Nutrition and cardiovascular disease

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Introduction: cardiovascular prevention in the XXI century

Cardiovascular disease (CVD) is the leading component of the non-communicable diseases (NCDs). Atherosclerotic and hypertensive diseases, mainly ischemic heart disease and stroke together with heart failure, whether resulting from ischemic heart disease or other causes, are the major CVD entities and represent the most important threats for population health in the XXI century. Ischemic heart disease and stroke have been projected for the year 2020 to rank first and second in frequency among causes of death, first and third among causes of years of life lost, and first and fourth among causes of disability-adjusted years of life lost (**1**). In summary, cardiovascular disease (CVD) still remains the leading cause of death worldwide and a major cause of disability (**1**). Furthermore, the projections of mortality from CVD for 2030 are somber and cumbersome (**2**).

Therefore, CVD constitutes a global health crisis and has an ubiquitous occurrence (**3**). In addition to the well-known burden of mortality and disability caused by CVD in high-income countries, the important high-level Meeting of the United Nations General Assembly on NCDs held in September 2011 denounced that CVD will exert a devastating impact specifically on the working-age populations (ages 35–64 years) of low- and middle-income countries by the year 2030 (**4**)

In this dramatic context, the available evidence to support that most of the burden of CVD is preventable through diet and lifestyle is huge (**2, 5)**. For no other chronic condition there is such a large body of scientific evidence on the effectiveness of preventive approaches. This body of evidence is mainly based on good-quality prospective observational cohorts and also in a few large randomized trials. Therefore, the prevention of CVD through diet and lifestyle, without any doubt, represents an

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absolute priority for public health. Diet is especially relevant in cardiovascular prevention and, consequently, the assessment of the *diet-heart hypothesis* has been one of the most active research areas in nutritional epidemiology during the last 50 years. (**6, 7**) The identification and targeting of dietary factors with the greatest potential for preventing CVD are of major scientific and public health importance.

Substantial advances in understanding the role of specific nutritional factors as determinants of CVD have accrued during the last 2 decades. The priority of overall food patterns over single foods or individual nutrients, the importance of carbohydrate quality rather than quantity, and the specific roles of each fat subtype, some foods or their combination, sodium intake and total energy balance represent several key findings of interest. In the present chapter we summarize the current understanding of dietary factors as determinants of the occurrence of CVD.

Hard Clinical End-Points

Many studies of nutritional epidemiology conducted to assess the diet-heart hypothesis have used as end-point intermediate biomarkers of cardiovascular risk (reductions in blood pressure, changes in lipids, inflammatory molecules or other biomarkers) as a proxy for the risk of ischemic heart disease or stroke.

This approach could be flawed for several reasons (**8**). In first place, the existence of multiple pathways leading from diet to heart disease speaks against the simplistic approach of giving a high value to changes in any single biomarker. Second, the induction period can be variable for the different pathways in which diverse biomarkers are involved and this fact severely limits the possibility of assessing at any time point any multiple combinations of biomarkers. Third, probably there are other pathways that are still less well known and can account for a substantial proportion of clinical events. Therefore, the most sensible approach to investigate the diet-heart hypothesis is the use of hard clinical events as the end-point. In the present review we will specially highlight the results of studies assessing hard clinical events.

Food Patterns

In nutritional epidemiology, food pattern analysis is a methodological approach which captures different combinations of food intake and better reflects the complexity of the diet and its relationships with disease risk. Food pattern analysis has mostly replaced the traditional single-nutrient analysis in relation to chronic diseases, because that

traditional approach has been challenged by several conceptual and methodological limitations. When an outcome is likely to be caused by a single nutrient, an exclusive focus on that nutrient may be the optimal approach; however, CVD has been associated with many dietary factors and the food pattern approach may be the most useful option because it goes beyond nutrients or foods and examines the effects of the overall diet (**9**). The focus on isolated nutrients or single foods makes it difficult to take into account any interaction between them. Many foods are consumed together and there can be a wide range of potential interactions between different nutrients and foods. Food patterns adequately capture between-food synergies. In this context, for the assessment of the association between dietary factors and CVD, to shift the focus to overall dietary patterns is more useful than the reductionist and overly optimistic approach of attributing all the effect to a single nutrient or food. It is very unlikely that the intake of a single nutrient or food could exert a sufficiently strong effect as to substantially change the incidence rates of CVD. Conversely, the additive effect of small changes in many nutrients is more likely to show an effect.

In summary, the current paradigm in nutritional epidemiology is to use food pattern analysis instead of other classical analytical approaches focused on single nutrients. In addition, dietary patterns overcome problems of confounding by other aspects of the diet.

In the next paragraphs we review the key components of food patterns that have been consistently shown to behave as determinants of CVD risk in high-quality longitudinal observational studies and large clinical trials.

Vegetables and fruits

Food patterns that emphasize the consumption of fruits and vegetables have been associated with substantial improvements in several vascular risk factors, including lipid levels, blood pressure (BP), insulin resistance, inflammatory biomarkers, endothelial function, and weight control (**10-14**). These benefits might be derived from several sources: a) the wide variety of phytochemicals, micronutrients, and fiber present in fruits and vegetables; b) the potentially improved bioavailability of these nutrients in their natural state when fruits and vegetables are consumed as fresh foods instead of cooked; c) the replacement of less healthful foods in the diet by fruit and vegetables. In prospective cohorts, greater fruit and vegetable consumption is associated with lower incidence of coronary heart disease (CHD) and stroke. A meta-analysis conducted by

Dauchet et al. (**15**) found stronger inverse associations with coronary heart disease (CHD) for the consumption of fruit than for vegetable consumption. The meta-analysis by He et al. (**16**) showed an inverse dose–response trend between both fruit and vegetables consumption and the risk of CHD. A narrative review by Ness and Powles (**17**) and two meta-analyses support the inverse association of fruit or vegetable consumption with stroke risk (**18, 19**). The meta-analysis by Dauchet (**18**) showed that stroke risk was reduced by 11% for each additional serving/d of fruit and by a non-significant 3% for each additional serving/d of vegetables. The estimates of relative risk in the meta-analysis by He et al. (**19**) were 0.72 (95 % CI: 0.66, 0.79) for fruit and 0.81 (95 % CI: 0.72, 0.90) for vegetables for the comparison between the highest (>=5 servings/d) and the lowest (<3 servings/d) categories of consumption.
Potential differences in health effects contributed by specific types of fruits, vegetables, or their juices require further investigation.

Dietary fiber and whole grain consumption

A pooled analysis of eleven cohort studies conducted by Pereira et al. (**20**) found that dietary fiber intake was inversely associated with the incidence of CHD events and also with CHD mortality. Each 10-g/d increment of energy-adjusted and measurement error-corrected total dietary fiber was associated with a 14% (RR of 0.86; 95% CI: 0.78-0.96) lower risk of all coronary events and a 27% (RR of 0.73; 95% CI: 0.61-0.87) relative reduction in the risk of coronary death.
Not only the fiber content, but also the degree of cereals processing (i.e. refined versus whole grains) is apparently important regarding their ability to provide an effective prevention against CVD. The American Heart Association (AHA) developed a pragmatic definition of whole grains based on the fiber content of whole wheat, ie, >=1.1 g of naturally occurring dietary fiber per 10 g of carbohydrate in the grain product (eg, bread or cracker) (**21**), but there is no universally accepted definition of whole grains. The term whole-grains usually includes bran, germ, and endosperm from the natural cereal. Whole grain products (eg, whole wheat breads, oats, barley, brown rice, brown pasta) are also known as “lente” carbohydrates because they have a slower (*lentus* in Latin language) gastrointestinal absorption and generally produce slower glycemic and insulinemic responses than highly processed refined grains (**22**). Bran is rich in dietary fiber, B vitamins, minerals, flavonoids, and tocopherols; germ contains numerous fatty acids, antioxidants, and phytochemicals. Endosperm essentially provides

starch (carbohydrate polysaccharides) and storage proteins (**23**). The degree of processing appears to act as an effect modifier of the effects of grain and carbohydrate consumption on the risk of CVD.

In large and well conducted longitudinal epidemiologic studies whole grain consumption has been consistently associated with lower incidence of CHD and possibly stroke. A meta-analysis on whole grains and CVD reported in its pooled estimate a significant 21% lower risk (95% CI: 15%-27%) of CVD events associated with the consumption of 2.5 serving/d vs 0.2 serving/d of whole grains (**24**). The higher dietary fiber in whole grains apparently contributes to these benefits. But also other additional characteristics of whole grains, including slower digestion (lower glycemic responses) and higher content of minerals, phytochemicals, and fatty acids are likely to play a key role in explaining these inverse associations (**25, 26**). Thus, similar to fruits and vegetables, health effects of whole grains may result from the interaction of synergistic effects of multiple elements that are unlikely to be matched by supplemental fiber alone, added bran, or isolated micronutrients. Another explanation of the beneficial effect of whole grains comes from dietary substitution for more highly refined/processed carbohydrates and starches that may themselves induce adverse cardiometabolic effects.

The removal of bran and germ that occurs in the refining process reduces dietary fiber and this implies that important benefits are lost, including potential reductions in blood cholesterol levels and blood pressure (**27, 28**). On the other hand, the refining process increases bioavailability and accelerates the digestion of starch in the remaining endosperm, which increases short-term and rapid glycemic responses (**29**).

Weight losses, improvements in glucose and insulin homeostasis, in endothelial function and in inflammatory biomarkers have been reported in small randomized trials of whole grains (**22, 24, 30**). These physiological benefits are consistent with the observed benefits in large epidemiologic studies using clinical end-points as outcome.

Fish and omega-3 fatty acids

The finding that populations with a high fish consumption such as Alaskan Native Americans, Greenland Eskimos, or Japanese living in fishing villages had low rates of CVD helped to generate the hypothesis that fish consumption may protect against atherosclerosis. Kromhout et al. (**31**) found in the Dutch arm of the Seven Countries

study that men who consumed 30 g/d of fish had 50% lower CHD mortality than those who rarely ate fish.

Subsequently, a wide collection of large cohort studies integrated in several meta-analyses and systematic reviews (**32-42**) have also found moderate inverse relationships between fish consumption and CVD (**43**).

In a recent dose-response meta-analysis including 18 studies, an increment of two servings a week of any fish was associated with a 4% (95% confidence interval 1% to 7%) reduced risk of cerebrovascular disease (**32**).

A previous review by He et al. (**40**) reported a 7% lower risk of CHD mortality for each 20 g/day increase in fish intake.

