Review Article

# Dietary Supplements and Cardiovascular Diseases

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**Abstract**

The market of nutritional supplements is expected to expand over 6%/year through 2018 due to growing interest in personal health, aging population, and promising personalized care products. The most used dietary supplements are fish oil, multivitamins, Vitamin D, and coenzyme Q10 (CoQ10) in this order, while probiotics is the fastest growing supplement. In the U.S., over 68% of the population use dietary supplements regularly. On the other hand, in the developed countries, cardiovascular diseases (CVDs) are the main cause of death and morbidity from the 1900s. The effects of most dietary supplements on cardiovascular risk and CVD have been studied for a long time. However, despite several studies explored the association of the various supplements to the cardiovascular risk, there is still a lack of consensus. Multivitamin supplementation has been advocated to reduce cardiovascular events; Vitamin D levels have been associated with the occurrence of coronary artery disease, heart failure, and atrial fibrillation; CoQ10 deficiency has been associated with myocardial dysfunction and with statin myopathy; probiotoics has been suggested to lower both blood pressure and circulating lipids. However, the study of the effects of dietary supplementations is not straightforward, since people assuming dietary supplements generally have a healthier diet and lifestyle, and randomized studies are rarely performed. In this review, we will summarize the findings linking dietary supplements to CVD with a special focus on novel insights.

**Keywords:** *Cardiovascular disease, cardiovascular risk, dietary supplements, multivitamins, probiotics, Vitamin D*

## Introduction

The United States (U.S.) nutritional supplements market is going to expand over 6%/year through 2018 due to growing interest in personal health, aging population, and promising personalized care products. In 2011, a survey of 10,000 consumers showed that the most used dietary supplements in the U.S. were fish oil, multivitamins, Vitamin D, and coenzyme Q10 (CoQ10), in this order.[1] However, in 2013 and first part of 2014, omega-3 and bone supplements sales in the U.S. declined, while probiotics was the fastest growing supplements category and it would remain so untill 2015.[1] The 2013 Council for Responsible Nutrition Consumer Survey on Dietary Supplements on 2012 U.S. residents over 18 years of age reported that 68% used dietary supplements regularly. The use of these supplements raised with age, varying from 64% of regular users between 18 and 34 years to 66% in the 35–55 years age group to 74% in the 55+ age group.[2]

Cardiovascular diseases (CVD) are the main cause of death in the U.S. from the 1900s.[3] In 2013, an estimated 83.6 million American adults (>1 in 3) have ≥1 types of CVD. Of these, 42.2 million are estimated to be ≥60 years of age.[4]

The efficacy of dietary supplements on global health has been deeply studied, but there is generally a lack of randomized trials and the understanding of their role is complicated by the fact that people assuming them generally have a healthier diet and lifestyle.

In our review, we will summarize the findings linking major dietary supplements to CVD with a special focus on novel insights. We will not discuss the role of omega 3 supplementation, since this supplement has been used in pharmacologic trials in cardiovascular field.

## Multivitamins

In the U.S., multivitamins are defined as a dietary supplement including three or more vitamins and minerals where each of them is contained at a tolerable dose, as defined by the Food and Drug Board.[5] Data on the



