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Review

Dietary Factors and the Risk of Coronary Heart Disease

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ABSTRACT: Coronary heart disease (CHD) is an important cause of morbidity and mortality in the US. A variety of dietary components and patterns have been suggested to decrease the risk of CHD. The current review examines the epidemiological evidence lending support to beneficial effects of dietary factors on CHD risk. The current literature strongly supports the notion that Mediterranean diet, omega-3 (n-3) fatty acids, flavonoids and polyphenols, dietary fiber, and whole grains confer protection against CHD. Overall, there is no evidence that vitamin intake reduces the risk of incident CHD and data on the role of garlic in CHD prevention are equivocal.

Key words: Coronary heart disease; Epidemiology; Diet; Omega-3 fatty acids; Mediterranean diet; Flavonoids

Coronary heart disease (CHD) is the leading cause of deaths in the United States [1]. About 785,000 new acute coronary events and 470,000 recurrent coronary events are estimated to have occurred in 2010[1]. Although a variety of pharmacological and invasive interventions are available to manage this problem, primary prevention remains a cost-effective solution [2]. Several dietary interventions have been shown to decrease the risk of CHD. This review examines the role of dietary factors including Mediterranean diet; fish and n-3 fatty acids; flavonoids and polyphenols; fiber and whole grain; vitamins; and garlic in the prevention of CHD.

Mediterranean diet and CHD

Mediterranean style diet is a collection of traditional dietary habits in countries adjoining the Mediterranean Sea. Its main constituents include higher amounts of fruit and vegetables, legumes, complex carbohydrates, low to moderate fish and poultry consumption; use of olive oil as main source of dietary fats, relatively low consumption of red meat, and low to moderate red wine consumption during meals. The role of some of these individual dietary constituents is presented in other sections of this review. Epidemiological evidence suggests that Mediterranean diet is associated with reduced risk of various chronic diseases, including Alzheimer's disease[3], mild cognitive impairment[4], stroke[5], and CHD[5].

The Seven Countries Study[6] was one of the earliest studies that aroused interest in this type of diet and chronic diseases. This study showed that a Mediterranean dietary pattern, typical of the Greek island of Crete, was associated with very low rates of CHD and various cancers. The Lyon Diet Heart Study randomized 605 subjects with history of myocardial infarction (MI) to either Mediterranean diet [more bread, more root vegetables, more fish, less meat (beef, lamb, and pork to be replaced by poultry), and canola oil based margarine] or prudent diet recommended by the American Heart Association[7]. After a mean follow up of 27 months, there were 16 cardiac deaths in the prudent diet group, vs. 3 in the Mediterranean diet group. The corresponding numbers for non-fatal MI were 17 and 5 respectively. There was a 73% risk reduction in non-fatal MI and cardiac mortality (RR=0.27, 95% CI 0.12-0.59, p

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value=0.001) after accounting for major confounding factors. Similarly, overall mortality was reduced by 70% (RR= 0.30, 95% CI 0.11-0.82) in the intervention group.

In another randomized trial, 1,000 patients with angina pectoris, MI or surrogate risk factors for CHD were allocated either to a diet rich in whole grains, fruits, vegetables, walnuts and almonds (intervention group), or to a local diet similar to the National Cholesterol Education Program prudent diet(control group)[8]. The intervention group had significantly fewer non-fatal MI (multivariate adjusted RR= 0.47; 95% CI 0.28-0.79), sudden cardiac deaths (adjusted RR= 0.33; 95% CI 0.13-0.86), and total cardiac endpoints (adjusted RR= 0.48; 95% CI 0.33-0.71) as compared to the control group. No statistically significant difference was found in the risk of fatal MI (adjusted RR= 0.67; 95% CI 0.31-1.42). Of note, about two-thirds of the participants in each group were vegetarian. After two years of follow up, the intervention group had a statistically significantly lower low- density lipoprotein (LDL), fasting blood glucose, BMI, blood pressure, and higher high-density lipoprotein (HDL) as compared to the control group.

The Mediterranean Diet, Cardiovascular Risks and Gene Polymorphisms (Medi-RIVAGE) study was a short term randomized trial to study the effect of Mediterranean diet on cardiovascular risk factors in subjects with moderate cardiovascular risk factors[9]. A total of 212 participants aged 18-70 years were advised to consume either a traditional Mediterranean diet, or an American Heart Association low fat diet. Reduction in LDL after 3 months tended to be greater with the Mediterranean diet (p value =0.09 for time-by-group interaction) than with the low-fat diet. It is possible that a poor compliance might explain the borderline significance in both dietary patterns.

In the Nurses' Health Study, there was a 29% reduced risk of CHD (RR= 0.71; 95% CI 0.62-0.82) and 39% reduced risk of cardiovascular disease (CVD) mortality (RR= 0.61; 95% CI 0.49-0.76) among women in the top quintile of Alternate Mediterranean Diet Score (aggregate of various components of Mediterranean diet calculated from food frequency questionnaire), as compared to the bottom quintile after 20 years of follow up[5]. Similarly, in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a follow up of apparently healthy 41,078 participants over 10 years suggested a 40% decreased risk of incident CHD in those with a high relative Mediterranean diet score (derived from degree of consumption of different Mediterranean diet constituents) as compared to those with low scores[10]. In another Spanish cohort of 13,609 participants free of known CVD at baseline, a similar risk reduction (RR= 0.41, 95% CI 0.18-0.95) in incident CVD was found in those with a higher Mediterranean diet score, as compared to those with a lower score[11].

