# Impact of Diet on Cardiovascular Diseases: Coronary Artery Disease

## Part III: Micronutrients, Supplements


## Abstract

Micronutrients are essential for the proper physiological functioning of the human body. They are only needed in trace amounts. However, low, or excess serum levels can result in wide-ranging undesirable health effects and increase mortality. Further, some micronutrients like arsenic are toxic if the body if exposed to them. The most common micronutrients involved with coronary artery disease include minerals like sodium, potassium, magnesium, calcium, and iron. Several other dietary supplements may also affect coronary artery disease. These include fish oil, curcumin, and probiotics. Micronutrients are often misunderstood in their role in preventing and reducing the impact of CAD and often end up being misused. In parts 1 and 2, the various macronutrients and their relationship with coronary artery disease were discussed. This section looks at several micronutrients that play a modulating role in atherosclerosis and coronary artery disease.



**Keywords:** coronary artery disease, sodium, potassium, iron, probiotics, vitamins




## Introduction

Globally, cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality in the world[1]. Ischemic heart disease (IHD) is a major player in CVDs. Its global burden is on the rise. According to GBD 2019, there were 197 million prevalent cases of IHD and 9.14 million deaths due to it in 2019[1]. The World Health Organization (WHO) estimates that three-quarters of deaths due to CVDs can be prevented by controlling lifestyle risk factors[2]. One lifestyle, diet, plays an important role in decreasing IHD burden. A study estimated that individuals can reduce their coronary heart disease (CHD) risk by 30% by following a heart-healthy dietary pattern[3]. A prudent diet can therefore play an important role in the quest for clean coronary arteries. The effect of macronutrients on CHD has been discussed earlier in Part I and Part II. This third and last part will discuss several micronutrients and supplements that also play a role.

## Discussion

Micronutrients (vitamins and minerals) are an essential component of the diet and are necessary for normal cellular and molecular function[4]. While micronutrients are only needed in trace amounts, their deficiency or excess can result in wide-ranging undesirable health effects[5-7]. These include developmental, and mental impairment, and several physical diseases including atherosclerotic coronary artery disease (CAD)[8].

### Sodium:

Sodium plays a major role in the etiology and pathogenesis of hypertension (HTN)[9]. This relationship is well-established[10]. HTN is a major risk factor for CAD[11]. HTN promotes atherosclerosis[12]. The worldwide sodium intake ranges between 3.5–5.5 g per day (corresponding to 9−12 g of salt per day). The WHO recommends that sodium intake should be limited to approximately 2.0 g per day (equivalent to approximately 5.0 g of salt per day) in healthy individuals[13]. A further decrease to less than 2 g/day (American Heart Association (AHA) recommends a reduction to 1.5 g/day) leads to a more significant blood pressure (BP) lowering:(- 3.39 mmHg for systolic BP and - 1.54 mmHg for diastolic BP[14]. This helps reduce atherosclerotic cardiovascular disease (ASCVD)[15]. High BP is dangerous. A 2-mmHg increase in BP increases mortality from CAD by 7 percent[16]. A heart-healthy diet reduces sodium intake[17].

**Potassium:**

A high intake of K is inversely related to CAD and CAD mortality. There is an inverse association between potassium and blood pressure[18-20]. A diet rich in potassium is associated with a reduction in BP[21]. In a study supported in part by the National Heart, Lung, and Blood Institute and the National Institute of Diabetes, Digestive and Kidney Diseases, mice fed a low-potassium diet demonstrated increased vascular calcification and artery stiffness[22]. In another study, it was estimated that for every 1,000 mg per day increase in urinary potassium excretion (indicating higher potassium intake), the risk of CVD (including CAD) was 18 percent lower[23].

**Magnesium:**

A systematic review and meta-analysis of prospective studies that comprised 313,041 individuals, found that higher dietary magnesium (Mg) intakes (up to approximately 250 mg/day) were associated with a significantly lower risk of IHD[24]. One study reported that higher dietary Mg (per 200 mg/day increment) was associated with a 22% lower risk of IHD (Risk Ratio or RR=0.78)[25]. Another study showed that higher levels of serum Mg (per 0.2 mmol/L increment) are associated with a 17% lower risk of IHD (RR=0.83) and 39% lower risk of fatal IHD (RR=0.61)[26]. Several other studies have found a similar inverse association[27,28]. Higher Mg is also noted to be potentially protective against sudden cardiac death[29]. Mg can prevent or delay atherosclerotic plaques[30]. Mg is also involved in the production of nitric oxide and prostaglandins, thus protecting the vascular endothelium in the coronary arteries[31]. Several epidemiological studies also indicate an inverse relationship between serum and dietary Mg and HTN[32], type 2 diabetes mellitus (T2DM)[33], and metabolic syndrome[34] – all risk factors for CAD.

**Calcium:** High calcium levels are statistically associated with a higher incidence of CHD[35]. Several studies report that calcium supplementation resulting in higher calcium levels increases the risk of cardiovascular events, coronary artery calcification, CAD, and myocardial infarction (MI)[36,37]. A genetic predisposition to higher serum calcium levels is also associated with an increased risk of CHD[38]. Possible mechanisms include effects on vascular calcification, vascular cells, blood coagulation, and altered gene expression[39]. Calcium supplements should not be used to prevent CAD/CHD.

**Iron:** Serum iron levels are related to the severity of CAD[40]. Many clinical studies suggest that the level of myocardial iron is a prognostic factor of heart failure following MI[41]. Sullivan et al. (1981) reported that depletion of body Fe stores reduced the risk of CAD[42]. A high dietary iron intake and high serum level of ferritin are positively linked with MI[43]. Supplementation has also been associated with an increased risk of nonfatal MI or fatal CAD[44]. Iron plays an important role in the production of free radicals and peroxidation of lipids, leading to oxidative stress, which leads to an increase in atherosclerosis[45,46].

**Selenium**: Several cohort studies have demonstrated a link between lower blood selenium (Se) levels and the increased occurrence of HTN and CAD[47]. The vascular benefits of Se are based on its antioxidative and detoxification effects[48].

**Manganese**: Manganese (Mn) is an element essential for health in trace amounts, but toxic at higher levels. In atherosclerotic subjects, the plasma levels of Mn are higher than in healthy individuals[49-51]. The urine of CAD patients also show higher Mn concentrations than that of healthy controls[52]. In another study, Mn concentration did not appear to be significantly increased in patients with CAD[53]. Its association with CAD is therefore unclear.

**Lead:** Chronic exposure to low lead (Pb) levels results in HTN that persists long after the cessation of Pb exposure[54]. Studies on Pb levels and CAD are sparse in the literature. Several small studies have identified a positive association of Pb exposure with CAD[55,56]. In a recent study, it was found that mean levels of serum Pb tended to be higher in CAD patients[57].

**Vitamins:** Previous experimental and epidemiologic evidence suggested that some antioxidant vitamins appear to be important in reducing the risk of CAD[58]. However, most individual, and multivitamin supplements have shown no efficacy in reducing CVD[59-61]. A study examined the efficacy of multiple vitamins and minerals on the secondary prevention of 1708 post-MI patients (age ≥50 years, ≥6 weeks after MI). In this study, consumption of high-dose multivitamins and minerals did not significantly reduce secondary cardiovascular events[62].

