; **34**: 362–66.
31 Kristo AS, Matthan NR, Lichtenstein AH. Effect of diets differing in glycemic index and glycemic load on cardiovascular risk factors: review of randomized controlled-feeding trials. *Nutrients* 2013; **5**: 1071–80.
32 Dong JY, Zhang YH, Wang P, Qin LQ. Meta-analysis of dietary glycemic load and glycemic index in relation to risk of coronary heart disease. *Am J Cardiol* 2012; **109**: 1608–13.
33 Fan J, Song Y, Wang Y, Hui R, Zhang W. Dietary glycemic index, glycemic load, and risk of coronary heart disease, stroke, and stroke mortality: a systematic review with meta-analysis. *PLoS One* 2012; **7**: e52182.
34 Ma XY, Liu JP, Song ZY. Glycemic load, glycemic index and risk of cardiovascular diseases: meta-analyses of prospective studies. *Atherosclerosis* 2012; **223**: 491–96.
35 Heuberger RA. Alcohol and the older adult: a comprehensive review. *J Nutr Elder* 2009; **28**: 203–35.
36 Mukamal KJ, Jensen MK, Grønbaek M *et al.* Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. *Circulation* 2005; **112**: 1406–13.
37 Rimm E. Alcohol and cardiovascular disease. *Curr Atheroscler Rep* 2000; **2**: 529–35.
38 Danaei G, Ding EL, Mozaffarian D *et al.* The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med* 2009; **6**: e1000058.
39 Thadhani R, Camargo CA Jr, Stampfer MJ, Curhan GC, Willett WC, Rimm EB. Prospective study of moderate alcohol consumption and risk of hypertension in young women. *Arch Intern Med* 2002; **162**: 569–74.
40 Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med* 2004; **38**: 613–19.
41 Patra J, Taylor B, Irving H *et al.* Alcohol consumption and the risk of morbidity and mortality for different stroke types – a systematic review and meta-analyis. *BMC Public Health* 2010; **10**: 258.
42 Temple NJ. What are the health implications of alcohol consumption? Temple NJ Wilson T & DR Jacobs (eds), 2012, pp. 323–34. *Nutritional Health: Strategies for Disease Prevention*, 3rd edn. New York, Humana Press.
43 Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G. Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation* 2002; **105**: 2836–44.
44 Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: a meta-analysis. *Eur J Epidemiol* 2011; **26**: 833–50.
45 Webster JL, Dunford EK, Hawkes C, Neal BC. Salt reduction initiatives around the world. *J Hypertens* 2011; **29**: 1043–50.
46 He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens* 2009; **23**: 363–84.
47 He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ* 2013; **346**: f1325.
48 Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 2013; **346**: f1326.
49 Bibbins-Domingo K, Chertow GM, Coxson PG *et al.* Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med* 2010; **362**: 590–99.
50 World Health Organization. Reducing salt intake in populations: Report of a WHO Forum and Technical Meeting, 5–7 October 2006, Paris, France. WHO: Geneva, Switzerland, 2007.
51 Brinsden HC, He FJ, Jenner KH, MacGregor G. Surveys of the salt content in UK bread: progress