What mechanisms underlie the apparent cardio-vascular benefits from the Mediterranean diet? A randomized controlled trial to study the effect of the Mediterranean diet on cardiovascular risk factors showed that Mediterranean diet was associated with decreased plasma glucose , lower systolic blood pressure, improved cholesterol-to- high density lipoprotein ratio, and lower C reactive protein (CRP) levels compared with low-fat diet[12]. The Mediterranean diet is low in saturated fats and rich in monounsaturated fats, mainly in form of olive oil. The latter is associated with improved cardiovascular risk factors, including obesity and diabetes [13-15]. In addition, the favorable effects of fruit and vegetables, fiber, and n-3 content of the Mediterranean diet on CHD (discussed in this review), may play a role.

Fish and n-3 fatty acids and CHD

The efficacy of fish and n-3 fatty acids in primary and secondary prevention of CHD has been shown in various clinical studies [16, 17]. In the Diet and Reinfarction (DART) Study, 2,033 survivors of MI (age under 70 years) were randomized to receive advice on eating at least two weekly portions (200-400 g) of fatty fish, to reduce their total fat intake or to increase their intake of cereal fiber [18]. Those who were not able to consume this quantity of fish were asked to consume fish oil (Maxepa) capsules as partial or total replacement for the fish consumption. Dietary compliance was monitored by food frequency questionnaires, and plasma marine n-3 fatty acids (i.e. eicosapentanoic acid -EPA) were measured in a subset of participants. After two years, 9.3% in the fish advice group vs. 12.8% in the control group had all cause death (multivariable adjusted RR= 0.71, 95% CI 0.54-0.93). Similarly, there were lower CHD deaths (7.7% vs. 11.4%), and CHD events (12.5% vs. 14.6%) in the fish consumption group compared to the control group.

The cardiovascular benefit of n-3 fatty acid supplementation was also seen in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)- Prevenzione trial[19]. In this open labeled trial with factorial design, of 11,324 MI survivors were given, in addition to the standard CHD medications (control group consisting of treatment with aspirin, beta blockers, nitrate, Angiotensin Converting Enzyme Inhibitors, and statins), either 1 g daily of n-3 fatty acids or vitamin E or both. N-3 fatty acids were associated with a 20% reduction in all-cause mortality, 30% reduction in CHD

death, and 45% reduction in sudden death as compared to control.

In the Japan EPA Lipid Intervention Study (JELIS), 18,645 hyperlipidemic patients were randomly assigned to receive either 1.8 g/d of EPA with statin (EPA group) or statin only. Of the total study population, 14,981 were subject to primary prevention and 3,664 to secondary prevention [20]. Post-treatment LDL concentrations decreased by 25% in both intervention and control groups. The 5-year cumulative rate of major coronary events was 2·8% in the EPA group and 3·5% in the control group, resulting in a significant relative risk reduction of 19% in the EPA group (p value=0·011). For the entire study population, non-fatal coronary event rate (including non-fatal MI, unstable angina, and events of angioplasty, stenting, or coronary artery bypass grafting) was significantly lower (19%) in the EPA group than in controls (RR=0.81; 95% CI 0.68–0.96), however, no statistically significant difference in coronary death was seen in the two groups. A statistically non-significant risk reduction in non fatal MI (RR=0.70; 95% CI 0.42–1.14), as well as fatal MI (RR= 0.64; 95% CI 0.21–1.94) and a significant risk reduction in unstable angina (RR=0.72; 95% CI 0.55–0.95) were seen in the secondary prevention subgroup. The lack of a true placebo and substantially underpowered subgroup analyses were some of the major limitations of that study.

The Alpha Omega trial was a randomized multi-center, double-blind, placebo-controlled trial to evaluate the role of the marine n−3 fatty acids EPA and docosahexaenoic acid (DHA) and of the plant-derived alpha-linolenic acid (ALA) in secondary prophylaxis of cardiovascular events [21]. 4,837 participants with history of MI were randomized to one of four trial margarines: margarine supplemented with a combination of EPA and DHA, margarine supplemented with ALA, margarine supplemented with EPA–DHA and ALA, or placebo margarine. Compared to placebo, neither EPA–DHA nor ALA reduced major cardiovascular events (hazard ratio with EPA–DHA, 1.01; 95% CI 0.87 -1.17; hazard ratio with ALA, 0.91; 95% CI 0.78 to 1.05).

In a pooled analysis of prospective cohort studies and randomized trials on n-3 fatty acids, and CHD mortality, a 36% lower risk of CHD death was evident with up to 250 mg/d of EPA-DHA consumption (RR = 0.64, 95% CI 0.50 – 0.80, p value<0.001) and little further benefit was seen with higher intakes (0.0% change per each additional 100 mg/d; RR =1.00, 95% CI 0.99 –1.01, p value= 0.94). Overall, the existing evidence suggests a decreased risk of all-cause mortality, and CHD mortality with use of dietary or supplemental n-3 fatty acids.

