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Coronary heart disease prevention: Nutrients, foods, and dietary patterns

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Abstract

Diet is a key modifiable risk factor in the prevention and risk reduction of coronary heart disease (CHD). Results from the Seven Countries Study in the early 1970s spurred an interest in the role of single nutrients such as total fat in CHD risk. With accumulating evidence, we have moved away from a focus on total fat to the importance of considering the quality of fat. Recent meta-analyses of intervention studies confirm the beneficial effects of replacing saturated fat with polyunsaturated fatty acids on CHD risk. Scientific evidence for a detrimental role of *trans* fat intake from industrial sources on CHD risk has led to important policy changes including listing *trans* fatty acid content on the “Nutrition Facts” panel and banning the use of *trans* fatty acids in food service establishments in some cities. The effects of such policy changes on changes in CHD incidence are yet to be evaluated. There has been a surging interest in the protective effects of vitamin D in primary prevention. Yet, its associations with secondary events have been mixed and intervention studies are needed to clarify its role in CHD prevention. Epidemiological and clinical trial evidence surrounding the benefit of B vitamins and antioxidants such as carotenoids, vitamin E, and vitamin C, have been contradictory. While pharmacological supplementation of these vitamins in populations with existing CHD has been ineffective and, in some cases, even detrimental, data repeatedly show that consumption of a healthy dietary pattern has considerable cardioprotective effects for primary prevention. Results from these studies and the general ineffectiveness of nutrient-based interventions have shifted interest to the role of foods in CHD risk reduction. The strongest and most consistent protective associations are seen with fruit and vegetables, fish, and whole grains. Epidemiological and clinical trial data also show risk reduction with moderate alcohol consumption. In the past decade, there has been a paradigm shift in nutritional epidemiology to examine associations between dietary patterns and health. Several epidemiological studies show that people following the Mediterranean style diet or the Dietary Approaches to Stop Hypertension (DASH) diet have lower risk of CHD and lower likelihood of developing hypertension. Studies using empirical or data driven dietary patterns have frequently identified two patterns — “Healthy or Prudent” and “Western”. In general, the “Healthy”, compared to the “Western” pattern has been associated with more favorable biological profiles, slower progression of atherosclerosis, and reduced incidence. Evidence on changes in dietary patterns and changes in CHD risk is still emerging. With the emergence of the concept of personalized nutrition, studies are increasingly considering the role of genetic factors in the

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modulation of the association between nutrients and CHD. More studies of genetic variation and dietary patterns in relation to CHD are needed.

Keywords

Heart disease; Epidemiology; Diet; Nutrients; Dietary patterns

1. Introduction

Heart disease is the leading cause of death for people of most ethnicities in the United States [1]. The most recent report from the American Heart Association indicates that an estimated 82,600,000 American adults (>1 in 3) have 1 or more types of cardiovascular disease (CVD). Of these, 40,400,000 are estimated to be >60 years (y) of age. It is estimated that >2200 Americans die of CVD each day, which is equivalent to 1 death every 39 s. While CVD death rates have declined over the years, the burden of the disease remains high [2]. The lifetime risk of developing coronary heart disease (CHD) after age 40 has been estimated to be 49% for men and 32% for women [3]. The total direct and indirect costs of CVD and stroke in the United States in 2007 are estimated at \$286 billion. CVD and stroke are the most costly diseases accounting for 15% of the total health expenditures in 2007 [2].

The importance of nutrition, in general, to the prevention of CHD is undisputable. Progress in understanding the role of diet on CHD has evolved in the past 100 years. Early evidence came from data on trends in food consumption and ecological studies which showed associations between prevalence and fat intake across and within countries [4,5]. For many years, research then focused on the role of single nutrient intakes, like saturated fat and cholesterol, through metabolic studies and clinical trials [6–8]. More recently, there have been major shifts in nutrition research to understand the role of foods and diet as a whole. In the current review, we briefly review the history, and then focus on the most recent epidemiological and clinical trial evidence from research on nutrients, foods, and dietary patterns on CHD risk. A synopsis of systematic reviews, pooled analyses, and meta-analyses that summarize the association between diet and CHD is presented in Table 1.

2. Nutrients

2.1. Dietary fat

Until very recently, most studies of diet and CVD focused on dietary lipids. This focus stemmed from the seminal work of Ancel Keys in the 1950s and 60s showing both ecological associations between fat intake, cholesterol and CHD, and responsiveness of blood cholesterol to changes in dietary fat [9–16].

2.1.1. Total fat—Until as recently as the 1990s, the focus of public health recommendations, including the USDA food guide pyramid, was to limit the intake of total (and particularly saturated) dietary fat to reduce CVD risk. Based on these recommendations, total fat was usually replaced with carbohydrate, which, while lowering total cholesterol, may conversely increase triglyceride concentration [17]. Importantly, a

2009 meta-analysis of several prospective studies found that intake of total fat was not significantly associated with CHD mortality (relative risk [RR] for highest vs. lowest category=0.94, 95% confidence interval [CI]: 0.71–1.18, P=0.58) or with CHD events (RR for highest vs. lowest category=0.93, 95% CI: 0.84–1.03, P=0.17) [18]. The misplaced focus on total dietary fat was demonstrated by findings from the Women's Health Initiative Dietary Modification Trial [19]. The intervention arm involved intensive behavior modification to reduce total fat intake to 20% of calories. After 6 y, fat intake decreased by approximately 8% in the intervention group compared to the control group, (saturated fatty acid [SFA] (2.9%), monounsaturated fatty acid [MUFA] (3.3%), and polyunsaturated fatty acid [PUFA] (1.5%)). However, this change in total fat intake had no significant effect on incidence of CHD (HR=0.97, 95% CI: 0.90–1.06), while trends toward lower risk of CHD were associated with lower intakes of saturated fat and *trans* fat.

Based on the most recent evidence, the 2006 American Heart Association (AHA) Diet and Lifestyle recommendations for CVD risk reduction relaxed guidelines for total fat intake, and rather, made recommendations for each type of fat. Specifically, the AHA now recommends limiting intake of saturated fat to <7% of energy, and *trans* fat to <1% of energy [20]. Likewise, the most recent Dietary Guidelines for Americans (2010) now recommend that saturated fat intake be <7% of total energy intake, with replacement with food sources of MUFA and PUFA [21].

2.1.2. Saturated fat—Although total fat was frequently targeted in interventions, saturated fat has long been recognized as the most important fat to avoid. The “diet–heart hypothesis” that high intake of saturated and low intake of polyunsaturated fat increase blood cholesterol, which, in turn, causes atherosclerosis, was central to most diet and CVD research in the latter half of the 1900s. In the Seven Countries Study, where 11,579 men aged 40–59 y were followed for 15 y, [4] differences in type of fat accounted for much of the risk of CHD death. Subsequent studies showed associations between intake of individual fatty acids and dietary cholesterol in relation to serum cholesterol and mortality from CHD. Strong positive associations were observed between 25-y CHD death rates and intake of the four major SFA, lauric, myristic, palmitic, and stearic acid ($r>0.8$, $P<0.001$), for the *trans* fatty acid elaidic acid ($r=0.78$, $P<0.001$), and for dietary cholesterol ($r=0.55$, $P<0.05$) [22]. Migration studies such as the Japanese Ni-Hon San Study provide unique opportunities to evaluate the role of environmental and lifestyle factors in CHD as differences in genetic factors are minimized. That study began in 1965 with men in Japan (Hiroshima and Nagasaki), and with Japanese-American men in Hawaii, and the San Francisco Bay Area of California. Saturated fat intake was lowest in Japan and highest among Japanese immigrants in California. Likewise, relative weight and serum cholesterol mirrored these higher saturated fat intakes, suggesting that the marked differences in CHD among men from these three areas may be attributable to differences in saturated fat intake [23].

In contrast, a recent meta-analysis of 16 prospective cohort studies on 347,747 subjects showed that, during 5–23 y of follow-up, intake of saturated fat was not associated with increased risk of CHD (RR=1.07, 95% CI: 0.96–1.19, P=0.22) [24]. However, of the 16 studies included, 7 adjusted for serum cholesterol concentrations. As indicated by Scarborough and Rayner [25], serum cholesterol lies in the causal pathway between

saturated fat and CHD and, therefore, controlling for serum cholesterol concentrations may be expected to attenuate estimates. Others argue that it is difficult to assess the effect of saturated fat alone, as lower intake of saturated fat implies an increased intake of some other source of energy to maintain balance [26]. Studies have also evaluated change in CHD risk when saturated fat is replaced with PUFA, MUFA, or carbohydrate. A pooled analysis of 11 prospective cohort studies showed that, for each 5% of energy intake from SFA replaced with PUFA, risk of coronary events and coronary death decreased by 13% (95% CI: 0.77–0.97) and 26% (95% CI: 0.61–0.89), respectively. Replacement with either MUFA or carbohydrate, instead of SFA, was not associated with difference in risk of coronary events or death [27]. In a systematic review and meta-analysis of 8 randomized clinical trials (RCTs) where saturated fat was replaced by PUFA, Mozaffarian et al. [28] noted an overall pooled risk reduction of 19% in the intervention groups (RR=0.81, 95% CI: 0.70–0.95, P=0.008) corresponding to a 10% reduced CHD risk (RR=0.90, 95% CI: 0.83–0.97) for each 5% energy from PUFA rather than SFA. It has been known from the Keys' early studies that the main underlying mechanism for the role of SFA in CHD risk is through increasing low density lipoprotein (LDL) concentration. Importantly, replacing SFA with unsaturated fatty acids increases the high-density lipoprotein (HDL):LDL ratio whereas replacement by carbohydrate has no effect on this ratio [29]. Further, replacing SFA with either PUFA or MUFA has been shown to be equally efficacious at reducing the total cholesterol (TC): HDL ratio [30].

2.1.3. Monounsaturated fatty acids—Much of the interest in the role of MUFA in the prevention of CHD stems from observed beneficial effects of the Mediterranean diet, which includes high consumption of olive oil. Oleic acid, found in olive oil, is the primary MUFA in the American diet. Epidemiologic evidence for the protective effect of MUFA against CHD has been mixed. In the Nurses' Health Study (NHS), marginal protection was observed (hazard ratio [HR]=0.81 (95% CI: 0.65–1.00, P=0.05)) [31]. Others found no differences in MUFA intake between CHD cases and controls [32,33]. In the Pooling Project of Cohort Studies on Diet and Coronary Disease [27], each 5% energy increment from MUFA rather than SFA was not associated with coronary events (HR=1.19, 95% CI: 1.00–1.42) or coronary death (HR=1.01, 95% CI: 0.73–1.41). The Strong Heart Study found that higher intakes of MUFA at baseline were associated with higher CHD mortality among American Indians aged 47–59 y but not among those aged 60–79 y. In studies of populations with diets without large contributions by high MUFA oils, it is often difficult to separate MUFA from SFA, as both are included in animal fat sources. In the Strong Heart Study, meat, poultry, and fish provided almost the same contributions of SFA (45%) and MUFA (46%) [34].

Together, the evidence shows that substitution of SFA with either MUFA or PUFA leads to reductions in total and LDL cholesterol. However, due to the greater degree of unsaturation (number of double bonds) present in PUFA, they are more susceptible to oxidative modification than MUFA. There is considerable evidence to show that a PUFA diet increases the oxidative susceptibility of LDL compared to a MUFA enriched diet (olive oil diet) [35–37]. This is potentially harmful as oxidized LDL is known to induce an inflammatory response and stimulate production of other reactive oxygen species, processes integral to the progression of atherosclerosis.

2.1.4. Trans fatty acids—*Trans* fatty acids (TFA) have at least one carbon–carbon double bond in the *trans*, rather than the typical *cis*, configuration. The process of hydrogenation (adding hydrogen to remove double bonds in monounsaturated or polyunsaturated oils) was invented early in the 20th century as a means to increase the shelf life of oils. Mass consumption of these fats, as margarine or shortening, increased in the US during World War II and later increased further, as butter was identified as a major source of SFA, contributing to elevated cholesterol concentrations [38]. Only recently has it been recognized that *trans* fat is at least as bad as SFA for CHD risk. A meta-analysis of 4 prospective studies showed that isocaloric substitution of 2% of total energy intake from carbohydrates with TFA was associated with increased CHD incidence (pooled RR=1.23; 95% CI, 1.11–1.37; P<0.001) [39]. The addition of 3 retrospective case–control studies to the meta-analysis increased the effect size of TFA on CHD further (pooled RR=1.29; 95% CI, 1.11–1.49; P<0.001). Erythrocyte TFA have been associated with higher plasma LDL cholesterol (P for trend=0.06), lower plasma HDL cholesterol (P for trend<0.01), higher plasma LDL:HDL (P for trend<0.01) [40] and increased risk for acute coronary syndrome (odds ratio [OR] for each 1-SD increase in *trans* oleic acid=1.24 (95% CI 1.06–1.45) [41]).

In controlled trials, each 1% energy replacement of TFA with SFA, MUFA, or PUFA decreased the TC:HDL ratio by 0.31, 0.54, and 0.67 respectively (P<0.05 for each). In prospective cohort studies, it was estimated that each 2% energy replacement of TFA with SFA, MUFA, or PUFA would lower CHD risk by 17% (95% CI: 7–25%), 21% (95% CI: 12–30%), or 24% (95% CI: 15–33%), respectively. Although benefit was greatest with replacement with plant oils, replacement with tropical oils or animal fats also showed benefit, especially for partially hydrogenated vegetable oils with high TFA (35–45%) content [42].

