

Impact of Diet on Cardiovascular Diseases: Coronary Artery Disease

Part I: Healthy Macronutrients

Abstract

Diet is a major modifiable factor in the prevention and management of cardiovascular diseases. These diseases impart the greatest non-communicable diseases burden globally. They are the leading cause of deaths in the world and account for 17.9 million deaths annually. This represents 31% of the total mortality. In 2016, 85% of the cardiovascular deaths in the world were due to ischemic heart disease and stroke. Premature mortality due to cardiovascular diseases is one of the main obstacles in increasing the human lifespan. Coronary artery disease is a major cardiovascular disease. It is caused by arterial atherosclerosis. This leads to progressive narrowing of the coronary arteries limiting blood flow to the myocardium. Plaque rupture may cause sudden blockage to the blood flow resulting in myocardial death. This can be associated with malignant ventricular arrhythmias and lead to death. Several lifestyle factors can prevent, reduce the progression, or even regress atherosclerosis. Diet is a major modifiable factor. A healthy diet can lead to a lower risk of coronary artery disease. It can also stem the progression and improve outcomes in those with established coronary artery disease. The role of diet in the pathogenesis of coronary artery disease is discussed in this 3-part manuscript. Part I looks at the healthier choices.

Keywords: coronary artery disease, plant-based diet, fish, dairy, coffee, chocolate

Introduction

Atherosclerotic cardiovascular disease (ASCVD) continues to be the leading global cause of morbidity and mortality¹. Hypertension (HTN), coronary heart disease (CHD), stroke, and congestive heart failure affect 48% of the US population or approximately 121.5 million Americans². Coronary artery disease (CAD) is the most prevalent ASCVD³. The coronary arteries arise from the base of the aorta and supply the heart with blood. Their wall is made up of three layers: the innermost layer (tunica intima), the middle layer (tunica media), and the outermost layer (tunica adventitia)^{4,5}. CAD results from an atherosclerotic process, affecting the structure and function of all these three layers⁶. It is characterized by a diseased endothelium, low-grade inflammation, monocyte recruitment, macrophage formation, lipid accumulation, and plaque formation within the intima⁷. Plaques may form in the coronary arteries but may also occur in different vascular beds resulting in peripheral artery disease, cerebrovascular disease, or aortic atherosclerosis⁸. In the coronaries, the plaque can grow, usually slowly, eventually impeding blood flow and clinically manifesting as angina⁹. Plaque rupture or erosion can occur suddenly. This is associated with local accumulation of tissue factors, platelet activation,

superimposed thrombosis, and rapid vessel occlusion, leading to myocardial infarction (MI), or even death¹⁰. Besides angina and MI, CAD may lead to other diseases of the heart (coronary heart disease or CHD) such as congestive heart failure, and malignant ventricular arrhythmias¹¹. CAD has a global prevalence of 2%–3%¹². It is estimated that it affected 110 million people in 2015 and was responsible for 8.92 million deaths that year¹³. Its incidence is increasing, especially in low to middle-income countries. It is expected that 82% of the future increase in CHD mortality will occur in these countries¹⁴.

This part I of this 3-part manuscript will discuss the role of beneficial macronutrients in the diet. Part 2 will discuss unhealthy macronutrients while part 3 will look at the role of micronutrients in the development and progression of CAD/CHD. Throughout the 3-part manuscript, CAD and CHD are used interchangeably.

Discussion

Nutrition plays an increasingly significant role in the primary and secondary prevention of several diseases¹⁵. “Let thy food be thy medicine and thy medicine be thy food.” Has been attributed to the Greek physician Hippocrates, indicating the concern regarding diet and health as far back as 400 B.C¹⁶. In 1747, James Lind, a Scottish surgeon in the Royal Navy, noted that citrus fruits treat scurvy¹⁷. The nutrition cardiovascular connection was first recognized in 1908, when a Russian scientist Alexander Ingotowski, demonstrated that high cholesterol intake caused the development of atherosclerosis in rabbits¹⁸. Diet has now become an important health issue, especially when it comes to coronary heart disease (CHD)¹⁹. A heart-healthy diet is associated with major CHD benefits²⁰⁻²⁴.

Plant-Based Diets: A plant-based diet is low in fat, cholesterol, salt, animal products, and sugar²⁵. Plant-based diets do not have to be vegan or vegetarian and many include a low intake of lean meats. These diets are rich in fruits, vegetables, whole grains, nuts, with a regular intake of green tea, dark chocolate, and coffee. They help reduce CHD²⁶. This has been verified by several studies. A large Finnish study reported an inverse relationship between intake of vegetables and risk of both CAD and cardiovascular death²⁷. Law, et al. reported that the risk of ischemic heart disease is about 15% lower at the 90th when compared to the 10th centile of fruit and vegetable consumption²⁸. The Lifestyle Heart Trial found that 82% of patients diagnosed with heart disease who followed a plant-based diet program had some level of regression of atherosclerosis. In this study, 91% had a reduction in the frequency of angina episodes, compared to 53% of the control group. The control group was fed the American Heart Association diet. They also showed a progression of atherosclerosis²⁹. Similarly, other researchers showed that compared with a control group, the plant-based diet group had a 73% decrease in coronary events and a 70% decrease in all-cause mortality³⁰. There are several mechanisms via which plant-based diets exert their beneficial effects. The five major beneficial actions of plant-based diets are: decrease in blood pressure (BP), change in the lipid profile, decrease in HbA1c, reduction of inflammation, and reduction of oxidative stress. Several studies have shown that plant-based diets help reduce BP³¹. The DASH diet is predominantly plant-based, with a small amount of lean meat. DASH diet is associated with a reduction in BP by a mean of 5.5/3.0 mm when compared to a control diet (irrespective of being normotensive or hypertensive)³². In a meta-analysis of 7 clinical trials

that excluded the DASH diet trials, Yokoyama et al analyzed data from 311 participants and found that consumption of vegetarian diets reduced systolic BP by 4.8 mm Hg and diastolic BP by 2.2 mm Hg compared with omnivorous diets³². The impact of an elevated BP on coronary artery disease is significant - a 2-mmHg increase in BP increases mortality from coronary artery disease by 7 percent³³. Plant-based diets also help lose body weight. Vegetable diet individuals eat 5% - 14% fewer calories than their meat-eating counterparts³⁴. The associated weight loss has beneficial effects on BP and lipids. Studies have suggested that there are reductions of 0.5–1 mmHg in BP, and 0.02 mmol/L in total cholesterol for every 1 kg of weight loss³⁵. Other studies have calculated that weight loss of 5–8 kg if sustained, resulted in a mean low density lipoprotein cholesterol (LDL-C) reduction of 5 mg/dL and an increase in high density lipoprotein cholesterol (HDL-C) of 2–3 mg/dL. A 3 kg weight loss reduced TG by 15 mg³⁶⁻³⁸. It has been shown that each 1% reduction in LDL-C or non-HDL-C is associated with a 1% decrease in CHD event risk (over 5 years)³⁹. Weight loss also helps decrease type 2 diabetes mellitus (T2DM) – 1 kg weight loss results in a 0.1% glycated hemoglobin (HbA1c) reduction⁴⁰. T2DM doubles the risk of developing coronary artery disease⁴⁰. Plant-based diets decrease inflammation as evidenced by lower C-reactive protein levels in these patients⁴¹⁻⁴³. Inflammation is associated with the progression of atherosclerosis and adverse CHD events⁴⁴⁻⁴⁷. Plant-based diets also have high antioxidant nutrients, resulting in a better vascular health⁴⁸. Compared to omnivores, they have less oxidative stress⁴⁹, less endothelial injury^{50,51}, thinner intimal medial wall⁵⁰, and reduced atherosclerosis^{50,51}.

People eating plant-based diets also have lower mortality. In one study there was a 24% lower mortality from ischemic heart disease (IHD) in vegetarians compared to non-vegetarians during > 10 years of follow-up period⁵². As mentioned before, plant-based diets are the only dietary pattern to have shown reversal of CAD⁵³. A significant number of patients (82%) in the Lifestyle Heart Trial noted a regression in atherosclerosis⁵⁴. However, not all plant foods are created equal^{55,56}. Prudent plant-based diets contain higher amounts of healthy foods such as fruits, vegetables, whole grains, nuts, legumes, polyunsaturated fatty acid (PUFA) oils, tea, and coffee and are associated with lower cardiovascular (CVD) risk⁵⁵. However, plant-based diets which included higher amounts of less healthy plant foods, such as refined grains, potatoes/fries, and foods/beverages high in added sugar, are linked to an increased risk⁵⁶.