A variety of mechanisms may be responsible for the observed cardiovascular benefits of n-3 fatty acids. In addition to improving lipid profile [22], n-3 fatty acids have been shown to suppress various inflammatory cytokines such as interleukin-6, interleukin-1 β and tumor necrosis factor-α [23, 24]. Additionally, lowering triglycerides, improved endothelial function and stability of atherosclerotic plaques [25], decreased platelet aggregation [26], and reduced risk of arrhythmias due to cardiomyocyte membrane stabilization [27] with use of n-3 fatty acids have also been suggested.

Flavonoids, polyphenols and CHD

Consumption of fruit and vegetables has been shown to lower the risk of CVD [28, 29]. Fruit and vegetables have a unique nutrient profile in that in general, they are rich in fiber, potassium, polyphenols, and other minerals like magnesium, various vitamins, and usually have low energy densities, and fat content. Flavonoids are a chemically related class of various plant derived bioactive molecules including flavanols, flavonols, flavones, isoflavones, flavanones, and anthocyanins. Flavonoids have been suggested to impart a protective role against cardiovascular events.

In the Zutphen Elderly Study, dietary intake of flavonoids was assessed by dietary history of 805 men aged 65-84 years [30] and major sources of flavonoid intake were tea (61%), onions (13%) and apples (10%). As compared to the lowest tertile of flavonoid intake, those in the highest tertile had a 68% reduced risk of CHD mortality (multivariable adjusted RR= 0.32, 95% CI 0.15-0.71, p value for trend 0.003). As compared to the lowest tertile (0-250 ml per day) of tea consumption, the highest tertile (>500 ml per day) was associated with a statistically significant 55% reduced risk of CHD mortality. Similarly, highest tertile (≥ 110 g per day) of apple consumption was associated with 49% reduced CHD mortality. In 34,492 postmenopausal women of the Iowa Women's Health Study, total flavonoid intake was associated with a decreased risk of CHD mortality after adjusting for age and energy intake (p value for trend 0.04)[31]. Although this association was attenuated after multivariate adjustment, a decreased risk was seen in each quintile of flavonoids compared with the lowest. Relative risks (95% CI) of CHD death from lowest to highest intake quintile were 1.0, 0.67 (0.49-0.92), 0.56 (0.39-0.79), 0.86 (0.63-1.18), and 0.62 (0.44-0.87), respectively. Consumption of broccoli was associated with a statistically significant 48% reduction in CHD mortality in the highest quintile of intake (RR=0.52, 95% CI 0.37-0.74). Other studies documenting an inverse

association between dietary flavonoids and CHD are the Rotterdam Study[32], Finnish mobile clinic health examination survey[33], Alpha-Tocopherol, Beta Carotene Cancer Prevention Study[34], and the Zutphen Elderly Study for catechins [35].

On the other hand, the Health Professionals Follow-up Study failed to find any significant protective effects of total flavonoid intake on the risk of nonfatal MI(multivariable adjusted RR=1.08; 95% CI 0.81-1.43)[36]. A statistically non-significant 36% risk reduction in CHD death was seen in subjects who had prevalent CHD (RR=0.64, 95% CI 0.39-1.04). Similarly, in the 38,445 female participants of the Women's Health Study, flavonoid intake did not protect against CVD[37]. This lack of protection was observed across different type of flavonoids. When individual foods were analyzed, apple, tea and broccoli, but not onions were associated with statistically non significant reduced risk of CVD. Insufficient power and lack of comprehensive control for potential confounding factors in some analyses were acknowledged by the authors. The Caerphilly Study suggested a positive association between flavonol intake and CHD mortality[38]. As compared to the lowest quintile of total flavonol consumption, the RR of CHD mortality in the highest quintile was 1.6 (95% CI 0.9- 2.9, p value = 0.2). Men with the highest consumption of tea (> 1.2 L, or > 8 cups/d) had an RR of 2.3 (95% CI 1.0-5.1, p value for trend 0.031) of dying from CHD in the follow-up period compared with men consuming < 300 mL/d (< 2 cups/d). Almost all men used milk in their tea, and it is possible that milk may attenuate antioxidant capacity of tea.

Polyphenol- rich foods such as cocoa have shown to have cardiovascular benefits. Decreased CHD mortality from cocoa consumption were demonstrated in the Zutphen Elderly Study [39]. As compared to the lowest tertile of cocoa consumption, the mean systolic blood pressure in the highest tertile of cocoa intake was 3.7 mm Hg lower (95% CI −7.1 to −0.3 mmHg, p value for trend 0.03) and the mean diastolic blood pressure was 2.1 mm Hg lower (95% CI −4.0 to −0.2 mm Hg, p value for trend 0.03). As compared to the lowest tertile of cocoa intake, the adjusted RR of cardiovascular death in the highest tertile was 0.50 (95% CI 0.32-0.78, p for trend 0.004) and the RR of all-cause mortality was 0.53 (95% CI 0.39-0.72, p for trend <0.001). In a cross-sectional analysis of 2,217 participants of the Family Heart Study, an inverse association between frequency of chocolate consumption and prevalent coronary artery calcification (CAC) scores was demonstrated [40]. As compared to the study participants who reported no chocolate consumption, the multivariable adjusted odds ratios (95% CI) for CAC for those reporting chocolate consumption of 1-3 times per month, once per week, and 2 or more times per week were 0.95 (0.66-1.36), 0.79 (0.54-1.15), and 0.69 (0.48-0.99) respectively (p for linear trend 0.029). Exclusion of subjects with known CHD or diabetes mellitus did not significantly change the odds ratio estimates but did modestly decrease the overall significance (p value = 0.07). In another paper, cross-sectional data from the Family Heart Study also suggested an inverse association between chocolate consumption and prevalent CHD[41]. Compared to subjects who did not report any chocolate intake, odds ratios (95% CI) for CHD were 1.01 (0.76-1.37), 0.74 (0.56-0.98), and 0.43 (0.28-0.67) for subjects consuming 1-3 times/month, 1-4 times/week, and 5+ times/week, respectively (p value for trend <0.0001).