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efficacy of the association of vitamins on cardiovascular risk are actually inconsistent. The U.S. Preventive Services Task Force (USPSTF) has recently revised the most recent evidence of the association between vitamin consumption and CVD and cancer risk.[6] In its report, the USPSTF assessed that there are no sufficient data to confirm the role of multivitamin on the prevention of cancer and cardiovascular events. The first issue is that observational studies on the association between vitamins and CVD are scant and unclear. In the Cancer Prevention Study II on >1 million U.S. adults, the death rates tended to be more elevated in nonvitamin consumers with no previous CVD rather than in regular or occasional users. However, the significance of this association decreased when the death risk was adjusted for cardiovascular risk factors.[7] In Sweden, where fruits and vegetables consumption is poor, one case–control study on the relationship between vitamin supplements and myocardial infarction (MI) showed an inverse association between a low intake of multivitamins and the incidence of MI.[8] By contrast, in 2011, one large multiethnic study on 182,099 participants showed no significant association between multivitamins intake for >10 years and CVD risk.[9] These different results can be partially explained by the intervention of modifiers such as dose and composition of vitamin complex, age group, ethnicity, baseline intake of nutrients, behavioral exercise, and drugs (e.g., statin treatment). Recently, 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 of CVD).[6] The consumption of a high-dose multivitamin and multimineral did not significantly reduce even secondary cardiovascular events. This outcome can be influenced either by high frequency of withdrawals and noncompliance of the patients. Another issue is that most of studies examined the efficacy on heart just of single or small combination of vitamins. Moreover, most of these agents have shown no efficacy in reducing CVD.[10-12] Some of them have also been addressed to increase toxicity and adverse events.

## Vitamin D

Vitamin D is a prohormone synthetized in skin through ultraviolet radiation of 7-dehydrocholesterol. Its functioning depends first on its liver metabolism to 25-hydroxyvitamin $D_3$ (25[OH]$D_3$) and second to kidney conversion to 1α, 25-dihydroxyvitamin $D_3$. The serum 25(OH)D level is the most commonly used assessment to establish total level of Vitamin D.[13] Vitamin D has a wide spectrum of effects in the body, varying from the role on calcium/phosphate homeostasis and muscle strength, to the action on cardiovascular, nervous, and immune systems. Vitamin D deficiency has been referred to rise the incidence of multiple chronic diseases such as CVD, cancer, multiple sclerosis, and diabetes.[14] The first hypothesis of the association between level of Vitamin D and CVD was made by Robert Scragg in 1981. He suggested that ultraviolet irradiation, by raising body levels of Vitamin D, lowered the risk of thrombosis, thus protecting from CVD. According to Scragg, this hypothesis provided possible reasons for seasonal and geographical variations in CVD mortality and morbidity.[15] Since then, many authors provided important information to the association between Vitamin D levels and cardiovascular risk. Most of the recent results support a direct association between Vitamin D deficiency and CVD. One of the strongest results comes from a meta-analysis of prospective studies from 1966 through February 2012 on 65,994 subjects. In this study, the authors found a significant graded inverse association between 25(OH)-Vitamin D, varying from 20 to 60 nmol/L, and cardiovascular risk (RR, 1.03; 95% CI: 1.00–1.06 for each 25 nmol/L decrease in Vitamin D).[15] However, these data should be confirmed by studies regarding the association of Vitamin D to the different manifestations of CVD. In fact, CVD refers to a spectrum of different diseases including heart disease, vascular diseases of the brain, and the kidney and peripheral artery disease.[16] Most of results derived from studies about the association between Vitamin D status and heart disease, such as coronary artery disease (CAD), heart failure (HF), and dysrhythmia.

## Coronary Artery Disease

A growing number of evidence supports the predictive role of low levels of Vitamin D for the development of CAD. Two recent studies on patients who underwent coronary angiography also showed significant association between low level of Vitamin D and angiographic severity of coronary artery stenoses in patients with CAD assessed with SYNTAX score (which combines several angiographic classifications of lesions based on functional impact, location, and complexity).[17-19] A larger cross-sectional study confirmed these results. In this study, Verdoia *et al*. supported the impact of hypovitaminosis D on the progress and extent of CAD, particularly when Vitamin D levels were <10 ng/ml.[20] The main issue is still he understanding of the precise molecular causal effect linking Vitamin D deficiency to the development of CAD. Low levels of Vitamin D are associated with increased insulin resistance (and thus can lead to diabetes), hyperlipidemia, and hypertension, which all together lead to CAD.[21-23] Several findings revealed a direct biological effect of Vitamin D on the endothelium and in angiogenesis.[24,25] In fact, Vitamin D can influence the development of coronary collateral circulation [Figure 1]. Artery collateralization (arteriogenesis) is a preserving process for ischemic tissue. In this process, nonfunctional vascular anastomoses are modified into collateral arteries which can bypass obstruction sites.[26] The molecular action of Vitamin D on arteriogenesis has been completely understood. Recent studies focused on Vitamin D action