Fruits and vegetables

Consuming fruits, along with green and yellow vegetables, is beneficial for the coronary vasculature⁵⁷ and help prevent the development of atherosclerotic plaque⁵⁸. The plaque vulnerability is also reduced⁵⁹. This results in a decreased risk of cardiovascular events, Liu et al in a prospective cohort study of 39,876 female health professionals, found that the relative risk (RR) between those with the lowest vegetable and fruit consumption (median value: 2.6 servings/day) and those with the highest consumption (median value: 10.2 servings/day) was 1.0 and 0.68, respectively⁶⁰. Joshipura and colleagues estimated that an increase in fruit and vegetable intake could reduce the burden of IHD by as much as 31%⁶¹. In a study of 42,148 men and 84,251 women, it was noted that the RR for CAD was 0.80 in the highest quintile of vegetable and fruit consumption⁶¹. In a systematic review and meta-analysis, for fruits and

vegetables combined, the summary RR per 200 g/day was 0.92 for CHD⁶². In a meta-analysis of nine cohort studies (222,081 men and women), there was a reduction in CHD risk by 4% for each additional portion of fruit and vegetable intake per day⁶³. Fruits and vegetables are rich in several biological compounds, including polyphenols⁶⁴ with immense cardiovascular benefits⁶⁵.

Whole grain. Whole grains contain all three parts of the grain: the bran, the germ, and the endosperm. Refined grains contain only the endosperm. Whole grains commonly used are barley, brown rice, buckwheat, bulgur (cracked wheat), millet, oatmeal, corn, quinoa, brown rice, rye, sorghum, teff, triticale, and wheat. Whole-grain intake is associated with a reduced risk of CHD⁶⁶. In the Atherosclerosis Risk in Communities study, done over 11 years, intake of whole grains was inversely associated with incident CAD⁶⁷. Intake of > 6 servings of whole grains per week results in less progression in coronary artery stenosis even after adjustments for age, cardiovascular risk factors, and dietary intakes of saturated and polyunsaturated fat, cholesterol, and alcohol⁶⁸. A reduced CHD risk was seen in a meta-analysis of 18 prospective studies, in individuals with a higher whole grain intake (RR 0.79)⁶⁹. Aune et al., in a meta-analysis of 45 studies noted a reduction of 21%, in the relative risk of CHD for the highest versus lowest category of whole-grain intake. They also found an inverse association between whole-grain intake and CHD mortality⁷⁰.

Legumes: Legumes (pods with seeds that split into two halves) include beans, peas, lentils, soybeans, and peanuts. Legumes are a good source of plant protein⁷¹. They also provide several essential minerals, dietary fiber (both soluble fiber and resistant starch), and numerous phytochemicals⁷². Their intake helps decrease CHD risk^{73,74}. Afshin, et al. in a systematic review and meta-analysis of five prospective cohort studies, found that consuming four 100-g servings of legumes weekly was associated with a 14% lower risk of CHD⁷³. More recently, in a meta-analysis (eight prospective cohort studies), the highest versus lowest legume intakes were associated with a 10% decreased risk incident CHD and CHD-related mortality⁷⁴. Benefits accrue from their effects in decreasing systolic BP⁷⁵, improving lipid profile⁷⁵, and improving insulin sensitivity⁷⁶.

Nuts: Common nuts such as almonds, hazelnuts, walnuts, pistachios, pecans, cashews, peanuts, Brazil nuts, macadamia nuts, and pine nuts are heart healthy⁷⁷. They have no cholesterol, have a low glycemic index and are high in fiber and nutrients⁷⁸. These nutrients include bioflavonoids, folate, vitamin E, and polyunsaturated fatty acids (PUFAs)⁷⁹. Epidemiological studies and randomized controlled trials indicate that nut consumption helps in weight loss⁸⁰. Further, the macronutrients and phytochemicals present in nuts lead to a reduced risk of CVD⁸¹. Eating one or two ounces of tree nuts per day helps decrease the risk MI, and cardiovascular death⁸². Cardiovascular benefits have also been noted in patients with T2DM. Diabetics who ate five 28-gram servings of nuts per week (compared to those eating less than a single serving per month) had a 20% lower risk of CHD, and a 34% lower risk of cardiovascular disease death⁸³.

Fiber: Dietary fiber is either water-soluble or water insoluble. The former is derived from the inner flesh of plants (such as oats, barley, legumes, lentils, apples, pears, plums, oranges, broccoli, Brussels sprouts, carrots, and peas, and most root vegetables) and helps reduce glucose and cholesterol concentrations⁸⁴. Insoluble fiber is derived from the outer skin of plants and

helps form stool bulk, which promotes laxation. Good sources are potatoes, apples, bananas, and avocados, zucchini, green beans, celery, cauliflower, tomatoes, and kiwi⁸⁵. Whole grains, nuts, and seeds are also good sources. In an umbrella review of 31 analytic studies, fiber intake was associated with a reduction in both total serum cholesterol and LDL-C concentration⁸⁶. Higher intakes of cereal fiber and whole-grain products decrease the progression of coronary atherosclerosis and stenosis⁸⁷. In addition, fiber intake is inversely associated with several other CAD/CHD risk factors such as metabolic syndrome⁸⁸, insulin resistance⁸⁹, HTN⁹⁰, and obesity⁹¹. Besides reducing lipid levels, fiber intake also causes high satiety, a decrease in the nutrient absorption rate, and may even affect the gut microbiota⁹². The American Heart Association (AHA) recommends >1.1 g fiber per 10 g of carbohydrate for good CVD health⁹³.

Dairy

Dairy products commonly consumed include fluid milk, fermented cheese, and fermented yogurt⁹⁴. The AHA and the European Society of Cardiology promote the consumption of low-fat dairy products for cardiovascular production⁹⁵. Milk and milk products lower BP, improve insulin resistance, and decrease inflammation and oxidative stress^{96,97}. These actions may help reduce atherosclerosis and CHD^{98,99}. Several meta-analyses indicate that dairy products may however have a neutral effect on CHD¹⁰⁰. In a systematic review and meta-analysis published in 2017, consumption of milk, yogurt, and cheese had no effect on the risk of CHD¹⁰¹. Jakobsen, et al. also found no association between total intake of dairy (both low-fat and high-fat dairy) and CHD¹⁰². There is some suggestion that intake of cheese may be inversely associated with the risk of CHD¹⁰². It appears that dairy intake has a neutral or a slight protective effect on cardiometabolic health¹⁰⁰⁻¹⁰². The AHA recommends the intake of low-fat dairy products for a healthy cardiovascular system¹⁰³.

Eggs:

The risk of eggs in increasing CAD due to their high cholesterol content (141-234 mg per egg) has been questioned in the past^{104,105}. In a 2016 meta-analysis, Alexander et al. found that consumption of one egg per day did not increase the risk of CHD¹⁰⁶. A systemic review and meta-analysis published in 2020, also found no association between egg intake and cardiovascular disease¹⁰⁷. In a prospective cohort study of 37,121 participants ≥ 20 years of age with a median follow-up of 7.8 years, there was no significant effect of egg consumption on mortality in US adults¹⁰⁸. A more recent population-based cohort study with 521,120 participants, with a mean follow-up of 16 years, suggested that whole egg consumption may result in higher CVD mortality and recommended that whole eggs be replaced with an equivalent amount of egg whites/egg substitutes¹⁰⁹. Some studies have reported a positive association between a higher egg intake and the relative risk of CVD and all-cause mortality in patients with type 2 diabetes¹¹⁰ - recent data appears to refute these findings¹¹¹. The AHA suggests one egg (or two egg whites) per day for people who eat them, as part of a healthy diet¹⁰³.

Poultry:

Meats are broadly divided into two groups - red (such as beef, pork, lamb) or white (such as chicken, turkey, rabbit). Poultry meats or white meats have a lower content of saturated fat and a

better unsaturated fatty acid profile¹¹²⁻¹¹⁴. White meat is also lower in heme iron. Both saturated fat and heme iron are recognized factors that promote atherosclerosis^{115,116}. Poultry intake was not associated with all-cause and CVD mortality in a meta-analysis¹¹⁷. A recent analysis of pooled data from 6 prospective cohort studies of US adults however found a positive association between poultry intake and incident CVD¹¹⁸. It is postulated that since fried chicken was included in the white meat category in this study, the results may have been skewed. Fried food consumption has been positively associated with adverse cardiovascular outcomes¹¹⁹. There is evidence that the substitution of one daily serving of red meat with white meat, mainly poultry, is associated with a 19% reduction of cardiovascular risk¹²⁰. Overall, white meat (non-fried) consumption has a neutral or inverse relationship with CAD.

Fish:

Oily fish is rich in omega PUFAs - eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)¹²¹. Several studies have demonstrated decreased CAD in fish eaters¹²². The reduction has also been seen in non-fatal myocardial infarction, fatal myocardial infarction, and sudden death¹²³⁻¹²⁵. In the Diet And Reinfarction Trial, consumption of oily fish twice a week was associated with a 32% reduction in CHD mortality¹²⁶. A 36% decreased mortality was noted in those consuming fatty fish or seafood (providing 250–500 mg/day of marine n-3 PUFA) when compared to those who consumed little or no seafood¹²⁷. Plant-based omega PUFA, alpha-linolenic acid (ALA), is also cardioprotective, although only 0.2% to 8% of ALA is converted to EPA. The risk reduction is 10% between the highest vs. lowest tertile of ALA intake¹²⁷.

Overall, higher fish intake (especially oily/fatty fish such as salmon, tuna, sardines, mackerel, and trout) 1 - 2 times per week, is beneficial for the primary and secondary prevention of CHD¹²⁸. The EPA and DHA fatty acids, besides having anti-inflammatory effects, induce a wide array of cardio-vascular effects. These include reduced platelet activation and aggregation and stabilization of atherosclerotic plaques¹²⁹.