The observed protective effects of flavonoid intake on CHD have been attributed to various mechanisms. Flavonoids have been shown to induce an acute and sustained increase in endothelium- dependent vasodilatation in people with cardiovascular risk factors [42-44], as well as those with established CHD [45-48]. Ingestion of dark chocolate has been shown to induce flow- mediated dilation of brachial artery, an effect that has been shown to last for as long as 8 hours[43]. An increase in circulating plasma nitric oxide storage forms following ingestion of various dietary flavonoids has been suggested [49]. These molecules have intrinsic vasodilator activity. Besides, reduction in blood pressure[50], total and low density lipoprotein cholesterol[51], and inhibition of platelet aggregation [52] seen with dietary flavonoid use may account for the observed benefits.

Dietary fiber and whole grains and CHD

Dietary fiber is a broad class of plant based non digestible non starch polysaccharides and lignins. Liu et al. have shown an inverse association between dietary fiber intake and the risk of MI and CVD[53]. In this prospective study of 39,876 female health professionals with no known history of CVD, as compared to the lowest quintile of fiber intake (median: 12.5 g/day), the highest quintile of fiber intake (median: 26.3 g/day) was associated with a 35% reduced risk of total CVD (RR=0.65, 95% CI 0.51- 0.84) and 54% reduced risk of MI (RR=0.46, 95% CI 0.30- 0.72). In a pooled analysis of 10 prospective cohort studies, every 10 g daily total dietary fiber intake was associated with a 14% reduced risk of all coronary events (RR=0.86; 95% CI 0.78-0.96), and a 27% decreased risk of coronary death (RR=0.73;95% CI 0.61-0.87)[54].

Mozaffarian et al. have shown that cereal fiber consumption is associated with a lower risk of incident

CVD, but not MI[55] in 3,588 men and women (mean age 72 years). In that study, cereal fiber consumption but not fruit or vegetable fiber consumption was inversely associated with incident CVD (RR=0.79; 95% CI 0.62-0.99) comparing the highest to the lowest quintile of cereal fiber intake. Comparing the 80th percentile with the 20th percentile of intake, higher cereal fiber intake, no statistically significant difference was in the risk of non fatal MI (RR= 0.94; 95% CI 0.76-1.16) or CHD death (RR= 0.87; 95% CI 0.67-1.13).

The advice to increase cereal fiber intake did not affect the rate of MI or CVD mortality in the DART study [18]. , a meta-analysis of 12 studies suggested that cereal fiber itself had the least influence on CHD risk; whole grain consumption was associated with a 26% reduction in the risk of incident CHD. Furthermore, the Iowa Women's Health suggested that fiber from whole grain, but not refined grain decreased all cause mortality [56]. Whole grains not only have fiber, but also other phytonutrients, which may be responsible for this observed effect.

The exact mechanism of cardioprotective effect of dietary fiber and cereal is uncertain. Increased fecal excretion of cholesterol[57], increased insulin sensitivity [58], reduced activity of pro-coagulant factors[59], and decreased risk of incident diabetes[60] with consumption of fiber and whole grain cereals have been suggested.

Vitamins and CHD

According to the "oxidative-modification hypothesis" of atherosclerosis, atherogenesis is initiated by oxidation of lipids in the LDL[61]. In vitro and in vivo studies suggest that such oxidative damage leads to endothelial cell damage[62], and foam cell accumulation[63]. Thus, antioxidants might be expected to limit atherosclerosis and its clinical manifestations such as MI. However, epidemiological studies have been controversial. Whereas some studies do suggest such protective role of antioxidant vitamins on CHD risk, many randomized trials have shown no benefit, and some suggest potential harm.

In a prospective study of 1,299 elderly Massachusetts residents, the multivariate RR of fatal MI and total cardiovascular death in the highest quartile of dietary carotene, as compared to the lowest were 0.27 (95% CI 0.10-0.74) and 0.59 (95% CI 0.37-0.94) respectively[64]. Similar findings were reported by Liu et al. in a cohort of US male physicians [65], and Osganian et al. in a cohort of female nurses consuming alpha and beta carotene from dietary sources[66]. In the latter cohort, total vitamin C intake (dietary as well as in form of supplements) has also been associated with decreased risk of CHD (RR=0.73; 95% CI 0.57- 0.94) [67]. Interestingly, a weaker, and statistically non- significant inverse association was seen between intake of vitamin C from diet alone and incident CHD in that study.

