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Optimum nutritional strategies for cardiovascular disease prevention and rehabilitation (BACPR)

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ABSTRACT

Nutrition has a central role in both primary and secondary prevention of cardiovascular disease yet only relatively recently has food been regarded as a treatment, rather than as an adjunct to established medical and pharmacotherapy. As a field of research, nutrition science is constantly evolving making it difficult for patients and practitioners to ascertain best practice. This is compounded further by the inherent difficulties in performing double-blind randomised controlled trials. This paper covers dietary patterns that are associated with improved cardiovascular outcomes, including the Mediterranean Diet but also low-carbohydrate diets and the potential issues encountered with their implementation. We suggest there must be a refocus away from macronutrients and consideration of whole foods when advising individuals. This approach is fundamental to practice, as clinical guidelines have focused on macronutrients without necessarily considering their source, and ultimately people consume foods containing multiple nutrients. The inclusion of food-based recommendations aids the practitioner to help the patient make genuine and meaningful changes in their diet. We advocate that the cardioprotective diet constructed around the traditional Mediterranean eating pattern (based around vegetables and fruits, nuts, legumes, and unrefined cereals, with modest amounts of fish and shellfish, and fermented dairy products) is still important. However, there are other approaches that can be tried, including low-carbohydrate diets. We encourage practitioners to adopt a flexible dietary approach, being mindful of patient preferences and other comorbidities that may necessitate deviations away from established advice, and advocate for more dietitians in this field to guide the multi-professional team.

INTRODUCTION

There are multiple modifiable risk factors for cardiovascular disease (CVD), many of which are modifiable via changes in diet and physical activity. This combination is widely recognised in clinical guidelines as being important in both primary and secondary prevention,[1–3] and nutritional education is an important element of cardiac rehabilitation (CR). However, the area of nutrition is frequently over complicated with conflicting information. Such an example is salt, with recent evidence suggesting the benefit of salt restriction is greatest in those already with hypertension (HTN),[4] and that both low and high intake may be associated with increased mortality.[5]

Patients with cardiac disease are becoming increasingly more complex due to the number of comorbidities present. Data from the National Audit of Cardiac Rehabilitation (NACR) show HTN to be the most common comorbidity (49.9%), followed by hypercholesterolaemia/dyslipidaemia (31.7%) and then diabetes (24.5%).[6] Poor diet is a significant modifiable risk factor in these comorbidities, and all outcomes reported by the NACR could likely be improved with increased emphasis on addressing lifestyle (nutrition and exercise).

The *Diet working group* was established by British Association for Cardiovascular Prevention and Rehabilitation (BACPR) and was actioned to provide a guide through current controversies in cardiovascular nutrition, in addition to signposting researchers to current gaps in evidence. The group sought views from professionals working in the area of CR and aims to provide specific recommendations to answer the many common questions encountered by healthcare professionals working in this field. This paper reviews both macronutrients and the key food groups healthcare professionals sought clarity on.

The objectives of this paper are to review the area of cardiovascular nutrition and provide recommendations for practitioners to help patients make healthy eating decisions. We also aim to identify current gaps in evidence and suggestions for future research.

MACRONUTRIENTS

Protein

Summary messages regarding dietary protein are presented in table 1. Detailed study[7–13] analysis examining protein intake and CVD are presented in online supplementary table 1.

There is a long-standing argument that high protein intakes lead to renal failure with a recent observational study suggesting that increased protein intake post-myocardial infarction (MI) was associated with a greater decline in renal function[7] and increased risk of mortality.[8] Of interest, dairy or plant protein sources showed a much weaker association when compared with animal protein, and the relationship between protein and outcome variables was stronger in those with predisposing disease, for example, diabetes. This indicates that the source of dietary protein may be important to consider. Indeed, randomised controlled trials show that the quality of meat (in addition to the whole diet) is likely to be an important factor to consider

Table 1 Protein

Macronutrient	Source and quality	Summary
Protein	Animal and plant Lean animal protein (defined by O'Connor *et al*[9]) as <10 g total fat, <5 g saturated fat and <95 mg cholesterol/100 g) is a better choice than fattier types Sources of animal protein include fish, poultry, meat, eggs and dairy. Processed meat is also included in this category as a source of protein Sources of plant protein include nuts and seeds (almonds, walnuts, cashews), pulses (including chickpeas, lentils, bean) Animal proteins are complete (contain the nine essential amino acids) whereas plant proteins do not. This has often led to plant protein being described as low quality	Higher intakes post-MI associated with more rapid decline in renal function and increased mortality.[7 8] This was more pronounced with protein derived from meat and less so with protein from dairy, fish, eggs or plant protein[7 8] Comorbidities such as diabetes are associated with a greater strength of association between higher animal protein intake and the decline in renal function,[7] in addition to all-cause mortality[8] Protein quality (considering total and saturated fat, and cholesterol) is likely an important factor to consider. The addition of lean 500 g/week of lean (<10 g total fat, <5 g saturated fat and <95 mg cholesterol), unprocessed beef or pork (equating to approximately 71 g/day) to a cardioprotective diet did not increase cardiovascular risk and improved 10-year cardiovascular risk score when compared with the same cardioprotective diet but with only 200 g/week or lean red meat[9] The comparator diet is important when examining the relationship between protein and CVD.[10] When analysed against plant protein, red meat yielded smaller decreases in TC and LDL-C, but when compared with low-quality carbohydrates or fish, yielded greater decreases in LDL-C and triglycerides. Variation in the definition of 'meat' could explain discrepancies in the literature. Some foods listed under meat include 'sausage, hamburger and bacon' which have a markedly different nutrient profile to beef, lamb and chicken[7] and hence different relationship with cardiovascular health[11] Protein is vital for muscle development and strength. Higher protein intakes of 1.5 g/kg/d in an elderly population improve appendicular muscle mass, the ratio of appendicular muscle to fat and increase gate speed comparison to lower protein intakes (0.8 g/kg/d). The protein used was predominantly from whey (high in leucine) which provides the stimulus for muscle growth, and no adverse outcomes were reported[12] Protein is an essential macronutrient and we suggest this should be obtained from a range of plant and animal sources. Those with established renal disease should be particularly mindful of protein intake. Good quality, low fat/low saturated fat/low cholesterol sources of protein should be encouraged as part of a cardioprotective diet

CVD, cardiovascular disease; LDL-C, low-density lipoproten-cholesterol; MI, myocardial infarction; TC, total cholesterol.

in explaining this relationship, with evidence suggesting that the addition of lean red meat to an already low saturated fat cardioprotective diet does not impact negatively on blood lipids.[9] The saturated fat content of the comparison diet[10] may be an additional piece of the puzzle in explaining the impact dietary protein (and its source) has on cardiovascular health.[11]

Protein provides the main components for muscle synthesis and consensus opinion suggests that protein intakes should be higher in the elderly[12] with intakes up to 1.5 g/kg/d being shown to improve body composition in an elderly, frail population.[13] Collectively, these studies highlight an important role for protein in cardiovascular health, especially when considering (a) source (animal vs plant); (b) quality and (c) overall diet quality.

CARBOHYDRATES

Summary messages regarding dietary carbohydrate are presented in table 2. Detailed study[14–19] analysis examining carbohydrate intake and CVD are presented in online supplementary table 1.

The Prospective Urban Rural Epidemiology study raised carbohydrates to the forefront of cardiovascular health with headline data showing higher carbohydrate intake was

Table 2 Carbohydrate

Macronutrient	Source and quality	Summary
Carbohydrates	Plant Refined and whole grain breads and cereals, pastas, rice, fruits and vegetables, and cakes, biscuits and sugar-sweetened beverages Carbohydrate sources that are based around refined white flour should be reduced/avoided and replaced with better quality sources (such as whole grain cereals and breads, or fruits and vegetables). Education may be required to explain to individuals that carbohydrates are not only found in breads, cereals and pastas but are also present in numerous vegetables and fruits	Sources of carbohydrate are important to the relationship of carbohydrates with cardiovascular health. Data from the PURE study indicated higher carbohydrate intake was associated with increased mortality although the sources and quality of carbohydrate was poor, likely explaining this relationship.[14] Additionally, the high percentage energy from carbohydrate likely displaced other beneficial nutrients (protein and fat) from the diet. There appear to be different associations between low-carbohydrate high animal fat and protein diets versus low-carbohydrate high plant fat and protein diets and mortality. A low-carbohydrate diet high in plant fat and protein was not associated with increased mortality, whereas a low-carbohydrate diet high animal fat and protein diet was.[15 16] Higher fibre intake is inversely associated with cardiovascular and all-cause mortality post-MI.[17] Prospective studies support a role for whole grains in cardiovascular health, with whole grain bread, pasta, cereals and oatmeal associated with reduced all-cause mortality, with similar observations for cardiovascular mortality.[11 18] However, randomised controlled trials do not support a role for specifically increasing whole grain consumption to reduce lipids, blood pressure and body mass index.[19] We recommend that patients are encouraged to consume good quality sources of carbohydrate, such as vegetables and whole grain cereals that are high in fibre as part of a cardioprotective diet. Reducing dietary carbohydrate may be advantageous to those with altered blood glucose control

MI, myocardial infarction; PURE, Prospective Urban Rural Epidemiology.

Table 3 Fat

Macronutrient	Source and quality	Summary
Fats	Animal and plant Sources of animal fat include fish, poultry, meat and dairy (including butter, cream and cheese). Eggs are not listed here due to their low fat content. The fatty acid profile can be affected by what the animal has been fed. Grass fed beef tends to have a lower total fat content than grain-fed beef. Fatty fish (mackerel, salmon, sardines, herring and trout contain the n3 polyunsaturated fats eicosapentaenoic acid and docosahexaenoic acid). Meat can also vary substantially regarding total and saturated fat content. Sources of plant fat include nuts and seeds, and vegetables (including oils). The fatty acid profile of oils varies hugely. Oils high in n6 polyunsaturated fats include soybean, sunflower, safflower and walnut. Oils that contain more n3 polyunsaturated fats include flaxseed, walnut and rapeseed. Olive oil contains predominantly n9 monounsaturated fats. Coconut oil (a plant-based oil) contains predominantly saturated fat.	Acknowledgement of the source is vital, especially considering saturated and polyunsaturated fats. The effect of reducing saturated fat on cardiovascular outcomes is greater when baseline saturated fat is high and the intervention diet leads to a greater decrease in saturated fat and TC.[20] Reducing saturated fat and replacement with unsaturated fats appears to convey the greatest cardiovascular benefit.[20] Industrial trans fats (found in pastries, cakes and deep fried foods) should be avoided as they are associated with increased total mortality.[21] Increasing consumption of n6 fatty acids appears to reduce the risk of MI and lower TC but has no significant effect on other cardiovascular outcomes such as CVD events, CHD events or stroke.[22] Reducing saturated fat and increasing marine polyunsaturated fats (specifically the n3 eicosapentaenoic acid and docosahexaenoic acid) is associated with decreased total and all-cause mortality.[21] Practical advice around this is to encourage individuals to increase consumption of oily fish (fresh or tinned). There appears no benefit from consuming n3 supplements for the prevention of fatal CVD, largely due to the dose of eicosapentaenoic acid and docosahexaenoic acid not being high enough for any substantial benefit on reducing CVD or fatal CHD.[23] Higher, purified doses of eicosapentaenoic acid *do* result in reductions in cardiovascular death[24] and the effect is likely due to a pleiotropic action of eicosapentaenoic acid (lipid lowering, anti-inflammatory, antiplatelet and antithrombotic actions). Based on meta-analyses, replacement of saturated fat with unsaturated fat appears to convey to greatest benefit for cardiovascular health. However, similar to protein and carbohydrate, manipulation of dietary fat and its constituents (saturated, monounsaturated and polyunsaturated) must acknowledge the source of these nutrients when focusing on cardiovascular health.

CHD, coronary heart disease ; CVD, cardiovascular disease; MI, myocardial infarction; TC, total cholesterol.

associated with increased all-cause and cardiovascular (CV) mortality.[14] However, recent meta-analyses examining the association between carbohydrate intake and cardiovascular health have suggested a U-shaped relationship between carbohydrate and all-cause mortality, specifically in those consuming a low-carbohydrate diet higher in animal protein and fat.[15 16]

Prospective cohort studies have shown fibre intake to be inversely associated with reduced cardiovascular and all-cause mortality post-MI.[17] In this study,[17] only cereal fibre was significantly associated with a reduction in cardiovascular and all-cause mortality in both men and women. One of the most prominent sources of cereal fibre is whole grain, and whole grain is frequently cited as being beneficial for health[11 18]; however, there is disparity between meta-analyses of cohort studies and results from randomised controlled trials.[19] Such discrepancy between this and prospective studies likely highlights the importance of adequately defining whole grain, and taking a whole diet approach when considering cardioprotective foods.

FATS

Summary messages regarding dietary fat are presented in table 3. Detailed study[20–24] analysis examining fat intake and CVD are presented in online supplementary table 1.

The correct balance of dietary fats is a key to cardiovascular health; however, as with carbohydrates and protein types, sources and amounts have made determining effects difficult. Saturated fat has long been suggested to be harmful for cardiovascular health; however, a recent meta-analysis[20] suggested that reducing saturated fat did not seem to effect total mortality or CVD mortality. However, a reduction in combined cardiovascular events of 17% was shown with a reduction in saturated fat. Greater decreases in events were seen for studies that replaced saturated fat with polyunsatured fats when compared with monounsaturated fats, carbohydrate or protein.[20] Thus, it would appear reducing saturated fat and replacement with unsaturated fat conveys the greatest cardiovascular benefit, not necessarily reducing saturated fat and replacing with refined carbohydrate, and some of this effect may be modified by where the saturated fat is found that is, dairy versus processed baked goods.

Increased trans fat intake is positively associated with total mortality, along with animal monounsaturated fats, alpha linolenic acid and arachidonic acid.[21] In this same study, marine n3 polyunsaturated fat and replacement of saturated fat with plant monounsaturated fat were associated with lower total and CVD mortality. This latter study acknowledges the subtypes of fat such as n3 (alpha linolenic acid, eicosapentaenoic acid and docosahexaenoic acid) and n6 fatty acids (linoleic acid and gamma-linoleic acid). Indeed, n6 fatty acids have been shown to reduce risk of MI, as well as reducing total cholesterol (TC), with these findings possibly relating to both baseline n6 intake and dose of n6 provided.[22] This latter point is similar to observations made in the most recent analysis of fish oil supplements and cardiovascular health. This analysis indicated no benefit from supplementation on reducing fatal coronary heart disease (CHD) or any CVD in people with or at high risk of CVD,[23] primarily due to the low dose of eicosapentaenoic acid and docosahexaenoic acid used in the included studies (226 to 1800 mg/day and 0 to 1700 mg/day, respectively). These null results contrast substantially with the positive effects seen with the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial utilising a highly purified form of eicosapentaenoic acid (4 g/day).[24] Further research into specific fat replacements for saturated fat is warranted and it is unclear whether there is additional benefit to maintaining a lower saturated fat diet while on lipid-lowering treatment. As with protein and carbohydrate, the source of the nutrient (ie, food) matters.

FOODS AND FOOD GROUPS

Detailed information considering food and food groups are shown in online supplementary table 2.

Fruits and vegetables

The grouping of fruits together with vegetables is inaccurate, similarly to the grouping of red and processed meat. This ignores distinct differences between fruits and vegetables in terms of their nutrient profile, and hence their association with disease. Fruits and vegetables high in nutrients are hypothesised to be cardioprotective and have consistently been associated with reduced CVD.[25] Hence, fruits and vegetables are cornerstones of cardioprotective dietary patterns (eg, dietary approaches to stop hypertension (DASH), Mediterranean) and dietary guidelines ubiquitously recommend them.[1–3]

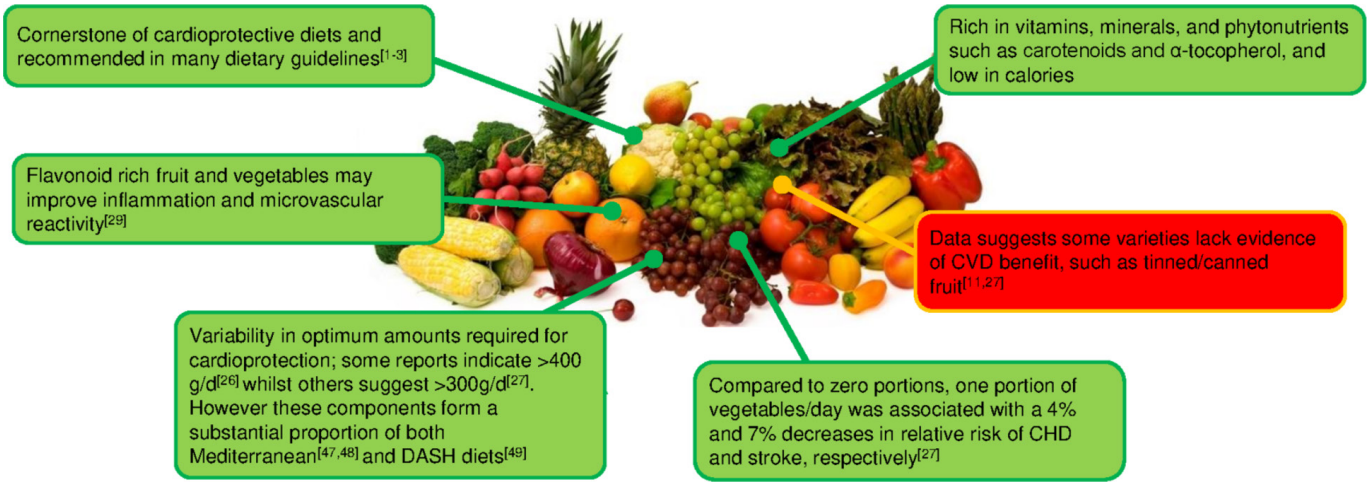

Figure 1 Fruits and vegetables

However, a systematic review and meta-analysis[26] is notable whereby there was an inverse association between both reported dietary intake and blood concentrations of vitamin C, carotenoids and α-tocopherol (markers of fruit and vegetable intake) with risk of CVD, and all-cause mortality. Interestingly, inverse associations between disease/mortality endpoints were stronger for measured biomarkers than for reported dietary intake suggesting that the methodology used to collect this information may be a unreliable.[26] Multiple studies have shown fruits and vegetables to be consistently associated with reduced CHD and stroke incidence, HTN, and CVD mortality.[26 27] However, debate exists on the physical amounts to be consumed, with some suggestions of CHD benefit over 400 g/day[26] and others showing little further benefit of over 300 g/day.[27] Existing randomised controlled trials have shown inconsistent effects on established cardiovascular risk markers such as inflammation, blood pressure or lipids,[28 29] and some varieties appear to lack evidence of CVD benefit altogether.[11 27] Indeed, tinned/canned fruit has been positively associated with all-cause and CVD mortality[11 27] although the reasons for this observation are not clear and could potentially reflect socioeconomic status. One review only found cardioprotective effects for raw vegetables[11]; however, more varieties were associated with reduced all-cause mortality. It is unclear whether the lack of cardioprotection is true or due to a lack of high-quality research on specific fruits and vegetables (figure 1).

Eggs

Eggs are a rich source of dietary cholesterol, typically containing 150–230 mg/egg. With the exception of eggs, prawns and liver, most foods rich in cholesterol are also high in saturated fat and it is well established that dietary saturated fat influences levels of circulating low-density lipoprotein-cholesterol (LDL-C) to a much greater extent than dietary cholesterol in foods.[30] However, the association of egg consumption (and dietary cholesterol) with CVD remains controversial and confusing for patients, particularly those with existing heart disease. The lack of good quality evidence to support the restriction of eggs has resulted in a recent changes to guidelines with many removing any reference to limiting egg and cholesterol intake,[1 3] although this is still highlighted in the most recent American guidelines from primary prevention of CVD.[2]

In a very recent analysis of prospective cohort data, Zhong *et al*[31] indicated higher consumption of eggs and dietary cholesterol was positively associated with incident CVD and all-cause mortality. These findings are inconsistent with those from previous prospective cohort studies[32–35] and a large review of meta-analyses[11] or other prospective studies[26] showing no association or a benefit to egg consumption However, in Zhong *et al*,[31] the effects of egg consumption were modest, and based on self-reported dietary intake at baseline (with an average follow-up of 17 years) in a US population that may not be representative of a UK diet.

In a prospective cohort study of 0.5 million Chinese adults,[32] a moderate level of egg consumption (up to <1 egg per day) was significantly associated with lower risk of CVD. This study demonstrated that each one-egg increment per week was associated with an 8% lower risk of haemorrhagic stroke. In a subgroup analysis of diabetic populations, greater egg intake was associated with increased rick of CVD and CHD.[34 35] The relationship between egg intake and diabetes incidence is not specifically covered here, but the role of egg intake and CVD incidence in people with diabetes requires further consideration made for the overall dietary pattern. However, eggs are a low in calories, high in protein and contain numerous micronutrients. Given their nutrient profile, eggs can form part of a healthy cardioprotective diet (figure 2).

Dairy

Dairy products have received a great deal of attention in terms of their effect on CVD risk primarily due to their saturated fat content of butter, whole milk and yoghurt, and most cheeses. However, there is increasing evidence that suggests dairy products may actually have a neutral or even a beneficial impact on CVD risk, and that some of the uncertainty in evidence may be related to the different types of dairy. This has been shown by Patterson *et al*[36] who also highlighted the importance of considering the calcium content of the food. In their analysis, the inverse association between total dairy intake and risk of MI was attenuated by adjustment for calcium with similar observations for cheese and MI risk.

Several recent systematic review and meta-analyses have continued to reinforce the inverse or neutral association between dairy intake and CV health.[37–40] In a thorough review of systematic reviews and meta-analyses, Fontecha *et al*[40] confirmed no association between total dairy intake and CVD. When considering specific subtypes of CVD and dairy, high-fat dairy was not associated with CHD risk, whereas low-fat dairy was associated

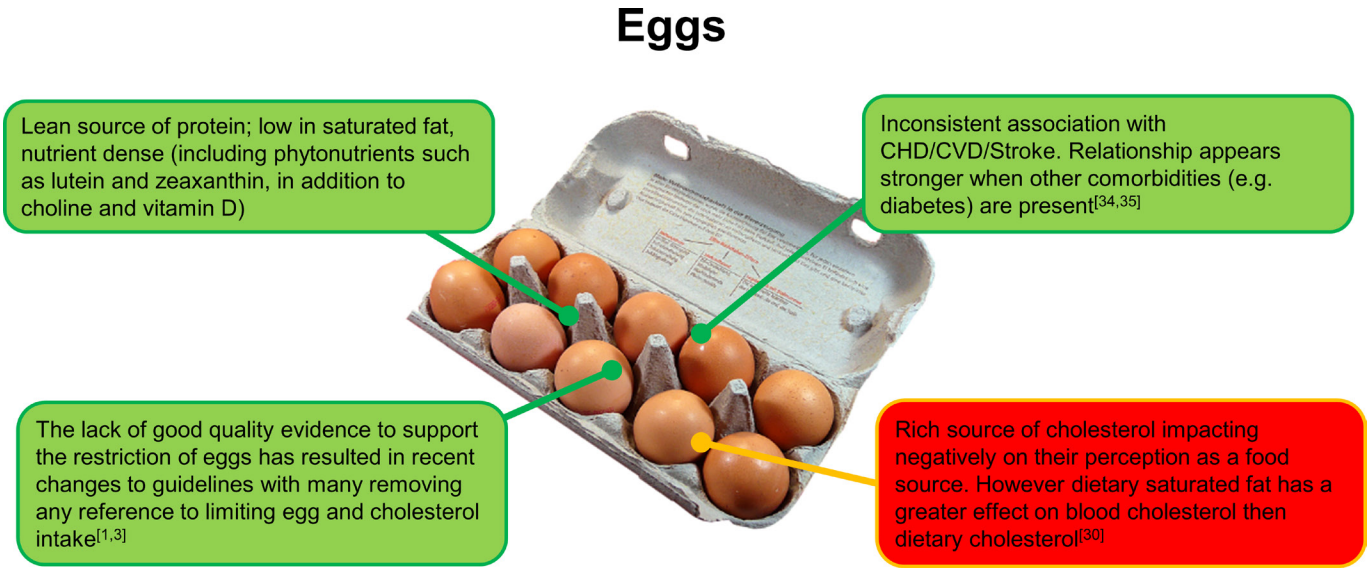

Figure 2 Eggs.

with lower risk. Milk, cheese and yoghurt all appeared to be neutral or inversely associated risk of CHD, stroke or CVD incidence. This paper also considered biomarkers in addition to the hard endpoints of CHD and stroke. Dairy product consumption was not associated with changes in TC or LDL-C. Similar results were also observed for systolic and diastolic blood pressure.

The effects of dairy intake appear to be relatively modest and in some studies, adjusting for total energy intake and consumption of other food groups (such as fruit, vegetables or red meat) can attenuate previously significant associations. Certain dairy products such as cheese are energy dense which could contribute to weight gain if consumed in excess. However, these same foods are high in amino acids known to stimulate muscle growth (leucine) and rich in calcium and phosphorus (figure 3).

Alcohol

The relationship between alcohol consumption and CVD is still a subject of controversial debate in both primary and secondary prevention. Several meta-analysis have indicated inconsistent relationships between alcohol intake and cardiovascular health.[41–45] A recent meta-analysis[41] of 45 studies has shown a significant reduction of CHD mortality for low-volume drinkers and current drinkers comparing to abstainers. In all studies combined, low-volume alcohol consumption was associated with a significantly lower risk of CHD mortality. However, in those studies that excluded participants with heart conditions, low-volume consumption was not associated with reduced CHD mortality.[41]

Drinking patterns are also important to consider in the context of alcohol intake, and compared with moderate drinkers, those individuals who consumed a moderate volume of alcohol but did so more inconsistently had a higher risk of CHD mortality.[43] This pattern of drinking may partly explain increased risk of an acute MI following a period of higher drinking[44] and indicates that alcohol use does not have a uniformly protective effect against MI. Patterns of high consumption (perhaps reflecting the social context of alcohol consumption such as binge drinking) must be considered.

A criticism of studies in this area is a lack of acknowledgement that alcohol may have a differential effect on specific types of CVD. Consuming >100 g ethanol/week had a higher risk of all-cause mortality although a J-shaped relationship existed for all

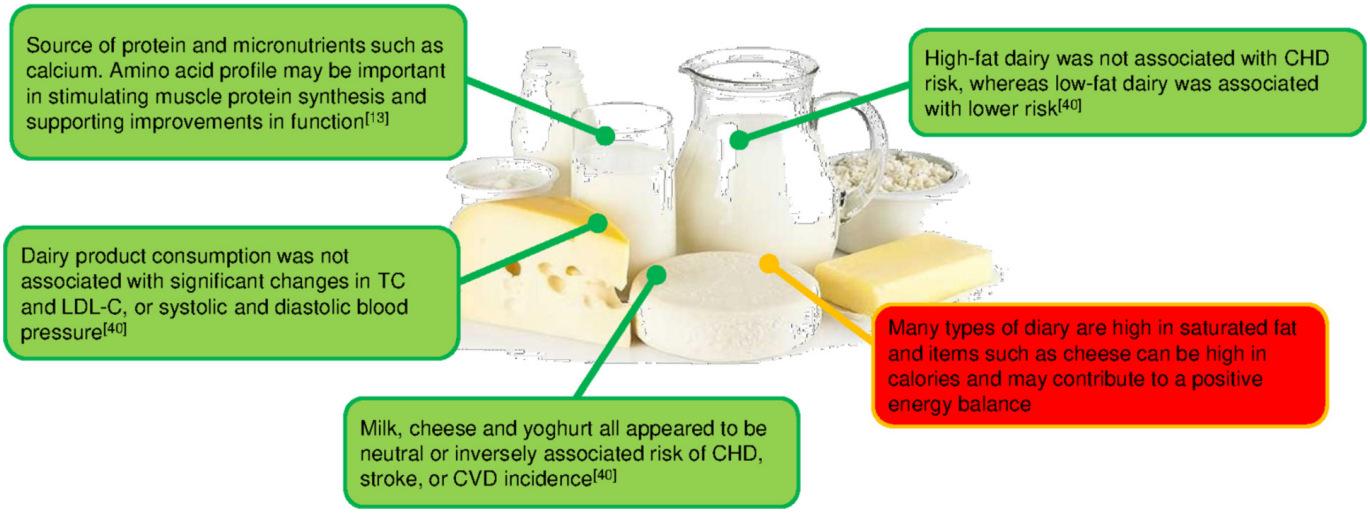

Figure 3 Dairy.

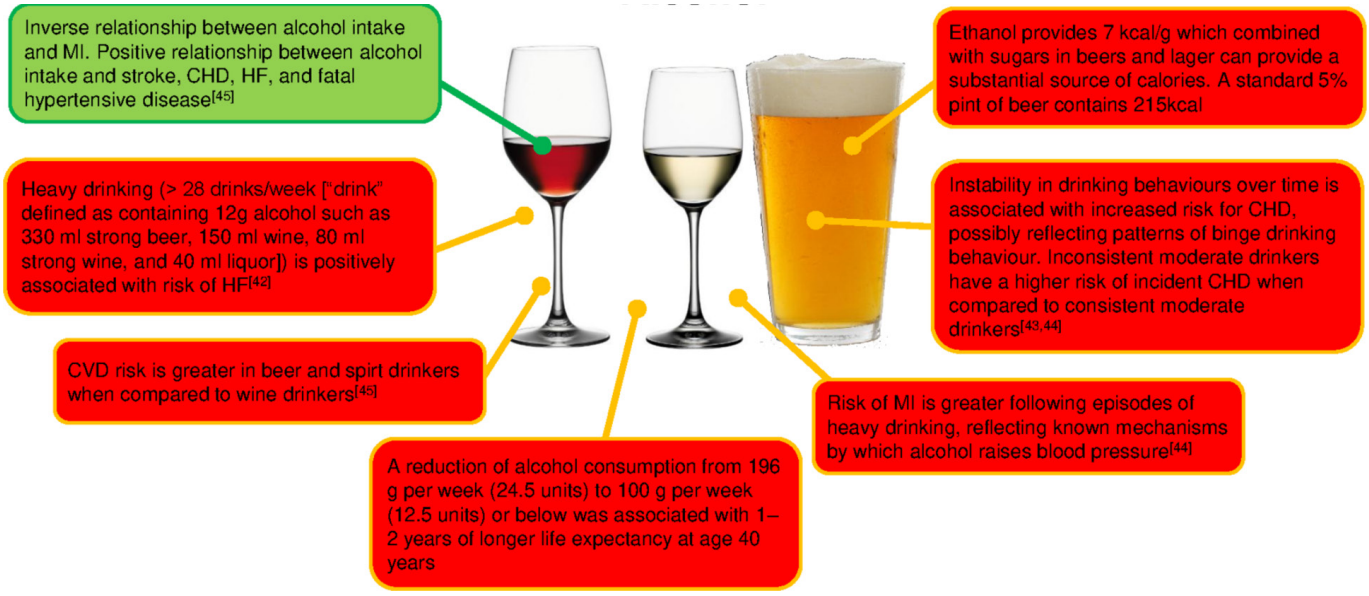

Figure 4 Alcohol.

CVD outcomes.[45] When this was disaggregated, alcohol intake (per 100 g/week higher consumption) was positively associated with stroke, CHD, HF and fatal hypertensive disease. With MI as the outcome, there was an inverse log-linear association with alcohol intake. These findings demonstrate how the consistency in frequency and low quantity of alcohol may play an essential role in cardioprotection and prevention. More evidence in needed in those individuals with a previous history of MI (figure 4).

WHOLE DIET APPROACHES

Studies considering whole diet approaches for CVD prevention are shown in online supplementary table 3.

The previous discussions have highlighted the complexities of nutrition. It is the view of the BACPR diet working group that nutrition research—especially that which impact directly on patients—be focused on food.

Improving diet quality post-MI is associated with a reduction in risk for all-cause mortality, with evidence to suggest it is the whole diet—rather than individual components—that drives this association.[46] The most widely studied diet pattern in relation to cardiovascular health is the 'Mediterranean' diet (MedDiet), with multiple studies suggesting this diet pattern is associated with lower all-cause mortality in both primary and secondary prevention of CVD.[47 48] Broadly speaking, this diet pattern contains a high nutrient density, is rich in fibre, has a relatively high intake of fat (predominantly from olive oil), low intake of saturated fat and a relatively low glycaemic index in comparison to Western diets. Traditionally, it is based around vegetables and fruits, nuts, legumes, and unrefined cereals, moderate fish and shellfish, and fermented dairy products in moderate amounts[48] but will clearly differ pending on geographical region (eg, Spain vs North Africa). Greater adherence to an 'Alternate MedDiet' characterised by a high intake of vegetables, legumes, fruit, nuts, whole-grain cereals, fish, a high intake of monounsaturated fats, and low consumption of saturated fat, red and processed meats was associated with a pooled relative risk for all-cause mortality of 0.81 in post-MI individuals.[47] In this same study, a two-point increase in the alternate MedDiet score was associated with a 7% decrease in all-cause mortality post-MI. This observed level of risk-reduction is also consistent across many other cohort studies examining the association between MedDiet adherence and all-cause and CV mortality.[48] The authors of this study make a clear point that pizza consumed in non-Mediterranean countries should be considered as a type of fast food as it is high in calories, sodium and saturated fat due to the manufacturing process. Similarly, using canola oil (high in polyunsaturated fat) is technically not part of the traditional MedDiet. This means healthcare professionals should be prepared to correct preconceived ideas regarding what is and is not, a MedDiet. Aside from oil type, authorities agree large component of the cardioprotective diet is fruit and vegetables. The established DASH diet (rich in fruits and vegetables, whole grains, low-fat dairy, nuts, legumes, and low in red and processed meat) is associated with decreased incidence of stroke, CVD, CHD, diabetes, in addition to improvements in biomarkers such as systolic and diastolic blood pressure, haemoglobin A1c (HbA1C) and fasting insulin.[49] The most recent analysis of this topic showed a benefit for greater incorporation of healthy plant foods into the diet, although this benefit was not seen with unhealthy sources (such as refined cereals). Compared with the lowest quintile, those individuals in the highest quintile of a plant-based diet had a lower risk of incident CVD, CVD mortality and all-cause mortality.[50] Significant reductions in CVD and mortality endpoints were not observed with an unhealthy plant-based diet. Comparing these studies, it can be determined that not all plant-based diets are created equal. More research is needed into plant-based diets and their direct effects post-MI.

A growing area of interest is low-carbohydrate diets and a criticism of the studies cited so far is a lack of consideration of patient subgroups (ie, those with MI vs those with MI +type 2 diabetes mellitus). In this latter group, more aggressive control of carbohydrate intake may be justified and lead to better clinical outcomes. There is a lack of robust clinical evidence for low-carbohydrate diets post-MI and more research is needed in this field. In one recent study, a very low-carbohydrate diet was effective at improving diabetes-related outcomes (HbA1c and diabetes-related drug use) in addition to reducing triglycerides and increasing high-density lipoprotein cholesterol.[51] The group did exhibit increases in TC and LDL-C which could be argued to

Table 4 Summary recommendations

Key principles	Examples	Special considerations
Adequate protein is essential to prevent muscle loss	Good quality animal and plant protein such as lean meat, fish, dairy and nuts	Older people and those with renal disease
Include higher fibre carbohydrate foods	Choose foods high in fibre, for example, wholemeal bread and pasta instead of refined versions. Include non-starchy vegetables	Portion control and reducing total carbohydrate required to improve glycaemia
Advise reductions in saturated fat on an individual basis and acknowledge the source	Reducing processed baked pastry goods is more advantageous than reducing dairy foods for equivalent amount of saturated fat	
Consider dairy intake in the context of the overall diet and health needs	As above	
Consume eggs as part of a reduced saturated fat healthy eating pattern	-	May need to consider amount of egg intake/ dietary cholesterol intake in individuals with familial hypercholesterolaemia
Eat foods naturally rich in unsaturated fats	Nuts, seeds, oily fish extra virgin olive oil is consumed as part of the traditional Mediterranean diet	-
Include plenty of fruit and vegetables	Root vegetables, green leafy vegetables, for example, kale, lettuce, spinach; cruciferous vegetables. A variety of fruits should be included	Ideally fresh or frozen fruit unless canned is the only source available. Be mindful of total carbohydrate and free sugar content particularly for those with dysglycaemia
For those who drink alcohol to consume within local government recommendations of no more than 14 units/week with 1–2 alcohol free days each week. Avoid binge drinking	-	-
Use a whole diet approach and tailor approaches to individual comorbidities and need	A traditional cardioprotective diet rich in vegetables, fruits, nuts, legumes, unrefined cereals, moderate seafood and fermented dairy food; low amounts of red and processed meats; olive oil as main culinary fat	Consider reducing the carbohydrate content particularly for those with dysglycaemia, and replacing with plant-based proteins and fats

be a negative consequence of the diet intervention, especially if extrapolated to a post-MI population. However, this same group showed previously that this increase in LDL-C was accompanied by a decrease in LDL particle number and an increase in LDL particle size[52] (suggestive of a more favourable lipid profile). However, it is worth highlighting that there is substantial variation in response to low-carbohydrate diets so monitoring of lipids is important. This study was criticised at the time for patients self-selecting their intervention (not randomised to either treatment or control arm) although this in many ways represents a 'real-world' approach whereby patients are given a choice in their treatment. It is crucial to examine the carbohydrate replacement element and its source (fat vs protein, and animal or plant sources) as this will also govern the impact this diet pattern has on CV health. Indeed, a recent meta-analysis has indicated a plant-based low-carbohydrate diet is inversely associated with lower risk of mortality whereas an animal-based low-carbohydrate diet was positively associated with the same outcome.[15] This highlights the importance for healthcare practitioners to explore diet choices with their patients, and not automatically assume plant-based or low-carbohydrate diets are 'good' and 'bad', respectively.

CONCLUSION

Recommendations from the working group are summarised in table 4. Focusing on macronutrients can be problematic with advice such as 'reduce saturated fat' and increase monounsaturated and polyunsaturated fats being vague and non-specific. The greatest improvement in cardiovascular outcomes will be seen when patients are provided with food-based advice. This requires those dispensing this information to have an understanding of nutritional science and an appreciation for the patients' comorbidities. While there is a large body of evidence for the role of the MedDiet, additional approaches should be used in the right groups of patients. Low-carbohydrate diets can be carefully planned and be very nutritious, although similar to plant-based diets they can also be poor quality if not planned appropriately. Nutritional advice needs to be patient-focused, flexible, and should be adapted to each individual with CVD and their other comorbidities. More specialised dietitians are required in this area to guide the multi-professional team and provide guidance and training to those involved in the individual's rehabilitation journey.