Alcohol:

The relationship between alcohol intake and CAD is complex and appears to be J- or U-shaped¹³⁰⁻¹³². It is well documented that low to moderate drinking imparts cardioprotection¹³³⁻¹³⁵. Low to moderate alcohol drinkers have less severe coronary lesions on angiography¹³⁶. They also have a reduced risk of MI and CHD mortality^{133,137}. On the other hand, heavier alcohol consumption¹³⁴ and binge drinking¹³⁸ is associated with increased CHD^{133,139} and CHD mortality¹⁴⁰. A recent Mendelian randomization study documented that heavy alcohol consumption was associated with an increased risk of subclinical coronary atherosclerosis¹⁴¹. The AHA recommends that men consume less than 2 standard drinks a day and women consume less than 1 standard drink a day. In the United States, one “standard” drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol)¹⁰³.

The beneficial effects of alcohol are due to several actions¹⁴²⁻¹⁴⁹. Low to moderate intake tends to increase HDL-C¹⁴² and apolipoprotein A-I¹⁴³. Alcohol intake has an inverse association with

T2DM¹⁴⁴. Alcohol helps alter the atherosclerotic plaque composition and provide stabilization¹⁴⁵. Alcohol also exerts several effects on factors involved in hemostasis, such as inhibition of platelet aggregation¹⁴⁶, lowering of fibrinogen levels¹⁴⁷, and decreasing plasma viscosity¹⁴⁸. It also increases levels of tissue plasminogen activator¹⁴⁹.

Coffee

Coffee is a widely consumed beverage in the world (average consumption of 2.9 cups/day)¹⁵⁰. Coffee intake in moderation appears to be cardiovascular protective^{151,152}. In a dose-response meta-analysis of the relationship of coffee intake and CVD risk (36 studies with 1,279,804 participants), moderate coffee consumption (3 to 5 cups per day), was associated with the lowest CVD risk, while heavy consumption did not increase CVD risk compared to non-consumers¹⁵¹. The 2015–2020 Dietary Guidelines for Americans indicate that consumption of 3 to 5 cups/d of coffee is associated with a reduced risk of CVD in adults¹⁵².

Its consumption has also been studied in relation to the incidence of CAD. Coronary artery calcium (CAC) detected by cardiac computed tomography is a subclinical marker of atherosclerosis, which predicts cardiovascular heart disease^{153,154}. In a study of 1570 adults (Rotterdam Coronary Calcification Study), there was a lower risk of coronary calcification in women consuming more than 3 cups of coffee per day¹⁵⁵. A lower prevalence of coronary atherosclerosis was also found in a cross-sectional study of 25,138 young and middle-aged adults, consuming 3 to 5 cups of coffee per day¹⁵⁶. Another recent study found that the inverse association between coffee intake and coronary calcification persisted even after adjustments for potential confounders, including cardiovascular risk factors¹⁵⁷.

The effect of coffee on CAD health is primarily based on the effects of coffee on BP¹⁵⁸ and lipid levels¹⁵⁹. Although coffee intake may increase the BP in the short-term, in the long-term, intake of coffee, over 2 weeks or more, does not appear to have a substantial impact on BP, in normotensive or hypertensive individuals¹⁵⁸. Coffee is a complex mixture of several compounds including caffeine, minerals, fiber, and other biologically active components, such as diterpene alcohols, cafestol, kahweol, and phenolic acids, that influence human homeostasis and metabolism¹⁶⁰. Coffee, particularly unfiltered coffee (such as French press, Scandinavian boiled coffee, or Turkish coffee) is rich in cholesterol-raising compounds (diterpenes, kahweol, and cafestol) and increases total cholesterol, LDL-C, and triglycerides (TG)^{161,162}. Consumption of filtered coffee does not affect blood lipids^{161,163}. The process of brewing releases oil droplets containing diterpenes from ground coffee beans and these are captured by the paper filter^{161,164}. A high intake of unfiltered coffee (6 cups per day) increases LDL-C by 17.8 mg/dL¹⁶⁵. Coffee also reduces the risk of T2DM – a major cause of CAD¹⁶⁶.

TEA

Tea is consumed in different parts of the world as green, black, or Oolong tea. Of the tea consumed worldwide, 78% is black tea; 20% and 2% is Oolong tea. Green tea is produced by steaming or drying the leaves of *Camellia sinensis* (without fermenting), leaving them rich in polyphenols and strong antioxidant actions. Green tea consumption was associated with a lower

incidence of CAD in a study population in Japan¹⁶⁷. A subsequent meta-analysis of 18 studies included 13 studies on black tea and 5 studies on green tea. While no significant association was seen with the risk of developing CAD with the consumption of black tea, the results were different for green tea. An increase in the intake of 1 cup/day of green tea was associated with a 10% decreased risk of CAD incidence (RR: 0.90)¹⁶⁸. The Harvard Health cites a study of 40,530 Japanese adults, where drinking more than five cups of green tea a day resulted in a 26% lower risk of death from a heart attack (and stroke) than people who drank less than one cup of green tea a day¹⁶⁹. Oolong tea is also helpful. It increases plasma LDL particle size, and this helps prevent LDL oxidation and helps retard atherosclerosis¹⁷⁰.

Polyphenols are the main functional extracts from green tea¹⁷¹. They account for up to 40% of the dry weight of green tea¹⁷². About 60% of all polyphenols are flavonoids. These have a strong antioxidant actions and also exhibit some anti-inflammatory activity. These induce favorable effects on endothelial function¹⁷³. Green tea also reduces LDL-C and TG levels¹⁷⁴. Studies show that dietary flavonoid intake is inversely related to the rate of mortality from CAD^{175,176}.

Comment [PKH1]: A strong antioxidant action

Comment [PKH2]: action

Chocolate:

Comment [PKH3]:

The medical literature is full of studies on the health benefits of cocoa. Its benefits on coronary heart disease have been extensively studied¹⁷⁷. Buijsse, et al. in 2006 reported that when comparing the consumption of >2.25 g cocoa/day (approximately equivalent to the cocoa contents found in 8.5 g of dark chocolate) with the consumption of <0.5 g cocoa/day (approximately equivalent to the cocoa contents in 1.4 g dark chocolate), the risk of CVD death was reduced by 50% in the former group¹⁷⁸. The National Heart, Lung, and Blood Institute Family Heart Study reported an inverse relation between chocolate intake and the prevalence of CAD¹⁷⁹. A subsequent study involving 20,915 adults reported a 12% reduction in CAD (Hazard Ratio=0.88)¹⁸⁰. A Swedish prospective study found that chocolate consumption (≥ 3 –4 servings/week) was associated with a lower risk of myocardial infarction and ischemic heart disease¹⁸¹. Two recent studies reported similar results^{182,183}. A study by Ho et al., published in 2021, also reported CAD protective effects associated with chocolate intake¹⁸⁴. Overall, chocolate is cardioprotective, but the amount needed varies according to the study. It may be safe to limit chocolate intake to <100 gm/week. Dark chocolate contains cocoa bean solids and is associated with most of the coronary health benefits¹⁸⁵. On the other hand, milk chocolate contains, besides cocoa butter and cocoa, sugar, milk powder, and lecithin. It is an energy-dense food and contains a relatively high amount of saturated fat and added sugar¹⁸⁶. In prospective studies, higher milk chocolate intake was associated with greater weight gain¹⁸⁷ and often worse cardiac outcomes¹⁸⁸.

Cocoa beans, the main ingredient of dark chocolate, contain several hundred plant chemicals with many of them exerting cardio-protective effects¹⁸⁹. These include polyphenols, which constitute about 10% of a whole bean's dry weight¹⁹⁰. These polyphenols exert beneficial effects on endothelial function, platelet aggregation, insulin sensitivity, oxidative damage, and inflammation^{191,192}. There is also BP reduction and lipid profile improvement associated with cocoa intake^{193,194}. Cocoa beans also contain fiber and methylxanthines (theobromine and caffeine)¹⁹⁵. Several studies suggest that theobromine may enhance flavanol-related decrease of blood pressure, increase flow-mediated dilatation, and increase HDL-C^{196,197}. The fat in cocoa (40–50% as cocoa butter - approximately 33% oleic acid, 25% palmitic acid, and 33% stearic

acid) appears to have a neutral effect on blood lipid levels¹⁹⁸. Cocoa is also rich in several minerals including potassium, phosphorus, zinc, and magnesium, and these may also play a beneficial role¹⁹⁵.

Conclusion

Coronary artery disease is a major cause of global morbidity and mortality. Lifestyle factors play an important role in its prevention and progression. A plethora of scientific studies has clearly shown the benefits of a plant-based diet. This diet is rich in fruits and vegetables, whole grains, legumes, nuts, and fiber. Oily fish provides EPA and DHA, which are also beneficial. Consumption of dairy and eggs appears to be neutral. Beverages like tea, coffee, and dark chocolate, are also cardioprotective. Alcohol is a double-edged sword, being associated with a reduction in CAD in low to moderate consumption. The deleterious impact of obesity and the consumption of red meat, saturated fats, refined carbohydrates, ultra-processed foods, and sugar-sweetened beverages is discussed in part 2 of this 3-part manuscript.