Numerous prospective cohort studies and randomized controlled trials have consistently failed to prove any protective role of vitamins and antioxidants in CHD. In a randomized controlled trial of 8,171 women aged 40+ years, a follow up of about 10 years did not reveal any effect of vitamin C (RR=1.02; 95% CI 0.92-1.13), vitamin E (RR= 0.94; 95% CI 0.85-1.04), or beta carotene (RR 1.02; 95% CI 0.92-1.13) supplementation on combined outcome of MI, stroke, coronary revascularization, or CVD death[68].

In the Vitamin E Atherosclerosis Prevention Study (VEAPS) [69] vitamin E supplementation did not reduce the progression of the common carotid artery intimal medial thickness after 3 years of follow up. However, a statistically significant reduction in circulating oxidized LDL was seen. The Primary Prevention Project (PPP) was an open-label 2x2 factorial trial of 300 mg of synthetic vitamin E and/or 100 mg of low-dose aspirin daily in 4,495 Italian men and women[70]. Although terminated prematurely because of strong treatment effect of aspirin, the trial did not suggest any statistically significant effect of vitamin E in reducing angina, MI or cardiovascular mortality. Similarly, in a randomized, double-blinded, placebo controlled factorial trial of more than 14,000 US male physicians, neither vitamin C nor vitamin E supplementation showed any effect on the risk of total MI and cardiovascular mortality after 8 years of follow up. Numerous other randomized trials examining the role of vitamin E in secondary prophylaxis of CVD have similarly been disappointing.

Overall, there is no evidence suggesting that vitamins confer beneficial effects on CHD endpoints.

Garlic and CHD

Although epidemiological studies have explored the role of garlic on cardiovascular risk factors, like hyperlipidemia, there are not many studies exploring the garlic-CHD association. In a small double blind placebo controlled study of 51 hyperlipidemic male and female patients with history of CHD received either time released garlic powder tablets, "Allicor", or placebo for 12 months[71]. As compared to baseline, Allicor was associated with a statistically significant reduction in total cholesterol (by 12.4%), and LDL (by 16.3%), but no significant differences in triglycerides, and HDL after 12 months of treatment. A statistically significant reduced risk of fatal and non-fatal MI as well as sudden cardiac death was seen in men (RR= 0.76, 95% CI 0.57-

0.94), but not women in the Allicor group. LDL reduction accounted for the decreased risk of MI and sudden cardiac death in men (r=0.463, p value=0.013). In another placebo controlled double-blind randomized trial of 65 asymptomatic patients [72], CAC progression was significantly lower in the aged garlic plus supplement group (OR 0.35, 95% CI 0.1–0.85), as compared to the placebo group. As compared to placebo, the aged garlic plus supplement group had a significant reduction in total cholesterol (RR=0.92, 95% CI 0.81–0.98, p value= 0.04) as well as LDL (RR=0.87, 95% CI 0.71–0.90, p value= 0.04). In addition, improvement in vascular function (as measured by digital thermal monitoring), as well as oxidative markers (such as autoantibodies to malondialdehyde (MDA)-LDL, apoB-immune complexes, oxidized phospholipids (OxPL) on apolipoprotein B-100 (OxPL/apoB), and lipoprotein (a) [Lp (a)] was observed in the garlic plus supplement group. Garlic has H_2S releasing capabilities, and various garlic derived molecules like diallyl disulfide and diallyl trisulfide attenuate deleterious effects of oxidized LDL on nitric oxide production[73]. In rat models, garlic derived molecules like *S*-propargylcysteine have been shown to protect from MI [74]. Hydrogen sulphide (H_2S) has been suggested to have cytoprotective role in reperfusion injuries[75]. Experimental reduction in H_2S levels has been shown to increase myocardial infarct size in animal models [76]. Sodium hydrogen sulfide inhibits human platelet aggregation induced by various pro-thrombotic agents like adenosine diphosphate (ADP), epinephrine, arachidonic acid, and thrombin[77]. Larger randomized controlled trials are needed to explore conclusively any association between garlic consumption and CHD.

Future Directions

Genetic makeup of an individual defines his/her susceptibility to disease, and environmental factors (i.e. diet and exercise) influence the risk of the disease. It is evident not only in clinical medicine, but also in epidemiological research that individuals respond differently to the same intervention. The concept of *nutrigenetics*, which studies the effect of gene variations on the organism's ability to digest, absorb and use food, and *nutrigenomics*, which explores how bioactive components within food affect gene expression and function, are based on these premises. With rapid expansion in these areas of research, it might be possible to utilize genetic information to identify population subgroups with differential responses to diet, and thus tailor dietary approaches to individual needs with the help of genetic and lifestyle information to effectively prevent or treat CHD[78].

In summary, this review provides strong evidence for the importance of dietary factors in the fight against CHD, suggesting that adherence to simple modifiable factors such as dietary factors could be relevant and cost-effective in the prevention of CHD. Although still emerging, data from nutrigenomics and metabolomics may help elucidate underlying biological response at the individual level and help design personalized nutrition to prevent CHD.

REFERENCES

[1] Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010; 121(7): e46-e215.

[2] Lindgren P, Fahlstadius P, Hellenius ML, Jonsson B, de Faire U. Cost-effectiveness of primary prevention of coronary heart disease through risk factor intervention in 60-year-old men from the county of Stockholm--a stochastic model of exercise and dietary advice. Prev Med 2003; 36(4): 403-409.