TFA are found naturally in small amounts in ruminant animals. Some epidemiologic evidence suggests that TFA from ruminant sources, in amounts consumed in diets, do not contribute importantly to risk of CHD [43,44]. However, a quantitative review of clinical trials concluded that animal and industrial TFA do not differ in their ability to raise LDL:HDL ratio [45]. In a recent editorial, Willett and Mozaffarian [46] noted that the amount of TFA from dairy sources in controlled feeding studies greatly exceeded the intake of ruminant TFA in usual diets. Given that TFA have no known health benefits beyond their energy value, that there is no safe level of consumption for industrial TFA, and that there is a clear association between intake of TFA and risk of heart disease, the Food and Drug Administration (FDA) required food manufacturers to list TFA on Nutrition Facts and some Supplement Facts panels from January 1st, 2006, although TFA levels of less than 0.5 g per serving can be listed as 0 g [47]. In March 2003, Denmark became the first country to pass legislation regulating that no more than 2% of fats and oils in any food product can contain TFA [48]. The cities of Boston [49] and New York [50] banned TFA usage in food service establishments.

2.1.5. N-3 fatty acids—In the mid 1970s, it was noted that Greenland Eskimos had low rates of ischemic heart disease (IHD), stimulating research on beneficial aspects of their diet. The protection was partly attributed to the anti-thrombotic effect of long-chained polyunsaturated fatty acids prevalent in diets rich in marine oils [51]. Several prospective

cohorts have shown protective associations between intake of n-3 fatty acids and or fish intake (see Section 3.2) and heart disease risk. For example, the Japan Public Health Center-Based Study Cohort I [52] reported a significant inverse association of eicosapentaenoic acid (EPA)+docosahexaenoic acid (DHA) intake with risk of myocardial infarction (MI) or nonfatal coronary events, although no significant associations were found with fatal coronary events or sudden cardiac death, possibly due to the low number of cases. The NHS showed that higher plasma concentrations of EPA and DHA were associated with lower prospective risk of nonfatal MI [53]. Recently, Danish men with intake of n-3 PUFA >1.08 g/day were shown to have 19% lower (95% CI: 0.64–1.04) incident acute coronary syndrome (fatal and non-fatal MI) compared with men in the lowest quintile (0.39 g/day) [54]. Evidence from prospective studies suggests that intake of 250 mg/day of EPA and DHA (about 1–2 servings/week of fatty fish) appears to be sufficient for primary prevention [55]. In contrast to these findings from cohort studies, however, three case–control studies found no protective effect of dietary intake, plasma or adipose concentrations of n-3 fatty acids on non-fatal MI [53,56,57].

Evidence suggests that n-3 fatty acid intake may be effective for secondary prevention. In 2 meta-analyses of RCT in patients with CHD, both dietary and non-dietary interventions of n-3 fatty acids reduced overall mortality by nearly 20% and fatal MI by 24–30% [58,59]. Recently, an Italian trial showed that 1 g/day of n-3 PUFA (n=3494) vs. placebo (n=3481) resulted in reduced CVD mortality or related hospital admission (HR=0.92, 95% CI: 0.849–0.999, P=0.009) in patients with chronic heart failure [60]. A recent systematic review of n-3 dietary supplements showed that an average dose of 1.8±1.2 g/day for a mean of 2.2±1.2 y decreased risk of CVD mortality and sudden cardiac death by 13% (95% CI: 0.79–0.95, P=0.002; 95% CI: 0.76–0.99, P=0.04 respectively), and nonfatal CVD events by 18% (95% CI: 0.85–0.99, P=0.02) [61].

The mechanisms underlying the protective effects of fish oil on CHD risk reduction include prevention of arrhythmias as well as lowering of heart rate and blood pressure, decreasing platelet aggregation, and lowering triglyceride concentration [62]. The latter appears to be due to decreased hepatic triglyceride secretion combined with enhanced clearance of triglycerides from plasma. A systematic review of 23 trials involving 1075 subjects with type 2 diabetes, found that n-3 PUFA significantly reduced triglyceride concentrations by 25%. Very low density lipoprotein (VLDL) and VLDL-triacylglycerol concentrations also decreased by 36% and 40%, respectively but LDL concentrations increased slightly by 5.7% (P=0.05) [63]. In addition to effects on lipoproteins, n-3 fatty acids may also have a direct effect on vascular function through uptake and incorporation into vascular smooth muscle and endothelial cells. N-3 fatty acids increase endothelium dependent vasodilation in patients with CHD through both NO-dependent and NO-independent pathways [64]. Further, n-3 fatty acids exert anti-inflammatory effects by reducing adhesion and migration of monocytes, and alter inflammatory gene-expression by decreasing activation of transcription factors such as nuclear factor kappa B (NFκB) and peroxisome proliferator-activated receptors [65]. Further evidence for n-3 fatty acids is presented below in relation to fish intake.

2.1.6. Plant-based n-3 fatty acids—While the major dietary source of n-3 fatty acids is fatty fish, alpha-linolenic acid (ALA) is a short chain n-3 PUFA found in plant sources such as rapeseed oil, soybeans, flaxseed, and walnuts. ALA has been proposed as an alternative to fish oils because it can be converted to EPA and DHA, the n-3 PUFA's found in fish. However, the extent of this conversion is limited. While the cardio-protective benefits of marine n-3 fatty acids are established, evidence for ALA is limited. Recently, however, declines in CHD mortality in Eastern Europe have been associated with consumption of oils rich in ALA [66].

Animal models have demonstrated that ALA has anti-arrhythmic properties [67,68]. A meta-analysis of 5 prospective studies showed that high ALA intake was associated with 21% lower risk of fatal heart disease (RR=0.79, 95% CI: 0.60–1.04), but with increased risk for prostate cancer [69]. The authors concluded that the protective effect of ALA on fatal CHD would probably outweigh the possible negative effects. In another systematic review of 14 human studies, ALA supplementation for at least 4 weeks was associated with reduced circulating concentrations of fibrinogen and fasting plasma glucose (P 0.01 for both), but not with significant modification of the lipid profile [70].

Since the publication of these meta-analyses, the NHS showed that dietary ALA was inversely associated with risk of sudden cardiac death (P for trend=0.02, RR for highest two quintiles (vs. lowest)=0.60–0.62) but not of other fatal CHD or nonfatal MI. The specificity of the association between dietary ALA and sudden cardiac death lends further support to the evidence that n-3 PUFA act primarily through anti-arrhythmic mechanisms [71]. In contrast, however, a case-control study in Seattle reported that higher red blood cell membrane ALA was associated with higher risk of sudden cardiac arrest (Quartile 4 vs. 1 OR=2.5, 95% CI: 1.3–4.8) after adjustment for red blood cell long-chain n-3 PUFA, TFA, and linoleic acid. The authors attributed the apparent discrepancy in their findings to metabolic processes under genetic control that may result in variations in cell membrane ALA [72].

While there are no current specific recommendations for ALA for CHD risk reduction, most epidemiologic evidence points to a protective role, and including ALA (2 to 3 g per day) in the diet has been recommended for both primary and secondary prevention of CHD [73]. There is a need for additional ALA trials to corroborate the strength of the existing evidence.

2.2. B vitamins

Evidence for a link between B vitamins and CHD comes from the homocysteine lowering effects of these vitamins. Homocysteine, a sulfur-containing amino acid, is a metabolite produced indirectly in the demethylation of methionine. Each 5 $\mu\text{mol/L}$ of homocysteine has been associated with approximately 20% increased risk of CHD events, independent of traditional CHD risk factors [74]. Several large epidemiological studies have shown associations between dietary intakes or concentrations of B vitamins (folate, vitamin B6 and vitamin B12), homocysteine, and CHD. A case-control study in the Boston area demonstrated that both dietary and plasma vitamin B6 and folate were lower in patients with first MI compared to control [75]. In the Kuopio Ischemic Heart Disease Risk Factor Study, dietary folate, but not vitamins B6 or B12, was inversely associated with acute coronary

events. After controlling for 21 CHD risk factors, men in the highest (vs. lowest) quintile of folate intake had 54% reduced risk of acute coronary events (95% CI: 0.25–0.81, $P=0.008$) [76]. In the NHS, the inverse association between folate intake and CHD was stronger among women who consumed up to 1 (RR=0.69, 95% CI: 0.49–0.97) or >1 alcoholic drink per day (RR=0.27, 95% CI: 0.13–0.58) relative to non consumers [77]. However, folate is cleaved during the metabolism of alcohol and, thus, alcohol may interfere with the effectiveness of folate in lowering homocysteine [78].

Most recently, in the Japan Collaborative Cohort Study, dietary folate, but not vitamin B12, was inversely associated with mortality from CHD among women (HR=0.57, 95% CI: 0.34–0.96, P for trend=0.03), and there was a trend for a protective effect of vitamin B6 (HR=0.47, 95% CI: 0.21–1.04, P for trend=0.06); but no associations were noted in men [79]. In another large prospective study in Japan, among non-supplement users, those in the highest vs. lowest quintile of vitamin B6 intake (medians=1.6 and 1.3 mg/day, respectively) had 40–50% lower risk of CHD or MI. Further, vitamin B12 intake was associated with nearly 50% reduction in risk of MI (RR=0.53, 95% CI: 0.29–0.95). The inverse association with MI was only marginal for folate (P -trend=0.05). Further, below-median intake of all three vitamins was associated with 70–80% excess risk of CHD [80]. In contrast, dietary folate was not associated with CHD mortality in the PROSPECT-EPIC cohort (Q4 vs. Q1 HR=1.05, 95% CI: 0.62–1.79), despite its association with lower homocysteine concentration [81].

Data from the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up showed a RR for heart disease of 2.4 (95% CI: 1.1–5.2) for persons in the lowest serum folate quartile (9.9 nmol/L) compared with those in the highest (21.8 nmol/L) quartile, among persons aged 35–55 y [82]. However, for ages 55 y, those in the lowest (vs. highest) quartile had 50% reduced risk of CHD (95% CI: 0.3–0.8). The authors suggested that low folate may more likely to lead to elevated homocysteine in younger than older adults. While no age stratification was performed in the Physician's Health Study, men with the lowest 20%, compared with those in the top 80%, of circulating concentrations of plasma folate (<2 ng/mL) and pyridoxal phosphate (PLP) had higher risk of MI, although this did not reach significance (Folate RR=1.3, 95% CI: 0.8–2.1; PLP RR=1.3, 95% CI: 0.9–2.1 [83]). A strong protective effect of folate concentration on acute coronary events was observed in the Kuopio Ischemic Heart Disease Risk Factor Study (RR=0.35, 95% CI: 0.17–0.73, $P=0.005$) [84] but not in the Atherosclerosis Risk In Communities study [85]. In the latter, those in the highest (vs. lowest) quintile of plasma PLP had 72% lower risk for CHD (95% CI: 0.10–0.70, $P=0.008$) [85].

Siri et al. [86] showed that low vitamin B12 concentrations were associated with an increased risk of coronary atherosclerosis (OR=2.91; 95% CI: 1.10–7.71), independent of total homocysteine, in patients with severe coronary atherosclerosis. Although low folate status was a determinant of elevated total homocysteine, neither folate (OR=0.58, 95% CI: 0.23–1.48) nor vitamin B6 (OR=0.86, 95% CI: 0.33–2.22) was associated with increased risk of coronary atherosclerosis. Studies have also shown conflicting results on CHD mortality, with some showing no association with B vitamin concentrations [87,88], and others showing significant protection [89,90].

The promise of early epidemiologic evidence for a protective effect of B vitamins on CHD paved the way for several randomized clinical trials of dietary supplementation of folic acid and other B vitamins. Unfortunately, a meta-analysis of 12 randomized trials, with a total of 16,958 participants with pre-existing vascular disease, showed that folic acid supplementation had no effect on CHD risk (RR=1.04, 95% CI: 0.92–1.17) [91]. Because all trials in the meta-analysis enrolled patients after 1996, when the U.S. FDA regulation for fortification of grain products was passed, a sensitivity analysis by country of study origin was conducted, but this did not change the results. Another meta-analysis of RCT showed that B vitamins had no effect on atherosclerosis progression in subjects who did not undergo percutaneous transluminal angioplasty [92]. However, a meta-analysis of 14 RCT suggested that folic acid improved flow mediated dilation, a marker of endothelial function, by 1.08% points (95% CI: 0.57–1.59, P=0.0005) [93]. Since these meta-analyses, large scale RCT in women at high risk for CVD [94] or patients with end-stage renal disease [95,96] also found no protective effect of supplementation with large doses of B vitamins on CVD mortality [94], MI [96], or fatal and nonfatal CVD events [95]. In a recent analysis, daily supplementation with 2 mg folic acid plus 1 mg vitamin B12 in 12,064 survivors of MI had no effect on major coronary events (RR=1.05, 95% CI: 0.97–1.13). Interestingly, these negative results with CVD are seen despite observed reduction in homocysteine by nearly 28% [97]. A Norwegian trial [98] in patients with CAD or aortic valve stenosis similarly showed no effect of either 0.8 mg folic acid+0.4 mg vitamin B12 +40 mg vitamin B6, folic acid+vitamin B12 or vitamin B6 alone, relative to placebo, on total mortality or CVD events, and it was terminated after 36 months [99]. Most recently, the Western Norway B Vitamin Intervention Trial also showed no benefit of folate/vitamin B12 or vitamin B6 on angiographic progression of CAD. Rather, post-hoc analysis suggested that folate/B12 might actually promote more rapid progression of CAD [100].