References

1. Global regional and national age-sex specific all-cause and cause-specific mortality for 240 causes of death 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013 *Lancet*. (2015) 385:117–71. [10.1016/S0140-6736\(14\)61682-2](https://doi.org/10.1016/S0140-6736(14)61682-2).
2. Virani S.S., Alonso A., Benjamin E.J., Bittencourt M.S., Callaway C.W., Carson A.P., Chamberlain A.M., Chang A.R., Cheng S., Delling F.N., et al. Heart disease and stroke statistics—2020 update: A report from the American Heart Association. *Circulation*. 2020;141:E139–E596. doi: [10.1161/CIR.0000000000000757](https://doi.org/10.1161/CIR.0000000000000757).
3. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. Roth GA, Johnson C, Abajobir A, et al. *J Am Coll Cardiol*. 2017;70:1–25.
4. Tellides G, Pober JS. Inflammatory and immune responses in the arterial media. *Circ Res*. 2015;116(2):312–22. <https://doi.org/10.1161/CIRCRESAHA.116.301312>.
5. Zorc-Pleskovic R, Pleskovic A, Vraspir-Porenta O, Zorc M, Milutinovic A. Immune cells and vasa vasorum in the tunica media of atherosclerotic coronary arteries. *Bosn J Basic Med Sci*. 2018;18(3):240–5. <https://doi.org/10.17305/bjbm.2018.2951>.
6. Wang D, Wang Z, Zhang L, Wang Y. Roles of cells from the arterial vessel wall in atherosclerosis. *Mediators Inflamm*. 2017;2017:8135934. <https://doi.org/10.1155/2017/8135934>.
7. Hansson G.K. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352(16):1685–1695.
8. Rahman MS, Woollard K. Atherosclerosis. *Adv Exp Med Biol*. 2017;1003:121-144. doi: [10.1007/978-3-319-57613-8_7](https://doi.org/10.1007/978-3-319-57613-8_7).
9. Ganz P, Abben RP, Barry WH. Dynamic variations in resistance of coronary arterial narrowings in angina pectoris at rest. *Am J Cardiol*. 1987 Jan 1;59(1):66-70. doi: [10.1016/s0002-9149\(87\)80071-1](https://doi.org/10.1016/s0002-9149(87)80071-1).

10. Bentzon J.F., Otsuka F., Virmani R., Falk E. Mechanisms of plaque formation and rupture. *Circ. Res.* 2014;114:1852–1866. doi: 10.1161/CIRCRESAHA.114.302721.64.
11. Olvera Lopez E, Ballard BD, Jan A. Cardiovascular Disease. 2021 Aug 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–.
12. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation.* 2019 Mar 5;139(10):e56-e528. doi: 10.1161/CIR.0000000000000659.
13. GBD 2015 Mortality Causes of Death Collaborators (October 2016). "Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015". *Lancet.* 388 (10053): 1459–1544. doi:10.1016/S0140-6736(16)31012-1
14. https://www.who.int/cardiovascular_diseases/en/cvd_atlas_14_deathHD.pdf?ua=1.
15. <https://www.who.int/initiatives/behealthy/healthy-diet>.
16. Witkamp RF, van Norren K. Let thy food be thy medicine...when possible. *Eur J Pharmacol* 2018;836:102–14.
17. Tröhler U. Lind and scurvy: 1747 to 1795. *J R Soc Med.* 2005 Nov;98(11):519-22. doi: 10.1258/jrsm.98.11.519. Erratum in: *J R Soc Med.* 2006 Jan;99(1):45.
18. Konstantinov I.E., Jankovic G.M. Alexander I. Ignatowski: A pioneer in the study of atherosclerosis. *Tex. Heart Inst. J.* 2013;40:246–249.
19. Esselstyn CB, Jr, Gendy G, Doyle J, et al. A way to reverse CAD? *J Fam Pract.* 2014;63:356–364.
20. Esselstyn CB. A plant-based diet and coronary artery disease: a mandate for effective therapy. *J Geriatr Cardiol.* 2017;14(5):317-320. doi:10.11909/j.issn.1671-5411.2017.05.004
21. Dietary Guidelines Advisory Committee . U.S. Department of Agriculture, Agricultural Research Service; Washington, DC: 2020. Scientific report of the 2020 dietary guidelines advisory committee: advisory report to the secretary of agriculture and the secretary of health and human services.
22. Arnett D.K., Blumenthal R.S., Albert M.A. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2019 Mar 7 doi: 10.1016/j.jacc.2019.03.010.
23. Grundy S.M., Stone N.J., Bailey A.L. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2018 doi: 10.1016/j.jacc.2018.11.003.
24. Jacobson T.A., Maki K.C., Orringer C.E. National lipid association recommendations for patient-centered management of dyslipidemia: Part 2. *J Clin Lipidol.* 2015 Nov-Dec;9(6 Suppl) doi: 10.1016/j.jacl.2015.09.002. S1-122.e1.

25. Blaney D, Diehl H. The optimal diet: the official CHIP cookbook. Hagerstown, MD: Autumn House Publishing; 2009. Jan 1.
26. Esselstyn CB., Jr Resolving the coronary artery disease epidemic through plant-based nutrition. *Prev Cardiol.* 2001 Autumn;4(4):171–7. DOI: <http://dx.doi.org/10.1111/j.1520-037X.2001.00538.x>.
27. Knekt P., Reunanen A., Jarvinen R., Seppanen R., Heliovaara M., Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *Am. J. Epidemiol.* 1994;139:1180–1189. doi: 10.1093/oxfordjournals.aje.a116964.
28. Law, M., Morris, J. By how much does fruit and vegetable consumption reduce the risk of ischaemic heart disease?. *Eur J Clin Nutr* 52, 549–556 (1998). <https://doi.org/10.1038/sj.ejcn.1600603>.
29. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA.* 1998 Dec 16;280(23):2001–7. DOI: <http://dx.doi.org/10.1001/jama.280.23.2001>.
30. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation.* 1999 Feb;99(6):779–85. DOI: <http://dx.doi.org/10.1161/01.CIR.99.6.779>.
31. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation.* 1999 Feb;99(6):779–85. DOI: <http://dx.doi.org/10.1161/01.CIR.99.6.779>.
32. Yokoyama Y, Nishimura K, Barnard ND, et al. Vegetarian diets and blood pressure: a meta-analysis. *JAMA Intern Med.* 2014;174:577-587.
33. Piano MR. Alcohol's Effects on the Cardiovascular System. *Alcohol Res.* 2017;38(2):219-241.
34. Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38 000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes Metab Disord.* 2003;27:728-734.
35. Avenell A, Broom I, Brown TJ, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess.* 2004;8(21):iii–iv. 1–182.
36. Arnett D.K., Blumenthal R.S., Albert M.A. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2019 Mar 7 doi: 10.1016/j.jacc.2019.03.010. pii: S0735-1097(19)33877-X.
37. Grundy S.M., Stone N.J., Bailey A.L. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2018 doi: 10.1016/j.jacc.2018.11.003.

38. Jacobson T.A., Maki K.C., Orringer C.E. National lipid association recommendations for patient-centered management of dyslipidemia: Part 2. *J Clin Lipidol*. 2015 Nov-Dec;9(6 Suppl) doi: 10.1016/j.jacl.2015.09.002. S1-122.e1.
39. Gummesson A, Nyman E, Knutsson M, Karpefors M. Effect of weight reduction on glycated haemoglobin in weight loss trials in patients with type 2 diabetes. *Diabetes Obes Metab*. 2017;19(9):1295–1305.
40. Prevalence of small vessel and large vessel disease in diabetic patients from 14 centres. The World Health Organisation Multinational Study of Vascular Disease in Diabetics. Diabetes Drafting Group. *Diabetologia*. 1985;28 Suppl:615–640.
41. Haghghatdoost F, Bellissimo N, Totosy de Zepetnek JO, Rouhani MH. Association of vegetarian diet with inflammatory biomarkers: a systematic review and meta-analysis of observational studies. *Public Health Nutr*. 2017;20:2713–2721. doi: 10.1017/S1368980017001768.
42. Craddock JC, Neale EP, Peoples GE, Probst YC. Vegetarian-Based Dietary Patterns and their Relation with Inflammatory and Immune Biomarkers: A Systematic Review and Meta-Analysis. *Adv Nutr*. 2019 May 1;10(3):433-451. doi: 10.1093/advances/nmy103.
43. Menzel J, Jabakhanji A, Biemann R, Mai K, Abraham K, Weikert C. Systematic review and meta-analysis of the associations of vegan and vegetarian diets with inflammatory biomarkers. *Sci Rep*. 2020;10(1):21736. Published 2020 Dec 10. doi:10.1038/s41598-020-78426-8.
44. Nissen S.E., Tuzcu E.M., Schoenhagen P., Brown B.G., Ganz P., Vogel R.A., Crowe T., Howard G., Cooper C.J., Brodie B., et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: A randomized controlled trial. *JAMA*. 2004;291:1071–1080. doi: 10.1001/jama.291.9.1071.
45. Cannon C.P., Braunwald E., McCabe C.H., Rader D.J., Rouleau J.L., Belder R., Joyal S.V., Hill K.A., Pfeffer M.A., Skene A.M., et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N. Engl. J. Med*. 2004;350:1495–1504. doi: 10.1056/NEJMoa040583.
46. Ridker P.M., Everett B.M., Thuren T., MacFadyen J.G., Chang W.H., Ballantyne C., Fonseca F., Nicolau J., Koenig W., Anker S.D., et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N. Engl. J. Med*. 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914.
47. Ridker P.M., Libby P., MacFadyen J.G., Thuren T., Ballantyne C., Fonseca F., Koenig W., Shimokawa H., Everett B.M., Glynn R.J. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: Analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) *Eur. Heart J*. 2018;39:3499–3507. doi: 10.1093/eurheartj/ehy310.
48. Tuso PJ, Ismail MH, Ha BJ, Bartolotto C. Nutritional update for physicians: plant-based diets. *Perm J*. 2013 Spring;17(2):61–6. DOI: <http://dx.doi.org/10.7812/TPP/12-085>.
49. Sebeková K, Boor P, Valachovicová M, et al. Association of metabolic syndrome risk factors with selected markers of oxidative status and microinflammation in healthy omnivores and vegetarians. *Mol Nutr Food Res*. 2006 Sep;50(9):858–68. DOI: <http://dx.doi.org/10.1002/mnfr.200500170>.