**Vitamin D**:

Cholecalciferol deficiency is associated with increased cardiovascular risk (including CAD), above and beyond established cardiovascular risk factors[63]. Clinical studies have reported a clear association between low cholecalciferol levels and CAD[64-70]. A meta-analysis calculated an adjusted relative risk of 1.4 for CAD when comparing the lowest to the highest categories of vitamin D levels. Recent large-scale observational studies have recognized that this relationship between plasma levels of 25(OH)D and coronary atherosclerosis is inverse in character. Further, greater vitamin D deficiency/insufficiency is associated with a more severe and extensive CAD[71]. Several mechanisms may explain this link between cholecalciferol deficiency and CVDs. Adequate levels of vitamin D are associated with decreased risk of endothelial dysfunction, calcification, and stiffness in the arteries[72]. Low cholecalciferol levels modulate plasma renin activity, raise blood pressure, increase insulin resistance, and lead to hyperlipidemia[73-77]. Vitamin D may also have a direct effect on angiogenesis[78,79], and help in the development of coronary collateral circulation[80]. However, the results obtained from a review of relevant randomized control trials did not clearly show cardiovascular improvements following cholecalciferol supplementation[81].

**Cadmium**: The literature is extremely sparse on cadmium (Cd) and CAD. One study reported that serum Cd levels were significantly decreased in patients with CAD[70].

**Zinc:** Zinc (Zn) is a major component of numerous enzymes within the human body. It controls the functioning of metalloenzymes, transcription factors, angiotensin-converting enzymes, desaturases, superoxide dismutases, and many others[82]. Consequently, deficiency of Zn leads to apoptosis, inflammation, and oxidative stress, all well known risk factors for CVDs[83]. Perturbations in Zn homeostasis affect the vascular endothelium[84]. Proatherogenic factors, released during Zn deficiency, increase the incidence of arrhythmias, strokes, CM, and many other CV system pathologies[85,86]. There is an inverse relationship between serum Zn concentrations and the risk of CVDs in high-risk populations[87].. Zn affects oxidative stress and reduces the oxidation of low-density lipoprotein (LDL-C), which has a protective effect against atherosclerosis[88]. In previous studies, it has been shown that in patients with CAD, serum Zn levels are lower than in healthy individuals. Kazemi et al in 2007, found that serum Zn level was significantly lower in coronary artery patients[89]. In a meta-analysis, Liu, et a., found that low Zn intake was associated with a higher prevalence of CAD. It was also associated with a higher incidence of MI[90]. In a study of patients undergoing coronary angiography, low serum Zn levels predicted mortality[91]. Although some studies have presented contradicting results[92], it appears that low serum Zn levels are detrimental for the heart. One study linked them with increased cardiovascular mortality[93]. Intracellular Zn plays a critical role in the redox signaling pathway, whereby certain triggers such as ischemia and infarction lead to the release of zinc from proteins and cause myocardial damage. In such states, replenishing with Zn has been shown to improve cardiac function and prevent further damage[94].

**Copper**: Copper (Cu) seriously affects the cardiovascular system, especially in the pathogenesis of CAD[95]. In acute coronary syndrome there is a positive link between serum Cu levels and elevated troponin T, troponin I and CK-MB values[96]. A MI is associated with a slight increase in serum Cu and a significant increase in urine Cu levels[97]. Shokrzadeh et al. measured the levels of Cu in patients with ischemic cardiomyopathy and found higher serum Cu levels in these patients when compared to healthy subjects[98]. Lutfi et al. did not find any significant association between CAD and Cu levels in Sudanese patients[99]. A recent Mendelian randomization study found an inverse association for genetically higher Cu levels with risk of CAD (Odds ratio = 0.92)[100]. Despite these studies, it is commonly believed that Cu levels are higher in patients with CAD. The lack of Cu leads to vascular elastic tissue degeneration and vascular smooth muscle proliferation, migration, and degeneration. It also impacts hypercholesterolemia and glucose tolerance and can increase chronic inflammation and oxidative stress[101].

## Supplements and CAD

### Probiotics

Probiotics may have a role in preventing or reducing atherosclerosis and beneficially affect CAD/CHD. Stepankova, et al, demonstrated that some intestinal bacteria prevent or slow down the progression of atherosclerotic lesions[102]. Several species, such as Eubacteria, Anaeroplasma, Roseburia, Oscillospira, and Dehalobacteria are effective in preventing atherosclerosis. In mice, a reduction in atherosclerotic plaque has been noted Lactobacillus rhamnosus GG supplementation despite being fed a high-fat diet for 12 weeks[103]. Probiotics may also help reduce BP, HbA1c, fasting blood glucose, and insulin resistance[104,105]. In a review of 26 clinical studies and two meta-analyses, Shimizu et al. found that LDL-C was reduced by 8.9–11.6% with L. reuteri supplementation[106]. LDL-C was lowered by 5% by E. faecium supplementation in mostly normal individuals[106]. Selective bacteria given as a probiotic supplement may be of value in reducing atherosclerosis.

**Multivitamins**

In 2011, one large multiethnic study on 182,099 participants showed no significant association between multivitamin intake for >10 years and CVD risk[107]. Antioxidant vitamins like vitamin C, vitamin E and beta carotene have no clinical benefit in reducing CAD – and their use in high doses is often harmful[108]. A study examined the efficacy of multiple vitamins and minerals on the secondary prevention of 1708 post-MI patients (age ≥50 years, ≥6 weeks after MI)[109]. The consumption of a high-dose multivitamin and multimineral did not significantly reduce secondary cardiovascular events[109]. No current results conclusively support the use of vitamin D supplementation as a strategy for CAD protection[110]. Minerals taken as a supplement also have not shown any CAD benefit[111]. Folic acid ingestion may be helpful. One recent Mendelian randomization study found that high genetically predicted folate levels were associated with decreased risk of CAD[112]. Daily supplementation with 0.5-5.0 mg of folic acid typically lowers plasma homocysteine levels by approximately 25%[113]. Hyper-homocysteinemia can cause endothelial injury, dysfunction of DNA, proliferation of smooth muscle cells, oxidative stress, decreased functioning of glutathione peroxidase, impaired nitric oxide synthase, and inflammation – all detrimental to the coronary arteries[114]. These data suggest that folic acid supplementation may reduce CAD[115]. However, supplementation for healthy people is not recommended by the AHA. Adequate intake of vitamins and minerals in their natural form (for example, in fruits and vegetables) is, however is CAD protective. Therefore, the AHA recommends the consumption of vegetables and fruits, especially green and yellow vegetables, but not antioxidant vitamin supplementation, to prevent atherosclerotic diseases such as CAD[116].

**CoQ10:**

Supplementation with CoQ10 (300 mg/day) increases antioxidant activity and lowers inflammation in patients who have CAD and are on statins therapy[117]. A meta-analysis (eight trials with 267 participants in the intervention group and 259 in the placebo group) showed that taking CoQ10 by CAD patients significantly decreased total cholesterol and increased HDL-C levels[118]. In patients who were post-MI reperfusion, CoQ10 decreased ventricular arrhythmias, improved LV function, and reduced total cardiac death[119,120]. Another study, a double-blind placebo-controlled trial of 144 subjects with acute MI, also showed that CoQ10 was beneficial when given 120 mg per day within the first 3 days of an MI[121]. However, its use as a supplement, in the prevention and management of CHD remains unclear.

**Fish Oils:**

Omega-3 polyunsaturated fatty acids (PUFAs) primarily eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), are derived from fish and are available as fish oils[122]. Several primary and secondary prevention trials have shown that omega-3 supplementation reduce several cardiovascular endpoints, such as angina, fatal and non-fatal MI, and sudden cardiac death[123-126]. Alexander et al. found that there was a 14%-16% CHD risk reduction in high-risk populations with their intake. Higher intakes of EPA + DHA > 1 g per day resulted in an 18% reduction of any CHD event, including sudden cardiac death. This higher intake also reduced CHD by 25% in individuals with triglycerides (TG) over 150 mg/dl[123]. They also help reduce stent restenosis[124], and CABG occlusion[125,126.] They can be used concomitantly with statins, for further stabilizing and promoting coronary plaque regression[127]. PUFAs improve the lipid profile - decrease very low-density lipoproteins and increase HDL-C[128]. In a dose of 2 to 4 gm/day (EPA + DHA), they also help reduce TG levels[129]. They retard atherosclerosis, plaque formation, coronary artery calcification, and promote atherosclerotic plaque stability[130,131]. They also lower glucose, improve insulin resistance[132-134] and reduce BP[135,136]. Eating oily fish may be better, as this also provides vitamin D, selenium, and other naturally occurring antioxidants which are not found in purified fish oil supplements. The AHA recommends consuming 1 serving of fatty fish or 1g of EPA/DHA-containing supplements twice a week for good cardiovascular health[116].