The discordance in findings from epidemiologic studies and clinical trials may be due, in part, to inclusion of different populations. Observational studies traditionally evaluate if risk in a population free from the disease at baseline is greater among those with inadequate vs. adequate B vitamin intakes, while RCTs are largely conducted in populations with existing CVD and often use doses of B-vitamins well above recommended intakes. Finally, most RCTs were conducted after U.S. fortification of all enriched flour, breads, rice, pasta, cornmeal, and other grain products with folic acid. Since fortification, the prevalence of low plasma folate concentrations has decreased [101]. While the plausible role of B vitamins cannot be dismissed, the original excitement about the use of supplements in secondary prevention has been dampened. Further research is needed to understand these complex relationships.

2.3. Carotenoids

Carotenoids are a class of more than 600 compounds that are responsible for the yellow, red, and orange pigments in plants. The most common carotenoids found in the human diet are α -carotene, β -carotene, β -cryptoxanthin, lycopene, lutein, and zeaxanthin. Known primarily as precursors to vitamin A, carotenoids are also important free radical quenchers [102] and act as potent antioxidants.

Evidence for a role of carotenoids in CVD first stemmed from studies that showed that higher intakes of fruit and vegetables were associated with lower risk of CVD. For example, among 22,071 US male physicians without heart disease, each serving of carotenoid-rich vegetables decreased the 12 y risk of CHD by 17% (RR=0.83, 95% CI: 0.71–0.98) [103]. However, studies on the association between dietary carotenoids and CVD risk have been inconsistent. In 73, 286 female nurses followed for 12 y, those in the highest intake quintiles of α -carotene (1518 μg) and β -carotene (7639 μg) had 20% (RR=0.80, 95% CI=0.65–0.99) and 26% (RR=0.74, 95% CI=0.59–0.93) lower risk of CAD, respectively compared to those in the lowest quintiles (α -carotene=209 μg , β -carotene=1720 μg). These protective associations were not evident for lutein/zeaxanthin, β -cryptoxanthin, or lycopene [104]. Similarly, over a mean 7.2 y, no significant associations were seen between dietary lycopene and total CVD, important vascular events, or MI (P for trend=0.34, 0.20, 0.09 respectively). However, women consuming 10 servings/week of tomato-based products reduced their CVD risk by about 30% (RR=0.71, 95% CI: 0.42–1.17) and risk of important vascular events by 65% (RR=0.35, 95% CI: 0.16–0.77) compared to those consuming <1.5 servings/week. Although dietary lycopene was not associated with CVD, the strong inverse associations noted for tomato-based products suggest that either dietary lycopene, or other nutrients in a high tomato dietary pattern, may have a role in CVD prevention [105].

In a case–control study in Italy, (760 MI patients and 682 controls) intakes of lycopene, total carotenoids and lutein+zeaxanthin were not associated with acute MI. However, acute MI risk was lower for the highest vs. lowest quintile of intakes of α -carotene (OR=0.71, 95% CI 0.51–0.98), β -carotene (OR=0.71, 95% CI 0.50–1.01), and β -cryptoxanthin (OR=0.64, 95% CI 0.46–0.88) [106]. In contrast, a case–control study in Costa Rica found that dietary lutein +zeaxanthin was associated with increased risk (P for trend=0.02) of nonfatal acute MI [107]. A pooled analysis of 9 cohorts, representing 4647 major incident CHD events and 293,172 subjects free of CHD at baseline, showed that energy-adjusted lutein intake was associated with lower risk of major CHD events (pooled RR=0.89, 95% CI: 0.75–1.04, P for trend=0.03) [108].

Further evidence comes from studies with circulating concentrations of carotenoids. The Physician's Health Study, [109] showed no association between baseline plasma total carotenoids and incident MI. However, among smokers, higher plasma β -carotene was associated with lower risk (P for interaction=0.02). In the same cohort, plasma lycopene was not associated with total CVD or important vascular events [110]. In contrast, higher plasma lycopene was associated with lower risk of total CVD (RR=0.66, 95% CI: 0.47–0.95) and important vascular events (RR=0.50, 95% CI: 0.28–0.90) in the Women's Health Study [111]. The differences in findings between the two cohorts may be explained by sex differences and that the women had longer follow-up time (4.8 vs. 2.1 y). Further, median plasma lycopene was much lower in the male physicians than in women (9.3 vs. 16.5 $\mu\text{g}/\text{dL}$).

In the placebo group of the Lipid Research Clinics Coronary Primary Prevention Trial, serum carotenoids were associated with 36% lower risk of CHD events (Q5 vs. Q1, RR=0.64, 95% CI: 0.44–0.92) [112]. In contrast to previous studies, plasma β -cryptoxanthin and lutein, rather than other carotenoids, were associated with lower (P for trend=0.03 for

both) risk of acute MI in the Singapore Chinese Health Study. Evidence for a mechanistic role for lutein/zeaxanthin and β -cryptoxanthin in CHD comes from the Los Angeles Atherosclerosis Study, where an 18-month change in intima-media thickness (IMT) was inversely related to oxygenated lutein, β -cryptoxanthin, and zeaxanthin ($P < 0.02$ for all) [113], and the ARIC study, where serum β -cryptoxanthin and lutein+zeaxanthin concentrations were inversely related to carotid IMT (OR per 1SD: 0.75, 95% CI: 0.59–0.94) [114].

In one observational study [115], it was noted that Lithuanian men had 4 times the risk of CHD and lower plasma β -carotene (377 vs. 510 nmol/L, $P < 0.01$) and lycopene (327 vs. 615 nmol/L, $P < 0.001$) concentrations than Swedish men. A study in Japan showed that high serum α -carotene and β -carotene, but not lycopene, were associated with 50% lower risk of CVD and heart disease mortality [116]. After 15-y of follow-up, comparable results were noted for both α - and β -carotene and CVD mortality in the Zutphen Elderly Study [117].

Several RCTs have been conducted to validate a causal role for carotenoids in CVD prevention. Despite overwhelming evidence from epidemiological studies, however, RCTs have failed to demonstrate a beneficial effect. In a meta-analysis of 8 RCTs of β -carotene vs. placebo, β -carotene supplementation of 15–50 mg for 1.4 to 12.0 y, actually showed a small but significant increase in CVD (OR=1.1, 95% CI: 1.03–1.17, $P=0.003$) and all-cause mortality (OR=1.07, 95% CI: 1.02–1.11, $P=0.003$) [118]. A more recent systematic review and meta-analysis of 12 high quality trials showed that β -carotene, alone or combined with vitamins A and E, significantly increased mortality by 7% (RR=1.07, 95% CI: 1.02–1.11) [119]. Sub-group analysis from the α -tocopherol β -carotene cancer prevention study, showed that, among men with previous MI, 20 mg/day of β -carotene (vs. placebo) for a mean 5.3 y increased the risk of fatal CHD (RR=1.75, 95% CI=1.16–2.64, $P=0.007$) [120]. Among male smokers with angina pectoris, β -carotene supplementation had no effect either on recurrence or progression [121]. Similarly, in the Women's Antioxidant Cardiovascular Study, there was no effect of β -carotene supplementation (RR=1.02, 95% CI: 0.92–1.13, $P=0.71$) on MI, stroke, coronary revascularization, or CVD death [122].

Emerging evidence for a potential role of lycopene, lutein, and zeaxanthin in atherosclerotic progression implies that the effect of carotenoids is complex and not likely due to a single carotenoid in isolation. Therefore, the use of β -carotene or other single carotenoid supplements is not recommended. Rather, efforts should be targeted to increasing the consumption of carotenoid rich fruit and vegetables.

2.4. Vitamin E

Vitamin E is the key fat-soluble antioxidant in the human body and is present in a complex of four isomers (α , β , γ , δ -tocopherols). It functions in both plasma and LDL as a chain-breaking antioxidant that prevents the propagation of free radical damage in biological membranes. The "oxidation modification hypothesis of LDL" supports a biological role for vitamin E in preventing CVD [123]. Oxidized LDL is a strong chemokine that induces adhesion and influx of monocytes, causing release of cytokines [124]. A number of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor- α (TNF- α), modulate monocyte adhesion to the endothelium. Studies in cell culture and

animals have consistently shown that vitamin E prevents this oxidative modification of LDL [125]. In addition to its role as a free radical scavenger, vitamin E is a potent anti-inflammatory agent, especially at high doses, and has been shown to reduce release of proinflammatory cytokines, chemokine IL-8, and plasminogen activator inhibitor-1, as well as decrease adhesion of monocytes to endothelium [126]. Finally, work in CVD patients has shown that vitamin E can decrease concentrations of C-reactive protein (CRP), a systemic marker of inflammation and CVD risk factor [127,128].

With the recognition that oxidized LDL is involved in atherogenesis, several large epidemiological cohorts have examined the role of vitamin E and CVD. An early study found a strong inverse association between plasma vitamin E and IHD [129] and angina [130]. Of 87,245 female nurses, those who took vitamin E supplements for >2 y (vs. non-supplement users) had 41% lower risk (95% CI: 0.38–0.91) of CHD [131]. Similarly, in 39,910 male health professionals, those who took vitamin E supplements in doses 100 IU/day for >2 y had 37% lower risk (95% CI: 0.47–0.84) [132]. Two European studies also found inverse association between the highest vs. lowest categories of vitamin E intake and risk of CHD [132] and coronary mortality [133]. In addition, there was an inverse association between dietary vitamin E and CHD mortality in 34,486 postmenopausal women in the Iowa Women's Health Study [134]; between supplement use and IHD incidence and mortality in a study of 4576 French-Canadian men [135]; and reduced risk of all-cause mortality among vitamin E supplement users in the Established Populations for Epidemiologic Studies of the Elderly [136]. The consistency in these findings and the biologic plausibility led many to support a causal explanation and to suggest that vitamin E supplements may reduce the risk of CVD.

In response, several RCTs were conducted. Again, however, the results have been disappointing. An early meta-analysis of 7 randomized placebo controlled trials of vitamin E supplementation, with doses ranging from 50 to 800 IU, showed no benefit for total or CVD mortality [118]. Subsequent meta-analyses and systematic reviews of more than 90 trials showed similar null results [137,138]. Most recently, a dose-response meta-analysis of 19 clinical trials involving 135,967 participants, with vitamin E doses ranging from 16.5 to 2000 IU/day showed increased risk of high-dose vitamin E (> 400 IU/day) on total mortality, and noted increased risk at dosages greater than 150 IU/day [139].

Despite a solid theory of the molecular basis of oxidative stress and its role in atherosclerosis, these clinical trials failed to support the role of vitamin E supplementation in preventing CVD. There are many potential explanations. Blumberg and Frei [140] note that “the antioxidant theory” of disease prevention has not been truly tested in RCT. Another potential explanation is that the correct form of vitamin E has not been studied. One report argued that the use of the more bioavailable RRR- α -tocopherol (as opposed to all-rac tocopherol present in synthetic vitamin E) at doses 4–8 folds greater than those used in trials may be required to obtain effective reduction of oxidative stress [141]. Moreover, because γ -tocopherol is suggested to have superior antioxidant and anti-inflammatory properties, consideration should be given to combined α - and γ -tocopherol supplementation. This is important, because α -tocopherol supplementation decreases γ -tocopherol concentration [142].

Together, the evidence does not support vitamin E supplementation, especially in secondary prevention. As with carotenoids, the contrast between observational and RCT results suggests that the protective effects of α -tocopherol occur in the presence of other nutrients and therefore, it is most effective and safe when obtained from foods.

2.5. Vitamin C

Vitamin C or ascorbic acid is a water-soluble vitamin and a highly effective antioxidant as it loses electrons easily. The free radical theory of aging, first posited by Harman [143], has long provided a biological basis for the progression of chronic disease. Because of its role as a free radical scavenger, vitamin C has been hypothesized to have a preventive role in CVD.

Several prospective studies have assessed the role of vitamin C, both dietary and supplemental, in CVD, with mixed results. A pooled analysis of 9 cohorts (with mean 10-y follow-up) showed that those taking >700 mg/day supplemental vitamin C, vs. none, had 25% lower incidence of CHD (RR=0.75, 95% CI: 0.60–0.93, P<0.001). Interestingly, among non-supplement users, those in the highest (median=152 mg), vs. lowest (median=45 mg), quintile of energy-adjusted vitamin C intake had a higher risk for major CHD events [108]. While the reasons for this discrepancy are not entirely clear, the authors attribute the observed associations in part to incomplete adjustments for other substances in plant foods. In contrast, a meta-analysis of 15 cohort studies, with 7415 incident CHD cases among 374,488 participants and median follow-up of 10 y, found that those in the lowest tertile of vitamin C exposure, relative to the highest, had 16% lower risk (95% CI: 0.73–0.95) of CHD [144].