50. Yang SY, Zhang HJ, Sun SY, et al. Relationship of carotid intima-media thickness and duration of vegetarian diet in Chinese male vegetarians. *Nutr Metab (Lond)* 2011 Sep 19;8(1):63. DOI: <http://dx.doi.org/10.1186/1743-7075-8-63>.
51. Tuso P, Stoll SR, Li WW. A plant-based diet, atherogenesis, and coronary artery disease prevention. *Perm J*. 2015;19(1):62-67. doi:10.7812/TPP/14-036.
52. Key, T., Fraser, G., Thorogood, M., et al. Mortality in vegetarians and non-vegetarians: A collaborative analysis of 8300 deaths among 76,000 men and women in five prospective studies. *Public Health Nutrition*, 1998. 1(1), 33-41. doi:10.1079/PHN19980006.
53. Kahleova H, Levin S, Barnard ND. Vegetarian Dietary Patterns and Cardiovascular Disease. *Prog Cardiovasc Dis*. 2018 May-Jun;61(1):54-61. doi: 10.1016/j.pcad.2018.05.002.
54. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet*. 1990 Jul 21;336(8708):129-33. doi: 10.1016/0140-6736(90)91656-u.
55. <https://www.acc.org/about-acc/press-releases/2017/07/17/13/33/not-all-plant-based-diets-are-created-equal>.
56. <https://www.hsph.harvard.edu/nutritionsource/carbohydrates/>.
57. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet*. 2006;367:320-6.
58. Zhu F, Qin Y, Bi Y, et al. Fresh vegetable and fruit consumption and carotid atherosclerosis in high-cardiovascular-risk population: a cross-sectional study in Jiangsu, China. *Cad Saude Publica*. 2021 Jun 9;37(5):e00033020. doi: 10.1590/01021-311X00033020.
59. Wang W, Wang Y, Gao X, Zhao Z, Li L, Yu B, Liu G, Lin P. Association between food and nutrients intakes and coronary plaque vulnerability in patients with coronary heart disease: An optical coherence tomography study. *Nutr Metab Cardiovasc Dis*. 2021 Jan 4;31(1):201-208. doi: 10.1016/j.numecd.2020.08.027.
60. Liu S, Manson JE, Lee IM, et al. Fruit and vegetable intake and risk of cardiovascular disease: the women's health study. *Am J Clin Nutr*. 2000;72:922-8.
61. Josphipura KJ, Hu FB, Manson JE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med*. 2001;134:1106-14.
62. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. 2017 Jun 1;46(3):1029-1056. doi: 10.1093/ije/dyw319.
63. Dauchet L, Amouyel P, Hercberg S, et al. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies *J Nutr* 2006; 136: 2588-2593.
64. Pandey K.B., Rizvi S.I. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid. Med. Cell. Longev*. 2009;2:270-278. doi: 10.4161/oxim.2.5.9498.
65. Williamson G. The role of polyphenols in modern nutrition. *Nutr. Bull*. 2017;42:226-235. doi: 10.1111/nbu.12278.

66. Helnæs A, Kyrø C, Andersen I, et al. Intake of whole grains is associated with lower risk of myocardial infarction: the Danish Diet, Cancer and Health Cohort. *Am J Clin Nutr* 2016;103:999-1007. doi: 10.3945/ajcn.115.124271.
67. Steffen LM, Jacobs DR Jr, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr*. 2003 Sep;78(3):383-90. doi: 10.1093/ajcn/78.3.383.
68. Erkkilä AT, Herrington DM, Mozaffarian D, Lichtenstein AH. Cereal fiber and whole-grain intake are associated with reduced progression of coronary-artery atherosclerosis in postmenopausal women with coronary artery disease. *Am Heart J*. 2005 Jul;150(1):94-101. doi: 10.1016/j.ahj.2004.08.013.
69. Tang G., Wang D., Long J., Yang F., Si L. Meta-Analysis of the Association Between Whole Grain Intake and Coronary Heart Disease Risk. *Am. J. Cardiol.* 2015;115:625–629. doi: 10.1016/j.amjcard.2014.12.015.
70. Aune D., Keum N., Giovannucci E., et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: Systematic review and dose-response meta-analysis of prospective studies. *BMJ*. 2016;353:i2716. doi: 10.1136/bmj.i2716.
71. Anderson JW, Smith BM, Washnock CS. Cardiovascular and renal benefits of dry bean and soybean intake. *Am J Clin Nutr*. 1999;70(3 Suppl):464S-474S.
72. Mudryj AN, Yu N, Aukema HM. Nutritional and health benefits of pulses. *Appl Physiol Nutr Metab*. 2014;39(11):1197-1204. ; Messina V. Nutritional and health benefits of dried beans. *Am J Clin Nutr*. 2014;100 Suppl 1:437S-442S.
73. Afshin A, Micha R, Khatibzadeh S, Mozaffarian D. Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr*. 2014;100(1):278-288.
74. Marventano S, Izquierdo Pulido M, Sanchez-Gonzalez C, et al. Legume consumption and CVD risk: a systematic review and meta-analysis. *Public Health Nutr*. 2017;20(2):245-254.
75. Jayalath VH, de Souza RJ, Sievenpiper JL, et al. Effect of dietary pulses on blood pressure: a systematic review and meta-analysis of controlled feeding trials. *Am J Hypertens*. 2014;27(1):56-64.
76. Becerra-Tomas N, Diaz-Lopez A, Rosique-Esteban N, et al. Legume consumption is inversely associated with type 2 diabetes incidence in adults: A prospective assessment from the PREDIMED study. *Clin Nutr*. 2018;37(3):906-913.
77. Tan SY, Tey SL, Brown R. Nuts and Older Adults' Health: A Narrative Review. *Int J Environ Res Public Health*. 2021;18(4):1848. Published 2021 Feb 14. doi:10.3390/ijerph18041848.
78. Tan S.Y., Tey S.L., Brown R. Can Nuts Mitigate Malnutrition in Older Adults? A Conceptual Framework. *Nutrients*. 2018;10:1448. doi: 10.3390/nu10101448.