**Aspirin**

Aspirin (ASA) is a cyclooxygenase-1 (COX-1) inhibitor. It binds irreversibly to platelets[137]. Low dose use has been used for both primary and secondary prevention of ASCVD. Recent clinical trials demonstrate an increased risk of bleeding (gastrointestinal and cerebral) associated with aspirin use, which often outweighed cardiovascular risk reduction in primary prevention[138,139]. The ACC/AHA guidelines recently recommended that aspirin be used for primary prevention only in patients 40-70 years of age who are at a high atherosclerotic vascular disease (ASCVD) risk and have a low bleeding risk, and who are unable to optimally control modifiable ASCVD risk factors[140]. Low-dose aspirin should not be administered on a routine basis for primary prevention of ASCVD among adults younger than 70 years[141]. The recommended dose is 81 mg daily after a PTCI or CABG[142]. Low dose ASA is available over-the-counter without a prescription. Many individuals use low dose aspirin routinely to prevent CAD/CHD – in view of the increased bleeding noted, this use should be cleared by a physician.

**Psyllium**

Psyllium husk, derived from the seeds of Plantago ovata, has a 70 to 30 ratio of soluble/ insoluble fiber. Psyllium consumption reduces several risk factors for CAD. It helps reduce BP. A meta-analysis of 11 trials with 592 participants revealed a significant reduction of 2.04 mmHg in systolic blood pressure with its use[143]. There is an improvement in hypercholesterolemia[144,145], HbA1c, and fasting blood glucose[146]. It slows gastric emptying and helps control body weight[147]. In an umbrella review, it was noted that consuming the highest amounts of dietary fiber intake can significantly reduce the incidence and mortality from CVD[148]. Lim and Lee showed that psyllium prevented MI in rats[149].

**Garlic:** Garlic supplementation with aged garlic extract reduces systolic BP by 7-16 mm Hg and diastolic BP by 5-9 mm Hg. Total cholesterol is reduced by 7.4-29.8 mg/dL[150]. However, supplementation benefits in CAD are still unconfirmed.

**Chlorella**

Chlorella products contain numerous nutrients and vitamins, including vitamin D and B12. A meta-analysis of 19 randomized controlled trials including 797 subjects showed that Chlorella supplementation improves TC, LDL-C and HDL-C levels, BP, fasting blood glucose, and body mass index[151]. Chlorella has multiple nutrients and antioxidant compounds that cause these beneficial effects[152].

**Curcumin**

Curcumin comes from turmeric. It has anti-inflammation properties and improves lipid levels[153]. It increases LDL-C size – smaller LDL-C particles are easier to oxidize[154]. LDL-C oxidation leads to atherosclerosis. Wongcharoen et al. reported that post coronary artery bypass grafting (CABG), curcumin in a dose of 4g per day given 3 days before and 5 days after the procedure, reduced inflammation, and reduced MI post CABG from 30% to 13%[155].

**L-carnitine**

L-carnitine (LC) is a derivative of amino acids lysine and methionine. It plays a role in energy metabolism and mitochondrial protection[156]. It facilitates the transport of long-chain fatty acids into the mitochondrial matrix. This is associated with reduced oxidative stress, inflammation, and necrosis of cardiac myocytes[157,158]. Clinical studies show that LC supplementation (1000 mg/d) increases HDL-C and Apo-A1 levels with a slight decrease in TG levels[159]. In one systemic review and meta-analysis (13 controlled trials with 3629 participants), supplementation with LC reduced angina by 40% and ventricular arrhythmias by 65% following an acute MI compared with placebo[160]. However, there is not enough data to currently recommend its use in patients with CHD.

**Vitamin K**:

Vitamin K is an essential bioactive compound required for optimal body function. Vitamin K has two main forms, namely, phylloquinone (K1) and menaquinones (K2). K1 is found primarily in green, leafy, and cruciferous vegetables. Vitamin K2 is found in some dairy products, pork, poultry, and fermented foods. Vitamin K2 is considered more important for vascular system health than vitamin K1. Vitamin K2 reduced incident CHD in a population of 4807 participants by 57%, when the upper versus lower tertile were compared[161]. Several studies have also documented the benefits of vitamin K1. A 16% reduction in CHD was noted in an NHS cohort of 72,874 female nurses, from lowest to highest quintile of vitamin K1 intake[162]. A similar reduction in CHD (13%-16%) was noted in a study of 40,087 men[163]. In the Multi-Ethnic Study of Atherosclerosis study, there was an inverse association between vitamin K1 dietary intake and coronary artery calcification, especially in those on antihypertensive drugs[164]. More studies are needed to determine the efficacy and proper supplementation dose. Both K1 and K2 are safely tolerated.

In summary, numerous nutritional supplements have demonstrated improvement in surrogate endpoints (BP, lipids, glucose, carotid IMT, coronary calcification, etc.). However, there are limited data that dietary supplements reduce hard CV endpoints related to CHD and MI. Supplements can have unpleasant and often dangerous side effects. They can also interact with prescribed medication. Consuming too much vitamin D or calcium increases CAD. Supplements that are over-the-counter are not regulated and may have a poor quality. Instead of relying on supplements, a healthy diet provides a full complement of micronutrients needed for healthy coronary arteries.

## Diet and other diseases/lifestyle factors

Besides obesity[165], type 2 diabetes mellitus[166], dyslipidemia[167], and HTN[168], a prudent diet also beneficially impacts other risk factors for CAD/CHD. These include depression[169], improper sleep[170], chronic kidney disease[171], and smoking[172].

## Conclusion

Coronary artery disease is a major cause of morbidity and mortality around the world. Although abstinence from tobacco smoking and physical exercise plays an important role in reducing this burden, the part played by diet is extremely significant. The calories in the diet should not exceed the caloric expenditure, to avoid becoming overweight or obese. Ideally, the BMI should be normal and there should be no visceral obesity. Even a weight loss of 5–10% of body weight if overweight/obese reduces blood pressure and induces beneficial metabolic changes. The diet should also be balanced. Most professional nutrition associations recommend that a normal diet comprise of macronutrients in the following percentages: 45%-65% carbohydrates; 10%-30% from proteins and 20%-30% from fats. An adequate intake of water (approximately 6 glasses per day) and micronutrients is also required. The ingredients in this balanced diet also matter. Ideally, the diet should be rich in vegetables (dark green, red, yellow, orange), fruits (preferably whole fruits), legumes (beans and peas), unsalted nuts (almonds, peanuts, pecans, pistachios, hazelnuts), whole grains, and fiber. The plant-based diet should provide an intake of viscous fiber of 5–10 g/day and plant sterols/stanols of 2 g/day. Meat should be eaten infrequently, with red meat restricted to lean cuts, and avoiding processed red meat. One egg a day appears to be safe in non-diabetics (and maybe even diabetics). Seafood intake, especially oily fish (DHA and EPA) is encouraged. Fat-free or low-fat dairy, including milk, yogurt, cheese are not restricted. Dietary saturated fat (fatty cuts of lamb, pork, beef, poultry with skin, beef fat, lard, bacon, sausage, hotdogs. whole milk & whole milk products: butter, ghee, cheese, cream, ice cream, yogurt made from whole milk; palm oil, palm kernel oil, coconut oil, and coconut cream) should be replaced with monounsaturated fatty acids and polyunsaturated fatty acids. Extra virgin olive oil and canola oil are good sources of monounsaturated fats. Plant-based omega-6 polyunsaturated fats are present in corn, safflower, sunflower, soybean oils, and sunflower seeds. Plant-based omega-3 polyunsaturated fats are available in flaxseed oil, canola oil, soybean oil, English walnuts, edamame, hemp seeds, chia seeds, flaxseeds, and fenugreek seeds. Overall, saturated fat intake should be reduced to 7% of total energy and dietary cholesterol to <200 mg/day. Trans fats (often labeled as partially hydrogenated fats) should be avoided (baked goods: pastries, cakes, donuts, cookies, fried foods: French fries, fried chicken, onion rings, and deep-fried snacks cooked in re-used oil, stick margarine, shortening; butter, meat, cheese, and dairy products). Refined carbohydrates and sugar-sweetened beverages should be avoided. Added sugars should be reduced to <10% of the total energy intake. Sodium intake should be reduced to 2300 mg per day (ideally to 1500 mg/day). Alcohol should be imbibed in low to moderate amounts. Filtered coffee, green tea, and dark chocolate intake are also beneficial. Supplementation with potassium, magnesium, iron, calcium, and vitamins is not recommended unless there is a deficiency. The role of probiotics is still unclear. Several common diets, such as the DASH diet, Mediterranean diet, and the vegetarian diet have CAD preventive effects. Plant-based diets are the only dietary pattern to have shown regression of atherosclerosis. A prudent diet will also help mitigate systemic atherosclerosis and its common manifestations - stroke, peripheral artery disease, and vasculogenic erectile dysfunction..