Despite its reputation as an antioxidant, vitamin C has been identified as a pro-oxidant under conditions of high oxidative stress. For example, among women with diabetes, supplemental vitamin C 300 mg/day, vs. none, was associated with increased risk for CVD (RR=1.69, 95% CI: 1.09–2.44, P for trend<0.01) and coronary artery disease (CAD) (RR=2.07, 95% CI: 1.27–3.38, P for trend<0.01) [145]. Most RCTs have incorporated vitamin C into a mixture including vitamin E and β -carotene, with largely null results in relation to CVD. The individual role of vitamin C has been evaluated in only two large RCT. The Women's Antioxidant Cardiovascular Study tested the effects of ascorbic acid (500 mg/day), vitamin E (600 IU every other day), and β -carotene (50 mg every other day) on the combined outcome of MI, stroke, coronary revascularization, or CVD death among 8171 female health professionals at increased risk, in a factorial design. After a mean of 9.4 y, there was no effect of ascorbic acid on the combined end point or on individual outcomes [122]. Similarly, in the Physicians' Health Study II, 400 IU of vitamin E every other day and 500 mg of vitamin C daily for a mean of 8 y had no effect on major cardiovascular events, total MI, or CVD mortality [146]. Despite the absence of apparent effect on CHD, 500 mg/day supplemental vitamin C, for at least 4 weeks, has been shown to decrease serum LDL cholesterol and triglyceride concentrations [147].

The evidence does not support a role for supplementation with antioxidant vitamins for preventing CHD risk. Still, dietary supplement sales in the US have been estimated to exceed \$20.3 billion [148]. NHANES 1999–2000 data showed that nearly 52% of Americans consumed dietary supplements, including 12.7% and 12.4% taking vitamins E

and C, respectively [149]. Nutrients and bioactive compounds in foods act synergistically or antagonistically in the complex food matrix to deliver the established health effects of foods. The disappointing results of RCT with dietary supplements suggest that this protection is lost when nutrients are isolated and consumed as a pill. Therefore, it appears that the benefit of antioxidant nutrients for protection against CVD is best obtained by eating a variety of healthy foods, rather than by taking supplements.

2.6. Vitamin D

Vitamin D is a fat-soluble nutrient that plays an important role in a hormone-like fashion. Its two major forms are vitamins D₂ (ergocalciferol) and D₃ (cholecalciferol). Vitamin D₃ can be synthesized by humans in skin cells upon exposure to ultraviolet-B radiation from sunlight. In the absence of sunlight, dietary intake of vitamin D is crucial. Vitamin D from diet and supplements is absorbed through the intestine, then converted to 25-hydroxyvitamin D₃ [25(OH)D] in the liver, and to 1,25 dihydroxyvitamin D₃ [1,25(OH)₂D₃], the active form of vitamin D, in the kidney. The discovery that cells other than kidney cells possess the enzyme capable of converting 25(OH)D to 1,25 (OH)₂D has shifted attention to the key hormonal functions of vitamin D. Recently, evidence has accumulated that 1,25(OH)₂D and its receptor (VDR) generate biological responses in several physiological systems, including the cardiovascular system. Zittermann et al. [150] summarized the underlying mechanisms for a potential role of vitamin D in CHD prevention. These include the inhibition of vascular smooth muscle proliferation, the suppression of vascular calcification, the down regulation of pro-inflammatory cytokines, the up regulation of anti-inflammatory cytokines, and the action of vitamin D as a negative endocrine regulator of the renin-angiotensin system.

Evidence for a role of vitamin D in CVD comes from ecologic studies, with an increase in heart disease events with geographic latitude, in gross agreement with the fact that vitamin D concentrations decline with latitude [150]. Several prospective cohort studies have investigated plasma 25-hydroxy (OH) vitamin D, a stable marker for vitamin D status, in relation to CVD. In the Framingham Offspring study [151], participants with low (<15 ng/mL) vs. higher 25(OH)D had an adjusted hazard ratio of 1.62 (95% CI: 1.11–2.36, P=0.01) for incident CVD events. Similarly, in the Health Professionals Follow-up Study (HPFS), men with 25(OH)D 15 ng/mL were at increased risk (RR=2.09, 95% CI: 1.24–3.54, P for trend=0.02) for MI, compared to those 30 ng/mL [152].

Men and women in the lowest quartile of 25(OH)D (<21 ng/mL) in the NHANES III were 1.3 times more likely to develop hypertension than those in the highest quartile (37 ng/mL) (95% CI: 1.13–1.49, P=0.001) [153]. In another NHANES analysis, participants with 25 (OH)D <10 ng/mL had significantly higher heart rate (2.1±0.6 beats/min) and mean systolic blood pressure (1.9±0.8 mm Hg) than those with 25(OH)D 35 ng/mL [154]. In addition, each 10 ng/mL lower 25 (OH)D was associated with a prevalence ratio of 1.35 for peripheral artery disease (ankle-brachial index <0.9) (95% CI: 1.15–1.59) [155]. Further, differences in vitamin D concentrations were found to explain nearly one-third of the excess risk of peripheral artery disease in black vs. white adults, after adjustment for established CVD risk factors [156]. Most recently, a meta-analysis of epidemiological studies summarized that

high vitamin D concentrations were associated with lower prevalence of cardiometabolic disorders (OR: 0.57, 95% CI: 0.48–0.68), and CVD (OR=0.67, 95% CI: 0.55–0.81) [157].

While the protective effect of vitamin D on CVD events is clearly supported by the evidence, the association with secondary CVD events has been mixed. For example, in two German clinics, 25(OH)D concentrations did not protect against secondary CVD events (Q4 vs. Q1: HR=0.79, 95% CI: 0.44–1.42) [158]. South Indian patients with CAD or acute MI were seen to actually have elevated serum 25(OH)D, compared to controls [159], although the validity and generalizability of these findings have been challenged [160]. However, no other study has shown this inverse relationship. In fact, most show the opposite. In the NHANES 2001–2004, those with CHD were more likely to have hypovitaminosis D (defined as 25(OH)D <30 ng/mL) (OR: 1.44, 95% CI: 1.10–1.89) [161]. Hypovitaminosis D has also been shown to be more prevalent in the presence of type 2 diabetes (34.0 vs. 16.4%, $P<0.001$) and to be associated with greater common carotid IMT (1.10 ± 0.15 vs. 0.87 ± 0.14 mm, $P<0.001$) [162] and prevalent CVD (OR: 1.70, 95% CI: 1.10–2.60) [163]. In the LURIC (Ludwigshafen Risk and Cardiovascular Health) study, the adjusted odds for fatal stroke in patients referred to coronary angiography was 0.67 (95% CI: 0.46–0.97, $P=0.03$) per z-score unit of 25(OH)D [164], and those in the lowest (vs. highest) quartile of 25(OH)D (median 7.6 vs. 28.4 ng/mL) were more likely to die from CVD (HR: 2.22, 95% CI: 1.57–3.13) [165]. Among 6219 participants in the Mini-Finland Health study [166], low vitamin D was associated with higher risk of cerebrovascular death (Q5 vs. Q1: HR=0.48, 95% CI: 0.31–0.75) but not coronary death (HR: 0.94, 95% CI: 0.70–1.18). NHANES data showed that serum 25 (OH)D was inversely associated with both all-cause [167] and CVD mortality [167,168]. Similar protective associations for all-cause and CVD mortality were also observed in an Italian cohort [169].

Despite the clear evidence from epidemiological studies for a protective role of vitamin D in CVD, randomized controlled trials are needed to prove a causal role. Three large RCTs have been conducted. In the Women's Health Initiative [170], with 36,282 postmenopausal women, aged 50–79 y, daily supplementation with 500 mg calcium carbonate and 200 IU of vitamin D did not affect coronary or cerebrovascular risk over a 7-y period. In a Norwegian study of 438 overweight or obese subjects [171], daily supplementation for one year with either 40,000 IU vitamin D3 per week or 20,000 IU per week did not have any effect on blood pressure or serum lipids. In a randomized double blind controlled trial in British doctors [172], 100,000 IU oral vitamin D₃ supplementation or placebo every four months over five years had no effect on CVD events (RR: 0.90, 95% CI: 0.77–1.06) or CVD mortality (RR=0.84, 95% CI: 0.65–1.10). Evidence from observational studies indicates that the greatest benefit is seen among groups who have low or sub-optimal concentrations of this vitamin. Future clinical trials need to be conducted in vitamin D deficient groups who are at high risk for heart disease before conclusions can be drawn.

3. Foods

3.1. Fruit and vegetables

The conflicting results between the apparent protective effects of nutrients as part of dietary intake and the lack of effectiveness of single nutrient supplementation in trials has led to a

focus on foods as protective against CVD. Among these, evidence is most consistent for fruit and vegetables. The global total mortality attributable to inadequate consumption of fruit and vegetables (FV) has been estimated to be up to 2.64 million deaths per year. It has been projected that by increasing FV consumption to 600 g/day, the worldwide burden of IHD and ischemic stroke could be reduced by 31% and 19%, respectively [173]. Epidemiological studies have consistently demonstrated that greater FV intakes are associated with lower risk of incident CVD events. A meta-analysis of nine studies, representing 91,379 men, 129,701 women, and 5007 CHD events, showed that risk of CHD decreased by 4% (RR: 0.96, 95% CI: 0.93–0.99, P=0.003) for each additional portion of fruit or vegetable intake; and by 7% (RR: 0.93, 95% CI: 0.89–0.96, P<0.0001) for fruit intake [174]. Another meta-analysis, of 12 studies, with 278,459 individuals and 9413 CHD events over 11 y, showed that, relative to <3 servings/day of fruit and vegetables, those consuming 3–5 or >5 servings/day had lower CHD risk of 7% (95% CI: 0.86–1.00, P=0.06) and 17% (0.77–0.89, P<0.0001), respectively [175]. In a Swedish study, men who ate fruit and vegetables daily had lower 12 y risk of CHD if they reported high intake of dairy fat (OR 0.39, 95% CI 0.21–0.73) [176]. A similar interaction was seen in the Baltimore Longitudinal Study of Aging, where the combination of high fruit and vegetable and low saturated fat intakes was more protective against mortality in aging men than either alone [177].

The benefits of fruit and vegetable intake appear to be dose related. A case-control study found that the benefit of fruit and vegetable intake consumption increased proportionally by the number of servings consumed (P for trend<0.0001) [178]. In the CARDIO2000 study, consumption of 5 (vs. <1) servings of fruit/day was associated with 72% lower risk of CHD (95% CI: 0.11–0.54, P<0.001), and of vegetables more than 3 days/week (vs. non-consumption) was associated with 70% lower risk for CHD (95% CI: 0.22–0.40, P<0.001) [179]. Most recently, the Diet, Cancer and Health cohort study showed that each 100 g/day intake of fruit and vegetables tended to be associated with lower risk of acute coronary syndrome for men (RR = 0.97, 95% CI = 0.93–1.01) and women (RR = 0.97, 95% CI=0.89–1.01) [180].

In addition to absolute quantity, frequency of fruit and vegetable intake has been associated with lower CVD risk. The Prospective Epidemiological Study of Myocardial Infarction (PRIME) in men aged 50–59 y from France and Northern Ireland found that frequency of citrus, but not other fruit, intake was associated with 5 y lower incidence of acute coronary events (tertile 3 vs. 1, RR: 0.64, 95% CI: 0.41–0.99) [181]. More recently, with 10-y of follow-up of this cohort, the protective effect of fruit and vegetables was significant only in current smokers [182].

The protective effect of fruit and vegetables also translates to lower risk of CVD mortality. In the Massachusetts Health Care Panel Study of 1299 elderly residents, those in the highest quartile of β -carotene rich fruit and vegetable intake (2.05 servings/day) had 41% lower risk of CVD mortality than those in the lowest quartile (<0.8 servings/day) (RR: 0.59, 95% CI: 0.37–0.94, P for trend=0.014). Strongest effects were seen with regular consumption of carrots and/or squash and salads and/or green leafy vegetables [183]. In the Alpha-Tocopherol, Beta-carotene Cancer Prevention (ATBC) study, there was a protective effect of

higher fruit and berry intake on CHD mortality (P for trend=0.008) [184]. Most recently, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk showed that fruit and vegetable intakes were each inversely associated with CVD mortality (Fruit HR=0.75, 95% CI: 0.66–0.85; Vegetable HR=0.88, 95% CI: 0.78–0.99) [185].

In contrast, several studies have not seen significant protective effects of fruit and vegetables on mortality, although most show protective trends. These include a study of adults in Maryland [186], the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study among middle-aged Finnish men [187], and the Adventist Health Study [188]. These studies may have had insufficient power, or inadequate ranges of intake to observe significant effects.

Despite the evidence from mechanistic studies and epidemiology, few randomized controlled trials have been conducted to confirm the causal role of fruits and vegetables in the prevention of CHD. The Dietary Approaches to Stop Hypertension (DASH) trial is discussed in the Dietary patterns section. The mechanisms by which fruit and vegetables exert their protective effects are not entirely clear but likely include antioxidant and anti-inflammatory effects. For example, we recently documented that greater variety in fruit and vegetable intake is associated with lower circulating concentrations of C-reactive protein, a marker of systemic inflammation [189]. Several bioactive components in fruits and vegetables such as carotenoids, vitamin C, fiber, magnesium, and potassium act synergistically or antagonistically to promote a holistic beneficial effect. The totality of the evidence supports current dietary guidelines to increase fruit and vegetable consumption.