Also Randomized Clinical Trials (RCTs) (mostly conducted in secondary prevention) have assessed the effect of fish consumption or fish oil supplementation on CVD outcomes (mainly reinfarctions). The pioneering Diet and Reinfarction Trial (DART) (**44**) demonstrated that participants who increased their fish consumption to twice a week had a significant 29% reduction in total mortality after two years. The GISSI-Prevenzione trial (**45**) found that daily supplementation with n-3 fatty acids led to a 10% to 15% reduction in the main endpoints (death, nonfatal MI, and stroke). The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS) (**46**) found that supplementation with eicosapentaenoic acid (EPA) (1800 mg/d) significantly reduced coronary events among patients receiving low-dose statin therapy after 4.6 years of follow-up. Fish and fish oil are among only a handful of dietary factors for which both long-term observational studies and RCTs of CVD outcomes have been successfully conducted.

The available evidence tend to suggest that greater cardiovascular benefits can be obtained with fish consumption and omega-3 fatty acids in secondary prevention than in primary prevention and in populations consuming low amounts of omega-3 fatty acids at baseline than among those with a higher baseline consumption of fish or omega-3 fatty acids (**35**). Fish and other seafood are good sources of long-chain omega-3 polyunsaturated fatty acids (PUFAs), which include docosahexaenoic acid (DHA) and EPA which are only synthesized from their plant derived precursor, alfa-linolenic acid, in low amounts (<5%) in humans. Average EPA plus DHA contents of different seafood species vary by >10-fold. Fatty (oily) fish such as salmon, sardines, trout, white tuna, anchovies, and herring have the highest concentrations (**43**).

Small randomized trials have found that long chain omega-3 fatty acids reduced triglyceride levels (**47**), systolic and diastolic BP (**48**), and resting heart rate (**49**). RCT and observational studies also suggest that these oils may also improve endothelial function, reduce inflammation, normalize heart rate variability, improve myocardial relaxation and efficiency, and, at high doses, limit platelet aggregation (**50**). These findings for physiological benefits are in agreement with the inverse association between fish consumption and the incidence of CHD and ischemic stroke, and especially risk of cardiac death.

However, some large trials using supplements of omega-3 fatty acids instead of the consumption of whole fish have found no effect on stroke (**32**).

Therefore, it is possible that the potential benefit of fish consumption on CVD could be attributed not simply to long chain omega 3 fatty acids but also to a wider array of nutrients (and their interactions) that are abundant in fish. For example, fish are also rich in vitamins D and in multiple B vitamins, which have been inversely associated with the risk of CVD. Also essential amino acids and trace elements present in fish (e.g., arginine, calcium, magnesium, potassium, iodine and selenium) may contribute to explain their reported favorable vascular effects. Another important issue to explain the cardiovascular protection by fish against CVD is that fish usually tend to replace in meals red or processed meats which are less healthy foods.

Probably the benefits of eating fish can be superior to those provided by fish oil supplements, although definitive evidence on this comparison is not yet available.

Potential adverse cardiovascular effects of methylmercury found in a few fish species are limited and conflicting; if present, the available evidence suggests that cardiovascular benefits of fish consumption are not counterbalanced for this potential adverse effect (**51, 52**).

Nuts, legumes and soy

Nuts are a good source of unsaturated fatty acids, fiber, minerals (potassium, calcium and magnesium), vitamins (folate and tocopherols) and other bioactive compounds, such as phytosterols and polyphenols (**53, 54**). In large prospective cohort studies, the consumption of tree nuts has been reported to be associated with lower CHD incidence (**55, 56**). Overall, cardiovascular benefits of modest nut consumption (>= 2 servings/wk versus never or almost never consumption) are supported by both effects on risk factors

in short-term trials and by the magnitude and consistency of reduced CVD risk observed in prospective cohort studies.

An important recent pooled analysis of primary data from 25 nut consumption trials including in total 583 participants, showed impressive benefits of nut consumption on blood lipids, with reductions in total blood cholesterol concentrations of 10.9 mg/dL (5.1% change) and in low-density lipoprotein cholesterol concentration (LDL-C) of 10.2 mg/dL (7.4% change). Reductions in triglyceride levels by 20.6 mg/dL (10.2%) were obtained only in subjects with blood triglyceride levels of at least 150 mg/dL but not in those with lower levels (**57**).

Beyond these short term trials and beyond observational studies, the large PREDIMED primary prevention randomized trial with 7,447 participants reported a 30% relative reduction in major cardiovascular events (stroke, myocardial infarction or cardiovascular death) versus a control diet after a 4.8-year intervention with Mediterranean diet supplemented with mixed nuts (mainly walnuts, but also almonds and hazel nuts) totaling a consumption of 30 g/d of mixed nuts. This finding, consistent with previous observational studies and small randomized trials on intermediate outcomes, provides a first line evidence to support the benefits of mixed nuts in cardiovascular prevention (**58**).

Epidemiological evidence for cardiovascular benefits from legumes (eg, peas, beans, lentils, and chickpeas) is weaker than for nuts, although they may also provide beneficial effects taking into account the overall package of micronutrients, phytochemicals and fiber provided by them. In a meta-analysis of RCTs, consumption of soy-containing foods showed an apparent beneficial effect lowering diastolic and systolic blood pressure even though the effects did not achieve statistical significance. Isolated soy protein or isoflavones (phytoestrogens) seem to have smaller effects, producing only modest reductions in LDL cholesterol and diastolic blood pressure (**59, 60**). More investigation of the effects of legumes on cardiovascular disease with well-conducted prospective cohorts and RCTs is required.

Dairy products

Dairy products are a good source of potentially beneficial nutrients, such as magnesium, potassium, calcium, and bioactive peptides. On the other hand, the main type of fat in dairy products is saturated fat, specifically palmitic acid with adverse effects on blood lipids. Based on the lower content of calories, SFA, and cholesterol of low-fat or non-fat

dairy products, together with the scarce nutritional advantage of whole-fat dairy, the majority of dietary guidelines and scientific organizations recommend low-fat or non-fat dairy consumption (**51**).

Furthermore, different studies have suggested that dairy products might be associated with lower blood pressure and reduced risk of hypertension. The consumption of low–fat dairy (but not of whole-fat diary) has been inversely associated with blood pressure and with the risk of hypertension (**61-63**). Potentially varying health effects of specific dairy foods (eg, milk, yogurt, cheese, and butter) require further study.

Meats and processed meats

Food patterns associated with lower CVD risk such as the Mediterranean diet (**58, 64, 65**), the Prudent Dietary pattern (**66**), the DASH diet (**67**), or the vegetarian diets (**68**) have a common denominator: they include a lower consumption of overall meats and specially of red and processed meats because diverse components of meats, such as SFA, cholesterol, heme iron and others could increase cardiometabolic risk. In addition, in processed meats high levels of salt and other preservatives might be detrimental for cardiovascular health. Available meta-analyses of prospective cohort studies evaluating the role of meat consumption on the risk of CHD, have found that total red meat consumption was associated with overall higher risk of CHD, although the association was not statistically significant (**55, 69**). Consumption of processed meats but not unprocessed red meats was associated with higher incidence of CHD (**69**). The adverse effects of preservatives (eg, sodium, phosphates, and nitrites) specially present in processed meats and/or their methods of cooking preparation (eg, high temperature commercial cooking/frying) could influence their health effects (**69**).

Sugar-sweetened beverages

Evidence from RCT, prospective cohorts, and ecological comparisons support positive associations between sugar-sweetened beverage (SSB) consumption and adiposity in children and adults (**70**). This direct association between SSB and obesity or weight gain is most consistent among large prospective cohort studies with long follow-up and without undue adjustment for total energy intake, because total energy intake is an intermediate link between exposure and outcome, and therefore, it should not be treated as a confounder. The detrimental effect of SSB on adiposity is nowadays considered a resolved issue (**71**).

In USA, the proportion of total dietary calories from sugar-sweetened beverages has increased to 222 calories/day per person in the period from 1965 to 2002. The same period that overweight/obesity was increasing rapidly (**72**). On average, an American teenage boy drinks approximately 300 Kcal/day of SSB and a teenage girl approximately 200 kcal (73). Most SSB intake by children occurs at home, not at school (**74**).

Results from limited short-term trials suggested that calories in liquid form may be less satiating and thereby increase the total amount of daily calories consumed (**75, 76**). SSB intake can also displace more healthful beverages, such as milk (**77**).

Reduced SSB consumption improved weight loss or reduced weight gain in both children and adults (**78**). In one multicomponent lifestyle intervention, the reduction of each 1-serving/d of SSB was associated with 0.65-kg greater weight loss (**79**).

A meta-analysis by Mattes et al. (**80**) including six RCTs reported that adding SSBs to the diets of participants significantly increased body weight in a dose-dependent manner. This finding have been confirmed by the most recent meta-analysis on this issue conducted by Malik et al (**70**).

In another meta-analysis of prospective cohorts, higher SSB intake was associated with higher incidence of diabetes mellitus (DM) and metabolic syndrome (**81**).

A direct positive association between SSB intake and the incidence of CHD was observed in the Nurses' Health Study (including 88 520 women observed for up to 24 years). This reported detrimental association persisted even after accounting for potential confounding factors. Among women who consumed two or more servings of SSBs per day a 35% higher risk of developing CHD was found in comparison with those who consumed less than 1 serving per month (relative risk = 1.35; 95% CI, 1.07 to 1.69; P for trend<0.001) (**82**). The combination of highly refined carbohydrate calories, a liquid form that may minimize satiety, absence of other beneficial nutrients/constituents, displacement of more healthful beverages, and very high intake in many population subgroups renders reduction in SSB a key dietary target for improving individual and population cardiometabolic health (**83**).

Alcoholic beverages

Light to moderate alcohol consumption (1 drink or less daily for women and 2 drinks or less daily for men) is associated with a reduced risk of CVD, whereas increasingly

excessive consumption results in a detrimental effect. This is a very consistent finding of many observational epidemiologic studies. However, there are no trials and therefore there is no experimental evidence on alcohol consumption and hard cardiovascular end-points. Alcohol consumption confers cardiovascular protection predominately through improvements in insulin sensitivity, reduced coagulation factors and, especially increased high-density lipoprotein cholesterol (**84**). On the other hand, habitual heavy alcohol intake is cardiotoxic, causing a large proportion of dilated cardiomyopathies of non-ischemic causes worldwide (**85**). The ensuing ventricular dysfunction is often irreversible, even when alcohol consumption is stopped; continued drinking in such patients is associated with increased mortality. Both acute binges and higher habitual intake of alcohol have also been associated with higher risk of atrial fibrillation (**86**). Conversely, in randomized trials and in the absence of weight gain, modest alcohol use reduces systemic inflammation, improves high-density lipoprotein cholesterol leves and insulin resistance (**87-89**). Consistent with these effects, individuals who drink alcohol moderately (up to 2 drinks/d for men and 1 drink/d for women) experience a lower incidence of CHD and DM compared with nondrinkers (**55, 90**).