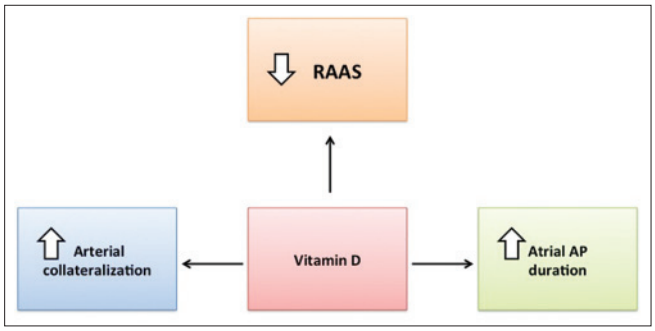


**Figure 1: Vitamin D has been demonstrated to increase arterial collateralization, to increase the duration of the atrial action potential, and to lower the activation of the renin-angiotensin-aldosterone system**

bound to its receptor in the nucleus. This complex promotes the transcription of several genes through the binding to specific gene target sequences.

## Heart Failure

There is a lack of consensus about Vitamin D action on HF and its consequences. In 2012, Gotsman *et al*. reported a high prevalence of Vitamin D deficiency among patients affected by HF. Low levels of Vitamin D were also predictive of poor outcome in HF patients.[27] In contrast, in 2013, Boxer *et al*. examined the role of high dose of Vitamin D supplementation (50,000 IU) in a randomized controlled study. After Vitamin D supplementation in, no improvement was found in HF patients' physical performance.[28] Moreover, a recent prospective study of 3731 men of 60–79 years old reported that the risk of HF in older men with and without MI or stroke was associated with the elevation in parathyroid hormone, recently denied to be an independent cardiovascular risk factor, but not with the 25(OH) D status.[29] How Vitamin D acts in HF is unclear. In animal models, Vitamin D status has been reported to downregulate the renin-angiotensin-aldosterone system (RAAS). In humans, it seems to be an inverse relation between Vitamin D and RAAS activation and activity [Figure 1].[30] The RAAS is overactivated in patients with HF, possibly leading to cardiac remodeling and activation of the sympathetic system.[31] Explanation could be found in Vitamin D status. Recently, the supplementation of 2000 UI for 6 weeks has been reported to lower plasma renin activity in HF patients.[32] Moreover, one recent study revealed that Vitamin D supplementation in HF patients with baseline low plasma levels lowered aldosterone concentration.[33]

## Atrial Fibrillation

The association between Vitamin D and atrial fibrillation (AF) is controversial. The first study which examined the possible role of Vitamin D in developing AF was a large European community-based cohort of 2930 participants in 2011.[34] After a follow-up of 9.9 years, the authors found no relationship between the incidence of new episodes of AF and Vitamin D status. Furthermore, in 2012, Qayyum *et al*. showed no association between Vitamin D level and type and adverse events related to AF.[35] However, recent smaller studies provided different results. In a recent comparative study of Vitamin D status in patients with nonvalvular AF, valvular AF and in control, Vitamin D deficiency was significantly related to nonvalvular AF.[36] The mechanisms which explain the effect of Vitamin D on the atrium are uncertain. A direct electromechanical action on the left atrium has been recently derived from a study on HF rabbits atrial tissue [Figure 1].[37] In this study, rapid atrial pacing and acetylcholine atrial stimulation both induce lower number, duration, and rate of AF episodes in the presence of 1,25[OH]2 D.