3.2. Fish

The primary source of n-3 fatty acids, described in the section above, is fatty fish. A meta-analysis of 11 cohort studies, representing 222,364 individuals and 11.8 y of follow-up, reported that individuals who consumed fish 2–4 times/week (vs. never or <once/month) had 23% lower risk of CHD mortality (pooled RR=0.77, 95% CI: 0.66–0.89). Those with higher frequency of consumption (>5 times/week) had greater reduction in risk (RR=0.62, 95% CI: 0.46–0.82). Each 20 g/day of fish intake was associated with 7% lower risk of CHD mortality (P for trend=0.03) [190]. In another meta-analysis, similar estimates were noted for fatal CHD (RR=0.83, 95% CI: 0.76–0.90, P<0.005) and total CHD (RR=0.86, 95% CI: 0.81–0.92, P<0.005) [191]. A meta-analysis of eight studies noted that compared to no fish consumption, low levels of fish consumption reduce CHD mortality by 17% and that each additional serving per week was associated with an incremental risk reduction of ~4%. However, no associations were seen with non-fatal MI [192].

The Japan Public Health Center-Based Study Cohort I [52] reported a significant inverse association of fish intake with risk of MI or nonfatal coronary events, although no significant associations were found with fatal coronary events or sudden cardiac death, possibly due to the low number of cases. Notably, those who consumed fish 8 times/week (median=180 g/day) had ~40% lower risk of CHD (95% CI: 0.38–1.04) compared to those consuming once per week (median=23 g/day). Among 5103 women with type 2 diabetes in the NHS, fish intake >5 times/week, compared to <1 serving/month, was significantly associated with CHD incidence (RR=0.36 (95% CI: 0.20–0.66)) and total mortality (RR=0.48 (95% CI: 0.29–0.80)) [193]. Protection has also been shown in populations with low fish

consumption. Dutch adults in the highest quartile of EPA+DHA intake (234 mg/day) had 49% lower risk of fatal CHD (95% CI: 6–73%) and 62% lower risk of fatal MI (95% CI: 23–81%) compared to those in the lowest quartile (40 mg/day). Similarly, those with >17.3 g/day of fish intake had 40–50% lower risk of fatal CHD (HR=0.52, 95% CI: 0.28–0.95) and fatal MI (HR=0.40, 95% CI: 0.19–0.86) [194]. In contrast, however, one meta-analysis [190] showed no significant association between fish intake and non-fatal MI (P for trend=0.40).

Evidence that the benefit of fish intake for CHD is due to n-3 PUFA comes from studies, showing that fatty but not lean fish is associated with protection. For example, a prospective cohort of 1373 men showed that fatty, but not lean, fish, consumption was associated with lower risk of sudden coronary death (HR=0.46, 95% CI: 0.27–0.78) [195]. Similarly, in the Estrogen Replacement and Atherosclerosis trial of 229 postmenopausal women, tuna and dark fish, but not other fish, were associated with smaller increases in stenosis in women [196]. Moderate consumption of fatty fish and marine omega-3 fatty acids was associated with lower incident heart failure in Swedish women [197], but not men [198].

In addition to the type and amount of fish consumed, the preparation method (baked vs. fried) of fish may impact CHD risk. In the Cardiovascular Health Study, modest consumption of tuna or other broiled or baked fish, but not of fried fish, was associated with a lower risk of incident heart failure [199], total IHD death (49%), especially arrhythmic IHD death (58%). Frying has been shown to increase the n-6:n-3 ratio, as n-3 fatty acids may be lost and replaced with frying oil [200].

Despite the established beneficial effect of fatty fish consumption on CHD, concerns exist regarding the potential effects of mercury and other contaminants found in fatty fish. One meta-analysis of 5 studies, found no significant association between higher mercury exposure and risk of CHD (pooled RR=1.12, 95% CI: 0.71–1.75) [55]. However, most of these studies excluded women and more studies are needed. Two studies found that fish oil consumption was protective of CHD after adjustment for hair or toenail mercury [201,202]. However, an earlier analysis of the Kuopio Ischaemic Heart Disease Risk Factor Study [203] found that high mercury content (>2.0 µg/g) attenuated the protective effects of n-3 fatty acids on CHD risk. Men in the highest quintile category of serum DHA+docosapentaenoic acid (DPA) had 44% reduced risk (P=0.014) of acute coronary events compared with men in the lowest fifth. However, when stratified by mercury exposure, men in the highest quintile of DHA+DPA with low hair mercury (< 2.0 µg/g) had 67% lower risk (P=0.016) of acute coronary events, relative to men in the same quintile of DHA+DPA intake with high hair content of mercury (>2.0 µg/g).

Together, the benefits of fatty fish consumption appear to outweigh the concerns of mercury exposure at this time, with the possible exception of pregnant women [204]. The most recent AHA Diet and Lifestyle recommendations for CVD risk reduction include consuming fatty fish at least twice a week [20]. Consumption of a variety of fish is recommended to minimize any potentially adverse effects due to environmental pollutants while maximizing the cardioprotective effects. The AHA recommends eating fish within the recommendations established by the FDA and Environmental Protection Agency [205].

3.3. Whole grains

The whole cereal grain is the fruit (or caryopsis) of plants belonging to the Poaceae (or Gramineae) family also known as grasses [206]. Two classical definitions for whole grains exist. The FDA definition states that “whole grains consist of the intact, ground, cracked or flaked caryopsis, whose principal anatomical components – the starchy endosperm, germ and bran – are present in the same relative proportions as they exist in the intact caryopsis” [207]. An “expanded definition” is used by studies that explicitly describe or define whole grain, but do not meet the FDA definition of whole grains, by including bran and germ, and studies that do not explicitly use the term “whole grains” but were in fact conducted with individual whole grains such as oats or barley [206].

The protective role of whole grains against CVD has been evaluated for some time. In the early 1970s, Trowell proposed the “fiber hypothesis” that “high consumption of natural starchy carbohydrates, taken with their full complement of fiber, is protective against hyperlipidemia and ischemic heart disease” [208]. The first study to test this hypothesis was conducted by Morris et al. [209] in 337 healthy middle-aged men in London and south-east England. They reported that men with high intake of dietary fiber from cereals had a lower incidence of CHD. Since then, the inverse association between whole grain intake and CVD has been reported in several large prospective cohorts.

A meta-analysis of seven large-prospective cohort studies [210] concluded that greater whole grain intake (pooled average 2.5 servings/day vs. 0.2 servings/day) was associated with 21% lower risk of CVD events (OR=0.79, 95% CI: 0.73–0.85) for both men and women. However, the association was weaker for incident stroke (OR=0.83, 95% CI: 0.68–1.02). Another meta-analysis of 13 studies, found that risk of CHD events for those with the highest (vs. lowest) intakes of whole grain was 29% lower (95% CI: 0.48–0.94). While the protective effect for total dietary fiber was similar to that of whole grains (RR=0.73, 95% CI: 0.65–0.83), cereal fiber was not associated with a significant risk reduction (RR=0.90, 95% CI: 0.80–1.01) [211].

Since the publication of these meta-analyses, additional studies have added to the evidence. With 26 y of follow-up, results from the NHS found that whole grain intake tended to be associated with lower risk of CVD-specific mortality among women with type 2 diabetes (Quintile 5 vs. 1, RR=0.70, 95% CI=0.46–1.06, P for trend=0.07) while bran intake was significantly associated with 35% lower risk of mortality (Q5 vs. Q1, RR = 0.65, 95% CI = 0.43–0.99, P for trend=0.04) [212]. In the ARIC study, 13.3 y incident heart failure risk decreased by 7% for each serving/day increase (RR=0.93, 95% CI: 0.87–0.99) in whole grain intake in African-American and white adults [213]. However, in the Multi-Ethnic Study of Atherosclerosis, whole grain intake showed little cross-sectional relationship with carotid IMT or coronary artery calcification, although reverse causality could be confounding this result [214].

Given the strength of evidence for a protective role of whole grains in prevention of CVD, an FDA supported health claim was approved that reads “diets high in plant foods – i.e., fruits, vegetables, legumes, and *whole grain* cereals – are associated with lower occurrence of CHD and cancers of the lung, colon, esophagus, and stomach” [215]. Applying the FDA

definition of whole grains, De Moura et al. [216] found insufficient evidence from 4 studies (2 observational, 2 randomized crossover design intervention studies) to support a health claim for whole grains and CVD risk. However, when using the expanded definition and including studies (15 intervention and 14 observational) that considered intake of fiber-rich bran and germ as well as whole grain, the results did support the CVD health claim.

The mechanisms underlying the protective effect of whole grains on CVD risk include its effects on insulin sensitivity [214,217], blood pressure [218], lipids [217,219], and inflammation [214]. Despite their beneficial health effects, only 8% of Americans meet the recommendation to consume at least three servings per day of whole grains [220]. The evidence appears to be sufficient to increase policy efforts focused on decreasing refined grain intake and improving whole grain intake in the general population.

3.4. Alcohol

A large body of literature has shown a U- or J-shaped relationship between alcohol intake and CHD risk, suggesting that, moderate alcohol consumption, compared to no or heavy alcohol consumption, is associated with decreased risk in both men and women, in many populations. Based on this evidence, the AHA recommends that if alcoholic beverages are consumed, they should be limited to no more than 2 drinks per day for men and 1 drink per day for women, ideally with meals [20]. One drink is defined as 1–1/2 fluid ounces (fl oz) of 80-proof spirits (such as bourbon, Scotch, vodka, gin, etc.), 1 fl oz of 100-proof spirits, 4 fl oz of wine or 12 fl oz of beer. In a pooled analysis of 8 prospective studies from North America and Europe including 192,067 women and 74,919 men initially free of CVD, the relative risk of CHD was 0.58 (95% CI: 0.49–0.68) in women and 0.69 (95% CI: 0.62–0.76) in men with daily intake of 30 g/day, corresponding to about 2 to 3 drinks. Higher levels of alcohol consumption were not associated with any discernable additional protection in women and with only modest protection in men [221].

In contrast to the protective effects of regular moderate consumption, a meta-analysis of 12 studies showed that irregular heavy drinking occasions (>60 g of pure alcohol or 5 drinks per occasion at least monthly) were associated with 45% higher risk (RR=1.45, 95% CI: 1.24–1.70) for IHD events [222]. Another meta-analysis, [223] showed that regular heavy drinkers (>2 days a week) had a 25% lower risk (pooled RR=0.75, 95% CI: 0.64–0.89) for CHD compared to abstainers. On the other hand, irregular heavy drinkers (2 days a week or less) had a significantly higher risk for CHD (pooled RR=1.10, 95% CI: 1.03–1.17) compared to non-drinkers.

In 9 nationally representative samples of US adults, light (current use of 3 drinks/week) and moderate (current use of >3 to 7 drinks/week for women and >3 to 14 drinks/week for men) alcohol consumption were associated with 31% (95% CI: 0.59–0.82) and 38% (95% CI: 0.50–0.77) lower risk of CVD mortality. No protective effect was noted for heavy alcohol (current use of >7 drinks/week for women and >14 drinks/week for men) consumption (summary RR=0.95, 95% CI: 0.82–1.10) [224]. Similar estimates of a protective effect were also noted for CVD mortality in patients with a history of CVD events [225] and for fatal and total CHD among patients with type 2 diabetes [226]. In both studies, protective effects were noted for intakes between <6 to 25 g/day.

All types of alcoholic beverages appear to be protective, although there is evidence that wine is more protective than other forms. In 1992, the term “French paradox” was first coined by Renaud and de Lorgeril [227] to explain low CHD death rates despite high intake of dietary cholesterol and saturated fat. The authors suggested that this paradox may be attributable, in part, to high wine consumption. In a Mediterranean cohort, wine intake was associated with greater protection against CVD than beer, and beer intake was associated with a better effect than spirits [228]. Other studies have contested the view that wine is more protective, suggesting that wine preference is associated with other protective lifestyle behaviors [229,230].

Several physiological mechanisms have been identified to explain the complex relationship between alcohol and CHD. In a meta-analysis of experimental studies, 30 g of ethanol/day increased concentrations of HDL-C by 3.99 mg/dL (95% CI: 3.25–4.73), and apolipoprotein A I by 8.82 mg/dL (95% CI: 7.79–9.86). In addition, moderate alcohol intake was suggestive of a favorable, but not significant, thrombolytic profile [231]. Other studies have noted lower CRP concentrations [232,233] and higher insulin sensitivity [234] in moderate alcohol consumers. Proponents of red wine suggest that the polyphenolic compound, resveratrol, has cardioprotective effects which include its antioxidant and antiapoptotic effects [235].

The evidence that risk of CVD is lowest in individuals who drink moderately is strong. However, recommendations for alcohol consumption must be made with caution, as the risks of heavy consumption are serious, including addiction, accidents, liver disease, and some cancers. For this reason, the AHA does not recommend that non-drinkers start using alcohol or that consumers increase the amount they drink.

4. Dietary patterns

The traditional approach in nutritional epidemiology has been to study the effects of single nutrients or foods on health outcomes. However, individuals do not consume single nutrients but, rather, meals consisting of a variety of foods with complex combinations of nutrients that are likely to be interactive or synergistic [236,237]. Pattern analysis provides an additional dimension to examining the relationship between diet and disease risk and suggests a more comprehensive approach to disease prevention or treatment, because the focus is on the entire diet rather than on just one food or nutrient [238]. Dietary pattern analysis using score-based approaches (diet indexes) is an “a priori” approach that is based on published dietary recommendations. Diet scores summarize dietary behavior into a single score, are easy to interpret, and are hypothesis-generating. Two scores that have been used to examine risk of CVD include those for the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet.

Another approach is to define empirically derived dietary patterns in order to explore the underlying structure of dietary patterns in the population, without a pre-assessment of their importance or quality. The two most commonly used approaches include principal components analysis (PCA) and cluster analysis. PCA is a form of factor analysis that reduces data into patterns based on inter-correlations between data. Cluster analysis

maximally separates individuals into different groups using Euclidian distance among foods or food groups to identify those consumed together by the same subsets of individuals [239].