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

made and further reductions possible. *BMJ Open* 2013; **3**: e002936.
52 Temple NJ. Population strategies to reduce sodium intake: the right way and the wrong way. *Nutrition* 2011; **27**: 387.
53 Yudkin J. Pure, white and deadly. London: Davis-Poynter Ltd, 1972.
54 Yudkin J. Sucrose and cardiovascular disease. Proc Nutr Soc 1972; **31**: 331–37.
55 Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr* 2009; **89**: 1037–42.
56 Winkelmayer WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. *JAMA* 2005; **294**: 2330–35.
57 Dhingra R, Sullivan L, Jacques PF *et al.* Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation* 2007; **116**: 480–88.
58 Crowe FL, Key TJ, Appleby PN *et al.* Dietary fibre intake and ischaemic heart disease mortality: the European Prospective Investigation into Cancer and Nutrition-Heart study. *Eur J Clin Nutr* 2012; **66**: 950–56.
59 Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. *Circulation* 2011; **123**: 2870–91.
60 Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *J Nutr* 2012; **142**: 1304–13.
61 Kelly SA, Summerbell CD, Brynes A, Whittaker V, Frost G. Wholegrain cereals for coronary heart disease. *Cochrane Database Syst Rev* 2007; **2**: CD005051.
62 Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002; **325**: 1202.
63 Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002; **288**: 2015–22.
64 Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. *BMJ* 1998; **316**: 894–98.
65 Homocysteine Lowering Trialists' Collaboration. Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials. *Am J Clin Nutr* 2005; **82**: 806–12.
66 Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. *JAMA* 2006; **296**: 2720–26.
67 Wang X, Qin X, Demirtas H *et al.* Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. *Lancet* 2007; **369**: 1876–82.
68 Lee M, Hong KS, Chang SC *et al.* Efficacy of homocysteine lowering therapy with folic acid in stroke prevention: a meta-analysis. *Stroke* 2010; **41**: 1205–12.
69 Huang T, Chen Y, Yang B, Yang J, Wahlqvist ML, Duo L. Meta-analysis of B vitamin supplementation on plasma homocysteine, cardiovascular and all-cause mortality. *Clin Nutr* 2012; **31**: 448–54.
70 Yang H, Lee M, Hong K, Ovbiagele B, Saver JL. Efficacy of folic acid supplementation in cardiovascular disease prevention: An updated meta-analysis of randomised controlled trials. *Eur J Int Med* 2012; **23**: 745–54.
71 Clarke R, Halsey J, Lewington S *et al.* Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality. *Arch Intern Med* 2010; **170**: 1622–31.
72 Moats C, Rimm EB. Vitamin intake and risk of coronary disease: observation versus intervention. *Curr Atheroscler Rep* 2007; **9**: 508–14.
73 Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003; **361**: 2017–23.
74 Bin Q, Hu X, Cao Y, Gao F. The role of vitamin E (tocopherol) supplementation in the prevention of stroke. A meta-analysis of 13 randomised controlled trials. *Thromb Haemost* 2011; **105**: 579–85.
75 HOPE and HOPE-TOO Investigators. Effect of long-term vitamin E supplementation on cardiovascular events and cancer. A randomised controlled trial. *JAMA* 2005; **293**: 1338–47.
76 Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Annals Intern Med* 2005; **142**: 37–46.
77 Boaz M, Smetana S, Weinstein T *et al.* Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. *Lancet* 2000; **356**: 1213–18.
78 Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a post

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

intervention follow-up. *JAMA* 2004; **290**: 476–85.
79 Goodman GE, Thornquist MD, Balmes J *et al.* The Carotene and Retinol Efficacy Trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. *J Natl Cancer Inst* 2004; **96**: 1743–50.
80 Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* 2007; **297**: 842–57.
81 Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev* 2008: CD007176.
82 National Institutes of Health State-of-the-Science Panel. National Institutes of Health State-of-the-Science Conference Statement: multivitamin/mineral supplements and chronic disease prevention. *Am J Clin Nutr* 2007; **85**: 257–64S.
83 Kokubo K, Iso H, Ishihara J *et al.* Association of dietary intake of soy, beans and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: the Japan Public Health Center-based (JPHC) study cohort 1. *Circulation* 2007; **116**: 2553–62.
84 Mink PJ, Scrafford CG, Barraj LM *et al.* Flavonoid intakes and cardiovascular disease mortality: a prospective study in postmenopausal women. *Am J Clin Nutr* 2007; **85**: 895–909.
85 Mursu J, Voutilainen S, Numi I, Tuomainen TP, Kurl S, Salonen JT. Flavonoid intake and the risk of ischaemic stroke and CVD mortality in middle aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Br J Nutr* 2008; **100**: 890–95.
86 McCullough ML, Peterson JJ, Patel R, Jacques PF, Shah R, Dwyer JT. Flavonoid intakes and cardiovascular disease mortality in a prospective cohort of US adults. *Am J Clin Nutr* 2012; **95**: 454–64.
87 Hooper L, Kroon PA, Rimm EB *et al.* Flavonoids, flavonoid rich foods and cardiovascular risk: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2008; **88**: 38–50.
88 Hooper L, Kay C, Abdelhomid A *et al.* Effect of chocolate, cocoa and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. *Am J Clin Nutr* 2012; **95**: 740–51.
89 Schottker B, Haug U, Schomburg L *et al.* Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. *Am J Clin Nutr* 2013; **97**: 782–93.
90 Schierbeck LL, Rejnmark L, Tofteng CL *et al.* Vitamin D deficiency in postmenopausal, healthy women predicts increased cardiovascular events: a 16-year follow-up study. *Eur J Endocrinol* 2012; **167**: 553–60.
91 Pittas AG, Chung M, Trikalinos T *et al.* Systematic review: vitamin D and cardiometabolic outcomes. *Ann Intern Med* 2010; **152**: 307–14.
92 Semba RD, Houston DK, Bandinelli S *et al.* Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults. *Eur J Clin Nutr* 2010; **64**: 203–9.
93 Kendrick J, Targher G, Smits G, Chonchol M. 25-hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National health and Nutrition Examination Survey. *Atherosclerosis* 2009; **205**: 255–60.
94 Ginde AA, Scragg R, Schwartz RS, Camargo CA Jr. Prospective study of serum 25-hydroxy vitamin D level, cardiovascular disease mortality, and all-cause mortality in older US adults. *J Am Geriatr Soc* 2009; **57**: 1595–603.
95 Szulc P, Claustrat B, Delmas PD. Serum concentrations of 17β-E2 and 25-hydroxycholecalciferol (25OHD) in relation to all-cause mortality in older men – the MINOS study. *Clin Endocrinol (Oxf)* 2009; **71**: 594–602.
96 Wang L, Song Y, Manson JE *et al.* Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes* 2012; **5**: 819–29.
97 Parker J, Hashmi O, Dutton D *et al.* Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. *Maturitas* 2010; **65**: 225–36.
98 Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. *Prev Med* 2010; **51**: 228–33.
99 Sokol SI, Tsang P, Aggarwal V *et al.* Vitamin D status and risk of cardiovascular events: lessons learned via systematic review and meta-analysis. *Cardio Rev* 2011; **19**: 192–201.
100 Sun Q, Pan A, Hu FB, Manson JE, Rexrode KM. 25-hydroxyvitamin D levels and the risk of stroke: a prospective study and meta-analysis. *Stroke* 2012; **43**: 1470–77.
101 Brondum-Jacobsen P, Nordestgaard BG, Schnohr P, Benn M. 25-hydroxyvitamin D and symptomatic ischemic stroke: an original study and meta-analysis. *Ann Neurol* 2013; **73**: 38–47.
102 Sokol SI, Tsang P, Aggarwal V, Melamed ML, Srinivas VS. Vitamin D status and risk of