[3] Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006; 59(6): 912-921.

[4] Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol 2009; 66(2): 216-225.

[5] Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. Circulation 2009; 119(8): 1093-1100.

[6] Aravanis C, Corcondilas A, Dontas AS, Lekos D, Keys A. Coronary heart disease in seven countries. IX. The Greek islands of Crete and Corfu. Circulation 1970; 41(4 Suppl): I88-100.

[7] de Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, Guidollet J, Touboul P, Delaye J. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994; 343(8911): 1454-1459.

[8] Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, Manor O, Pella D, Berry EM. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet 2002; 360(9344): 1455-1461.

[9] Vincent-Baudry S, Defoort C, Gerber M, Bernard MC, Verger P, Helal O, Portugal H, Planells R, Grolier P, Amiot-Carlin MJ, Vague P, Lairon D. The Medi-RIVAGE study: reduction of cardiovascular disease risk factors after a 3-mo intervention with a Mediterranean-type diet or a low-fat diet. Am J Clin Nutr 2005; 82(5): 964-971.

[10] Buckland G, Gonzalez CA, Agudo A, Vilardell M, Berenguer A, Amiano P, Ardanaz E, Arriola L, Barricarte A, Basterretxea M, Chirlaque MD, Cirera L, Dorronsoro M, Egues N, Huerta JM, Larranaga N, Marin P, Martinez C, Molina E, Navarro C, Quiros JR, Rodriguez L, Sanchez MJ, Tormo MJ, Moreno-Iribas C. Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. Am J Epidemiol 2009; 170(12): 1518-1529.

[11] Martinez-Gonzalez MA, Garcia-Lopez M, Bes-Rastrollo M, Toledo E, Martinez-Lapiscina EH, Delgado-Rodriguez M, Vazquez Z, Benito S, Beunza JJ. Mediterranean diet and the incidence of cardiovascular disease: A Spanish cohort. Nutr Metab Cardiovasc Dis 2010.

[12] Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, Fiol M, Gomez-Gracia E, Lopez-Sabater MC, Vinyoles E, Aros F, Conde M, Lahoz C, Lapetra J, Saez G, Ros E. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 2006; 145(1): 1-11.

[13] Ros E. Dietary cis-monounsaturated fatty acids and metabolic control in type 2 diabetes. Am J Clin Nutr 2003; 78(3 Suppl): 617S-625S.

[14] Kris-Etherton PM. AHA Science Advisory. Monounsaturated fatty acids and risk of cardiovascular disease. American Heart Association. Nutrition Committee. Circulation 1999; 100(11): 1253-1258.

[15] Martinez-Gonzalez MA, Sanchez-Villegas A. The emerging role of Mediterranean diets in cardiovascular epidemiology: monounsaturated fats, olive oil, red wine or the whole pattern? Eur J Epidemiol 2004; 19(1): 9-13.

[16] Patel JV, Tracey I, Hughes EA, Lip GY. Omega-3 polyunsaturated fatty acids: a necessity for a comprehensive secondary prevention strategy. Vasc Health Risk Manag 2009; 5: 801-810.

[17] Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr 2003; 77(2): 319-325.

[18] Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989; 2(8666): 757-761.

[19] Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999; 354(9177): 447-455.

[20] Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007; 369(9567): 1090-1098.

[21] Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 2010; 363(21): 2015-2026.

[22] Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, Ballantyne CM, Ginsberg HN. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007; 29(7): 1354-1367.

[23] Calder PC. Polyunsaturated fatty acids and inflammation. Prostaglandins Leukot Essent Fatty Acids 2006; 75(3): 197-202.

[24] Zhao G, Etherton TD, Martin KR, Gillies PJ, West SG, Kris-Etherton PM. Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. Am J Clin Nutr 2007; 85(2): 385-391.

[25] Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, Gallagher PJ, Calder PC, Grimble RF. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. Lancet 2003; 361(9356): 477-485.

[26] Cerbone AM, Cirillo F, Coppola A, Rise P, Stragliotto E, Galli C, Giordano M, Tremoli E, Di Minno G. Persistent impairment of platelet aggregation following cessation of a short-course dietary supplementation of moderate amounts of N-3 fatty acid ethyl esters. Thromb Haemost 1999; 82(1): 128-133.

[27] Leaf A, Kang JX, Xiao YF, Billman GE. n-3 fatty acids in the prevention of cardiac arrhythmias. Lipids 1999; 34 Suppl: S187-189.

[28] He FJ, Nowson CA, Lucas M, MacGregor GA. Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. J Hum Hypertens 2007; 21(9): 717-728.

[29] Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. J Nutr 2006; 136(10): 2588-2593.

[30] Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet 1993; 342(8878): 1007-1011.

[31] Yochum L, Kushi LH, Meyer K, Folsom AR. Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. Am J Epidemiol 1999; 149(10): 943-949.

[32] Geleijnse JM, Launer LJ, Van der Kuip DA, Hofman A, Witteman JC. Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam Study. Am J Clin Nutr 2002; 75(5): 880-886.