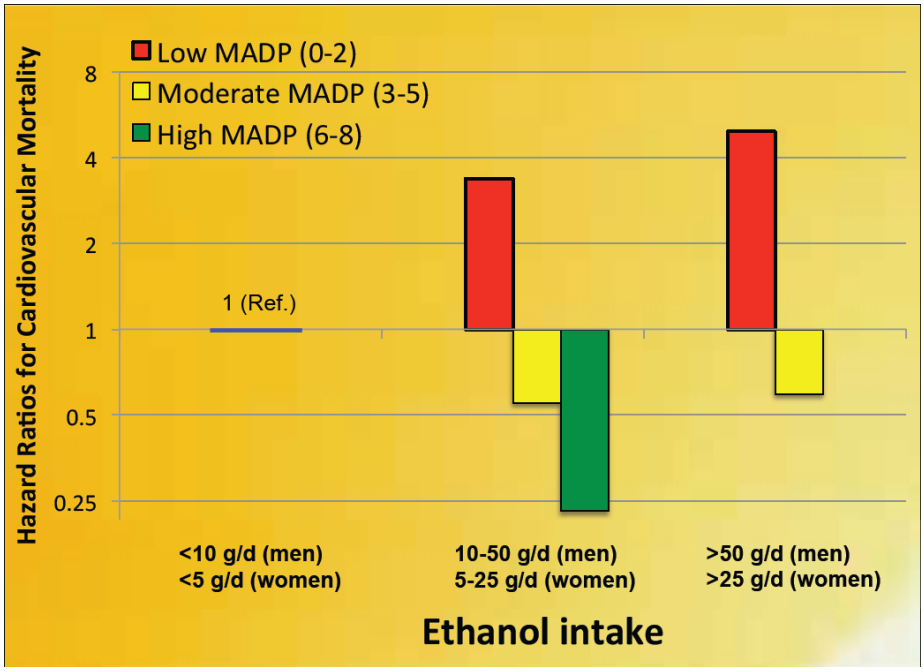
In these observational studies, benefits of moderate alcohol intake could be overestimated, because the non-exposed group (nondrinkers) frequently includes former drinkers, those who have received a medical advice to quit drinking because of some chronic disease and other individuals who avoid alcohol because of poor health (**91**), and because heavy alcohol consumers are generally underrepresented in large longitudinal epidemiologic studies. Some non-alcohol components, including resveratrol and other polyphenols present in wine, more than in beer, and in beer more than in liquors, could have potential benefits. In this line of thought it can be expected to find greater benefits from moderate consumption of wine than from beer consumption and greater benefits from beer that from liquors. However, most available evidence supports the direct effects of alcohol itself irrespective of the type of beverage (**87-89, 92**) because moderate intake of alcohol regardless whether it comes from wine, beer or liquors has been found to be associated with reduced rates of CHD in different populations (**93**). Further research on this issue is needed.

A growing interest in the drinking pattern has received confirmation by epidemiological findings, because a lowest cardiovascular risk has been observed among individuals who drink moderately on several days of the week, rather than among those who

concentrate the same amount of alcohol in 1 or 2 drinking occasions during the week (i.e. binge drinkers) (**94**).

Other different adverse effects of alcohol, even in moderate doses, also need to be taken into account. Interestingly, increased alcohol intake leads to higher weight gain because an average serving of alcohol contributes aprox. 120 to 200 kcal that, as discussed previously, may be less satiating than calories from solid foods (**95**). Alcohol-related accidents, homicides, suicides, and social problems explain why alcohol use has an overall net adverse effect on population mortality (**96**). Thus, alcohol use, especially among younger adults, is not advisable at all as a population-based strategy to reduce CVD risk. For adults who already drink alcohol, no more than moderate use can be encouraged.

An alcohol drinking pattern that is likely to be especially healthy can be denominated the "Mediterranean Alcohol Drinking Pattern Score" (MADP). This pattern reflects the traditional way of consuming alcohol in Mediterranean countries and it is based on the idea of including in the pattern several dimensions of the drinking habits, in an analogy to the food pattern approach that is currently accepted as the most sensible method in nutritional epidemiology. Beyond the total amount of alcohol consumed, it seems interesting to capture other aspects of the conformity to a traditional MADP. We used data from the prospective cohort study of the SUN Project (**97**) to define a MADP which positively scored moderate alcohol intake, alcohol intake spread out over the week, low spirits consumption, wine preference, wine consumed during meals and avoidance of binge-drinking. Each 2-point increment in the MADP was associated with lower risk of cardiovascular mortality [HR (95%CI): 0.49 (0.31-0.79)]. Better adherence to the MADP was associated with reduced cardiovascular mortality as compared with abstention or departure from this pattern, throughout categories of ethanol intake. This reduction goes beyond the inverse association usually observed for moderate alcohol drinking (Figure 1).



Phytochemicals

The beneficial effects of the incredibly rich combination of natural phytochemicals present in fruit and vegetables are probably superior to those of every thinkable polypill containing any mixture of artificial elements. There are more than 8000 phytochemicals present in whole foods. These compounds differ in solubility, molecular size and polarity, characteristics that may affect their bioavailability and their biological properties in cells, organs and tissues. A supplement given as a pill simply cannot mimic this balanced natural combination of bioactive compounds present in fruit, vegetables, extra-virgin olive oil or red wine. Phytochemicals are naturally occurring compounds in plant foods. They include plant sterols, flavonoids, and sulfur-containing compounds (**98**). For example, over 4000 different classes of flavonoids have been described. Their major dietary sources are tea, broccoli, kale, celery, onions, garlic, apples, and red wine.

A meta-analysis of seven cohort studies found that participants in the highest tertile of flavonol intake had a 20% (95% CI: 7%-31%) lower risk of fatal CHD than those in the lowest tertile (**99**). In a meta-analysis of RCTs, flavonoids-rich foods such as cocoa and soy, decreased cardiovascular risk factors (**59**). In particular, dark chocolate reduced systolic and diastolic blood pressure.

Plant sterols occur naturally in fruits, vegetables, vegetables oils, nuts, and grains. Over 40 plant sterols (phytoesterols) have been identified. Except for the methyl groups in the

side chain sterols are structurally similar to dietary cholesterol. They inhibit cholesterol absorption in human intestines. Plant sterols lower blood cholesterol (**100**). One major concern is that plant sterols modestly lower blood concentrations of carotenoids and some fat-soluble vitamins. Therefore, the long-term effects of food enriched with these phytochemicals need to be assessed.

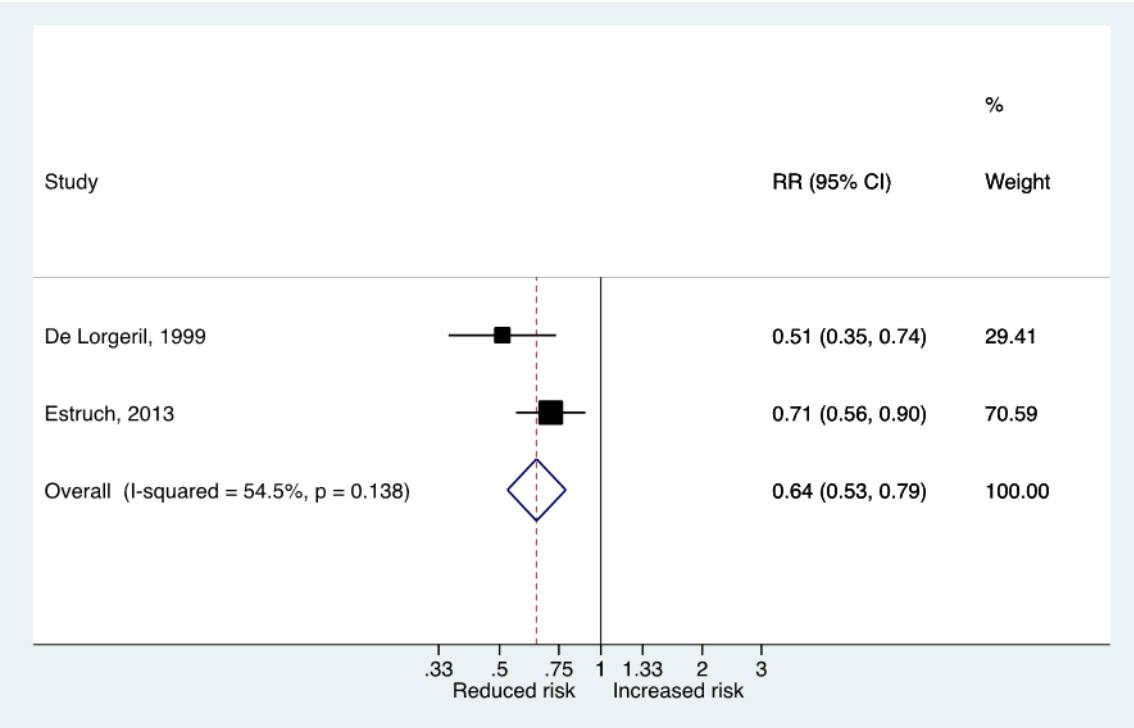
The Mediterranean diet

The available scientific evidence demonstrates that overall dietary patterns can improve health and prevent CVD in a greater extent than isolated food or nutrients (**58**, **101**). Using different research approaches several healthful dietary patterns have been identified. They share several key common characteristics, including an emphasis on fruits, vegetables, other plant foods such as legumes and nuts, and (in many patterns) whole grains and fish; with limited or occasional dairy products (mainly low-fat dairy); and often with very limited amounts of red meats or processed meats and fewer sugared beverages, refined carbohydrates and other processed foods. These dietary patterns are each generally consistent with food-based priorities for CVD health ideal metrics.