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Online Supplementary Table 1 Macronutrients and their association or effect on CV outcomes

Study	Participant characteristics	Study Design	Measures and time points	Key observations
Esmeijer et al.[7]	4837 participants in original cohort Excluded 671 Total participants: *n* 2248 Time since MI: 4.0 (1.9-6.4) years <0.80 g/kg ideal bodyweight: Age: 69±6 years 77% men BMI: 27.6±3.6 kg/m2 Ethnicity: 99% white High blood pressure: 57% SBP: 144±22 mmHg DBP: 82±11 mmHg Serum LDL-C: 2.7±0.9 mmol/L Plasma Glucose: 6.0±1.8 mmol/L Current smoker: 20% BP lowering drugs: 90% RAS drugs: 52% Diabetes prevalence: 18% Glucose lowering drugs: 14% Lipid-modifying drugs: 88% Anti-thrombotic drugs: 98% Current smoker Serum cystatin C: 1.02±0.29 mg/L Serum creatinine: 1.05±0.37 mg/dL eGFRcysC: 77±20 mL/min/1.73 m^2 eGFRcr–cysC: 75±19 mL/min/1.73 m^2 0.80 to <1.00 g/kg ideal bodyweight: Age: 69±5 years 83% men BMI: 27.4±3.5 kg/m2 Ethnicity: 99% white High blood pressure: 58% SBP: 144±21 mmHg DBP: 82±11 mmHg Serum LDL-C: 2.7±0.8 mmol/L Plasma Glucose: 6.0±1.9 mmol/L Current smoker: 18% BP lowering drugs: 87%	Prospective cohort study Participants taken from the Alpha Omega Cohort (low-dose omega-3 fatty acids) Present study included patients with available blood samples at baseline and after 41 months follow-up Participants grouped based on protein intake (g/kg ideal body weight) at baseline: <0.80, 0.80 to <1.00, 1.00 to <1.20 ≥1.20 g/kg <0.80 g/kg ideal bodyweight: 1346 ± 316 kcal/d, 173 ± 49 g/d carbohydrates (51 ± 8% total energy), 52 ± 20 g/d total fat (35 ± 8% total energy), 46 ± 8 g/d protein (14 ± 3% total energy), 25 ± 8 g/d animal protein (8 ± 3 % total energy), 9 ± 7 g/d from meat (3 ± 2 % total energy), 10 ± 5 g/d from dairy (3 ± 2 % total energy), 21 ± 5 g/d plant protein (6 ± 1 % total energy) 0.80 to <1.00 g/kg ideal bodyweight: 1659 ± 364 kcal/d, 204 ± 57 g/d carbohydrates (49 ± 7% total energy), 66 ± 23 g/d total fat (36 ± 7% total energy), 61 ± 6 g/d protein (15 ± 3% total energy), 36 ± 7 g/d animal protein (9 ± 3 % total energy), 15 ± 7 g from meat (4 ± 2 % total energy), 14 ± 7 g/d from dairy (3 ± 2 % total energy), 25 ± 6 g/d plant protein (6 ± 1 % total energy) 1.00 to <1.20 g/kg ideal bodyweight: 1874 ± 359 kcal/d, 228 ± 58 g/d carbohydrates/d (48 ± 7% total energy), 75 ± 22 g/d total fat (36 ± 7% total energy), 73 ± 8 g/d protein (16 ± 3% total energy), 45 ± 8 g/d animal protein (10 ± 3 % total energy), 18 ± 7g/d from meat (4 ± 2 % total energy), 18 ± 8 g/d from dairy (4 ± 2	Primary outcome; association between dietary protein intake and risk of kidney function decline in post-MI individuals Bloods taken at baseline and 41 months follow up. Cystatin C measured at baseline and 41 months. GFR based on cystatin C (eGFRcysC) and combined creatinine–cystatin C (eGFRcr–cysC) at baseline and after 41 months, using the Chronic Kidney Disease Epidemiology Collaboration equations from 2012. Diet data and anthropometry measured at baseline. Diet data collected using 203 item FFQ. Questionnaires checked by registered dietitian and nutrient content calculated using 2006 Dutch Food Composition tables. 41 month diet data not collected. Protein intake expressed as g/kg ideal body weight to avoid erroneously high requirements in overweight and obese subjects. Linear regression used to study association of kidney function decline and baseline intake of total protein, types of protein (meat vs. dairy) sources of protein (animal vs. plant). Models adjusted for age, sex and total energy intake, education, alcohol, smoking, physical activity, RAS blocking drugs, intake of fat (MUFA, PUFA, SFA and TFA), dietary sodium, diabetes and systolic blood pressure.	For whole cohort, annual change in eGFRcysC and eGFRcr–cysC was −1.30 (−1.43, −1.17) and −1.71 (−1.87, −1.56) mL/min/1.73 m2, respectively. Total energy, all macro and micronutrients increased with each protein category. Annual change in eGFRcysC was doubled in those individuals with protein intake >1.2 when compared to those with < 0.8 g/kg ideal body weight (1.60 [−1.92,−1.28] vs. −0.84 [−1.21, −0.46] mL/min/1.73 m2, respectively. Significant inverse association between intake of animal protein and both eGFRcysC and eGFRcr–cysC. Significance not observed with plant protein. With eGFR as outcome, the annual decline in renal function was significantly slower with dairy vs. meat for every 5 g protein (−0.05 [−0.13, 0.03] vs. −0.11 [−0.20, −0.02]). With change in eGFRcr–cysC as outcome, there was no significant difference between dairy and meat. <u>3-fold stronger association between protein intake and eGFR decline in patients with diabetes</u> **Summary** **In patients with established CVD, higher protein intakes were associated with accelerated decline in renal function. Note that "meat" category contained "processed meats" such as sausage, hamburger,**

	RAS drugs: 56% Diabetes prevalence: 18% Glucose lowering drugs: 12% Lipid-modifying drugs: 85% Anti-thrombotic drugs: 97% Serum cystatin C: 0.99±0.26 mg/L Serum creatinine: 1.04±0.35 mg/dL eGFRcysC: 80±20 mL/min/1.73 m^2 eGFRcr–cysC: 77±19 mL/min/1.73 m^2 1.00 to <1.20 g/kg ideal bodyweight: Age: 69±5 years 80% men BMI: 27.7±3.6 kg/m2 Ethnicity: 99% white High blood pressure: 57% SBP: 145±22 mmHg DBP: 82±11 mmHg Serum LDL-C: 2.7±0.8 mmol/L Plasma Glucose: 6.0±1.8 mmol/l Current smoker: 13% BP lowering drugs: 84% RAS drugs: 52% Diabetes prevalence: 17% Glucose lowering drugs: 12% Lipid-modifying drugs: 88% Anti-thrombotic drugs: 98% Serum cystatin C: 0.95 ± 0.22 mg/L Serum creatinine: 1.01 ± 0.30 mg/dL eGFRcysC: 83±19 mL/min/1.73 m^2 eGFRcr–cysC: 79±19 mL/min/1.73 m^2 ≥1.20 g/kg ideal bodyweight: Age: 69±5 years 78% men BMI: 27.8±3.7 kg/m2 Ethnicity: 99% white High blood pressure: 55% SBP: 142±20 mmHg DBP: 81±10 mmHg Serum LDL-C: 2.7±0.7 mmol/L Plasma Glucose: 6.1±2.1 mmol/L Current smoker:14%	% total energy), 28 ± 6 g/d plant protein (6 ± 1 % total energy) ≥1.20 g/kg ideal bodyweight: 2250 ± 469 kcal/d, 268 ± 68 g/d carbohydrates (48 ± 7% total energy), 90 ± 27 g/d total fat (36 ± 6% total energy), 92 ± 14 g/d protein (17 ± 3% total energy), 60 ± 12 g/d animal protein (11 ± 3 % total energy), 22 ± 8 g/d from meat (4 ± 2 % total energy), 27 ± 12 g/d from dairy (5 ± 2 % total energy), 33 ± 8 g/d plant protein (6 ± 1 % total energy)		**bacon therefore “meat” includes processed and unprocessed foods**

	BP lowering drugs: 88% RAS drugs: 57% Diabetes prevalence: 19% Glucose lowering drugs: 13% Lipid-modifying drugs: 86% Anti-thrombotic drugs: 99% Serum cystatin C: 0.93±0.21 mg/L Serum creatinine: 0.98±0.31 mg/dL eGFRcysC: 85±18 mL/min/1.73 m^2 eGFRcr–cysC: 82±18 mL/min/1.73 m^2			
Virtanen et al.[8]	2682 participants in original cohort Excluded 41 Total participants: *n* 2641 1094 history of T2DM, CVD, or cancer at baseline 1547 free of disease at baseline 100% men Ethnicity not reported SBP and DBP not reported Plasma Glucose not reported Quartile 1 Age: 53.7±4.6 years BMI: 26.5±3.4 kg/m2 Current smoker: 33.5% Serum TC:HDL-C: 4.77±1.48mmol/L Serum TAG: 1.25±0.74 mmol/L Serum CRP: 2.60±5.35 mg/L Serum ferritin: 155±162 µg/L eGFR: 84.9 ± 13.4 mL/min High blood pressure: 61.4% HTN medication: 20.2 Diabetes: 3.8% Glucose lowering medication: 0.8% CVD: 40.2% CVD medication: 2.4% Lipid modifying medication: 0.2% Quartile 2 Age: 53.2±4.9 years BMI: 26.6±3.5 kg/m2 Current smoker: 32.9%	Prospective cohort study Participants taken from the Kuopio Ischaemic Heart Disease Risk Factor Study. Baseline examinations took place 1984-1989. Follow-up in 2014. Participants grouped based on protein intake (g/d) at baseline: Quartile 1 <83.9 g/d, Quartile 2 83.9–92.1 g/d Quartile 3 92.2–101.5 g/d Quartile 4 >101.5 g/d Quartile 1: 2532 ± 671 kcal/d, carbohydrates 43.6 ± 7.2 % total energy, total fat 39.9 ± 6.5% total energy, 76.4 ± 7.3 g/d protein (12.9 ± 1.1% total energy), 49.0 ± 8.9 g/d animal protein (8.2 ± 1.4 % total energy), 25.2 ± 6.4 g/d plant protein (4.2 ± 1.0 % total energy), unprocessed red meat (58 ± 40 g/d), processed red meat[a] (69 ± 61 g/d), fish (27 ± 33 g/d), egg (31 ± 25 g/d), non fermented dairy (486 ± 308 g/day), fermented dairy (113 ± 143 g/d). Quartile 2: 2336 ± 577 kcal/d, carbohydrates 48.3 ± 6.1 % total energy, total fat 38.6 ± 5.6 % total energy, 88.0 ± 2.4 g/d protein (14.9 ± 0.7 % total energy), 59.5 ± 6.4 g/d animal protein (10.1 ± 1.2 % total energy), 26.3 ± 5.7 g/d plant protein (4.5 ± 1.1 % total energy), unprocessed red meat (66 ± 46 g/d), processed red meat[a] (62 ± 52 g/d), fish (35 ±	Primary outcome; association between dietary protein intake and risk of disease death Anthropometry and bloods taken at study baseline. Diet data collected using a 4-day (including 1 weekend day) food record. Questionnaires checked by nutritionist and nutrient content analysed using NUTRICIA 2.5 software. Ratio between intakes of animal and plant protein in the diet was calculated, with a higher ratio showing greater Deaths determined from national Causes of Death Register with the use of the Finnish personal identification code. Deaths were coded according to the International Classification of Diseases (ICD), 10th revision, codes. Person-years of follow-up were calculated from the baseline to the date of death or the end of follow-up. Cox proportional hazards regression models were used to estimate HRs in exposure quartiles, with the lowest category (quartile 1) as the reference. Models were adjusted for age (years), examination year, and energy intake (kcal/d), education years, income (euros per year), marital status (married/unmarried); pack-years of smoking (cigarette packs smoked per day × years smoked, alcohol intake (g/week), leisure-time physical activity (kcal/d); BMI (in kg/m2), diagnosis of T2DM, CVD, cancer, or HTN at baseline or use of cardiac, hypercholesterolemia, hypertension, or diabetes medications (yes/no), fibre, SFA, MUFA, PUFA, and TFA (all g/d).	1255 deaths recorded during mean follow-up of 22.31 ± 7.89 years. Men in the highest compared with the lowest quartile of total protein intake had a borderline statistically significant 17% increased risk of mortality (95% CI: −1, 39%; P-trend = 0.07) Relationship between total protein and mortality was stronger in those with previous disease history vs. those men without (HR 1.04; 95% CI: 1.01, 1.07; per 5 g/d increase vs. HR 1.01; 95% CI: 0.98, 1.04; *P*=0.05, *P*=0.07 [depending on model], respectively) Men in highest vs. lowest quartile of animal protein intake had a trend toward 13% increased mortality risk (95% CI: -5, 35%; *P*-trend = 0.04). Participants in the highest meat intake quartile had a 23% (95% CI: 4, 47%; *P*-trend = 0.01) higher risk of mortality vs. those in the lowest quartile. Adjusting for additional nutrients increased the risk (HR 1.36; 95% CI: 1.09, 1.70; *P*-trend = 0.01). Those with the highest ratio of animal:plant protein in the diet (higher animal protein intake) had 23%

	Serum TC:HDL-C: 4.89±1.54mmol/L Serum TAG: 1.33±0.84 mmol/L Serum CRP: 2.28±3.87 mg/L Serum ferritin: 163±149 µg/L eGFR: 84.8 ± 12.5 mL/min High blood pressure: 58.8% HTN medication: 24.8 Diabetes: 4.7 Glucose lowering medication: 0.6% CVD: 36.5% CVD medication: 3.2% Lipid modifying medication: 0.8% Quartile 3 Age: 52.7±5.2 years BMI: 26.8±3.6 kg/m2 Current smoker: 30.9% Serum TC:HDL-C: 4.88±1.56mmol/L Serum TAG: 1.31±0.84 mmol/L Serum CRP: 2.46±3.72 mg/L Serum ferritin: 163±135 µg/L eGFR: 85.4 ± 12.2 mL/min High blood pressure: 59.5% HTN medication: 22.2% Diabetes: 7.3% Glucose lowering medication: 1.4% CVD: 38.3% CVD medication: 2.6% Lipid modifying medication: 0.6% Quartile 4 Age: 52.7±5.2 years BMI: 27.6±3.7 kg/m2 Current smoker: 30.0% Serum TC:HDL-C: 4.76±1.40mmol/L Serum TAG: 1.37±0.85 mmol/L Serum CRP: 2.42±3.47 mg/L Serum ferritin: 193±160 µg/L eGFR: 85.6 ± 13.1 mL/min High blood pressure: 61.7% HTN medication: 23.3% Diabetes: 8.0%	37 g/d), egg (30 ± 24 g/d), nonfermented dairy (504 ± 305 g/day), fermented dairy (165 ± 191 g/d). Quartile 3: 2360 ± 577 kcal/d, carbohydrates 42.2 ± 5.8 % total energy, total fat 38.7 ± 5.6 % total energy, 96.6 ± 2.7 g/d protein (16.5 ± 1.0 % total energy), 68.7 ± 6.1 g/d animal protein (11.7 ± 1.3 % total energy), 25.7 ± 5.4 g/d plant protein (4.4 ± 1.0 % total energy), unprocessed red meat (76 ± 45 g/d), processed red meat[a] (69 ± 56 g/d), fish (46 ± 46 g/d), egg (31 ± 23 g/d), nonfermented dairy (543 ± 347 g/day), fermented dairy (195 ± 211 g/d). Quartile 4: 2534 ± 630 kcal/d, carbohydrates 41.2 ± 6.4 % total energy, total fat 37.4 ± 5.9 % total energy, 111.8 ± 9.7 g/d protein (18.8 ± 2.1% total energy), 83.6 ± 11.8 g/d animal protein (14.1 ± 2.3 % total energy), 26.1 ± 6.5 g/d plant protein (4.4 ± 1.0 % total energy), unprocessed red meat (97 ± 60 g/d), processed red meat[a] (76 ± 75 g/d), fish (35 ± 29 g/d), egg (31 ± 25 g/d), nonfermented dairy (564 ± 366 g/day), fermented dairy (273 ± 273 g/d).		increased risk of mortality (95% CI: 2, 49%; P-trend = 0.01) Men consuming more animal protein had a higher BMI, were more likely to smoke and have T2DM. Consumption of fish, eggs, dairy, or plant protein were not associated with mortality in this cohort. **Summary** **Greater intake of animal protein associated with increased risk of mortality. The relationship with total protein and mortality was greatest in those with predisposing disease. No comment on protein quality.**

	Glucose lowering medication: 2.0% CVD: 36.1% CVD medication: 3.2% Lipid modifying medication: 0.9%			
O'Connor et al.[9]	261 participants approached 69 assessed for eligible 19 excluded 50 participants randomized 9 dropped out Total participants: *n* 41 31% men Age: 46±2 years Med-Red Body mass: 91.2±1.5 kg Body fat: 37.2±1.0 % SBP: 118±2 mmHg DBP: 80±1 mmHg Plasma glucose: 5.4±0.1 mmol/L TC: 4.9±0.1 mmol/L LDL-C: 3.1±0.1 mmol/L HDL-C: 1.2±0.1 mmol/L TAG: 1.4±0.1 mmol/L ApoB: 1±0.0 g/L Insulin: 85.4±7.6 pmol/L CRP: 21.9±2.9 HOMA-IR: 2.981±0.299 10-year risk (%): 4.6±0.5 Vascular Age: 45±2 years 14-point Med Diet Score: 4±0 Med-Control Body mass: 90.6±1.5 kg Body fat: 36.6±1.0 % SBP: 120±2 mmHg DBP: 78±1 mmHg Plasma glucose: 5.3±0.1 mmol/L TC: 4.9±0.1 mmol/L LDL-C: 3.0±0.1 mmol/L HDL-C: 1.3±0.1 mmol/L TAG: 1.4±0.1 mmol/L ApoB: 0.9±0.0 g/L Insulin: 77.1±6.9 pmol/L CRP: 21.9±2.9	Randomized, crossover, controlled feeding trial 16 week duration Two 5-week controlled feeding intervention with 4 week of self-selected unrestricted "wash-out". Intervention consisted of a "Mediterranean Pattern" with daily macronutrients targets of 40% of total energy as carbohydrate, 22% protein, and 40% fat. Daily fat intakes were targeted at 7% of total energy as SFA and 20% MUFA. All foods were provided. Mediterranean Patterns contained ∼500 g (Med-Red) and ∼200 g (Med-Control) of lean, unprocessed beef or pork per week. Med-Red 2601 ± 428 kcal/d, carbohydrates 42 ± 1 % total energy, total fat 40 ± 1 % total energy, MUFA 22 ± 1 total energy, PUFA 8 ± 0 % total energy, SFA 7 ± 0 total energy, protein 18 ± 0 % total energy, 476 g red meat/wk, 112 g poultry/wk, 336 g seafood/wk, 2 eggs/wk, 560g nuts, seed, soy/wk, 3 servings dairy/d. 14-point Med Diet Score: 12 Med-Control 2573 ± 405 kcal/d, carbohydrates 42 ± 2 % total energy, total fat 40 ± 1 % total energy, MUFA 21 ± 1 total energy, PUFA 9 ± 1 % total energy, SFA 8 ± 0 total energy, protein 19 ± 1 % total energy, 196 g red meat/wk, 420 g poultry/wk, 336 g seafood/wk, 3 eggs/wk, 616 g nuts, seed, soy/wk, 2 servings dairy/d. 14-point Med Diet Score: 13 Note that these are prescribed diets. It is not clear if participants consumed other food during the study intervention.	Primary outcome: assess the effects of consuming a Mediterranean Pattern with different amounts of red meat on cardiometabolic disease risk factors Anthropometry (body mass and composition), bloods (full lipid profile) and Framingham Heart Study 10-year CV risk and vascular age taken at baseline and during the last week of the study. Baseline food intakes determined prior to randomisation and during washout to determine return to self-selected eating pattern	Greater reduction of body mass in Med-Red vs. Med-Control group (−1.6 ± 0.5 vs. −1.0 ± 0.5 kg, respectively). TC decreased significantly in both Med-Red and Med-Control (-0.4 ± 0.1 vs. -0.2 ± 0.1 mmol/L, respectively). Decrease in Med-Red was significantly greater than Med-Control. Significant decrease in LDL-C in Med-Red group vs. baseline value (3.1 ± 0.1 vs. 2.8 ± 0.1 mmol/L, respectively). Significant reduction in ApoB in Med-Red vs. Med-Control (-0.1 ± 0.0 vs. 0.0 ± 0.0 g/L, respectively) No significant change in TC:HDL-C, TAG, CRP, glucose, insulin, and HOMA-IR between groups. Significant reductions in SBP in Med-Red and Med-Control groups over time (-3 ± 2 vs. -5 ± 2 mmHg, respectively) Both Med-Red and Med-Control improved 10-year CV risk score (-0.7 ± 0.4 and -0.5 ± 0.4 years) and improved vascular age. **Summary** **This short-term study shows adopting a Mediterranean diet pattern improves cardiometabolic risk irrespective of red meat intake providing the meat is lean and unprocessed.**

	HOMA-IR: 2.679±0.297 10-year risk (%): 4.6±0.5 Vascular Age: 45±2 years 14-point Med Diet Score: 4±0 No statistically significant difference in any baseline parameter between groups Ethnicity and medication use not reported			
Guasch-Ferré et al.[10]	Articles via PubMed: 366 Excluded 267 due to inappropriate articles (literature reviews, editorials, not RCT design, outcomes of interest not reported, control and red meat consumption not different) 99 Articles assessed for eligibility Excluded 66 due to acute feeding trials, lipids not reported, red meat intake not reported, no comparison group. Articles in final meta-analysis: 36 20 studies used a cross-over design Sample size for studies ranged from 8-191 participants Mean ages ranged from 22-70 years of age Included both normolipidaemic (n=26 studies) and hyperlipidaemic (n=11 studies) participants Red meat consumption ranged from 46.5-500 g/d in intervention diets and 0-266 g/d in comparison diets Minimally-processed red meat was consumed in 24 studies; processed red meat was consumed in 5 studies, and the extent of red meat processing was not reported in 8 studies	Meta-analysis of RCTs comparing red meat consumption vs. other comparison diets Articles soured from PubMed (up to 2017) Study quality score from National Heart, Lung and Blood Institute (Quality Assessment of Controlled Intervention Studies): Score ranging from 0 to 28 points Research question developed using PICOS Inclusion criteria were: Participants aged ≥18 years and not pregnant, intervention and comparison diets that prescribed differing amounts of red meat, reporting, ≥1 cardiovascular risk factor as a dependent variable (i.e. TC, LDL-C, HDL-C, TAGs, apolipoproteins [A1 and B], or blood pressure), and use of a RCT study design. As a minimum the study needed to be at least 2 weeks in duration Meat defined as “all forms of beef, pork, lamb, veal, goat, and non-bird game (eg, venison, bison, elk)” Processed meat defined as “preserved by smoking, curing, salting, and/or the addition of chemical preservative.”	Primary outcomes changes or differences in blood concentrations of TC, LDL-C, HDL-C, ApoA1, ApoB, or blood pressure.	When combining all studies examining red meat vs. all comparison diets, there was no significant effects of red meat on TC, LDL-C, HDL-C, TC:HDL-C, HDL-C:LDL-C, VLDL-C, ApoA1, or ApoB. Red meat yielded lesser decreases in TAGs (WMD 0.065 mmol/L; 95% CI, 0.000, 0.129). Lean red meat gave created decreases in TC and LDL-C (WMD -0.05 mmol/L; 95% CI: -0.12, -0.02; P=0.04; WMD -0.08 mmol/L; 95% CI: -0.15, -0.02, P=0.03, respectively) relative to all comparison diets. No significant differential effects of red meat were observed for total cholesterol or LDL-C when dietary SFA intake in the red meat group was higher or similar to that in the comparison diet. When compared with high-quality plant protein, red meat yielded smaller decreases in TC (WMD 0.264 mmol/L; 95% CI: 0.144, 0.383; P<0.001) and LDL-C (WMD 0.198 mmol/L; 95% CI: 0.065, 0.330; P=0.003). Red meat decreased TC (WMD -0.109 mmol/L; 95% CI: -0.211, -0.007; P<0.036) and LDL-C (WMD

				–0.173 mmol/L; 95% CI: -0.260, -0.086; P<0.001) when compared to fish-only diets Red meat showed no significant difference on any lipid variable when compared with chicken or poultry diets When poultry and fish were combined, red meat decreased TC to a greater extent (WMD -0.092 mmol/L; 95% CI: -0.177, -0.008; P=0.032) and TAG to a lesser extent (WMD 0.224 mmol/L; 95% CI: 0.077, 0.371; P=0.003). When compared with carbohydrates, red meat yielded lesser decreases in HDL-C (WMD 0.139 mmol/L; 95% CI, 0.004, 0.275; P=0.043) when usual diet was the comparison (WMD 0.081 mmol/L; 95% CI, 0.008, 0.153; P=0.030). In comparison with carbohydrates, red meat yielded greater decreases in TAG concentrations (WMD -0.181 mmol/L; 95% CI: -0.349, -0.013; P=0.035) and also with combined animal protein sources (WMD -0.093 mol/L; 95% CI: -0.176, -0.011, P=0.027). **Summary** **Relative to all diets combined, red meat had no significant impact on TC, LDL-C, HDL-C, ApoA1, B, BP but gave lesser decreases in TAG. When compared with specific control diets, swapping red met for high-quality plant protein led to beneficial changes in lipids.**
Kwok et al.[11]	Potentially relevant records: 3011 Excluded 2670 341 reviews or studies reviewed in detail Excluded 308	Review of evidence from systematic reviews and meta analyses Identified food categories/groups based on UK ‘EatWell guide’, ‘the five food groups’	Primary outcomes included death (all-cause) or cardiovascular disease (stroke, cerebrovascular disease, cerebrovascular accident, CHD, ischaemic heart disease, coronary artery disease, acute myocardial infarction,	For all-cause mortality the evidence was ranked as Level 2 for refined grains, green leafy vegetables/salad and tinned fruit.

	Articles in final meta-analysis: 33 16 reviews on all-cause mortality 17 reviews on cardiovascular disease None of the included studies were based on RCT data Follow up periods not reported.	in the 2015-2020 Dietary guidelines for Americans, and 'Food guide pyramid' from the Centre for Nutrition Policy and Promotion in the United States Searched PubMed (August 2018) for most recent and highest quality systematic review and meta analysis evaluating the dietary components and associated adverse outcomes. Quality assessment of studies performed using WHO strength of evidence: Level 1a/b convincing evidence Level 2 probable evidence Level 3 possible evidence Level 4 limited/contrasting Inclusion criteria were Studies had to have the dietary component of interest and some form of quantitative association with either CVD or mortality Food item consumption and its association with outcome can be quantified as a dose–response relationship and highest compared to lowest consumers of food items.	acute coronary syndrome, HF, cardiac failure, cardiac insufficiency)	For CVD only fish had Level 2 evidence. <u>All-cause mortality</u> 2 or fewer studies for the assessment of whole grain bread, pasta, whole grain breakfast cereals, or oats/oatmeal. In a dose-response analysis all food items above were associated with a significantly reduced risk of all-cause mortality (whole grain bread: RR 0.85; 95% CI: 0.82, 0.89; pasta: RR 0.85; 95% CI: 0.74, 0.99; wholegrain breakfast cereal: RR 0.88; 95% CI: 0.83, 0.92; oats/oatmeal: RR 0.88; 95% CI: 0.83, 0.92). Intake of refined grains and fibre were associated with a significant dose–response reduction in all-cause mortality (163,634 participants; RR 0.95; 95% CI: 0.91, 0.99; and 875,390 participants; RR 0.90; 95% CI: 0.86, 0.94, respectively) No association was found between rice (453,723 participants) and all-cause mortality Fish consumption was associated with a benefit for all-cause mortality (RR 0.98; 95% CI: 0.97, 1.00). Processed meat was associated with a 25% increased risk of all-cause mortality (1,1423,969 participants, RR 1.25; 95% CI: 1.07, 1.45). No associations were found between white and red meat, and eggs. Root vegetables (451,151 participants, RR 0.76; 95% CI: 0.66, 0.88), green leafy vegetables/salad (568,725 participants, RR 0.78; 95% CI: 0.71, 0.86), cooked vegetables (631,480 participants, RR 0.89; 95% CI: 0.80, 0.99) and cruciferous vegetables

				(531,147 participants, RR 0.90; 95% CI: 0.85, 0.95) were associated with lower all-cause mortality. Tinned fruit was associated with increased all-cause mortality (147,712 participants, RR 1.14; 95% CI: 1.07, 1.21). Comparing high and low consumers of alcohol suggested a reduction in all-cause mortality (844,414 participants, RR 0.87; 95% CI: 0.83, 0.92) Coffee displayed a dose-response relationship for reduced all-cause mortality (941,247 participants, RR 0.96; 95% CI: 0.94, 0.97). Dairy products such as butter, yoghurt, cheese, milk were not significantly associated with mortality. Increased nut intake was associated with lower all-cause mortality (819,448 participants, RR 0.78; 95% CI: 0.72, 0.84). Specifically tree nuts (202,751 participants, RR 0.82; 95% CI: 0.75, 0.90) and peanuts (265,252 participants, RR 0.77; 95% CI: 0.69, 0.86). <u>Cardiovascular Disease</u> A dose-response relationship existed for whole grain bread (177,389 participants, RR 0.87; 95% CI: 0.80, 0.95), whole grain breakfast cereals (206,200 participants, RR 0.84; 95% CI: 0.78, 0.90), bran (118,085 participants, RR 0.85; 95% CI: 0.79, 0.90), and fibre (1,279,690 participants, RR 0.91; 95% CI: 0.88, 0.94) Inverse associations were seen for red meat (1,319,147 participants, RR 1.15; 95% CI: 1.05, 1.26), and processed meat (1,186,761 participants, RR 1.24; 95% CI: 1.09, 1.40).

				Only raw vegetables displayed a dose-response association of benefit (451,151 participants, RR 0.86; 95% CI: 0.81, 0.90). Comparing the highest and lowest consumption of alcohol showed an inverse association with risk of CVD (1,184,974 participants, RR 0.75; 95% CI: 0.70, 0.80). Yogurt, cheese, milk and butter showed no evidence of a dose–response association for benefit or harm with CVD Nut intake was associated with reduced risk of CVD (376,228 participants, RR 0.79; 95% CI: 0.70, 0.88). Specifically tree nuts (130,987 participants, RR 0.75; 95% CI: 0.67, 0.84) and peanuts (265,252 participants, RR 0.64; 95% CI: 0.50, 0.81). Olive oil showed a dose-response with reduced CVD risk (476,714 participants, RR 0.82; 95% CI: 0.70, 0.96). Comparing highest and lowest consumers, increased soy consumption was associated with lower risk of CVD (718,279 participants, RR 0.83; 95% CI: 0.75, 0.93). A dose-response relationship existed for chocolate intake (per 20g/week) and reduced CVD risk (369,599 participants, RR 0.982; 95% CI: 0.972, 0.992) **Summary** **In this comprehensive review of systematic reviews and meta analyses key foods from specific food groups show differential associations with all-cause mortality and CVD. Current evidence suggests that specifically green leafy**

				vegetables/salad is strongly associated with reduced all-cause mortality, and foods such as yoghurt, butter, cheese, show no association. This review also highlights significant associations between processed meat and all-cause mortality, but not with red or white meat, or eggs. Foods that appear harmful include processed meat and tinned fruit for all-cause mortality and processed meat and red meat for CVD.
Park et al.[13]	355 participants assessed for eligible 235 excluded 120 participants randomized (40 to each arm) 21 dropped out 40 included in ITT analysis <u>Protein intake of 0.8 g/kg/d</u> Age: 76.83 ± 3.86 years Men: 40% Weight: 58.73 ± 9.71 kg BMI: 24.16 ± 33.82 kg/m2 ASM*: 15.19 ± 3.10 kg ASM height2: 6.19 ± 0.79 kg/m2 ASM/weight: 26.00 ± 3.99 % ASM/BMI: 0.64 ± 0.16 ASM:fat ratio: 1.08 ± 0.46 CHS Score: 1.70 ± 0.83 Frailty status 13% Hypertension: 55% Hyperlipidaemia: 18 % Diabetes: 28 % Osteoporosis: 18 % Arthritis: 5 % MNA Score: 20.04 ± 2.40 <u>Protein intake of 1.2 g/kg/d</u> Age: 77.30 ± 3.67 years Men: 35% Weight: 59.73 ± 9.98 kg BMI: 24.36 ± 3.04kg/m2 ASM: 15.53 ± 3.56 kg ASM height2: 6.29 ± 0.93 kg/m2 ASM/weight: 26.03 ± 3.89 %	Randomised, double-blind, placebo-controlled trial 12 week duration Randomised to 1 of 3 interventions: Protein intake of 0.8 g/kg/d Protein intake of 1.2 g/kg/d Protein intake of 1.5 g/kg/d All participants were asked to maintain usual diet and exercise. Participants were provided with 5 x 10 g packs containing placebo (9.6 g maltodextrin) or protein powders (9.3 g whey protein). <u>Baseline</u> <u>Protein intake of 0.8 g/kg/d</u> 1233.49 ± 296.31 kcal/d, carbohydrates 202.19 ± 49.36 g/d, total fat 26.61 ± 12.21 g/d, protein 48.36 ± 15.54 g/d, protein 0.84 ± 0.28 g/kg, MNA score 20.04 ± 2.40 <u>Protein intake of 1.2 g/kg/d</u> 1216.28 ± 290.01 kcal/d, carbohydrates 203.52 ± 47.97 g/d, total fat 26.55 ± 11.41 g/d, protein 45.18 ± 12.73 g/d, protein 0.77 ± 0.24 g/kg, MNA score 20.69 ± 2.11 <u>Protein intake of 1.5 g/kg/d</u> 1224.43 ± 263.03 kcal/d, carbohydrates 204.60 ± 39.02 g/d, total fat 23.38 ± 9.37 g/d,	Primary outcome: muscle mass as measured by dual-energy X-ray absorptiometry (DEXA). Secondary outcome measure was frailty. 1 screening visit and 3 visits at weeks 0 (baseline), 6, and 12. Cardiovascular Health study (CHS), frailty criteria, the Mini Nutritional Assessment (MNA), demographic and medical information, BMI, and 3-d dietary intake were measured during screening. Medical and clinical information, KLoSHA frailty criteria, the timed up-and-go (TUG) test, and hematologic and urinary measurements were assessed at weeks 0, 6 and 12. Muscle mass measured at weeks 0 and 12. 3-d dietary intake and adverse effects were assessed at weeks 2, 4, 6, 8, 10, and 12.	Post intervention ASM indicators were significantly (P<0.05) higher in the 1.5 g protein/kg/d then in the 0.8 g/kg/d group Protein intakes were higher in the 1.2 g/kg/d and 1.5 g/kg/d. Carbohydrate intake was higher in 0.8 g/kg/d protein group. There were no differences in fat intake between groups. Gait speed was significantly higher in the 1.5 g/kg/d group vs. 0.8 g/kg/d group. There was no difference between 0.8 g/kg/d and 1.2 g/kg/d. Only blood urea nitrogen was significantly increased by protein intake of 1.2 and 1.5 g/kg/d compared with protein intake of 0.8 g/kg/d at weeks 6 and 12 **Summary** **Protein intake high in leucine (whey) leads to improvements in muscle and physical performance in elderly subjects with some cardiovascular risk factors.** **Including a variety of plant and animal proteins (especially rich in leucine) may help preserve muscle mass in aging individuals**.

	ASM/BMI: 0.64 ± 0.14 ASM:fat ratio: 1.08 ± 0.57 CHS Score: 1.78 ± 0.89 Frailty status 20% Hypertension: 70% Hyperlipidaemia: 25 % Diabetes: 45 % Osteoporosis: 5 % Arthritis: 13 % MNA Score: 20.69 ± 2.11 <u>Protein intake of 1.5 g/kg/d</u> Age: 76.80 ± 3.70 years Men: 30% Weight: 56.28 ± 8.67 kg BMI: 23.65 ± 2.53 kg/m2 ASM: 14.19 ± 2.78 kg ASM height2: 5.93 ± 0.71 kg/m2 ASM/weight: 25.19 ± 2.74 % ASM/BMI: 0.60 ± 0.11 ASM:fat ratio: 0.98 ± 0.49 CHS Score: 1.93 ± 0.94 Frailty status 30% Hypertension: 58% Hyperlipidaemia: 20 % Diabetes: 23% Osteoporosis: 18% Arthritis: 13 % MNA Score: 20.89 ± 1.93 * appendicular skeletal muscle mass	protein 44.84 ± 11.58 g/d, protein 0.80 ± 0.21 g/kg, MNA score 20.89 ± 1.93 <u>12 weeks</u> <u>Protein intake of 0.8 g/kg/d</u> 1470.02 ± 343.40 kcal/d, carbohydrates 248.68 ± 54.30 g/d, total fat 24.43 ± 11.36 g/d, protein 52.28 ± 21.83 g/d, protein 0.90 ± 0.38 g/kg, MNA score 23.10 ± 2.76 <u>Protein intake of 1.2 g/kg/d</u> 1392.22 ± 277.22 kcal/d, carbohydrates 215.70 ± 39.19 g/d, total fat 22.74 ± 9.65 g/d, protein 69.91 ± 16.98 g/d, protein 1.18 ± 0.23 g/kg, MNA score 23.91 ± 2.51 <u>Protein intake of 1.5 g/kg/d</u> 1386.21 ± 272.23 kcal/d, carbohydrates 214.80 ± 44.42 g/d, total fat 19.05 ± 8.11 g/d, protein 76.36 ± 16.69 g/d, protein 1.37 ± 0.26 g/kg, MNA score 24.11 ± 2.25		
Seidelmann et al.[15]	Total participants: *n* 15,428 Q1 Participants: *n* 3086 Age: 53.7±5.7 years Men: 53% BMI: 28.0±0.1 kg/m2 Current smoker: 33% Former smoker: 35% Never smoker: 32% High blood pressure: 35% Diabetes: 13% Ethnicity: 76% white, 24% Black, <1% Asian, <1% Native American Highest exercise activity: 15%	Prospective cohort study and meta-analysis Participants taken from the Atherosclerosis Risk in Communities (ARIC) study. Participants based on quintiles of total energy from carbohydrate Q1: 1558 ± 11 kcal/d, carbohydrates 37 ± 5.7% total energy, animal fat 26.3 ± 0.1 % total energy, plant fat 12.5 ± 0.1 % total energy, animal protein 16.9 ± 0.1 % total energy, plant protein 3.9 ± 0.02 % total energy), dietary fibre 13.5 ± 0.1 g/d. Glycaemic index 71.8 ± 0.1, Glycaemic load 100.6 ± 1.1	Primary outcome was all-cause mortality Diet data collected using a 66-item semi-quantitative FFQ at visit 1 and visit 3. The Harvard Nutrient Database was used to derive nutrient intakes from the FFQ responses. Participants examined at follow-up visits, with the second visit occurring between 1990 and 1992, the third between 1993 and 1995, the fourth between 1996 and 1998, the fifth between 2011 and 2013, and the sixth between 2016 and 2017. Models adjusted for age, race and gender, ARIC test centre, total energy consumption, diabetes, cigarette smoking, physical activity, income level and education	Median follow-up of 25 years, with 6283 deaths occurring. Participants in lower carbohydrate quartiles had higher prevalence of diabetes, exercised less, had higher BMI, and smoking. Significant U-shaped association between carbohydrate intake and risk of mortality (P<0.0001). Intake of 50-55% energy had lowest risk but carbohydrate intakes of 30% energy had highest risk (HR 1.37; 95% CI: 1.16, 1.63). Risk was also increased in those consuming >65% energy from

	Q2 Participants: *n* 3086 Age: 54.3±5.7 years Men: 48% BMI: 27.9±0.1 kg/m2 Current smoker: 27% Former smoker: 34% Never smoker: 40% High blood pressure: 33% Diabetes: 13% Ethnicity: 75% white, 25% Black, <1% Asian, <1% Native American Highest exercise activity: 17% Q3 Participants: *n* 3085 Age: 54.3±5.8 years Men: 45% BMI: 27.6±0.1 kg/m2 Current smoker: 26% Former smoker: 32% Never smoker: 42% High blood pressure: 34% Diabetes: 11% Ethnicity: 73% white, 27% Black, <1% Asian, <1% Native American Highest exercise activity: 19% Q4 Participants: *n* 3086 Age: 54.3±5.8 years Men: 42% BMI: 27.6±0.1 kg/m2 Current smoker: 23% Former smoker: 31% Never smoker: 46% High blood pressure: 34% Diabetes: 11% Ethnicity: 71% white, 28% Black, <1% Asian, <1% Native American Highest exercise activity: 19% Q5 Participants: *n* 3085 Age: 54.3±5.8 years Men: 36% BMI: 27.4±0.1 kg/m2	Q2: 1655 ± 11 kcal/d, carbohydrates 44 ± 2.5% total energy, animal fat 22.4 ± 0.1 % total energy, plant fat 13.6 ± 0.1 % total energy, animal protein 14.8 ± 0.1 % total energy, plant protein 4.3 ± 0.02 % total energy), dietary fibre 16.5 ± 0.1 g/d, Glycaemic index 74.1 ± 0.1, Glycaemic load 134.6 ± 1.1 Q3: 1660 ± 11 kcal/d, carbohydrates 49 ± 2.2% total energy, animal fat 19.9 ± 0.1 % total energy, plant fat 13.6 ± 0.1 % total energy, animal protein 13.5 ± 0.1 % total energy, plant protein 4.5 ± 0.02 % total energy), dietary fibre 17.7 ± 0.1 g/d, Glycaemic index 74.9 ± 0.1, Glycaemic load 151.1 ± 1.1 Q4: 1646 ± 11 kcal/d, carbohydrates 53 ± 2.8% total energy, animal fat 17.6 ± 0.1 % total energy, plant fat 13.2 ± 0.1 % total energy, animal protein 12.3 ± 0.1 % total energy, plant protein 4.6 ± 0.02 % total energy), dietary fibre 18.7 ± 0.1 g/d, Glycaemic index 76.0 ± 0.1, Glycaemic load 166.8 ± 1.1 Q5: 1607 ± 11 kcal/d, carbohydrates 61 ± 6.3% total energy, animal fat 13.6 ± 0.1 % total energy, plant fat 13.6 ± 0.1 % total energy, animal protein 11.5 ± 0.1 % total energy, plant protein 4.8 ± 0.02 % total energy), dietary fibre 19.8 ± 0.1 g/d, Glycaemic index 76.7 ± 0.1, Glycaemic load 191.7 ± 1.1 Explored association between different sources of fat and protein using animal- and plant-based scores.	Updated meta analysis: Grouped data into 2 categories due to carbohydrate intake: 1) North American and European; and 2) Asian and Multinational studies. Mean Carbohydrate intake in group 1 approximately 50% total energy; mean carbohydrate intake in group 2 approximately 61%. Group 1 compared low-carbohydrate consumption with moderate carbohydrate consumption. Group 2 compared moderate carbohydrate consumption with high carbohydrate consumption	carbohydrate (HR 1.16; 95% CI: 1.02, 1.33). Updated meta-analysis including data from ARIC: Relationship between carbohydrate consumption and mortality was dependent on carbohydrate range used. Low carbohydrate diet was associated with a significantly increased risk of all-cause mortality vs. moderate carbohydrate diets (pooled HR 1.20; 95% CI: 1.09, 1.32; p<0.0001). High carbohydrate diet was associated with a significantly increased risk of all-cause mortality vs. moderate carbohydrate diets (pooled HR 1.23; 95% CI: 1.11, 1.36; p<0.0001). Plant-based LCD associated with higher average intake of vegetables but lower fruit intake. Animal-based lower carbohydrate diet was associated with lower average intake of both fruit and vegetables Plant-based LCD had higher average PUFA, and lower SFA when compared to the animal-based low carbohydrate diet. In ARIC and updated meta-analysis, increased, substitution of carbohydrate for animal protein was associated with increased all-cause mortality (HR 1.18; 95% CI: 1.08, 1.29; P<0.0001). Substitution of carbohydrate for plant protein and fat was associated with reduced all-cause mortality (HR 0.82; 95% CI: 0.78, 0.87; P<0.0001). **Summary** **There is a U-Shaped relationship between carbohydrate intake and mortality. Source of fat and protein**

	Current smoker: 22% Former smoker: 29% Never smoker: 48% High blood pressure: 37% Diabetes: 10% Ethnicity: 69% white, 30% Black, 1% Asian, <1% Native American Highest exercise activity: 20% Updated meta-analysis with results from ARIC and 2 other studies: Participants: *n* 432,179 8 studies in meta analysis Sample size for studies ranged from 9200-135,335 participants Majority of studies in MA excluded patients with CVD or diabetes			**modified this relationship, with LCDs containing more plant protein and fat being more beneficial than those containing more animal fat and protein.** **Of note this is note evidence for vegan diets, as some nutrients are present in animal products and not vegetables products ie. B12. This is specifically focussing on shifting balance**.
Li et al.[16]	Total participants: *n* 4098 2258 from Nurses' Health study and 1840 men from Health Professional Follow-Up study All free from CVD, cancer, stroke at baseline. All free from stroke at time of MI. Ethnicity not reported SBP and DBP not reported Plasma Glucose not reported <u>Women</u> Q1 Participants: *n* 407 Age at diagnosis: 65.1±8.4 years BMI: 25.8±5.4 kg/m2 Current smoker: 9% Former smoker: 55% Never smoker: 36% High blood pressure: 66% Diabetes: 13% Physical activity: 14.3±18.2 MET hrs/wk Elevated cholesterol: 75% Lipid modifying medication: 44% Aspirin use: 65% Q3	Prospective cohort design Participants taken from Nurses' Health Study the Health Professional Follow-Up Study Participants grouped into quintiles of adherence to low carbohydrate diet score <u>Women</u> Q1: Post-MI total LCDS: 3.5±2.0 Pre-MI total LCDS: 11.3±6.7 Post-MI plant-based LCDS: 6.3±2.4 Pre-MI plant-based LCDS: 12.0±5.4 Post-MI animal-based LCDS: 2.7±1.7 Pre-MI animal-based LCDS: 11.1±7.9 1581 ± 534 kcal/d, carbohydrates 64.4 ± 5.6 % total energy, SFA 6.9 ± 2.0% total energy, TFA 1.2 ± 0.6 % total energy, omega 3 0.6 ± 0.3 % total energy, animal fat 9.5 ± 3.4 % total energy, vegetable fat 12.3 ± 4.0 % total energy, animal protein 9.3 ± 2.7 % total energy, vegetable protein 6.0 ± 1.4 % total energy, cereal fibre 6.7 ± 3.3 g/d, alcohol 3.7 ± 7.5 g/d, chicken/turkey 0.3 ± 0.2 servings/d, total fish 0.2 ± 0.2 servings/d, total fruit 2.6 ± 1.3 servings/d, total vegetables 2.8 ± 1.3 servings/d, total red meat 0.8 ± 0.4	Primary outcomes were all-cause and cardiovascular mortality and their relationship to LCDs (animal or plant) Food intakes determined using validated FFQ every 4 years pre-MI and post-MI FFQ before death. Nutrient content was calculated from the Harvard University Food Composition Database and multiplied by the frequency of consumption. Participants divided into 11 strata for each macronutrient. Those in highest stratum were assigned scores of 10 for fat, 10 for protein, and 0 for carbohydrate. Score ranged from 0 (lowest fat and protein, and highest carbohydrate intake) to 30 (highest fat and protein, and lowest carbohydrate intake). <u>Higher scores mean great adherence to a specific type of LCD</u> MI was confirmed based on the World Health Organization's criteria. Covariates chosen a priori ad included medication use, medical history, and lifestyles factors that have been reported to be associated with MI risk Models adjusted for time since MI onset, age at diagnosis calendar year, total caloric intake physical activity, aspirin use, diabetes, high blood pressure, lipid-lowering medication use, alcohol consumption, currently married, body mass index, CABG, and pre-MI score.	During follow-up, 682 total and 336 CVD deaths for women, and 451 total and 222 CVD deaths for men. Median survival time was 8 years for women and 9 years for men Diabetes prevalence was higher in those with high LCDS In women, total LCDS was associated with increased all-cause mortality post-MI (HR 1.31; 95% CI: 0.99, 1.73; P_{trend}=0.02). Total LCDS was not significantly associated with all-cause mortality in men (HR 0.90; 95% CI 0.64, 1.27; P_{trend}=0.94). Combined, total LCDS was not significantly associated with all-cause mortality (HR 1.13; 95% CI: 0.91, 1.40; P_{trend}=0.27) Higher animal-based post-MI LCDS were associated with increased all-cause mortality in women (HR 1.33; 95% CI: 1.01, 1.77; P_{trend}=0.001) but not men (HR 1.27; 95% CI: 0.89, 1.81; P_{trend}=0.23). Combined higher animal based LCDS were associated with