[33] Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. BMJ 1996; 312(7029): 478-481.
[34] Hirvonen T, Pietinen P, Virtanen M, Ovaskainen ML, Hakkinen S, Albanes D, Virtamo J. Intake of flavonols and flavones and risk of coronary heart disease in male smokers. Epidemiology 2001; 12(1): 62-67.
[35] Arts IC, Hollman PC, Feskens EJ, Bueno de Mesquita HB, Kromhout D. Catechin intake might explain the inverse relation between tea consumption and ischemic heart disease: the Zutphen Elderly Study. Am J Clin Nutr 2001; 74(2): 227-232.
[36] Rimm EB, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. Ann Intern Med 1996; 125(5): 384-389.
[37] Sesso HD, Gaziano JM, Liu S, Buring JE. Flavonoid intake and the risk of cardiovascular disease in women. Am J Clin Nutr 2003; 77(6): 1400-1408.
[38] Hertog MG, Sweetnam PM, Fehily AM, Elwood PC, Kromhout D. Antioxidant flavonols and ischemic heart disease in a Welsh population of men: the Caerphilly Study. Am J Clin Nutr 1997; 65(5): 1489-1494.
[39] Buijsse B, Feskens EJ, Kok FJ, Kromhout D. Cocoa intake, blood pressure, and cardiovascular mortality: the Zutphen Elderly Study. Arch Intern Med 2006; 166(4): 411-417.
[40] Djousse L, Hopkins PN, Arnett DK, Pankow JS, Borecki I, North KE, Curtis Ellison R. Chocolate consumption is inversely associated with calcified atherosclerotic plaque in the coronary arteries: The NHLBI Family Heart Study. Clin Nutr 2010.
[41] Djousse L, Hopkins PN, North KE, Pankow JS, Arnett DK, Ellison RC. Chocolate consumption is inversely associated with prevalent coronary heart disease: The National Heart, Lung, and Blood Institute Family Heart Study. Clin Nutr 2010.
[42] Balzer J, Rassaf T, Heiss C, Kleinbongard P, Lauer T, Merx M, Heussen N, Gross HB, Keen CL, Schroeter H, Kelm M. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. J Am Coll Cardiol 2008; 51(22): 2141-2149.
[43] Hermann F, Spieker LE, Ruschitzka F, Sudano I, Hermann M, Binggeli C, Luscher TF, Riesen W, Noll G, Corti R. Dark chocolate improves endothelial and platelet function. Heart 2006; 92(1): 119-120.
[44] Grassi D, Necozione S, Lippi C, Croce G, Valeri L, Pasqualetti P, Desideri G, Blumberg JB, Ferri C. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. Hypertension 2005; 46(2): 398-405.
[45] Duffy SJ, Keaney JF, Jr., Holbrook M, Gokce N, Swerdloff PL, Frei B, Vita JA. Short- and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. Circulation 2001; 104(2): 151-156.
[46] Stein JH, Keevil JG, Wiebe DA, Aeschlimann S, Folts JD. Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary artery disease. Circulation 1999; 100(10): 1050-1055.
[47] Farouque HM, Leung M, Hope SA, Baldi M, Schechter C, Cameron JD, Meredith IT. Acute and chronic effects of flavanol-rich cocoa on vascular function in subjects with coronary artery disease: a randomized double-blind placebo-controlled study. Clin Sci (Lond) 2006; 111(1): 71-80.
[48] Widlansky ME, Hamburg NM, Anter E, Holbrook M, Kahn DF, Elliott JG, Keaney JF, Jr., Vita JA. Acute EGCG supplementation reverses endothelial dysfunction in patients with coronary artery disease. J Am Coll Nutr 2007; 26(2): 95-102.
[49] Loke WM, Hodgson JM, Proudfoot JM, McKinley AJ, Puddey IB, Croft KD. Pure dietary flavonoids quercetin and (-)-epicatechin augment nitric oxide products and reduce endothelin-1 acutely in healthy men. Am J Clin Nutr 2008; 88(4): 1018-1025.
[50] Taubert D, Roesen R, Lehmann C, Jung N, Schomig E. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. JAMA 2007; 298(1): 49-60.
[51] Polagruto JA, Wang-Polagruto JF, Braun MM, Lee L, Kwik-Uribe C, Keen CL. Cocoa flavanol-enriched snack bars containing phytosterols effectively lower total and low-density lipoprotein cholesterol levels. J Am Diet Assoc 2006; 106(11): 1804-1813.
[52] Freedman JE, Parker C, 3rd, Li L, Perlman JA, Frei B, Ivanov V, Deak LR, Iafrati MD, Folts JD. Select flavonoids and whole juice from purple grapes inhibit platelet function and enhance nitric oxide release. Circulation 2001; 103(23): 2792-2798.
[53] Liu S, Buring JE, Sesso HD, Rimm EB, Willett WC, Manson JE. A prospective study of dietary fiber intake and risk of cardiovascular disease among women. J Am Coll Cardiol 2002; 39(1): 49-56.
[54] Pereira MA, O'Reilly E, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. Arch Intern Med 2004; 164(4): 370-376.
[55] Mozaffarian D, Kumanyika SK, Lemaitre RN, Olson JL, Burke GL, Siscovick DS. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. JAMA 2003; 289(13): 1659-1666.
[56] Jacobs DR, Pereira MA, Meyer KA, Kushi LH. Fiber from whole grains, but not refined grains, is inversely associated with all-cause mortality in older women: the Iowa women's health study. J Am Coll Nutr 2000; 19(3 Suppl): 326S-330S.
[57] Vahouny GV, Tombes R, Cassidy MM, Kritchevsky D, Gallo LL. Dietary fibers: V. Binding of bile salts, phospholipids and cholesterol from mixed micelles by bile acid sequestrants and dietary fibers. Lipids 1980; 15(12): 1012-1018.
[58] Hallfrisch J, Scholfield DJ, Behall KM. Diets containing soluble oat extracts improve glucose and insulin