**References**


1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study [published correction appears in J Am Coll Cardiol. 2021 Apr 20;77(15):1958-1959]. J Am Coll Cardiol. 2020;76(25):2982-3021. doi:10.1016/j.jacc.2020.11.01.
2. Simão AF, Précoma DB, Andrade JP De, Filho HC, Francisco J, Saraiva K, et al. Special article, I cardiovascular prevention Guideline of the Brazilian Society of Cardiology – executive summary. 2014;420–431.
3. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr. 2012 Jun;142(6):1009-18. doi: 10.3945/jn.111.157222.
4. Bailey R.L., West K.P., Jr., Black R.E. The epidemiology of global micronutrient deficiencies. Ann. Nutr. Metab. 2015;66(Suppl. 2):22–33. doi: 10.1159/000371618.
5. World Health Organization. Nutritional Anemias: Tools for Effective Prevention and Control. World Health Organization; Geneva, Switzerland: 2017. ;Lozoff B. Iron deficiency and child development. Food Nutr. Bull. 2007;28:S560–S571. doi: 10.1177/15648265070284S409.
6. Sanghvi T., Van Ameringen M., Baker J., et al. Vitamin and mineral deficiencies technical situation analysis: A report for the Ten Year Strategy for the Reduction of Vitamin and Mineral Deficiencies. Food Nutr. Bull. 2007;28:S160–S219.
7. Black R.E., Allen L.H., Bhutta Z.A., Caulfield L.E., de Onis M., Ezzati M., Mathers C., Rivera J. Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: Global and regional exposures and health consequences. Lancet. 2008;371:243–260. doi: 10.1016/S0140-6736(07)61690-0.

8. Reunanen A, Knekt P, Marniemi J. et al. Serum calcium, magnesium, copper and zinc and risk of cardiovascular death. Eur J Clin Nutr. 1996;50:431–437.
9. Appel L.J., Brands M.W., Daniels S.R., Karanja N., Elmer P.J., Sacks F.M. Dietary approaches to prevent and treat hypertension: A scientific statement from the American Heart Association. Hypertension. 2006;47:296–308. doi: 10.1161/01.HYP.0000202568.01167.B6.
10. Welsh CE, Welsh P, Jhund P, et al. Urinary sodium excretion, blood pressure, and risk of future cardiovascular disease and mortality in subjects without prior cardiovascular disease. Hypertension. 2019;73:1202–1209. doi: 10.1161/HYPERTENSIONAHA.119.12726.
11. https://www.heart.org/.
12. Graudal N.A., Hubeck-Graudal T., Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database Syst. Rev. 2017;11:4–10. doi: 10.1002/14651858.CD004022.pub4.
13. World Health Organization. Guideline: Sodium Intake for Adults and Children. World Health Organization; Geneva, Switzerland: 2012.
14. Aburto N.J., Ziolkovska A., Hooper L., Elliott P., Cappuccio F.P., Meerpohl J.J. Effect of lower sodium intake on health: Systematic review and meta-analyses. BMJ. 2013;346:f1326. doi: 10.1136/bmj.f1326.
15. Graudal N.A., Hubeck-Graudal T., Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database Syst. Rev. 2017;11:4–10. doi: 10.1002/14651858.CD004022.pub4.
16. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903–1913.
17. Gibbs J., Gaskina E., Jia C. The effect of plant-based dietary patterns on blood pressure: a systematic review and meta-analysis of controlled intervention trials. J Hypertens. 2020;38 000–000.
18. Binia A, Jaeger J, Hu Y, Singh A, Zimmermann D. Daily potassium intake and sodium-to-potassium ratio in the reduction of blood pressure: a meta-analysis of randomized controlled trials. J Hypertens. 2015;33:1509–1520. doi: 10.1097/HJH.0000000000000611.
19. Perez V, Chang ET. Sodium-to-potassium ratio and blood pressure, hypertension, and related factors. Adv Nutr. 2014;5:712–741. doi: 10.3945/an.114.006783.
20. McDonough AA, Veiras LC, Guevara CA, Ralph DL. Cardiovascular benefits associated with higher dietary K(+) vs. lower dietary Na(+): evidence from population and mechanistic studies. Am J Physiol Endocrinol Metab. 2017;312:E348–e356. doi: 10.1152/ajpendo.00453.2016.
21. Filippini T, Naska A, Kasdagli MI, Torres D, Lopes C, Carvalho C, Moreira P, Malavolti M, Orsini N, Whelton PK, Vinceti M. Potassium Intake and Blood Pressure: A Dose-

Response Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2020 Jun 16;9(12):e015719. doi: 10.1161/JAHA.119.015719.

22. Yong Sun, Chang Hyun Byon, Youfeng Yang,et al. Dietary potassium regulates vascular calcification and arterial stiffness. JCI Insight. 2017;2(19):e94920. https://doi.org/10.1172/jci.insight.94920.
23. https://news.harvard.edu/gazette/story/2021/11/less-sodium-more-potassium-lowers-risk-of-cardiovascular-disease/.
24. Liana C Del Gobbo, Fumiaki Imamura, Jason HY Wu, Marcia C de Oliveira Otto, Stephanie E Chiuve, Dariush Mozaffarian, Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies, The American Journal of Clinical Nutrition, Volume 98, Issue 1, July 2013, Pages 160–173, https://doi.org/10.3945/ajcn.112.053132
25. Gröber U, Schmidt J, Kisters K. Magnesium in Prevention and Therapy. Nutrients. 2015;7(9):8199-8226. Published 2015 Sep 23. doi:10.3390/nu7095388
26. Del Gobbo L.C., Imamura F., Wu J.H., de Oliveira Otto M.C., Chiuve S.E., Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: A systematic review and meta-analysis of prospective studies. Am. J. Clin. Nutr. 2013;98:160–173. doi: 10.3945/ajcn.112.053132.
27. Rooney MR, Alonso A, Folsom AR, Michos ED, Rebholz CM, Misialek JR, Chen LY, Dudley S, Lutsey PL. Serum magnesium and the incidence of coronary artery disease over a median 27 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study and a meta-analysis. Am J Clin Nutr. 2020 Jan 1;111(1):52-60. doi: 10.1093/ajcn/nqz256.
28. Larsson SC, Burgess S, Michaëlsson K. Serum magnesium levels and risk of coronary artery disease: Mendelian randomisation study. BMC Med. 2018 May 17;16(1):68. doi: 10.1186/s12916-018-1065-z.
29. Peacock J.M., Ohira T., Post W., Sotoodehnia N., Rosamond W., Folsom A.R. Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study. Am. Heart. J. 2010;160:464–470. doi: 10.1016/j.ahj.2010.06.012.
30. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An update on physiological, clinical and analytical aspects. Clinica chimica acta; international journal of clinical chemistry. 2000 Apr;294(1-2):1–26.
31. Shechter M, Sharir M, Labrador MJ, Forrester J, Silver B, Bairey Merz CN. Oral magnesium therapy improves endothelial function in patients with coronary artery disease. Circulation. 2000 Nov 07;102(19):2353–8.
32. Kostov K, Halacheva L. Role of Magnesium Deficiency in Promoting Atherosclerosis, Endothelial Dysfunction, and Arterial Stiffening as Risk Factors for Hypertension. Int J Mol Sci. 2018 Jun 11;19(6):1724. doi: 10.3390/ijms19061724.
33. Rodrguez-Moran M., Menda L.E.S., Galvn G.Z., Guerrero-Romero F. The role of magnesium in type 2 diabetes: A brief based-clinical review. Magnes. Res. 2011;24:156–162.