In this context, the Mediterranean Diet (MeDiet) is defined as the traditional dietary pattern found in Greece, Southern Italy, Spain and other olive-growing countries of the Mediterranean basin in the early 1960s (**102**). It consists in an abundant use of olive oil as the major culinary fat, a high consumption of plant-based foods (fruits, vegetables, legumes, nuts and seeds, and whole grain cereals), frequent but moderate intake of wine (especially red wine), usually with meals, consumption of fresh fish and seafood, moderate consumption of dairy products (especially yogurt and cheese), poultry and eggs, and low consumption of sweet desserts, red and processed meat. Randomized trials of dietary intervention constitute hallmarks in the acquisition of knowledge in this field. The availability of a randomized trial (the Lyon Diet Heart Study) showing a protective effect on CVD hard clinical end-points was a strong point to support the causal effect of the MeDiet (**55, 103**). The Lyon trial was a secondary prevention trial because it only included survivors of a previous myocardial infarction and the number of observed events was modest. Surprisingly, the Lyon trial gave no special consideration to olive oil, which is traditionally accepted as the hallmark of the Mediterranean diet and the major source of fat in Mediterranean countries. However, results of the Lyon trial were subsequently confirmed also for primary prevention by the recent *PREvención con DIeta MEDiterránea* (PREDIMED) trial conducted in 7,447

initially healthy participants, without any previous history of CVD (**58, 104**). Participants in the PREDIMED trial were men and women from 55 to 80 years at high cardiovascular risk because they were diabetics or had at least 3 major vascular risk factors. They were randomly allocated to one of three diets: a MeDiet rich in nuts, a MeDiet rich in extra-virgin olive oil, and a control group receiving advice to reduce the intake of fat. A significant reduction in the risk of a combined cardiovascular end-point (myocardial infarction, stroke or cardiovascular death) was observed for both groups allocated to MeDiet. The trial was stopped after a median follow-up of 4.8 years because early evidence of benefit. The hazard ratio for a combined end-point of myocardial infarction, stroke or cardiovascular death was 0.70 (95% confidence interval (CI): 0.54-0.92) for the MeDiet with extra-virgin olive oil and 0.72 (95% CI: 0.54-0.96) for the MeDiet with nuts.

We conducted a random effect meta-analysis to combine these two trials and found a relative 38% reduction in the risk of CVD after intervention with a MeDiet with pooled risk ratio of 0.62 (95% CI: 0.45-0.85) (**105**). There was no evidence of heterogeneity and we repeated the meta-analysis also using a fixed-effects model (Figure 1). We did not include another published trial (the Indo-Mediterranean Diet Heart Study) because its validity has been seriously questioned (**106**).



(From reference 104)

Together with the evidence from randomized trials, examining the evidence from observational studies is also important given that even randomized clinical trials are not completely free of limitations (i.e subject compliance, disease latency, duration of exposure, or lifestyle changes) (**55**).

A meta-analysis published by Sofi in 2010 (**107**), found a growing accrual of evidence supporting a substantial beneficial effect of the MeDiet on CVD clinical end-points. After that meta-analysis other 7 new prospective observational studies were published (**108-114**), up to August 2013. Two of these studies (**108, 109**) provided separated estimates for men and women. We repeated the meta-analysis adding these 9 new estimates to those already included in the meta-analysis by Sofi.

The Northern Manhattan Study (n: 2568) (**110**) reported that a dietary pattern resembling the MeDiet was inversely associated with a composite outcome of CVD (ischemic stroke, myocardial infarction, or vascular death). Nevertheless the estimate for 1-point increase was not statistically significant. The Greek European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, which had previously assessed only fatal coronary events (**64**), reported now the results for 636 cases of coronary heart disease (CHD) including both fatal and non-fatal cases (**108**). Better adherence to the MeDiet was associated with a non-significant lower CHD incidence, and a statistically significant reduction in mortality from CHD. Other results from this same cohort reported a significant inverse association with cerebrovascular disease (**111**). The Dutch cohort of the EPIC study also found that higher adherence to a MeDiet was associated with lower risk of a combined CVD end-point (fatal CVD, nonfatal myocardial infarction and nonfatal stroke) (**112**). Among more than 77,000 adults living in the Subartic region (North Sweden), the Västerboten Intervention Program (**109**) showed that higher adherence to a MeDiet was associated with a significant reduction in cardiovascular mortality among women, but not among men. The authors concluded that the benefits of the MeDiet go beyond the Mediterranean geographical area and can be borrowed by other populations.

Two Italian rural male cohorts of the Seven Countries Study (n: 1139) (**113**) estimated a significant 26% relative reduction in CHD mortality for each 2.7-point increment in the Mediterranean Adequacy Index (MAI) (HR: 0.74; 95% CI: 0.55-0.99) after 20 years of follow-up. Since the authors used an index that ranges from 0 to over 100, when we converted the estimates to a 2-point increment within a 0 to 9 scale, the magnitude of the association was unusually strong.

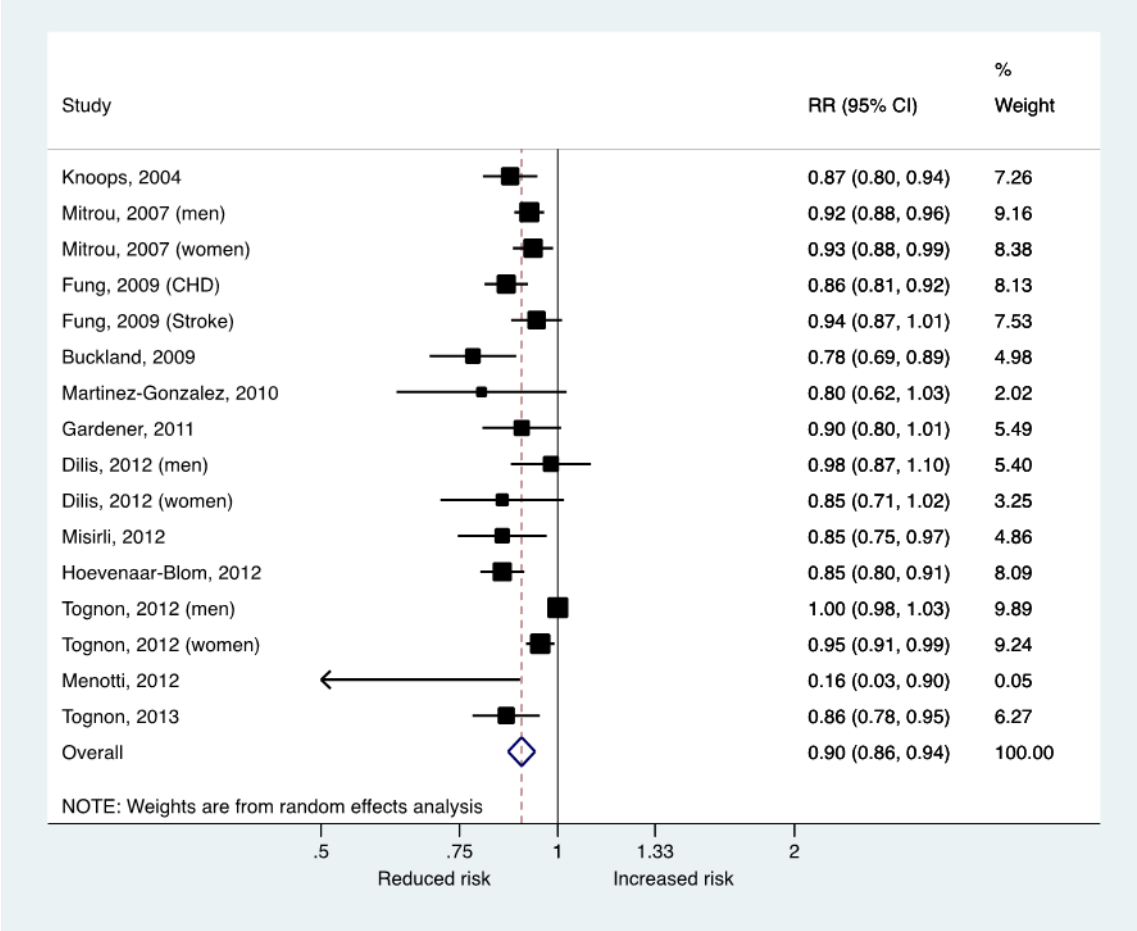
The Danish MONICA cohort (**114**) assessed 1,849 men and women and found a significant 8% relative reduction in the risk of CVD for each 1-unit increase in adherence to an 8-point scale.

The MORGEN study conducted in the Netherlands (**115**) included 8,128 men and 9,759 women aged 20-65 years and assessed a MeDiet operationalized according to 8 of the 9 items of the MDS proposed by Trichopoulou (**64**) (moderate alcohol consumption was excluded). They found a non-significant inverse association with a combined CVD end-point (fatal CVD, nonfatal myocardial infarction and stroke). We did not include these results in our meta-analysis because they were partly included in the EPIC-NL study (**112**).

Two cohort studies conducted in Spain (**116, 117**) consistently showed a very similar inverse association, though the EPIC-Spain cohort (**116**) had narrower confidence intervals. They were published ahead of print almost simultaneously and shortly before the meta-analysis by Sofi (**107**). They were already included in that previous meta-analysis.

We included 9 estimates from 7 new prospective cohort studies in our meta-analysis together with 7 of the 8 previous estimates included in the meta-analysis by Sofi (**107**). The initial report from the Greek EPIC cohort on CHD mortality (**64**) was excluded because it was subsequently updated (**108**). Our new random-effect meta-analysis with 16 estimates showed that each two-point increment in a 0 to 9 MDS was associated with a 10% relative reduction in the risk of CVD (risk ratio: 0.90; 95% CI: 0.86-0.94) (Figure 2). These results were highly consistent with the previous pooled estimate reported by Sofi (**107**). Therefore, our updated meta-analysis supported an inverse linear association between MeDiet and CVD. However, there was evidence of statistical heterogeneity (I^2=77.5%; p<0.001). After removing from the meta-analysis those studies with end-points that only included fatal CVD (**109, 103, 118**), we observed not only a slightly stronger inverse association (risk ratio: 0.87; 95% CI: 0.85-0.90) but also that evidence of heterogeneity was not present any more (I^2=19.8%, p=0.26). A possible explanation for the heterogeneity due to studies which only included fatal CVD cases as outcome might be explained by the fact that mortality from CVD is not only related to incidence but also to the quality and timeliness of medical care. Another potential explanation may be related to differences in the methods used for case ascertainment. Visual inspection of the funnel plots and the Egger's test (p=0.001) suggested a potential possibility of publication bias. However, when we excluded the 3 studies

based only on CVD fatal cases, the potential for publication bias disappeared (p=0.69 in the Egger's test).