	Participants: *n* 491 Age at diagnosis: 64.9±8.4 years BMI: 26.6±5.2 kg/m2 Current smoker: 9% Former smoker: 59% Never smoker: 32% High blood pressure: 69% Diabetes: 21% Physical activity: 14.7±16.9 MET hrs/wk Elevated cholesterol: 72% Lipid modifying medication: 52% Aspirin use: 62% Q5 Participants: *n* 424 Age at diagnosis: 64.4±8.6 years BMI: 28.2±5.9 kg/m2 Current smoker: 16% Former smoker: 57% Never smoker: 27% High blood pressure: 72% Diabetes: 36% Physical activity: 12.4±17.4 MET hrs/wk Elevated cholesterol: 78% Lipid modifying medication: 48% Aspirin use: 61% <u>Men</u> Q1 Participants: *n* 410 Age at diagnosis: 66.0±9.0 years BMI: 25.3±3.4 kg/m2 Current smoker: 12% Former smoker: 49% Never smoker: 39% High blood pressure: 54% Diabetes: 8% Physical activity: 35.6±34.0 MET hrs/wk Elevated cholesterol: 67% Lipid modifying medication: 51% Aspirin use: 84% Q3	servings/d, high-fat dairy 1.1 ± 0.9 servings/d, low-fat dairy 1.1 ± 0.8 servings/d Q3: Post-MI total LCDS: 13.4±1.1 Pre-MI total LCDS: 15.2±6.8 Post-MI plant-based LCDS: 13.9±0.8 Pre-MI plant-based LCDS: 14.6±5.2 Post-MI animal-based LCDS: 13.0±1.4 Pre-MI animal-based LCDS: 15.7±7.2 1628 ± 515 kcal/d, carbohydrates 53.9 ± 4.1 % total energy, SFA 9.0 ± 2.3% total energy, TFA 1.4 ± 0.6 % total energy, omega 3 0.7 ± 0.3 % total energy, animal fat 13.3 ± 4.0 % total energy, vegetable fat 14.5 ± 4.8 % total energy, animal protein 12.8 ± 3.3 % total energy, vegetable protein 5.8 ± 1.3 % total energy, cereal fibre 6.3 ± 2.9 g/d, alcohol 4.6 ± 9.3 g/d, chicken/turkey 0.4 ± 0.2 servings/d, total fish 0.3 ± 0.2 servings/d, total fruit 2.4 ± 1.2 servings/d, total vegetables 2.9 ± 1.2 servings/d, total red meat 1.0 ± 0.5 servings/d, high-fat dairy 1.2 ± 0.9 servings/d, low-fat dairy 1.1 ± 0.8 servings/d Q5: Post-MI total LCDS: 24.0±2.6 Pre-MI total LCDS: 19.3±6.9 Post-MI plant-based LCDS: 22.0±2.2 Pre-MI plant-based LCDS: 17.7±5.2 Post-MI animal-based LCDS: 25.5±2.5 Pre-MI animal-based LCDS: 19.8±7.3 1607 ± 536 kcal/d, carbohydrates 43.2 ± 5.7 % total energy, SFA 12.0 ± 2.5 % total energy, TFA 1.2 ± 0.7 % total energy, omega 3 0.9 ± 0.4 % total energy, animal fat 19.3 ± 5.4 % total energy, vegetable fat 17.0 ± 6.2 % total energy, animal protein 15.5 ± 3.8 % total energy, vegetable protein 5.2 ± 1.2 % total energy, cereal fibre 5.2 ± 2.7 g/d, alcohol 3.6 ± 7.2 g/d, chicken/turkey 0.4 ± 0.2 servings/d, total fish 0.3 ± 0.2 servings/d, total fruit 2.4 ± 1.2 servings/d, total vegetables 2.9 ± 1.2 servings/d, total red meat 1.1 ± 0.6 servings/d, high-fat dairy 1.4 ± 1.1 servings/d, low-fat dairy 0.9 ± 0.9 servings/d	For women, additional adjustments were made for postmenopausal hormone use status, and smoking. For men, additional adjustments were made for heart failure, LVEF, acute therapy during hospitalization (received either angioplasty or thrombolytics, or none), and smoking.	increased all-cause mortality (HR 1.33; 95% CI: 1.06, 1.65; P_{trend}=0.02) Higher plant-based post-MI LCDS were not associated with all-cause mortality in either men (HR 0.85; 95% CI: 0.61, 1.18; P_{trend}=0.28) or women (HR 1.04; 95% CI: 0.79, 1.37; P_{trend}=0.93) Higher animal-based post-MI LCDS were associated with increased cardiovascular mortality (Pooled HR 1.51; 95% CI: 1.09, 2.07; P_{trend}=0.02) Higher plant-based post-MI LCDS were not associated with increased cardiovascular mortality (Pooled HR 0.92; 95% CI: 0.68, 1.25; P_{trend}=0.59) In women, an increase in total LDCS from pre- to post-MI was associated with increased risk of all-cause mortality (HR 1.35; 95% CI: 0.99, 1.84; P_{trend}=0.01). A greater increase in animal-based LCDS was associated with higher all-cause mortality (HR 1.35; 95% CI: 0.99, 1.84; P_{trend}=0.0005) and cardiovascular mortality (HR 1.97; 95% CI: 1.29, 3.03; P_{trend}=0.0006). This relationship was not observed with plant-based LCDS Changes in LCDS in men were not associated with all-cause and CVD mortality. A greater increase in plant-based LCDS was not associated with increased mortality in either men or women. **Summary** **LCDs – especially based around animal products – are associated with increased all-cause and CVD mortality, especially in women. Low-carbohydrate plant-based diets are not associated with increased all-cause or CVD mortality. Low carb**

	Participants: *n* 382 Age at diagnosis: 66.1±9.1 years BMI: 26.61±3.7 kg/m2 Current smoker: 11% Former smoker: 52% Never smoker: 37% High blood pressure: 56% Diabetes: 17% Physical activity: 32.9±48.7 MET hrs/wk Elevated cholesterol: 64% Lipid modifying medication: 56% Aspirin use: 84% Q5 Participants: *n* 321 Age at diagnosis: 66.1±9.3 years BMI: 26.8±3.8 kg/m2 Current smoker: 16% Former smoker: 58% Never smoker: 26% High blood pressure: 47% Diabetes: 24% Physical activity: 32.1±38.5 MET hrs/wk Elevated cholesterol: 65% Lipid modifying medication: 47% Aspirin use: 79%	 <u>Men</u> Q1: Post-MI total LCDS: 4.1±2.2 Pre-MI total LCDS: 12.2±7.3 Post-MI plant-based LCDS: 6.9±2.2 Pre-MI plant-based LCDS: 12.2±5.0 Post-MI animal-based LCDS: 2.4±1.7 Pre-MI animal-based LCDS: 11.2±7.9 2006 ± 632 kcal/d, carbohydrates 64.1 ± 6.1 % total energy, SFA 6.2 ± 2.0 % total energy, TFA 1.2 ± 0.7 % total energy, omega 3 0.6 ± 0.3 % total energy, animal fat 8.0 ± 3.2 % total energy, vegetable fat 13.1 ± 4.3 % total energy, animal protein 9.0 ± 2.7 % total energy, vegetable protein 6.5 ± 1.6 % total energy, cereal fibre 9.5 ± 4.1 g/d, alcohol 8.1 ± 12.3 g/d, chicken/turkey 0.4 ± 0.2 servings/d, total fish 0.3 ± 0.2 servings/d, total fruit 3.2 ± 1.5 servings/d, total vegetables 3.5 ± 1.6 servings/d, total red meat 0.7 ± 0.5 servings/d, high-fat dairy 0.9 ± 0.8 servings/d, low-fat dairy 1.1 ± 0.8 servings/d Q3 Post-MI total LCDS: 12.4±1.1 Pre-MI total LCDS: 15.4±6.3 Post-MI plant-based LCDS: 14.0±0.8 Pre-MI plant-based LCDS: 15.2±4.9 Post-MI animal-based LCDS: 13.0±1.4 Pre-MI animal-based LCDS: 15.3±7.0 1880 ± 595 kcal/d, carbohydrates 53.8 ± 4.2 % total energy, SFA 8.2 ± 2.2 % total energy, TFA 1.4 ± 0.6 % total energy, omega 3 0.8 ± 0.4 % total energy, animal fat 12.1 ± 3.6 % total energy, vegetable fat 14.6 ± 4.9 % total energy, animal protein 12.5 ± 3.3 % total energy, vegetable protein 6.0 ± 1.3 % total energy, cereal fibre 8.5 ± 3.7 g/d, alcohol 9.4 ± 12.8 g/d, chicken/turkey 0.4 ± 0.2 servings/d, total fish 0.4 ± 0.3 servings/d, total fruit 2.6 ± 1.3 servings/d, total vegetables 3.3 ± 1.4 servings/d, total red meat 1.0 ± 0.5 servings/d, high-fat dairy 1.1 ± 1.0 servings/d, low-fat dairy 1.3 ± 1.0 servings/d		**can be interpreted differently, and care should be given to exploring if they are based around animal or plant products**

		Q5 Post-MI total LCDS: 24.3±2.7 Pre-MI total LCDS: 19.9±6.3 Post-MI plant-based LCDS: 21.8±2.6 Pre-MI plant-based LCDS: 17.9±5.3 Post-MI animal-based LCDS: 24.8±2.8 Pre-MI animal-based LCDS: 20.3±6.7 1927 ± 658 kcal/d, carbohydrates 41.1 ± 6.2 % total energy, SFA 11.7 ± 2.7 % total energy, TFA 1.8 ± 0.7 % total energy, omega 3 0.8 ± 0.6 % total energy, animal fat 19.5 ± 6.0 % total energy, vegetable fat 17.2 ± 6.1 % total energy, animal protein 15.2 ± 3.7 % total energy, vegetable protein 5.2 ± 1.4 % total energy, cereal fibre 6.0 ± 2.5 g/d, alcohol 8.9 ± 11.4 g/d, chicken/turkey 0.4 ± 0.3 servings/d, total fish 0.3 ± 0.2 servings/d, total fruit 2.0 ± 1.2 servings/d, total vegetables 3.0 ± 1.4 servings/d, total red meat 1.5 ± 0.8 servings/d, high-fat dairy 1.4 ± 1.3 servings/d, low-fat dairy 1.1 ± 1.0 servings/d		
Li et al.[17]	Total participants: *n* 4098 2258 from Nurses' Health study (NHS) and 1840 men from Health Professional Follow-Up study (HPFS) All free from CVD, cancer, stroke at baseline. All free from stroke at time of MI. Ethnicity not reported SBP and DBP not reported Plasma Glucose not reported <u>Women</u> Q1 Participants: *n* 433 Age at diagnosis: 64.5±8.8 years BMI: 26.3±5.4 kg/m2 Current smoker: 24% Former smoker: 51% Never smoker: 25% High blood pressure: 67% Diabetes: 19% Physical activity: 9.4±13.5 MET hrs/wk Elevated cholesterol: 71% Lipid modifying medication: 42%	Prospective cohort design Participants taken from Nurses' Health Study the Health Professional Follow-Up Study Grouped on quintiles of fibre intake (g/d) Women Q1 Post-MI fibre intake: 12.4±2.0 g/d Pre-MI fibre intake: 14.0±4.6 g/d 1619 ± 538 kcal/d, SFA 11.1 ± 3.2 % total energy, TFA 1.8 ± 0.8 % total energy, omega 3 0.7 ± 0.3 % total energy, alcohol 6.0 ± 12.8 g/d, cereal fibre 4.0 ± 1.7 g/d, fruit fibre 1.3 ± 0.6 g/d, legume fibre 0.2 ± 0.1 g/d Q3 Post-MI fibre intake: 19.2±0.8 g/d Pre-MI fibre intake: 17.5±4.6 g/d 1637 ± 526 kcal/d, SFA 9.2 ± 2.3 % total energy, TFA 1.5 ± 0.5 % total energy, omega 3 0.7 ± 0.3 % total energy, g/d, alcohol 4.3 ± 9.1 g/d, cereal fibre 5.9 ± 2.2 g/d, fruit fibre 4.0 ± 0.64 g/d, legume fibre 1.0 ± 0.1 g/d	Primary outcomes of all-cause and cardiovascular mortality MI was confirmed according to symptoms plus either diagnostic electrocardiographic changes or increased levels of cardiac enzymes, including cardiac specific troponin Diet intakes assessed using a validated FFQ every 4 years from 1976-2006 for NHS and from 1986-2006 for HPFS. Covariates chosen a priori and included medication use, medical history, and lifestyles factors. In HPFS, also considered clinical characteristics such as ST elevation MI (Y/N), site of MI, type or revascularisation, LVEF, initial creatinine levels, and HF during hospital stay (Y/N) Models adjusted for time since MI onset, age at diagnosis, calendar year. total caloric intake, physical activity, aspirin use, diabetes, high blood pressure, use of lipid lowering drugs, alcohol consumption, SFA intake, n3 fatty acid intake, TFA intake, married, BMI, CABG, folate intake, and pre-MI intake.	Median follow-up post MI was 8.7 years for women and 9.0 years for me. 682 total and 336 cardiovascular deaths for women, and 451 total and 222 cardiovascular deaths for men. In basic models (adjusted for age and time since MI) higher post-MI fibre intake was associated with lower all-cause mortality in both men and women (HR 0.63; 95% CI: 0.47, 0.86; Ptrend=0.0008, and HR 0.50; 95% CI: 0.39, 0.64; Ptrend=<0.0001, respectively). Adjustment for lifestyle characteristics attenuated these associations although combined HR showed association (HR 0.75; 95% CI: 0.58, 0.97; P_{trend}=0.03). A similar relationship was observed between post-MI fibre intake and cardiovascular mortality, with addition of lifestyle factors attenuating any significant association.

	Aspirin use: 61% Q3 Participants: *n* 437 Age at diagnosis: 64.9±8.5 years BMI: 27.6±6.2 kg/m2 Current smoker: 9% Former smoker: 61% Never smoker: 30% High blood pressure: 74% Diabetes: 27% Physical activity: 13.4±18.4 MET hrs/wk Elevated cholesterol: 80% Lipid modifying medication: 50% Aspirin use: 62% Q5 Participants: *n* 457 Age at diagnosis: 65.1±8.2 years BMI: 26.3±5.2 kg/m2 Current smoker: 4% Former smoker: 58% Never smoker: 38% High blood pressure: 70% Diabetes: 24% Physical activity: 20.1±20.8 MET hrs/wk Elevated cholesterol: 79% Lipid modifying medication: 55% Aspirin use: 64% <u>Men</u> Q1 Participants: *n* 367 Age at diagnosis: 65.8±9.5 years BMI: 26.4±3.7 kg/m2 Current smoker: 9% Former smoker: 54% Never smoker: 28% High blood pressure: 59% Diabetes: 13% Physical activity: 25.9±33.6 MET hrs/wk Elevated cholesterol: 68% Lipid modifying medication: 48% Aspirin use: 78%	Q5 Post-MI fibre intake: 28.7±4.4 g/d Pre-MI fibre intake: 22.2±6.6 g/d 1592 ± 518 kcal/d, SFA 7.0 ± 2.1 % total energy, TFA 1.0 ± 0.5 % total energy, omega 3 0.8 ± 0.4 % total energy, alcohol 2.9 ± 5.4 g/d, cereal fibre 8.4 ± 4.0 g/d, fruit fibre 8.7 ± 2.6 g/d, legume fibre 3.4 ± 1.6 g/d <u>Men</u> Q1 Post-MI fibre intake: 16.0±2.4 g/d Pre-MI fibre intake: 17.3±4.9 g/d 1878 ± 620 kcal/d, SFA 10.8 ± 3.0 % total energy, TFA 1.8 ± 0.8 % total energy, omega 3 0.7 ± 0.5 % total energy, alcohol 13.4 ± 17.1 g/d, cereal fibre 5.3 ± 2.1 g/d, fruit fibre 1.8 ± 0.7 g/d, legume fibre 0.4 ± 0.3 g/d Q3 Post-MI fibre intake: 24.4±1.0 g/d Pre-MI fibre intake: 22.3±5.6 g/d 1946 ± 646 kcal/d, SFA 8.8 ± 2.4 % total energy, TFA 1.5 ± 0.6 % total energy, omega 3 0.7 ± 0.3 % total energy, alcohol 9.1 ± 12.3 g/d, cereal fibre 7.8 ± 2.8 g/d, fruit fibre 5.1 ± 0.5 g/d, legume fibre 1.7 ± 0.2 g/d Q5 Post-MI fibre intake: 37.0±5.8 g/d Pre-MI fibre intake: 27.8±8.3 g/d 1925 ± 621 kcal/d, SFA 6.1 ± 2.0 % total energy, TFA 0.9 ± 0.5 % total energy, omega 3 0.9 ± 0.5 % total energy, alcohol 6.3 ± 10.3 g/d, cereal fibre 11.2 ± 4.8 g/d, fruit fibre 11.4 ± 3.5 g/d, legume fibre 5.3 ± 2.1 g/d	For women, additional adjustments were made for postmenopausal hormone use status, and smoking For men, additional adjustments were made for heart failure, LVEF, acute therapy during hospitalization (received either angioplasty or thrombolytics, or none), and smoking.	Pooled HR of 0.85 (95% CI: 0.74, 0.97) for all-cause mortality for a 10 g/d increase in intake. Only cereal fibre was inversely associated with lower all-cause and cardiovascular mortality (pooled HR 0.73; 95% CI: 0.58, 0.91 and pooled HR 0.72; 95% CI: 0.52, 0.99, respectively). No association was observed for fruit or legume fibre. Pre-MI fibre was not associated with post-MI all-cause mortality (pooled HR 1.17; 95% CI: 0.92, 1.48) and cardiovascular mortality (pooled HR 1.10; 95% CI 0.77, 1.55). In fully adjusted models a greater increase in fibre intake from pre to post-MI was associated with significantly lower all-cause mortality in women (HR 0.64; 95% CI 0.48, 0.86; P_{trend}=0.005), but not men. The pooled HR was 0.69 (95% CI: 0.55, 0.87; P_{trend}=0.002) suggesting increasing fibre intake from pre- to post-MI was beneficial. In both men and women, an increase in fibre intake from pre- to post MI was associated with lower cardiovascular mortality (HR 0.65; 95% CI 0.42, 0.99; P_{trend}=0.09 and 0.65; 95% CI: 0.39,1.08; P_{trend}=0.04) **Summary** **Overall this study showed a modest association between intake of fibre post MI lower all-cause and cardiovascular mortality, and that in those individuals who increased their fibre intake the most saw greater benefit. This relationship appeared to be driven by cereal fibre.**

	Q3 Participants: *n* 373 Age at diagnosis: 66.1±8.9 years BMI: 26.1±3.6 kg/m2 Current smoker: 4% Former smoker: 52% Never smoker: 36% High blood pressure: 58% Diabetes: 13% Physical activity: 37.0±54.0 MET hrs/wk Elevated cholesterol: 63% Lipid modifying medication: 57% Aspirin use: 82% Q5 Participants: *n* 358 Age at diagnosis: 66.1±8.9 years BMI: 25.6±3.7 kg/m2 Current smoker: 1% Former smoker: 47% Never smoker: 41% High blood pressure: 50% Diabetes: 15% Physical activity: 40.4±35.0 MET hrs/wk Elevated cholesterol: 64% Lipid modifying medication: 50% Aspirin use: 81%			
Zhang et al.[18]	Potentially relevant records: 343 236 articles excluded based on title Full texts assessed for eligibility: 109 Excluded 92 due to duplicates, 1 not published, 28 not relevant outcomes, 6 comments/editorials, 4 review/meta analysis Articles in final meta-analysis: 17 (19 prospective cohort studies) Total number of participants in analysis: 1,041,962 6 studies reported whole grain, 11 studies reported whole grain foods.	Meta-analysis of prospective cohort studies examining whole grain foods or diets on total mortality, cardiovascular mortality, and cancer mortality, and cardiovascular risk factors in healthy people or those with cardiovascular disease Articles sourced from Pubmed and Web of Science till January 2016 Quality of evidence was assessed using Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). Publication bias assessed using Begg's Test Inclusion criteria were:	Primary outcomes were all-cause mortality, CVD mortality, and cancer mortality Additional factors extracted included participants' age and sex, definition of whole grain or whole grain products, methods for whole grain assessment, confounders adjusted for in the analysis, whole grain intake in each category, type of intake (whole grain products or whole grain), RR and 95% CIs in each category. Data on dietary changes or BMI not extracted.	For the outcome of total mortality there were 661,752and 84,646 deaths. 9 studies reported on total mortality. Pooled RR comparing highest and lowest categories of intake was 0.84 (95% CI: 0.81, 0.88). Subgroup analysis suggested the inverse association between whole grain and mortality was stronger in women (RR 0.85; 95% CI: 0.81, 0.89) than men (RR 0.90; 95% CI: 0.85, 0.95), and in studies with a follow-up of 15-20 years (RR 0.75; 95% CI: 0.67, 0.84). Each 28 g/d serving of wholegrain associated with 9% reduction in in risk

	11 studies from America, 7 from Europe, and 1 from the Mediterranean area. All used FFQ for assessing dietary intake	Studies must be prospective cohort studies, report effect on risk of all-cause and/or cause-specific mortality, report RR, HR and 95% CI.		of all-cause mortality (pooled RR 0.91; 95% CI: 0.90, 0.93). For the outcome of CVD mortality, there were 595,585 participants and 23,482 deaths. 8 studies reported on cardiovascular mortality. Pooled RR comparing highest and lowest categories of intake was 0.83 (95% CI: 0.80, 0.87). Each 28 g/d serving of wholegrain associated with 14% reduction in in risk of cardiovascular mortality (pooled RR 0.86 95% CI: 0.83, 0.89). **Summary** **Data form prospective cohort studies suggest increased wholegrain consumption is associated with lower all-cause and CVD mortality.**
Kelly et al.[19]	Potentially relevant records: 15,283 After duplicates: 11,104 Full-texts assessed for eligibility: 414 Excluded 401 due to inappropriate articles (not wholegrain, not RCT, intervention < 12 weeks, not relevant comparison, macronutrient intake not reported, not adults, ongoing studies) Articles in final meta-analysis: 9 All studies were parallel RCTs Total number of participants in analysis: 1414 Interventions included oats (n=1), range of foods based on wheat (n=5), mixture of rye and wheat (n-1), whole grain brown rice (n=1), and whole grain wheat and oats (n=1). In 7 studies the control diet was described as refined. 1 study described the control diet as usual and 1 described control as white rice.	Meta-analysis of RCTs examining wholegrain* foods or diets on total mortality, cardiovascular events, and cardiovascular risk factors in healthy people or those with cardiovascular disease Articles sourced from CENTRAL (2016), MEDLINE (1946-August 2016), Embase (1980-week 35 2016), CINHAL PLUS (1937-August 2016), ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) Quality of evidence was assessed using GRADE. Study bias assessed using Cochrane 'Risk of Bias' tool Inclusion criteria were: Studies must be RCTs, including cross-over and parallel-group designs. Study duration needed to be at least 12 weeks. Participants ≥18 years, had raised lipids, BP, were overweight or obese, or had MetS or DM.	Primary outcomes were total cardiovascular mortality, Cardiovascular events (e.g. fatal and non-fatal myocardial infarction, unstable angina, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, stroke). Secondary outcomes were blood lipids, blood pressure, quality of life, and adverse events. Considered confounding variables such as bodyweight and dietary fibre	Substantial variation in definition of "wholegrain" No studies reported effect of whole grain on total cardiovascular mortality or cardiovascular events 8 studies reported total cholesterol with data from 7 being analysed. Pooled analysis (722 participants) showed no effect on total-cholesterol (MD 0.07; 95% CI: -0.07, 0.21). 1 study reported medians and showed no difference in TC between intervention and control. 1 study could not be combined due to reporting of results as % change rather than absolute values. In this study, TC decreased by 5.4% in the intervention vs. -2.9% in the control. 9 studies reported LDL-C, with data from 7 being summarised. Pooled analysis (770 participants) showed no effect on LDL-C (MD 0.06; 95% CI: -0.05, 0.16). 1 study reported medians and showed no difference in LDL-C between intervention and control. 1

	3 studies included overweight or obese participants, 2 included participants with MetS, 1 included participants with risk factors for MetS, 1 included participants with a BMI 18.5-35 kg/m2 or signs of MetS or hypercholesterolaemia, 1 included participants with MetS or DM Foods were provided in 8/9 studies. 1 study gave participants information regarding whole grain foods	Excluded studies that did not meet inclusion criteria, or listed diabetes or changes in risk factors (IGT, IR, glucose or insulin outcomes, weight, BMI, and anthropometric outcomes) if they did not also measure lipids or blood pressure. *wholegrain defined by authors as foods based on milled wholegrains i.e. wholemeal of oatmeal		study could not be combined due to reporting of results as % change rather than absolute values. In this study, LDL-C decreased by 8.7% in the intervention vs. 4.3% in the control. 8 studies reported HDL-C, with data from 7 being summarised. Pooled analysis (772 participants) showed no effect on HDL-C (MD -0.02; 95% CI: -0.05, 0.01 8 studies reported TAG, with data from 7 being summarised. Pooled analysis (771 participants) showed no effect (MD 0.03; 95% CI: -0.08, 0.13). 8 studies reported SBP, with data from 7 being summarised. Pooled analysis (768 participants) showed no effect (MD 0.04; 95% CI: -1.67, 1.75). 8 studies reported DBP, with data from 7 being summarised. Pooled analysis (768 participants) showed no effect (MD 0.16; 95% CI: -0.89, 1.21). 2 studies reported adverse events. 1 study showed similar events between intervention and control and included RTI, sinusitis, and pharyngitis). Events considered to relate to the intervention included nausea (2/77), flatulence (2/77). No studies reported QoL **Summary** **Combined RCT data does not support a clear role for wholegrains in reducing CV risk factors, whereas observation data does. Interpretation of this is that single changes to consume more wholegrains needs to be as part of a whole dietary change.**
Hooper et al.[20]	Potentially relevant records: 1459 Excluded 1327 records	Meta-analysis of RCTs examining effect of reducing SFA intake and replacing it with	Primary outcomes were all-cause mortality, cardiovascular mortality, and combined CVD events	There was no clear effect of reducing SFA compared to usual or control diets

	Full-texts assessed for eligibility: 132 Excluded 127 as did not meet inclusion criteria 5 potential RCTs with authors contacted 5 excluded (following further data from 4 authors and no reply from 1). No new studies included 48 RCTs in original 2012 meta analysis Excluded 33 15 RCTs eligible Articles in final meta analysis: 15 (17 intervention arms) Total number of participants in analysis: 58,509 6 studies included only people at high risk of CVD, 4 included participants at moderate risk, and 5 at low risk. 7 studies included only men, 3 included only women, and 5 both men and women Trial duration ranged from 2 to >8 years. Interventions varied. 16 intervention arms included advice to alter intake, 4 arms provided supplements, and 1 provided all food.	carbohydrate, PUFA or MUFA and/or protein on mortality and cardiovascular morbidity Articles sourced from CENTRAL (March 2014), MEDLINE (February 2014) and Embase (to 2014). Checked trials in systematic reviews. Quality of evidence was assessed using GRADE. Study bias assessed using Cochrane 'Risk of Bias' tool Inclusion criteria were: RCTs of at least 24 months duration. Adults aged over 18 years of age, healthy or with comorbidities (previous cancer, CVD, diabetes), using or not using lipid-lowering medication The intervention had to be dietary advice, supplementation of fats, oils or modified or low-fat foods, or a provided diet, and the control group usual diet, placebo or a control diet. Excluded studies that did not meet inclusion criteria, those with participants who were acutely ill, or where allocation was not truly randomised	(cardiovascular deaths, cardiovascular morbidity (non-fatal myocardial infarction, angina, stroke, heart failure, peripheral vascular events, atrial fibrillation) and unplanned cardiovascular interventions (coronary artery bypass surgery or angioplasty). Secondary outcomes included CHD mortality, CHD events, MI, stroke, T2 diabetes incidence, lipids, body weight, BMI, blood pressure, and QoL	on total mortality (55,858 participants, RR 0.97; 95% CI: 0.90, 1.05). Subgrouping did not suggest any additional effects, nor were effects seen when replacement of SFA was considered. Reducing SFA had no clear effect on reducing CV mortality when compared with usual diets (53,421 participants, RR 0.95; 95% CI: 0.80, 1.12). Subgrouping did not suggest important effects of reduced SFA on CV mortality, expect when baseline SFA was >18% total energy (RR 0.70; 95% CI: 0.51, 0.96) or when the reduction in SFA was >8% total energy (RR 0.70; 95% CI: 0.51, 0.96). Decreasing SFA reduced CV events when compared with usual diets (53,300 participants, RR 0.83; 95% CI: 0.72, 0.96). Heterogeneity was observed in students examining this outcome. Subgroups suggested replacing SFA with PUFA had the greatest effect (RR 0.73; 95% CI: 0.58, 0.92), with no clear benefit for replacing SFA with MUFA, carbohydrate, or protein. Those studies which reduced TC by at least 0.2 mmol/L reduced CV events by 26% (RR 0.74; 95% CI: 0.59, 0.92) Reducing SFA had a marginal effect on MI (53,167 participants, RR 0.90; 95% CI: 0.80, 1.01). Subgrouping suggested reduction in MI in studies of men only (but not women) and in studies that reduced serum total cholesterol by at least 0.2 mmol/L, but not in other subgroups Reducing SFA had no clear effect on stroke when compared with usual diets (50,952 participants, RR 1.00; 95% CI: 0.89, 1.12).

				Reducing SFA did not suggest any benefit on CHD mortality when compared to usual diets (53,159 participants, RR 0.98; 95% CI: 0.84, 1.15) Reducing SFA may decreased the risk of CHD events (53,199 participants, RR 0.87; 95% CI: 0.74, 1.03). Heterogeneity was high between studies, and partly explained by the degree of SFA at baseline and the level of cholesterol lower achieved There was no clear benefit of reducing SFA on the diagnosis of diabetes (48,835 participants, RR 0.96; 95% CI: 0.90, 1.02). Compared with usual diet, reducing SFA decreased TC (7115 participants, MD -0.24 mmol/L; 95% CI: -0.36, -0.13, P_{effect} 0.0001) and LDL-C (3291 participants, MD -0.19 mmol/L; 95% CI: -0.33, -0.05, P_{effect} 0.006). Decreasing SFA had no clear effect on HDL-C (5174 participants, MD -0.01 mmol/L, 95% CI: -0.02 to 0.01, P_{effect} 0.21) or TAG (3845 participants, MD -0.08 mmol/L; 95% CI: -0.21, 0.04, P_{effect} 0.20). There was no clear effect of SFA on TC/HDL-C ratio (2985 participants, MD -0.10; 95% CI: -0.33, 0.13, P_{effect} 0.40), LDL-C/HDL-C ratio (50 participants, MD -0.36; 95% CI: -0.92, 0.20), Lp(a) (28,820 participants, MD 0.00; 95% CI: -0.00, 0.00, P_{effect} 1.00), or HOMA (2832 participants, MD -0.00; 95% CI: -0.04, 0.04, P_{effect} 1.00). Reducing SFA intake decreased glucose when compared to usual diets (249 participants, MD -1.69 mmol/L; 95% CI: -2.55, -0.82, P_{effect} 0.0001).

				Reducing SFA intake resulted in small reductions in body weight (4541 participants, MD -1.97 kg; 95% CI: -3.67, -0.27, and BMI (5553 participants, MD -0.50; 95% CI: -0.82, -0.19) **Summary** **This study suggests reducing SFA has no effect on total mortality. Reducing SFA and replacing with PUFA had the greatest effect on CV events. Replacing with protein, MUFA or carbohydrate did not have any effect. Some of these effects are mediated by the level of SFA consumed initially, and the level of cholesterol reduction achieved. The ideal type of unsaturated fat to replace SFA with is unclear**.
Zhuang et al.[21]	Total participants: *n* 617,119 567,169 complete questionnaires satisfactorily. Excluded duplicates, individuals moving out of state, and those who died before study entry Final sample: *n* 521,120 participants for analysis <u>Quintile of Saturated Fat Intake</u> <u>Q1</u> Age: 63.2 years Male: 55.2% Race: 89.6% White, 4.3% Black, 2.2% Hispanic, 2.2% Asian BMI: 25.1 kg/m2 Current smoker: 6.7% Physical activity (>5 times/wk): 27.4% History of Hypercholesterolaemia: 22.6% History of hypertension: 24.3% Heart Disease: 18.8% Stroke: 2.1% Cancer: 8.9% Diabetes: 6.1% Fair or poor health: 10.6% Daily aspirin use: 18.7%	Prospective cohort design. Participants taken from National Institutes of Health-American Association of Retired Persons Diet and Health Study Participants enrolled between1995-1996 with 16 years follow up Grouped on quintiles of dietary fat intake <u>Quintile of Saturated Fat Intake</u> Q1: 1545.1 kcal/d, total fat 20.5 % total energy, SFA 5.8 % total energy, MUFA 7.5 % total energy, PUFA 5.2 % total energy, TFA 1.3 % total energy, total protein 14.7 % total energy, omega-3 0.6 % total energy, ALA 0.5 % total energy, marine omega-3 0.04 % total energy, omega-6 4.6 % total energy, LA 4.5 % total energy, AA 0.04 % total energy, omega-6/omega 3 ratio 8.2, alcohol 2.6 g/d Q3: 1683.4 kcal/d, total fat 30.6 % total energy, SFA 9.2 % total energy, MUFA 11.7 % total energy, PUFA 4 7.1 % total energy, TFA 2.1 % total energy, total protein 15.5 % total energy, omega-3 0.7 % total energy, ALA 0.6 % total energy, marine omega-3 0.04 % total energy, omega-6 6.4 % total energy, LA 6.3	Primary outcomes were total mortality and cardiovascular mortality Diet measured at baseline using validated 124 item FFQ + Diet History Questionnaire. Total energy intake was also calculated based on the Continuing Survey of Food Intakes by Individual. Sub study 2 non-consecutive 24 hr recall baseline (validation) Models adjusted age and sex, race, marital status, BMI, education, household income, smoking status, physical activity, alcohol consumption, history of hypertension, history of hypercholesterolaemia, perceived health condition, history of heart disease, stroke, diabetes, cancer at baseline, multivitamin use, aspirin use, hormones for women, total energy and energy from protein and other fatty acids. Evaluated effect of replacing SFA with other types of fat Mortality determined from annual linkage to Social Security administration Death Master File >99% follow-up rate for mortality Cause of death was determined by annual linkage to National Death Index Plus classified into 22 categories-9/10th ICD-9 and 10	During a follow-up of 16 years (7,307,097 person-years), 129,328 deaths (85,037 in the men and 44, 291 in the women) were documented Dietary intakes of SFAs and TFAs positively associated with total mortality in multivariable fully adjusted models. When substituting for carbohydrates, those in the highest quintile of SFA intake had the highest rate of total mortality when compared against the lowest quintile (HR 1.29; 95% CI: 1.25, 1.33; P_{trend}<0.0001) PUFA intake was inversely associated with total mortality (HR 0.93; 95% CI: 0.91, 0.95; P_{trend}<0.0001) Each 1 SD increment of energy as PUFA related to a 2% lower total mortality. Animal MUFA was correlated with higher total mortality (HR 1.09; 95% CI: 1.06, 1.13; P_{trend}<0.0001) whereas

	Q3 Age: 62.8 years Male: 59.3% Race: 91.6% White, 3.9% Black, 1.9% Hispanic, 1.1 % Asian BMI: 26.6 kg/m2 Current smoker: 10.4% Physical activity (>5 times/wk): 17.6% History of Hypercholesterolaemia: 26.1% History of hypertension: 23.8% Heart Disease: 13.3% Stroke: 2.0% Cancer: 9.0% Diabetes: 9.4% Fair or poor health: 12.7% Daily aspirin use: 14.4% Q5 Age: 62.6 Male: 61.5% Race: 93.9% White, 2.7% Black, 1.3% Hispanic, 0.5% Asian BMI: 27.1 kg/m2 Current smoker: 19.7% Physical activity (>5 times/wk): 14.1% History of Hypercholesterolaemia: 29.7% History of hypertension: 21.6% Heart Disease: 10.8% Stroke: 2.2% Cancer: 9.2% Diabetes: 11.5% Fair or poor health: 15.9% Daily aspirin use: 12.0% Quintile of PUFA Intake Q1 Age: 62.8 years Male: 61.5% Race: 90.8% White, 3.2% Black, 2.6% Hispanic, 1.6% Asian BMI: 25.8 kg/m2 Current smoker: 10.6% Physical activity (>5 times/wk): 23.1%	% total energy, AA 0.05 % total energy, omega-6/omega 3 ratio 9.0, alcohol 1.9 g/d Q5: 1874.5 kcal/d, total fat 38.6 % total energy, SFA 13.2 % total energy, MUFA 14.4 % total energy, PUFA 7.5% total energy, TFA 2.4 % total energy, total protein 15.5 % total energy, omega-3 0.8 % total energy, ALA 0.7 % total energy, marine omega-3 0.04 % total energy, omega-6 6.7 % total energy, LA 6.6 % total energy, AA 0.05 % total energy, omega-6/omega 3 ratio 8.4, alcohol 1.3 g/d Quintile of PUFA Intake Q1: 1638.8 kcal/d, total fat 21.2 % total energy, SFA 6.9 % total energy, MUFA 7.9 % total energy, PUFA 4.5 % total energy, TFA 1.4 % total energy, total protein 14.9 % total energy, omega-3 0.5 % total energy, ALA 0.4 % total energy, marine omega-3 0.03 % total energy, omega-6 3.9 % total energy, LA 3.9 % total energy, AA 0.04 % total energy, omega-6/omega 3 ratio 7.7, alcohol 2.9 g/d Q3: 1704.8 kcal/d, total fat 30.2 % total energy, SFA 9.3 % total energy, MUFA 11.5 % total energy, PUFA 6.8 % total energy, TFA 2.1 % total energy, total protein 15.7 % total energy, omega-3 0.7 % total energy, ALA 0.6 % total energy, marine omega-3 0.04 % total energy, omega-6 6.0 % total energy, LA 6.0 % total energy, AA 0.05 % total energy, omega-6/omega 3 ratio 8.80, alcohol 1.9 g/d Q5: 1697.1 kcal/d, total fat 38.0 % total energy, SFA 10.5 % total energy, MUFA 14.3 % total energy, PUFA 9.8 % total energy, TFA 2.5 % total energy, total protein 14.9 % total energy, omega-3 1.0 % total energy, ALA 0.9 % total energy, marine omega-3 0.04 % total energy, omega-6 8.8 % total energy, LA 8.8 % total energy, AA 0.05 % total energy, omega-6/omega 3 ratio 9.3, alcohol 1.2 g/d	Sensitivity analysis excluding existing CVD at baseline done to exclude reverse causality observed similar results.	plant MUFA was inversely associated with total mortality (HR 0.94; 95% CI: 0.91, 0.97; P_{trend}<0.0004) Comparing highest vs. lowest quintiles of intake, increased SFA was associated with increased CVD (HR 1.27; 95% CI: 1.21, 1.34; P_{trend}<0.0001) Each 1 SD increment in SFA was related to 7% higher CVD mortality. Total MUFA was not significantly associated CVD, although animal MUFA was inversely associated with CVD mortality (HR 1.09; 95% CI: 1.03, 1.16; P_{trend}=0.0015). Plant MUFA was associated with lower CVD mortality (HR 0.94; 95% CI: 0.89, 0.99; P_{trend}=0.015). Comparing highest vs. lowest quintiles of intake, increased TFA was associated with increased CVD (HR 1.06; 95% CI: 1.03, 1.16; P_{trend}<0.0001) Comparing highest vs. lowest quintiles of intake, increased PUFA intake was associated with decreased CVD mortality (HR 0.94; 95% CI: 0.90, 0.98; P_{trend}=0.0074) Total omega-3 intake was not associated with CVD mortality. Higher intakes of omega-3 were associated with lower CVD mortality (HR 0.90; 95% CI: 0.87, 0.94; P_{trend}=<0.0001). Total omega-6 was inversely associated with CVD mortality. Higher intakes of LA were associated with lower CVD mortality (HR 0.92; 95% CI: 0.87, 0.98; P_{trend}=0.0038). Higher intake of AA was associated with increased CVD mortality (HR 1.11 95% CI: 1.06-1.16). In isocaloric substitution analysis, replacing 2% energy from SFA with

	History of Hypercholesterolaemia: 25.8% History of hypertension: 23.3% Heart Disease: 15.4% Stroke: 2.2% Cancer: 8.9% Diabetes: 6.2% Fair or poor health: 11.8% Daily aspirin use: 16.1% <u>Q3</u> Age: 62.8 years Male: 59.8% Race: 92.6% White, 3.3% Black, 2.6% Hispanic, 1.0% Asian BMI: 26.5 kg/m2 Current smoker: 11.1% Physical activity (>5 times/wk): 18.5% History of Hypercholesterolaemia: 26.1% History of hypertension: 23.4% Heart Disease: 13.8% Stroke: 2.0% Cancer: 8.9% Diabetes: 9.1% Fair or poor health: 12.4% Daily aspirin use: 14.8% <u>Q5</u> Age: 62.9 years Male: 60.7% Race: 91.0% White, 4.6% Black, 1.4% Hispanic, 1.3% Asian BMI: 26.6 kg/m2 Current smoker: 14.0% Physical activity (>5 times/wk): 16.6% History of Hypercholesterolaemia: 26.5% History of hypertension: 23.5% Heart Disease: 12.9% Stroke: 2.2% Cancer: 9.4% Diabetes: 12.2% Fair or poor health: 15.0% Daily aspirin use: 13.5%	<u>Quintile of MUFA Intake</u> Q1: 1546.7 kcal/d, total fat 20.3 % total energy, SFA 5.9 % total energy, MUFA 7.3 % total energy, PUFA 4.8 % total energy, TFA 1.2 % total energy, total protein 14.9 % total energy, omega-3 0.5 % total energy, ALA 0.5 % total energy, marine omega-3 0.04 % total energy, omega-6 4.2 % total energy, LA 4.1 % total energy, AA 0.03 % total energy, omega-6/omega 3 ratio 7.8, alcohol 2.5 g/d Q3: 1685.1 kcal/d, total fat 30.3 % total energy, SFA 9.3 % total energy, MUFA 11.4 % total energy, PUFA 6.8 % total energy, TFA 2.1 % total energy, total protein 15.4 % total energy, omega-3 0.7 % total energy, ALA 0.6 % total energy, marine omega-3 0.04 % total energy, omega-6 6.1 % total energy, LA 6.0 % total energy, AA 0.05 % total energy, omega-6/omega 3 ratio 8.7, alcohol 2.0 g/d Q5: 1860.3 kcal/d, total fat 39.7 % total energy, SFA 12.1 % total energy, MUFA 15.3 % total energy, PUFA 8.9 % total energy, TFA 2.8 % total energy, total protein 15.5 % total energy, omega-3 1.0 % total energy, ALA 0.8 % total energy, marine omega-3 0.04 % total energy, omega-6 8.0 % total energy, LA 7.9 % total energy, AA 0.06 % total energy, omega-6/omega 3 ratio 9.4, alcohol 1.1 g/d		TFA was associated with a 3% increase in total and CVD mortality. Replacing 5% energy from MUFA was associated with a 16% and 13% reduction in total and CVD mortality, respectively. Replacing 5% energy from SFA with PUFA was associated with a 18% and 15% reduction in total and CVD mortality, respectively. Isocaloric replacement of SFA with ALA showed not benefit on total and CVD mortality. Replacing 0.1% energy from SFA with EPA and DHA was associated with a 4% reduction in total and CVD mortality. Replacing 2% of energy from SFA with omeage-6 PUFA was associated with lower risk of total and CVD mortality (0.92; 95% CI: 0.91, 0.93; p<0.0001 and 0.94; 95% CI: 0.92, 0.96; p<0.0001, respectively). Replacing SFA with AA increased mortality and CVD mortality. **Summary** **In this large cohort, increased intake of SFA, TFA and animal-MUFA was associated with higher total and CVD mortality. Greater intakes of plant MUFAs, marine omega-3 PUFAs and LA were associated with lower total and CVD mortality.**