34. Piuri G, Zocchi M, Della Porta M, Ficara V, Manoni M, Zuccotti GV, Pinotti L, Maier JA, Cazzola R. Magnesium in Obesity, Metabolic Syndrome, and Type 2 Diabetes. Nutrients. 2021 Jan 22;13(2):320. doi: 10.3390/nu13020320.
35. Reid IR, Gamble GD, Bolland MJ. Circulating calcium concentrations, vascular disease and mortality: a systematic review. J Intern Med. 2016 Jun;279(6):524-40. doi: 10.1111/joim.12464.
36. Tankeu AT, Ndip Agbor V, Noubiap JJ. Calcium supplementation and cardiovascular risk: A rising concern. J Clin Hypertens (Greenwich). 2017 Jun;19(6):640-646.
37. Bolland M., Avenell A., Baron J., Grey A., Maclennan G., Gamble G., et al. . (2010a) Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 341: c3691.
38. Larsson SC, Burgess S, Michaëlsson K. Association of Genetic Variants Related to Serum Calcium Levels With Coronary Artery Disease and Myocardial Infarction. JAMA. 2017 Jul 25;318(4):371-380. doi: 10.1001/jama.2017.8981.
39. Reid IR, Birstow SM, Bolland MJ. Calcium and Cardiovascular Disease. Endocrinol Metab (Seoul). 2017;32(3):339-349. doi:10.3803/EnM.2017.32.3.339.
40. Bagheri B, Shokrzadeh M, Mokhberi V, et al.. Association between Serum Iron and the Severity of Coronary Artery Disease. Int Cardiovasc Res J. 2013 Sep;7(3):95-8.
41. Bulluck H, Rosmini S, Abdel-Gadir A, White SK, Bhuva AN, Treibel TA, et al. Residual Myocardial Iron Following Intramyocardial Hemorrhage During the Convalescent Phase of Reperfused ST-Segment-Elevation Myocardial Infarction and Adverse Left Ventricular Remodeling. Circ Cardiovasc Imaging 2016;9. doi:10.1161/CIRCIMAGING.116.004940.
42. Sullivan JL. Iron and the sex difference in heart disease risk. Lancet. 1981;1:1293–1294.
43. Quintana Pacheco D.A., Sookthai D., Wittenbecher C. Red meat consumption and risk of cardiovascular diseases-is increased iron load a possible link? Am J Clin Nutr. 2018;107(1):113–119. doi: 10.1093/ajcn/nqx014.
44. Ascherio A, Willett WC, Rimm EB. et al. Dietary iron intake and risk of coronary disease among men. Circulation. 1994;89:969–974.
45. Neven E, De Schutter T, Behets G, Gupta A, D'Haese P. Iron and vascular calcification. Is there a link? Nephrol Dial Transplant. 2011;26:1137–45.
46. Woollard KJ, Sturgeon S, Chin-Dusting JP, Salem HH, Jackson SP. Erythrocyte hemolysis and hemoglobin oxidation promote ferric chloride-induced vascular injury. J Biol Chem 2009;284:13110–8. doi:10.1074/jbc.M8090952005.
47. Liu L., Lin G., Wang H., Zhang B., Du S. Selenium exposure and incident hypertension among Chinese adults (P24-020-19) Curr. Dev. Nutr. 2019;3(Suppl. S1) doi: 10.1093/cdn/nzz044.P24-020-19.
48. Kiełczykowska M, Kocot J, Paździor M, Musik I. Selenium - a fascinating antioxidant of protective properties. Adv Clin Exp Med. 2018 Feb;27(2):245-255. doi: 10.17219/acem/67222.
49. Volkov NF. The cobalt, manganese and zinc content in the blood and internal organs of atherosclerotic patients. Ter Arkh. 1962;34:52–56.

50. Bala IuM, Plotko SA, Furmenko G. Content of manganese, nickel, zinc, copper, silver and lead in the blood, aorta, liver, kidneys and pancreas of atherosclerotic patients. Ter Arkh. 1967;39:105–111.
51. Masironi R. Trace elements and cardiovascular diseases. Bull World Health Organ. 1969;40:305–312.
52. Kanabrocki EL, Scheving LE, Olwin JH. et al. Circadian variation in the urinary excretion of electrolytes and trace elements in men. Am J Anat. 1983;166:121–148.
53. Kromhout D. Blood lead and coronary heart disease risk among elderly men in Zutphen the Netherlands. Environ Health Perspect. 1988;78:43-46.
54. Navas-Acien A, Guallar E, Silbergeld EL. et al. Lead Exposure and Cardiovascular Disease—A Systematic Review. Environ Health Perspect. 2007;115:472–482.
55. EPA (U.S. Environmental Protection Agency) 2006. Air Quality Criteria for Lead (Final). Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158823.
56. Lustberg M, Silbergeld E. Blood lead levels and mortality. Arch Intern Med. 2002;162:2443–2449.
57. Cebi A, Kaya Y, Gungor H, Demir H, Yoruk IH, Soylemez N, Gunes Y, Tuncer M. Trace Elements, Heavy Metals and Vitamin Levels in Patients with Coronary Artery Disease. Int J Med Sci 2011; 8(6):456-460. doi:10.7150/ijms.8.456. Available from https://www.medsci.org/v08p0456.htm.
58. Adams AK, Wermuth EO, Mcbride PE. Antioxidant vitamins and the prevention of coronary heart disease. Am Fam Physician. 1999;60:895–904.
59. Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: The Women's Health Study: A randomized controlled trial. JAMA. 2005;294:56–65.
60. Leppälä JM, Virtamo J, Fogelholm R, Huttunen JK, Albanes D, Taylor PR, et al. Controlled trial of alpha-tocopherol and beta-carotene supplements on stroke incidence and mortality in male smokers. Arterioscler Thromb Vasc Biol. 2000;20:230–5.
61. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med. 1996;334:1145–9.
62. Moyer VA. U.S. Preventive Services Task Force. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: U.S. Preventive services Task Force recommendation statement. Ann Intern Med. 2014;160:558–64.
63. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet. 1998;351:805–806; Wang TJ, Pencina MJ, Booth SL. et al. Vitamin D Deficiency and Risk of Cardiovascular Disease. Circulation. 2008;117:503–511.
64. Carrie W, Nemerovski PD, Michael P. et al. Vitamin D and Cardiovascular Disease. Pharmacotherapy. 2009;29:691–708.
65. Lind L, Hanni A, Lithell H. et al. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens. 1995;8:894–901.
66. Watson KE, Abrolat ML, Malone LL. et al. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation. 1997;96:1755–1760.