(From Reference 104)

The disappointing results of low-fat diets

The Mediterranean diet is relatively high in total fat. But as reviewed above, a wide body of consistent evidence supports the benefits of the Mediterranean diet in cardiovascular prevention. In contrast, it is important to highlight the disappointing results found after using low-fat diets as a paradigm of a healthy diet to prevent CVD (**119-121**). In sharp contrast with the MeDiet, the long-term compliance and sustainability of low-fat diets seem suboptimal. In any case, nutritional quality should be a higher priority than reducing fat intake (**121**). In addition to have a higher potential for long-term adherence than low-fat diets, the MeDiet has passed the tests of long-term sustainability, effectiveness, and nutritional quality (**122, 123**). The MeDiet represents a considerably more palatable alternative than the usual low-fat approaches for promoting

healthy eating. Also, it has a strong background of a millenary tradition without any evidence of harm. A traditional MeDiet is a relatively low-cost non-pharmaceutical means of preventing CVD. It can be easily adopted by large sectors of the population. The promotion of this dietary pattern seems a feasible tool for the prevention of CVD in Public Health Nutrition.

The Dietary Approaches to Stop Hypertension (DASH) diet.

The food pattern known as DASH (Dietary Approaches to Stop Hypertension) emphasizes the consumption of fruits, vegetables, and low-fat dairy products; include whole grains, poultry, fish, and nuts; and it is low in red meat, saturated fat, sweets, and sugar-sweetened beverages (**13, 124**). The original DASH diet was low in total fat (27% energy) and higher (55% energy) in carbohydrates; additional modifications to build new DASH-type dietary patterns have been evaluated with an exchange of approximately 10% energy of carbohydrate for vegetable sources of monounsaturated fat or protein (**124**). In controlled feeding trials, each of these DASH diets significantly lowered BP and improved blood lipids in comparison with usual Western diets (**13, 125**). This finding highlights the greater importance of specific food choices rather than macronutrient composition for maximization of CVD benefits. BP reduction was greatest when DASH diets were combined with reduced sodium intake (**13**). In several observational studies, a better adherence to a DASH-type dietary pattern was associated with lower risk of CVD (**51**). Currently very few US adults, even those with elevated BP, follow a DASH dietary pattern (**126**).

Vegetarian diets

A vegetarian dietary pattern includes several types of vegetarian diets: pesco-vegetarians (who consume fish); lacto-ovo-vegetarians (who consume milk and eggs); and strict vegans (who consume no animal products). Potentially different cardiometabolic effects of these different vegetarian diets are not established. Few RCTs of vegetarian diets have been conducted. Two small trials demonstrated that vegetarian diets versus typical Western diets reduced blood pressure (**127, 128**). However, three other trials found no differences between lacto vegetarian or vegan dietary pattern and conventional dietary recommendations for improving weight loss, BP, blood lipids, or insulin resistance (**129-134**). In several observational studies, vegetarians versus non-vegetarians improved health outcomes (**51, 135-140**). Several

characteristics of vegetarian diets could explain these relationships, including high consumption of plant-based foods and low consumption of meats, processed meats, and other processed and fast foods (**137**).

Because vegetarians are often generally more health conscious, other lifestyle characteristics, in addition to diet, may play a role as potential confounders on the observed lower rates of CVD. Overall, vegetarian diets have been studied less extensively than Mediterranean or DASH patterns, and although the foods that are not consumed (animal products) are their strictly defining feature, the more salient features for CVD benefits may be the foods that are typically consumed, in particular more fruits, vegetables, legumes, nuts, and vegetable oil (**83**).

In a collaborative reanalysis of 5 prospective studies mortality from CHD was reported to be significantly lower by 24% among vegetarians compared to nonvegetarians (**135**). Subsequently, a meta-analysis of 7 cohort studies confirmed a lower cardiovascular mortality in vegetarians, but inconsistent results for the association between vegetarian diets and death from any cause were found (**140**). More recently, a 5-year follow-up of the Adventist Health Study-2 cohort showed an overall association of vegetarian dietary patterns with lower mortality **(139)**. Most available comparisons between vegetarians and non-vegetarians relied on a single measurement of diet at baseline, but dietary patterns may change over time and the length of exposure to vegetarianism may account for heterogeneity in results from different cohorts. When vegetarians were separated according to the length of their exposure to vegetarianism, the cardiovascular benefit was present only among those who have been vegetarian for at least 5 years **(135)**.

The team of the PREDIMED trial evaluated a moderate pro-vegetarian diet. Since a pure vegetarian diet might not easily be embraced by many individuals, consuming preferentially plant-derived foods instead of animal-derived foods (i.e., a pro-vegetarian food pattern) would be a more easily understood message for health promotion. A pro-vegetarian food pattern was found to be related with a reduction in mortality from any cause, and especially in cardiovascular mortality (**138**).

Okinawa diet

One of the regions with lowest rates of CHD in the world is the Japanese region Okinawa. Therefore, Japanese diets have been proposed as another healthful dietary pattern (**141**). This traditional dietary pattern is characterized by soybean products, fish, seaweeds, fruits, vegetables, and green tea and low meat consumption (**142**). However, Japanese diets often contain high sodium because of soy sauce and added salt at home, likely contributing to the relatively high incidence of stroke and some cancers. Very low-fat Japanese diets have also been associated with higher stroke risk, specially hemorrhagic stroke (**143**). Food staples of traditional Okinawan diets are rich in antioxidant and relative low in calories. They include orange-yellow root vegetables and green leafy vegetables; wide varieties of seaweeds; tofu; and herbaceous plants (**144**). Due to the appropriate energy balance age-related weight gain is avoid. This is also an important advantage of the Okinawan food pattern (**141**). Japanese dietary patterns seem another good option for CHD prevention, although the reason for relatively high rates of some cancer and stroke requires further investigation. Scientific evidence for benefits of these dietary patterns remains more limited than evidence supporting the Mediterranean diet or the DASH diet.

Quality of carbohydrates:

The importance of carbohydrate quality, rather than quantity, has been one of the most important new insights related to diet and cardiometabolic health. Although carbohydrates have traditionally been classified as simple (eg, monosaccharides and disaccharides) versus complex (eg, starch and glycogen), several additional characteristics are relevant in determining cardiometabolic effects (**83**). These include dietary fiber content; bran and germ content; food structure (eg, intact, minimally processed, refined, or liquid); and potentially glycemic responses or induction of hepatic de novo lipogenesis following ingestion. The concept of the glycemic index (GI) defines the different glycemic responses to various carbohydrate-containing foods. The GI is measured as the 2-hour area under the curve for blood glucose levels after ingesting a test food compared with a standard weight (50g) of reference carbohydrate (glucose or white bread). In order to take into account the quantity of carbohydrates consumed for each food was developed the glycemic load (GL) derived from the product of the GI value of a food and its carbohydrate content. In the Nurses' Health Study, a higher dietary GL was associated with higher risk of CHD (**145**).

Our group of research has developed a score called Carbohydrate Quality Index (CQI) to evaluate the quality of carbohydrates. The criteria for a maximum CQI were: higher dietary fiber, higher ratio whole grains/total grains, higher ratio solid carbohydrates/total carbohydrates, and lower glycemic index. Based on the position of each subject according to the quintiles of each criterion, the score ranges from 4 points (lowest quality) to 20 points (highest quality). We observed that those subjects with the highest score (in the fifth quintile) exhibited a very low prevalence of inadequate nutrient intake (adjusted Odds Ratio: 0.03; 95% CI: 0.01-0.08 vs the first quintile) in the elderly subjects at high CVD risk of the PREDIMED trial. Similar results were observed in the young Mediterranean cohort of the SUN Project (**146**).

Quality of fats

Earlier results from epidemiologic studies on the "diet-heart" hypothesis were based on ecological data relating dietary intake of saturated fat and cholesterol to rates of coronary heart disease (CHD) in different countries. In the pioneering Seven Coutries Study conducted by Keys (**147**), there was a strong correlation between intake of saturated fat as a percentage of calories and coronary death rates across 16 defined populations in 7 countries (r=0.84). Noteworthy, the correlation between energy from total fat and CHD incidence was modest (r=0.39). Interestingly, the regions with the lowest (Crete) and the highest (Finland) CHD rates in the Seven Countries study had the same amount of total fat intake (approx.. 40% of energy) which was the highest fat intake among the 16 populations of this pioneering ecological study.

Results from migration studies also suggested that changes in diet (especially increased saturated fat intake) and lifestyle rather than genetic factors were responsible for the differences in CHD rates among three Japanese populations living in Japan, Hawaii, and San Francisco (**148**). However, concurrent changes in multiple aspects make it difficult to identify specific causal factors.

Beyond international comparisons or migration studies, several prospective cohort studies have directly addressed the specific associations between subtypes of dietary fat and the risk of CHD. Hu et al. (**149**) conducted a detailed prospective analysis among 80,082 women aged 34 to 59 years in the Nurses' Health Study. This large cohort study, with good control of confounding showed that the type of fat was more important than the quantity of fat. Higher intake of saturated and trans fatty acids was associated with

higher CHD risks, whereas greater intake of polyunsaturated and monounsaturated fats was associated with lower risk.

In a meta-analysis of four prospective cohort studies involving nearly 140,000 individuals, Mozaffarian et al. (**150**) estimated that each 2% increase in energy intake from trans fatty acids was associated with a 23% increase risk for CHD (pooled relative risk of 1.23; 95% CI: 1.11-1.37; $p<0.001$). Trans fatty acids raise low-density lipoprotein (LDL) cholesterol and lower high-density lipoprotein (HdL) cholesterol in comparison to natural cis-unsaturated fatty acids (**151**).

Two traditional trials conducted with the objective of replacing saturated by polyunsaturated fat, one conducted among institutionalized patients in a Los Angeles Veterans hospital (**152**) and another in a Finnish mental hospital (**153**), found statistically significant reductions in serum cholesterol and in nonfatal myocardial infarction (MI) and coronary deaths associated with this change in fat subtypes. Total fat intake was not reduced. By contrast, prevention trials that lowered total fat did not find any significant reduction in serum cholesterol or in the rate of CHD events. In the Medical Research Council low-fat trial (**154**) there was no effect on the rate of reinfarction. Similarly, in the Women's Health Initiative Randomized Controlled Dietary Modification Trial previously cited (**119**); reduction in total fat intake did not significantly reduce the risk of CHD, stroke, or total CVD in postmenopausal women.

Recently, a controversy has emerged supporting that saturated fat intake is not the major risk factor for CVD (**155**). Indeed, the results of a meta-analysis which included several prospective cohort studies did not support any significant association between saturated fat intake and CVD risk (**156**). The key issue here might be the substitution. It saturated fat is substituted for refined carbohydrates the effect will be essentially null because both are very likely associated with moderate adverse effects.