4.1. Mediterranean dietary pattern

Interest in the Mediterranean dietary pattern first started in the 1960s when Ancel Keys, in the Seven Countries Study, found that populations living near the Mediterranean Sea had the lowest incidence of chronic diseases and higher life expectancy compared to other parts of the world [240]. The Mediterranean dietary pattern has been described as (i) daily consumption of unrefined cereals and cereal products, vegetables (2–3 servings), fruit (4–6 servings), olive oil, dairy products (1 or 2 servings), and red or white wine (1–2 wine glasses); (ii) weekly consumption of potatoes (4–5 servings), fish (4–5 servings), olives, pulses, and nuts (more than 4 servings) and eggs and sweets (1–3 servings); (iii) monthly consumption of red meat and meat products (4–5 servings) [241].

Several indexes have been developed to describe the Mediterranean diet and these have been used frequently in relation to CHD events and CHD mortality [242]. A meta-analysis of 8 prospective studies, representing 514,816 participants and 33,576 deaths, showed that a two-point increase in the adherence score was associated with a 9% lower risk of CVD mortality (pooled RR=0.91, 95% CI: 0.87–0.95) [243]. Other studies have also consistently found an association between the Mediterranean diet and CVD. For example, in the ATTICA study, greater adherence to the diet score was associated with lower odds of CVD after 5-y of follow-up (OR per 1/55 points=0.94, P<0.0001) [244]. Importantly, significant inverse associations were also seen with serum lipids, blood pressure, inflammation, and coagulation markers related to CVD, documenting that the Mediterranean diet also has effects on mechanisms underlying the pathogenesis of CHD [245]. Applying the same score to a case–control study (CARDIO2000) in Greece, investigators found similar protective associations in the primary prevention of acute coronary syndrome. Each 10-unit increase in score was associated with 27% lower odds (95% CI: 0.66–0.89) of acute coronary syndrome [246]. The same group also demonstrated that greater adherence to the Mediterranean diet was effective in secondary prevention among patients. Adherence to the diet was associated with 12% lower likelihood of 2-y recurrent CVD events (OR=0.88, 95% CI: 0.80–0.98, P=0.04) [247]. Two prospective-cohort studies in Spain, [248,249], also showed that the Mediterranean diet reduced incident CHD events by 6–13% per point increase in the score.

While the use of Mediterranean diet scores in Mediterranean populations is well accepted, it is less clear how well they apply to non-Mediterranean populations. Fung et al. [250] created an alternate Mediterranean diet score that focuses on higher consumption of plant foods, including plant proteins, MUFA, and fish and lower consumption of animal products and saturated fat. Use of this alternative score in the NHS, showed that women in the top (vs. lowest) quintile of the score were at lower risk for CHD (RR=0.71, 95% CI: 0.62–0.82, P for trend<0.0001). When a traditional Mediterranean diet score was used with the NHANES III data, greater adherence was associated with better profile of cardioprotective lipids, glucose metabolism, inflammation, and coagulation measures [251]. Most recently, Rumawas et al. [252] developed another score that also accounts for overconsumption, arguing that this may be more appropriate for Western diets.

Convincing evidence for the protective role of the Mediterranean diet comes from the Lyon Diet Heart Study, a randomized secondary prevention trial comparing a Mediterranean diet with standard advice to follow a prudent Western-type diet on recurrence after a first MI. At 27-months, a reduction in the rate of coronary events of 76% was seen in the Mediterranean diet group and the decision was made to stop the trial [253]. A final report showed that the protective effect was maintained up to 4 y after the first infarction [254]. Despite the overwhelming evidence, some methodological limitations, including incomplete dietary assessment at baseline and conclusion, have been noted [255].

A second trial, The Heart Institute of Spokane Diet Intervention and Evaluation Trial (THIS-DIET), compared a Mediterranean diet with a conventional “heart-healthy” low-fat diet in relation to CVD events and survival after first MI. Both diets were low in saturated fat (7% kcal) and cholesterol (200 mg/day), but the Mediterranean diet also contained greater n-3 fatty acids (>0.75%kcal). Survival over 46 months did not differ between diet groups, but both intervention diets were associated with better odds of survival (OR=0.28, 95% CI: 0.13–0.63, P=0.002) compared to usual care [256]. Another trial, the Prevencion con Dieta Mediterranea Study is evaluating the effect of the Mediterranean diet in a primary prevention setting. This multicenter, randomized, controlled, 4-y clinical trial will compare Mediterranean diets with 1) virgin olive oil or 2) mixed nuts, with a standard low-fat diet on CVD events. In a preliminary analysis at the end of 3-months, both Mediterranean diets had favorable effects on plasma glucose, systolic blood pressure, and TC:HDL ratio. However, CRP decreased only in those following the diet with olive oil (–0.54 mg/L, 95% CI: –1.04 to –0.03 mg/L) [257].

Consistent epidemiological and clinical trial evidence supports the role of the Mediterranean diet in the prevention of CHD. However, the dramatic effects seen in the Lyon Diet Heart Study need to be replicated in primary prevention trials. Further, such studies must also be conducted in non-Mediterranean populations to determine if the favorable effects transfer to other groups. Finally, there are few data on the factors contributing to a greater adherence of the Mediterranean diet.

4.2. DASH dietary pattern

The Dietary Approaches to Stop Hypertension (DASH) diet is a success story in hypertension control. This pattern is rich in fruit, vegetables, and low-fat dairy products, includes whole grains, poultry, fish, and nuts, and limits saturated fat, red meat, sweets, and sugar-containing beverages. Compared with the control diet, the DASH diet provided lower total fat, saturated fat, and dietary cholesterol, and higher potassium, magnesium, calcium, fiber, and protein. In the initial randomized controlled trial, sodium was held constant across diets while alcohol was limited to two drinks per day [258]. After an 8-week intervention, 70% of participants (with untreated hypertension at baseline) following the DASH diet, compared with 45% increasing only fruit and vegetables, and 23% on the control diet achieved normal blood pressure [259].

Because hypertension is a CVD risk factor, several prospective cohort studies have examined associations between adherence to a DASH dietary pattern and incident CVD events. In the NHS, 14% lower risk of CHD was seen in the highest (vs. lowest) quintile (95% CI: 0.67–

0.85, P for trend<0.001) of DASH diet score [260] A cross-sectional analysis in a subgroup showed that a higher DASH score, indicating greater adherence, was also significantly associated with lower plasma CRP ($P=0.008$ for trend) and interleukin-6 ($P=0.04$ for trend). In the Swedish mammography cohort, after 7-y of follow-up, women with the greatest adherence to the DASH diet had 37% lower risk of heart failure (95% CI: 0.48–0.81, P for trend<0.001) [261]. Similarly, Swedish men, aged 45–79 y, in the highest (vs. lowest) quartile of the DASH score had 22% fewer heart failure events (95% CI: 5%–35%, P for trend=0.006) [262].

The Iowa Women's Health Study also found that women with the highest adherence to the DASH diet had 23% lower risk of CHD mortality (95% CI: 0.52–0.86, P for trend=0.01), but this became non-significant after adjustment for other risk factors [263]. Similarly, among adults with hypertension in the NHANES III follow-up study, a DASH-like diet was not significantly associated with mortality from CVD [264].

In addition to its effects on blood pressure and incident CHD, the DASH diet appears to have beneficial effects on several CVD risk factors, including TC, LDL-C [265], inflammation [260], and homocysteine [266]. As a whole, the evidence for the protective role of the DASH dietary pattern in prevention of CVD is strong. It is noteworthy that the DASH dietary pattern is consistent with current U.S. dietary guidelines for CVD risk reduction. This diet should be especially promoted among populations with a high risk for hypertension.

4.3. Other dietary patterns

4.3.1. Hypothesis driven dietary patterns—The Healthy Eating Index (HEI) measures how well American diets conform to the major recommendations of the Dietary Guidelines for Americans and the original Food Guide Pyramid. While the HEI was associated with a 28% lower risk of CVD (RR=0.72, 95% CI: 0.60–0.88; $P<0.001$) in the HPFS [267], no significant effect was found in the NHS (RR=0.86, 95% CI: 0.72–1.03) [268]. However, trends were in the expected direction and approached significance (P for trend=0.085). On the other hand, Kant et al. [269] found that a diet quality score based on the sum of the number of foods recommended by current dietary guidelines (Recommended Food Score, RFS) was strongly associated with lower risk of CHD mortality (RR=0.67, 95% CI: 0.47–0.95). A modified version of the RFS was evaluated by Michels and Wolk [270] in the Swedish Mammography cohort. This RFS excluded juices, due to their high sugar content, potatoes due to their high glycemic index, and chicken, because poultry was not considered a health-promoting food by itself but rather because it may be substituted for red meat and red meat consumption. In addition to the RFS, the authors extended the concept to non-recommended foods to build the non-recommended food score (NRFS). In this cohort, the RFS, but not the NRFS, strongly predicted CHD mortality (HR=0.47, 95% CI: 0.33–0.68, P for trend<0.0001). In another study, both RFS (HR=1.27, 95% CI: 1.05–1.54) and NRFS (HR=0.71, 95% CI: 0.54–0.93) showed statistically significant associations with CVD mortality [271].

The Diet Quality Index (DQI) is a measure of adherence to 8 food group and nutrient-based recommendations from the Committee on Diet and Health of the National Research Council

Food and Nutrition Board [272]. Seymour et al. [273] found that the DQI was associated with circulatory-disease mortality but only in women (medium-low quality diet vs. highest-quality diet RR=1.86, 95% CI: 1.19–2.89). The lack of association among men may partly be due to the fact that national dietary guidance has changed since the development of the DQI. Similarly, Osler and others found that a healthy diet index, a pattern rich in whole-grain breads, fruit, and vegetables, was not associated with CHD [274] or CVD mortality [275] after adjustment for confounding due to CVD risk factors. The lack of association between diet scores and CHD may reflect some of the limitations of pattern analysis using this approach. For example, some diet scores dichotomize components thus limiting the full range of amounts of foods consumed. Scores that include a range of points for each component do not consider variability in amounts at the extremes. The value of the score may depend on the amount of subjectivity introduced in the interpretation of the guidelines that form the basis of the score. Finally, the summation of equally weighted dietary component scores implies that each component is equally important and additively related to disease prevention [276].

In addition to diet scores based on diet quality, scores that reflect adherence to specific recommendations have been developed. Halton et al. [277] created the “low-carbohydrate-diet score” to classify women in the NHS according to the relative intakes of fat, protein, and carbohydrate. During 20-y of follow-up, the relative risk of CHD comparing highest and lowest deciles of the “low-carbohydrate-diet score” was 0.94 (95% CI: 0.74–1.19, P for trend=0.19). When the score was adjusted to focus on vegetable sources of protein and fat, significance improved (RR = 0.70, 95% CI: 0.56–0.88, P for trend=0.002). Meanwhile, Stampfer et al. [278] showed that a diet score reflecting a diet low in TFA and glycemic load, high in cereal fiber, marine omega-3 fatty acids, and folate with a high ratio of PUFA: SFA strongly predicted the risk of CHD. In women with 3 low-risk factors (diet score in the upper 2 quintiles, non-smoking, and moderate to vigorous exercise 30 min/day), the relative risk for coronary events was 0.43 (95% CI: 0.33–0.55).

A case-control study in Norwegian men and postmenopausal women (aged 45–75 y) showed that a plant-centered dietary pattern was associated with a reduced risk of first MI. Of the 39 food groups that formed that healthy dietary pattern score, the risk of MI was significantly higher per SD of butter and margarine (OR=1.66, 95% CI: 1.12–2.46), and lower per SD of tomatoes (OR=0.53, 95% CI: 0.35–0.79), high-fat fish (OR=0.57, 95% CI: 0.38–0.86), wine (OR=0.58, 95% CI: 0.41–0.83), salad (OR=0.59, 95% CI: 0.40–0.87), whole-grain breakfast cereal (OR=0.64, 95% CI: 0.45–0.90), cruciferous vegetables (OR=0.66, 95% CI: 0.47–0.93), and non-hydrogenated vegetable oil (OR=0.68, 95% CI: 0.49–0.95) [279]. In addition to this healthy dietary pattern, the Southern European Atlantic Diet (SEAD), the traditional diet of northern Portugal and Galicia, was also associated with lower odds of nonfatal acute MI (OR=0.90, 95% CI: 0.85–0.96). The SEAD differs from the Mediterranean diet by higher consumption of red meat, pork, and fish, and lower consumption of olive oil, nuts and fruits. However, like the Mediterranean diet, the SEAD is characterized by high intake of vegetables, whole foods and wine consumption during meals [280].