67. Doherty TM, Tang W, Dascalos S. et al. Ethnic origin and serum levels of 1,25-dihydroxyvitamin D3 are independent predictors of coronary calcium mass measured by electron-beam computed tomography. Circulation. 1997;96:1477–1481.
68. Scragg R, Jackson R, Holdaway IM. et al. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. Int J Epidemiol. 1990;19:559–563.
69. Zittermann A, Schleithoff SS, Tenderich G. et al. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure. J Am Coll Cardiol. 2003;41:105–112.
70. Cebi A, Kaya Y, Gungor H, Demir H, Yoruk IH, Soylemez N, Gunes Y, Tuncer M. Trace elements, heavy metals, and vitamin levels in patients with coronary artery disease. Int J Med Sci. 2011;8(6):456-60. doi: 10.7150/ijms.8.456.
71. Norouzi H, Ziaie N, Saravi M, Norouzi A, et al. Association of vitamin D deficiency and premature coronary artery disease. Caspian J Intern Med. 2019 Winter;10(1):80-85. doi: 10.22088/cjim.10.1.80.
72. Al Mheid I, Quyyumi AA. Vitamin D and cardiovascular disease: controversy unresolved. J Am Coll Cardiol. 2017;70:89–100.
73. Carrie W, Nemerovski PD, Michael P. et al. Vitamin D and Cardiovascular Disease. Pharmacotherapy. 2009;29:691–708.
74. Lind L, Hanni A, Lithell H. et al. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens. 1995;8:894–901.
75. Lavie CJ, Lee JH, Milani RV. Vitamin D and cardiovascular disease will it live up to its hype? J Am Coll Cardiol. 2011;58:1547–56.
76. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension. 2007;49:1063–9.
77. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol. 2010;106:963–8.
78. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol. 2005;289:F8–28.
79. Chung I, Han G, Seshadri M, Gillard BM, Yu WD, Foster BA, et al. Role of vitamin D receptor in the antiproliferative effects of calcitriol in tumor-derived endothelial cells and tumor angiogenesis in vivo . Cancer Res. 2009;69:967–75.
80. de Groot D, Pasterkamp G, Hoefer IE. Cardiovascular risk factors and collateral artery formation. Eur J Clin Invest. 2009;39:1036–47.
81. Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, Murphy J, Khaw KT, Camargo CA Jr. Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study : A Randomized Clinical Trial. JAMA Cardiol. 2017 Jun 1;2(6):608-616. doi: 10.1001/jamacardio.2017.0175.
82. Maxfield L, Crane JS. Available online at: https://www.ncbi.nlm.nih.gov/journals/NBK493231/ (accessed March 22, 2021).

83. Jurowski K, Szewczyk B, Nowak G, Piekoszewski W. Biological consequences of zinc deficiency in the pathomechanisms of selected diseases. J Biol Inorg Chem. (2014) 9:1069–79. 10.1007/s00775-014-1139-0.
84. Beattie JH, Gordon M-J, Duthie SJ, McNeil CJ, Horgan GW, Nixon GF, et al. Suboptimal dietary zinc intake promotes vascular inflammation and atherogenesis in a mouse model of atherosclerosis. Molec Nutr. Food Res. (2012) 56:1097–105. 10.1002/mnfr.201100776.
85. Huang L, Teng T, Bian B, Yao W, Yu X, Wang Z, et al. Zinc levels in left ventricular hypertrophy. Biol Trace Elem Res. (2017) 176:48–55. 10.1007/s12011-016-0808-y.
86. Hashemian M, Poustchi H, Mohammadi-Nasrabadi F, Hekmatdoost A. Systematic review of zinc biochemical indicators and risk of coronary heart disease. ARYA Arther. (2015) 11:357–65).
87. Chu A, Foster M, Samman S. Zinc status and risk of cardiovascular diseases and type 2 diabetes mellitus-A systematic review of prospective cohort studies. Nutrients. (2016) 8:707. 10.3390/nu8110707.
88. Little PJ, Bhattacharya R, Moreyra AE, Korichneva IL. Zinc and cardiovascular disease. Nutrition. 2010;26:1050–7.
89. Kazemi-Bajestani SM, Ghayour-Mobarhan M, Ebrahimi M, et al. Serum zinc concentrations are lower in Iranian patients with angiographically defined coronary artery disease than in subjects with a normal angiogram. Journal of trace elements in medicine and biology: organ of the Society for Minerals and Trace Elements (GMS) 2007;21(1):22–8.
90. Liu B, Cai Z-Q, Zhou Y-M. Deficient zinc levels and myocardial infarction. Biol Trace Elem Res. (2015) 165:41–50. 10.1007/s12011-015-0244-4.
91. Pilz S, Dobnig H, Winklhofer-Roob BM, Renner W, Seelhorst U, Wellnitz B, et al. . Low serum zinc concentrations predict mortality in patients referred to coronary angiography. Br J Nutr. (2009) 101:1534–40. 10.1017/S0007114508084079.
92. Dastani M, Mokhtari M, Khameneh Bagheri R, et al. A Pilot study on correlation between Zinc and Magnesium serum concentrations and coronary slow flow phenomenon. Acta Biomed. 2021 Sep 2;92(4):e2021279. doi: 10.23750/abm.v92i4.9471.
93. Reunanen A, Knekt P, Marniemi J. et al. Serum calcium, magnesium, copper and zinc and risk of cardiovascular death. Eur J Clin Nutr. 1996;50:431–437.
94. Little PJ, Bhattacharya R, Moreyra AE, Korichneva IL. Zinc and cardiovascular disease. Nutrition. 2010 Nov-Dec;26(11-12):1050-7. doi: 10.1016/j.nut.2010.03.007.
95. Nourmohammadi I, et al. Serum levels of Zn,Cu,Cr and Ni in Iranian Subjects with Atherosclerosis, in Arch Irn Med. 2001;4:21–4.
96. Altekin E, Coker C, Sisman AR, Onvural B, Kuralay F, Kirimli O. The relationship between trace elements and cardiac markers in acute coronary syndromes. J Trace Elem Med Biol. 2005;18:235–42.
97. Lukaski HC, Klevay LM, Milne DB. Effects of dietary copper on human autonomic cardiovascular function. Eur J Appl Physiol. 1988;58:74–80.

98. Shokrzadeh M, Ghaemian A, Salehifar E, Aliakbari S, Saravi SS, Ebrahimi P, et al. Serum zinc and copper levels in ischemic cardiomyopathy. Biol Trace Elem Res. 2009;127:116–23.
99. Lutfi MF, Elhakeem RF, Khogaly RS, et al. Frontiers in Physiology, 06 Jul 2015, 6:191) DOI: 10.3389/fphys.2015.00191.
100. Jäger S, Cabral M, Kopp JF, Hoffmann P, Ng E, Whitfield JB, Morris AP, Lind L, Schwerdtle T, Schulze MB. Blood copper and risk of cardiometabolic diseases-A Mendelian randomization study. Hum Mol Genet. 2021 Sep 15:ddab275. doi: 10.1093/hmg/ddab275.
101. Medeiros D, Pellum L, Brown B. Serum lipids and glucose as associated with hemoglobin levels and copper and zinc intake in young adults. Life Sci. 1983 Apr 18;32(16):1897-904. doi: 10.1016/0024-3205(83)90069-3.
102. Stepankova R, Tonar Z, Bartova J, et al. Absence of microbiota (germ-free conditions) accelerates the atherosclerosis in ApoE-deficient mice fed standard low cholesterol diet. J Atheroscler Thromb. 2010;17:796-804.
103. Chan YK, Brar MS, Kirjavainen PV, et al. High fat diet induced atherosclerosis is accompanied with low colonic bacterial diversity and altered abundances that correlates with plaque size, plasma A-FABP and cholesterol: a pilot study of high fat diet and its intervention with Lactobacillus rhamnosus GG (LGG) or telmisartan in ApoE(-/-) mice. BMC Microbiol. 2016;16:264.
104. Khalesi S, Sun J, Buys N, Jayasinghe R. Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. Hypertension. 2014 Oct;64(4):897-903. doi: 10.1161/HYPERTENSIONAHA.114.03469.
105. Tao YW, Gu YL, Mao XQ, Zhang L, Pei YF. Effects of probiotics on type II diabetes mellitus: a meta-analysis. J Transl Med. 2020 Jan 17;18(1):30. doi: 10.1186/s12967-020-02213-2. Erratum in: J Transl Med. 2020 Feb 28;18(1):105.
106. J.M. Shimizu, M. Hashiguchi, T. Shiga, et al. Meta-analysis: effects of probiotic supplementation on lipid profiles in Normal to mildly hypercholesterolemic individuals. PloS One, 10 (10) (2015), Article e0139795.
107. Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Multivitamin use and the risk of mortality and cancer incidence: The multiethnic cohort study. Am J Epidemiol. 2011;173:906–14.
108. https://www.nccih.nih.gov/health/antioxidants-in-depth.
109. Moyer VA. U.S. Preventive Services Task Force. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: U.S. Preventive services Task Force recommendation statement. Ann Intern Med. 2014;160:558–64.
110. Manson JE, Cook NR, Lee IM, et al. VITAL Research Group. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med. 2019 Jan 3;380(1):33-44. doi: 10.1056/NEJMoa1809944.
111. Kim J, Choi J, Kwon SY et al. Association of Multivitamin and Mineral Supplementation and Risk of Cardiovascular Disease. A Systematic Review and Meta-