In any case, all these results suggest that overall dietary patterns play a more important role than total amount of macronutrients as nutritional determinants of CHD.

Salt intake

There is compelling evidence that higher intake of sodium chloride (salt) is associated with elevated levels of BP (**157**). Through its effects on BP, a reduction in salt intake will reduce stroke and CHD, as a meta-analysis of prospective observational studies has supported (**158-161**). Long-term follow-up of salt-reduction trials is also consistent with lower CVD event rates after salt reduction (**162, 163**).

Foods consumed in restaurants, pre-prepared, or packaged foods account for more than 50% of sodium intake in Western countries. The rest is derived from naturally occurring sources or added at home (**162**). In Asian countries, most sodium is from soy sauce or is added at home (**162**). Structural or policy-level approaches are very well suited for reducing population average levels of salt intake. Projected benefits are enormous. A national effort that reduced US salt intake by 3 g/d (<1.2 g/d less sodium) could annually prevent between 60 000 and 120 000 CHD events and 32 000 to 66 000strokes, saving 194 000 to 392 000 quality-adjusted life-years and $10 to $24 billion in healthcare costs (**164, 165**). The best approach to reduce BP is that of using sodium reduction in combination with the DASH diet.

Nutritional interventions

Targeted goals to the individuals are more effective than any generic advice (**166, 167)**. Clinical providers can help patients to accomplish targeted changes in the healthful dietary patterns and implement simple office-based assessments to inquire about and help them to set dietary goals. Clinic-based strategies are facilitated by health care systems changes, including scheduled visits for individual/group education; sustained in-person, telephone, or electronic feedback.

In the context of a Mediterranean dietary pattern, in order to have a feasible, reliable and fast tool to evaluate adherence to the Mediterranean diet, the PREDIMED trial intervention team developed and validated an instrument for rapid estimation of adherence to the Mediterranean diet (**168**). This tool has been demonstrated to be very useful in clinical practice. The score proposed was an adaptation of a previously validated 9-item index selecting the best cut-off points to discriminate between cases of myocardial infarction and controls (**169**). This 14-point screener was designed to assess adherence to the Mediterranean diet and to allow for immediate feedback to participants. This 14-point score includes the following 14 questions:

	Frequency[1]
1. Do you use olive oil as the principal source of fat for cooking?	Yes
2. How much olive oil do you consume per day (including that used In frying, salads, meals eaten away from home, etc)?	>=4 Tablespoon[2]
3. How many servings of vegetables do you consume per day? Count garnish and side servings as ½ point; a full serving is 200 g.	>=2
4. How many pieces of fruit (including fresh-squeezed juice) do you consume per day?	>=3
5. How many servings of red meat, hamburger, or sausages do you consume per day? A full serving is 100-150 g.	<1
6. How many servings (12 g) of butter, margarine, or cream do you consume per day?	<1
7. How many carbonated and/or sugar-sweetened beverages do you consume per day?	<1
8. Do you drink wine? How much do you consume per week?	>=7 cups[3]
9. How many servings (150 g) of pulses do you consume per week?	>=3
10. How many servings of fish/seafood do you consume per week?	>=3
11. How many times do you consume commercial (not homemade) pastry such as cookies or cake per week?	<2
12. How many times do you consume nuts per week? (1 serving= 30 g)	>=3
13. Do you prefer to eat chicken, turkey, or rabbit instead of beef, pork, hamburgers, or sausages?	Yes
14. How many times per week do you consume boiled vegetables, pasta, rice, or other dishes with "sofrito" (a sauce of tomato, garlic, onion, and leeks sauted in olive oil?	>=2

[1] Criterion to score 1 point. Otherwise, 0 recorded

[2] 1 tablespoon = 13.5 g

[3] 1 cup = 100 ml

Questionnaire from reference 165.

The 14-score PREDIMED screener showed a reasonable absolute agreement with the information gathered from the full-length food-frequency questionnaire and it has

shown strong inverse associations with metabolic syndrome and its components (**170**), cardiovascular risk factors (**171**), cardiovascular clinical end-points (**172**) or obesity indexes such as body mass index, waist circumference, and waist-to-height ratio (**173**).

Summary

During the two last decades the body of knowledge on nutritional determinants of cardiovascular disease has considerably increased. Although there is still a long road to cover the gaps in knowledge, a vast amount of high quality studies are available to support the beneficial cardiovascular role of plant-based food patterns, tree nuts, virgin olive oil, whole grains, fish consumption and moderate consumption of alcohol. These studies also support the detrimental role of processed foods, high salt intake, trans-fats, SSB and processed meats.

The evidence knowledge can be summarized in the following dietary goals to reduce CVD:

- ✓ Consume more fruits
- ✓ Consume more vegetables
- ✓ Consume more whole grains. Increase your intake of fiber
- ✓ Consume more legumes
- ✓ Consume more fish
- ✓ Consume more nuts
- ✓ Consume low-fat dairy instead of whole fat dairy
- ✓ Use virgin olive oil
- ✓ For hydration: drink water
- ✓ If you consume alcohol: max. 2 daily servings for men, 1 daily serving for women. Otherwise, no alcohol consumption is recommended.
- ✓ Reduce your portion sizes
- ✓ Do not forget physical activity (min. 150 min/wk moderate activity)
- ✓ Consume less precooked and fried foods
- ✓ Consume less meats and processed meats
- ✓ Consume less refined sugars and partially hydrogenated vegetable oils
- ✓ Do not put on weight. If you are overweight/obese try to lose weight.

REFERENCES

1) Mathers CD, Lopez AD, Murray CJL. The burden of disease and mortality by condition: data, methods, and results for 2001. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL , eds. Global Burden of Disease and Risk Factors. Washington, DC: International Bank for Reconstruction and Development/World Bank; 2006:45–240.
2) Mathers CD, Longcars D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. PLoS Med. 2006;3:e442.
3) Labarthe DR, Dunbar SB. Global cardiovascular health promotion and disease prevention: 2011 and beyond. Circulation 2012;125:2667-76.
4) United Nations General Assembly. Political Declaration of the High-Level Meeting of the General Assembly on the Prevention and Control of Non-Communicable Diseases. New York, NY: United Nations; September 16, 2011. A/66/L.
5) US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors.US Burden of Disease Collaborators. JAMA 2013;310:591-608.
6) Mozaffarian D, Ludwig DS. Dietary guidelines in the 21st century: a time for food. JAMA 2010;304:681-2.
7) Kris-Etherton PM, Etherton TD, Carlson J, Gardner C. Recent discoveries in inclusive food-based approaches and dietary patterns for reduction in risk for cardiovascular disease. Current Opinion Lipidol 2002;13:397-407.
8) Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA 2002;288:2569-78.
9) Martinez-Gonzalez MA, Martin-Calvo N. The major European dietary patterns and metabolic syndrome. Rev Endocr Metab Disord 2013;14:265–271.
10) Estruch R, Martínez-González MA, Corella D, et al; PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 2006;145:1-11.
11) Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004;292:1440-6.
12) Elmer PJ, Obarzanek E, vollmer WM, Simons-Morton D, Stevens VJ, Young DR, Lin PH, Champagne C, Harsha DW, Svetkey LP, Ard J, Brantley PJ, Proschan MA, Erlinger TP, Appel LJ. Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. Ann Intern Med 2006;144:485-95.
13) Miller ER 3rd, Erlinger TP, Appel LJ. The effects of macronutrients on blood pressure and lipids: an overview of the DASH and OmniHeart trials. Curr Atheroscler Rep 2006;8:460-5.
14) Svendsen M, Blomhoff R, Holme I, Tonstad S. The effect of an increased intake of vegetables and fruit on weight loss, blood pressure and antioxidant defense in subjects with sleep related breathing disorders. Eur J Clin Nutr 2007;61:1301-11.
15) Dauchet L, Amouyel P, Hercberg S et al. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. J Nutr 2006;136:2588–93.
16) He FJ, Nowson CA, Lucas M et al. (2007) Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. J Hum Hypertens 2007;21:717–28.
17) Ness AR & Powles JW. Fruit and vegetables, and cardiovascular disease: a review. Int J Epidemiol 1997;26:1–13.
18) Dauchet L, Amouyel P & Dallongeville J. Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies. Neurology 2005;65:1193–7.
19) He FJ, Nowson CA & MacGregor GA (2006) Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. Lancet 2006;367:320–6.
20) Pereira MA, O'Reilly E, Augustsson K et al. Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. Arch Intern Med 2004;164:370–6.
21) Lichtenstein AH, Appel LJ, brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Eterton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006;114:82-96.
22) De Munter JS, Hu FB, Spiegelman D, et al. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. PLoS Med 2007;4:e261.
23) Sabelli PA, Larikins BA. The development of endosperm in grasses. Plant Physiol 2009;149:14-26.
24) Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: a meta-analysis. Nutr Metab Cardiovasc Dis 2008;18:283-90.
25) Jacobs DR Jr, Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy. Am J Clin Nutr 2003;78:508S-13S.
26) Jacobs DR Jr, Tapsell LC. Food, not nutrients, is the fundamental unit in nutrition. Nutr Rev 2007;65:439-50.
27) Anderson JW, Randles KM, Kendall CW, Jenkins DJ. Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. J Am Coll Nutr 2004;23:5-17.
28) Whelton SP, Hyre Ad, Pedersen B, Yi Y, Whelton PK, He J. Effect of dietary fiber intake on blood pressure: a meta-analysis of randomized, controlled clinical trials. J Hypertens 2005;23:475-81.
29) Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002;287:2414-23.
30) Katcher HI, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain-enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. Am J Clin Nutr 2008;87:79-90.
31) Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205-9.
32) Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S, Ward H, Johnson L, Crowe F, Hu FB, Franco OH. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. BMJ 2012;345:e6698.
33) Xun P, Qin B, Song Y, Nakamura Y, Kurth T, Yaemsiri S, Djousse L, He K. Fish consumption and risk of stroke and its subtypes: accumulative evidence from a meta-analysis of prospective cohort studies. Eur J Clin Nutr 2012;66:1199-207.