## Supplementation

The benefits of Vitamin D supplementation have been largely studied. Recently, Vitamin D supplements have been found to protect against bone fractures, cancer mortality, and overall mortality in elderly people.[38-40] In contrast, the effects of dietary Vitamin D supplementation on cardiovascular system are still under discussion. Large trials' analyses reported that Vitamin D supplements could prevent HF in the elderly but showed no protection against MI and stroke.[41] A recent small randomized double-blind placebo-controlled trial confirmed these results. This study showed that after 6 months of Vitamin D supplementation, elderly patients with HF had significant improvement in ejection fraction (EF).[42]

## Probiotics

Probiotics refer to viable bacteria or yeasts present in fermented dairy products, but also contained in drugs. They exhibit a wide spectrum of health benefits after ingestion, starting from better lactose tolerance and digestion, immune system reinforcement, and cancer inhibition. Nevertheless, much of literature has studied their activity of improving lipid metabolism and blood pressure (BP) profile, which are two strong independent cardiovascular risk factors. The first hypothesis of probiotics efficacy in lowering serum cholesterol refers to a study on dietary habits and cholesterolemia in the African Masaai.[43] The tribesmen were reported to assume regularly high dose of fermented whole milk and meat. Despite their dietary intake, they had low rate of CVD and low level of blood cholesterol. Thus, this inspired further studies to examine the association between cholesterolemia and fermented milk consumption.

Unfortunately, most of past and current results of the effect of probiotics on cardiovascular risk derive from studies *in vitro*. Furthermore, the precise mechanisms that make probiotics lowering lipids and BP are still unclear. Probiotics have been suggested either to promote cholesterol assimilation by growing cells, to bind it to cellular surface, or to insert it into the cellular membrane.[44,45] Gut microflora can also transform cholesterol into coprostanol, thus making

it eliminable with defection. This reduces cholesterol absorption and total cholesterol level. Different species of bacteria have been tested for this effect. In one study, Sterolibacterium denitrificans was shown to synthetize the enzymes which lead to cholesterol conversion into fundamental cofactors for coprostanol production.[46] This result is consistent with the fact that some probiotics act on cholesterol according to bacterial genus, species or strain; thus, it makes even more difficult to confirm the power of probiotics on lowering blood lipids. *In vivo* studies on animals reported that this action is partly due to Lactobacilli with bile salt hydrolase (BSH) activity.[47] Bile acids synthesis and elimination are the most important sources of cholesterol excretion in the feces.[48] These BSH bacilli have been shown to provoke the deconjugation of bile acids [Figure 2]. On one side, deconjugated bile acids are easily eliminated with defecation, thus raising the necessity of cholesterol to produce bile acids de novo. On the other side, the deconjugation of bile salts makes cholesterol hardly absorbable. Probiotics have also been investigated in improving BP profile. Recently, the consumption of probiotics for >8 weeks has been reported to reduce both systolic and diastolic BP, especially in subjects with high baseline BP consuming different species of probiotics.[49]

## Coenzyme Q10

CoQ10, or ubiquinone, is an organic molecule which is placed in the mitochondria, where it serves the electron reaction chain for cellular energy production, and in the plasma and subcellular elements where it is involved in other functions.[50] Some of these functions have been suggested to impact on CVD and cardiovascular risk factors. $CoQ_{10}$ deficiency, in fact, was revealed in serum and myocardial biopsies of patients with different CVD, from cardiomyopathy to HF.[51,52] According to some literature, $CoQ_{10}$ supplementation improves different cardiovascular conditions in many ways. Some authors reported that $CoQ_{10}$ supplementation enhance myocardial contractility, thus improving the EF of HF patients.[53] Other authors

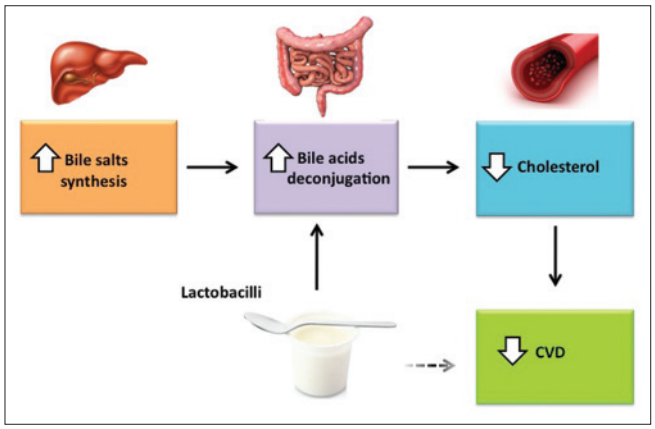


**Figure 2: Probiotics have been demonstrated to increase bile salts synthesis and bile acids deconjugation, and to lower circulating cholesterol, thus possibly protecting from cardiovascular diseases**