Analysis. Circulation: Cardiovascular Quality and Outcomes. 10 Jul 2018https://doi.org/10.1161/CIRCOUTCOMES.117.004224
112. Yuan S, Mason AM, Carter P, Burgess S, Larsson SC. Homocysteine, B vitamins, and cardiovascular disease: a Mendelian randomization study. BMC Med. 2021 Apr 23;19(1):97. doi: 10.1186/s12916-021-01977-8.
113. Liakishev AA. Homocysteine lowering with folic acid and B vitamins in vascular disease. Kardiologiia. 2006;46(5):70. doi: 10.1016/s0749-4041(08)70686-9.
114. Pushpakumar S, Kundu S, Sen U. Endothelial dysfunction: the link between homocysteine and hydrogen sulfide. Ingenta Connect. 2014;21(32):3662–3672.
115. Kaye AD, Jeha GM, Pham AD, et al. Folic Acid Supplementation in Patients with Elevated Homocysteine Levels. Adv Ther. 2020 Oct;37(10):4149-4164. doi: 10.1007/s12325-020-01474-z.
116. AHA vitamins Alyson Haslam and Vinay Prasad. Multivitamins Do Not Reduce Cardiovascular Disease and Mortality and Should Not Be Taken for This Purpose. Circulation: Cardiovascular Quality and Outcomes. 10 Jul 2018https://doi.org/10.1161/CIRCOUTCOMES.118.004886.
117. Lee BJ, Tseng YF, Yen CH, Lin PT. Effects of coenzyme Q10 supplementation (300 mg/day) on antioxidation and anti-inflammation in coronary artery disease patients during statins therapy: a randomized, placebo-controlled trial. Nutr J. 2013 Nov 6;12(1):142. doi: 10.1186/1475-2891-12-142.
118. Jorat MV, Tabrizi R, Mirhosseini N, et al. The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis. 2018 Oct 9;17(1):230. doi: 10.1186/s12944-018-0876-4.
119. Chello M, Mastroroberto P, Romano R, et al. Protection by coenzyme Q10 from myocardial reperfusion injury during coronary artery bypass grafting. Ann Thorac Surg 1994; 58: 1427–1432.
120. Singh RB, Wander GS, Rastogi A, et al. Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction. Cardiovasc Drugs Ther 1998; 12: 347–353.
121. Singh RB, Wander GS, Rastogi A, et al. Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction. Cardiovasc Drugs Ther 1998; 12: 347–353.
122. 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.
123. Alexander DD, Miller PE, Van Elswyk ME, et al. A meta-analysis of randomized controlled trials and prospective cohort studies of eicosapentaenoic and docosahexaenoic long-chain omega-3 fatty acids and coronary heart disease risk. Mayo Clin Proc 2017: 92: 15–29.
124. Gajos G, Zalewski J, Rostoff P, et al. Reduced thrombin formation and altered fibrin clot properties induced by polyunsaturated omega-3 fatty acids on top of dual

antiplatelet therapy in patients undergoing percutaneous coronary intervention (OMEGA-PCI clot). Arterioscler Thromb Vasc Biol 2011; 31: 1696–1702.

125. Arnesen H. n-3 fatty acids and revascularization procedures. Lipids 2001; 36(Suppl.): S103–S106.

126. Arnesen H, Seljeflot I. Studies on very long chain marine n-3 fatty acids in patients with atherosclerotic heart disease with special focus on mechanisms, dosage and formulas of supplementation. Cell Mol Biol (Noisy-le-grand) 2010; 56: 18–27.

127. Fan H, Zhou J, Yuan Z. Meta-Analysis Comparing the Effect of Combined Omega-3 + Statin Therapy Versus Statin Therapy Alone on Coronary Artery Plaques. Am J Cardiol. 2021 Jul 15;151:15-24. doi: 10.1016/j.amjcard.2021.04.013.

128. Pucci G, Cicero AF, Borghi C, et al. Emerging biologic therapies for hypercholesterolaemia. Expert Opin Biol Ther 2017; 15: 1–11.;, Jacobson TA, Glickstein SB, Rowe JD, et al. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. J Clin Lipidol 2012; 6: 5–18.

129. Shearer GC, Savinova OV, Harris WS. Fish oil -- how does it reduce plasma triglycerides?. Biochim Biophys Acta. 2012;1821(5):843-851. doi:10.1016/j.bbalip.2011.10.011.

130. Sekikawa A, Miura K, Lee S, et al. Long chain n-3 polyunsaturated fatty acids and incidence rate of coronary artery calcification in Japanese men in Japan and white men in the USA: population based prospective cohort study. Heart 2014; 100: 569–573. ;115.

131. Abedin M, Lim J, Tang TB, et al. N-3 fatty acids inhibit vascular calcification via the p38-mitogen-activated protein kinase and peroxisome proliferator-activated receptor-gamma pathways. Circ Res 2006; 98: 727–729.

132. Jans A, Konings E, Goossens GH, et al. PUFAs acutely affect triacylglycerol-derived skeletal muscle fatty acid uptake and increase postprandial insulin sensitivity. Am J Clin Nutr 2012; 95: 825–836.

133. García-López S, Villanueva Arriaga RE, Nájera Medina O, et al. One month of omega-3 fatty acid supplementation improves lipid profiles, glucose levels and blood pressure in overweight schoolchildren with metabolic syndrome. J Pediatr Endocrinol Metab 2016; 29: 1143–1150.

134. Sawada T, Tsubata H, Hashimoto N, et al. Effects of 6-month eicosapentaenoic acid treatment on postprandial hyperglycemia, hyperlipidemia, insulin secretion ability, and concomitant endothelial dysfunction among newly-diagnosed impaired glucose metabolism patients with coronary artery disease. An open label, single blinded, prospective randomized controlled trial. Cardiovasc Diabetol 2016; 15: 121.

135. ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011; 364: 818–828.

136. White WB, Gulati V. Managing hypertension with ambulatory blood pressure monitoring. Curr Cardiol Rep 2015; 17: 2.), Houston M. The role of nutrition and nutraceutical supplements in the treatment of hypertension. World J Cardiol 2014; 6: 38–66.