79. Kornsteiner-Krenn M., Wagner K.H., Elmadfa I. Phytosterol content and fatty acid pattern of ten different nut types. *Int. J. Vitam. Nutr. Res.* 2013;83:263–270. doi: 10.1024/0300-9831/a000168.
80. Jackson C.L., Hu F.B. Long-term associations of nut consumption with body weight and obesity. *Am. J. Clin. Nutr.* 2014;100:408S–411S. doi: 10.3945/ajcn.113.071332.
81. Eaton S.B., Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N. Engl. J. Med.* 1985;312:283–289. doi: 10.1056/NEJM198501313120505.
82. Guasch-Ferré M, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, Rexrode KM, Li Y, Hu FB, Bhupathiraju SN. Nut consumption and risk of cardiovascular disease. *Journal of the American College of Cardiology.* 2017 Nov 21;70(20):2519-32.
83. Liu G, Guasch-Ferré M, Hu Y, Li Y, Hu FB, Rimm EB, Manson JE, Rexode K, Sun Q. Nut Consumption in Relation to Cardiovascular Disease Incidence and Mortality among Patients with Diabetes Mellitus. *Circulation Research.* 2019 Feb 19.
84. Jacobson T.A., Maki K.C., Orringer C.E. National lipid association recommendations for patient-centered management of dyslipidemia: Part 2. *J Clin Lipidol.* 2015 Nov-Dec;9(6 Suppl) doi: 10.1016/j.jacl.2015.09.002. S1-122.e1.
85. <https://www.diabetes.co.uk/nutrition/insoluble-fibre.html>.
86. McRae MP. Dietary Fiber Is Beneficial for the Prevention of Cardiovascular Disease: An Umbrella Review of Meta-analyses. *J Chiropr Med.* 2017 Dec;16(4):289-299. doi: 10.1016/j.jcm.2017.05.005.
87. Erkkilä AT, Herrington DM, Mozaffarian D, Lichtenstein AH. Cereal fiber and whole-grain intake are associated with reduced progression of coronary-artery atherosclerosis in postmenopausal women with coronary artery disease. *Am Heart J.* 2005 Jul;150(1):94-101. doi: 10.1016/j.ahj.2004.08.013.
88. Chen J.P., Chen G.C., Wang X.P., Qin L., Bai Y. Dietary fiber and metabolic syndrome: A meta-analysis and review of related mechanisms. *Nutrients.* 2018;10:24. doi: 10.3390/nu10010024
89. Morimoto N., Kasuga C., Tanaka A., Kamachi K., Ai M., Urayama K.Y., Tanaka A. Association between dietary fibre: Carbohydrate intake ratio and insulin resistance in Japanese adults without type 2 diabetes. *Br. J. Nutr.* 2018;119:620–628. doi: 10.1017/S0007114517003725.
90. Aljuraiban G.S., Griep L.M., Chan Q., et al. Total, insoluble and soluble dietary fibre intake in relation to blood pressure: The Intermap Study. *Br. J. Nutr.* 2015;114:1480–1486. doi: 10.1017/S0007114515003098.
91. Du H., van der A.D., Boshuizen H.C., et al. Dietary fiber and subsequent changes in body weight and waist circumference in European men and women. *Am. J. Clin. Nutr.* 2010;91:329–336. doi: 10.3945/ajcn.2009.28191.
92. Anderson J.W., Baird P., Davis R.H., et al. Health benefits of dietary fiber. *Nutr. Rev.* 2009;67:188–205. doi: 10.1111/j.1753-4887.2009.00189.x.
93. Lloyd-Jones D.M., Hong Y., Labarthe D., et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart

- Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703.
94. Yu E, Hu F. Dairy products, dairy fatty acids, and the prevention of cardiometabolic disease: a review of recent evidence. *Curr Atheroscler Rep*. (2018) 20:24. doi: 10.1007/s11883-018-0724-z.
 95. Poppitt SD. Cow's Milk and Dairy Consumption: Is There Now Consensus for Cardiometabolic Health? *Front Nutr*. 2020 Dec 8;7:574725. doi: 10.3389/fnut.2020.574725.
 96. Ballard KD, Bruno RS. Protective role of dairy and its constituents on vascular function independent of blood pressure-lowering activities. *Nutr Rev* 2015; 73: 36–50.
 97. Fekete AA, Givens DI, Lovegrove JA. The impact of milk proteins and peptides on blood pressure and vascular function: a review of evidence from human intervention studies. *Nutr Res Rev*. 2013 Dec;26(2):177-90. doi: 10.1017/S0954422413000139.
 98. Ghosh S, He W, Gao J, Luo D, Wang J, Chen J, Huang H. Whole milk consumption is associated with lower risk of coronary artery calcification progression: evidences from the Multi-Ethnic Study of Atherosclerosis. *Eur J Nutr*. 2021 Mar;60(2):1049-1058. doi: 10.1007/s00394-020-02301-5.
 99. Chrysant SG, Chrysant GS. An update on the cardiovascular pleiotropic effects of milk and milk products. *J Clin Hypertens (Greenwich)* 2013; 15: 503–510.
 100. Poppitt SD. Cow's Milk and Dairy Consumption: Is There Now Consensus for Cardiometabolic Health? *Front Nutr*. 2020 Dec 8;7:574725. doi: 10.3389/fnut.2020.574725.
 101. Guo J, et al. Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Eur. J. Epidemiol*. 2017;32:269–287. doi: 10.1007/s10654-017-0243-1.
 102. Jakobsen MU, Trolle E, Outzen M, Mejborn H, Grønberg MG, Lyndgaard CB, Stockmarr A, Venø SK, Bysted A. Intake of dairy products and associations with major atherosclerotic cardiovascular diseases: a systematic review and meta-analysis of cohort studies. *Sci Rep*. 2021 Jan 14;11(1):1303. doi: 10.1038/s41598-020-79708-z.
 103. <https://www.heart.org/>.
 104. Hu FB, Stampfer MJ, Rimm EB, et al. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA* 1999;281:1387-94. doi: 10.1001/jama.281.15.1387.
 105. Kritchevsky SB, Kritchevsky D. Egg consumption and coronary heart disease: an epidemiologic overview. *J Am Coll Nutr*. 2000 Oct;19(5 Suppl):549S-555S. doi: 10.1080/07315724.2000.10718979.
 106. Alexander DD, Miller PE, Vargas AJ, Weed DL, Cohen SS. Meta-analysis of Egg Consumption and Risk of Coronary Heart Disease and Stroke. *J Am Coll Nutr*. 2016 Nov-Dec;35(8):704-716. doi: 10.1080/07315724.2016.1152928.
 107. Drouin-Chartier JP, Chen S, Li Y, et al. Egg consumption and risk of cardiovascular disease: three large prospective US cohort studies, systematic review, and updated meta-analysis. *BMJ*. 2020;368:m513. doi:10.1136/bmj.m513.

108. Xia PF, Pan XF, Chen C, Wang Y, Ye Y, Pan A. Dietary Intakes of Eggs and Cholesterol in Relation to All-Cause and Heart Disease Mortality: A Prospective Cohort Study. *J Am Heart Assoc.* 2020 May 18;9(10):e015743. doi: 10.1161/JAHA.119.015743.
109. Zhuang P, Wu F, Mao L, et al. Egg and cholesterol consumption and mortality from cardiovascular and different causes in the United States: A population-based cohort study. *PLoS Med.* 2021;18(2):e1003508. Published 2021 Feb 9. doi:10.1371/journal.pmed.1003508.
110. Li Y, Zhou C, Zhou X, Li L. Egg consumption and risk of cardiovascular diseases and diabetes: a meta-analysis. *Atherosclerosis.* 2013 Aug;229(2):524-30. doi: 10.1016/j.atherosclerosis.2013.04.003.
111. Nicholas R Fuller, Amanda Sainsbury, Ian D Caterson, et al. Effect of a high-egg diet on cardiometabolic risk factors in people with type 2 diabetes: the Diabetes and Egg (DIABEGG) Study—randomized weight-loss and follow-up phase, *The American Journal of Clinical Nutrition*, Volume 107, Issue 6, June 2018, Pages 921–931.
112. Micha R., Wallace S.K., Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus. *Circulation.* 2010;121:2271–2283. doi: 10.1161/CIRCULATIONAHA.109.924977.
113. Micha R., Michas G., Mozaffarian D. Unprocessed red and processed meats and risk of coronary artery disease and type 2 diabetes—An updated review of the evidence. *Curr. Atheroscler. Rep.* 2012;14:515–524. doi: 10.1007/s11883-012-0282-8.
114. Micha R., Michas G., Lajous M., Mozaffarian D. Processing of meats and cardiovascular risk: Time to focus on preservatives. *BMC Med.* 2013;11:136. doi: 10.1186/1741-7015-11-136.
115. Fang X., An P., Wang H., Wang X., Shen X., Li X., Min J., Liu S., Wang F. Dietary intake of heme iron and risk of cardiovascular disease: A dose–response meta-analysis of prospective cohort studies. *Nutr. Metab. Cardiovasc. Dis.* 2015;25:24–35. doi: 10.1016/j.numecd.2014.09.002.
116. Han M., Guan L., Ren Y., Zhao Y., Liu D., Zhang D., Liu L., Liu F., Chen X., Cheng C., et al. Dietary iron intake and risk of death due to cardiovascular diseases: A systematic review and dose-response meta-analysis of prospective cohort studies. *Asia Pac. J. Clin. Nutr.* 2020;29:309–321.
117. Abete I, Romaguera D, Vieira AR, Lopez de Munain A, Norat T. Association between total, processed, red and white meat consumption and all-cause, CVD and IHD mortality: a meta-analysis of cohort studies. *Br J Nutr.* 2014;112(5):762-775. doi:10.1017/S000711451400124X.
118. Zhong VW, Van Horn L, Greenland P, Carnethon MR, Ning H, Wilkins JT, Lloyd-Jones DM, Allen NB. Associations of Processed Meat, Unprocessed Red Meat, Poultry, or Fish Intake With Incident Cardiovascular Disease and All-Cause Mortality. *JAMA Intern Med.* 2020 Apr 1;180(4):503-512. doi: 10.1001/jamainternmed.2019.6969.
119. Tong T.Y.N., Appleby P.N., Key T.J., et al. The associations of major foods and fibre with risks of ischaemic and haemorrhagic stroke: A prospective study of 418,329 participants in the EPIC cohort across nine European countries. *Eur. Heart J.* 2020;41:2632–2640. doi: 10.1093/eurheartj/ehaa007.