	Quintile of MUFA intake Q1 Age: 63.0 years Male: 53.2% Race: 90.3% White, 3.8% Black, 2.3% Hispanic, 1.9% Asian BMI: 25.3 kg/m2 Current smoker: 7.4% Physical activity (>5 times/wk): 27.0% History of Hypercholesterolaemia: 24.3% History of hypertension: 23.9% Heart Disease: 17.3% Stroke: 2.1% Cancer: 9.1% Diabetes: 6.0% Fair or poor health: 10.4% Daily aspirin use: 17.7% Q3 Age: 62.9 years Male: 58.9% Race: 91.9% White, 3.7% Black, 1.8% Hispanic, 1.1% Asian BMI: 26.5 kg/m2 Current smoker: 10.9% Physical activity (>5 times/wk): 17.8% History of Hypercholesterolaemia: 26.8% History of hypertension: 23.5% Heart Disease: 13.1% Stroke: 2.0% Cancer: 8.6% Diabetes: 6.2% Fair or poor health: 12.1% Daily aspirin use: 14.4% Q5 Age: 62.6 years Male: 63.8% Race: 92.8% White, 3.6% Black, 1.3% Hispanic, 0.8% Asian BMI: 27.3 kg/m2 Current smoker: 17.8% Physical activity (>5 times/wk): 14.2%			

	History of Hypercholesterolaemia: 27.4% History of hypertension: 22.8% Heart Disease: 12.5% Stroke: 2.3% Cancer: 9.1% Diabetes: 13.3% Fair or poor health: 16.9% Daily aspirin use: 13.1%			
Hooper et al.[22]	Potentially relevant records: 20,846 Full-texts assessed for eligibility: 2155 Excluded 1216 full texts, abstracts and trials registry entries Excluded 192 trials due to duration <52 weeks, intervention was not omeaga-6, or did not collect data on one key review outcome Articles in final meta analysis: 19 (17 included in quantitative analysis) and 2 narratively. Total number of participants in analysis: 6461 Participants followed for one to eight years. 10 studies recruited both men and women, 10 trials included participants at low risk of CVD, 3 trials included people at moderate risk of CVD, and 5 included people with existing CVD Articles in final meta analysis: 193 (49 trials) included in quantitative analysis. Total number of participants in analysis: 24,272 Participants followed for 1 to 4 years. 44 studies recruited both men and women, 5 trials did not report sex of participants	Meta-analysis of RCTs examining effect omega-6 fats on total mortality, cardiovascular events, CHD events, MACCE, and stroke in healthy people or those with CVD Articles sourced from CENTRAL, MEDLINE and Embase to May 2017, Clinical trials.gov; WHO International trials platform to Sept 2016. Checked trials in systematic reviews. Quality of evidence was assessed using GRADE. Study bias assessed using Cochrane 'Risk of Bias' tool Inclusion criteria were: RCTs of at least 12 months duration. Higher versus lower omega 6 fat (including LA, GLA, DGLA, AA or any combination). Intervention had to be dietary supplementation, a provided diet or dietary advice with aim to increase or decrease intake of omega-6 fats or dietary component high in omega-6 fats e.g. sunflower oil if no clear aim stated. Intervention to achieve increase or decrease by 10% of baseline omega 6 intake Diet versus usual diet; no advice, no supplementation or placebo, with lower omega 6 intake. Excluded studies which aimed to increase omega 6 and 3.	Primary outcomes were all-cause mortality, CVD mortality, CVD events (all available data on fatal and not fatal MI; angina and/or stroke), CHD events (MI (fatal or /non fatal) or angina, Major Adverse cardiac and cerebrovascular events (where it was possible to assess the numbers of participants experiencing fatal or non fatal MI; unstable angina and stoke), Stroke (total, fatal and non-fatal, ischaemic and haemorrhagic. Secondary outcomes were Myocardial infarction (MI, total, fatal and non-fatal), Angina, Sudden cardiac death, Atrial fibrillation (AF) (new or recurrent, ventricular tachycardia and/or ventricular fibrillation), Heart failure, Revascularisation (angioplasty or coronary artery bypass grafting), Peripheral arterial disease (PAD), Serum lipids (including TC, fasting TAGs, HDL-C, LDL-C), BMI, body weight and other measures of adiposity	10 trials reported all-cause mortality Pooled analysis (4506 participants) showed no effect of higher vs. lower intake of omega-6 on all-cause mortality (RR 1.00; 95% CI: 0.88, 1.12) None of the subgroup analysis considering omega-6 type, intervention type, energy replacement, primary or secondary prevention of CVD, dose, duration, statin use, baseline omega-6 intake or sex suggested important differences in mortality between higher or lower omega-6 fats and all-cause mortality. 7 trials reported CVD mortality Pooled analysis (4019 participants) showed no effect of higher vs. lower intake of omega-6 on CVD mortality (RR 1.09; 95% CI: 0.76, 1.55). Significant heterogeneity was observed in these studies with some showing protective effects whilst others showing harm. Subgrouping by primary or secondary prevention of CVD did not suggest important differences between subgroups but did reduce heterogeneity and suggested harmful effects of omega-6 fat in secondary prevention trials (RR 1.28; 95% CI: 1.04, 1.57). 7 trials reported CVD events. Pooled analysis (4962 participants) showed no effect of higher vs. lower intake of omega-6 on CVD events (RR 0.97; 95% CI: 0.81, 1.15).This was not altered by subgroup analysis.

	16 trials included participants with existing CVD 13 trials provided 0.6 - <1% energy from PUFA, 17 trials provided 1-<2% energy, 8 trials gave 2-<5% energy, and 11 trials gave ≥5% energy as PUFA. Baseline omega-6 intake was <5% energy in 3 trials, 5% to <8% in 3 trials, and at least 8% in 1 trial. 12 trials did not report baselines omeaga-3 intake. In the majority of studies (9), as LA increased, SFA decreased. MUFA decreased in 5, carbohydrate and protein in 1, and carbohydrates in 1. For 3 trials it was unclear what was replaced in the diet.			7 trials reported CHD events. Pooled analysis (3997 participants) showed no effect of higher vs. lower intake of omega-6 on CHD events (RR 0.88; 95% CI: 0.66, 1.17). Where omega-6 fat replaced MUFA, there was an increased risk of CHD events, while omega-6 fat replacing carbohydrates appeared to reduce CHD event risk 2 trials reported MACCEs. Pooled analysis (2879 participants) showed no effect of higher vs. lower intake of omega-6 on MACCEs (RR 0.84; 95% CI: 0.59, 1.20). 4 trials reported stroke. Pooled analysis (3730 participants) showed no effect of higher vs. lower intake of omega-6 on stoke (RR 1.36; 95% CI: 0.45, 4.11). Studies were heterogeneous and CIs very wide. In subgroup analysis increasing omega-6 fat was protective in primary prevention but not secondary prevention. 7 trials reported MI. Pooled analysis (4606 participants) showed increasing omega-6 was associated with reduced risk of MI (RR 0.88; 95% CI: 0.76, 1.02). Studies were heterogeneous and CIs very wide. There were no differences with subgroup analysis 10 trials suggested increased omega-6 fats reduces TC (4280 participants, MD -0.33 mmol/L; 95% CI -0.50, -0.16). 5 trials indicated increasing omega-6 has no effect on TAG (834 participants, MD -0.01 mmol/L; 95% CI: -0.23, 0.21), 4 trials showed no effect on HDL-C (1995 participants, MD −0.01 mmol/L; 95% CI: −0.03, 0.02), and 2 trials showed no effect on LDL-C (MD −0.04 mmol/L; 95% CI: −0.21, 0.14)

				Increasing omega-6 had little or no effect on adiposity (based on BMI). **Summary** **Low quality evidence suggests increasing omega-6 fats may make no difference to all-cause mortality, CVD events, CVD mortality, CHD events or stroke. Increasing omega 6 may reduce MI risk although this is based on low quality evidence. High quality evidence suggests increasing omega-6 may lower TC but has no effect on adiposity, LDL-C, HDL-C or TAGs**
Aung et al.[23]	Potentially relevant records: 41,406 Texts screened for CV endpoints: 983 Excluded 354 as not human or clinical trial Excluded 548 as study length <6 months 81 reports reviewed against inclusion criteria Excluded 73 due to sample size <500, duration <1 year, and major vascular outcomes <10 events Articles in final meta-analysis: 10 All studies were parallel RCTs Total number of participants in analysis: 77,917 8 studies had double-blind design and were placebo-controlled. 2 had open label design 61.4% of participants were men, with a mean age at entry was 64 years 66.4% of participants had a prior history of CHD, 28% had prior stroke, and 37% had prior diabetes.	Meta-analysis of RCTs examining association of omega-3 supplements with risk of fatal and non-fatal CHD and major vascular events Articles sourced from PUBMED and MEDLINE, plus hand searching of reference lists review articles or previous meta analyses. Used PRISMA guidelines for the conduct of meta analyses and RCTs. Not clear how bias or quality was determined. Inclusion criteria were: Studies must be RCTs, including cross-over and parallel-group designs. Must be trials or marine-derived very long chain omega-3 FA supplements vs. placebo All required use of supplements but no restrictions on EPA or DHA Studies must be 1 year in duration Must contain >500 participants	Primary outcomes included nonfatal MI; death caused by CHD; ischemic, haemorrhagic, and unclassified stroke; coronary or non-coronary arterial revascularization events; major vascular events (a composite of first occurrence of nonfatal MI or death caused by CHD; nonfatal or fatal stroke; or any revascularization procedure); and all-cause mortality. Deaths caused by CHD included sudden cardiac deaths, deaths due to ventricular arrhythmias, and heart failure in patients with CHD, MI, or deaths occurring after coronary revascularization or heart transplant.	Omega-3 supplementation had no significant association with any CHD event (RR 0.96; 95% CI: 0.90, 1.01; P = 0.12), CHD death (RR 0.93; 95% CI: 0.83, 1.03; P =0.05), nonfatal MI (RR, 0.97; 95% CI: 0.87, 1.08; P =0.40), major vascular events (RR 0.97; 95% CI: 0.93, 1.01; P=0.10), stroke (RR 1.03; 95% CI: 0.93, 1.13; P=0.56), or revascularisaztion events (RR 0.99; 95% CI: 0.94, 1.04; P=0.61) Considering history of CHD, diabetes, pre-treatment levels of cholesterol, HDL-C, LDL-C, TAGs or prior use of statin therapy, intake of omega 3 supplements in each subgroup had no significant association with major vascular events Study design (open vs. blind) did not influence lack of association between omega-3 supplementation of non-fatal MI, CHD death, or any CHD. Omega-supplementation was not associated with all-cause mortality (RR 0.96; 95% CI: 0.92, 1.01; P=0.16) **Summary**

	9/10 trials used a combination of EPA and DHA. EPA dose ranged from 226-1800 mg/d and DHA ranged from 0-1700 mg/d.			**This meta-analysis of RCTs does not support the use of omega-3 supplements for the prevention of fatal CHD, nonfatal MI, stroke, revascularization events, or any major vascular events in those with no or pre-existing CVD. Important consideration is DOSE given**
Bhatt et al.[24] .	19,212 participants eligible Excluded 11,033. 8179 participants randomized (40 to each arm) Randomised 1:1 to either placebo (*n* 4089) or intervention (*n* 4090). <u>Intervention</u> Age: 64 (57.0-69.0) years Age ≥ 65 years: 45.4% Male: 71.6% White: 90.3% BMI: 30.8 (27.8-34.5) kg/m2 BMI ≥ 30 kg/m2: 57.0% CV risk category: 70.7% secondary; 29.3% primary Ezetimibe use: 6.4% Statin Intensity: 6.2% low, 61.9% moderate, 31.5% high, 0.3% missing Diabetes: 0.7% T1, 57.9% T2, no diabetes 41.5%, missing 0% hsCRP: 2.2 (1.1-4.5) mg/L TAG: 2.4 (2.0-3.1) mmol/L HDL-C: 1.0 (0.9-1.2) mmol/L LDL-C: 1.9 (1.6-2.3) mmol/L Prior Atherosclerotic Coronary Artery Disease and Related Morbidities: 58.4% Prior Atherosclerotic Cerebrovascular Disease and Related Morbidities: 15.7% Prior Atherosclerotic Peripheral Artery Disease: 9.5% Prior Non-Atherosclerotic Cardiovascular Disease: 89.2% Prior Cardiac Arrhythmias: 5.6% Prior Non-Cardiac/Non-Atherosclerotic Vascular Disorders: 87.3% Anti-diabetic medication: 53.6%	Randomised, double-blind, placebo-controlled trial. Eligible patients randomized in a 1:1 fashion to either icosapent ethyl (2 g twice daily with food) or matching placebo Randomization was stratified by primary vs. secondary prevention, use of ezetimibe, and geographic region	Primary outcome was the total of first plus subsequent ischaemic events consisting of the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Secondary endpoint was hard MACE (defined as "cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke"). Follow-up visits continued at 4 and 12 months and annually thereafter until approximately 1,612 primary efficacy endpoint events occurred, after which patients made a final end-of-study visit.	After a median follow-up of 4.9 years there were 1,606 primary end point events Icosapent ethyl significantly reduced rates of first occurrence of the primary end point vs. placebo (HR 0.75; 95% CI: 0.68, 0.83; p<0.0001). Icosapent ethyl significantly reduced rates of second occurrence of the primary end point vs. placebo (HR 0.68; 95% CI: 0.60, 0.78; p<0.0001). Total key secondary endpoint event rates were significantly reduced to 32 from 44 per 1,000 patient-years for icosapent ethyl versus placebo, respectively (RR 0.72; 95% CI: 0.63, 0.82; p<0.0001) Times to first, second, third or fourth occurrence of the primary endpoint were significantly reduced with Icosapent ethyl **Summary** **Icosapent ethyl is a derivative of EPA. Recent studies have questioned the role of omega-3 supplementation in primary and secondary prevention of CVD, and it is clear from these that one of the issues has potentially been the dose of EPA and DHA used. REDUCE-IT used a dose of 4000 mg/d. This trial was also not focussed on LDL-C. Ongoing trials such as STRENGTH, RESPECT EPA, & EVAPORATE will reveal more information on the role of omega-3 supplementation and CVD.**

	Anti-hypertensive medication: 95.3% Anti-platelet medication: 79.7% Anticoagulant: 9.4% No antithrombotic: 14.3% ACEi: 51.7% ARB: 27.1% Beta blocker: 71.0% <u>Placebo</u> Age: 64 (57.0-69.0) years Age ≥ 65 years: 46.6% Male: 70.8% White: 90.2% BMI: 30.8 (27.9-34.7) kg/m2 BMI ≥ 30 kg/m2: 57.8% CV risk category: 70.7% secondary; 29.3% primary Ezetimibe use: 6.4% Statin Intensity: 6.5% low, 63.0% moderate, 30.0% high, 0.5% missing Diabetes: 0.7% T1, 57.8% T2, no diabetes 41.4%, missing 0.1% hsCRP: 2.2 (1.1-4.5) mg/L TAG: 2.4 (2.0-3.1) mmol/L HDL-C: 1.0 (0.9-1.2) mmol/L LDL-C: 2.0(1.6-2.3) mmol/L Prior Atherosclerotic Coronary Artery Disease and Related Morbidities: 58.5% Prior Atherosclerotic Cerebrovascular Disease and Related Morbidities: 16.2% Prior Atherosclerotic Peripheral Artery Disease: 9.5% Prior Non-Atherosclerotic Cardiovascular Disease: 89.1% Prior Cardiac Arrhythmias: 5.9% Prior Non-Cardiac/Non-Atherosclerotic Vascular Disorders: 87.2% Anti-diabetic medication: 53.7% Anti-hypertensive medication: 95.2% Anti-platelet medication: 79.1% Anticoagulant: 9.5% No antithrombotic: 14.7% ACEi: 52.1% ARB: 26.8% Beta blocker: 70.4%			

Online Supplementary Table 2 Food Groups and their association with CV outcomes

Study	Participant characteristics	Study Design	Measures and time points	Key observations
Aune et al.[25]	Potentially relevant records: 46,082 Excluded 44,823 based on title or abstract Full-texts assessed for eligibility: 1259 Excluded 934 as reported other exposures than vitamin C, E, or carotenoids 325 relevant papers assessed. 230 excluded due to reviews, cross-sectional studies, or supplement use. Articles in final meta-analysis: 99 (69 cohort studies) Follow-up ranged from 4-32 years	Meta-analysis of prospective cohort studies assessing relationship between blood concentrations of vitamin C, E, and carotenoids with risk of CHD, stroke, CVD, total cancer, and all-cause mortality Articles sourced from PubMed and EMBASE to February 2017 PRIMSA criteria followed for reporting of meta analyses Quality of evidence assessed using Newcastle-Ottawa scale Study bias assessed using funnel plots and Egger's test Inclusion criteria unclear	Primary outcomes were risk of CHD, stroke, CVD, total cancer, and all-cause mortality	11 studies reported dietary vitamin C intake in relation to CHD. Pooled analysis (240,824 participants) suggested a significant 12% reduction per 100 mg/d (RR 0.88; 95% CI: 0.79, 0.98) in CHD risk with increased vitamin C intake 12 studies reported dietary vitamin C intake in relation to stroke. Pooled analysis (296,066 participants) suggested a significant 8% reduction per 100 mg/d (RR 0.92; 95% CI: 0.87, 0.98) in stroke risk with increased vitamin C intake. There was substantial heterogeneity observed in studies 10 studies reported vitamin C intake in relation to CVD. Pooled analysis (296,066 participants) suggested a significant 11% reduction per 100 mg/d (RR 0.89; 95% CI: 0.85, 0.94) in stroke risk with increased vitamin C intake 16 studies reported vitamin C intake in relation to total mortality. Pooled analysis (296,066 participants) suggested a significant 11% reduction per 100 mg/d (RR 0.89; 95% CI: 0.85, 0.94) in stroke risk with increased vitamin C intake 16 studies reported blood vitamin C concentration in relation to CHD. Pooled analysis (7514 participants) suggested a significant 26% reduction (RR 0.89; 95% CI: 0.85, 0.94) in CHD

				risk per 50 µmol/L increase in vitamin C concentration 16 studies reported blood vit C concentration in relation to stroke. Pooled analysis (27,843 participants) suggested a significant 30% reduction (RR 0.70; 95% CI: 0.61, 0.81) in CHD risk per 50 µmol/L increase in vitamin C concentration 6 studies reported blood vitamin C concentration in relation to stroke. Pooled analysis (45,273 participants) suggested a significant 24% reduction (RR 0.76; 95% CI: 0.61, 0.81) in stroke risk per 50 µmol/L increase in vitamin C concentration 8 studies reported blood vit C concentration in relation to total mortality. Pooled analysis (48,060 participants) suggested a significant 28% reduction (RR 0.72; 95% CI: 0.66, 0.79) in mortality risk per 50 µmol/L increase in vitamin C concentration 5 studies reported total dietary carotenoids in relation to CHD. Pooled analysis (91,838 participants) suggested a significant 15% reduction (RR 0.85; 95% CI: 0.77, 0.93) in CVD risk per 5000 µg/d increase in carotenoids intake 2 studies reported total dietary carotenoids in relation to CVD. Pooled analysis (135,971 participants) suggested a significant 20% reduction (RR 0.80; 95% CI: 0.70, 0.90) in CVD risk per 5000 µg/d increase in carotenoids intake 5 studies reported total dietary carotenoids in relation to mortality. Pooled analysis (189,079 participants) suggested a significant 12% reduction (RR 0.88; 95% CI: 0.83, 0.93) in CVD

				risk per 5000 µg/d increase in carotenoids intake 3 studies reported blood carotenoid concentration in relation to CHD. Pooled analysis (3040 participants) suggested a significant 17% reduction (RR 0.83; 95% CI: 0.72, 0.95) in CHD risk per 100 µg/dL increase in blood carotenoids 7 studies reported blood carotenoid concentration in relation to mortality. Pooled analysis (18,559 participants) suggested a significant 26% reduction (RR 0.74; 95% CI: 0.62, 0.88) in CHD risk per 100 µg/dL increase in blood carotenoids 4 studies reported total dietary β-carotene in relation to CHD. Pooled analysis (99,345 participants) suggested a significant 18/% reduction (RR 0.82; 95% CI: 0.68, 0.98) in CVD risk per 5000 µg/d increase in β-carotene intake 7 studies reported total dietary β-carotene in relation to stroke. Pooled analysis (201,587 participants) suggested a significant 19% reduction (RR 0.81; 95% CI: 0.66, 0.98) in CVD risk per 5000 µg/d increase in β-carotene intake 5 studies reported total dietary β-carotene in relation to mortality. Pooled analysis (143,140 participants) suggested a significant 8% reduction (RR 0.92; 95% CI: 0.85, 0.98) in mortality risk per 5000 µg/d increase in β-carotene intake No significant association between dietary β-carotene and CVD 3 studies reported blood β-carotene in relation to CHD. Pooled analysis (2933 participants) suggested a significant

				20% reduction (RR 0.80; 95% CI: 0.66, 0.97) in CVD risk per 25 µg/dL increase in β-carotene 3 studies reported blood β-carotene in relation to stroke. Pooled analysis (30,144 participants) suggested a significant 15% reduction (RR 0.85; 95% CI: 0.74, 0.97) in CVD risk per 25 µg/dL increase in β-carotene 8 studies reported blood β-carotene in relation to CVD. Pooled analysis (24,428 participants) suggested a significant 14% reduction (RR 0.86 95% CI: 0.78, 0.96) in CVD risk per 25 µg/dL increase in β-carotene 7 studies reported blood β-carotene in relation to mortality. Pooled analysis (23,141 participants) suggested a significant 19% reduction (RR 0.81; 95% CI: 0.72, 0.90) in mortality risk per 25 µg/dL increase in β-carotene 3 studies reported blood β-cryptoxanthinin relation to mortality. Pooled analysis (14,985 participants) suggested a significant 16% reduction (RR 0.84; 95% CI: 0.76, 0.94) in mortality risk per 15 µg/dL increase in β-cryptoxanthin. No significant association existed between blood β-cryptoxanthin and CHD, stroke, or CVD No significant associations were observed between dietary lycopene and CHD, stroke, CVD, or mortality. No significant associations were observed between blood lycopene and CHD, stroke, CVD, or mortality. No significant associations were observed between dietary vitamin E and CHD, stroke, CVD, or mortality.

				4 studies reported blood α-Tocopherol concentration in relation to stroke. Pooled analysis (69,386 participants) suggested a 10% reduction (RR 0.90; 95% CI: 0.86, 0.95) in stroke risk per 500 μg/dL increase in blood α-Tocopherol 9 studies reported blood α-Tocopherol concentration in relation to mortality. Pooled analysis (52,376 participants) suggested a 6% reduction (RR 0.94; 95% CI: 0.89, 0.99) in mortality risk per 500 μg/dL increase in blood α-Tocopherol Blood α-Tocopherol was not significantly associated with CHD or CVD **Summary** **This meta-analysis showed an inverse association between dietary intake and blood concentration of vitamin C and risk of CHD, stroke, CVD, and all-cause mortality. Dietary carotenoid intake as well as intake of specific carotenoids (β-carotene, lycopene) were inversely associated with CHD, stroke, and mortality, whereas blood concentrations of carotenoids (total, β-carotene, α-carotene, lycopene, β-cryptoxanthin) were inversely associated with CVD, total cancer, and/or all-cause mortality.**
Yip et al.[26]	Potentially relevant records: 4736 Screened 959 abstracts Full-text articles assessed for suitability: 87 Excluded 23 due to not meta analyses, were comparative risk assessment of used biomarkers Articles in final meta analysis: 64	Review of evidence from systematic reviews and meta analyses examining the association between fruit and vegetable intake and the burden of disease Search PubMed, Ovid, EBSCOhost, Google Scholar databases, Australian Institute of Health and Welfare, and World Cancer Research Fund International websites (April 2018)	Primary outcomes were incidence and/or mortality RR, odds ratio, or HR over a given time span for high-vs low intakes. Secondary outcomes included incidence and/or mortality RR, odds ratio, or hazard ratio over a time span per gram(s) of fruit and/or vegetable intake	For each 100 g/d increases in fruit intake, there was a 14% decreased risk of stroke (RR 0.86; 95 % CI 0.84, 0.88). Risk of CVD was decreased by 10% for each 100 g/d increase in fruit intake (RR 0.90; 95% CI: 0.88, 0.92)

	None of the included studies were based on RCT data Follow up periods not reported.	Quality assessment of studies performed using Assessing the Methodological Quality of Systematic Reviews (AMSTAR) checklist. For cohort studies the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies was used Inclusion criteria were Only meta analyses examining the direct associations of fruit and/or vegetables intake with burden of disease were considered Studies must quantify the pooled RR directly associated with dietary fruit and/or vegetables as in grams or servings. Studies were excluded if they showed only associations of subgroups (i.e. celery and mushrooms), used biomarkers (either biomarkers of fruit and vegetable intake or biomarkers of disease), examined cooking methods, or if they investigated specific disease interventions		CHD risk was reduced by 9% for every 100 g/d increase in fruit intake (RR 0.91; 95% CI: 0.89, 0.93) Risk of hypertension was reduced by 3% for each 100 g/d increase in fruit (RR 0.97; 95% CI: 0.96, 0.99) All-cause mortality risk was reduced by 11% for every 100 g/d of fruit intake (RR 0.89; 95% CI: 0.88, 0.90). In general, clear increases in protective associations were observed within the first 300 g/day of intakes but little further increase thereafter. Each 100 g/d increase in tinned fruit was associated with a 19% increase in all-cause mortality (RR 1.19; 95% CI: 1.06, 1.26). In those consuming ≥34 g/d vs. <17 g/d tinned fruit there was a 23% increased risk of CVD mortality (RR 1.23; 95% CI: 1.05, 1.43) For each 100 g/d increase in vegetables there was a 14% decrease in CHD (RR 0.86; 95% CI: 0.84, 0.89). Risk of stroke was decreased by 12% (RR 0.88; 95% CI: 0.80, 0.95) for every 100 g/d increase in vegetables. CVD risk was decreased by 7% (RR 0.93; 95% CI: 0.92, 0.95) for each 100 g/d increase in vegetables. CVD mortality was reduced by 5% and all-cause mortality by 13% (RR 0.95; 95% CI: 0.91, 0.99 and RR 0.87; 95% CI: 0.84, 0.90, respectively) for each 100g increase in vegetables. Clear increases in different degrees of protective associations were observed

				within the first 300 g/day of intakes but little further increase thereafter. For fruit and vegetables combined, each 100 g/d increases was associated with a 8% decreased risk for all-cause mortality (RR 0.91; 95% CI: 0.90, 0.93). CVD mortality risk was reduced by 7% (RR 0.93; 95% CI: 0.89, 0.97) for each 100 g/d increase in fruit and vegetables. Risk of stroke was decreased by 7% for each 100 g/d increase in fruit and vegetables (RR 0.93; 95% CI: 0.91, 0.95) CVD risk was decreased by 4% for each 100 g/d increase in fruit and vegetables (RR 0.96; 95% CI: 0.94, 0.98) Risk of CHD was decreased by 4% for each 100 g/d increase in fruit and vegetables (RR 0.96; 95% CI: 0.95, 0.97) Risk of hypertension was decreased by 1% for each 100 g/d increase in fruit and vegetables (RR 0.99; 95% CI: 0.99, 0.99) Clear increases in protective associations were observed within the first 300 g/day of intake, little further increase thereafter. **Summary** **Evidence from this study shows increased fruit and vegetable intakes are associated with reduced burden of CVDs. In this analysis increased consumption of tinned fruit was associated with increased all-cause and CVD mortality.**

Bechthold et al.[27]	Potentially relevant records: 16,623 Excluded 16,382 after title/abstract screening Full texts assessed: 261 Excluded 138 due to not relevant exposure/outcome, not relevant study design, secondary prevention, or meta analysis Articles in final meta-analysis: 123 Whole grain: 16 Refined grain: 8 Vegetables: 32 Fruits: 30 Nuts: 12 Legumes: 13 Eggs: 16 Dairy: 24 Fish: 47 Red meat: 15 Processed meat: 13 Sugar sweetened beverages: 9	Meta-analysis of prospective studies examining association between different food groups and risk of CHD, stroke, and HF Articles sourced from PUBMED and EMBASE (until March 2017), plus hand searching of reference lists review articles or previous meta analyses. Used MOOSE guidelines for the conduct of meta analyses. Inclusion criteria were: Prospective design Must contain information on 1 of 12 predefined food groups Participants ≥ 18 years Considering CHD including myocardial infarction and other coronary artery diseases (like angina); stroke (haemorrhagic, ischemic); and HF as outcomes Exclusion criteria studies including populations suffering from chronic disease studies reporting only fatal outcomes Studies aggregating outcomes as total CVD, and not reporting on CHD, stroke or HF separately Applied the NutriGrade scoring system (max 10 points) which comprises the following items: (i) risk of bias/study quality/study limitations (max. 2 points), (ii) precision (max. 1 point), (iii) heterogeneity (max. 1 point), (iv) directness (max. 1 point), (v) publication bias (max. 1 point), (vi) funding bias (max. 1 point), (vii) effect size (max. 2 points), and (viii) dose-response (max. 1 point)	Primary outcomes included CHD (including MI and other coronary artery diseases (like angina)); stroke (haemorrhagic, ischemic); and HF	<u>Wholegrains</u> 7 studies (6,834 cases), 7 studies (11,114 cases) and 5 studies (6,455 cases) were included in high vs. low intake for CHD, stroke, and HF, respectively. Compared with low intakes, high intakes of wholegrain were associated with lower risk of CHD (RR 0.85; 95% CI: 0.81, 0.90), stroke (RR 0.91; 95% CI: 0.82, 1.02) and HF (RR 0.91; 95% CI: 0.85, 0.97). Each additional daily 30 g of whole grains were inversely associated with risk of CHD (RR 0.95; 95% CI: 0.92, 0.98, and HF (RR 0.96; 95% CI: 0.95, 0.97) Risk of CHD decreased by 17% with increasing intake of whole grains up to ~100 g/d. No benefit for increasing intake was apparent above this intake <u>Refined Grains</u> 5 studies (3286 cases), 6 studies (11,434 cases) and 1 study (1018 cases) were included in high vs. low intake for CHD, stroke, and HF, respectively Compared with low intakes, high intakes of refined grains were associated with increased risk of CHD (RR 1.11; 95% CI: 0.99, 1.25). No association was observed for stroke or HF <u>Vegetables</u> 19 studies (19,402 cases), 16 studies (12,442 cases) and 3 study (6,267 cases) were included in high vs. low intake for CHD, stroke, and HF, respectively Compared with low intakes, a high intakes of vegetables was associated with lower risk of CHD (RR 0.92; 95% CI: 0.87, 0.98) and stroke (RR 0.87;

				95% CI: 0.82, 0.93). No association was observed with HF. Each additional daily 100 g of vegetables were inversely associated with risk of CHD (RR 0.97; 95% CI: 0.96, 0.99), stroke (RR 0.92; 95% CI: 0.86, 0.98), and HF (RR 0.96; 95% CI: 0.94, 0.98) <u>Fruits</u> 17 studies (17,827 cases), 17 studies (30,523 cases) and 3 study (6,267cases) were included in high vs. low intake for CHD, stroke, and HF, respectively Compared with low intakes, a high intakes of fruits was associated with lower risk of CHD (RR 0.89; 95% CI: 0.84, 0.93), stroke (RR 0.83; 95% CI: 0.77, 0.89) and HF (RR 0.95; 95% CI: 0.88, 1.02). Each additional daily 100 g of fruits were inversely associated with risk of CHD (RR 0.94; 95% CI: 0.90, 0.97) and stroke (RR 0.90; 95% CI: 0.84, 0.97). There was no association with risk of HF (RR 0.98; 95% CI: 0.94, 1.01) <u>Nuts</u> 54 studies (5480 cases), 6 studies (7490 cases) and 3 studies (3613 cases) were included in high vs. low intake for CHD, stroke, and HF, respectively Comparing low vs. high intakes suggested a trend for reduced risk of CHD (RR 0.80; 95% CI: 0.62, 1.03). This was not observed for stroke and HF Each additional daily 100 g of fruits were inversely associated with risk of CHD (RR 0.94; 95% CI: 0.90, 0.97) and stroke (RR 0.90; 95% CI: 0.84, 0.97). There was no association with risk of HF (RR 0.98; 95% CI: 0.94, 1.01)

				Legumes 10 studies (8228 cases) and 6 studies (6333 cases) were included in high vs. low intake for CHD and stroke, respectively Comparing the highest to the lowest categories of legume intake, an inverse association between legume intake and risk of CHD (RR 0.91; 95% CI: 0.84, 0.99), but not with risk of stroke (RR 0.98; 95% CI: 0.88, 1.10) A small inverse association was observed for each additional daily intake of 50 g of legumes and risk of CHD (RR 0.96; 95% CI: 0.92, 1.01), but not for stroke (RR 1.00; 95% CI: 0.88, 1.13) Eggs 11 studies (14,370 cases), 6 studies (6333 cases), and 4 studies (5059 cases) were included in high vs. low intake for CHD, stroke, and HF respectively. Comparing the highest to the lowest categories of egg intake, no association between egg intake and risk of CHD (RR 0.99; 95% CI: 0.94, 1.05) or risk of stroke (RR 0.99; 95% CI: 0.93, 1.05) was observed. A positive association between egg intake and risk of HF (RR 1.25; 95% CI: 1.12, 1.39) was present There was no association between each increment of 50 g of daily egg intake and risk of CHD (RR 1.00; 95% CI: 0.95, 1.06) or stroke (RR 0.99; 95% CI: 0.93, 1.05) but with risk of HF (RR 1.16; 95% CI: 1.03, 1.31) Dairy 13 studies (15,790 cases), 12 studies (16,887 cases), and 3 studies (4057 cases) were included in high vs. low

				intake for CHD, stroke, and HF respectively. Comparing the highest to the lowest categories of dairy intake, no associations were observed between dairy intake and risk of CHD (RR 0.99; 95% CI: 0.92, 1.07), stroke (RR 0.96; 95% CI: 0.90, 1.01), or HF (RR 1.00; 95% CI: 0.90,1.10) Each additional daily 200 g of dairy were not associated with risk of CHD (RR 0.99; 95% CI: 0.96, 1.02) or stroke (RR 0.98; 95% CI: 0.96, 1.00), but were positively associated with risk of HF (RR 1.08; 95% CI: 1.01, 1.15). No significant differences could be observed for low-fat and high-fat dairy and risk of CHD and stroke. <u>Fish</u> 22 studies (16,732 cases), 20 studies (14,360 cases), and 8 studies (7945 cases) were included in high vs. low intake for CHD, stroke, and HF respectively. Comparing the highest to the lowest categories, a small inverse association between fish intake and risk of CHD (RR 0.94; 95% CI: 0.88,1.02) or stroke (RR 0.95; 95% CI: 0.89, 1.01), and a stronger inverse association between fish intake and risk of HF (RR 0.89; 95% CI: 0.80, 0.99) was observed Each additional daily 100 g of fish were inversely associated with risk of CHD (RR 0.88; 95% CI: 0.79, 0.99), stroke (RR 0.86; 95% CI: 0.75, 0.99), and HF (RR 0.80; 95% CI: 0.67, 0.95) <u>Red Meat</u> 3 studies (6659 cases), 7 studies (10,541 cases), and 5 studies (9229 cases) were included in high vs. low intake for CHD, stroke, and HF, respectively.

				Comparing the highest to the lowest categories, a positive association between red meat intake and risk of CHD (RR 1.16; 95% CI: 1.08, 1.24,), stroke (RR 1.16; 95% CI: 1.08, 1.25), and HF (RR 1.12; 95% CI: 1.04, 1.21) was observed Each additional daily 100 g of red meat were positively associated with risk of CHD (RR 1.15; 95% CI: 1.08,1.23,), stroke (RR 1.12; 95% CI: 1.06, 1.17), and HF (RR 1.08; 95% CI: 1.02, 1.14) <u>Processed meat</u> 5 studies (7038 cases), 6 studies (9492 cases), and 3 studies (7077 cases) were included in high vs. low intake for CHD, stroke, and HF, respectively. Comparing the highest to the lowest categories, a positive association between processed meat intake and risk of CHD (RR 1.15; 95% CI: 0.99, 1.33), stroke (RR 1.16; 95% CI: 1.07, 1.26), and HF (RR 1.27; 95% CI: 1.14, 1.41) Each additional daily 50 g of processed meat were positively associated with risk of CHD (RR 1.27; 95% CI: 1.09, 1.49), stroke (RR 1.17; 95% CI: 1.02, 1.34), and HF (RR 1.12; 95% CI: 1.05, 1.19) <u>Sugar-sweetened beverages</u> 5 studies (8470 cases), 7 studies (11,187 cases), and 2 studies (8603 cases) were included in high vs. low intake for CHD, stroke, and HF, respectively. Comparing the highest to the lowest categories, a positive association between SSB intake and risk of CHD (RR 1.10; 95% CI: 1.01, 1.20) and stroke (RR 1.09; 95% CI: 1.01, 1.18), but no association with HF risk (RR

				1.11; 95% CI: 0.88, 1.39) were observed Each additional daily 250 ml of SSB were positively associated with risk of CHD (RR 1.17; 95% CI: 1.11, 1.23,), stroke (RR 1.07; 95% CI: 1.02, 1.12), and HF (RR 1.08; 95% CI: 1.05, 1.12) **Summary** **This meta-analysis of prospective cohort studies confirms previously understood thinking around cardioprotective components. It also highlights foods which appear to show little or no association with CHD, stroke, or HF (eggs and dairy)**
Macready et al.[28]	307participants assessed for eligibility 86 excluded 221 participants randomized to one of 3 arms: High flavonoid (HF): *n* 74 Low flavonoid (LF): *n* 70 Control (CT): *n* 77 Total drop outs: 67 <u>HF Group</u> Age: 50 ± 1 years Men: 62% Nonsmoker: 86.2% BMI: 27.6 ± 0.3 kg/m2 Waist circumference: 93.4 ± 0.8 Mean 24-hr SBP: 126 ± 2 mmHg Mean 24-hr DBP: 77 ± 1 mmHg Blood glucose: 5.6 ± 0.0 mmol/L TC: 5.7 ± 0.2 mmol/L TAG: 1.3 ± 0.1 mmol/L HDL-C: 1.5 ± 0.0 mmol/L LDL-C: 3.9 ± 0.1 mmol/L LDI-Ach AUC*: 1190 ± 96 LDI-SNP AUC*: 1470 ± 155 PWV*: 8.4 ± 0.2 m/s PWA Aix*: 24.9 ± 1.6 % PWA AIx HR75*: 18.1 ± 1.7 % DVP-SI*: 8.0 ± 0.3 m/s DVP-RI*: 69.2 ± 2.0 m/s HR*: 61 ± 1 bpm	Single-blind, dose-dependent, parallel randomised controlled trial 18 week duration Only those with an RR of CVD >1.5, established by using a methodology adapted from the Framingham CVD risk scoring tool, were recruited and randomly assigned to 1 of 3 dietary groups: High flavonoid (HF): n 74 Low flavonoid (LF): n 70 Control (CT): n 77 Portions of F&Vs were defined as 80 g for fresh, frozen, or canned items or 40 g for dried items and ≥150 mL fresh juice Used USDA flavonoids database to define HF and LF foods. HF and LF foods were defined as >15 mg/100 g and as <5 mg/100 g of total flavonoids, respectively, with adjustments made to account for fresh, dry, or canned F&V weight.	Primary outcome was vascular function and was powered based on microvascular reactivity Participants attended 4 clinic visits (week 0, 6, 12, and 18) 2 week run in on habitual diet followed by baseline (week 0 visit). HF and LF participants' target intake of F&Vs was increased over and above habitual intake by 2, 4, and 6 (+2, +4, and +6) 80-g portions/d over 3 consecutive 6-wk periods (+2, +4 , and +6) Vascular function, 24hr ambulatory BP, fasting blood samples (lipids), and 24-hr urine collected at each visit. 3-d dietary intake and adverse effects were assessed at weeks 2, 4, 6, 8, 10, and 12. Compliance assessed with 2 24-hr dietary recalls and biomarkers of F&V intake (plasma vitamin C, folate, and carotenoids, and urinary flavonoids and potassium)	Dose-dependent increase in dietary and urinary flavonoids in the HF group, with no change in other groups (P = 0.0001). Dietary intakes of folate (P=0.035), non-starch polysaccharides (P=0.001), vitamin C (P=0.0001), and carotenoids (P=0.0001) increased in both intervention groups compared with the control group Men in the HF group showed improved endothelium-dependent vasodilation (measured by LDI-Ach-AUC) with +2 target portions /d, remaining elevated with +4 and +6 portions/d (P=0.017). There was no significant effect of HF treatment in women. Women in the LF treatment arm showed improvements in endothelium-independent microvascular reactivity (measured via LDI-SNP AUC) with +2 portions/d (P=0.0002) but increased in those consuming +6 portions/d (P=0.0309) CRP was significantly reduced in men consuming +4 and +6 portions/d

	CRP*: ICAM*: VCAM*: E-selectin*: vWF*: TNF-α*: IL-6*: NO*: Fibrinogen*: <u>LF Group</u> Age: 51 ± 1 years Men: 58% Nonsmoker: 86.4% BMI: 28.0 ± 0.3 kg/m2 Waist circumference: 93.9 ± 0.7 cm Mean 24-hr SBP: 128 ± 2 mmHg Mean 24-hr DBP: 77 ± 1 mmHg Blood glucose: 5.7 ± 0.0 mmol/L TC: 5.6 ± 0.1 mmol/L TAG: 1.4 ± 0.0 mmol/L HDL-C: 1.6 ± 0.0 mmol/L LDLC: 3.7 ± 0.1 mmol/L LDI-Ach AUC*: 960 ± 71 LDI-SNP AUC*: 975 ± 78 PWV*: 8.5 ± 0.3 m/s PWA Aix*: 25.1 ± 1.7 % PWA AIx HR75*: 20.3 ± 1.7 % DVP-SI*: 7.9 ± 0.2 m/s DVP-RI*: 69.7 ± 1.8 % HR*: 63 ± 1 bpm CRP*: 1.8 ± 0.2 µg/mL ICAM*: 903 ± 36 ng/mL VCAM*: 654 ± 24 ng/mL E-selectin*: 36.0 ± 1.9 ng/mL vWF*: 92.6 ± 4.9 % of normal PAI-1*: 3.3 ± 0.4 ng/mL TNF-α*: 1.1 ± 0.1 pg/mL IL-6*: 1.3 ± 0.1 pg/mL NO*: 10.4 ± 0.3 µmol/L Fibrinogen*: 3.2 ± 0.1 g/L <u>CT Group</u> Age: 52 ± 1 years Men: 63% Nonsmoker: 89.5% BMI: 27.3 ± 0.4 kg/m2 Waist circumference: 92.3 ± 1.0 com			compared with baseline and +2 portions/d (P=0.001). Men in the HF and LF groups had significantly lower CRP at +2 (P = 0.0126) and +4 target portions (P = 0.001) compared with control men. Significant reductions in VACM (P=0.0468), E-selectin (men; P=0.0005, women: P=0.0047) were also observed in both HF and LF groups. NO was significantly increased in the HF arm (P=0.0293) with +4 portions/d compared with LF and CT groups. NO decreased in the CT group (P=0.0299). **Summary** **This study demonstrates that +2 portions of flavonoid-rich fruits and vegetables (berries, citrus fruit, apples, grapes, peppers, onions, broccoli, and herbs) per day improves arterial function and +4 portions/day reduces inflammation (especially in men with increased CVD risk). This is evidence to increase consumption of flavonoid-rich fruits and vegetables, and highlights the need to focus on specific types of fruit and vegetables, rather than as a whole category.**

	Mean 24-hr SBP: 125 ± 2 mmHg Mean 24-hr DBP: 76 ± 1 mmHg Blood glucose: 5.5 ± 0.0 mmol/L TC: 5.2 ± 0.2 mmol/L TAG: 1.3 ± 0.0 mmol/L HDL-C: 1.5 ± 0.0 mmol/L LDL-C: 3.4 ± 0.1mmol/L LDI-Ach AUC*: 1180 ± 124 LDI-SNP AUC*: 1209 ± 117 PWV*: 8.2 ± 0.2 m/s PWA Aix*: 25.1 ± 1.8 m/s PWA AIx HR75*: 18.2 ± 1.8 DVP-SI*: 8.2 ± 0.3 m/s DVP-RI*: 72.9 ± 1.9 m/s HR*: 61 ± 1 m/s CRP*: 2.0 ± 0.3 µg/mL ICAM*: 932 ± 31 ng/mL VCAM*: 641 ± 24 ng/mL E-selectin*: 34.8 ± 1.4 ng/mL vWF*: 75.4 ± 5.6 % of normal PAI-1*: 3.4 ± 0.4 ng/mL TNF-α*: 1.8 ± 0.4 pg/mL IL-6*: 1.3 ± 0.1 pg/mL NO*: 10.6 ± 0.3 µmol/L Fibrinogen*: 3.2 ± 0.1 g/L			
McEvoy et al.[29]	105 participants recruited and commenced 4 week run-in 13 lost prior to randomisation 92 randomised to 1 of 3 arms: 2 portions/d: *n* 29 4 portions/d: *n* 31 7 portions/d: *n* 32 89 participants completed study <u>2 portions/d</u> Age: 55.9 ± 4.9 years Men: 55% Current smoker: 17% Weight: 87.1 ± 11.4 kg BMI: 31.3 ± 2.4 kg/m2 Waist circumference: 104 ± 8.1 cm Waist-to-hip ratio: 0.96 ± 0.08 Body fat: 39.6 ± 7.7 % 24-hr SBP: 127.0 ± 13.9 mmHg 24-hr DBP: 76.4 ± 10.9 mmHg TC: 5.55 ± 0.95 mmol/L	Randomised controlled parallel trial 12 week duration (excluding 4 week run-in) Participants recruited from hospital outpatient clinics and from the general public. All participants were low F&V consumers (≤2 portions/d or ≤160 g/d), overweight (BMI: >27 and ≤35 kg/m2), and without pre-existing CVD or diabetes but had a combination of risk factors that placed them at high total risk (estimated multifactorial CVD risk ≥20% over 10 y) of developing atherosclerotic CVD for the first time Randomly assigned to 1 of 3 groups: 2 portions/d (160 g/d) 4 portions/d (320 g/d) 7 portions/d (560 g/d)	Primary outcomes were changes in blood pressure, lipids, or inflammatory markers (hsCRP). 4 week run-in where F&V intake was restricted to <2 portions/d. Participants given personalised dietetic advice to increase F&V intake and encourage variety. All participants received F&V. Compliance with the study protocol was monitored weekly via telephone during the intervention period and determined with use of self-reported dietary data collected pre- and post-intervention using a 4-d food record. Anthropometry, blood pressure, lipids, and hsCRP measured at baseline (week 0) and week 12	No significant change in self-reported F&V intake in 2 portions/d group. Mean F&V intake increased to 3.8 and 7.1 portions/d within the 4 and 7 portions/d groups, respectively (P<0.0001). Mean change in self-reported F&V intake was significantly correlated with mean change in lutein status (P<0.0001) and mean change in β-cryptoxanthin status (P = 0.03). Increasing F&V intake had no impact on either SBP or DBP Increasing F&V had no significant impact on any measured lipid parameter. In the 2 portions/d group LDL-C increased (P=0.05) but remained unchanged in the 4 and 7 portions/d groups (P=0.70 and P=0.37, respectively).