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

cardiovascular events: lessons learned via systematic review and meta-analysis. *Cardio Rev* 2011; **19**: 192–201.
103 Elamin MB, Elnour NOA, Elamin KB *et al.* Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; **96**: 1931–42.
104 Wang L, Manson JE, Song Y, Sesso HD. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 2010; **152**: 315–23.
105 Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press: 2011.
106 Manson JE, Bassuk SS, Lee IM *et al.* The VITamin D and OmegA-3 Trial (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials* 2012; **33**: 159–71.
107 Rashid MN, Fuentes F, Touchon RC, Wehner PS. Obesity and the risk for cardiovascular disease. *Prev Cardiol* 2003; **6**: 42–47.
108 Prospective Studies Collaboration, Whitlock G, Lewington S, *et al.* Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; **373**: 1083–96.
109 Denke MA, Sempos CT, Grundy SM. Excess body weight. An under-recognised contributor to high blood cholesterol levels in white American men. *Arch Intern Med* 1993; **153**: 1093–103.
110 Zhou B, Wu Y, Yang J, Li Y, Zhang H, Zhao L. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. *Obes Rev* 2002; **3**: 147–56.
111 Haslam D, Sattar N, Lean M. ABC of obesity. Obesity – time to wake up. *BMJ* 2006; **333**: 640–42.
112 Folsom AR, Stevens J, Schreiner PJ, McGovern PG. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. Atherosclerosis Risk in Communities Study Investigators. *Am J Epidemiol* 1998; **148**: 1187–94.
113 Ellekjaer H, Holmen J, Vatten L. Blood pressure, smoking and body mass in relation to mortality from stroke and coronary heart disease in the elderly. A 10-year follow-up in Norway. *Blood Press* 2001; **10**: 156–63.
114 Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA* 2002; **288**: 1994–2000.
115 Manson JE, Greenland P, LaCroix AZ *et al.* Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med* 2002; **347**: 716–25.
116 Lakka TA, Venalainen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *N Engl J Med* 1994; **330**: 1549–54.
117 Joliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2000: CD001800.
118 Kohl HW 3rd, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, Kahlmeier S; Lancet Physical Activity Series Working Group. The pandemic of physical inactivity: global action for public health. *Lancet* 2012; **380**: 294–305.
119 Heath GW, Parra DC, Sarmiento OL, *et al.* Evidence-based intervention in physical activity: lessons from around the world. *Lancet* 2012; **380**: 272–81.
120 Thompson PD, Lim V. Physical activity in the prevention of atherosclerotic coronary heart disease. *Curr Treat Options Cardiovasc Med* 2003; **5**: 279–85.
121 Blair SN, Connelly JC. How much physical activity should we do? The case for moderate amounts and intensities of physical activity. *Res Q Exerc Sport* 1996; **67**: 193–205.
122 Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJ, Martin BW; Lancet Physical Activity Series Working Group. Correlates of physical activity: why are some people physically active and others not? *Lancet* 2012; **380**: 258–71.
123 Brownson RC, Boehmer TK, Luke DA. Declining rates of physical activity in the United States: what are the contributors? *Ann Rev Public Health* 2005; **26**: 421–43.
124 Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U; Lancet Physical Activity Series Working Group. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet* 2012; **380**: 247–57.
125 Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr* 2005; **81**: 230–42S.
126 Woodside JV, McCall D, McGartland C, Young IS. Micronutrients: dietary intake v. supplement use. *Proc Nutr Soc* 2005; **64**: 543–53.
127 Woodside JV, Young IS, McKinley MC. Fruits and vegetables: measuring intake and encouraging increased consumption. *Proc Nutr Soc* 2013; **72**: 236–45.