In addition to the literature on CHD endpoints, a considerable amount of research has focused on the biological mechanisms that lead to the development of CHD. Both the HEI and the alternate Mediterranean diet index were associated with inflammation and markers of endothelial dysfunction [281]. Likewise, a Mediterranean diet score in a Greek population was inversely associated with systolic blood pressure, CRP, fibrinogen, total antioxidant capacity, total serum cholesterol, and body mass index (BMI) ($P < 0.05$) [245]. In the Multi-Ethnic Study of Atherosclerosis, Nettleton et al. [282] created a Comprehensive Healthy Dietary Pattern by summing weighted categorical ranks of 36 narrowly defined food groups. The Comprehensive Healthy Dietary Pattern was associated with lower urinary albumin:creatinine ratio, common carotid IMT, measures of adiposity, and inflammatory markers, triacylglycerol, and insulin concentrations. However, this pattern was not associated with blood pressure, LDL, coronary artery calcification, internal carotid IMT, or the ankle-brachial index. Most recently, we developed a diet and lifestyle score based on the AHA 2006 Diet and Lifestyle Recommendations. Greater adherence to the recommendations was positively associated with plasma HDL cholesterol ($P = 0.001$), inversely with serum insulin ($P = 0.0003$) and CRP ($P = 0.02$) concentrations, waist circumference ($P < 0.0001$), and 10-y risk of CHD score ($P = 0.01$ in women). In addition, among those with BMI < 25 , the score was inversely associated with serum glucose concentration ($P = 0.01$) [283].

4.3.2. Empirically derived dietary patterns—A growing number of observational studies are examining associations between empirically dietary patterns and CHD, primarily using principal components or cluster analysis. One of the first studies to relate cluster defined dietary patterns to CVD is the Seven Countries study [284]. They found that participants in a dietary cluster characterized by high alcohol intake had the highest mortality from CHD or stroke (14.4 deaths per 100 in 15 y) and that those in a cluster with high intake of PUFA had the lowest mortality (5.4 deaths per 100 in 15 y). However, these results were only adjusted for age and geographical area and residual confounding remains a strong possibility. In the Whitehall II study, 4 clusters were identified —unhealthy, characterized by white bread, processed meat, French fries, and full-cream milk; sweet, characterized by white bread, biscuits, cakes, processed meat, and high-fat dairy products; Mediterranean-like, defined by fruit, vegetables, rice, pasta, and wine; Healthy, with high intake of fruit, vegetables, whole-meal bread, and low-fat dairy, and low intake of alcohol. Compared to the unhealthy cluster, the healthy cluster was associated with reduced risk of fatal CHD and non-fatal MI by 29% (95% CI: 0.51–0.98) after adjustment for confounding due to age, sex, ethnicity, dietary energy misreporting, social position, smoking status, and leisure-time physical activity. After further adjustment for obesity, blood pressure, blood pressure medication, and lipids, the association was attenuated, but approached significance (P for trend = 0.07) [285]. It is interesting to note that the Mediterranean-like cluster was characterized by high intake of butter, which is not in line with the traditional Mediterranean diet. Further, attributes of the Mediterranean-style diet were split between this and the Healthy cluster [286]. The Framingham Nutrition studies identified 5 distinct clusters — heart healthy, light eating, wine and moderate eating, high fat, and empty calorie clusters. Compared to the heart healthy cluster, participants in the empty calorie cluster had more than twice the odds of carotid atherosclerosis (OR = 2.28, 95% CI: 1.12–4.62, $P < 0.05$) [287].

Similarly, women who consumed a heart-healthy diet and who had never smoked had more than 80% lower odds for subclinical heart disease compared with smokers whose diets were less-heart healthy (OR=0.17, 95% CI: 0.07–0.36, P=0.0001) [288].

Factor analysis has been used in several large-scale epidemiological studies to derive dietary patterns. Most studies that use this approach have focused on 2 major patterns — the “Prudent” pattern, generally characterized by vegetables, fruit, legumes, fish, poultry, and whole grains, and the “Western” pattern by red meat, processed meat, refined grains, French fries, and sweets/desserts. In both the NHS [238] and the HPFS [278], the prudent pattern was associated with reduced risk for CHD (Q5 vs. Q1 NHS RR=0.76, 95% CI: 0.60–0.98, P for trend=0.03; Q5 vs. Q1 HPFS RR=0.70, 95% CI: 0.56–0.86, P for trend=0.0009) while the Western pattern was associated with significantly increased risk (Q5 vs. Q1 NHS RR=1.46, 95% CI: 1.07–1.99, P for trend=0.02; Q5 vs. Q1 HPFS RR=1.64, 95% CI: 1.24–2.17, P for trend<0.0001). In the Nurses cohort, [289] the prudent diet was also associated with 28% lower CVD mortality (95% CI: 13–40%). Similar results were shown in the World Health Organization-Monitoring Trends and Determinants in Cardiovascular Disease study in Denmark, where the prudent pattern was associated with lower CVD mortality (RR for 1 SD increase=0.63, 95% CI: 0.44–0.90) in women, but not men [275]. No associations were noted for the Western pattern [274].

Principal components analysis has also been applied to diets of ethnic populations. Such studies have typically identified a “traditional” pattern, in addition to healthy and Western type patterns. For example, in the Ohsaki National Health Insurance Cohort study, Shimazu et al. [290] found that a Japanese pattern which loaded heavily on soybean products, fish, seaweeds, vegetables, fruit, and green tea was not associated with mortality from CHD or stroke (HR=0.82, 95% CI: 0.82–1.29, P for trend=0.29). On the other hand, the animal food pattern, defined by high intakes of animal-derived products, coffee, and alcoholic beverages, showed a significant trend toward higher CHD mortality risk (HR=1.50, 95% CI: 0.95–2.37, P for trend= 0.05). The lack of protective association between the traditional Japanese pattern and CHD mortality may be due to the fact that this pattern was related to higher sodium consumption. Similarly, in the Korean National Health and Nutrition Survey, none of the three patterns identified (traditional, western, drinker) was associated with hypertension. Unlike findings from Western populations, the vegetable rich traditional dietary pattern did not show a protective effect against hypertension in Korean males. The Korean dietary practice of consuming salted vegetables may have played a role in these findings [291]. Likewise, in a population of Costa Rican adults, a vegetable pattern was not associated with lower odds of MI (Q5 vs. Q1 OR=0.92, 95% CI: 0.57–1.50, P for trend=0.92). However, a staple pattern characterized by use of palm oil for cooking, and intake of refined grains, legumes, coffee, added sugar, and red meat was associated with nearly a 3.5 times greater odds of MI (Q5 vs. Q1 OR=3.53, 95% CI: 1.98–6.31, P for trend=0.0002) [292]. In the Multi-Ethnic Study of Atherosclerosis [293] a healthy pattern featuring whole grains and fruit was associated with lower risk of CVD (Q5 vs. Q1 HR=0.54, 95% CI: 0.33–0.91) while an unhealthy pattern high in fats and processed meat, was associated with a greater risk (Q5 vs. Q1 HR=1.82, 95% CI: 0.99–3.35). Most notably, the association between CVD and the healthy pattern remained strong even after adjustment for waist circumference, blood pressure, lipids, or inflammatory markers. Consistent with findings using a Mediterranean

diet score, two studies, one in a Greek population and the other in an Australian population, found that consumption of empirically defined dietary patterns characterized by Mediterranean type foods were associated with lower CVD mortality [294] and 5-y incidence of CVD [295].

In support of their likely causal importance to CHD outcomes, patterns identified by cluster or factor analysis have also been shown to be associated with numerous CHD risk factors, including better blood lipid profile [296,297], lower CRP [297,298], and lower homocysteine [298] concentrations. On the other hand, less healthy Western, meat, or sweets patterns have been associated with poor lipid profile [299–301], higher blood glucose [299], and higher glycated hemoglobin [302].

Most recently, reduced rank regression (RRR) has emerged as a unique way of identifying dietary patterns. By applying RRR to food groups and choosing biochemical markers for CHD as response variables, linear combinations of dietary intake variables that best explain the variance in the response variables is attained [303]. However, this method does not describe the actual reported behavioral dietary patterns in the population [239]. Using coronary artery disease (CAD) biomarkers as response variables, a dietary pattern was constructed with high meat, margarine, poultry, and sauce, and low wine, vegetables, and whole grain cereals. After adjustment, this dietary pattern was, not surprisingly, strongly associated with the risk of CAD (Q5 vs. Q1 RR=12.3, 95% CI: 4.9–30.9, P for trend<0.0001) [303]. Similarly, in the Whitehall II study, a pattern of foods associated with blood lipids was able to predict CHD risk (Q4 vs. Q1 HR=1.57, 95% CI: 1.08–2.27) after adjustment for confounders [304]. Patterns derived by RRR have also been shown to be associated with sub-clinical markers of CVD. In the Multi-Ethnic Study of Atherosclerosis, a dietary pattern based on variations in CRP, interleukin-6, homocysteine, and fibrinogen concentrations was associated with both coronary calcification (Agatston score>0: OR (95% CI) for quartile 5 compared with quartile 1=1.34 (1.05, 1.71)) and common carotid IMT (> 1.0 mm: OR (95% CI) for quartile 5 compared with quartile 1=1.33 (0.99, 1.79)) [305]. In the Insulin Resistance Atherosclerosis Study, a pattern derived in association with pro-inflammatory and pro-thrombotic marker was associated with rate of coronary artery atherosclerosis progression, independent of traditional CVD risk factors [306].

These RRR analyses are useful for hypothesis generation and confirmation of other observations, but because the patterns are identified in relation to intermediate markers rather than actual behavior, it is not surprising that they relate to the outcomes already predicted by the intermediate factors, nor is it clear to what extent the patterns themselves would be predictive of events in other population samples. More work is needed to clarify the utility of this approach. However, the fact that they identify the same foods as those identified by other methods to predict CHD risk is a supportive contribution to the body of evidence.

5. Concluding remarks

CVD continues to remain a significant problem in developed countries and is a growing health concern worldwide. Although death rates from CVD have decreased in many

countries, due to advances in the field of medicine, the prevalence of CVD risk factors continues to increase. Diet is a centrally important modifiable risk factor in the prevention of CVD. Early efforts focused on identifying protective nutrients, like vitamin E, folic acid, and β -carotene, have proven to be disappointing when tested in clinical trials. Rather, the evidence now suggests that a complicated set of many nutrients interact to influence CVD risk. Therefore, it is important to focus on whole foods and dietary patterns to impact on CVD risk reduction. This paradigm shift in our thinking from nutrients to dietary patterns has also been reflected in the Dietary Guidelines. While the first Dietary Goals released in 1977 focused on reduction of specific nutrients such as fat and cholesterol, the recently released 2010 Dietary Guidelines consider diet as a whole and integrate nutrient and energy recommendations into a healthy pattern that is nutrient dense but energy balanced. Much has been learned about the importance of healthy diet in the prevention of CHD. As we continue to identify the roles of nutrients and other compounds in foods in the complex pathways that contribute to CHD risk or protection, the field is increasing its focus on genetic modulation of these pathways so that better guidance may be developed for subsets of the population at differential risk.

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Table 1
Summary of meta-analyses and pooled analyses of the effect of nutrients, foods, and dietary patterns on CHD outcomes.

Study	Study design	Exposure	Outcome	Results
<i>Dietary fats</i>				
Skeaff and Miller, 2009 [18]	Prospective cohort studies 280,000 participants	Total fat (highest vs. lowest fat intakes) 5% increase in total fat intake	CHD events CHD death	Total fat (highest vs. lowest): CHD events: RR=0.93 (95% CI: 0.84–1.03) CHD death: RR=0.94 (95% CI: 0.74–1.18) Per 5% increase in total fat intake: CHD events: RR=1.02 (95% CI: 0.98–1.05) CHD death: RR=1.06 (95% CI: 0.88–1.28)
Siri-Tarino et al. 2010 [24]	16 prospective cohort studies 347,747 participants 5–23 y follow-up	Saturated fat	CHD	Pooled RR for extreme quantities: RR=1.07 (95% CI: 0.96–1.19)
Jakobsen et al. 2009 [27]	11 prospective cohort studies 344,696 participants 4–10 y follow-up	5% lower energy intake from saturated fat and a concomitant higher energy from i) PUFA ii) MUFA	CHD events CHD death	i) PUFA replacing SFA CHD events: HR=0.87 (95% CI: 0.77–0.97) CHD death: HR=0.74 (95% CI: 0.61–0.89) ii) MUFA replacing SFA CHD events: HR=1.19, 95% CI: 1.00–1.42 CHD death: HR=1.01 (95% CI: 0.73–1.41)
Mozaffarian et al. 2010 [28]	8 RCT 13,614 participants	PUFA for SFA	CHD	(RR=0.81, 95% CI: 0.70–0.95, P=0.008) for 10% reduced CHD risk (RR=0.90, 95% CI: 0.83–0.97) for each 5% energy from PUFA rather than SFA
Mozaffarian et al. 2006 [39]	4 prospective studies: 139,836 participants 3 retrospective case-control studies: 2430 participants	Isocaloric substitution of 2% of total energy intake of carbohydrates with TFA	CHD	4 prospective studies: RR=1.23 (95% CI: 1.11–1.37) 4 prospective studies+3 retrospective case-control studies: RR=1.29 (95% CI: 1.11–1.49)
Mozaffarian and Clarke, 2009 [42]	4 prospective cohort studies 139,836 participants	2% higher energy from <i>trans</i> fatty acid intake	CHD events	RR=1.23 (95% CI: 1.11–1.37)
Yezebe and Lievre, 2004 [58]	10 RCT 14,727 patients	n-3 fatty acids	Fatal and non-fatal MI	Death due to MI: RR=0.76 (95% CI: 0.66–0.88) Non-fatal MI: RR=1.03 (95% CI: 0.87–1.19)
Bucher et al. 2002 [59]	11 RCT Intervention group: 7951 patients Control group: 7855 patients	Dietary or non-dietary n-3 PUFA vs. control diets or placebo	Fatal and non-fatal MI	Death due to MI: RR=0.7 (95% CI: 0.6–0.8) Non-fatal MI: RR=0.8 (95% CI: 0.5–1.2)
Marik and Varon, 2009 [61]	11 RCT 39,044 patients	Dietary EPA/DHA supplements vs. placebo Average dose of EPA/DHA=1.8±1.2 g/day Mean duration of follow-up=2.2±1.2 y	CVD death Sudden cardiac death Non-fatal CVD events	CVD deaths: OR=0.87 (95% CI: 0.79–0.95) Sudden cardiac death: OR=0.87 (95% CI: 0.76–0.99) Nonfatal CVD events: OR=0.92 (95% CI: 0.85–0.99)
Brouwer et al. 2004 [69]	5 prospective cohort studies	Intake of ALA	Mortality from heart disease	RR=0.79 (95% CI: 0.60–1.04)
<i>B vitamins</i>				
Bazzano et al. 2006 [91]	12 RCT 16,958 participants	Folic acid supplementation vs. placebo/usual care	CVD CHD	RR=0.95 (95% CI: 0.88–1.03) for CVD RR=1.04 (95% CI: 0.92–1.17) for CHD