	LDL-C: 3.36 ± 0.94 mmol/L HDL-C: 1.34 ± 0.30 mmol/L TAG: 2.00 ± 0.83 mmol/L TC:HDL-C: 4.32 ± 1.21 Blood glucose: 5.48 ± 0.49 Antihypertensive medication: 28 % Lipid-lowering medication: 41 % F&V portions: 1.71 ± 0.98 <u>4 portions/d</u> Age: 57.7 ± 5.9 years Men: 71% Current smoker: 19% Weight: 90.4 ± 9.4 kg BMI: 31.0 ± 2.5 kg/m2 Waist circumference: 105 ± 6.6 cm Waist-to-hip ratio: 0.98 ± 0.05 Body fat: 36.7 ± 6.4 % 24-hr SBP: 126.5 ± 10.9 mmHg 24-hr DBP: 76.5 ± 7.7 mmHg TC: 5.35 ± 1.10 mmol/L LDL-C: 3.18 ± 1.00 mmol/L HDL-C: 1.27 ± 0.38 mmol/L TAG: 1.98 ± 0.79 mmol/L TC:HDL-C: 4.42 ± 1.10 Blood glucose: 5.64 ± 0.63 Antihypertensive medication: 39 % Lipid-lowering medication: 42 % F&V portions: 1.70 ± 0.70 <u>7 portions/d</u> Age: 54.4 ± 6.8 years Men: 66% Current smoker: 34% Weight: 87.8 ± 9.9 kg BMI: 30.6 ± 2.1 kg/m2 Waist circumference: 103 ± 6.2 cm Waist-to-hip ratio: 0.96 ± 0.05 Body fat: 37.6 ± 7.4 % 24-hr SBP: 129.7 ± 11.7 mmHg 24-hr DBP: 76.9 ± 8.3 mmHg TC: 5.70 ± 1.12 mmol/L LDL-C: 3.57 ± 1.05 mmol/L HDL-C: 1.22 ± 0.33 mmol/L TAG: 2.02 ± 0.97 mmol/L TC:HDL-C: 4.93 ± 1.44 Blood glucose: 5.54 ± 0.60 Antihypertensive medication: 28 %	1 F&V portion was defined as an 80-g serving		No evidence of a dose-response effect of increasing F&V intake on hsCRP concentrations (P_{trend}=0.33). **Summary** **This study suggests no direct effects of increasing fruit and vegetable intake on blood pressure, lipids, or inflammation. No information was provided on what fruits and vegetables were consumed**

	Lipid-lowering medication: 25 % F&V portions: 1.62 ± 0.81			
Zhong et al.[31]	Total participants: *n* = 29,615 Mean age: 51.6 ± 13.5 years *ARIC:* Men: 45.6%, Women: 54.4% Age: 54.3±5.8 years Ethnicity: Black 24%, White 76% Current smoker: 26.3% BMI: 27.7 ± 5.3kg/m^2 SBP: 121.1 ± 18.7 mmHg HDL-C: 1.3 ± 0.4 mmol/L Non-HDL-C: 4.25 ± 1.44 mmol/L Diabetes: 10.8 % Antihypertensive medication: 31% Lipid lowering medication: 3% Hormonal therapy: 10.1% Total energy 1534 kcals/d (IQR 1189-1960), Egg intake 0.14/d (IQR 0.07-0.43), dietary cholesterol 227 mg/d (IQR 0-6.2), alcohol 0g/d (IQR 0-6.2), aHEI**-2010 score 40.6±8.7 CARDIA: Men: 43.6% Women: 56.4% Age: 25.7±3.1 years Ethnicity: Black 48%, White 52% Current smoker: 29.8% BMI: 24.6 ± 5.1kg/m^2 SBP: 110.4 ± 10.9mmHg HDL-C: 1.4 ± 0.3 mmol/L Non-HDL-C: 3.2 ± 0.9 mmol/L Diabetes: 0.8% Antihypertensive medication: 2.5% Lipid lowering medication: 0% Hormone therapy: 2.5% Total energy 2460 kcal/d (IQR 1802-3348) egg intake 0.42/d (IQR 0.17-0.87), dietary cholesterol 384 ± 259-567 mg/d, alcohol 1.2 g/d (IQR 0-13.2), aHEI-2010 score 43.4 ± 11.1 FHS	Meta-analysis of prospective cohort studies Participants taken from the Atherosclerosis Risk in Communities (ARIC) Study, Coronary Artery Risk Development in Young Adults (CARDIA) Study, Framingham Heart Study (FHS), Framingham Offspring Study (FOS), Jackson Heart Study (JHS), and the Multi-Ethnic Study of Atherosclerosis (MESA) Exclusion criteria: CVD at baseline, participants consuming <500 Kcals/day and > 6000 Kcals/day, or missing data from study variables.	Primary outcomes were incident CVD (including fatal and non-fatal CHD, stroke, heart failure and other CVD deaths), and all-cause mortality. Each study assessed self-reported usual dietary intake (dietary assessment method not reported but all cohorts used different dietary assessment tools (except the two Framingham cohorts) Diet data were harmonized cohort by cohort, only baseline measures were included in the study (start dates between 1985 and 2005). Consumption frequencies were converted into estimated numbers per day using the middle value (e.g. 3-4 times/week =0.5 times per day). One serving was standardised across cohorts and food groups were constructed using the same definitions. Ingredients from mixed dishes were considered and appropriate portions determined for each cohort. Models adjusted for age, sex, race/ethnicity, education total energy, smoking status, physical activity score, alcohol intake, co-use of hormone therapy, BMI, diabetes, systolic BP, use of anti-hypertensive medication, HDL-C, non-HDL-C, and use of lipid lowering medication To further evaluate whether dietary cholesterol or egg intake within different dietary patterns altered the association with incident CVD and all-cause mortality, major food groups were adjusted individually or incorporated into 3 diet pattern scores: alternate Healthy Eating Index 2010 (aHEI- 2010) score, alternate Mediterranean Diet (MedDiet) score or Dietary Approaches to Stop Hypertension (DASH). Median follow up 17.5 years, interquartile range 13.0-21.7, maximum 31.3 years (1985-2016)	Mean cholesterol intake was 285±184 mg/d Mean egg consumption was 0.34±0.46 eggs/d Higher consumption of dietary cholesterol or eggs was significantly associated with higher risk of incident CVD and all-cause mortality in a dose dependant manner. Each additional 300mg of dietary cholesterol consumed per day was significantly associated with higher risk of incident CVD (HR 1.17; 95%CI 1.09, 1.26, adjusted ADR 3.24%; 95%CI 1.39, 5.08*) and all-cause mortality (HR 1.18; 95% CI: 1.10, 1.26], adjusted ARD 4.43%; 95% CI: 2.51, 6.36). *each additional 300mg cholesterol per day is associated with a 3.24% greater absolute risk of CVD over the follow-up period (i.e. 32 additional cases of CVD per 1000 participants). Each additional half egg consumed per day was significantly associated with higher risk of incident CVD (adjusted HR 1.06; 95% CI: 1.03, 1.10], adjusted ARD 1.11%; 95% CI: 0.32, 1.89) and all-cause mortality (adjusted HR 1.08; 95% CI: 1.04-1.11, adjusted ARD 1.93%; 95% CI: 1.01,2.76) Association between dietary cholesterol and incident CVD and all-cause mortality were no longer significant after adjusting for consumption of eggs, processed and unprocessed meat. The dietary cholesterol content of eggs fully explained the association between egg consumption and incident CVD, and

	Men: 34.2% Women: 65.8%, Age: 73.4 ± 3 years Ethnicity: White 100% Current smoker: 10.2% BMI: 26.6 ± 4.7kg/m^2 SBP: 146 ± 20.6 mmHg HDL-C: 1.3 ± 0.4 mmol/L Non-HDL-C: 4.4 ± 1.0 mmol/L Diabetes: 9.6 % Antihypertensive medication: 43% Lipid lowering medication: 5.9% Hormone therapy: 4.9% Total energy 1676 kcal/d (IQR 1802-3348), egg intake 0.14/d (IQR 0.07-0.43), dietary cholesterol 221 mg/d (IQR 152-308), alcohol 1.2 g/d (IQR 0-13.2), aHEI-2010 score 50.9 ± 9.6 FOS Men: 45.4% Women: 54.6% Age: 73.4±3 years Ethnicity: White 100% Current smoker: 19.2% BMI: 27.3 ± 4.8kg/m^2 SBP: 125 ± 18.1 mmHg HDL-C: 1.3 ± 0.4 vmmol/L Non-HDL-C: 4.0 ± 1.0 mmol/L Diabetes: 6 % Antihypertensive medication: 17% Lipid lowering medication: 6.2% Hormone therapy: 10.3% Total energy 1786 kcal/d (IQR 1413-2233), egg intake 0.14/d (IQR 0.07-0.43), dietary cholesterol 209mg/d, (IQR 153-280), alcohol 3.2 g/d (IQR 0-13.2), aHEI-2010 score 45.8±9.4 JHS Men: 37.7% Women: 62.3%, Ethnicity: Black 100% Age: 49.3 ± 10.6 years Current smoker: 11.9% BMI: 31.9 ± 7.3 kg/m^2 SBP: 124.4 ± 15.3 mmHg HDL-C: 1.3 ± 0.4 mmol/L			largely explained the association between egg consumption and all-cause mortality. The significant associations of dietary cholesterol consumption with CVD and all-cause mortality were independent of the fat amount and quality of the diet Authors found the effect of egg and dietary cholesterol remained after accounting for the beneficial effect of different dietary models; aHEI-2010 score (HR 1.18; 95% CI: 1.10, 1.26), MedDiet (HR 1.18; 95% CI: 1.10, 1.26), DASH (HR 1.19; 95% CI: 1.11, 1.27). **Summary** **This is a statistically strong study representing the ethnically diverse US population. However, the authors themselves report that the effect of increasing egg intake on incident CVD is modest and the clinical significance of this unknown. The study findings were based on a single measure of self-reported dietary intake at baseline when the average follow-up time was 17 years. This does not take into account any changes to habitual cholesterol or egg intake during that time. The results are very much in contrast to the null effects of egg consumption of CVD risk in other recent studies**.

	Non-HDL-C: 3.8 ± 1.0 mmol/L Diabetes: 11% Antihypertensive medication: 40.3% Lipid lowering medication: 7.3% Hormone therapy: 14% Total energy 1999 kcal/d (IQR 1446-2736), egg intake 0.32/d (IQR 0.09-0.65), dietary cholesterol 306mg/d (IQR 196-473), alcohol 0.1 g/d (IQR 0-1.7) aHEI-2010 score 51 ± 9.8 MESA Men: 47.6% Women: 52.4% Age: 61.4±9.6 years Ethnicity: Black 26.6%, Hispanic 22.2%,Chinese 11.8 %, White 39.4% Education: < high school 17.8%, high school 17.4%, ≥college64.9% Current smoker: 13.1% BMI: 28.3 ± 5.4kg/m^2 SBP: 125.9 ± 20.9mmHg HDL-C: 1.3 ± 0.4 mmol/L Non-HDL-C: 3.7 ± 0.7 mmol/L Diabetes: 12.4% Antihypertensive medication: 36.3 % Lipid lowering medication: 16.1 % Hormone therapy: 15.5 % Total energy 1515 kcal/d (IQL 1095-2065), egg intake 0.14/d (IQR 0.04-0.29), dietary cholesterol 209 mg/d (IQR 133-326), alcohol, 0.5g/d (IQR 0.1-5.3), aHEI-2010 score 51 ± 9.8			
Qin et al.[32]	512 896 Chinese participants in original cohort. Participants recruited between 2004-2008 from 10 geographical locations. Excluded participants with baseline cancer, CHD or stroke, self-reported diabetes of on-site fasting plasma glucose ≥ 7.0 mmol/L <u>Never/rarely</u> Participants: *n* 42,046 Age: 52.3 ± 10.8 years Men: 33.9 %	Prospective cohort study (China Kadoorie Biobank (CKB) Study. Baseline assessment of habitual frequency of egg consumption over the previous year was used to inform groups: never or rarely 1 to 3 days per month 1 to 3 days per week 4 to 6 days per week daily No details on habitual diet were provided	Primary outcomes were morbidity or mortality from CVD, IHD, haemorrhagic stroke and ischaemic stroke, as well as major coronary events (MCE) including fatal IHD death and incident non-fatal MI. Baseline data collected between 2004 and 2008 to completion, which occurred at diagnosis of CVD endpoint, death, loss to follow-up or 31st December 2015 (whichever came first). Used a non-validated, qualitative food frequency questionnaire to assess diet data Covariates collected at baseline questionnaire, including anthropometric data, socio-demographic information,	Median follow-up 8.9 years (IQR 2.15 years) At baseline 13.1% of participants reported daily consumption of eggs (usual amount 0.76 eggs/day) and 9.1% reported never or rare consumption. Among the 461,213 subjects, there were 83,977 CVD incident cases, 9,985 CVD deaths and 5,103 MCE. Compared to non-consumers, daily egg consumption was associated with lower risk of CVD (HR 0.89; 95% CI: 0.87, 0.92).

	BMI: 23.7 ± 3.5 kg/m2 Current drinking: 19.3 % Current smoking: 34.1 % Physical activity: 21.5 13.5 MET h/d Hypertension: 36.9 % Family history of CVD: 20.2 % Diet pattern New affluence: 10.3 % Traditional southern: 64.6 % Multivitamin use: 2.7 % <u>1–3 days/month</u> Participants: *n* 92,568 Age: 51.2 ± 10.6 years Men: 38.9 % BMI: 23.5 ± 3.3 kg/m2 Current drinking: 17.9 % Current smoking: 32.6 % Physical activity: 22.1 ± 14.4 MET h/d Hypertension: 34.1 % Family history of CVD: 19.3 % Diet pattern New affluence: 10.2 % Traditional southern: 64.1 % Multivitamin use: 2.6 % <u>1–3 days/week</u> Participants: *n* 2,169,00 Age: 50.2 ± 10.3 years Men: 42.2 % BMI: 23.5 ± 3.3 kg/m2 Current drinking: 18.6 % Current smoking: 32.1 % Physical activity: 21.9 ±14.1 MET h/d Hypertension: 32.2 % Family history of CVD: 19.6 % Diet pattern New affluence: 19.0 % Traditional southern: 56.6 % Multivitamin use: 3.4 % <u>4–6 days/week</u> Participants: *n* 49,182 Age: 49.7 ± 10.3 years Men: 42.3 % BMI: 23.5 ± 3.3 kg/m2		lifestyle behaviours (smoking, alcohol intake, physical activity and diet), medical history (self reported HTN and use of BP lowering medication, aspirin and statins, family history of CHD or stroke Logistic regression or multiple linear regression (for continuous variable) was conducted to compare age, sex-, site adjusted proportions or means of baseline characteristics by frequency of egg intake. HR and 95% CI were estimated for the associations between egg consumption and CVD. The multivariate model was adjusted for all covariates listed in participant characteristics.	Multivariate-adjusted HR (95% CI) for IHD was 0.88 (0.84-0.93), MCE 0.86 (0.76-0.97, haemorrhagic stroke 0.74 (0.67-0.82), and ischaemic stroke 0.90 (0.85-0.95). Daily consumers had an 11% lower risk of IHD, 18% lower risk of CVD death, and 28% lower risk of haemorrhagic stroke death compared to non-consumers. Each one-egg increment per week was associated with an 8% lower risk of haemorrhagic stroke (HR 0.92; 95% CI: 0.90, 0.95). Similar associations were observed for CVD and haemorrhagic stroke mortality HRs (daily consumption *vs* non consumption) were 0.82 (95% CI: 0.75, 0.89) and 0.72 (95% CI: 0.62, 0.84), respectively. The inverse associations with mortality from IHD and ischaemic stroke were non-significant. Further analysis demonstrated that egg consumption was not associated with morbidity of mortality of any CVD endpoint among diabetic patients (diagnosed during study). Among Chinese adults, a moderate level of egg consumption (up to <1 egg per day) was significantly associated with lower risk of CVD. **Summary** **Inconsistent with other studies. There is potential misclassification of egg consumption due to a non-validated FFQ and recall issues, change of habitual egg consumption after developing disease (reverse causality). This study did not contain any groups that eat more than one egg per day, and so no association could be made with >1 egg per day and CVD**.

	Current drinking: 18.5 % Current smoking: 31.5 % Physical activity: 21.9 ± 13.2 MET h/d Hypertension: 30.5 % Family history of CVD: 20.3 % Diet pattern New affluence: 35.6 % Traditional southern: 41.0 % Multivitamin use: 4.4 % <u>7 days/week</u> Participants: *n* 60,427 Age: 51.6 ± 10.9 years Men: 44.2 % BMI: 23.4 ± 3.4 kg/m2 Current drinking: 21.0 % Current smoking: 32.7 % Physical activity: 21.7 ± 13.9 MET h/d Hypertension: 29.0 % Family history of CVD: 21.0 % Diet pattern New affluence: 55.6 % Traditional southern: 23.7 % Multivitamin use: 6.5 %			
Alexander et al.[33]	Potentially relevant records: 245 After duplicates: 150 Excluded 84 due to study design, experimental or non-english Full texts assessed: 66 Excluded 49 due to diet pattern, missing RR for eggs, or study population with disease Number of studies in qualitative synthesis: 17 Articles in final meta analysis: 15 Approximately 276,000 participants for stroke outcome and 308,000 participants for CHD outcome Studies primarily conducted in the US, with others in Japan, Australia, Spain, and UK.	Systematic review and meta-analysis Searched PubMed (August 2015), EMBASE, and Cochrane Collaboration reports Followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting of systematic reviews and meta-analyses Bias assessed using Eggers's regression method Inclusion criteria were Prospective design Human populations Published in English Provide risk estimates and measure of variance for egg intake and CV outcomes (CHD and stroke)	Primary outcomes were incident stroke, incident CHD including mortality, incident coronary events, incident MI, incident haemorrhagic stroke, incident CVD, IHD mortality, stroke mortality, incident hospitalized or fatal HF, ischaemic stroke Follow-up of 6-26 years Relative risks comparing the highest to the lowest categories of egg intake were combined across all studies to produce summary associations. Generally these were 1 egg per day vs < 2 eggs per week. Random effects meta-analysis was used to generate summary relative risk estimates (SRREs) for high *vs* low intake and stratified intake dose-response analysis. Heterogeneity was examined in subgroups where sensitivity and regression analysis were conducted on increasing egg intake.	<u>Stroke</u> Comparing high (1 egg/d). vs. low (<2 eggs/week) egg intake, a significant 12% lower risk of stroke was observed (SRRE 0.88; 95% CI: 0.81, 0.97). Heterogeneity between studies was low Subgroup analysis based on location of study indicated a significant reduction in stroke risk in US studies (SRRE 0.90; 95% CI: 0.82, 0.99) but not in studies performed in Japan (SRRE 0.82; 95% CI: 0.58, 1.18) <u>CHD</u> Comparing high vs low egg intake, a non-significant SRRE 0.97 (95% CI: 0.88, 1.07) was observed. Subgroup analysis based on location showed no association between egg intake and CHD in US studies (SRRE

	7 studies included in the meta-analysis of egg intake and stroke 7 studies included in the meta-analysis for CHD. Studies adjusted for CHD and stroke risk factors such as age, race, BMI, physical activity, smoking, alcohol and BP. Some studies in the meta-analysis included participants with T2Dm, HTN and hyperlipidaemia.	Studies were excluded if they were case–control, cross-sectional, ecologic and experimental animal studies, or case reports, case series, commentaries, and letters to the editor.		0.99; 95% CI: 0.90, 1.10) or studies undertaken in Japan (SRRE 0.83; 95% CI: 0.61,1.11). Daily (or more) intake of eggs was not associated with risk of CHD (SRRE 0.99; 95% CI: 0.89, 1.09). No apparent trend was observed in the stratified intake dose–response analyses for egg consumption and CHD risk **Summary** **These finding are relatively consistent with those of Shin et al and Rong et al. Also, some studies included in these meta-analysis report increased risks between egg consumption and CHD and stroke risk among people with diabetes, however, methodological reasons such as not capturing any changes in dietary intake and lifestyle behaviours following a diabetes diagnosis may bias results. Many of these associations are not statistically significant and may not reflect an independent relationship. More studies are needed which take into account the overall dietary patterns and foods consumed with eggs that may increase risk of T2DM.**
Rong et al.[34]	Potentially relevant records: 1440 After duplicates: 1317 Excluded 1301 due to study design, non-human, or did not study CHD or stroke as outcome Full texts assessed: 16 Excluded 8 due to insufficient data, fewer than 3 categories of egg intake Articles in final meta analysis: 8 6 studies (9 reports) examined CHD as an outcome 6 studies (8 reports) considered stroke	Meta-analysis of prospective cohort studies examining the association between egg intake and CHD or stroke Searched PubMed and EMBASE (June 2013). Used reference lists from relevant papers and review articles Used MOOSE guidelines for the conduct of meta analyses. Quality assessed using the Newcastle-Ottawa scale Begg and Egger tests for publication bias Inclusion criteria were	Primary outcomes were CHD, CHD mortality, MI, IHD, IHD mortality, stroke and stroke mortality Length of follow-up was 8 to 26 years	Summary RR for CHD for an increase in one egg per day was 0.99 (95% CI: 0.85, 1.15, P_{trend}=0.88). RR for stroke for an increment of one egg consumed per day was 0.91 (95% CI: 0.81-1.02, Ptrend=0.10). This meta-analysis did not identify any association between egg consumption and risk of CHD or stroke. A higher intake of eggs (up to one per day) was not associated with increased risk of CHD or stroke. In a sub-group analysis of diabetic populations, the RR of CHD comparing

	263,938 participants for CHD outcome and 210,404 participants for stroke outcome Studies primarily conducted in the US	Prospective design Egg consumption was the exposure Outcomes of CHD or stroke Relative risk and 95% CI reported for at least 3 quantitative categories of egg intake Studies were excluded if they were reviews, editorials, non-human studies, and letters without sufficient data Articles reporting both CHD and stroke were treated as two separate reports as were results stratified by gender.		the highest with the lowest egg consumption was 1.54 (95% CI: 1.14-2.09; P=0.01). Diabetic subjects with a higher egg consumption had a 25% (95% CI: 0.57, 0.99, P=0.04) lower risk of haemorrhagic stroke. RR for ischaemic and total stroke in persons with diabetes were 0.91 (95% CI: 0.82, 1.01) and 0.80 (95% CI: 0.29, 2.15), respectively. Associations between egg consumption and risk of coronary heart disease and stroke were similar in subgroup analyses, which were defined by sex, study location, number of cases or participants, duration of follow-up, repeated egg consumption measurements, study quality, and whether diet variables or cholesterol levels were controlled for in models **Summary** **Studies with larger sample sizes and longer follow-up times are required to confirm these sub group results. . In long-term follow up, subjects may have changed diet; approximately half of the studies had updated diet information during the follow-up, but others have intake date from baseline only.**
Shin et al.[35]	Potentially relevant records: 72 Excluded 53 due to study design, non-human, or did not study CVD, mortality, or T2DM as outcome Full texts assessed: 19 Excluded 3 due to not reporting HR with 95% CI or use of continuous variable for egg intake Articles in final meta analysis: 16 8 studies examined CVD as an outcome; 4 studies IHD and 5 studies stroke	Meta-analysis of prospective cohort studies examining the association between egg intake and CHD or stroke Searched PubMed and EMBASE (March 2013). Used MOOSE guidelines for the conduct of meta analyses. Inclusion criteria were Prospective design Egg consumption was the exposure Outcomes of CHD or stroke	Primary outcomes were CVD, IHD, mortality, T2DM and stroke Egg consumption assessed by using a self-administered or interview-based FFQ and categorized into 3–6 groups.	<u>CVD risk</u> In 348,420 participants there were 9389 cases of incident CVD; from 239,729 participants there were 5401 cases of stroke; and from 241,900 participants there were 4189 Comparison of the highest egg consumption category (≥1 egg/day) with the lowest (≤1 egg per week or never) resulted in a pooled HR of: 0.96 (95% CI: 0.8, 1.05) for overall CVD. <u>Mortality</u>

	6 studies considered mortality, with 3 examining IHD mortality and 3 examining stroke mortality 3 studies considered diabetes as an outcome 4 reported CVD in persons with diabetes 3 examined mortality in persons with diabetes For CVD, the number of participants and duration of the follow-up ranged from 1600 to 90,735 and from 6 to 20 years, respectively For mortality, number of individuals and duration of the follow-up ranged from 4077 to 37,130 and from 9 to 20 y, respectively. For T2DM number of participants and duration of follow-up ranged from 1669 to 36,295 and from 11 to 20 y, respectively In persons with T2DM, number of patients and duration of follow-up ranged from 341 to 5672 and from 7 to 20 y, respectively	Hazard ratios and 95% CI reported for at least 3 quantitative categories of egg intake Studies were excluded if they were reviews, editorials, non-human studies, and letters without sufficient data Articles reporting both CHD and stroke were treated as two separate reports as were results stratified by gender.		In 103,202 participants there were 510 deaths from IHD and 1818 deaths from stroke. Comparison of the highest egg consumption category (≥1 egg/day) with the lowest (≤1 egg per week or never) resulted in pooled HR of: 1.13 (95% CI: 0.95, 1.33) for overall mortality, 0.98 (95% CI: 0.77, 1.24) for IHD mortality, and 0.92 (95% CI: 0.56, 1.50) for stroke mortality <u>Risk of Diabetes</u> In 69,297 participants there were 4889 cases of T2DM. Comparison of the highest egg consumption category (≥1 egg/day) with the lowest (≤1 egg per week or never) resulted in pooled HR of 1.42 (95% CI: 1.09, 1.86) <u>Risk of CVD and mortality in those with T2DM</u> In 7549 participants, comparing highest (≥1 egg/day) with the lowest (≤1 egg per week or never) category of egg consumption the pooled HR was 1.69; 95% CI: 1.09, 2.62). Egg consumption was not linked with mortality. **Summary** **Egg consumption was not associated with increased risk of CVD and cardiac mortality in the general population. However, this study observed an increased risk of incidence of T2DM with higher egg consumption, and increased risk of CVD in subjects with diabetes**
Patterson et al.[36]	Total participants at 1997: *n* 38,984 Excluded participants with cancer, CVD, diabetes, or those with unusually high or low energy intake (*n* 6010)	Prospective cohort design. Participants taken from Swedish Mammography Cohort with baseline data gathered in 1997	Primary outcome was incidence of MI Diet measured at baseline using validated 96-item FFQ. FFQ was validated against the mean intake of four 7-d weighed diet records.	Over an average follow up of 11.6 years there were 1392 cases of the primary endpoint. Comparing highest vs lowest quintiles, women in the highest quintile of total dairy foods were more likely to

	Final sample: *n* 33,636 women Q1 Participants: *n* 6798 Age: 52.9 years Never smoked: 58.4 % Past smoker: 25.7 % Current smoker: 26.3 % Physical activity: 42.2 MET h/d Waist-to-hip ratio >0.8: 46.3 BMI: 25.0 kg/m2 Alcohol consumption 0-<2.5 g ethanol/d: 46.9 % 2.5-<15.0 g ethanol/d: 43.4 % ≥15.0 g ethanol/d: 9.7 % High blood pressure: 19.8 % Elevated cholesterol: 8.7 % Family history of MI: 13.4 % Aspirin use: 41.2 % HRT use (ever): 49.4 % Q2 Participants: *n* 6912 Age: 61 years Never smoked: 52.4 % Past smoker: 23.1 % Current smoker: 22.6 % Physical activity: 42.4 MET h/d Waist-to-hip ratio >0.8: 46.1 % BMI: 24.9 kg/m2 Alcohol consumption 0-<2.5 g ethanol/d: 44.1 % 2.5-<15.0 g ethanol/d: 47.5 % ≥15.0 g ethanol/d: 8.4 % High blood pressure: 19.2 % Elevated cholesterol: 7.5 % Family history of MI: 12.9 % Aspirin use: 42.3 % HRT use (ever): 51.2 % Q3 Participants: *n* 6629 Age: 61.6 years Never smoked: 54.3 % Past smoker: 22.1 % Current smoker: 22.0 % Physical activity: 42.5 MET h/d	All women were followed from baseline until date of first MI, death, or end of the follow-up period Participants grouped on quintiles of total dairy intake Q1: 2.2 servings/d Q2: 3.5 servings/d Q3: 4.5 servings/d Q4: 6.0 servings/d Q5: 8.4 servings/d Total dairy intake was the sum of milk [full-fat (≥3.0% fat), semi-skimmed (≤1.5% fat), skimmed (0.5% fat), and pancakes], cultured milk/yogurt [full-fat (≥3.0% fat) and low-fat (≤1.5% fat)], cheese [full-fat (>17% fat), low-fat (≤17% fat), and cottage cheese/quark], cream and crème fraiche (full-fat and low-fat) intakes. Subgroup analysis performed by assigning participants to 5 groups based on the same cut-offs used for quintiles of total dairy food intake but using a sum of dairy food that excluded cheese (i.e., the sum of milk, cultured milk/yogurt, and cream). <u>Q1</u> Fruit and vegetables 366 g/d, whole grain foods 91 g/d, total dairy 181 g, milk 44 % total dairy, cultured milk/yoghurt 35 % total dairy, cheese 18 % total dairy, cream and crème fraiche 3.3 % total dairy <u>Q2</u> Fruit and vegetables 390 g/d, whole grain foods 104 g/d, total dairy 297 g, milk 41 % total dairy, cultured milk/yoghurt 40 % total dairy, cheese 18 % total dairy, cream and crème fraiche 1.5 % total dairy <u>Q3</u> Fruit and vegetables 394 g/d, whole grain foods 114 g/d, total dairy 384 g, milk 41 % total dairy, cultured milk/yoghurt 38 % total dairy, cheese 20 % total dairy, cream and crème fraiche 1.3 % total dairy	Incident cases of MI (fatal and nonfatal; International Classification of Diseases, 10th edition, code I21) from baseline (September 15, 1997) through December 31, 2008, from the Cause of Death Registry and through December 31, 2009, from the National Hospital Discharge Registry by computerized record linkage of the cohort population to the registries using the national registration number that each resident in Sweden is assigned Models adjusted for smoking status, physical activity, waist-to-hip ratio, alcohol consumption, diagnosis of hypertension, diagnosis of high cholesterol, family history of myocardial infarction, education, aspirin usage, hormone therapy usage, energy intake, dairy food groups and consumption of fruit and vegetables and whole-grain foods.	be highly educated, and have higher intakes of whole grain food. Total dairy food consumption (8.4 servings/d) was inversely associated with risk of MI (HR 0.77; 95% CI: 0.63, 0.95, P_{trend}=0.047). Milk and cultured milk/yoghurt were not associated with risk of MI in multivariate-adjusted models (HR 1.14; 95% CI: 0.95, 1.36, P_{trend}=0.115, and HR 0.89; 95% CI: 0.75, 1.05, P_{trend}=0.149, respectively). Women in the highest quintile of cheese intake (6.0 servings/d) had a significantly lower risk of MI vs. low cheese consumers (HR 0.74; 95% CI: 0.60, 0.91, P_{trend}=0.006). When cheese was removed from total dairy variable, total diary was not associated with MI (HR for highest vs. lowest quintile 0.83; 95% CI: 0.57, 1.21). At intakes reported in the study (0.4 servings/d), cream and full-fat crème fraiche were not associated with MI risk Women who reported using butter on bread but not in cooking had a 34% significantly higher risk compared with women who did not use butter at all The association for total dairy food was attenuated and became non-significant after adjustment for calcium and phosphorous (HR for the highest vs. the lowest quintile: 0.85; 95% CI: 0.62, 1.16 and 0.83; 95% CI: 0.63, 1.06, respectively. The association for cheese was attenuated and became non-significant after adjustment for calcium (HR for the highest vs. the lowest quintile: 0.81; 95% CI: 0.62, 1.05).