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

128 Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies. *Neurology* 2005; **65**: 1193–97.
129 Dauchet L, Amouyel P, Hercberg S *et al.* Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr* 2006; **136**: 2588–93.
130 He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet* 2006; **367**: 320–26.
131 He FJ, Nowson CA, Lucas M, MacGregor GA. Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. *J Hum Hypertens* 2007; **21**: 717–28.
132 Takachi R, Inoue M, Ishihara J *et al.* Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-Based Prospective Study. *Am J Epidemiol* 2008; **167**: 59–70.
133 Dauchet L, Montaye M, Ruidavets JB *et al.* Association between the frequency of fruit and vegetable consumption and cardiovascular disease in male smokers and non-smokers. *Eur J Clin Nutr* 2010; **64**: 578–86.
134 Oude Griep LM, Geleijnse JM *et al.* Raw and processed fruit and vegetable consumption and 10-year coronary heart disease incidence in a population-based cohort study in the Netherlands. *PLoS One* 2010; **5**: e13609.
135 Bendinelli B, Masala G, Saieva C *et al.* Fruit, vegetables, and olive oil and risk of coronary heart disease in Italian women: the EPICOR Study. *Am J Clin Nutr* 2011; **93**: 275–283.
136 Crowe FL, Roddam AW, Key TJ *et al.* Fruit and vegetable intake and mortality from ischaemic heart disease: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heart study. *Eur Heart J* 2011; **32**: 1235–43.
137 John JH, Ziebland S, Yudkin P, Roe LS, Neil HA; Oxford Fruit and Vegetable Study Group. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. *Lancet* 2002; **359**: 1969–74.
138 Appel LJ, Moore TJ, Obarzanek E *et al.* A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997; **336**: 1117–24.
139 Broeksmans WMR, Klopping-Ketelaars WAA, Kluft C *et al.* Fruit and vegetables and cardiovascular risk profile: a diet controlled intervention study. *Eur J Clin Nutr* 2001; **55**: 636–42.
140 McCall DO, McGartland CP, McKinley MC *et al.* Dietary intakes of fruit and vegetables improves microvascular function in hypertensive subjects in a dose-dependent manner. *Circulation* 2009; **119**: 2153–60.
141 Berry SE, Mulla UZ, Chowienczyk PJ *et al.* Increased potassium intake from fruit and vegetables or supplements does not lower blood pressure or improve vascular function in UK men and women with early hypertension: a randomized controlled trial. *Br J Nutr* 2010; **104**: 1839–47.
142 McCall DO, McGartland CP, McKinley MC *et al.* The effect of increased dietary fruit and vegetable consumption on endothelial activation, inflammation and oxidative stress in hypertensive volunteers. *Nutr Metab Cardiovas Dis* 2011; **21**: 658–64.
143 George TW, Paterson E, Waroonphan S, Gordon MH, Lovegrove JA. Effects of chronic consumption of fruit and vegetable puree-based drinks on vasodilation, plasma oxidative stability and antioxidant status. *J Hum Nutr Diet* 2012; **25**: 477–87.
144 Chen ST, Maruthur NM, Appel LJ. The effect of dietary patterns on estimated coronary heart disease risk: results from the Dietary Approaches to Stop Hypertension (DASH) trial. *Circ Cardiovasc Qual Outcomes* 2010; **3**: 484–89.
145 Sacks FM, Svetkey LP, Vollmer WM *et al.* DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001; **344**: 3–10.
146 Appel LJ, Champagne CM, Harsha DW *et al.* Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA* 2003; **289**: 2083–93.
147 Blumenthal JA, Babyak MA, Hinderliter A *et al.* Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Arch Int Med* 2010; **170**: 126–35.
148 Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu F. Adherence to a DASH-Style diet and risk of coronary heart disease and stroke in women. *Arch Intern Med* 2008; **168**: 713–20.
149 Parikh A, Lipsitz SR, Natarajan S. Association between a DASH-like diet and mortality in adults with hypertension: findings from a population