34) Larsson SC, Orsini N. Fish consumption and the risk of stroke: a dose-response meta-analysis. Stroke 2011;42:3621-3.
35) Jacobson TA. Beyond lipids: the role of omega-3 fatty acids from fish oil in the prevention of coronary heart disease. Curr Atheroscler Rep 2007;9:145-53.
36) Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr. 2006 Jul;84(1):5-17.
37) Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, König A, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and stroke risk. Am J Prev Med 2005;29:347-52.
38) König A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and coronary heart disease mortality. Am J Prev Med 2005;29:335-46.
39) Yzebe D, Lievre M. Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials. Fundam Clin Pharmacol. 2004 Oct;18(5):581-92.
40) He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation 2004;109:2705-11.
41) He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Goldbourt U, Greenland P. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke 2004;35:1538-42.
42) Whelton SP, He J, Whelton PK, Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease. Am J Cardiol 2004;93:1119-23.
43) Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA 2006;296:1885-99.
44) Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989;2:757-61.
45) GISSI Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardio. Lancet 1999;354:447-55.
46) Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acido n major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090-8.
47) Eslick GD, Howe PR, Smith C, Priest R, Bensoussan A. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. Int J Cardiol 2009;136:4-16.
48) Geleijnse JM, giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens 2002;20:1493-99.
49) Mozaffarian D, Geelen A, Brouwer IA, Geleijnse JM, Zock PL, Katan MB. Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. Circulation 2005;112:1945-52.
50) Mozaffarian D, Wu JHY. Omega-3 fatty acids and cardiovascular disease-effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 2011;58:2047-6.
51) Dietary Guidelines Advisory Committee. 2010 Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans. US Department of Agriculture, Agricultural Research Service. http://www.cnpp.usda.gov/DGAs2010-DGACReport.htm (Accessed October 23, 2013).
52) Mozaffarian D, Shi P, Morris JS, Spiegelman D, Grandjean P, Siscovick DS, Willet WC, rim EB. Mercury exposure and risk of cardiovascular disease in two US cohort. New Engl J Med 2011;364:1116-25.
53) Ros E, Mataix J. Fatty acid composition of nuts-implications for cardiovascular health. Br J Nutr. 2006;11:S29–S35.
54) Ros E, Tapsell LC, Sabate J. Nuts and berries for heart health. Curr Atheroscler Rep. 2010;11:397–406.
55) Mente A, de Koning L, Shannon HS, Anand SS. A systematic revie of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med 2009;169:659-69.
56) Kelly JH Jr, Sabate J. Nuts and coronary heart disease: and epidemiological perspective. Br J Nutr 2006;96:S61-S7.
57) Sabate J, Oda K, Ros E. Nut consumption and blood lipid levels: A pooled analysis of 25 intervention trials. Arch Intern Med. 2010;170:821–7.
58) Estruch R, Ros E, Salas-Salvadó J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279-90.
59) Hooper L, Kroon PA, Rimm EB, Cohn JS, Harvey I, Le Cornu KA, Ryder JJ, Hall WL, Cassidy A. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2008;88:38-50.
60) Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M. Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition committee. Circulation 2006;113:1034-44.
61) McGrane MM, Essery E, Obbagy J, Lyon J, Macneil P, Spahn J, Van Horn L. Dairy Consumption, Blood Pressure, and Risk of Hypertension: An Evidence-Based Review of Recent Literature. Curr Cardiovasc Risk Rep 2011;5:287-298.
62) Alonso A, Beunza JJ, Delgado-Rodríguez M, Martínez JA, Martínez-González MA. Low-fat dairy consumption and reduced risk of hypertension: the Seguimiento Universidad de Navarra (SUN) cohort. Am J Clin Nutr 2005;82:972-9.
63) Toledo E, Alonso A, Martinez-Gonzalez MA. Differential Association of Low-Fat and Whole-Fat Dairy Products with Blood Pressure and Incidence of Hypertension. Curr Nutr Rep 2012;1:197-204.
64) Trichopoulou A, Costacou T, Bamia C, Trichopulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;26:2599-2608.
65) Martinez-Gonzalez MA, Gea A. Mediterranean diet: the whole is more than the sum of its parts. Br J Nutr. 2012;108:577-8.
66) Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB. Dietary patterns and the risk of coronary heart disease in women. Arch Intern Med 2001;161:1857-6.
67) Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med 2008;168:713-20.

68) Dominique Ashen M. Vegetarian Diets in Cardiovascular Prevention. Curr Treat Options Cardiovasc Med 2013 Aug 9. [Epub ahead of print].
69) Micha R, Wallace S, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes: a systematic review and meta-analysis. Circulation 2010;121:2271-83.
70) Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. Am J Clin Nutr 2013;98:1084-102.
71) Hu FB. Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. Obes Rev 2013;14:606-19.
72) Duffey KJ, Popkin BM. Shifts in patterns and consumption beverages between 1965 and 2002. Obesity (Silver Spring) 2007;15:2739-47.
73) Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:e21-e181.
74) Wang YC, bleich SN, Gortmaker SL. Increasing caloric contribution from sugar-sweetened beverages and 100% fruit juices among US children and adolescents, 1988-2004. Pediatrics 2008;121:e1604-14.
75) Stull AJ, Aplzan JW, Thalacker-Mercer AE, Iglay HB, Campbell WW. Liquid and solid meal replacement products differentially affect postprandial appetite and food intake in older adults. J Am Diet Assoc 2008;108:1226-30.
76) Zijlstra N, Mars M, de Wijk RA, Westerterp-Plantenga MS, de Graaaf C. The effect of viscosity on ad libitum food intake. Int J Obes (Lond) 2008;32:676-83.
77) Keller KL, Kirzner J, Pietrobelli A, St-Onge MP. Faith MS. Increased sweetened beverage intake is associated with reduced milk and calcium intake in 3-to 7-year-old children at multi-item laboratory lunches. J Am Diet Assoc 2009;109:497-501.
78) Wolff E, Sansinger ML. Soft drinks and weight gain: how strong is the link? Medscape J Med 2008;10:189.
79) Chen L, Appel LJ, Loria C, Lin PH, champagne CM, Elmer PJ, Ard Jd, Mitchell D, Batch BC, Svetkey LP, Caballero B. Reduction in consumption of sugar-sweetened beverages is associated with weight loss: the PREMIER trial. Am J Clin Nutr 2009;89:1299-306.
80) Mattes RD, Shikany JM, Kaiser KA, Allison DB. Nutritively sweetened beverage consumption and body weight: a systematic review and meta-analysis of randomized experiments. Obes Rev 2011; 12: 346–365.
81) Malik VS, Popkin BM, bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care 2010;33:2477-83.
82) Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr. 2009;89:1037–1042.
83) Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. Circulation 2011;123:2870-91.
84) Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. BMJ 2011;342:d636.
85) Laonigro I, Correale M, Di Biase M, Altomare E. Alcohol abuse and heart failure. Eur J Heart Fail 2009;11:453-62.
86) Conen D, Tedrow UB, Cook NR, Moorthy MV, Buring JE, Albert CM. Alcohol consumption and risk of incident atrial fibrillation in women. JAMA 2008;300:2489-96.
87) Rim EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. BMJ 1999;319:1523-8.
88) Shai I, Wainstein J, Harman-Boehm I, Raz I, Fraser D, Rudich A, Stampfer MJ. Glycemic effects of moderate alcohol intake among patients with type 2 diabetes: a multicenter, randomized, clinical intervention trial. Diabetes Care 2007;30:3011-6.
89) Joosten MM, Beulens JW, Kersten S, Hendriks HF. Moderate alcohol consumption increases insulin sensitivity and ADIPOQ expression in postmenopausal women: a randomized, crossover trial. Diabetologia 2008;51:1375-81.
90) Koppes LL, Dekker Jm, Hendriks HF, Bouter LM, Heine RJ. Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. Diabetes Care 2005;28:719-25.
91) Fillmore KM, Stockwell T, Chikritzhs T, Bostrom A, Kerr W. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies and new hypotheses. Ann Epidemiol 2007;17:S16-S23.
92) Mukamal KJ, rim EB. Alcohol consumption: risks and benefits. Curr Ahteroscler Rep 2008;10:536-43.
93) Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Revie of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits. BMJ 1996;312:731-6.
94) Mukamal KJ, Jensen MK, Gronbaek M, Stampfer MJ, Manson JE, Pischon T, Rimm EB. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. Circulation 2005;112:1406-13.
95) Sayon-Orea C, Martinez-Gonzalez MA, Bes-Rastrollo M. Alcohol consumption and body weight: a systematic review. Nutr Rev 2011;69:419-31.
96) Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, Ezzati M. The preventable cause of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med 2009;6:e1000058.
97) Gea A, Bes-Rastrollo M, Toledo E, Garcia-Lopez M, Beunza JJ, Estruch R, Martinez-Gonzalez MA. Mediterranean Alcohol-Drinking Pattern and mortality in the SUN Project: A prospective cohort study (submitted).
98) Rajaram S. The effect of vegetarian diet, plant foods, and phytochemicals on hemostatis and thrombosis. Am J Clin Nutr 2003;78:552S-8S.
99) Huxley RR, Neil HA. The relation between dietary flavonol intake and coronary heart disease mortality: a meta-analysis of prospective cohort studies. Eur J Clin Nutr 2003;57:904-8.
100) Law M. Plant sterol and stanol margarines and health. BMJ 2000;320:861-4.
101) Appel LJ. Dietary patterns and longevity: expanding the blue zones. Circulation 2008;118:214-5.
102) Willett WC, Sacks F, Trichopoulou A, et al. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr 1995;61,Suppl.6:S1402-S1406.
103) De Lorgeril M, Salen P, Martin JL, Monajud I, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation 1999;99:779-785.
104) Martinez-Gonzalez MA, Corella D, Salas-Salvado J, et al. Cohort profile: design and methods of the PREDIMED study. Int J Epidemiol 2012;41:377-85.