showed that the addition of $CoQ_{10}$ could influence the endothelial function.[54] Both coronary arteries tone and peripheral perfusion are controlled by the endothelium. Impaired flow-dependent, endothelium-mediated vasodilation (flow-dependent dilatation) is a typical condition of chronic HF where vessels are not able to face the variability in blood supply, partly because of nitric oxide degeneration by reactive oxygen species (ROS).[55] In recent years, one study showed that CoQ10 attenuates the oxidized low-density lipoprotein (oxLDL)-induced production of ROS, the oxLDL-altered proapoptotic responses of the endothelial cells and increase the antioxidant activity.[56] Another recent study reported that long-term supplementation with $CoQ_{10}$ in 420 HF failure patients improves both HF symptoms and New York Heart Association class and reduces all-cause mortality.[57] However, according to a 2014 Cochrane systematic review, the $CoQ_{10}$ supplementation was not confirmed neither to improve nor to worsen the conditions of patients with HF; thus, further evidence are needed.[58] The protective effect of $CoQ_{10}$ against lipid peroxidation has been recently studied in patients with atherosclerosis. Lee *et al*. showed that the supplementation of 150 mg/day of $CoQ_{10}$ in 43 patients with CAD is associated with lower oxidative stress, can improve antioxidant enzyme functions, and diminishes the level of pro-inflammatory interleukin 6.[59] This anti-inflammatory activity has also been proved in synergy with the Mediterranean diet, showing that the addiction of $CoQ_{10}$, especially in the elderly, reduces the expression of both pro-inflammatory and stress genes.[60,61] Some studies also analyzed the association between $CoQ_{10}$ supplementation and cholesterolemia. Hypercholesterolemia increases the risk of CVD, particularly of CAD. The synthesis of both cholesterol and $CoQ_{10}$ is dependent on the activity of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statins are commonly used drugs in the treatment of hypercholesterolemia as they inhibit HMG-CoA reductase. Thus, statins act also by blocking the production of $CoQ_{10}$. The deficiency in $CoQ_{10}$ and its consequences on mythocondrial functions could partly explain the incidence of myopathies induced by the use of statins, particularly in patients with genetic susceptibility.[62] Therefore, the supplementation of $CoQ_{10}$ could be necessary to avoid this adverse event. However, there is still no significant association between statins treatment, $CoQ_{10}$ depletion and the incidence of statins-induced myophaties.[63] Furthermore, there is no consensus about the improvement of these myopathies with $CoQ_{10}$ supplements.[64,65]

## Conclusions

In our work, we reviewed the role of the most used dietary supplements in cardiovascular risk. The market of nutritional supplements has increased and is going to further due to growing interest in personal health, aging population, and promising personalized care products.

The effects of most dietary supplements on cardiovascular risk and CVD have been studied for a long time. However, despite several studies explored the association of the various supplements to the cardiovascular risk, analyzing the effects of dietary supplementations is not straightforward since patients assuming dietary supplements generally have a healthier diet and lifestyle, and randomized studies are rarely performed.

Low Vitamin D levels have been associated with CAD, HF and AF; CoQ10 deficiency has been associated with myocardial dysfunction and to statin myopathies; multivitamin supplementation has been advocated to reduce cardiovascular events; probiotoics has been suggested to lower both BP and circulating lipids.

The growing importance of these dietary supplements could lead to the opportunity to perform ad hoc studies to clarify their role and the exact importance of each one in the determination of cardiovascular risk and CVD.

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### Conflicts of interest

There are no conflicts of interest.

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