120. Hu F.B. Protein, body weight, and cardiovascular health. *Am. J. Clin. Nutr.* 2005;82:242S–247S. doi: 10.1093/ajcn/82.1.242S.
121. Siscovick DS, Barringer TA, Fretts AM, et al. Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association. *Circulation.* 2017;135(15):e867–e884. doi:10.1161/CIR.0000000000000482.
122. Lee JH, O’Keefe JH, Lavie CJ, Harris WS. Omega-3 fatty acids: cardiovascular benefits, sources and sustainability. *Nature reviews Cardiology.* 2009;6:753–8. ; Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *Journal of the American College of Cardiology.* 2009;54:585–94.
123. H. Iso, M. Kobayashi, J. Ishihara, S. Sasaki, K. Okada, Y. Kita, et al. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: The Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation,* 113 (2006), pp. 195-202.
124. M.L. Daviglius, J. Stamler, A.J. Orenca, A.R. Dyer, K. Liu, P. Greenland, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med,* 336 (1997), pp. 1046-1053.
125. C. Wang, W.S. Harris, M. Chung, A.H. Lichtenstein, E.M. Balk, B. Kupelnick, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr,* 84 (2006), pp. 5-17.
126. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish and fibre intakes on death and myocardial re-infarction: Diet And Re-infarction Trial (DART). *Lancet.* 1989; 2: 757–761.
127. Wang D.D., Li Y., Chiuve S.E., Stampfer M.J., Manson J.E., Rimm E.B., Willett W.C., Hu F.B. Association of specific dietary fats with total and cause-specific mortality. *JAMA Intern Med.* 2016;176:1134–1145.
128. Anand S, Hawkes C, de Souza RJ, et al. Food consumption and its impact on cardiovascular disease: Importance of solutions focused on the globalized food system. *J Am Coll Cardiol* 2016;66(14):1590-1614. <https://doi.org/10.1016/j.jacc.2015.07.050>.
129. Philip C. CALDER; n–3 Fatty acids and cardiovascular disease: evidence explained and mechanisms explored. *Clin Sci (Lond)* 1 July 2004; 107 (1): 1–11. doi: <https://doi.org/10.1042/CS20040119>.
130. Corrao G, Bagnardi V, Zamboni A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med* 2004;38:613-9. [10.1016/j.ypmed.2003.11.027](https://doi.org/10.1016/j.ypmed.2003.11.027).
131. O’Keefe JH, Bhatti SK, Bajwa A, et al. Alcohol and cardiovascular health: the dose makes the poison...or the remedy. *Mayo Clin Proc* 2014; 89: 382–393.
132. O’Keefe EL, DiNicolantonio JJ, O’Keefe JH, et al. Alcohol and CV health: Jekyll and Hyde J-curves. *Prog Cardiovasc Dis* 2018; 61: 68–75.
133. Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. *BMJ.* 2011;342:d671.

134. Mostofsky E, Chahal HS, Mukamal KJ, et al. Alcohol and immediate risk of cardiovascular events: A systematic review and dose-response meta-analysis. *Circulation*. 2016;133(10):979–987.
135. Au Yeung SL, Jiang C, Cheng KK, et al. Moderate alcohol use and cardiovascular disease from Mendelian randomization. *PLoS One*. 2013;8(7):e68054. Published 2013 Jul 16. doi:10.1371/journal.pone.0068054.
136. Chagas P, Mazocco L, Piccoli JDCE, Ardenghi TM, Badimon L, Caramori PRA, Pellanda L, Gomes I, Schwanke CHA. Association of alcohol consumption with coronary artery disease severity. *Clin Nutr*. 2017 Aug;36(4):1036-1039. doi: 10.1016/j.clnu.2016.06.017.
137. Zhao J, Stockwell T, Roemer A, Naimi T, Chikritzhs T. Alcohol Consumption and Mortality From Coronary Heart Disease: An Updated Meta-Analysis of Cohort Studies. *J Stud Alcohol Drugs*. 2017;78(3):375–386. 10.15288/jsad.2017.78.375.
138. Bagnardi V, Zatonski W, Scotti L, La Vecchia C, Corrao G. Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis. *J Epidemiol Community Health* 2008;62:615-9. 10.1136/jech.2007.065607.
139. Mukamal KJ, Maclure M, Muller JE, Sherwood JB, Mittleman MA. Prior alcohol consumption and mortality following acute myocardial infarction. *JAMA*. 2001;285(15):1965–1970. 10.1001/jama.285.15.1965.
140. Grabas MP, Hansen SM, Torp-Pedersen C, Bøggild H, Ullits LR, Deding U, Nielsen BJ, Jensen PF, Overgaard C. Alcohol consumption and mortality in patients undergoing coronary artery bypass graft (CABG)-a register-based cohort study. *BMC Cardiovasc Disord*. 2016 Nov 11;16(1):219. doi: 10.1186/s12872-016-0403-3.
141. Yun KE, Chang Y, Yun SC, Davey Smith G, Ryu S, Cho SI, Chung EC, Shin H, Khang YH. Alcohol and coronary artery calcification: an investigation using alcohol flushing as an instrumental variable. *Int J Epidemiol*. 2017 Jun 1;46(3):950-962. doi: 10.1093/ije/dyw237.
142. Mori T.A., Burke V., Beilin L.J., Puddey I.B. Randomized Controlled Intervention of the Effects of Alcohol on Blood Pressure in Premenopausal Women. *Hypertension*. 2015;66:517–523. doi: 10.1161/HYPERTENSIONAHA.115.05773.
143. Gaziano JM, Buring JE, Breslow JL, Goldhaber SZ, Rosner B, VanDenburgh M, Willett W, Hennekens CH. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *New Engl J Med* 1993;329:1829–1834.
144. Knott C, Bell S, Britton A. Alcohol Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Dose-Response Meta-analysis of More Than 1.9 Million Individuals From 38 Observational Studies. *Diabetes Care*. 2015 Sep;38(9):1804-12. doi: 10.2337/dc15-0710.
145. Gisbertz SS, Derksen WJ, de Kleijn DP, Vink A, Bots ML, de Vries JP, Moll FL, Pasterkamp G. The effect of alcohol on atherosclerotic plaque composition and cardiovascular events in patients with arterial occlusive disease. *J Vasc Surg* 2011;54:123–131.

146. Pace-Asciak CR, Hahn S, Diamandis EP, Soleas G, Goldberg DM. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. *Clin Chim Acta*, (2):207-219 19957.
147. Dimmitt SB, Rakic V, Puddey IB, Baker R, Oostryck R, Adams MJ, Chesterman CN, Burke V, Beilin LJ. The effects of alcohol on coagulation and fibrinolytic factors: a controlled trial. *Blood Coagul Fibrinolysis*, (1):39-45 19988-10.
148. Mukamal KJ, Jadhav PP, D'Agostino RB, Massaro JM, Mittleman MA, Lipinska I, Sutherland PA, Matheney T, Levy D, Wilson PW, Ellison RC, Silbershatz H, Muller JE, Toftler GH. Alcohol consumption and hemostatic factors: analysis of the Framingham Offspring cohort. *Circulation*, (12):1367-1373 200110.
149. Yarnell JW, Sweetnam PM, Rumley A, Lowe GD. Lifestyle and hemostatic risk factors for ischemic heart disease : the Caerphilly Study. *Arterioscler Thromb Vasc Biol*, (1):271-279 2000.MED: 10634829.
150. <http://www.gallup.com/poll/184388/americans-coffee-consumption-steady-few-cut-back.aspx>.
151. Ding M., Bhupathiraju S.N., Satija A., van Dam R.M., Hu F.B. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation*. 2014;129(6):643–659. doi: 10.1161/CIRCULATIONAHA.113.005925.
152. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015- 2020 Dietary Guidelines for Americans. 8th ed. 2015. Available at: <http://health.gov/dietaryguidelines/2015/guidelines/>. Accessed January 28, 2017.
153. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) *Circulation*. 2007;115:402–26.
154. Haberl R, Becker A, Leber A, Knez A, Becker C, Lang C, et al. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol*. 2001;37:451–7.
155. van Woudenberg GJ, Vliegthart R, van Rooij FJ, Hofman A, Oudkerk M, Witteman JC, et al. Coffee consumption and coronary calcification: the Rotterdam Coronary Calcification study. *Arterioscler Thromb Vasc Biol*. 2008;28:1018–23.
156. Choi Y, Chang Y, Ryu S, Cho J, Rampal S, Zhang Y, et al. Coffee consumption and coronary artery calcium in young and middle-aged asymptomatic adults. *Heart*. 2015;101:686–91.
157. Miranda AM, Steluti J, Goulart AC, Benseñor IM, Lotufo PA, Marchioni DM. Coffee Consumption and Coronary Artery Calcium Score: Cross-Sectional Results of