	Waist-to-hip ratio >0.8: 45.9 % BMI: 25.0 kg/m2 Alcohol consumption 0-<2.5 g ethanol/d: 44.4 % 2.5-<15.0 g ethanol/d: 47.3 % ≥15.0 g ethanol/d: 8.3 % High blood pressure: 18.9 % Elevated cholesterol: 7.4 % Family history of MI: 13.2 % Aspirin use: 43.8 % HRT use (ever): 50.5 % Q4 Participants: *n* 6573 Age: 61.9 years Never smoked: 53.8 % Past smoker: 22.6 % Current smoker: 22.0 % Physical activity: 42.7 MET h/d Waist-to-hip ratio >0.8: 46.0 % BMI: 24.8 kg/m2 Alcohol consumption 0-<2.5 g ethanol/d: 44.9 % 2.5-<15.0 g ethanol/d: 46.9 % ≥15.0 g ethanol/d: 8.2 % High blood pressure: 18.7 % Elevated cholesterol: 6.8 % Family history of MI: 13.1 % Aspirin use: 43.7 % HRT use (ever): 51.4 % Q5 Participants: *n* 6724 Age: 61.7 years Never smoked: 52.4 % Past smoker: 22.0 % Current smoker: 24.1 % Physical activity: 42.0 MET h/d Waist-to-hip ratio >0.8: 45.7 % BMI: 24.8 kg/m2 Alcohol consumption 0-<2.5 g ethanol/d: 46.8 % 2.5-<15.0 g ethanol/d: 44.3 % ≥15.0 g ethanol/d: 8.9 % High blood pressure: 18.4 % Elevated cholesterol: 6.7 % Family history of MI: 13.4 % Aspirin use: 45.3 %	 Q4 Fruit and vegetables 406 g/d, whole grain foods 121 g/d, total dairy 461 g, milk 40 % total dairy, cultured milk/yoghurt 37 % total dairy, cheese 21 % total dairy, cream and crème fraiche 1.1 % total dairy Q5 Fruit and vegetables 423 g/d, whole grain foods 140 g/d, total dairy 673 g, milk 38 % total dairy, cultured milk/yoghurt 37 % total dairy, cheese 24 % total dairy, cream and crème fraiche 0.8		Total low-fat or full fat milk intake was not associated with MI risk (comparing highest vs. lowest HR 1.03; 95% CI: 0.89, 1.18, P_{trend}=0.660 and HR 1.10 95% CI: 0.92, 1.31, P_{trend}=0.283, respectively). Higher intakes of full fat cheese (4.0 servings/d) was associated with a significantly lower risk of MI (HR comparing highest vs. lowest: 0.83; 95% CI: 0.68, 1.01, P_{trend}=0.035). Adjusting for calcium attenuated this association. **Summary** **This cohort study showed a non-linear association between dairy intake and risk of MI, and subsequent analysis showed different types of dairy food have different associations with risk of MI. A high intake of cheese was associated with a significantly lower risk of MI, whereas the use of butter on bread was associated with an increased risk. Studies should focus on individual dairy components in future analysis**

	HRT use (ever): 51.2 %			
Alexander et al.[37]	Potentially relevant records: 5928 Screened 5928 by title After duplicates 1649 Excluded 1596 due to study design or clinical outcomes Full texts assessed: 53 Excluded 21 due to calcium supplementation or diet pattern Articles in final meta analysis: 31 None of the included studies were based on RCT data Studies published between 1996-2015 with baseline dietary assessment between 1965 – 2001 Study countries included USA, Europe, the Nordic countries, Australia and Japan Over 1,000,000 total participants	Systematic review and meta-analysis of prospective cohort studies investigating dairy consumption and CVD Searched PubMed and EMBASE. Additional records found through screening bibliographies Followed PRISMA guidelines for reporting of systematic reviews and meta-analyses Exposure was total dairy intake, specific dairy products (e.g. milk, cheese, yoghurt), Ca from dairy products (reported as an analytical variable in the individual studies) and low- and full-fat dairy intake Inclusion criteria were Prospective design Adult population English language Provide risk estimates and measures of variance for dairy intake and CVD Studies were excluded if they studied dietary patterns i.e. dairy product patterns and CVD outcomes	Primary outcomes included CVD, CHD and stroke. Results expressed as summary relative risk estimates (SRREs)	<u>Total Diary Intake</u> 4 studies reported a composite of 'total dairy intake' with 'total CVD'. Comparing low and high intakes, total dairy intake was associated with a 12% lower risk of total CVD (SRRE 0.88; 95% CI: 0.75, 1.04) 7 studies total dairy intake and CHD reporting a SRRE of 0.91 (95% CI: 0.80 - 1.04). Significant heterogeneity was reported. Subgroup analysis of US-only studies showed no relationship between total dairy and risk of CHD (SRRE 0.99; 95% CI: 0.92, 1.07). Studies with a follow-up ≤15 years showed a significant SRRE for CHD risk (0.81; 95% CI: 0.71, 0.93). Studies with a follow-up ≥15 years showed no relationship. No clear relationship was observed for either full-fat diary or low-fat diary and CHD risk (SRRE 1·05; 95 % CI 0·93, 1·19, and SRRE 0·90; 95 % CI 0·82, 0·98, respectively) 7 studies reported on the association between total diary and stroke. Total dairy was significantly inversely related to stroke (SRRE 0·91; 95 % CI 0·83, 0·99). There was modest heterogeneity which was explained by duration of follow-up, fat content, and amount consumed. Studies with a follow-up ≥15 years resulted in an SRRE of 0.88 (95% CI: 0·82, 0·95). Both full-fat dairy intake (SRRE 0·91; 95 % CI 0·84, 0·99) and low-fat dairy intake (SRRE 0·90; 95 % CI 0·83,0·96) were associated inversely and significantly with stroke. <u>Milk</u>

				4 studies reported milk in association with total CVD. The SSRE was 0.94 (95% CI: 0.86, 1.03). 6 studies reported the association between total milk and CHD. Comparing low and high intakes total milk was not associated with CHD risk (SRRE 1.05; 95% CI: 0.95, 1.16). Subgroup analysis considering location or suggested a lower risk in UK-based studies (SSRE 0.84; 95% CI: 0.67, 1.05) and a positive association in women (SSRE 1.15; 95% CI: 1.00, 1.33). 7 studies reported the association between total milk and stroke. Comparing low and high intakes total milk was not significantly associated with risk of stroke (SRRE 0.90; 95% CI 0.79, 1.02) although there was substantial heterogeneity. No effect was observed in subgroup analysis considering sex or duration of follow-up <u>Cheese</u> 3 studies suggested an inverse non-statistically significant association with total CVD (SRRE 0.89; 95% CI: 0.78, 1.01). 5 studies showed a significant inverse relationship between cheese intake and CHD risk (SRRE 0.82; 95% CI: 0.72, 0.93). >1.5 servings of cheese was associated with significant inverse SRRE (0.86; 95% CI: 0.79, 0.94). 4 studies showed a significant inverse association with cheese intake and risk of stroke (SRRE 0.87; 95% CI: 0.77, 0.99). Similar responses were observed to CHD risk, with >1.5 servings associated with lower risk of stroke (SRRE 0.92; 95% CI: 0.87, 0.97). 3 studies examined the relationship between yoghurt and total CVD, and 4

				studies examined the relationship with CHD. Yoghurt intake was not associated with either outcome. <u>Calcium from dairy products</u> In 4 studies diary calcium was not associated significantly with total CHD (SRRE 0.94; 95% CI: 0.82, 1.08). Comparing low vs. high, diary calcium was significantly and inversely associated with lower risk of stroke (SRRE 0.69; 95% CI: 0.60, 0.81). **Summary** **Evidence from this meta analysis suggests that specific dairy components may be associated with lower risk of CHD and stroke. This is important given the content of dairy (SFA, protein) and demonstrates the importance of considering the whole food matrix, rather than individual nutrients.**
Soedamah-Muthu et al.[38]	No information provided on number of articles searched for in this updated systematic review and meta analysis, only number of newly added texts Previous meta analysis relevant to this updated one include: Gijsbers L, Ding EL, Malik VS, de Goede J, Geleijnse JM, Soedamah-Muthu SS. Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies. Am J Clin Nutr. 2016;103(4):1111–1124 Guo J, Astrup A, Lovegrove JA, Gijsbers L, Givens DI, Soedamah-Muthu SS. Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies.	Systematic review and meta-analysis of prospective cohort studies investigating dairy consumption and cardiometabolic disease Searched PubMed (July 2018). Additional records found through reference lists of recent reviews. Followed PRISMA guidelines for reporting of systematic reviews and meta-analyses Exposure was total dairy intake, specific dairy products (e.g. milk, cheese, yoghurt), Ca from dairy products (reported as an analytical variable in the individual studies) and low- and full-fat dairy intake Inclusion criteria were Prospective design Adult population Reported data on dairy consumption in relation to T2DM, CHD, and stroke	Primary outcomes included diabetes and CHD	26 cohort studies examined the relationship between total dairy (per 200 g/d) and diabetes. There was a borderline significant association between total dairy and risk of diabetes (RR 0.97; 95% CI: 0.95, 1.00). Per 200 g/d increment in low fat dairy was associated with a 4% lower risk of diabetes (RR 0.96; 95% CI: 0.92, 1.00). Comparing 80 g/d vs.0 g/d of yoghurt, there was an inverse significant association with diabetes (RR 0.86; 95% CI: 0.83, 0.90). Substantial heterogeneity was noted in all studies for diabetes outcome. 15 cohorts were included for the association between total dairy and milk in relation to CHD. Total dairy or milk was not association with incident CHD per 200 g/d increment (RR 1.00; 95%

	Eur J Epidemiol. 2017 Apr; 32(4):269-287. de Goede J, Soedamah-Muthu SS, Pan A, Gijsbers L, Geleijnse JM. Dairy consumption and risk of stroke: a systematic review and updated dose-response meta-analysis of prospective cohort studies. J Am Heart Assoc. 2016;5(5). 10.1161/JAHA.115.002787	Studies were excluded if they were on animals, children <18 years of age, or patient populations If dairy intake was only reported in servings, without the actual portion size, portion sizes of 177 g for total, low-fat, and full-fat dairy; 244 g for total, low-fat and full-fat milk; 244 g for yogurt; and 43 g for cheese were used to estimate grams per day		CI: 0.98, 1.03 and RR 1.01; 95% CI: 0.97, 1.04, respectively). Total dairy was not significantly associated with stroke (RR 0.98; 95% CI: 0.96, 1.01). Low fat and full fat diary had a similar significant inverse relationship per 200g/d increment with stroke (RR 0.97; 95% CI: 0.95, 0.99, and RR 0.96; 95% CI: 0.93, 0.99, respectively). An increment of 200 g/d of milk intake was associated with an 8% lower risk of stroke (RR 0.92; 95% CI: 0.88, 0.97). **Summary** **In this updated meta-analysis of observational studies examining diary intake with T2DM, CHD, and stroke, yoghurt intake was inversely associated with diabetes, and total dairy or milk was not associated with CHD. This study suggests a neutral or small beneficial associations between dairy components and cardiometabolic disease.**
Buziau et al.[39]	Total participants: *n* 8748 For T2DM cohort: *n* 7633 For CVD cohort: *n* 7679 <u>Tertile of energy-adjusted dairy intake</u> <u>T1</u> Participants: *n* 2916 Age: 52.5 ± 1.5 years BMI <25 kg/m2: 42 % 25-29 kg/m2: 31.7 % ≥ 30 kg/m2: 26.3 % Never smoked: 58.4 % Past smoker: 25.7 % Current smoker: 26.3 % Alcohol* Non-drinker: 13.9 % Rarely drinker: 26.9 % Low-risk drinker: 52.2 % Risky drinker: 7.0 %	Prospective cohort design. Participants taken from The Australian Longitudinal Study on Women's Health Study used women from 1946–1951 cohort Group on tertiles of energy-adjusted total dairy intake Maximum follow-up of 15 years Dairy products (g/d) were classified as "yogurt," "total cheese" (all types of cheese), "total fermented dairy" (sum of yogurt and total cheese), "total nonfermented dairy" (all types of milk), and "total dairy" (sum of total fermented dairy and nonfermented dairy). <u>T1</u> Total dairy 204-233 g/d,	Primary outcomes were self-reported physician-diagnosed T2DM and CVD Diet measured using validated 101-item FFQ and a 10-point scale (ranging from never to ≥3 times/d), except for milk (quantity of milk/d). Australian Food Composition Database (NUTTAB95) was used to compute energy and nutrient intakes BMI, weight, and physical activity were self-reported Models were adjusted for age, education, smoking status, alcohol consumption, and physical activity level, BMI, dietary variables and total energy intake. To minimize the possibility of reverse causality, ORs were estimated, excluding women with self-reported disease diagnosis within the first 3 y of follow-up	Women in the highest tertile of energy-adjusted total dairy intake were more likely to have a lower BMI and to be higher educated, a never smoker, classified as rarely drinker, and physically active. During follow-up, 701 cases of T2DM were reported. Women in highest tertile of yoghurt intake had lower odds of developing T2DM (OR 0.81; 95% 0.67, 0.99, P_{trend}=0.041). Adjustment for diet variables attenuated this relationship (OR 0.88; 95% CI: 0.71, 1.08, P_{trend}=0.21). Other categories (total cheese, total fermented dairy intake, total nonfermented dairy, and total dairy) were not associated with T2DM risk in fully adjusted models

	Physical activity <600 MET min/wk: 60.8 % 600-1199 MET min/wk: 18.4 % ≥1200 MET min/wk: 20.8 % <u>T2</u> Participants: *n* 2916 Age: 52.5 ± 1.5 years BMI <25 kg/m2: 44.5 % 25-29 kg/m2: 32.9 % ≥ 30 kg/m2: 22.6 % Never smoked: 62.1 % Past smoker: 24.7 % Current smoker: 13.2 % Alcohol* Non-drinker: 11.9 % Rarely drinker: 25.7 % Low-risk drinker: 56.5 % Risky drinker: 5.6 % Physical activity <600 MET min/wk: 55.0 600-1199 MET min/wk: 21.0 % ≥1200 MET min/wk: 24.0 % <u>T3</u> Participants: *n* 2916 Age: 52.5 ± 1.5 years BMI <25 kg/m2: 45.8 % 25-29 kg/m2: 33.3 % ≥ 30 kg/m2: 20.9 % Never smoked: 62.1 % Past smoker: 24.1 % Current smoker: 13.8 % Alcohol* Non-drinker: 11.2 % Rarely drinker: 28.7 % Low-risk drinker: 56.1 % Risky drinker: 4.1 % Physical activity <600 MET min/wk: 53.1 % 600-1199 MET min/wk: 22.9 % ≥1200 MET min/wk: 24.1% *rarely drinker" (any alcohol consumption <1 time/mo), "low-risk	1610 ± 543 kcal/d, total fat 36.6 ± 5.6 % total energy, SFA 14.4 ± 3.3 % total energy, MUFA 13.1 ± 2.4 % total energy, PUFA 5.8 ± 1.9 % total energy, protein 20.5 ± 3.7 % total energy, total carbohydrate 43.6 ± 7.2 % total energy, sugars 18.4 ± 5.7 % total energy, starch 24.9 ± 5.1 total energy, fibre 20.0 ± 8.0 % total energy, alcohol 10 ± 14 g/d, fruit 282 ± 200 g/d, vegetables 139 ± 63 g/d, whole-grain bread 34 ± 14 g/d, red meat 48 ± 46 g/d, processed meat 20 ± 22 g/d, fish 38 ± 44 g/d, sugar-sweetened beverages 0.6 ± 0.9 servings/d, coffee 1.3 ± 1.2 servings/d, tea 1.5 ± 1.2 servings/d <u>T2</u> Total dairy 281-395 g/d 1569 ± 528 kcal/d, total fat 34.5 ± 5.6 % total energy, SFA 13.6 ± 3.4 % total energy, MUFA 12.1 ± 2.3 % total energy, PUFA 5.6 ± 2.0 % total energy, protein 20.8 ± 3.2 % total energy, total carbohydrate 45.4 ± 6.4 % total energy, sugars 21.0 ± 5.4 % total energy, starch 24.1 ± 4.6 % total energy, fibre 20.0 ± 8.0 % total energy, alcohol 10 ± 13 g/d, fruit 289 ± 179 g/d, vegetables 133 ± 59 g/d, whole-grain bread 35 ± 16 g/d, red meat 40 ± 36 g/d, processed meat 17 ± 16 g/d, fish 34 ± 37 g/d, sugar-sweetened beverages 0.5 ± 0.7 servings/d, coffee 1.4 ± 1.2 servings/d, tea 1.6 ± 1.2 servings/d <u>T3</u> Total dairy 420-631 g/d 1555 ± 477 kcal/d, total fat 32.6 ± 6.1 % total energy, SFA 13.1 ± 3.7 % total energy, MUFA 11.3 ± 2.3 % total energy, PUFA 5.2 ± 2.1 % total energy, protein 21.7 ± 3.2 % total energy, total carbohydrate 46.5 ± 6.0 % total energy, sugars 23.4 ± 5.4 % total energy, starch 22.8 ± 4.6 total energy, fibre 20 ± 78 % total energy, alcohol 9 ± 13 g/d, fruit 293 ± 176 g/d, vegetables 130 ± 57 g/d, whole-grain bread 34 ± 16 g/d, red meat 34 ± 32 g/d, processed meat 15 ± 14 g/d, fish 32 ± 35 g/d, sugar-sweetened beverages 0.4 ± 0.7		835 cases of new CVD occurred during follow-up. Comparing highest vs. lowest tertiles, women with the highest intake of yoghurt and total fermented dairy had significantly lower risk of CVD compared (OR 0.84; 95% CI: 0.70, 1.00, P_{trend}=0.05, and OR 0.80; 95% CI: 0.67, 0.97, P_{trend}=0.017, respectively). Adjustment for other dietary variable and total energy attenuated this relationship for yoghurt and total fermented dairy (OR 0.87; 95% CI: 0.72,1.04, Ptrend=0.13, and OR 0.83; 95% CI: 0.69, 1.00, Ptrend=0.048). No association was seen for total cheese, total nonfermented dairy, or total dairy. **Summary** **In this prospective cohort study, higher intakes of total fermented dairy and lower risk of CVD. Dairy may also be a marker of a healthy diet, as women in this cohort who consumed that highest total dairy also had lowest prevalence of obesity, and consumed higher quantities of vegetables, and lower amounts of SFA, sugar-sweetened beverages, and processed meats.** .

	drinker" (≤14 drinks/wk), and "risky drinker" (≥15 to 28 drinks/wk)"	servings/d, coffee 1.5 ± 1.2 servings/d, tea 1.7 ± 1.2 servings/d		
Fontecha et al.[40]	Potentially relevant records: 2940 After duplicates: 2172 Full texts assessed: 31 Full texts assessed: 53 Excluded 15 due to texts being narrative reviews or not reporting data for dairy products consumption Articles in final overview of reviews for CVD events: 17 Reports published between 2004-2017. Sample size ranged from 2350 to 764,917 with participants followed for 5-83 years. Age ranged from 8-103 years 11 studies reported total dairy 9 on regular vs. low fat 2 fermented dairy information 9 studies on milk consumption 2 on high vs low fat milk consumption 2 on nonfermented milk consumption 1 on fermented milk consumption Cheese, butter and cream considered in 9 studies For updated meta analysis: 12	Overview of systematic reviews and meta-analyses Searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science databases from their inception to April 2018. Reference lists were also reviewed Followed Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting of systematic reviews and meta-analyses Bias assessed using AMSTAR 2. Only systematic reviews and meta-analyses addressing the relation between dairy product consumption and cardiovascular outcomes were considered. Meta-analyses had to include longitudinal studies, written in English, and followed systematic review methodology For RCTs on biomarkers, prospective, parallel and cross-over designs were eligible. Studies were required to provide a dietary supplement or specific diet containing dairy. Studies were excluded if a supplement could confound the effect of the milk or dairy product administered.	Primary outcomes for CV events were cardiovascular outcomes were incidence and mortality of CVD, CHD, and stroke. Some studies reported risk of IHD, MI, HF, and ischaemic and haemorrhagic stroke For RCTs and biomarkers of cardiometabolic risk SBP), DBP, and plasma lipids (TC, LDL-C, HDL-C, and TAGs) were considered	The maximum number of cardiovascular events, including fatal and nonfatal outcomes, was 11,019 for CVD, 37,049 for CHD, and 39,352 for stroke <u>Total dairy products</u> Collectively, total dairy intake was not associated with CVD 5 meta-analyses reported risk of CHD (total, incidence or mortality). Total dairy was neutral for CHD risk with similar results for high fat dairy. A significant lower risk was found for low-fat products (RR 0.90; 95% CI: 0.82, 0.98). 1 meta-analysis indicated total dairy was associated with a lower risk of MI (RR 0.83; 95% CI: 0.66, 0.99). 4 meta-analyses considered a dose-response relationship between total dairy and CHD. 3 studies found no differences with an increase of 200 g/d. 1 study showed significantly reduced risk with increments of 300 and 600 g/d (RR 0.88; 95% CI: 0.80, 0.96 and RR 0.90; 95% CI: 0.79, 0.94, respectively). 7 meta-analyses reported the association between stroke and total dairy intake. 6 studies found a significant inverse association between total dairy intake and stroke. 5 meta-analyses reported the association between regular- and low-fat dairy and stroke. Both high fat and low fat dairy was inversely associated with stroke. 4 meta-analyses examined the link with total dairy intake and ischaemic stroke risk. 1 meta-analysis found a significant

				inverse association (RR 0.79 95% CI: 0.68 – 0.91) with 3 reporting no association. <u>Milk</u> 2 meta-analyses reported associations between milk and CVD incidence, with 1 showing a protective effect (RR 0.84; 95% CI: 0.78, 0.90). 2 meta-analyses showed no association between milk intake and increased CHD or IHD risk 5 studies analysed fatal and non-fatal stroke in association with total milk intake. 1 reported a significant inverse relationship (RR 0.83; 95% CI: 0.77, 0.90) with 4 showing no association. Dose response analysis for milk was reported in 2 meta-analyses. Incremental intakes of 200 g/d were associated with lower CVD (RR 0.94; 95% CI: 0.89, 0.96) but no relationship was found with 244g/d increments, or increased milk intake and CHD incidence. 1 study suggested higher risk of haemorrhagic stroke for each 200 g/d increment of high-fat milk vs low-fat milk (RR 1.04; 95% CI: 1.02, 1.06). <u>Cheese</u> 3 meta-analyses analysed the relationship between high vs. low cheese intake and CVD risk. One study suggested an inverse association (RR 0.90; 95% CI: 0.82, 0.99) and 2 showed no association. No associations were observed with either high- or low-fat cheese and CVD risk, or dose-responses of 10 g/d or 50 g/d. 2 studies showed a significantly reduced risk for CHD associated with increased cheese intake, and 2 showed

				no association. There were no differences with either high- or low-fat cheese and associations (null) will CHD risk. Dose-responses for cheese intake of 50 g/d and 75 g/d were associated with lower CHD risk. 5 studies reported on the association between cheese intake and stroke. 4 studies showed a significant inverse association with stroke, and 1 showed no significant association. 1 dose response analysis of cheese intake and risk of stroke showed a significantly lower risk of stroke when cheese intake was increased by 50 g/d or 75 g/d (RR 0.86; 95% CI: 0.77, 0.99, and RR 0.92; 95% CI: 0.87, 0.97, respectively). <u>Yoghurt and Fermented products</u> 2 meta-analyses reported on the association between yoghurt intake and CVD, showing no significant association. No significant association was also observed between yoghurt and CHD risk (3 meta-analyses), or risk of stroke (2 meta-analyses). Increments of 50 or 100 g/d were not associated with fatal and non-fatal CHD events 1 study suggested consumption of fermented milk was significantly inversely associated with risk of stroke (RR 0.80; 95% CI: 0.71, 0.89), and an increment of 200 g/d of fermented dairy was associated with lower risk of CVD, but not CHD risk <u>Butter and Cream</u> No significant association were found for butter and CVD (1 meta-analysis), CHD (2 meta-analyses), and stroke (4 meta-analyses). <u>Dairy Products and Cardiometabolic Biomarkers</u> Increased fermented dairy intake was associated with lower TC and LDL-C in

				4 meta-analyses. 1 meta-analysis found no differences in LDL-C when comparing whole-fat dairy with low-fat dairy products. 8 studies examined the effect of dairy consumption on blood pressure. 6 reported a significant decreased in SBP and 5 reported a significant decreased in DBP. In updated meta-analysis, no significant changes in TC (-0.06 mmol/L; 95% CI: -0.19, 0.07 mmol/L), LDL-C (-0.06 mmol/L; 95% CI: -0.16, 0.03 mmol/L) were seen relating to total dairy consumption. Heterogeneity was high for TC and LDL-C Dairy product consumption did not result in significant changes in SBP (-0.41 mmHg; 95% CI: -1.73, 0.91) or DBP (−0.77 mmHg; 95% CI: -1.81, 0.27). Heterogeneity was low for BP trials. **Summary** **This is the most comprehensive study to date combining multiple systematic reviews and meta-analyses, multiple types of dairy, in addition to biomarkers and hard CV end-points. The main findings suggest that total dairy products (either regular or low-fat) have a null or slightly beneficial association with CV health (risk of CVD, CHD, or stroke). Thus advice to limit them based on their SFA content may not be beneficial, and more research is needed into fermented dairy.**
Zhao et al.[41]	Potentially relevant records: 2768 Excluded 2515 due to unreported outcomes for diseases of interest or quantifying alcohol exposure 65 studies excluded for not being original.	Updated Meta-Analysis of Cohort Studies quantifying the association between alcohol consumption and CHD mortality. Searched PubMed and EMBASE (March 2013).	Primary outcome was presence or absence of mortality from CHD. CHD defined as per ICD-10; I20-I25 as per WHO, 2010 Weighted RR estimates adjusted for between-study variation, abstainer group biases, mean age, sex of study population, alcohol measure accuracy ethnicity (mainly	Pooled 269 risk estimates showed a significantly higher risk among former drinkers (RR 1.25; 95% CI: 1.03, 1.51, P=0.0215) and a significantly lower risk among low-, medium-, and high-volume drinkers (RR 0.80; 95% CI: 0.69, 0.93; 0.80; 95% CI: 0.69, 0.94; and 0.86; 95%

	88 studies excluded due to the combining morbidity and mortality, no alcohol categories, restricted to sample with pre-existing conditions, duplicate/published in different journals. 87 studies excluded for meta-analysis of all-cause of mortality. Articles in final meta-analysis: 45 45 unique studies selected included 269 estimates of the risk relationship between level of alcohol consumption and CHD mortality. There were 2,913,140 subjects of all ages, ethnicity and medical conditions and 65,476 deaths available for the analysis 17 reported RR estimates for men and women separately, 21 for men only, 2 for women only, and 5 for both sexes combined. Only 7 studies (53 risk estimates) were free from abstainer bias. 25 studies (132 risk estimates) had both former and occasional drinker bias, 8 studies (41 risk estimates) had only former drinker bias, and 5 studies (43 risk estimates) had only occasional drinker bias. 5 studies were conducted in Asian countries (3 in China, 2 in Japan) and 40 in countries with mainly White populations (22 in the United States, 18 in Australia or European countries).	Followed PRISMA guidelines followed for identifying relevant studies. Inclusion criteria were: Studies must be prospective in design Published in English Report mortality from CHD as an outcome Minimum of three levels of alcohol consumption quantified for human subjects Studies were excluded if they did not meet inclusion criteria Participants grouped based on daily alcohol use in grams of ethanol assessed at baseline and compared with a reference group of variously defined “nondrinkers”: Former drinkers now completely abstaining; Current occasional drinkers: up to one drink per week (<1.30 g per day); Current low-volume drinkers: up to two drinks or 1.30–24.99 g per day; Current medium-volume drinkers: up to four drinks or 25–44.99 g per day; Current high-volume drinkers: up to six drinks or 45–64.99 g per day; Current higher volume drinkers: six drinks, 65 g, or more per day. Studies were classified on the presence or absence of abstainer biases by whether abstainers included both occasional drinkers and former drinkers, abstainers included occasional drinkers only, abstainers included former drinkers only, and abstainers included neither occasional drinkers nor former drinkers. Subgroups of studies were stratified by gender, mean age, and ethnicity and control for heart health in order to explore variation in the effects of alcohol use on CHD mortality according to different values of these variables.	White vs. not), control of heart health at baseline, socioeconomic status, and smoking status in individual studies. Covariates included the presence of former and/or occasional drinker biases, mean age of cohort at baseline, gender of study participants, primarily White ethnicity of study population or not, alcohol measure accuracy, control of social status, smoking status, and indication of prior heart conditions	CI: 0.73, 1.01, respectively,) compared with abstainers The mean estimates indicated significantly decreased risk of CHD mortality among male drinkers who drank 1.3–24.99 g/d (RR 0.86; 95% CI: 0.74, 0.99, P=0.0382) and 25-44.99 g/d (RR 0.84; 95% CI: 0.72, 0.97, P=0.162). In women, those who drank 1.3–24.99 and day had a lower risk of CHD mortality compared with abstainers (RR 0.81; 95% CI: 0.66, 0.99, P=0.443). However, fully adjusted RRs were significantly higher among both male former (RR 1.37; 95% CI: 1.12, 1.67, P=0.0026) and marginally higher among male occasional drinkers (RR 1.24; 95% CI: 1.00, 1.55, P=0.0526) but not for women. Fully adjusted models for the studies with mean age older than age 55 years at baseline showed significantly increased RRs for former drinkers (RR 1.34; 95% CI 1.08, 1.65, P=0.0078 and decreased RRs for low (RR 0.81; 95% CI: 0.69, 0.95, P=0.0080), medium (RR 0.77; 95% CI: 0.66, 0.90, P=0.0015) and all current drinkers (RR 0.83; 95% CI: 0.75, 0.92, P=0.0074). In participants aged 19-55 years, compared to abstainers both former drinkers and occasional drinkers had a significantly increased risk of CHD mortality (RR 1.45; 95% CI: 1.08, 1.95, P=0.0136, and RR 1.44; 95% CI: 1.09, 1.89, P=0.101, respectively. In studies that controlled for heart-health at baseline (i.e. excluded participants with heart conditions) fully-adjusted models showed no significant associations between alcohol intake and

				CHD mortality. The only significant association was observed comparing former drinkers vs. abstainers (RR 1.39; 95% CI: 1.03, 1.86, P=0.0295). In studies that included all participants (i.e. did not control for heart health at baseline), compared with abstainers decreased RRs for current low volume (0.78; 95% CI: 0.68,0.89, P=0.0005), medium volume (0.76; 95% CI: 0.66, 0.88, P=0.0002), high volume (0.84, 95% CI: 0.72, 0.99, P=0.0319), and all current drinkers (0.83, 95% CI: 0.76, 0.91, P=0.0041) were observed. In studies that were regarded as higher quality (n=5; free from former drinker bias, controlled for smoking, had a mean age up to 60 years, followed up to a mean age of 55 years, and had adequate measures of alcohol exposures) comparing former drinkers vs. abstainers was the only category to show a positive association with risk of CHD mortality (RR 1.40; 95% CI: 1.08, 1.84, P=0.0186) Fully adjusted models showed a significantly increased risk among former drinkers (RR 1.28) and decreased risk among low- (RR 0.81) and medium-volume drinkers (RR 0.83) compared with abstainers in the White populations. In Asian populations, the RR estimates were similar to the White populations but were not significant. **Summary** **In this analysis of prospective cohort studies, CHD risk was significantly lower in individuals classed as low- and medium-volume drinkers, and did not suggest high intakes of alcohol were associated with increased risk. However alcohol intake was self-reported at 1 time point – not capturing changes during life – or**

				risk estimates were based on small study populations (i.e. heavy drinkers in Asian populations). Because of additional confounding variables and this study is not able to support the concept that alcohol intake is cardioprotective
Larsson et al.[42]	Initial sample: 48,850 men, 39,227 women. Sample excluded due to missing personal identification number, death, diagnosis of ischaemic heart disease, HF, or cancer before baseline, and not provided information on alcohol consumption. Analysis sample: 40,590 men, 4,022 women. Age: 45–79 years old men, 49–83 years women. All participants free of IHD and HF at baseline <u>COSM</u> <u>Never Drinkers</u> Participants: *n* 1844 Age: 64.3 years BMI: 25.6 kg/m2 Postsecondary education: 15.8 % Family history of MI: 11.4 % Current smokers: 6.4 % Walk/bicycle = 40 min/day: 33 % Exercise = 2 h/week: 53.6 % Aspirin use = 7 tablets/week: 4.2 % Hypertension: 20.4 % Hypercholesterolemia: 9.4 % Diabetes: 9 % Atrial fibrillation: 1.7 % mDASH diet score: 20.6 <u>Former Drinkers</u> Participants: *n* 2357 Age: 63.7 years BMI: 26.1 kg/m2 Postsecondary education: 11.6 % Family history of MI: 16 % Current smokers: 32.1 % Walk/bicycle = 40 min/day: 37.3 %	Participants taken from the Cohort of Swedish Men (COSM) and Swedish Mammography Cohort (SMC). Men were categorised into eight groups according to their alcohol drinking status and number of drinks consumed per week: never (lifetime abstainers), former, current drinkers: occasional drinkers <1, numbers of drinks between 1–6, 7–14, 15–21, 22–28, and 28 per week. Because of lower alcohol consumption in women than in men, the two highest categories were collapsed into one category (i.e. highest category >21 drinks/week).	Primary outcomes were risk of MI and HF. Outcomes were determined from the Swedish National Patient Register and the Swedish Cause of Death Register. ICD-10 code I21 used to define MI and and I50 and I11.0 for HF. Validated FFQs at baseline were given in 1997. Patients were followed–up until December 2010. Average alcohol consumption in the past year prior to baseline was assessed with six questions on alcoholic beverages, including: class I beer (alcohol by volume, 2.25%), class II beer (2.8–3.5%), class III beer (>3.5%), wine (12%), strong wine (>18%), and liquor. Weekly alcohol consumption was calculated by multiplying the frequency of consumption of each alcoholic beverage by the amount consumed per occasion. One drink was defined as 12 g alcohol (ethanol). Covariates data on education, family history of myocardial infarction, smoking, weight, height, physical activity, aspirin use, history of hypertension, hypercholesterolemia, and diabetes were identified using the baseline questionnaire, participants provided. Self-reported history of hypertension and diabetes was complemented with data on diagnosis of these diseases in the Swedish National Patient and Diabetes Registers. Data on atrial fibrillation were acquired from the Swedish National Patient Register. Follow -up time from January 1, 1998 until the first of the following. Multivariable models were adjusted for age (as the time scale in all analyses), education, family history of myocardial infarction before 60 years of age; smoking; BMI; walking/bicycling; exercise; use of aspirin; and history of hypertension; Hypercholesterolemia; diabetes; and atrial fibrillation. The multivariable model was also	Compared with individuals consuming small (<1drink/wk) amounts of alcohol, heavy drinkers (> 28 drinks/wk in men and > 21 drinks/wk in women) were younger and less active, more likely to be current smokers, and have a family history of MI. In women, hypertension was more prevalent in never and former drinkers than in heavy drinkers During the 12 years of follow-up there were 3678 cases of MI in men and 1500 cases of MI in women. 1905 men and 1328 women were diagnosed with HF. Alcohol consumption was statistically significantly inversely associated with risk of MI in both men and women (P for trend < 0.001). In multivariable analysis compared with <1 drink/wk men who consumed >28 drinks/wk had a lower risk of MI (HR 0.70; 95% CI: 0.15, 0.67). In women who consumed >15-21 drinks/week the HR was 0.32 (95% CI: 0.15, 0.67). In women, heavy intakes of alcohol (>21 drinks/wk) attenuated the inverse relationship between alcohol and risk of MI. Alcohol intake was not associated with incident HF in either men or women although heavy intakes were associated with increased risk in men (HR 1.45; 95% CI: 1.09, 1.93). This was not observed in women. In men the HRs for <1 drink/wk, 1-6 drinks/wk, 7-14 drinks/wk, 15-21 drinks/wk and 22-28 drinks/wk were 1.07 (95% CI: 0.91, 1.26), 1.12 (95%

	Exercise = 2 h/week: 57.9 % Aspirin use = 7 tablets/week: 8.8 % Hypertension: 25.5 % Hypercholesterolemia: 15.1 % Diabetes: 13 % Atrial fibrillation: 3.2 % mDASH diet score: 20.4 <u><1 drink/wk</u> Participants: *n* 3572 Age: 62 years BMI: 25.8 kg/m2 Postsecondary education: 14.9 % Family history of MI: 14.7 % Current smokers: 20.9 % Walk/bicycle = 40 min/day: 33.7 % Exercise = 2 h/week: 56.5 % Aspirin use = 7 tablets/week: 5.7 % Hypertension: 23.2 % Hypercholesterolemia: 12.4 % Diabetes: 9 % Atrial fibrillation: 1.9 % mDASH diet score: 20.5 <u>1-6 drinks/wk</u> Participants: *n* 16,423 Age: 59.8 years BMI: 25.6 kg/m2 Postsecondary education: 16.6 % Family history of MI: 14.2 % Current smokers: 23.2 % Walk/bicycle = 40 min/day: 32.9 % Exercise = 2 h/week: 58.6 % Aspirin use = 7 tablets/week: 5.7 % Hypertension: 21.6 % Hypercholesterolemia: 12.9 % Diabetes: 7.6 % Atrial fibrillation:1.9 % mDASH diet score: 20.9 <u>7-14 drinks/wk</u> Participants: *n* 10,001 Age: 57.7 years BMI: 25.6 kg/m2 Postsecondary education: 19.8 % Family history of MI: 14.2 % Current smokers: 25.4 % Walk/bicycle = 40 min/day: 32 %		controlled for overall diet using a modified Dietary Approaches to Stop Hypertension diet score (mDASH diet score) ranges from 7 (minimal adherence) to 35 (maximal adherence).	CI: 0.94, 1.34), 0.92 (95% CI: 0.72, 1.17), and 1.12 (95% CI: 0.82, 1.55), respectively. In women the HRs for <1 drink/wk, 1-6 drinks/wk, 7-14 drinks/wk, 15-21 drinks/wk and >21 drinks/wk were 0.93 (95% CI: 0.81, 1.06), 0.90 (95% CI: 0.70, 1.16), 0.62 (95% CI: 0.29, 1.31), and 0.73 (95% CI: 0.32, 1.63), respectively. In men, risk of HF was higher in never and former drinkers (HR 1.24; 95% CI: 0.99, 1.54 and 1.40, 95% CI: 1.15, 1.71, respectively). The relationship was absent in women **Summary** **This study shows divergent associations between alcohol intake and risk of MI or HF. The difference between men and women's HF risk may be due to a small number of women who drank heavily, thus meaning lower statistical power. Similarly the intake of ethanol may have been inadequate to have an impact on BP. This is shown by the baseline data where the prevalence of hypertension is lower in the heavy drinking group than the light drinkers. Similar to other studies a limitation is that alcohol consumption was self-reported and measured at baseline only, and other types of CVD (or comorbidities) were not examined**

	Exercise = 2 h/week: 60.7 % Aspirin use = 7 tablets/week: 5.6 % Hypertension: 21.6 % Hypercholesterolemia: 13.4 % Diabetes: 6.6 % Atrial fibrillation: 2.1 % mDASH diet score: 20.9 <u>15-21 drinks/wk</u> Participants: *n* 3586 Age: 56.7 years BMI: 25.9 kg/m2 Postsecondary education: 20.1 % Family history of MI: 14.6 % Current smokers: 30.1 % Walk/bicycle = 40 min/day: 32 % Exercise = 2 h/week: 57.8 % Aspirin use = 7 tablets/week: 6.6 % Hypertension: 22.8 % Hypercholesterolemia: 15.3 % Diabetes: 6.4 % Atrial fibrillation: 2.2 % mDASH diet score: 20.7 <u>22-28 drinks/wk</u> Participants: *n* 1332 Age: 56.4 years BMI: 26.1 kg/m2 Postsecondary education: 20.4 % Family history of MI: 14.6 % Current smokers: 34.3 % Walk/bicycle = 40 min/day: 29.9 % Exercise = 2 h/week: 58.4 % Aspirin use = 7 tablets/week: 6.9 % Hypertension: 24.4 % Hypercholesterolemia: 14.9 % Diabetes: 6.7 % Atrial fibrillation: 2 % mDASH diet score: 20.4 <u>>28 drinks/wk</u> Participants: *n* 1475 Age: 56.5 years BMI: 26.2 kg/m2 Postsecondary education: 17.6 % Family history of MI: 16.5 % Current smokers: 42.5 % Walk/bicycle = 40 min/day: 29.5 %			

	Exercise = 2 h/week: 53.6 % Aspirin use = 7 tablets/week: 7.9 % Hypertension: 27.9 % Hypercholesterolemia: 16.9 % Diabetes: 9.2 % Atrial fibrillation: 1.9 % mDASH diet score: 19.9 <u>SMC</u> <u>Never Drinkers</u> Participants: *n* 4126 Age: 67.6 years BMI: 25.9 kg/m2 Postsecondary education: 12.4 % Family history of MI: 16.7 % Current smokers: 10.2 % Walk/bicycle = 40 min/day: 35.9 % Exercise = 2 h/week: 52.6 % Aspirin use = 7 tablets/week: 9.7 % Hypertension: 22.3 % Hypercholesterolemia: 7.8 % Diabetes: 6 % Atrial fibrillation: 1.1 % mDASH diet score: 22.1 <u>Former Drinkers</u> Participants: *n* 908 Age: 62.3 years BMI: 25.4 kg/m2 Postsecondary education: 14.3 % Family history of MI: 19.7 % Current smokers: 38 % Walk/bicycle = 40 min/day: 35.3 % Exercise = 2 h/week: 52.2 % Aspirin use = 7 tablets/week: 12.7 % Hypertension: 26.4 % Hypercholesterolemia: 7.6 % Diabetes: 7.7 % Atrial fibrillation: 2.2 % mDASH diet score: 21.8 <u><1 drink/week</u> Participants: *n* 8076 Age: 63.2 years BMI: 25.4 kg/m2 Postsecondary education: 15 % Family history of MI: 17.3 % Current smokers: 21.4 %			

	Walk/bicycle = 40 min/day: 37.6 % Exercise = 2 h/week: 55.6 % Aspirin use = 7 tablets/week: 9.4 % Hypertension: 21.6 % Hypercholesterolemia: 8.4 % Diabetes: 4.8 % Atrial fibrillation: 1.1 % mDASH diet score: 22.5 <u>1-6 drinks/week</u> Participants: *n* 16,382 Age: 59.6 years BMI: 24.7 kg/m2 Postsecondary education: 21.5 % Family history of MI: 16.4 % Current smokers: 24.5 % Walk/bicycle = 40 min/day: 35.9 % Exercise = 2 h/week: 58.9 % Aspirin use = 7 tablets/week: 8.2 % Hypertension: 19.3 % Hypercholesterolemia: 7.6 % Diabetes: 2.7 % Atrial fibrillation: 1 % mDASH diet score: 22.9 <u>7-14 drinks/wk</u> Participants: *n* 3628 Age: 57.6 years BMI: 24.5 kg/m2 Postsecondary education: 28.4 % Family history of MI: 16.1 % Current smokers: 31.1 % Walk/bicycle = 40 min/day: 36 % Exercise = 2 h/week: 57.5 % Aspirin use = 7 tablets/week: 9.6 % Hypertension: 18.4 % Hypercholesterolemia: 6.7 % Diabetes: 2.3 % Atrial fibrillation: 0.9 % mDASH diet score: 22.6 <u>15-21 drinks/wk</u> Participants: *n* 609 Age: 56.9 kg/m2 BMI: 24.5 kg/m2 Postsecondary education: 34.5 % Family history of MI: 17.1 % Current smokers: 36 %			

	Walk/bicycle = 40 min/day: 37.2 % Exercise = 2 h/week: 56.4 % Aspirin use = 7 tablets/week: 7.2 % Hypertension: 16 % Hypercholesterolemia: 7.8 % Diabetes: 1.5 % Atrial fibrillation: 0.7 % mDASH diet score: 22.2 <u>>21 drinks/wk</u> Participants: *n* 293 Age: 58 years BMI: 25 kg/m2 Postsecondary education: 29.4 % Family history of MI: 17.8 % Current smokers: 39.7 % Walk/bicycle = 40 min/day: 31.6 % Exercise = 2 h/week: 48.4 % Aspirin use = 7 tablets/week: 10.2 % Hypertension: 20.5 % Hypercholesterolemia: 7.6 % Diabetes: 5.5 % Atrial fibrillation: 1.2 % mDASH diet score: 21.7			
O'Neill et al.[43]	Initially participant records 62,799. 19,277 participants were excluded due to attrition or having experienced a CHD event prior to the study baseline. 8390 participants were not included due to incomplete data linkage. Total participants: *n* 35,132 62.1% male <u>EPIC-N</u> Record count: 7462 Age: 68.3 ± 8.0 years Male: 42.5 % Non smoker: 50.3 % Current smoker: 4.4% Ex-smoker: 43.9 % Unknown: 1.4 % BMI: 25.7 ± 3.6 kg/m2 High blood pressure: 29.2 % Drinker type: Consistent non-drinker: 5.7 %	Meta-analysis of six cohort studies using individual participant data. Participants taken from 5 British cohort studies: the European Prospective Investigation of Cancer, Norfolk Cohort (EPIC-N); the Medical Research Council's National Survey of Health and Development 1946 (NSHD); West of Scotland Twenty-07: 1930s (T07-1930s); West of Scotland Twenty-07: 1950s (T07-1950s) and Whitehall II (WII) and an additional French cohort: Gaz et Electricité (GAZEL) Participants grouped based on weekly alcohol intake: Consistent non-drinker: 0 g at each wave of data collection; Former drinker 0 g at last wave but intake >0 g at any earlier wave; Consistently moderate Male: 1–168 g at each wave, Female: 1–112 g at each wave;	Primary outcome was CHD incidence, determined from linked health records and survey data. Secondary outcomes included CHD mortality. CHD events included ICD-9: 410-414 and ICD-10: I20-I25. Non-fatal CHD events were identified using the Royal College of General Practitioners' codebook (codes 1940, 1945 and 195 Survival time was calculated for all participants as time (in years) between the end of the alcohol assessment period and date of CHD event, death from non-CHD causes, study dropout or last date of data linkage (study specific), whichever occurred first. Initial model accounting weekly alcohol intake and for age, sex and intake assessment interval, followed by an extended model that additionally included smoking status (no smoker, current smoker, ex- smoker, unknown) and socioeconomic status (high position, intermediate, low, unknown) covariates. Additional clinical data were obtained on BMI and self-reported high blood pressure or use of antihypertensive medication. All covariates	In pooled analysis, 4.9% of total participants experienced an incident (fatal or non-fatal) CHD event after a median follow-up of 12.6 ± 4.3 years 0.9% of participants died due to CHD (mean follow-up 13.7 ± 4.1 years). With alcohol defined according to a single intake measurement (none, moderate, or heavy), there was no significance difference in risk of incident CHD between moderate and heavy consumers. Those identified as "none" had a significantly increased risk in comparison to those who drank within recommended amounts (HR 1.29; 95% CI: 1.11, 1.43) In comparison to consistent moderate drinkers, consistent non-drinkers, former drinkers, and inconsistent moderate drinkers had an increased risk

	Former drinker: 22.6 % Consistent moderate drinker: 43.8 % Inconsistent moderate drinker: 7.1 % Consistent heavy drinker: 3.0 % Inconsistent heavy drinker: 4.0 % Unknown: 13.8 % Intake interval: 12.9 ± 1.9 <u>GAZEL</u> Record count: 14,247 Age: 57.4 ± 3.5 years Male: 74.1 % Non smoker: 69.9 % Current smoker: 13.1% Ex-smoker: 13.1 % Unknown: 3.9 % BMI: 25.8 ± 3.6 kg/m2 High blood pressure: 26.9 % Drinker type: Consistent non-drinker: 5.6 % Former drinker: 9.4 % Consistent moderate drinker: 31.1% Inconsistent moderate drinker: 18.8 % Consistent heavy drinker: 11.5 % Inconsistent heavy drinker: 9.7 % Unknown: 13.9 % Intake interval: 10.0 ± 0.1 <u>NSHD (1946)</u> Record count: 2979 Age: 53.3 ± 1.1 years Male: 49.2 % Non smoker: 25.7 % Current smoker: 36.7 % Ex-smoker: 35.8 % Unknown: 1.9 % BMI: 27.4 ± 4.8 kg/m2 High blood pressure: 66.8 % Drinker type: Consistent non-drinker: 7.0 % Former drinker: 9.4 % Consistent moderate drinker: 19.8 % Inconsistent moderate drinker: 20.0 % Consistent heavy drinker: 3.1 % Inconsistent heavy drinker: 8.1 % Unknown: 32.5 %	Inconsistently moderate Male: 1–168 g for most but not all waves, Female: 1–112 g for most but not all waves; Consistently heavy Male: >168 g at each wave, Female: >112 g at each wave Inconsistently heavy Male: >168 g for most but not all waves Female: >112 g for most but not all waves Age-stratified modelling of the longitudinal drinker typology was also performed between participants aged ≤55 vs >55 years at this study's baseline to compare associations with the incident CHD outcome A single one-off measure of alcohol intake was analyzed (none, moderate or heavy consumption)	were assessed at the commencement of the follow-up period for all CHD during follow up, all CHD person years, fatal CHD during follow up, and fatal CHD person year.	of incident CHD (HR 1.47; 95% CI: 1.21, 1.78; 1.31; 95% CI: 1.13, 1.52; and 1.18; 95% CI: 1.02, 1.37, respectively). These relationships were attenuated when BMI, and hypertension were included in the model When analysed according to age (up to 55 years or above 55 years), consistent non-drinkers aged <55 years and former drinkers showed increased risk of CHD compared to consistent moderate drinkers (HR 1.97; 95% CI: 1.29, 3.02; HR 1.60; 95% CI: 1.09, 2.37, respectively). In those aged >55, consistent non-drinkers, former drinkers, and inconsistent moderate drinkers all displayed increased risk of CHD (HR 1.38; 95% CI: 1.11, 1.71, HR 1.27; 95% CI: 1.08, 1.51, and HR 1.25; 95% CI: 1.06, 1.48, respectively). In men, former drinkers were at significantly greater risk of incident CHD compared to consistently moderate drinkers after maximal adjustment for confounding factors (HR 1.29; 95% CI: 1.06, 1.56). In women, former drinkers (HR 1.38; 95% CI: 1.07, 1.78) and consistent non-drinkers (HR 1.91; 95% CI: 1.43, 2.55) showed increased risk compared to their consistently moderate intake counterparts With fatal CHD as the outcome, similar relationships were observed. Non-drinkers had a significantly increased risk of fatal CHD in comparison to moderate drinkers (HR 1.44; 95% CI: 1.08, 1.93). No association was observed for heavy drinkers.