Study	Study design	Exposure	Outcome	Results
<i>Carotenoids</i>				
Knekt et al. 2004 [108]	9 prospective cohort studies	Minimum duration of 6 months Energy adjusted dietary intakes of α-carotene β-carotene Lutein Lycopene β-cryptoxanthin Total carotene	CHD incidence CHD mortality	Highest vs. lowest energy-adjusted dietary intake quintile α-carotene (Median intake 1508 µg/day vs. 100 µg/day) RR=0.90, 95% CI:0.77–1.04, P-trend=0.22 β-carotene (Median intake 5231 µg/day vs. 662 µg/day) RR=0.92, 95% CI: 0.79–1.06, P-trend=0.29 Lutein (Median intake 6029 µg/day vs. 739 µg/day) RR=0.89, 95% CI: 0.75–1.04, P-trend=0.03 Lycopene (Median intake 11,015 µg/day vs. 43 µg/day) RR=0.99, 95% CI: 0.85–1.14, P-trend=0.42 β-cryptoxanthin (Median intake 212 µg/day vs. 10 µg/day) RR=0.94, 95% CI: 0.79–1.12, P-trend=0.48 Total carotene (Median intake 1375 µg RE vs. 221 µg RE) RR=0.91, 95% CI: 0.78–1.06, P-trend=0.24 Highest vs. lowest energy-adjusted dietary+supplemental intake quintile for CHD incidence β-carotene: RR=0.88, 95% CI: 0.71–1.10, P-trend=0.44 Total carotene: RR=0.88, 95% CI: 0.68–1.16, P-trend=0.50 Highest vs. lowest energy-adjusted dietary+supplemental intake quintile for CHD mortality β-carotene: RR=0.84, 95% CI: 0.65–1.07, P-trend=0.34 Total carotene: RR=0.96, 95% CI: 0.73–1.25, P-trend=0.81
Vivekananthan et al. 2003 [118]	6 RCT Dose: 15–50 mg Follow-up=1.4–12.0 y	β-carotene treatment vs. placebo	CVD death	β-carotene treatment vs. placebo: 3.4 vs. 3.1% OR=1.1, 95% CI: 1.03–1.17, P=0.003
<i>Vitamin E</i>				
Vivekananthan et al. 2003 [118]	6 RCT Dose: 50–800 IU Follow-up=1.4–12.0 y	Vitamin E vs. placebo	CVD death	Vitamin E treatment vs. placebo: 6.0 vs. 6.0%, OR=1.0, 95% CI: 0.94–1.06, P=0.94
Eidelman et al. 2004 [137]	7 RCT Dose: 30–400 mg	Synthetic or natural vitamin E	CVD death Nonfatal MI	CVD death: OR=0.98, 95% CI: 0.94–1.03 Nonfatal MI: OR=1.00, 95% CI: 0.92–1.09
Shekelle et al. 2004 [138]	5 RCT	Vitamin E alone vs. placebo Vitamin E in combination vs. placebo	CVD death Fatal MI Non-fatal MI	CVD death Vitamin E alone vs. placebo (5 RCT): RR=0.97, 95% CI, 0.80 to 1.19 Vitamin E in combination vs. placebo (4 RCT): RR=1.03, 95% CI, 0.81 to 1.32 Fatal MI Vitamin E alone vs. placebo (5 RCT): RR=0.97, 95% CI: 0.74 to 1.27 Vitamin E in combination vs. placebo (4 RCT): RR=1.02, 95% CI: 0.77 to 1.37 Non-fatal MI Vitamin E alone vs. placebo (5 RCT): RR=0.72, 95% CI, 0.51 to 1.02 Vitamin E in combination vs. placebo (4 RCT): RR=0.99, 95% CI, 0.89 to 1.10
Knekt et al. 2004 [108]	9 cohort studies	Dietary vitamin E	CHD incidence CHD mortality	Energy-adjusted dietary vitamin E (Highest vs. lowest quintile) CHD incidence: RR=0.84, 95% CI: 0.71–1.00, P-trend=0.17

Study	Study design	Exposure	Outcome	Results
<i>Vitamin C</i>				
Knekt et al. 2004 [108]	9 cohort studies	Supplemental vitamin E (250 mg/day vs. none) Vitamin E (dietary+supplemental)	CHD incidence CHD mortality	Supplemental vitamin E (250 mg/day vs. none) CHD incidence: RR=0.94, 95% CI: 0.81–1.09, P-trend=0.52 CHD mortality: RR=0.98, 95% CI: 0.64–1.48, P-trend=1.00 Energy-adjusted Vitamin E (dietary+supplemental) (Highest vs. lowest quintile) CHD incidence: RR=0.95, 95% CI: 0.81–1.12, P-trend=0.85 CHD mortality: RR=1.01, 95% CI: 0.70–1.45, P-trend=0.89
Ye and Song, 2008 [144]	15 cohort studies 374,488 participants Median follow-up ~10 y	Dietary vitamin C Supplemental vitamin C (700 mg/day vs. none) Vitamin C (dietary+supplemental)	CHD incidence CHD mortality	Energy-adjusted dietary vitamin C (Highest vs. lowest quintile) CHD incidence: RR=1.23, 95% CI: 1.04–1.45, P-trend=0.07 Supplemental vitamin C (700 mg/day vs. none) CHD incidence: RR=0.75, 95% CI: 0.60–0.93, P-trend <0.001 CHD mortality: RR=0.76, 95% CI: 0.58–0.99, P-trend=0.17 Energy-adjusted Vitamin E (dietary+supplemental) (Highest vs. lowest quintile) CHD incidence: RR=0.88, 95% CI: 0.75–1.03, P-trend=0.007 CHD mortality: RR=1.08, 95% CI: 0.81–1.44, P-trend=0.61
Parker et al. 2010 [157]	16 studies	Vitamin C intake	CHD risk	Highest vs. lowest tertile of baseline vitamin C intake RR=0.84 (95% CI, 0.73–0.95) For each 30 mg/day increase in vitamin C, the overall RR for CHD=1.01 (95% CI, 0.99–1.02)
<i>Vitamin D</i>				
Dauchet et al. 2006 [174]	9 studies 91,379 men 129,701 women	Fruit and vegetable intake	CHD events	For each additional portion, RR=0.96 (95% CI: 0.93–0.99)
He et al. 2007 [175]	12 studies 278, 459 individuals 11 y	Fruit and vegetable intake (servings/day)	CHD events	3–5 servings/day vs. <3 servings/day, RR=0.93 (95% CI: 0.86–1.00) >5 servings/day vs. <3 servings/day, RR=0.83 (95% CI: 0.77–0.89)
<i>Fish</i>				
He et al. 2004 [190]	11 cohort studies 222,364 individuals 11.8 y	Fish	CHD mortality	2–4 times/week vs. never or <once/month, RR=0.77 (95% CI: 0.66–0.89) 5 times/week vs. never or <once/month, RR=0.62 (95% CI: 0.46–0.82)
Whelton et al. 2004 [191]	19 studies (14 cohort and 5 case-control studies)	Fish	Fatal CHD Total CHD	RR for those consuming any amount of fish vs. those consuming little to no fish RR=0.83, 95% CI: 0.7Low level of fish consumption vs. no fish consumption: i) CHD mortality risk reduction=17% (95% CI: 9% to 25%). ii) Non-fatal MI risk reduction=27% (95% CI: 21% to 34%) Each additional fish serving per week reduces i) CHD mortality risk incrementally by 3.9% (95% CI: 1.1% to 6.6%) ii) Non-fatal MI risk incrementally by 0.8% (95% CI: –1.2% to 2.8%) 6–0.90

Study	Study design	Exposure	Outcome	Results
Konig et al. 2005 [192]	7 observational studies Individuals with no pre-existing CHD	Fish (servings/week)	CHD mortality Non-fatal MI	RR=0.86, 95% CI: 0.81–0.92
<i>Whole grains</i>				
Mellen et al. 2008 [210]	7 prospective cohort studies	Whole grain intake (servings/day)	CVD events	2.5 servings/day vs. 0.2 servings/day, OR=0.79 (95% CI: 0.73–0.85)
Anderson, 2003 [211]	13 studies	Whole grain intake	CHD events	Highest vs. lowest intakes, RR=0.71 (95% CI: 0.48–0.94)
<i>Alcohol</i>				
Hvidtfeldt et al. 2010 [221]	8 studies 192,067 women 74,919 men	Alcohol (g/day)	CHD	<p>Women</p> <p>0.1–4.9 g/day vs. none: RR=0.78 (95% CI: 0.69–0.90)</p> <p>5.0–14.9 g/day vs. none: RR=0.68 (95% CI: 0.59–0.80)</p> <p>15.0–29.9 g/day vs. none: RR=0.52 (95% CI: 0.40–0.67)</p> <p>30.0–59.9 g/day vs. none: RR=0.53 (95% CI: 0.39–0.70)</p> <p>60 g/day vs. none: RR=0.93 (95% CI: 0.55–1.58)</p> <p>P-trend<0.0001</p> <p>Men</p> <p>0.1–4.9 g/day vs. none: RR=0.96 (95% CI: 0.86–1.08)</p> <p>5.0–14.9 g/day vs. none: RR=0.83 (95% CI: 0.74–0.92)</p> <p>15.0–29.9 g/day vs. none: RR=0.72 (95% CI: 0.64–0.82)</p> <p>30.0–59.9 g/day vs. none: RR=0.66 (95% CI: 0.57–0.76)</p> <p>60–89.9 g/day vs. none: RR=0.58 (95% CI: 0.44–0.77)</p> <p>90 g/day vs. none: RR=0.77 (95% CI: 0.53–1.13)</p> <p>P-trend<0.0001</p>
Roerecke and Rehm. 2010 [222]	12 studies	Irregular heavy drinking occasions (>60 g of pure alcohol or 5 drinks per occasion at least monthly)	IHD events	Irregular heavy drinking occasions vs. regular moderate drinking RR=1.45, 95% CI: 1.24–1.70
Bagnardi et al. 2008 [223]	6 studies (4 cohort and 2 case-control)	Regular heavy drinkers (>2 days a week)	CHD	Regular heavy drinkers vs. abstainers: pooled RR=0.75, 95% CI: 0.64–0.89 Heavy irregular or binge drinkers vs. abstainers: pooled RR=1.10, 95% CI: 1.03–1.17
Mukamal et al. 2010 [224]	9 iterations of the National Health Interview Survey, an annual survey of a nationally representative sample of U.S. adults between 1987 and 2000g	Usual volume Frequency Quantity of alcohol consumption Binge drinking	CVD mortality	Lifetime infrequent drinkers vs. abstainers: RR=0.95 (95% CI: 0.88–1.02) Former drinkers vs. abstainers: RR=1.02 (95% CI: 0.94–1.11) Light drinkers vs. abstainers: RR=0.69 (95% CI: 0.59–0.82) Moderate drinkers vs. abstainers: RR=0.62 (95% CI: 0.50–0.77) Moderate drinkers vs. abstainers: RR=0.95 (95% CI: 0.82–1.10)
Costanzo et al. 2010 [225]	8 prospective studies 16,351 patients with a history of CVD	Alcohol (g/day)	CVD mortality	Significant maximal protection on CVD mortality (average 22%) at approximately 26 g/day.
Koppes et al. 2006 [226]	Type-2 diabetes patients	Alcohol (g/day)	CHD mortality CHD incidence	<p>CHD mortality</p> <p><6 g/day vs. none: RR=0.64, 95% CI: 0.49–0.82</p> <p>6 to <18 g/day vs. none: RR=0.75, 95% CI: 0.28–1.98</p> <p>18 g/day vs. none: RR=0.34, 95% CI: 0.22–0.53</p> <p>CHD incidence</p> <p><6 g/day vs. none: RR=0.75, 95% CI: 0.61–0.93</p> <p>6 to <18 g/day vs. none: RR=0.57, 95% CI: 0.39–0.83</p> <p>18 g/day vs. none: RR=0.59, 95% CI: 0.41–0.81</p>

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Study	Study design	Exposure	Outcome	Results
<i>Dietary patterns</i> Sofi et al. 2008 [243]	4 prospective studies	Mediterranean diet score	CHD mortality	Risk of mortality from CVD associated with two point increase in adherence score for Mediterranean diet RR=0.91 (95% CI: 0.87-0.95)