137. Drugs and Lactation Database (LactMed) [Internet]. National Library of Medicine (US); Bethesda (MD): 2006.
138. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164(12):826-835. doi:10.7326/M15-2112.
139. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis [published correction appears in JAMA. 2019 Jun 11;321(22):2245]. JAMA. 2019;321(3):277-287. doi:10.1001/jama.2018.20578.
140. Mogul A, Leppien EE, Laughlin E, Spinler SA. Aspirin for primary prevention of cardiovascular disease: a review of recent literature and updated guideline recommendations. Expert Opin Pharmacother. 2021 Jan;22(1):83-91. doi: 10.1080/14656566.2020.1817389.
141. 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. JACC Journals › JACC › Archives › Vol. 74 No. 10.
142. O'Gara PT, Kushner FG, Ascheim DD et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 127, 529–555 (2013).
143. Clark CCT, Salek M, Aghabagheri E, Jafarnejad S. The effect of psyllium supplementation on blood pressure: a systematic review and meta-analysis of randomized controlled trials. Korean J Intern Med. 2020;35(6):1385-1399. doi:10.3904/kjim.2019.049.
144. Taneja A, Bhat CM, Arora A, Kaur AP. Effect of incorporation of isabgol husk in a low fibre diet on faecal excretion and serum levels of lipids in adolescent girls. Eur J Clin Nutr. 1989;43:197–202.
145. Hashem MA, Abd-Allah NA, Mahmoud EA, Amer SA, Alkafafy M. A Preliminary Study on the Effect of Psyllium Husk Ethanolic Extract on Hyperlipidemia, Hyperglycemia, and Oxidative Stress Induced by Triton X-100 Injection in Rats. Biology (Basel). 2021 Apr 16;10(4):335. doi: 10.3390/biology10040335**.**
146. Ziai SA, Larijani B, Akhoondzadeh S, et al. Psyllium decreased serum glucose and glycosylated hemoglobin significantly in diabetic outpatients. J Ethnopharmacol. 2005 Nov 14;102(2):202-7. doi: 10.1016/j.jep.2005.06.042.
147. Delargy HJ, O'Sullivan KR, Fletcher RJ, Blundell JE. Effects of amount and type of dietary fibre (soluble and insoluble) on short-term control of appetite. Int J Food Sci Nutr. 1997;48:67–77.
148. 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.

149. Lim SH, Lee J. Supplementation with psyllium seed husk reduces myocardial damage in a rat model of ischemia/reperfusion. Nutrition Research and Practice, 07 May 2019, 13(3):205-213. DOI: 10.4162/nrp.2019.13.3.205.
150. Varshney R, Budoff MJ. Garlic and Heart Disease. J Nutr. 2016 Feb;146(2):416S-421S. doi: 10.3945/jn.114.202333.
151. Fallah A.A., Sarmast E.D., Dehkordi S.H., Engardeh J., Mahmoodnia L., Khaledifar A., Jafari T. Effect of Chlorella supplementation on cardiovascular risk factors: A meta-analysis of randomized controlled trials. Clin. Nutr. 2018;37:1892–1901. doi: 10.1016/j.clnu.2017.09.019.
152. Bito T, Okumura E, Fujishima M, Watanabe F. Potential of Chlorella as a Dietary Supplement to Promote Human Health. Nutrients. 2020 Aug 20;12(9):2524. doi: 10.3390/nu12092524.
153. Qin S, Huang L, Gong J, et al. Efficacy and safety of turmeric and curcumin in lowering blood lipid levels in patients with cardiovascular risk factors: a meta-analysis of randomized controlled trials. Nutr J. 2017;16(1):68. Published 2017 Oct 11. doi:10.1186/s12937-017-0293-y.
154. Moohebati M, Yazdandoust S, Sahebkar A, et al. Investigation of the effect of short-term supplementation with curcuminoids on circulating small dense low-density lipoprotein concentrations in obese dyslipidemic subjects: a randomized double-blind placebo-controlled cross-over trial. ARYA Atheroscler. 2014;10:280.
155. Wongcharoen W, Jai-Aue S, Phrommintikul A, et al. Effects of curcuminoids on frequency of acute myocardial infarction after coronary artery bypass grafting. Am J Cardiol 2012; 110: 40–44.
156. Kendler BS. Carnitine: an overview of its role in preventive medicine. Prev Med. 1986; 15: 373–390.
157. Ribas GS, Vargas CR, Wajner M. L-carnitine supplementation as a potential antioxidant therapy for inherited neurometabolic disorders. Gene. 2014;533:469–76. doi: 10.1016/j.gene.2013.10.017.
158. Wang ZY, Liu YY, Liu GH, Lu HB, Mao CY. l-Carnitine and heart disease. Life Sci. 2018 Feb 1;194:88-97. doi: 10.1016/j.lfs.2017.12.015.
159. Lee BJ, Lin JS, Lin YC, Lin PT. Effects of L-carnitine supplementation on lipid profiles in patients with coronary artery disease. Lipids Health Dis. 2016 Jun 17;15:107. doi: 10.1186/s12944-016-0277-5.
160. DiNicolantonio JJ, Lavie CJ, Fares H, et al. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. Mayo Clin Proc 2013; 88: 544–551.
161. Geleijnse JM, Vermeer C, Grobbee DE, et al. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. J Nutr 2004; 134: 3100–3105.
162. Houston M. The role of noninvasive cardiovascular testing, applied clinical nutrition and nutritional supplements in the prevention and treatment of coronary heart disease. Ther Adv Cardiovasc Dis. 2018;12(3):85-108. doi:10.1177/1753944717743920

163. Erkkilä AT, Booth SL, Hu FB, et al. Phylloquinone intake and risk of cardiovascular diseases in men. Nutr Metab Cardiovasc Dis 2007; 17: 58–62.
164. Shea MK, Booth SL, Miller ME, et al. Association between circulating vitamin K1 and coronary calcium progression in community-dwelling adults: the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr 2013; 98: 197–208.
165. Lecube A, López-Cano C. Obesity, a Diet-Induced Inflammatory Disease. Nutrients. 2019 Sep 24;11(10):2284. doi: 10.3390/nu11102284.
166. Neuenschwander M, Ballon A, Weber KS, Norat T, Aune D, Schwingshackl L, Schlesinger S. Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies. BMJ. 2019 Jul 3;366:l2368. doi: 10.1136/bmj.l2368.
167. Trautwein EA, McKay S. The Role of Specific Components of a Plant-Based Diet in Management of Dyslipidemia and the Impact on Cardiovascular Risk. Nutrients. 2020 Sep 1;12(9):2671. doi: 10.3390/nu12092671.
168. Filippou CD, Tsioufis CP, Thomopoulos CG, et al. Dietary Approaches to Stop Hypertension (DASH) Diet and Blood Pressure Reduction in Adults with and without Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Adv Nutr. 2020 Sep 1;11(5):1150-1160. doi: 10.1093/advances/nmaa041.
169. Francis HM, Stevenson RJ, Chambers JR, Gupta D, Newey B, Lim CK. A brief diet intervention can reduce symptoms of depression in young adults - A randomised controlled trial. PLoS One. 2019 Oct 9;14(10):e0222768. doi: 10.1371/journal.pone.0222768.
170. Binks H, E Vincent G, Gupta C, Irwin C, Khalesi S. Effects of Diet on Sleep: A Narrative Review. Nutrients. 2020 Mar 27;12(4):936. doi: 10.3390/nu12040936.
171. Ko GJ, Obi Y, Tortorici AR, Kalantar-Zadeh K. Dietary protein intake and chronic kidney disease. Curr Opin Clin Nutr Metab Care. 2017 Jan;20(1):77-85. doi: 10.1097/MCO.0000000000000342.
172. Nédó E, Paulik E. Association of smoking, physical activity, and dietary habits with socioeconomic variables: a cross-sectional study in adults on both sides of the Hungarian-Romanian border. BMC Public Health. 2012;12:60. Published 2012 Jan 20. doi:10.1186/1471-2458-12-60.