	Intake interval: 17.0 ± 0.0 <u>T07 (1930s)</u> Record count: 869 Age: 64.4 ± 1.2 years Male: 42.6 % Non smoker: 36.0 % Current smoker: 31.3% Ex-smoker: 32.0 % Unknown: 0.7 % BMI: 26.7 ± 4.4 kg/m2 High blood pressure: 17.5 % Drinker type: Consistent non-drinker: 13.6 % Former drinker: 10.7 % Consistent moderate drinker: 21.7 % Inconsistent moderate drinker: 16.2 % Consistent heavy drinker: 3.0 % Inconsistent heavy drinker: 4.7 % Unknown: 30.4 % Intake interval: 8.2 ± 1.0 <u>T07 (1950s)</u> Record count: 1002 Age: 45.2 ± 1.2 years Male: 44.3 % Non smoker: 41.5 % Current smoker: 34.4 % Ex-smoker: 23.6 % Unknown: 0.5 % BMI: 26.4 ± 4.6 kg/m2 High blood pressure: 5.4 % Drinker type: Consistent non-drinker: 8.7 % Former drinker: 9.3 % Consistent moderate drinker: 25.7 % Inconsistent moderate drinker: 17.6 % Consistent heavy drinker: 3.0 % Inconsistent heavy drinker: 7.4 % Unknown: 26.8 % Intake interval: 9.1 ± 1.0 <u>WII</u> Record count: 8573 Age: 55.7 ± 6.0 years Male: 67.8 %			In contrast to CHD incidence, inconsistent moderate drinkers did not have an increased risk of fatal CHD (HR 1.04; 95% CI: 0.72, 1.52). Only former drinkers displayed a significantly elevated risk (HR 1.54; 95% CI: 1.07, 2.22). The HR was similar for non-consistent and former drinkers (1.52 and 1.54, respectively). Increased risk was not observed in inconsistent moderate, heavy, or inconsistent heavy drinkers although CIs were large in the latter group. Only women consistent non-drinkers displayed a significantly increased risk of fatal CHD (HR 2.62; 95% CI: 1.25, 5.49) **<u>Summary</u>** **This meta-analysis suggests that risk of CHD is higher in those who either never consume alcohol or used to consume alcohol, in comparison to those with moderate consumption in line with Government recommendations. Those individuals who drank moderately, but were inconsistent, also had higher risk of CHD suggesting that this may relate to patterns of intake i.e. binge drinking. Collectively, these data show consistency is important. In his study drinking trajectories were based on volume and researchers were not able to examine the effects of heavy drinking episodes. For accurate determination of the role alcohol has in CVD/CHD risk, patterns of consumption, type, volume all should be considered.** **This finding suggests that the absence of an effect in heavy drinkers should be interpreted with caution, given the known risk associate with large alcohol consumption and that the adherence for low alcohol could have**

	Non smoker: 38.7 % Current smoker: 8.3 % Ex-smoker: 31.4 % Unknown: 21.6 % BMI: 26.1 ± 3.9 kg/m2 High blood pressure: 17.2 % Drinker type: Consistent non-drinker: 5.9 % Former drinker: 6.8 % Consistent moderate drinker: 31.2 % Inconsistent moderate drinker: 17.8 % Consistent heavy drinker: 3.0 % Inconsistent heavy drinker: 6.3 % Unknown: 25.8 % Intake interval: 11.2 ± 0.8			**health benefits in reducing long term CHD**
Leong et al.[44]	Initially participant records: 12,461 Individuals with a first MI; 14,637 Hospital controls: 58 % Community controls: 36 % Other: 3 % of controls (World Health Organization's Monitoring of Trends and Determinants in Cardiovascular Disease -MONICA study and an undocumented source). Excluded 54 controls and 266 cases due to missing records on alcohol consumption. Analysis sample: 12,195 cases and 14,583 controls. <u>Cases:</u> Total participants: *n* 12,195 Age: 58 ± 12 years Male: 76 % Geographic region Western Europe: 5 % Eastern and Central Europe: 14 % Middle East: 13 % Africa: 4 % South Asia: 14 % China and Hong Kong: 25 % Southeast Asia and Japan: 8 %	Case–control study on patterns of alcohol consumption and risk of MI. Data obtained from MI undertaken in from 52 countries in Asia, Europe, the Middle East, Africa, Australia, and North and South America. Alcohol exposure was characterised by asking the frequency of alcohol beverage consume: <1 time per month, <1 time per week, 1–2 times per week, 3–4 times per week, 5–6 times per week. Daily Alcohol use was defined as the consumption of ≥1 alcoholic beverage within the previous 12 months. It was also asked how many alcoholic beverages were consumed in the 24 hours before the onset of MI symptoms and in the period 24 to 48 hours before the onset of MI symptoms. Heavy episodic drinking: ≥6 alcoholic drinks within 24 hours before MI. Also assessed if a period of heavy drinking may act as a trigger for acute MI. Time for trigger was identified as 24 hours prior to MI. 24 – 48 hours prior to MI was considered as control	Primary outcome was risk of MI Information on age, ethnicity, dietary patterns, physical activity, tobacco use, marital status, education, employment, psychosocial factors and cardiovascular risk factors was obtained. Height, weight, waist, and hip circumference were measured in a standardized manner. Serum TC, HDL-C, TAG, and ApoB and A1 concentrations were measured in a core laboratory; low-density LDL-C concentration was calculated from these measurements. Smoking was classified as current, former (no smoking within the previous year), or never. Marital status was considered single, married/common-law partner, separated/ divorced, and widowed. Participants' highest level of education was categorised as less than grade 9, grades 9 to 12, or university/ college/ trade school. Logistic regression was used to evaluate the relationship between MI and alcohol use to account for the paired recruitment of cases and controls within ±5 years of age of each other. The effect of alcohol exposure was adjusted for Dietary Risk score, exercise, smoking, marital status, employment, education level, depression, stress at work or at home, and financial stress Analysis was stratified by geographic region, and the estimates for each region were meta-analysed.	Alcohol consumption within the previous year was associated with a significantly lower risk of MI. The fully-adjusted OR was 0.87 (95% CI: 0.80, 0.94; P=0.001). Subgroup analysis based sex suggested a lower risk of MI in women (OR 0.73; 95% CI: 0.61, 0.78; P<0.001) but not men. The protective association of alcohol against MI was greater in individuals ≥45 years of age. For those aged 45-65 years the OR was 0.85 (95% CI: 0.76, 0.95) and for those aged >65 years the OR was 0.87 (95% CI: 0.75, 1.01). Alcohol use in European/North America/Australian/New Zealand populations was associated with a lower risk of MI (OR 0.71; 95% CI: 0.59, 0.85). In South Asian populations this was associated with increased risk (OR 1.4, 95% CI: 1.1, 1.8). Country-base analysis indicated respective ORs for Sri Lanka, Pakistan, Nepal, India, and Bangladesh of 1.4 (95% CI: 0.30, 6.6), 1.2 (95% CI: 0.61, 2.2), 0.85 (95% CI: 0.42, 1.7), 1.3 (95% CI: 0.80, 2.1), and

	Australia and New Zealand: 5 % South America and Mexico: 10 % North America: 2 % Consumed alcohol in previous year: 45 % Current smoker: 45 % N cigarettes smoked per day among ever smokers <20: 43 % ≥20: 57 % Diabetes mellitus: 18 % Hypertension: 39 % Daily fruit or vegetable consumption: 80 % Dietary Risk score: −4.1 ± 5.4 Undertakes leisure-time exercise: 15 % Home or work stress None: 25 % Some periods: 48 % Several periods: 19 % Permanent: 8 % Financial stress Little or none: 44 % Moderate: 41 % Severe: 15 % Depressed: 8 % Marital status Never: 3 % Married/common-law partner: 82 % Separated/divorced: 4 % Widowed: 11 % Education <Grade 9: 45 % Grade 9–12: 26 % >Grade 12: 29 % Employment Employed: 50 % Retired: 35 % Unemployed: 6 % Home duties: 9 % BMI: 26.1 ± 4.15 kg/m2 Waist-to-hip ratio: 0.93 ± 0.084 ApoB: 0.95 (0.78–1.1) mmol/L ApoA1: 1.1 (0.96–1.3) mmol/L ApoB/ApoA1 ratio: 0.86 (0.70–1.1) Total cholesterol: 5.2 (4.4–6.0) mmol/L		Models adjusted for age (categorized as <45, 45–65, and >65 years), sex, geographic region, dietary Risk score, exercise, smoking, marital status, employment, education level, depression, stress at work or at home, financial stress, body mass index, waist-to-hip ratio, serum ratio of ApoB to ApoA1; TC, HDL-C, LDL-C, and TAG concentrations, and history of hypertension or diabetes mellitus.	1.0 (95% CI: 0.40, 2.7). In participants of South Asian origin living *outside* of the South Asian countries, the OR for MI with alcohol use was 0.80 (95% CI: 0.53, 1.2; P=0.3). The inverse association between alcohol intake and MI was absent when alcohol intake exceeded >4 times/week. Compared with non-drinkers, ORs for <1x/week, 1-4x/week and >4x/week were 0.89 (95% CI: 0.81, 0.96), 0.84 (95% CI: 0.75-0.94), and 0.88 (95% CI: 0.76, 1.01), respectively. Consuming any alcohol in the hazard period (up to 24 hours prior to MI) was not associated with increased MI risk (OR 1.0; 95% CI: 0.91, 1.2; P=0.7). Heavy drinking (≥6 drinks) during the hazard period was associated with increased risk of MI (OR 1.4; 95% CI: 1.1, 1.9; P=0.001). Using sex-specific definition of heavy drinking (≥5 drinks for men and (≥4 drinks for women) showed similar associations (OR 1.4; 95% CI: 1.2, 1.8; P=0.001). The association between heavy drinking and risk of MI was more pronounced in those aged over 45 years; ORs for those <45, 45–65, and >65 years of age were 0.84 (95% CI: 0.51, 1.4; P=0.5), 1.6 (95% CI: 1.1, 2.2; P=0.01), and 5.3 (95% CI: 1.6, 18; P=0.008). **Summary** **In this study moderate alcohol intake was inversely associated with risk of MI in most geographical locations studied, however alcohol intake was positively associated with risk of MI in South Asian populations. Small quantities of alcohol in the 24 hour period prior to MI did not appear to be associated with increase of MI. However heavy drinking was associated with increased risk,**

	HDL-C: 0.99 (0.82–1.2) mmol/L LDL-C: 3.3 (2.7–4.0) mmol/L TAG: 1.6 (1.1–2.3) mmol/L <u>Controls</u> Total participants: *n* 14,583 Age: 57 ± 12 years Male: 74 % Geographic region Western Europe: 5 % Eastern and Central Europe: 13 % Middle East: 12 % Africa: 5 % South Asia: 15 % China and Hong Kong: 21 % Southeast Asia and Japan: 8 % Australia and New Zealand: 5 % South America and Mexico: 13 % North America: 3 % Consumed alcohol in previous year: 47 % Current smoker: 26 % N cigarettes smoked per day among ever smokers <20: 57 % ≥20: 43 % Diabetes mellitus: 7 % Hypertension 7 % Daily fruit or vegetable consumption: 85 % Dietary Risk score: −5.3 ± 5.4 Undertakes leisure-time exercise: 23 % Home or work stress None: 27 % Some periods: 53 % Several periods: 16 % Permanent: 4 % Financial stress Little or none: 49 % Moderate: 39 % Severe: 12 % Depressed: 7 % Marital status Never: 5 % Married/common-law partner: 82 % Separated/divorced: 4 % Widowed: 9 %			**especially in older individuals, and is supported by mechanistic work that shows increases in blood pressure and clotting following a heavy drinking episode.**

	Education <Grade 9: 38 % Grade 9–12: 25 % >Grade 12: 37 % Employment Employed: 55 % Retired: 31 % Unemployed: 5 % Home duties: 9 % BMI: 25.8 ± 4.15 kg/m2 Waist-to-hip ratio: 0.91 ± 0.084 ApoB: 0.90 (0.76–1.1) mmol/L ApoA1: 1.2 (1.0–1.4) mmol/L ApoB/ApoA1 ratio: 0.75 (0.60–0.93) TC: 5.1 (4.3–5.9) mmol/L HDL-C: 1.0 (0.82–1.3) mmol/L LDL-C: 3.1 (2.5–3.8) mmol/L TAGs: 1.6 (1.1–2.4) mmol/L			
Wood et al.[45]	Total participants: *n* 599,912 Total sample in analysis: 83 studies Age: 57 ± 9 years Male: 56 % Current smoker: 21 % <u>Emerging Risk Factors Collaboration</u> Assessment period: June 2017 Initial sample: 142 studies, 2,334,435 participants. Sample excluded due to missing information available on drinking status, drinking amount, plus-age, sex, history of diabetes and smoking, baseline of CVD, 1 year of follow-up, non or ex-drinkers at baseline survey. Analysis sample: 81 studies Total participants: *n* 247,504 Age: 57.1 (8.7) years Male: 66 % Smoking status Not current: 65 % Current: 35 % Diabetes: 4 % BMI: 26.1 (3.8) km/m2 HDL-C: 1.40 (0.41) mmol/L TC: 5.8 (1.7) mmol/L SBP: 136.5 (19.0) mmHg	Data from three large-scale data sources: Emerging Risk Factors Collaboration (EFRC), EPIC-CVD, and the UK Biobank. Baseline alcohol consumption was categorised into eight predefined groups according to the amount in grams consumed per week: >0–≤25, >25–≤50, >50–≤75, >75–≤100, >100–≤150, >150–≤250, >250–≤350, and >350 g per week. Data were harmonised across the contributing studies using a conversion of 1 unit=8 g of pure alcohol to a standard scale of grams per week, enabling a common analytical approach despite variation in the methods used (e.g., self-administered vs interview-led questionnaires; food frequency questionnaires vs dietary recall surveys), and in consumption scales over different periods of ascertainment. Alcohol type (wine, beer, and spirits), consumption frequency (≤2 days per week or >2 days per week) and episodic heavy drinking (binge drinkers ≥100 g per drinking occasion or non-binge drinkers <100 g per drinking occasion) were investigated.	Primary outcomes was association between alcohol intake and all-cause mortality, total CVD, and specific CV subtypes (stroke, MI, CHD, HF and other CV deaths) HRs were adjusted for usual levels of available potential confounders or mediators: body-mass index (BMI); SBP; HDL-C; LDL-C; TC; fibrinogen; baseline measures for smoking amount (in pack-years); level of education reached (no schooling or primary education only vs secondary education vs university); occupation (not working vs manual vs office vs other); self-reported physical activity level (inactive vs moderately inactive vs moderately active vs active); self-reported general health (scaled 0–1 where low scores indicate poorer health); self-reported red meat consumption; self-reported use of anti-hypertensive drugs.	40,310 deaths from all-causes, (including 11,762 vascular and 15,150 neoplastic deaths)39,018 first incident CVD outcomes, including 12,090 stroke events, 14,539 MI events, 7990 coronary disease events excluding MI, 2711 HF events, and 1121 deaths from other CVDs. Approximately 50% reported drinking more than 100 g of alcohol per week, and 8.4% drank more than 350 g per week. Baseline alcohol consumption was positively correlated with male sex, smoking status and amount, systolic blood pressure, HDL-C level, fibrinogen, and lower socioeconomic status with a median 96 g/week. A positive, curvilinear association between alcohol intake and all-cause mortality was observed, with lowest risk in those consuming <100 g/week. With all CVD outcomes as an outcome, a J-shaped relationship existed. However subgroup analysis suggested

	Weekly alcohol consumption: 87·7 (2.2–522.4) g/week >0–≤25 g per week: 22 % >25–≤50 g per week: 14 % >50–≤75 g per week: 11% >75–≤100 g per week: 7 % >100–≤150 g per week: 15% >150–≤250 g per week: 13 % >250–≤350 g per week: 10 % ≤350 g per week: 10 % <u>EPIC-CVD</u> Assessment period: April 2018 Initial sample: 23 European centres from 10 countries involving 35,455 participants. Sample excluded due to missing information available on drinking status, drinking amount, plus-age, sex, history of diabetes and smoking, baseline of CVD, 1 year of follow-up, non or ex-drinkers at baseline survey. Analysis sample: 22 European centres from 9 countries Total participants: *n* 26,036 Weekly alcohol consumption: 61.9 (2.6–404.0) g/week >0–≤25 g per week: 30 % >25–≤50 g per week: 14 % >50–≤75 g per week: 11 % >75–≤100 g per week: 9 % >100–≤150 g per week: 10% >150–≤250 g per week: 12 % >250–≤350 g per week: 7 % ≤350 g per week: 7 % <u>UK Biobank</u> Assessment period: May 2017 Initial sample: 502,627 participants. Sample excluded due to missing information available on drinking status, drinking amount, plus-age, sex, history of diabetes and smoking, baseline of CVD, 1 year of follow-up, non or ex-drinkers at baseline survey. Total participants: *n* 326,372 Weekly alcohol consumption: 103.9 (11.8–420.8) g/week	Cumulative survival from 40 years of age onwards in different categories of baseline alcohol consumption were also calculated. Results were modelled from age 40 years and enabled estimation of years of life lost between light drinkers (defined as those consuming >0–≤100 g/week of alcohol) and pre-defined groups of >100–≤200, >200–≤350, and >350 g per week.		different associations between alcohol intake and types of CVD. The relationship between alcohol intake and all-cause mortality was greater in those who consumed more beer or spirits as opposed to wine, and in those drinking alcohol less frequently (i.e. binge drinkers). Similar observations were seen for CVD and subtypes, although to a lesser extent. Compared with the 0-25 g/week, alcohol consumed had positive and linear associations with stroke (HR per 100 g/week higher consumption 1.14; 95% CI: 1.10, 1.17), coronary disease excluding MI (1.06; 95% CI: 1.00, 1.11), HF (1.09; 95% CI: 1.03, 1.15), fatal hypertensive disease (1.24; 95% CI: 1.15, 1.33), and fatal aortic aneurysm (1.15; 95% CI: 1.03, 1.28). For MI, there was an inverse log-linear relationship (0.94; 95% CI: 0.91, 0.97). In comparison to those who reported drinking >0–≤100 g (mean usual 56 g) alcohol per week, those who reported drinking >100–≤200 g (mean usual 123 g) per week, >200–≤350 g (mean usual 208 g) per week or >350 g (mean usual 367 g) per week had shorter life expectancy at age 40 years of approximately 6 months, 1–2 years, or 4–5 years respectively. Men who reported consuming above the UK upper limit of 112 g per week had a shorter life expectancy at age 40 years of 1.6 years (95% CI: 1.3, 1.8), compared with men who reported drinking below these respective upper limits. Thus, men who reported drinking less than 100 g alcohol per week had approximately a 1–2 years longer life expectancy at age 40 years than those who reported drinking 196 g per week.

	>0–≤25 g per week: 12 % >25–≤50 g per week: 12 % >50–≤75 g per week: 13 % >75–≤100 g per week: 11 % >100–≤150 g per week: 17% >150–≤250 g per week: 18 % >250–≤350 g per week: 8 % ≤350 g per week: 8 %			Women who reported drinking above either the UK threshold (112 g per week) had approximately 1.3 (1.1, 1.5) years shorter life expectancy at age 40 years compared with women who reported drinking below these thresholds. **Summary** **This study showed that among current drinkers, the threshold for lowest risk of all-cause mortality was approximately 100 g per week. No clear thresholds were found for CVD subtypes other than MI. Importantly this study suggests different relationships between alcohol and subtypes of CVD, in part mediated by changes in risk factors. For example, alcohols known stimulatory effect on BP may explain the positive relationship between alcohol intake and stroke, but the HDL-C-raising effect may account for the inverse association with risk of MI. As with other studies of this type, results are limited by the nature of how alcohol intake was determined (self-reported) and the potential for reverse causality.** **These data support adoption of lower limits of alcohol consumption than are recommended in most current guidelines.**

Online Supplementary Table 3 Whole diet approaches to be considered for CVD prevention

Study	Participant characteristics	Study Design	Measures and time points	Key observations
Li et al.[46]	Total participants: *n* 4398 2258 from Nurses' Health study (NHS) and 1840 men from Health Professional Follow-Up study (HPFS) Included men and women who were free of CVD, stroke, or cancer at the time of enrolment, survived a first MI during follow-up, and had no history of stroke at the time of initial MI onset <u>Women</u> Q1 Participants: *n* 439 Age at diagnosis: 64.7 ± 8.7 years BMI: 27.2 ± 6.1 kg/m2 Physical activity: 8.4 ± 15.6 MET h/wk Never smoked: 32 % Past smoker:48 % Current smoker: 20 % Diabetes: 23 % High blood pressure: 69 % Elevated cholesterol: 68 % Lipid-lowering medication: 43 % CABG Surgery: 52 % Q3 Participants: *n* 476 Age at diagnosis: 64.8 ± 8.6 years BMI: 27.0 ± 5.5 kg/m2 Physical activity: 15.1 ± 20.3 MET h/wk Never smoked: 33 % Past smoker: 55 % Current smoker: 11 % Diabetes: 22 % High blood pressure: 68 % Elevated cholesterol: 77 % Lipid-lowering medication: 50 %	Prospective cohort design Participants taken from Nurses' Health Study the Health Professional Follow-Up Study Participants grouped into quintiles of AHEI2010 <u>Women</u> Q1: AHEI2010 Post-MI: 38.9 ± 4.5 Pre-MI: 42.8 ± 8.6 1716 ± 511 kcal/d, SFA 10.4 ± 3.0 % total energy, omega 3 fats 0.6 ± 0.2 % total energy, TFA 1.8 ± 0.7 % total energy, alcohol 4.2 ± 12.8 g/d, folate intake 404 ± 196 µg/d, cereal fibre 5.0 ± 2.5 g/d red and processed meats 1.3 ± 0.9 servings/d, nuts and legumes 0.3 ± 1.3 servings/d, sugar-sweetened beverages 1.5 ± 1.1 servings/d, total vegetables 2.3 ± 1.3 servings/d, total fruits 1.1 ± 0.8 servings/d, fruit juice 1.0 ± 0.8 servings/d Q3: AHEI2010 Post-MI: 53.6 ± 1.6 Pre-MI: 51.45 ± 8.5 1579 ± 520 kcal/d, SFA 9.1 ± 2.7 % total energy, omega 3 fats 0.7 ± 0.2 % total energy, TFA 1.4 ± 0.6 % total energy. alcohol 3.5 ± 7.4 g/d, folate intake 507 ± 268 µg/d, cereal fibre 6.1 ± 2.7 g/d, red and processed meats 1.0 ± 0.6 servings/d, nuts and legumes 0.3 ± 0.3	Primary outcomes were all-cause and CVD mortality. CVD mortality was defined as fatal CHD, and fatal stroke. Food intakes determined using validated FFQ every 4 years. Nutrient content was calculated from the FFQ using USDA National Nutrient Database for Standard Reference (v 10-23) Diet quality was measured using Alternative Healthy Eating Index 2010 (AHEI2010) For each 11 component of AHEI2010, a maximum score of 10 was given for: red meat and processed meat (< 1 servings/day), nuts and legume (1 servings/day), sugar-sweetened beverages and fruit juice (< 1 servings per month), total vegetables (> 5 servings/day), total fruit (> 4 servings/day), PUFA (> 10% energy), TFA (< 0.5% energy), alcohol (women:0.5 – 1.5 drinks/day, men:1.5 – 2.5 drinks/day), long-chain (n-3) fats (EPA+DHA), 250 mg/day), whole grains (women: 75 g/day, men: 90 g/day), sodium (lowest decile, mg/d). A minimum score of 0 was given for: red meat and processed meat (≥ 1.5 servings/day), nuts and legume (0 servings/day), sugar-sweetened beverages and fruit juice (≥ 1 servings per day), total vegetables (0 servings/day), total fruit (0	During follow-up, there were 882 all-cause and 336 CVD deaths for women, and 451 all-cause and 222 CV deaths for men. Median survival time after MI was 8.7 years for women and 9.0 years for men In women, greater AHEI2010 was associated with significantly lower all-cause mortality (HR 0.66; 95% CI: 0.49, 0.88; P_{trend}<0.001). This was not observed in men (HR 0.98; 95% CI: 0.66, 1.44; P_{trend}=0.72). Pooled results suggested increased adherence to AHEI2010 was associated with lower all-cause mortality (HR 0.76; 95% CI: 0.60, 0.96; P_{trend}=0.02). During the post-MI period, MI survivors who were in the fifth quintile of the AHEI2010 had a better prognosis A greater increase in the AHEI2010 score from pre- to post-MI was significantly associated with lower all-cause (pooled HR 0.71; 95% CI: 0.56, 0.91; P_{trend}=0.006) and cardiovascular mortality (pooled HR 0.60; 95% CI: 0.41, 0.86; P_{trend}=0.006) Removal of alcohol did not significantly affect the relationship between Post-MI AHEI2010 and pooled all-cause mortality (HR 0.73; 95% CI: 0.58, 0.93; P_{trend}=0.01). Removal of alcohol from the AHEA2010 attenuated the

	CABG Surgery: 57 % Q5 Participants: n 469 Age at diagnosis: 64.9 ± 8.6 years BMI: 26.3 ± 4.9 kg/m2 Physical activity: 20.0 ± 21.9 MET h/wk Never smoked: 28 % Past smoker: 64% Current smoker: 8 % Diabetes: 22 % High blood pressure: 68 % Elevated cholesterol: 78 % Lipid-lowering medication: 56 % CABG Surgery: 60 % <u>Men</u> Participants: *n* 364 Age at diagnosis: 65.8 ± 9.3 years BMI: 26.3 ± 3.5 kg/m2 Physical activity: 26.6 ± 35.2 MET h/wk Never smoked:31 % Past smoker: 52 % Current smoker: 8 % Diabetes: 14 % High blood pressure: 57 % Elevated cholesterol: 63 % Lipid-lowering medication: 45 % CABG Surgery: 72 % <u>Q3</u> Participants: n 369 Age at diagnosis: 65.8 ± 9.2 years BMI: 26.2 ± 3.8 kg/m2 Physical activity: 36.7 ± 50.4 MET h/wk Never smoked: 37 % Past smoker: 51 % Current smoker: 4 % Diabetes: 16 % High blood pressure: 62 % Elevated cholesterol: 63 % Lipid-lowering medication: 52 % CABG Surgery: 76 % <u>Q5</u>	servings/d, sugar-sweetened beverages 1.0 ± 1.1 servings/d, total vegetables 1.6 ± 1.0 servings/d, total fruits 1.6 ± 1.0 servings/d, fruit juice 0.8 ± 0.9 servings/d Q5: AHEI2010 Post-MI: 70.2 ± 5.2 Pre-MI: 60.5 ± 10.7 1593 ± 498 kcal/d, SFA 7.9 ± 2.3 % total energy, omega 3 fats 0.9 ± 0.5 % total energy, TFA 1.1 ± 0.5 % total energy, alcohol 5.3 ± 6.8 g/d, folate intake 586 ± 310 µg/d, cereal fibre 7.2 ± 3.3 g/d, red and processed meats 0.8 ± 0.6 servings/d, nuts and legumes 0.7 ± 0.7 servings/d, sugar-sweetened beverages 0.6 ± 0.7 servings/d, total vegetables 2.2 ± 1.2 servings/d, total fruits 2.2 ± 1.2 servings/d, fruit juice 0.5 ± 0.6 servings/d <u>Men</u> <u>Q1</u> AHEI2010 Post-MI: 41.9 ± 5.4 Pre-MI: 44.3 ± 8.6 2047 ± 670 kcal/d, SFA 10.3 ± 2.9 % total energy, omega 3 fats 0.6 ± 0.3 % total energy, TFA 1.9 ± 0.8 % total energy, alcohol 11.1 ± 18.1 g/d, folate intake 600 ± 339 µg/d, cereal fibre 6.7 ± 3.7 g/d, red and processed meats 1.7 ± 1.0 servings/d, nuts and legumes 0.3 ± 0.3 servings/d, sugar-sweetened beverages 1.7 ± 1.5 servings/d, total vegetables 1.2 ± 0.9 servings/d, total fruits 1.2 ± 0.9 servings/d, fruit juice 1.1 ± 1.1 servings/d Q3 AHEI2010 Post-MI: 57.7 ± 1.6 Pre-MI: 52.2 ± 8.9 1933 ± 632 kcal/d, SFA 8.5 ± 2.7 % total energy, omega 3 fats 0.7 ± 0.4 % total energy, TFA 1.4 ± 0.6 % total energy,	servings/day), PUFA (≤ 2% energy), TFA (≥ 4% energy), alcohol (women: 0 or > 2.5 drinks/day, men: 0 or > 3.5 drinks/day), long-chain (n-3) fats (EPA+DHA), 0 mg/day), whole grains (0 g/day), sodium (highest decile, mg/d). Covariates considered medication use, medical history, and lifestyle factors previously associated with MI risk Performed secondary analyses in which alcohol component was removed to evaluate the contribution of a healthy diet independent of alcohol intake.	relationship between the change in score and all-cause and CV mortality (HR 0.81; 95% CI: 0.64, 1.04; P_{trend}=0.12 and HR 0.82; 95% CI: 0.57, 1.18; P_{trend}=0.28) Collectively this study highlights that greater adherence to a cardioprotective diet was associated with a 24% lower all-cause and 26% lower CV mortality. Improving diet quality after a heart attack was also associated with lower all-cause and cardiovascular mortality. The relationship with the change in score and all-cause and CV mortality was attenuated with the removal of alcohol, suggesting that alcohol intake was associated with lower all-cause and CV mortality The individuals in this study also had pre-existing CVD which adds to the relevance for practice.

	Participants: *n* 362 Age at diagnosis: 66.0 ± 9.0 years BMI: 25.3 ± 3.5 kg/m2 Physical activity: 41.2 ± 35.1 MET h/wk Never smoked: 39 % Past smoker: 47 % Current smoker: 4 % Diabetes: 12 % High blood pressure: 50 6% Elevated cholesterol: 70 % Lipid-lowering medication: 57 % CABG Surgery: 79 %	alcohol 8.0 ± 11.5 g/d, folate intake 710 ± 357 µg/d, cereal fibre 7.8 ± 3.1 g/d, red and processed meats 1.4 ± 0.8 servings/d, nuts and legumes 0.5 ± 0.5 servings/d, sugar-sweetened beverages 1.4 ± 1.3 servings/d, total vegetables 2.0 ± 1.4 servings/d, total fruits 2.0 ± 1.4 servings/d, fruit juice 1.1 ± 1.1 servings/d Q5: AHEI2010 Post-MI: 74.1 ± 5.6 Pre-MI: 63.0 ± 9.0 1889 ± 577 kcal/d, SFA 7.0 ± 2.4 % total energy, omega 3 fats 1.0 ± 0.6 % total energy, TFA 1.0 ± 0.5 % total energy, alcohol 9.7 ± 9.6 g/d, folate intake 838 ± 454 µg/d, cereal fibre 9.6 ± 4.2 g/d, red and processed meats 1.0 ± 0.7 servings/d, nuts and legumes 1.0 ± 0.9 servings/d, sugar-sweetened beverages 0.8 ± 0.9 servings/d, total vegetables 2.7 ± 1.8 servings/d, total fruits 2.7 ± 1.8 servings/d, fruit juice 0.7 ± 0.7 servings/d		
Lopez-Garcia et al.[47]	Total participants: *n* 17,415 11,278 from Nurses' Health study (NHS) and 6137 men from Health Professional Follow-Up study (HPFS) Included men and women with non-fatal CV event Ethnicity not reported SBP and DBP not reported Plasma Glucose not reported <u>Men</u> Q1 Participants: *n* 1586 Age: 68±9 years BMI: 26.5±3.8 kg/m2 Current smoker: 9% Physical activity: 27.3±33.8 MET hrs/wk Aspirin: 55% Diuretic: 12% B-Blocker: 22% Calcium Channel Blocker: 21%	Prospective cohort design Participants taken from Nurses' Health Study the Health Professional Follow-Up Study Followed STROBE criteria for reporting data from observational studies Participants grouped into quintiles of alternative Mediterranean Diet Score s (aMED) score <u>Men</u> Q1: aMED Score 2.19 ± 0.83 SFA 10.3 ± 2.9% total energy, TFA 1.7 ± 0.7 % total energy, MUFA 11.6 ± 3.3 % total energy, PUFA 5.4 ± 1.7 % total energy, omega 3 0.14 ± 0.03 % total energy, vegetable protein 5.0 ± 1.1 % total energy, vegetables 1.9 ± 1.1 servings/d, legumes 0.3 ± 0.3	Primary endpoint was death from any cause, CVD mortality, and cancer mortality Food intakes determined using validated FFQ every 4 years. Nutrient content was calculated from the FFQ using USDA National Nutrient Database for Standard Reference (v 10-23) CV events defined as MI, stroke, angina pectoris, CABG and angioplasty aMED score calculated by awarding 1 point if intake was above cohort median for vegetables, legumes, fruit, nuts, whole-grain cereals, fish, and MUFAs:SFAs, and 1 point for intake below cohort median for red and processed meats. Alcohol intake of 5 to	Following a median follow-up of 7.7 years for mean and 5.8 years for women there were 1142 and 666 deaths from CVD in mean and women, respectively. In men, a higher aMED score was associated with a significant reduction in all-cause and cardiovascular mortality. This relationship was not observed in women (due to adjustment for physical activity). In pooled estimates, greater aMED scores was associated with decreased all-cause mortality (P_{trend}=<0.001) A 2-point increased in aMED was associated with a 7% reduction in risk of all-cause mortality (0.93; 95% CI: 0.89, 0.9).

	Other BP medication: 11% Lipid modifying medication: 24% Q2 Participants: *n* 1239 Age: 69 ± 9 years BMI: 26.3 ± 3.6 kg/m2 Current smoker: 9% Physical activity: 28.9 ± 32.1 MET hrs/wk Aspirin: 46% Diuretic: 11% B-Blocker: 19% Calcium Channel Blocker: 18% Other BP medication: 9% Lipid modifying medication: 23% Q3 Participants: *n* 1032 Age: 68 ± 8years BMI: 26.0 ± 3.5kg/m2 Current smoker: 9% Physical activity: 31.8 ± 31.4 MET hrs/wk Aspirin: 60% Diuretic: 11% B-Blocker: 21% Calcium Channel Blocker: 22% Other BP medication: 10% Lipid modifying medication: 29% Q4 Participants: *n* 938 Age: 69 ± 9 years BMI: 26.1 ± 3.6kg/m2 Current smoker: 9% Physical activity: 35.8 ± 37.0 MET hrs/wk Aspirin: 52% Diuretic: 8% B-Blocker: 19% Calcium Channel Blocker: 19% Other BP medication: 7% Lipid modifying medication: 23% Q5 Participants: *n* 1342 Age: 69 ± 8years	servings/day, fruit 1.8 ± 1.1 servings/d, nuts 0.2 ± 0.3 servings/d, whole grain 0.9 ± 1.0 servings/d, fish 0.2 ± 0.2 servings/d, MUFA:SFA 1.1 ± 0.2, red and processed meat 0.9 ± 0.7 servings/d, alcohol 9.0 ± 15.7 g/d. Q2 aMED Score 3.77 ± 0.39 SFA 9.0 ± 2.7 % total energy, TFA 1.5 ± 0.7 % total energy, MUFA 11.1 ± 3.2 % total energy, PUFA 5.6 ± 1.7% total energy, omega 3 0.17 ± 0.19 % total energy, vegetable protein 5.6 ± 1.2 % total energy, vegetables 2.5 ± 1.5 servings/d, legumes 0.4 ± 0.3 servings/day, fruit 2.4 ± 1.6 servings/d, nuts 0.4 ± 0.5 servings/d, whole grain 1.4 ± 1.2 servings/d, fish 0.3 ± 0.2 servings/d, MUFA:SFA 1.2 ± 0.2, red and processed meat 0.8 ± 0.7 servings/d, alcohol 9.9 ± 15.3 g/d. Q3 aMED Score 4.85 ± 0.33 SFA 8.1 ± 2.6% total energy, TFA 1.3 ± 0.6 % total energy, MUFA 10.5 ± 3.3 % total energy, PUFA 5.6 ± 1.7 % total energy, omega 3 0.18 ± 0.22% total energy, vegetable protein 6.0 ± 1.3 % total energy, vegetables 3.1 ± 1.6 servings/d, legumes 0.5 ± 0.4 servings/day, fruit 2.8 ± 1.6 servings/d, nuts 0.5 ± 0.6 servings/d, whole grain 1.7 ± 1.4 servings/d, fish 0.4 ± 0.4 servings/d, MUFA:SFA 1.3 ± 0.3, red and processed meat 0.7 ± 0.7 servings/d, alcohol 9.5 ± 14.3 g/d. Q4 aMED Score 5.70 ± 0.43 SFA 8.0 ± 2.6% total energy, TFA 1.3 ± 0.6 % total energy, MUFA 10.6 ± 3.3 % total energy, PUFA 5.7 ± 1.7 % total energy, omega 3 0.21 ± 0.23 % total energy, vegetable protein 6.2 ± 1.4 % total energy, vegetables 3.8 ± 2.1 servings/d, legumes 0.6 ± 0.5	15 g/d for women and 10 to 15 g/d for men received 1 point. Multivariable models were adjusted for age, BMI, smoking status, physical activity, parental history of MI before age 65 y, menopausal status and use of hormone therapy in women, multivitamin use, and medication use (aspirin, diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other antihypertensive medication, statins and other cholesterol lowering drugs, insulin, and oral antidiabetic medication) Impact of alcohol was assessed by adjusting for alcohol intake (never, 0.1–4.9, 5.0–14.9, or ≥15.0 g/d) and similarly with olive oil (never or <1 time/mo, 1–3 times/mo, 1 time/wk, or ≥2 times/wk	For men, MUFA:SFA showed an inverse relationship with mortality. In women, whole-grain intake, MUFA:SFA ratio, and moderate alcohol intake showed an inverse association Results did not differ when stratified on BMI (> or < 30 kg/m2) or activity level, or smoking status. Adjusting for alcohol intake slightly attenuated the relationship between aMED score and all-cause mortality (pooled adjusted RR for all-cause and cardiovascular mortality for a 2-point increase in the aMED score: 0.95 [95% CI: 0.90, 1.00] and 0.99 [95% CI: 0.89, 1.10], respectively). Adjustment for olive-oil did not change the associated between a 2-point increase in aMED and total and cardiovascular mortality (0.93; 95% CI: 0.89, 0.98 and 0.97: 95% CI: 0.89, 1.06, respectively). Only 14.3% of mean and 10.3% of women consumed olive oil ≥2 times/wk. **Summary** **Collectively these data show an association between a reduction in mortality with increased adherence to a Mediterranean-style diet in men and women with a history of CVD. The lack of effect with individual components likely suggest a synergistic effect and reinforces previous discussions regarding diet components such as whole grains.** **The individuals in this study also had pre-existing CVD which adds to the relevance for practice.**

	BMI: 25.7 ± 3.5 kg/m2 Current smoker: 9% Physical activity: 40.9 ± 38.1 MET hrs/wk Aspirin: 50% Diuretic: 6% B-Blocker: 19% Calcium Channel Blocker: 16% Other BP medication: 8% Lipid modifying medication: 25% <u>Women</u> Q1 Participants: *n* 2274 Age: 68±9 years BMI: 26.9 ± 6.6 kg/m2 Current smoker: 16% Physical activity: 9.4 ± 14.4 MET hrs/wk Aspirin: 65% Diuretic: 14% B-Blocker: 24% Calcium Channel Blocker: 17% ACEi: 11% Other BP medication: 10% Statins: 23% Other lipid modifying medication: 4% Insulin: 5% Oral antidiabetic drugs: 6% Q2 Participants: *n* 1970 Age: 67 ± 9 years BMI: 26.7 ± 6.5 kg/m2 Current smoker: 14% Physical activity: 11.0 ± 18.8 MET hrs/wk Aspirin: 68% Diuretic: 14% B-Blocker: 26% Calcium Channel Blocker: 19% ACEi: 12% Other BP medication: 8% Statins: 26% Other lipid modifying medication: 3% Insulin: 5% Oral antidiabetic drugs: 7%	servings/day, fruit 3.1 ± 1.7 servings/d, nuts 0.5 ± 0.7 servings/d, whole grain 1.9 ± 1.4 servings/d, fish 0.4 ± 0.3 servings/d, MUFA:SFA 1.3 ± 0.3, red and processed meat 0.68 ± 0.7 servings/d, alcohol 10.4 ± 13.5 g/d. Q5 aMED Score 7.05 ± 0.79 SFA 7.0 ± 2.0% total energy, TFA 1.2 ± 0.5 % total energy, MUFA 10.4 ± 3.2 % total energy, PUFA 5.8 ± 1.7 % total energy, omega 3 0.25 ± 0.26 % total energy, vegetable protein 6.7 ± 1.4 % total energy, vegetables 4.5 ± 2.1 servings/d, legumes 0.7 ± 0.6 servings/day, fruit 3.8 ± 1.8 servings/d, nuts 0.7 ± 0.8 servings/d, whole grain 2.3 ± 1.5 servings/d, fish 0.5 ± 0.3 servings/d, MUFA:SFA 1.5 ± 0.3, red and processed meat 0.5 ± 0.5 servings/d, alcohol 11.0 ± 11.6 g/d. <u>Women</u> Q1 aMED Score 2.19 ± 0.83 SFA 11.5 ± 3.2% total energy, TFA 1.9 ± 0.7 % total energy, MUFA 11.8 ± 3.3 % total energy, PUFA 5.4 ± 1.7 % total energy, omega 3 0.09 ± 0.12 % total energy, vegetable protein 4.8 ± 1.2 % total energy, vegetables 1.6 ± 0.9 servings/d, legumes 1.9 ± 3.3 servings/day, fruit 1.4 ± 1.0 servings/d, nuts 0.1 ± 0.3 servings/d, whole grain 0.7 ± 1.0 servings/d, 0.1 ± 0.1 servings/d, MUFA:SFA 1.0 ± 0.2, red and processed meat 0.9 ± 0.8 servings/d, alcohol 3.6 ± 9.9 g/d. Q2 aMED Score 3.77 ± 0.39 SFA 10.3 ± 3.2 % total energy, TFA 1.7 ± 0.7 % total energy, MUFA 11.5 ± 3.8 % total energy, PUFA 5.6 ± 1.8% total energy, omega 3 0.11 ± 0.15 % total energy, vegetable protein 5.3 ± 1.4 % total energy, vegetables 2.1 ± 1.4		