105) Martinez-Gonzalez MA, Bes-Rastrollo M. Dietary patterns, Mediterranean diet, and cardiovascular disease. Current Opinion Lipid (submitted).
106) Horton R. Expression of concern: Indo-Mediterranean Diet Heart Study. Lancet 2005;366:354-356.
107) Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr 2010;92:1189-1192.
108) Dilis V, Katsoulis M, Lagiou P, et al. Mediterranean diet and CHD: the Greek European Prospective Investigation into Cancer and Nutrition cohort. Br J Nutr 2012;108:699-709.
109) Tognon G, Nilsson LM, Lissner L, et al. The Mediterranean diet score and mortality are inversely associated in adults living in the Subartic region. J Nutr 2012;142:1547-1553.
110) Gardener H, Wright CB, Gu Y, et al. Mediterranean diet and risk of ischemic stroke, myocardial infarction, and vascular death: the Northern Manhattan Study. Am J Clin Nutr 2011;94:1458-1464.
111) Misirli G, Benetou V, Lagiou P, et al. Relation of the traditional Mediterranean diet to cerebrovascular disease in a Mediterranean population. Am J Epidemiol 2012;176:1185-1192.
112) Hoevenaar-Blom M, Nooyens ACJ, Kromhout D, et al. Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. Plos ONE 2012;7:e45458.
113) Menotti A, Alberti-Fidanza A, Fidanza F. The association of the Mediterranean Adequacy Index with fatal coronary events in an Italian middle-aged male population followed for 40 years. Nutr Metab Cardiovasc Dis 2012;22:369-375.
114) Tognon G, Lissner L, Sæbye D, et al. The Mediterranean diet in relation to mortality and CVD: a Danish cohort study. Br J Nutr. 2013 Jul 3:1-9. [Epub ahead of print].
115) Hoevenaar-Blom MP, Spijkerman AM, Kromhout D, Verschuren WM. Insufficient sleep duration contributes to lower cardiovascular disease risk in addition to four traditional lifestyle factors: the MORGEN study. Eur J Prev Cardiol. 2013 Jul 3. [Epub ahead of print].
116) Buckland G, González CA, Agudo A, et al. Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. Am J Epidemiol 2009;170:1518-29.
117) Martinez-Gonzalez MA, Garcia-Lopez M, Bes-Rastrollo M, et al. Mediterranean diet and the incidence of cardiovascular disease: a Spanish cohort. Nutr Metab Cardiovasc Dis 2011;21:237-44.
118) Mitrou PN, Kipnis V, Thiébaut AC, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. Arch Intern Med 2007;167:2461-8.
119) Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:655-666.
120) Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145-154.
121) Despres JP, Poirier P. Looking back at Look AHEAD-giving lifestyle a chance. Nat Rev Cardiol 2013;10:184-186.
122) Serra-Majem L, Bes-Rastrollo M, Román-Viñas B, Pfrimer K, Sánchez-Villegas A, Martínez-González MA. Dietary patterns and nutritional adequacy in a Mediterranean country. Br J Nutr. 2009;101 Suppl 2:S21-8.
123) Martínez-González MA, Salas-Salvado J, Estruch R. Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes. N Engl J Med 2013 (in press).
124) Swain Jf, McCarron PB, Hamilton EF, Sacks FM, Appel LJ. Characteristics of the diet patterns tested in the Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart): options for heart-healthy diet. J Am Diet Assoc 2008;108:257-65.
125) Appel LJ, Sacks FM, Carey VJ, et al. Effects of protein, monounsaturated fat, and carbohyrdrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA 2005;294:2455-64.
126) Mellen PB, Gao SK, vitolins MZ, Goff DC Jr. Deteriorating dietary habits among adults with hypertension: DASH dietary accordance, NHANES 1988-1994 and 1999-2004. Arch Intern Med 2008;168:308-14.
127) Margetts BM, Beilin LJ, Vandongen R, Armstrong BK. Vegetarian diet in mild hypertension: a randomised controlled trial. BMJ (Clin Res Ed) 1986;293:1468-71.
128) Sciarrone SE, Strahan MT, Beilin LJ, Burke V, Rogers P, Rouse IR. Ambulatory blood pressure and heart rate responses to vegetarian meals. J Hypertens 1993;11:277.85.
129) Hakala P, Karvetti Rl. Weight reduction on lactovegetarian and mixed diets: changes in weight, nutrient intake, skinfold thicknesses and blood pressure. Eur J Clin Nutr 1989;43:421-30.
130) Barnard ND, Cohen J, Jenkings DJ, Turner-McCrievy G, Gloede L, Green A, Ferdowsian H. A low-fat vegan diet and a conventional diabetes diet in the treatment of type 2 diabetes: a randomized, controlled, 74-wk clinical trial. Am J Clin Nutr 2009;89:1588S-96S.
131) Burke LE, Styn Ma, Steenkiste Ar, Music E, Warziski M, Choo J. A randomized clinical trial testing treatment preference and two dietary options in behavioral weight management: preliminary results of the impact of diet at 6 months: PREFER study. Obesity (Silver Spring) 2006;14:2007-17.
132) Burke LE, Hudson AG, Warziski MT, Styn MA, Music E, Elci OU, Sereika SM. Effects of a vegetarian diet and treatment preference on biochemical and dietary variables in overweight and obese adults: a randomized clinical trial. Am J Clin Nutr 2007;86:588-96.
133) Fung TT, Rexrode KM, Mantzoros Cs, Manson JE, Willet WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. Circulation 2009;119:1093-100.
134) Nunez-Cordoba JM, Valencia-Serrano F, Toledo E, Alonso A, Martinez-Gonzalez MA. The Mediterranean diet and incidence of hypertension: the Seguimiento Universidad de Navarra (SUN) Study. Am J Epidemiol 2009;169:339-46.
135) Key TJ, Fraser GE, Thorogood M, et al. Mortality in vegetarians and non-vegetarians: a collaborative analysis of 8300 deaths among 76,000 men and women in five prospective studies. Public Health Nutr 1998;1:33-41.
136) Fraser GE. Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh-day Adventists. Am J Clin Nutr 1999;70:532S-8S.
137) Craig WJ, Mangels AR. Position of the American Dietetic Association: vegetarian diets. J Am Diet Assoc 2009;109:1266-82.
138) Martinez-Gonzalez MA, Sanchez-Tainta A, Corella C, et al. A pro-vegetarian food pattern and reduction in total mortality in the PREDIMED study. Am J Clin Nutr 2014 (in press).
139) Orlich MJ, Singh PN, Sabaté J, Jaceldo-Siegl K, Fan J, Knutsen S, Beeson WL, Fraser GE. Vegetarian dietary patterns and mortality in Adventist Health Study 2. JAMA Intern Med 2013;173:1230-8.

140) Huang T, Yang B, Zheng J, Li G, Wahlqvist ML, Li D. Cardiovascular disease mortality and cancer incidence in vegetarians: a meta-analysis and systematic review. Ann Nutr Metab 2012;60:233-40.
141) Wilcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. Ann N Y Acad Sci 2007;1114:434-55.
142) Shimazu T, Kuryama S, Hozawa A, et al. Dietary patterns and cardiovascular disease mortality in Japan: a prospective cohort study. Int J Epidemiol 2007;36:600-9.
143) Ding EL, Mozaffarian D. Optimal dietary habits for the prevention of stroke. Semin Neurol 2006;26:11-23.
144) Willcox DC, Willcox BJ, todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. J Am Coll Nutr 2009;28:500S-16S.
145) Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronoray heart disese in US women. Am J Clin Nutr 2000;71:1455-61.
146) Sanchez-Tainta A, Zazpe I, Bes-Rastrollo M, et al. Nutritional adequacy according to carbohydrates and fat quality in the PREDIMED trial. (submitted).
147) Keys A. Seven Countries: a multivariate analysis of death and coronary heart disease. Cambridge, MA: Harvard University Press;1980.
148) Kato H, tillotson J, Nichaman MZ, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Am J Epidemiol 1973;97:372-85.
149) Hu FB, stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491-9.
150) Mozaffarian D, Katan MB, Ascherio A, et al. Trans fatty acis and cardiovascular disease. N Engl J Med 2006;337:1491-9.
151) Hu FB. Diet and lifestyle influences on risk of coronary heart disease. Current Atheroscler Rep 2009;11:257-63.
152) Dayton s, Pearce ML, Hashimoto S, et al. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation 1969;40:1S-63S.
153) Turpeinen O, Karvonen MJ, Pekkarienn M, et la. Dietary prevention of coronary heart disease: the Finnish Mental Hospital Study. Int J Epidemiol 1979;8:99-118.
154) Morris JN, Ball KP, Antonis A, et al. Controlled trial of soya-bean oil in myocardial infarction. Lancet 1968;2:693-9.
155) Malhotra A. Saturated fat is not the major issue. BMJ 2013;347:f6340.
156) Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am J Clin Nutr 2010;91:535-46.
157) He FJ, MacCregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. J Hum Hypertens 2009;23:363-84.
158) Strazzulo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009;339:b4567.
159) Cook NR, Ctuler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease otucomes: observational follow-up of the Trials Of Hypertension Prevention (TOHP). BMJ 2007;334:885-8.
160) Appel LJ. At the tipping point: accomplishing population-wide sodium reduction in the United States. J Clin Hypertens (Greenwich) 2008;10:7-11.
161) Ikehara S, Iso H, Date C, Kikuchi S, Watanabe Y, Inaba Y, Tamakoshi A; JACC Study Group. Salt preference and mortality from stroke and coronary heart disease for Japanese men and women: the JACC study. Prev Med 2012;54:32-7.
162) Brown IJ, Tzoulaki I, Candeias v, Elliott P. Salt intakes around the world: implications for public health. Int J Epidemiol 2009;38:791-813.
163) Risk Factor Monitoring and methods branch web site, Applied Research program, National Cancer Institute. Sources of sodium among the US population, 2005-06. http://riskfactor.cancer.gov/diet/foodsources/sodium/ (Accessed October 23, 2013).
164) Bibbins-Domingo K, Chjertow GM, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 2010;362:590-9.
165) Smith-Spangler CM, Juusola JL, Enns EA, Owens DK, Garber AM. Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. Ann Intern Med 2010;152:481-7.
166) World Health Organization. Intervention on diet and physical activity: what works. Geneva, Switzerland: WHO Press; 2009.
167) Artinian NT, Fletcher GF, Mozaffarian D, et al. Intervention to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. Circulation 2010;122:406-41.
168) Schroder H, Fito M, Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, et al. A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. J Nutr 2011;141:1140-5.
169) Martinez-Gonzalez MA, Fernandez-Jarne E, Serrano-Martinez M, Wright M, Gomez-Gracia E. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. Eur J Clin Nutr 2004;58:1550-2.
170) Babio N, Bullo M, Basora J, Martinez-Gonzalez MA, Fernandez-Ballart J, Marquez-Sandoval F, et al. Adherence to the Mediterranean diet and risk of metabolic syndrome and its components. Nutr Metab Cardiovasc Dis 2009;19:563-70.
171) Sanchez-Tainta A, Estruch R, Bullo M, Corella D, Gomez-Gracia E, Fiol M, et al. Adherence to a Mediterranean-type diet and reduced prevalence of clustered cardiovascular risk factors in a cohort of 3,204 high-risk patients. Eur J Cardiovasc Rehabil 2008;15:589-93.
172) Schröder H, Martinez-Gonzalez MA, Fito M, et al. Baseline adherence to the Mediterranean diet and major cardiovascular events in the PREDIMED trial (submitted).
173) Martinez-Gonzalez MA, Garcia-Arellano A, Toledo E, Salas-Salvado J, Buil-Cosiales P, Corella D, et al. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. PLOS One 2012;7:e43134.