- ELSA-Brasil (Brazilian Longitudinal Study of Adult Health). *J Am Heart Assoc.* 2018 Mar 24;7(7):e007155. doi: 10.1161/JAHA.117.007155.
158. Mesas A.E., Leon-Muñoz L.M., Rodriguez-Artalejo F., Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. *Am J Clin Nutr.* 2011;94(4):1113–1126. doi: 10.3945/ajcn.111.016667
159. Farias-Pereira R, Park CS, Park Y. Mechanisms of action of coffee bioactive components on lipid metabolism. *Food Sci Biotechnol.* 2019 Aug 12;28(5):1287-1296. doi: 10.1007/s10068-019-00662-0.
160. Godos J, Pluchinotta FR, Marventano S, Buscemi S, Li Volti G, Galvano F, Grosso G. Coffee components and cardiovascular risk: beneficial and detrimental effects. *Int J Food Sci Nutr.* 2014;65:925–936.
161. Ranheim T, Halvorsen B. Coffee consumption and human health- beneficial or detrimental? Mechanisms for effects of coffee consumption on different risk factors for cardiovascular disease and type 2 diabetes mellitus. *Mol Nutr Food Res.* 2005;49:274–284.
162. Cai L, Ma D, Zhang Y, Liu Z, Wang P. The effect of coffee consumption on serum lipids: a meta- analysis of randomized controlled trials. *Eur J Clin Nutr.* 2012;66:872–877. ; Cano- Marquina A, Tarín JJ, Cano A. The impact of coffee on health. *Maturitas.* 2013;75:7–21.
163. Rebello SA, van Dam RM. Coffee consumption and cardiovascular health: getting to the heart of the matter. *Curr Cardiol Rep.* 2013;15:403.
164. Cano- Marquina A, Tarín JJ, Cano A. The impact of coffee on health. *Maturitas.* 2013;75:7–21.
165. Geeta Sikand, Tracy Severson. Top 10 dietary strategies for atherosclerotic cardiovascular risk reduction. *American Journal of Preventive Cardiology*, Volume 6, June 2021, Pages 100174.
166. Kolb H, Martin S, Kempf K. Coffee and Lower Risk of Type 2 Diabetes: Arguments for a Causal Relationship. *Nutrients.* 2021 Mar 31;13(4):1144. doi: 10.3390/nu13041144.
167. Sano J, Inami S, Seimiya K, Ohba T, Sakai S, Takano T, Mizuno K. Effects of green tea intake on the development of coronary artery disease. *Circ J.* 2004 Jul;68(7):665-70. doi: 10.1253/circj.68.665.
168. Wang Z.M., Zhou B., Wang Y.S., Gong Q.Y., Wang Q.M., Yan J.J., Gao W., Wang L.S. Black and green tea consumption and the risk of coronary artery disease: A meta-analysis. *Am. J. Clin. Nutr.* 2011;93:506–515. doi: 10.3945/ajcn.110.005363.
169. <https://www.health.harvard.edu/heart-health/green-tea-may-lower-heart-disease-risk>.
170. Shimada K, Kawarabayashi T, Tanaka A, et al. Oolong tea increases plasma adiponectin levels and low-density lipoprotein particle size in patients with coronary artery disease. *Diabetes Res Clin Pract.* 2004;65:227–234. doi: 10.1016/j.diabres.2004.01.003.

171. Higdon JV, Frei B. Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. *Crit Rev Food Sci Nutr* 2003;43:89–143.
172. Clement Y. Can green tea do that? A literature review of the clinical evidence. *Prev. Med.* 2009;49:83–87. doi: 10.1016/j.ypmed.2009.05.005.
173. Deka A., Vita J.A. Tea and cardiovascular disease. *Pharmacol. Res.* 2011;64:36–145. doi: 10.1016/j.phrs.2011.02.008.
174. Hooper L., Kroon P.A., Rimm E.B., Cohn J.S., Harvey I., Le Cornu K.A., Ryder J.J., Hall W.L., Cassidy A. Flavonoids, flavonoid-rich foods, and cardiovascular risk: A meta-analysis of randomized controlled trials. *Am. J. Clin. Nutr.* 2008;88:38–50.
175. Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen Elderly Study. *Lancet* 1993; 342: 1007 – 1011.
176. Mukamal KJ, Maclure M, Muller JE, Sherwood JB, Mittleman MA. Tea consumption and mortality after acute myocardial infarction. *Circulation* 2002; 105: 2476 – 2481.
177. Magrone T, Russo MA, Jirillo E. Cocoa and Dark Chocolate Polyphenols: From Biology to Clinical Applications. *Front Immunol.* 2017 Jun 9;8:677. doi: 10.3389/fimmu.2017.00677.
178. 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):411–17.) Several studies have focused on the benefits of cocoa intake on CAD.
179. 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* 2011;30(2):182–7.
180. Kwok CS, Boekholdt SM, Lentjes MAH, Loke YK, Luben RN, Yeong JK, Wareham NJ, Myint PK, Khaw K-T. Habitual chocolate consumption and risk of cardiovascular disease among healthy men and women. *Heart* 2015;101(16):1279–87.
181. Larsson S.C., Akesson A., Gigante B., Wolk A. Chocolate consumption and risk of myocardial infarction: A prospective study and meta-analysis. *Heart.* 2016;102:1017–1022. doi: 10.1136/heartjnl-2015-309203.
182. Steinhaus D.A., Mostofsky E., Levitan E.B., Dorans K.S., Hakansson N., Wolk A., Mittleman M.A. Chocolate intake and incidence of heart failure: Findings from the Cohort of Swedish Men. *Am. Heart J.* 2017;183:18–23. doi: 10.1016/j.ahj.2016.10.002.
183. Morze J, Schwedhelm C, Bencic A, et al. Chocolate and risk of chronic disease: a systematic review and dose-response meta-analysis. February 2020 *European Journal of Nutrition.* DOI: 10.1007/s00394-019-01914-9.
184. Ho YL, Nguyen XT, Yan JQ, et al. Chocolate consumption and risk of coronary artery disease: the Million Veteran Program. *Am J Clin Nutr.* 2021 May;113(5):1137–1144. doi: 10.1093/ajcn/nqaa427.
185. Engler MB, Engler MM, Chen CY, et al. Flavonoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. *J Am Coll Nutr.* 2004;23:197-204.

186. Duyf RL, Birch LL, Byrd-Bredbenner C, et al. (2015) Candy consumption patterns, effects on health, and behavioral strategies to promote moderation: summary report of a roundtable discussion. *Adv Nutr* 6(1):139 s–146 s. <https://doi.org/10.3945/an.114.007302>.
187. Greenberg JA, Buijsse B (2013) Habitual chocolate consumption may increase body weight in a dose-response manner. *PLoS One* 8(8):e70271. <https://doi.org/10.1371/journal.pone.0070271>.
188. Steinhaus D.A., Mostofsky E., Levitan E.B., Dorans K.S., Hakansson N., Wolk A., Mittleman M.A. Chocolate intake and incidence of heart failure: Findings from the Cohort of Swedish Men. *Am. Heart J.* 2017;183:18–23. doi: 10.1016/j.ahj.2016.10.002.
189. Krittanawong C, Narasimhan B, Wang Z, Hahn J, Virk HUH, Farrell AM, Zhang H, Tang WW. Association between chocolate consumption and risk of coronary artery disease: a systematic review and meta-analysis. *Eur J Prev Cardiol.* 2020 Jul 22:2047487320936787. doi: 10.1177/2047487320936787.
190. Rusconi M., Conti A. Theobroma cacao L., the Food of the Gods: A scientific approach beyond myths and claims. *Pharmacol. Res.* 2010;61:5–13. doi: 10.1016/j.phrs.2009.08.008.
191. Lin X, Zhang I, Li A, Manson JE, Sesso HD, Wang L, Liu S (2016) Cocoa Flavanol intake and biomarkers for cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Nutr* 146(11):2325–2333. <https://doi.org/10.3945/jn.116.237644>.
192. Katz DL, Doughty K, Ali A (2011) Cocoa and chocolate in human health and disease. *Antioxid Redox Signal* 15(10):2779–2811. <https://doi.org/10.1089/ars.2010.3697>.
193. Ried K, Fakler P, Stocks NP (2017) Effect of cocoa on blood pressure. *Cochrane Database Syst Rev* 4:Cd008893. <https://doi.org/10.1002/14651858.CD008893.pub3>.
194. Lin X, Zhang I, Li A, Manson JE, Sesso HD, Wang L, Liu S (2016) Cocoa Flavanol intake and biomarkers for cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Nutr* 146(11):2325–2333. <https://doi.org/10.3945/jn.116.237644>.
195. Latif R. Chocolate/cocoa and human health: A review. *Neth. J. Med.* 2013;71:63–68.
196. Babar A, Bujold E, Leblanc V, Lavoie-Lebel E, Paquette J, Bazinet L, Lemieux S, Marc I, Abdous B, Dodin S (2018) Changes in endothelial function, arterial stiffness and blood pressure in pregnant women after consumption of high-flavanol and high theobromine chocolate: a double blind randomized clinical trial. *Hypertens Pregnancy* 37(2):68–80. <https://doi.org/10.1080/10641955.2018.1446977> 61.
197. Neufingerl N, Zebregs YE, Schuring EA, Trautwein EA (2013) Effect of cocoa and theobromine consumption on serum HDLcholesterol concentrations: a randomized controlled trial. *Am J Clin Nutr* 97(6):1201–1209. <https://doi.org/10.3945/ajcn.112.047373>.

198. Ding E.L., Hutfless S.M., Ding X., Girotra S. Chocolate and prevention of cardiovascular disease: A systematic review. *Nutr. Metab. (Lond.)* 2006;3 doi: 10.1186/1743-7075-3-2.

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