	Q3 Participants: *n* 2103 Age: 67 ± 8 years BMI: 26.5 ± 6.3 kg/m2 Current smoker: 12% Physical activity: 13.4 ± 16.8 MET hrs/wk Aspirin: 67% Diuretic: 17% B-Blocker: 26% Calcium Channel Blocker: 21% ACEi: 12% Other BP medication: 10% Statins: 26% Other lipid modifying medication: 4% Insulin: 5% Oral antidiabetic drugs: 6% Q4 Participants: *n* 1978 Age: 67 ± 8 years BMI: 26.6 ± 6.1 kg/m2 Current smoker: 8% Physical activity: 14.1 ± 16.9 MET hrs/wk Aspirin: 71% Diuretic: 15% B-Blocker: 26% Calcium Channel Blocker: 21% ACEi: 13% Other BP medication: 9% Statins: 26% Other lipid modifying medication: 3% Insulin: 5% Oral antidiabetic drugs: 6% Q5 Participants: *n* 2953 Age: 67 ± 8years BMI: 26.2 ± 5.7 kg/m2 Current smoker: 7% Physical activity: 18.8 ± 22.4 MET hrs/wk Aspirin: 72% Diuretic: 15% B-Blocker: 26% Calcium Channel Blocker: 21% ACEi: 12%	servings/d, legumes 1.9 ± 3.1 servings/day, fruit 1.9 ± 1.4 servings/d, nuts 0.2 ± 0.4 servings/d, whole grain 1.0 ± 1.3 servings/d, fish 0.2 ± 0.2 servings/d, MUFA:SFA 1.1 ± 0.3, red and processed meat 0.8 ± 0.7 servings/d, alcohol 4.3 ± 9.9 g/d. Q3 aMED Score 4.85 ± 0.33 SFA 9.7 ± 3.1 % total energy, TFA 1.6 ± 0.7 % total energy, MUFA 11.4 ± 3.9 % total energy, PUFA 5.6 ± 1.8 % total energy, omega 3 0.12 ± 0.13 % total energy, vegetable protein 5.6 ± 1.3 % total energy, vegetables 2.6 ± 1.5 servings/d, legumes 2.0 ± 3.2 servings/day, fruit 2.3 ± 1.4 servings/d, nuts 0.3 ± 0.5 servings/d, whole grain 1.3 ± 1.4 servings/d, fish 0.2 ± 0.2 servings/d, MUFA:SFA 1.2 ± 0.3, red and processed meat 0.8 ± 0.8 servings/d, alcohol 4.3 ± 9.4 g/d. Q4 aMED Score 5.70 ± 0.43 SFA 9.0 ± 2.9% total energy, TFA 1.5 ± 0.6 % total energy, MUFA 11.1 ± 3.6 % total energy, PUFA 5.7 ± 1.8 % total energy, omega 3 0.15 ± 0.15 % total energy, vegetable protein 5.9 ± 1.4 % total energy, vegetables 3.1 ± 1.7 servings/d, legumes 2.1 ± 3.2servings/day, fruit 2.6 ± 1.5 servings/d, nuts 0.4 ± 0.5 servings/d, whole grain 1.5 ± 1.5 servings/d, fish 0.3 ± 0.3 servings/d, MUFA:SFA 1.2 ± 0.3, red and processed meat 0.7 ± 0.6 servings/d, alcohol 4.0 ± 8.1 g/d. Q5 aMED Score 7.05 ± 0.79 SFA 8.0 ± 2.4% total energy, TFA 1.3 ± 0.6 % total energy, MUFA 11.0 ± 3.5% total energy, PUFA 6.0 ± 1.8 % total energy, omega 3 0.18 ± 0.17 % total energy, vegetable protein 6.4 ± 1.5 % total energy, vegetables 4.2 ± 1.9		

	Other BP medication: 9% Statins: 29% Other lipid modifying medication: 4% Insulin: 3% Oral antidiabetic drugs: 5%	servings/d, legumes 2.2 ± 3.2 servings/day, fruit 3.3 ± 1.6 servings/d, nuts 0.5 ± 0.6 servings/d, whole grain 2.1 ± 1.7 servings/d, fish 0.4 ± 0.3 servings/d, MUFA:SFA 1.4 ± 0.4, red and processed meat 0.6 ± 0.6 servings/d, alcohol 4.9 ± 8.0 g/d.		
Martínez-González et al.[48]	Articles in final meta-analysis: 27 Total number of participants in analysis: 271,479 Exposure to MedDiet assessed using range of screening tools	Cumulative MA of observational studies (prospective cohort and clinical trials) Articles sourced from PubMed, Embase, Google Scholar, and Web of Science till May 2017 Inclusion criteria were: Studies must be clinical trial or prospective cohort studies, original articles, primary prevention of mortality or incidence of CVD through the MedDiet, exposure must be adherence to MedDiet, and outcome was mortality from CVD or incidence of CV events (defined as CHD or stroke) Excluded studies that did not meet inclusion criteria, those which did not consider adherence to MedDiet on CV incidence or mortality from CVD. Computed a relative risk with 95% confidence interval for an increase of two points in adherence to the MedDiet No comments on assessment of study quality or publication bias	Primary outcomes CVD mortality or incidence of CV events Collected information on study design, sample size and sample characteristics, dietary assessment method, average duration of follow-up, number of non-fatal and fatal events, and results and covariates in the fully adjusted model	Follow-up ranged from 4.8-17.3 years. Each 2-point increment in a 0-9 MedDiet was associated with an 11% reduction in CVD risk (RR 0.89; 95% CI: 0.86, 0.91). Lyon Heart Study and PREDIMED accounted for 0.62% and 1.32% of total evidence **Summary** **Data form prospective cohort studies and clinical trials suggest that increased adherence to a Mediterranean diet is associated with reduced CV mortality or incidence of CVD. The study does not include the updated PREDIMED study published in 2018. This would not change the outcomes of this review**
Chiavaroli et al.[49]	Potentially relevant records: 125 After duplicates: 77 Excluded 60 due to not being systematic review and meta analysis, or did not assess effect of DASH on CV outcomes Full-texts assessed for eligibility: 14 Excluded 10 due to not being most recent systematic review and meta analysis, no pairwise meta-analysis performed, no cardiometabolic outcomes reported	Umbrella review of systematic reviews and meta analyses examining the DASH diet and cardiometabolic outcomes. Articles sourced from Medline and Embase (inception to January 3 2019). Quality of evidence was assessed using GRADE and reporting of evidence following Preferred Reporting Items for	Primary outcome was incident CVD in prospective cohort studies and SBP in trials. Secondary outcomes included incident CHD, stroke, and diabetes in prospective cohort studies. Secondary outcomes in controlled trials included DBP, blood lipids, glycaemic control, insulin, adiposity, and inflammation	1 meta analysis of prospective studies assessed the relationship between DASH diet and CVD incidence (including 783,732 participants with 32,927 events). Consumption of the DASH diet was associated with a 20% reduction in CVD incidence (RR 0.80; 95% CI: 0.76, 0.85). 1 meta analysis of prospective studies assessed the relationship between

	Articles in final meta-analysis: 7 3 systemic reviews and meta analyses of prospective cohort studies 4 systematic review and meta analyses of RCTs Total number of participants from prospective cohort studies: 942,140 Total number of participants from RCTs: 4414 Of systematic review and meta analyses of prospective cohort studies, 1 included composite CVD outcomes, 1 included stroke incidence, 1 included diabetes incidence, 1 included overall mortality Of systematic review and meta analyses of RCTs, 0 included HbA1c, 2 included glycaemic control, 1 included blood pressure, 1 included lipid parameters, 1 included body weight and adiposity, ands 1 included inflammation	Systematic Reviews and Meta-Analyses (PRISMA) Study bias assessed using Cochrane 'Risk of Bias' tool or New Castle Ottawa score.		DASH diet and CHD incidence (including 144,337 participants with 7260 events). Consumption of the DASH diet was associated with a 21% reduction in CVD incidence (RR 0.79; 95% CI: 0.71, 0.88). 1 meta analysis of prospective studies assessed the relationship between DASH diet and Stroke incidence (including 150,191 participants with 4413 events). Consumption of the DASH diet was associated with a 19% reduction in CVD incidence (RR 0.81; 95% CI: 0.72, 0.92). 1 meta analysis of prospective studies assessed the relationship between DASH diet and diabetes incidence (including 158,408 participants with 23,612 events). Consumption of the DASH diet was associated with a 18% reduction in CVD incidence (RR 0.82; 95% CI: 0.74, 0.92) although significant heterogeneity was noted between studies 1 meta analysis of RCTs assessed the effect of the DASH diet on BP outcomes (including 1918 participants). DASH diet reduced SBP (MD -5.20 mmHg; 95% CI: -7.00, -3.40 mmHg) and DBP (MD -2.60 mmHg; 95% CI: -3.50, -1.70 mmHg)). There was large heterogeneity in outcomes. 1 meta analysis of RCTs studies assessed the effect of the DASH diet on lipid outcomes. DASH diet reduced TC (1673 participants, MD -0.20 mmol/L; 95% CI: -0.31, -0.10 mmol/L), LDL-C (1673 participants, MD -0.10 mmol/L; 95% CI: -0.20, -0.01 mmol/L)). There was no effect on HDL-C or TAG. Large heterogeneity in studies noted.

				2 RCTs showed DASH diet reduced HbA1c (654 participants, MD -0.53% (95% CI: -0.62, -0.43%)). 1 meta analysis of RCTs studies assessed the effect of the DASH diet on glucose outcomes (blood glucose, insulin, and HOMA-IR). DASH diet reduced insulin (760 participants, MD -0.15 µU/mL; 95% CI: -0.22 to -0.08 µU/mL)). There was no effect seen on blood glucose of HOMA-IR 1 meta analysis of RCTs studies assessed the effect of the DASH diet on body weight. DASH diet reduced bodyweight (1211 participants, MD -1.42 kg; 95% CI: -2.03, -0.82 kg)). 1 meta analysis of RCTs studies assessed the effect of the DASH diet on CRP. No effect was seen but subgroup analysis showed an effect when compared to unhealthy or usual diets (MD -9.62 nmol/L; 95% CI: -15.62, −3.62 nmol/L) or when follow-up was ≥ 8 weeks **Summary** **This study shows that adoption of the DASH diet is associated with reduced incident stroke, CVD, and CHD. The DASH diet shows modest effects on CV risk factors such as cholesterol, insulin, and inflammation. DASH is high in fruits and vegetables, whole grains, fish and poultry, and limiting fatty meats, and SSBs**
Kim et al.[50]	Total participants: *n* 12,168 <u>Characteristics based on plant-based diet scores:</u> Q1 Participants: *n* 2717 Age: 53.7±5.8 years Women: 42.3% BMI <25kg/m2: 19.5%	Prospective cohort study and meta-analysis Participants taken from the Atherosclerosis Risk in Communities (ARIC) study. Established 4, plant-based diet scores (plant-based diet index [PDI], healthy plant-based diet index [hPDI], less healthy [unhealthy] plant-based diet	Primary outcome was all-cause mortality (defined as deaths attributable to any cause), CV mortality, and incident CV disease (defined as composite outcome of CHD, stroke, and HF) Diet data collected using a 66-item semi-quantitative	Median follow-up of 25 years, there were 1565 deaths from CVD and 5436 deaths from all-causes. Those in highest quintiles of PDI, hPDI, and pro-vegetarian index were more likely to be women, white, more physically active, less likely to be obese, have diabetes or hypertension

	BMI 25-30kg/m2: 22.6% BMI ≥30kg/m2: 27.5% Current smoker: 33.8% Activity index: 2.3±0.7 High blood pressure: 36.5% Diabetes: 11.5% Fasting glucose: 6.1±2.4 mmol/L Lipid-lowering medication: 1.2% eGFR: 105.2±16.4 mL/min/1.73m2 Ethnicity: 43.2% Black Q2 Participants: *n* 2864 Age: 53.7±5.6 years Women: 55.2% BMI <25kg/m2: 21.7% BMI 25-30kg/m2: 24.4% BMI ≥30kg/m2: 24.7% Current smoker: 27.8% Activity index: 2.4±0.8 High blood pressure: 32.3% Diabetes: 11.4% Fasting glucose: 6.1±2.4 mmol/L Lipid-lowering medication: 1.3% eGFR: 103.3±15.8 mL/min/1.73m2 Ethnicity: 31.3% Black Q3 Participants: *n* 2308 Age: 53.7±5.7 years Women: 60% BMI <25kg/m2: 18.9% BMI 25-30kg/m2: 18.4% BMI ≥30kg/m2: 19.4% Current smoker: 23.2% Activity index: 2.4±0.8 High blood pressure: 31.2% Diabetes: 10.5% Fasting glucose: 6.0±2.1 mmol/L Lipid-lowering medication: 2.5% eGFR: 102.9±14.9 mL/min/1.73m2 Ethnicity: 24.1% Black Q4 Participants: *n* 1992 Age: 54.2±5.7 years Women: 61.5% BMI <25kg/m2: 16.9% BMI 25-30kg/m2: 17.2%	index [uPDI], and provegetarian diet index). hPDI included whole grains, fruits, vegetables, nuts, legumes, tea, and coffee. uPDI included fruit juices, refined grain, potatoes, sugar-sweetened beverages, sweets, and desserts. Higher PDI scores represented higher intakes of healthy and less healthy plant foods. Higher hPDI scores represented higher intakes of healthy plant foods, and lower intakes of less-healthy plant foods. Higher uPDI scores represented higher intakes of less healthy plant foods, and lower intakes of healthy plant foods. Higher pro-vegetarian diet scores represented higher intakes of plant foods (regardless of healthfulness). Higher scores of all four scores represented lower intakes of animal foods. <u>PDI Score Quintiles</u> <u>Q1</u> PDI Score (median): 44 (28-46) Healthy Plant Food: 5.4±2.8 servings/d Unhealthy Healthy Plant Food: 4.6±2.3 servings/d 1715 ± 593 kcal/d, carbohydrates 43.7 ± 8.0 % total energy, total fat 35.4 ± 5.9 % total energy, SFA 13.2 ± 2.7 % total energy, MUFA 13.9 ± 2.6 % total energy, PUFA 4.9 ± 1.2 % total energy, total protein 18.7 ± 3.9 % total energy, animal protein 15.2 ± 3.9 % total energy, plant protein 3.6 ± 0.8 % total energy, fibre 8.3 ± 2.7 g/1000 kcal, animal foods: 5.6 ± 2.8 servings/d, fruits and vegetables 2.8 ± 1.7 servings/d, red and processed meats 1.5 ± 0.8 servings/d, dairy 1.8 ± 1.4 servings/d, fish or seafood 0.3 ± 0.3 servings/d, margarine 1.0 ± 0.9 servings/d, alcohol 68.9 ± 137.9 g/wk Q2: PDI Score (median): 49 (47–50) Healthy Plant Food: 6.3±2.9 servings/d	FFQ at visit 1 and visit 3. The Harvard Nutrient Database was used to derive nutrient intakes from the FFQ responses. Participants examined at follow-up visits, with the second visit occurring between 1990 and 1992, the third between 1993 and 1995, the fourth between 1996 and 1998, the fifth between 2011 and 2013, and the sixth between 2016 and 2017. Models adjusted for BMI, age, race and gender, ARIC test centre, total energy consumption, alcohol intake, margarine intake, total cholesterol, lipid-lowering medication, renal function, diabetes, cigarette smoking, and education level	when compared to those in the lowest quintiles Those in the highest quintile of uPDI were more likely to be male, younger, smoke, obese, and have HTN Those in highest quintiles of PDI, hPDI, and pro-vegetarian index consumed more fruits and vegetables, less red and processed meat, more plant protein and carbohydrate (as percentage of total energy), fibre, and micronutrients such as potassium, magnesium and iron. Those in the highest quintile of uPDI consumed less fruit and vegetables, more red and processed meat, and had a higher intake of total energy and carbohydrate as a percentage of energy. In fully adjusted models, compared with Q1 the highest quintile of PDI was associated with a 16% lower risk of incident CVD (HR 0.84; 95% CI: 0.76, 0.94; P_{trend}<0.001), a 31% lower risk of CVD mortality (HR 0.69; 95% CI: 0.58, 0.81; P_{trend}<0.001), and a 24% lower risk of all-cause mortality (HR 0.76; 95% CI: 0.69, 0.83; P_{trend}<0.001) In fully adjusted models, compared with Q1 the highest quintile of hPDI was associated with a 16% lower risk of CVD mortality (HR 0.84; 95% CI: 0.71, 1.01; P_{trend}=0.03), and a 9% lower risk of all-cause mortality (HR 0.91; 95% CI: 0.83, 1.00; P_{trend}=0.03) In fully adjusted models, compared with Q1 the highest quintile of pro-vegetarian diet index was associated with a 15% lower risk of incident CVD (HR 0.85; 95% CI: 0.77, 0.94; P_{trend}<0.001), a 32% lower risk of CVD mortality (HR 0.68; 95% CI: 0.58, 0.80; P_{trend}0.001), and a 18% lower risk of all-

	BMI ≥30kg/m2: 13.7% Current smoker: 19.2% Activity index: 2.5±0.8 High blood pressure: 30.6% Diabetes: 9.4% Fasting glucose: 5.9±1.8 mmol/L Lipid-lowering medication: 3.4% eGFR: 102.1±13.9 mL/min/1.73m2 Ethnicity: 19.2% Black Q5 Participants: *n* 2287 Age: 53.9±5.8 years Women: 60.6% BMI <25kg/m2: 22.8% BMI 25-30kg/m2: 17.3% BMI ≥30kg/m2:14.6% Current smoker: 19.2% Activity index: 2.6±0.8 High blood pressure: 27.0% Diabetes: 7.0% Fasting glucose: 5.7±1.6 mmol/L Lipid-lowering medication: 3.8% eGFR: 101.9±13.2 mL/min/1.73m2 Ethnicity: 12.9% Black <u>Characteristics based on Pro-Vegetarian index score</u> Q1 Participants: *n* 2970 Age: 53.4±5.7 years Women: 46.5% BMI <25kg/m2: 21.8% BMI 25-30kg/m2: 24.3% BMI ≥30kg/m2: 28.9% Current smoker: 32.9% Activity index: 2.3±0.8 High blood pressure: 34.1% Diabetes: 10.4% Fasting glucose: 6.1±2.3 mmol/L Lipid-lowering medication: 1.1% eGFR: 104.5±15.9 mL/min/1.73m2 Ethnicity: 35.5% Black Q2 Participants: *n* 2687 Age: 53.7±5.7 years Women: 55.5%	Unhealthy Healthy Plant Food: 4.7±2.4 servings/d 1569 ± 555 kcal/d, carbohydrates 47.4 ± 7.8 % total energy, total fat 33.3 ± 5.7 % total energy, SFA 12.2 ± 2.4 % total energy, MUFA 13.0 ± 2.6 % total energy, PUFA 4.9 ± 1.2 % total energy, total protein 18.5 ± 3.9 % total energy, animal protein 14.4 ± 3.8 % total energy, plant protein 4.2 ± 0.9 % total energy, fibre 10.1 ± 3.0 g/1000 kcal, animal foods: 4.5 ± 2.0 servings/d, fruits and vegetables 2.8 ± 1.7 servings/d, red and processed meats 1.2 ± 0.7 servings/d, dairy 1.6 ± 1.2 servings/d, fish or seafood 0.3 ± 0.3 servings/d, margarine 1.0 ± 0.9 servings/d, alcohol 45.2 ± 95.2 g/wk Q3: PDI Score (median): 52 (51–53) Healthy Plant Food: 7.0±2.9 servings/d Unhealthy Healthy Plant Food: 4.9±2.4 servings/d 1548 ± 537 kcal/d, carbohydrates 50.0 ± 7.4% total energy, total fat 32.0 ± 5.7 % total energy, SFA 11.5 ± 2.3 % total energy, MUFA 12.4 ± 2.5 % total energy, PUFA 4.9 ± 1.2 % total energy, total protein 18.3 ± 3.7 % total energy, animal protein 13.8 ± 3.6 % total energy, plant protein 4.6 ± 0.9 % total energy, fibre 11.4 ± 3.3 g/1000 kcal, animal foods: 4.0 ± 1.8 servings/d, fruits and vegetables 3.1 ± 1.7 servings/d, red and processed meats 1.0 ± 0.7 servings/d, dairy 1.5 ± 1.1 servings/d, fish or seafood 0.3 ± 0.3 servings/d, margarine 1.0 ± 0.9 servings/d, alcohol 36.4 ± 80.7 g/wk Q4: PDI Score (median): 55 (54–56) Healthy Plant Food: 7.7±2.8 servings/d Unhealthy Healthy Plant Food: 5.1±2.4 servings/d 1573 ± 524 kcal/d, carbohydrates 52.1 ± 7.2 % total energy, total fat 30.7 ± 5.9 % total energy, SFA 10.9 ± 2.3 % total		cause mortality (HR 0.82; 95% CI: 0.76 – 0.89; P_{trend}<0.001) <u>No significant associations were observed with uPDI and any of the primary outcomes</u> Food group analysis showed that higher intakes of whole grains were associated with lower incidence of CVD, CVD mortality, and all-cause mortality. Refined grains showed no association. Higher intake of red and processed meat and eggs was associated with increased risk of CVD incidence, CVD mortality, and all-cause mortality. Increased poultry appeared to be significantly associated with reduced all-cause mortality. Fish or seafood, or diary was not significantly associated with any outcomes. Individual components such as vegetables, fruits, nut, and legumes were not significantly associated with any of the outcomes. Higher intake of potatoes, which were classified as less healthy plant foods for hPDI and uPDI, was inversely associated with incident CVD and all-cause mortality **Summary** **Overall this study shows that a healthy-plant based diets conveys a modest reduction in CV incidence, mortality, and all-cause mortality.** **A poorly constructed plant-based diet containing refined grains, fruit juices and increased sweets and desserts is not associated with any benefit to CV health, although in this study it was not associated with increased risk. This may be due to the scoring of potatoes and how they are consumed**

	BMI <25kg/m2: 19.8% BMI 25-30kg/m2: 23.1% BMI ≥30kg/m2: 24.2% Current smoker: 27.3% Activity index: 2.4±0.8 High blood pressure: 31.4% Diabetes: 11.6% Fasting glucose: 6.1±2.4 mmol/L Lipid-lowering medication: 1.7% eGFR: 103.7±15.5 mL/min/1.73m2 Ethnicity: 31.7% Black Q3 Participants: *n* 1911 Age: 53.6±5.7 years Women: 59.2% BMI <25kg/m2: 15.4% BMI 25-30kg/m2: 16.1% BMI ≥30kg/m2: 15.4% Current smoker: 24.0% Activity index: 2.4±0.8 High blood pressure: 31.4% Diabetes: 10.2% Fasting glucose: 5.9±2.0 mmol/L Lipid-lowering medication: 2.3% eGFR: 103.3±15.3 mL/min/1.73m2 Ethnicity: 27.9% Black Q4 Participants: *n* 2266 Age: 54.0±5.7 years Women: 59.5% BMI <25kg/m2: 20.3% BMI 25-30kg/m2: 18.3% BMI ≥30kg/m2: 16.5% Current smoker: 22.8% Activity index: 2.5±0.8 High blood pressure: 31.4% Diabetes: 9.8% Fasting glucose: 5.9±1.8 mmol/L Lipid-lowering medication: 2.9% eGFR: 102.5±14.3 mL/min/1.73m2 Ethnicity: 21.5% Black Q5 Participants: *n* 2334 Age: 54.6±5.8 years Women: 58.4%	energy, MUFA 11.9 ± 2.7 % total energy, PUFA 4.9 ± 1.2 % total energy, total protein 17.9 ± 3.5 % total energy, animal protein 13.0 ± 3.4 % total energy, plant protein 4.9 ± 1.0 % total energy, fibre 12.3 ± 3.4 g/1000 kcal, animal foods: 3.8 ± 1.7 servings/d, fruits and vegetables 3.5 ± 1.7 servings/d, red and processed meats 0.9 ± 0.6 servings/d, dairy 1.5 ± 1.1 servings/d, fish or seafood 0.3 ± 0.3 servings/d, margarine 1.1 ± 1.0 servings/d, alcohol 32.4 ± 66.3 g/wk Q5: PDI Score (median): 59 (57–74) Healthy Plant Food: 9.0±3.0 servings/d Unhealthy Healthy Plant Food: 6.0±2.6 servings/d 1698 ± 521 kcal/d, carbohydrates 54.6 ± 7.2% total energy, total fat 29.8 ± 5.6 % total energy, SFA 10.3 ± 2.3 % total energy, MUFA 11.5 ± 2.6 % total energy, PUFA 5.0 ± 1.2 % total energy, total protein 17.0 ± 3.1 % total energy, animal protein 11.6 ± 3.2 % total energy, plant protein 5.3 ± 1.1 % total energy, fibre 13.4 ± 3.5 g/1000 kcal, animal foods: 3.6 ± 1.8 servings/d, fruits and vegetables 4.1 ± 1.9 servings/d, red and processed meats 0.8 ± 0.7 servings/d, dairy 1.5 ± 1.0 servings/d, fish or seafood 0.3 ± 0.2 servings/d, margarine 1.1 ± 0.9 servings/d, alcohol 28.6 ± 59.4 g/wk <u>Pro-vegetarian diet index score</u> Q1: Pro-vegetarian diet index score (median +range): 27 (15-29) Healthy Plant Food: 5.5±2.7 servings/d Unhealthy Healthy Plant Food: 4.7±2.3 servings/d 1618 ± 585 kcal/d, carbohydrates 44.3 ± 8.1 % total energy, total fat 35.2 ± 5.8 % total energy, SFA 13.2 ± 2.6 % total energy, MUFA 13.8 ± 2.5 % total energy, PUFA 4.8 ± 1.1 % total energy,		**in different populations (boiled/baked vs. chips).**

	BMI <25kg/m2: 22.7% BMI 25-30kg/m2: 18.2% BMI ≥30kg/m2:18.9% Current smoker: 16.8% Activity index: 2.6±0.8 High blood pressure: 29.4% Diabetes: 8.2% Fasting glucose: 5.5±1.8 mmol/L Lipid-lowering medication: 3.8% eGFR: 101.6±13.6 mL/min/1.73m2 Ethnicity: 16.5% Black	total protein 18.7 ± 4.0 % total energy, animal protein 15.2 ± 4.0 % total energy, plant protein 3.5 ± 0.8 % total energy, fibre 8.0 ± 2.3 g/1000 kcal, animal foods: 5.2 ± 2.3 servings/d, fruits and vegetables 2.1 ± 1.4 servings/d, red and processed meats 1.4 ± 0.8 servings/d, dairy 1.8 ± 1.3 servings/d, fish or seafood 0.3 ± 0.3 servings/d, margarine 1.0 ± 0.9 servings/d, alcohol 60.3 ± 123.4 g/wk Q2: Pro-vegetarian diet index score (median +range): 31 (30/32) Healthy Plant Food: 6.3±2.8 servings/d Unhealthy Healthy Plant Food: 4.8±2.4 servings/d 1567 ± 561 kcal/d, carbohydrates 47.7 ± 7.9 % total energy, total fat 33.3 ± 5.7 % total energy, SFA 12.2 ± 2.4 % total energy, MUFA 13.0 ± 2.6 % total energy, PUFA 4.9 ± 1.2 % total energy, total protein 18.4 ± 3.9 % total energy, animal protein 14.3 ± 3.8 % total energy, plant protein 4.2 ± 0.8 % total energy, fibre 10.0 ± 2.7 g/1000 kcal, animal foods: 4.4 ± 2.0 servings/d, fruits and vegetables 2.7 ± 1.6 servings/d, red and processed meats 1.2 ± 0.8 servings/d, dairy 1.6 ± 1.2 servings/d, fish or seafood 0.3 ± 0.3 servings/d, margarine 1.0 ± 0.9 servings/d, alcohol 43.1 ± 89.3 g/wk Q3: Pro-vegetarian diet index score (median +range): 33 (33-34) Healthy Plant Food: 6.9±2.8 servings/d Unhealthy Healthy Plant Food: 4.9±2.4 servings/d 1574 ± 551 kcal/d, carbohydrates 49.7 ± 7.6% total energy, total fat 32.2 ± 5.7 % total energy, SFA 11.6 ± 2.3 % total energy, MUFA 12.5 ± 2.6 % total energy, PUFA 4.9 ± 1.2 % total energy, total protein 18.2 ± 3.7 % total energy, animal protein 13.7 ± 3.6 % total energy,		

		plant protein 4.5 ± 0.9 % total energy, fibre 11.3 ± 3.0 g/1000 kcal, animal foods: 4.2 ± 1.9 servings/d, fruits and vegetables 3.1 ± 1.6 servings/d, red and processed meats 1.0 ± 0.7 servings/d, dairy 1.6 ± 1.2 servings/d, fish or seafood 0.3 ± 0.3 servings/d, margarine 1.0 ± 0.9 servings/d, alcohol 39.4 ± 87.9 g/wk Q4: Pro-vegetarian diet index score (median +range): 36 (35-37) Healthy Plant Food: 7.5±2.9 servings/d Unhealthy Healthy Plant Food: 5.2±2.5 servings/d 1619 ± 527 kcal/d, carbohydrates 51.6 ± 7.5 % total energy, total fat 31.0 ± 5.8 % total energy, SFA 11.0 ± 2.3 % total energy, MUFA 12.0 ± 2.6 % total energy, PUFA 5.0 ± 1.2 % total energy, total protein 17.8 ± 3.6 % total energy, animal protein 13.0 ± 3.5 % total energy, plant protein 4.8 ± 0.9 % total energy, fibre 12.2 ± 3.1 g/1000 kcal, animal foods: 4.0 ± 1.8 servings/d, fruits and vegetables 3.6 ± 1.7 servings/d, red and processed meats 0.9 ± 0.6 servings/d, dairy 1.5 ± 1.1 servings/d, fish or seafood 0.3 ± 0.3 servings/d, margarine 1.1 ± 0.9 servings/d, alcohol 38.9 ± 91.1 g/wk Q5: Pro-vegetarian diet index score (median +range): 40 (38-40) Healthy Plant Food: 9.0±3.1 servings/d Unhealthy Healthy Plant Food: 5.6±2.6 servings/d 1739 ± 514 kcal/d, carbohydrates 54.4 ± 7.4% total energy, total fat 29.5 ± 5.8 % total energy, SFA 10.1 ± 2.2 % total energy, MUFA 11.5 ± 2.7 % total energy, PUFA 5.1 ± 1.2 % total energy, total protein 17.4 ± 3.2 % total energy, animal protein 11.9 ± 3.3 % total energy, plant protein 5.5 ± 1.1 % total energy, fibre 14.1 ± 3.6 g/1000 kcal, animal		

		foods: 3.7 ± 1.8 servings/d, fruits and vegetables 4.5 ± 2.0 servings/d, red and processed meats 0.9 ± 0.7 servings/d, dairy 1.5 ± 1.0 servings/d, fish or seafood 0.2 ± 0.3 servings/d, margarine 1.2 ± 1.0 servings/d, alcohol 31.4 ± 68.5 g/wk		
Athinarayanan et al.[51]	2 year follow-up data Total participants: *n*=349 <u>Continuous Care Intervention</u> *n*=262 Age: 53.8±8.4 years Female: 66.79±2.92 % BMI: 40.42±8.81 kg Waist Circumference: 124.5±14.3 cm Weight: 114.56±0.60 kg Spine bone mineral density: 1.20 ± 0.16 g/cm2 Central abdominal fat: 5.77±1.69 kg Android:gynoid ratio: 1.27±0.33 Lower extremity lean mass: 18.45±4.05 kg Years since T2 Diabetes Diagnosis: 8.44±7.22 HbA1c: 7.6±1.5 % C-peptide: 4.36±2.15 nmol/L Plasma glucose: 9.1±0.2 mmol/L Insulin: 27.73±1.26 mIU/L HOMA-IR: 9.09±0.41 MetS (prevalence): 88.6±2.0 % SBP: 131.9±14.1 mmHg DBP: 82.1±8.3 mmHg TC: 4.7±1.1 mmol/L LDL-C: 2.7±0.9 mmol/L HDL-C: 1.1±0.3 mmol/L TAG: 2.2±1.6 mmol/L ALT: 30.65±22.7 U/L AST: 23.69±15.19 U/L ALP: 74.11±22.14 U/L Bilirubin: 9.2±3.6 µmol/L NAFLD-Liver Fat Score: 3.43±3.84 NAFLD-Fibrosis Score: -0.23±1.36 eGFR: 80.48±13.62 mL/s/m2 Creatinine: 0.88±0.01 µmol/L TSH: 2.32±1.74 mIU/L	Open label, non-randomized controlled study. Intervention consisted of a personalised nutrition recommendation designed to maintain nutritional ketosis. <u>Continuous Care Intervention (CCI)</u> Dietary protein was set at 1.5 g/kg of an "ideal" body weight and titrated against blood ketone levels. Fats were included to satiety and participants were encouraged to consume adequate intake of omega-3 (EPA and DHA) and omega 6 (LA), with the remainder from MUFA and SFA. Each participant was instructed to consumer 3-5 serving of non-starchy vegetables and adequate mineral and fluid intakes. Participants were advised to consume a multivitamin, 1000-2000 IU Vit D3, and up to 1000 mg omega-3 daily. Participants in this group selected how they wishes to receive their education: 1) group education sessions or 2) web-based viewed through an app. <u>Usual Care (UC)</u> Patients with T2 diabetes referred to local diabetes education programme and were counselled by RDs on diabetes self-management, nutrition, and lifestyle. No detail is provided on the specific macronutrients consumed, or the sources of protein of fa tin the diet.	Primary outcomes were retention, HbA1c, weight, fasting glucose and insulin, HOMA-IR or c-peptide. Secondary outcomes included lipids, liver markers, calculated liver scores (fibrosis and fatty-liver), kidney function tests, thyroid function (TSH and free T4), inflammatory markers (hs-CRP and WBC), and changes in medication use and insulin dose. Prevalence and resolution of T2 diabetes, MetS, liver steatosis and fibrosis were assessed at baseline and 2 years Anthropometry was performed at baseline, 1-year and 2 year follow-up. Missing values were estimated from 40 imputations from logistic regression	HbA1C decreased by 0.9 units (P<0.0001) during the 2 year period. HbA1C increased by 0.4 units in the usual care group Fasting glucose, HOMA-IR and insulin all significantly (P<0.0001) decreased in the CCI group, and either stayed the same or increased in the usual care group. Weight decreased by -11.94±0.96 kg in the CCI group (P<0.0001) and increased in the usual care group (+1.28±1.63 kg). Central abdominal fat and the android:gynoid ratio all improved over the 2 year period. At 2 years, 74% of CCI group achieved 5% weight loss compared to 14% of the UC group. Diabetes medication (excluding metformin) decreased significantly in the CCI group over the 2 year period (56.9% to 26.8%, P<0.0001). Those individuals taking insulin observed a significant reduction in daily insulin units (81.9 to 15.5 U/day, P<0.0001) in the CCI group. A significant (P<0.0001) reduction in SBP and DBP was observed in the CCI group, but not in the usual care group. SBP decreased by -5.8±1.2 mmHg and DBP decreased by 3.1±1.2 mmHg. HDL-C and LDL-C all significantly (P<0.001) increased in the CCI group. HDL-C increased by 0.29±0.07 mmol/L

	Free T4: 11.8±2.2 pmol/L hs-CRP: 8.54±14.49 nmol/L WBC: 7.24±1.89× 10^9/L Diabetes Medication: 56.87±3.07 % Sulfonylurea: 23.66±2.63 % Insulin: 29.77±2.83 % TZD: 1.53±0.76 % SGLT2: 10.31±1.88 % DPP-4: 9.92±1.85 % GLP-1: 13.36±2.11 % Metformin: 71.37±2.80 % <u>Usual Care Intervention</u> *n*=87 Age: 52.3±9.5 years Female: 58.62±5.31 % BMI: 36.72±7.26 kg Waist Circumference: 117.9±14.3 cm Weight: 111.07±1.09 kg Years since T2 Diabetes Diagnosis: 7.85±7.32 years HbA1c: 7.6±1.8 % C-peptide: 4.18±2.48 nmol/L Plasma glucose: 8.4±0.4 mmol/L Insulin: 27.57±2.29 mIU/L HOMA-IR: 8.66±0.92 MetS (prevalence): 91.4±3.1 % SBP: 129.8±13.6 mmHg DBP: 82.0±8.9 mmHg TC: 4.8±1.2 mmol/L LDL-C: 2.6±0.9 mmol/L HDL-C: 1.0±0.3 mmol/L TAG: 3.2±4.5 mmol/L ALT: 27.4±19.81 U/L AST: 23.90±19.39 U/L ALP: 77.36±26.29 U/L Bilirubin: 9.4±4.8 µmol/L NAFLD Score: 3.10±3.63 NAFLD-Fibrosis Score: -0.80±1.41 eGFR: 79.17±13.73 mL/s/m2 Creatinine: 0.90±0.02 µmol/L TSH: 3.80±17.07 mIU/L Free T4: 11.3±3.7 pmol/L hs-CRP: 8.89±8.62 WBC: 8.14±2.39× 10^9/L Diabetes Medication: 66.67±5.08% Sulfonylurea: 23.66±2.63 % Insulin: 45.98±5.37 %			and LDL-C by 0.20±0.02 mmol/L. HDL-C decreased in the usual care group. TAG decreased significantly in the CCI group only (-0.50±0.16 mmol/L) ALT, AST, ALP, NAFLD-Liver Fat Score and NAFLD-Liver Fibrosis Score all significantly reduced in the CCI group (P<0.0001). eGFR increased by 2.73±0.72 mL/S/m2 is the CCI group whereas no change was seen in the usual care group. At 2 years, 27.2% and 6.5% of CCI and usual care patients showed resolution of MetS (P=$4.9x10^{-15}$). Diabetes remission was observed in 17.6% of CCI participants and 0 of the usual care participants at 2 years **Summary** **Long term follow up for the ketogenic diet shows substantial improvement in cardiometabolic risk factors in individuals with established diabetes. Results may not be as impressive as DiRECT but the severity of T2DM is greater in Virta Health. Long term follow-up is needed to examine the role these improvements may have on CV and all-cause mortality**.

	TZD: 1.15±1.15 % SGLT2: 14.94±3.84 % DPP-4: 8.05±2.93 % GLP-1: 16.09±3.96 % Metformin: 60.92±5.26 % No statistically significant difference in any baseline parameter between groups Ethnicity and medication use not reported			

Table legends

Table 1

AA, arachidonic acid; ALA, alpha linolenic acid; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASM, appendicular skeletal muscle mass; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CHS, cardiovascular health study frailty score; CRP, c-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DGLA, Dihomo-γ-linolenic acid; DHA, docosahexaenoic acid; DM, diabetes mellitus; eGFRcycC, estimated glomerular filtration rate from cystatin C measurements; eGFRcr-cysC, estimated glomerular filtration rate from creatinine and cystatin C measurements; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; HOMA-IR, homeostatic model assessment of insulin resistance; GLA, gamma-Linolenic acid; HDL-C, high density lipoprotein cholesterol; HTN, hypertension; LA, linoleic acid; low carbohydrate diet, LCD; LCDS, low carbohydrate score; LDL-C, low density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular events; MD, mean difference; MetS, metabolic syndrome; MI, myocardial infarction; MNA, mini nutritional assessment; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; QoL, quality of life; RAS, renin-angiotensin system; SBP, systolic blood pressure; SFA, saturated fat; T2DM, type 2 diabetes; TAG, triacylglycerol; TC, total cholesterol; TFA, trans fatty acid; , VLDL, very low density lipoprotein; WMD, weighted mean difference

Table 2

aHEI, alternate healthy eating index; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DASH, dietary approaches to stop hypertension; DBP, diastolic blood pressure; DVP-SI, digital volume pulse–stiffness index; DVP-RI, digital volume pulse–reflection index; FFQ, food frequency questionnaire; F&V, fruits and vegetables, HDL-C, high density lipoprotein cholesterol; HF, heart failure; HRT, hormone replacement therapy; hsCRP, high-sensitivity C-reactive protein ICAM, intercellular adhesion molecule; IHD, ischaemic heart disease; LDI-Ach, laser Doppler imaging with acetylcholine; LDI-SNP, laser Doppler imaging with sodium nitroprusside; LDL-C, low density lipoprotein cholesterol; MCE, major coronary events; mDASH; modified DASH; MedDiet, Mediterranean Diet; MI, myocardial infarction; MUFA, monounsaturated fat; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PUFA, polyunsaturated fat; PWA AIx, pulse wave analysis augmentation index; PWA AIx HR75, pulse wave analysis augmentation index with correction to a heart rate of 75 beats/min; PWV, pulse wave velocity; SBP, systolic blood pressure; SFA, saturated fat; TAG, triacylglycerol; TC, total cholesterol; TFA, trans fatty acid; VCAM, vascular cell adhesion molecule; vWF, von Willebrand factor

Table 3

aHEI, alternate healthy eating index; ALT, alanine aminotransferase; alternative Mediterranean diet (aMED); AST, aspartate aminotransferase; ALP, alkaline phosphatase; ApoA1, ACEi, angiotensin convertor enzyme inhibitor; apolipoprotein A1; ApoB, apolipoprotein B; BP, blood pressure; BMI, body mass index; CABG, coronary artery bypass graft; CHD, coronary heart disease; CVD, cardiovascular disease; DASH, dietary approaches to stop hypertension; DBP, diastolic blood pressure; DPP-4, Dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FFQ, food frequency questionnaire; GLP-1, Glucagon-like peptide-1; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hPDI, healthy plant-based diet index; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; HTN, hypertension; IHD, ischaemic heart disease; LDL-C, low density lipoprotein cholesterol; MD, mean difference; MedDiet, Mediterranean Diet; MetS, metabolic syndrome; MI, myocardial infarction; MUFA, monounsaturated fat; NAFLD, non-alcoholic fatty liver disease; PDI, plant-based diet index; PUFA, polyunsaturated fat; SBP, systolic blood pressure; SFA, saturated fat; SGLT2, Sodium-glucose co-transporter-2; TAG, triacylglycerol; TC, total cholesterol; TFA, trans fatty acid; TSH, thyroid stimulating hormone; TZD, thiazolidinediones; uPDI, unhealthy plant-based diet index; WBC, white blood cells