responses of moderately hypercholesterolemic men and women. Am J Clin Nutr 1995; 61(2): 379-384.
[59] Sundell IB, Ranby M. Oat husk fiber decreases plasminogen activator inhibitor type 1 activity. Haemostasis 1993; 23(1): 45-50.
[60] Kochar J, Djousse L, Gaziano JM. Breakfast cereals and risk of type 2 diabetes in the Physicians' Health Study I. Obesity (Silver Spring) 2007; 15(12): 3039-3044.
[61] Diaz MN, Frei B, Vita JA, Keaney JF, Jr. Antioxidants and atherosclerotic heart disease. N Engl J Med 1997; 337(6): 408-416.
[62] Hessler JR, Morel DW, Lewis LJ, Chisolm GM. Lipoprotein oxidation and lipoprotein-induced cytotoxicity. Arteriosclerosis 1983; 3(3): 215-222.
[63] Quinn MT, Parthasarathy S, Steinberg D. Endothelial cell-derived chemotactic activity for mouse peritoneal macrophages and the effects of modified forms of low density lipoprotein. Proc Natl Acad Sci U S A 1985; 82(17): 5949-5953.
[64] Gaziano JM, Manson JE, Branch LG, Colditz GA, Willett WC, Buring JE. A prospective study of consumption of carotenoids in fruits and vegetables and decreased cardiovascular mortality in the elderly. Ann Epidemiol 1995; 5(4): 255-260.
[65] Liu S, Lee IM, Ajani U, Cole SR, Buring JE, Manson JE. Intake of vegetables rich in carotenoids and risk of coronary heart disease in men: The Physicians' Health Study. Int J Epidemiol 2001; 30(1): 130-135.
[66] Osganian SK, Stampfer MJ, Rimm E, Spiegelman D, Manson JE, Willett WC. Dietary carotenoids and risk of coronary artery disease in women. Am J Clin Nutr 2003; 77(6): 1390-1399.
[67] Osganian SK, Stampfer MJ, Rimm E, Spiegelman D, Hu FB, Manson JE, Willett WC. Vitamin C and risk of coronary heart disease in women. J Am Coll Cardiol 2003; 42(2): 246-252.
[68] Cook NR, Albert CM, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, Manson JE. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. Arch Intern Med 2007; 167(15): 1610-1618.
[69] Hodis HN, Mack WJ, LaBree L, Mahrer PR, Sevanian A, Liu CR, Liu CH, Hwang J, Selzer RH, Azen SP. Alpha-tocopherol supplementation in healthy individuals reduces low-density lipoprotein oxidation but not atherosclerosis: the Vitamin E Atherosclerosis Prevention Study (VEAPS). Circulation 2002; 106(12): 1453-1459.
[70] de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet 2001; 357(9250): 89-95.
[71] Sobenin IA, Pryanishnikov VV, Kunnova LM, Rabinovich YA, Martirosyan DM, Orekhov AN. The effects of time-released garlic powder tablets on multifunctional cardiovascular risk in patients with coronary artery disease. Lipids Health Dis 2010; 9: 119.
[72] Budoff MJ, Ahmadi N, Gul KM, Liu ST, Flores FR, Tiano J, Takasu J, Miller E, Tsimikas S. Aged garlic extract supplemented with B vitamins, folic acid and L-arginine retards the progression of subclinical atherosclerosis: a randomized clinical trial. Prev Med 2009; 49(2-3): 101-107.
[73] Lei YP, Liu CT, Sheen LY, Chen HW, Lii CK. Diallyl disulfide and diallyl trisulfide protect endothelial nitric oxide synthase against damage by oxidized low-density lipoprotein. Mol Nutr Food Res 2010; 54 Suppl 1: S42-52.
[74] Wang Q, Liu HR, Mu Q, Rose P, Zhu YZ. S-propargyl-cysteine protects both adult rat hearts and neonatal cardiomyocytes from ischemia/hypoxia injury: the contribution of the hydrogen sulfide-mediated pathway. J Cardiovasc Pharmacol 2009; 54(2): 139-146.
[75] Nicholson CK, Calvert JW. Hydrogen sulfide and ischemia-reperfusion injury. Pharmacol Res 2010; 62(4): 289-297.
[76] Sivarajah A, McDonald MC, Thiemermann C. The production of hydrogen sulfide limits myocardial ischemia and reperfusion injury and contributes to the cardioprotective effects of preconditioning with endotoxin, but not ischemia in the rat. Shock 2006; 26(2): 154-161.
[77] Zagli G, Patacchini R, Trevisani M, Abbate R, Cinotti S, Gensini GF, Masotti G, Geppetti P. Hydrogen sulfide inhibits human platelet aggregation. Eur J Pharmacol 2007; 559(1): 65-68.
[78] Simopoulos AP. Nutrigenetics/Nutrigenomics. Annu Rev Public Health 2010; 31: 53-68.