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press

based follow up study. *Am J Hypertens* 2009; **22**: 409–16.
150 Folsom AR, Parker ED, Harnack LJ. Degree of concordance with DASH diet guidelines and incidence of hypertension and fatal cardiovascular disease. *Am J Hypertens* 2007; **20**: 225–32.
151 Fitzgerald KC, Chiuve SE, Buring JE, Ridker PM, Glynn RJ. Comparison of associations of adherence to a Dietary Approaches to Stop Hypertension (DASH)-style diet with risks of cardiovascular disease and venous thromboembolism. *J Thromb Haemost* 2012; **10**: 189–98.
152 Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rate to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations: monitoring trends and determinants in cardiovascular disease. *Lancet* 1999; **353**: 1547–57.
153 Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 2010; **92**: 1189–96.
154 Gardener H, Wright CB, Gu Y *et al.* Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: the Northern Manhattan Study. *Am J Clin Nutr* 2011; **94**: 1458–64.
155 Dilis V, Katsoulis M, Lagiou P, Trichopoulos D, Naska A, Trichopoulou A. Mediterranean diet and CHD: the Greek European prospective investigation into cancer and nutrition cohort. *Br J Nutr* 2012; **108**: 699–709.
156 Menotti A, Alberti-Fidanza A, Fidanza F. The association of the Mediterranean Adequacy Index with fatal coronary events in an Italian middle aged male population followed for 40 years. *Nutr Metab Cardiovasc Dis* 2012; **22**: 369–75.
157 Hoevenaar-Blom MP, Nooyens ACJ, Kromhout D *et al.* Mediterranean style diet and 12-year incidence of cardiovascular diseases: The EPIC-NL cohort study. *PLoS ONE* 2012; **7**: e45458.
158 de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999; **99**: 779–85.
159 Estruch R, Ros E, Salas-Salvado J *et al.* Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; **368**: 1279–90.
160 Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol* 2002; **13**: 3–9.
161 Schulze MB, Hu FB. Dietary patterns and risk of hypertension, type 2 diabetes mellitus and coronary heart disease. *Curr Atheroscler Rep* 2002; **4**: 462–67.
162 Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA* 2002; **288**: 2569–78.
163 Agnoli C, Krogh V, Grioni S *et al.* A priori-defined dietary patterns are associated with reduced risk of stroke in a large Italian cohort. *J Nutr* 2011; **141**: 1552–58.
164 Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB. Dietary patterns and the risk of coronary heart disease in women. *Arch Intern Med* 2001; **161**: 1857–62.
165 Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med* 2000; **343**: 16–22.
166 Fung TT, Stampfer MJ, Manson JE, Rexrode KM, Willett WC. Prospective study of major dietary patterns and stroke risk in women. *Stroke* 2004; **35**: 2014–19.
167 Heidemann C, Schulze MB, Franco OH, van Dam RM, Mantzoros CS, Hu FB. Dietary patterns and risk of mortality from cardiovascular disease, cancer, and all causes in a prospective cohort of women. *Circulation* 2008; **118**: 230–37.
168 Stricker MD, Onland-Moret NC, Boer JM *et al.* Dietary patterns derived from principal component- and k-means cluster analysis: long-term association with coronary heart disease and stroke. *Nutr Metab Cardiovasc Dis* 2013; **23**: 250–56.
169 Johnson MA. Strategies to improve diet in older adults. *Proc Nutr Soc* 2013; **72**: 166–72.
170 Gariballa S, Sinclair A. Ageing and older people. In Geissler C, Powers H (eds), pp. 319–34. *Human Nutrition*. London: Elsevier, 2005.

https://doi.org/10.1017/S0959259813000191 Published online by Cambridge University Press