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REVIEW

Dietary recommendations for prevention of atherosclerosis

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Abstract

This review aims at summarizing updated evidence on cardiovascular disease (CVD) risk associated with consumption of specific food items to substantiate dietary strategies for atherosclerosis prevention. A systematic search on PubMed was performed to identify meta-analyses of cohort studies and RCTs with CVD outcomes. The evidence is highly concordant in showing that, for the healthy adult population, low consumption of salt and foods of animal origin, and increased intake of plant-based foods—whole grains, fruits, vegetables, legumes, and nuts—are linked with reduced atherosclerosis risk. The same applies for the replacement of butter and other animal/tropical fats with olive oil and other unsaturated-fat-rich oil. Although the literature reviewed overall endorses scientific society dietary recommendations, some relevant novelties emerge. With regard to meat, new evidence differentiates processed and red meat—both associated with increased CVD risk—from poultry, showing a neutral relationship with CVD for moderate intakes. Moreover, the preferential use of low-fat dairies in the healthy population is not supported by recent data, since both full-fat and low-fat dairies, in moderate amounts and in the context of a balanced diet, are not associated with increased CVD risk; furthermore, small quantities of cheese and regular yogurt consumption are even linked with a protective effect. Among other animal protein sources, moderate fish consumption is also supported by the latest evidence, although there might be sustainability concerns. New data endorse the replacement of most high glycemic index (GI) foods with both whole grain and low GI cereal foods. As for beverages, low consumption not only of alcohol, but also of coffee and tea is associated with a reduced atherosclerosis risk while soft drinks show a direct relationship with CVD risk. This review provides evidence-based support for promoting appropriate food choices for atherosclerosis prevention in the general population.

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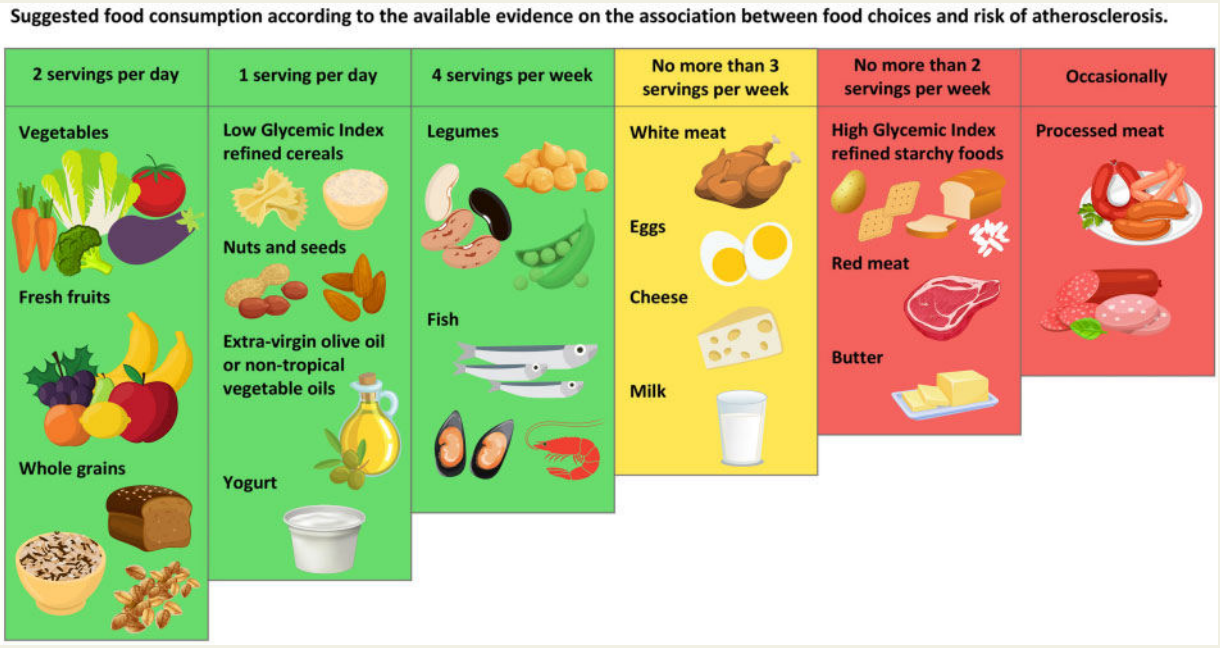
Graphical Abstract



Keywords Atherosclerosis • Coronary heart disease • Cardiovascular disease • Diet • Dietary recommendations • Food choices • Prevention

1. Introduction

There is strong evidence that dietary factors can influence the development of atherosclerosis directly, or through their effects on traditional risk factors, such as plasma lipids, blood pressure, and plasma glucose. However, this evidence is only partially based on randomized clinical trials (RCTs) with hard endpoints. In fact, although RCTs occupy the highest position in the hierarchy of evidence among the various study designs, those on diet and atherosclerotic events are relatively few and do not always provide consistent results.[1]

This inconsistency is partly due to methodological problems in the study conduct and interpretation. In fact, to reliably detect effects on chronic diseases, trials must evaluate changes in eating behaviours in large, compliant, and representative populations over long periods. This is not always feasible since, among other reasons, long-term compliance to recommended dietary modifications is difficult to achieve; moreover, trial planning must balance costs and statistical power. In addition, most trials focus on single dietary changes; however, when the energy intake is kept constant, eating less of one macronutrient implies necessarily eating more of others and the type of the replacement can influence the outcomes.[1]

Against this background, it must be acknowledged that the difficulties in conducting clinical trials designed to adequately test dietary strategies for prevention of atherosclerosis make it unlikely that the present research gaps in nutrition research will be filled in the future by this type of studies.

Therefore, it is reasonable to assume that if the evidence from RCTs were the only adequate scientific support for dietary recommendations for atherosclerosis prevention, very few dietary changes would pass the scrutiny for inclusion in guidelines. This would limit drastically the possibility to reduce the risk of atherosclerosis in a large number of people who do not qualify for lifelong drug treatment. For these reasons, it is reasonable to embrace also observational studies with hard endpoints in the evidence in support to dietary recommendations for prevention of atherosclerotic vascular disease. Long-term prospective cohort studies, tough based on self-reported dietary assessments and limited by residual confounding, allow a more successful control for confounding factors than cross sectional studies and hold several strengths that complement trial shortcomings.[2]

However, in the interpretation of the epidemiological evidence, it should always be considered that foods are mixtures of different nutrients and non-nutrient bioactive compounds and that characteristics other than nutrient combination (i.e. physical features of the foods, processing and cooking procedures) modulate the bioavailability of nutrients and, in turn, their metabolic effects. Therefore, in recent years research on diet and atherosclerosis has given more and more emphasis to foods and dietary patterns rather than to the nutrient's composition of the diet. This approach can also facilitate the translation of the information derived from nutritional research into clinical recommendations. In fact, the general public and practising physicians would find it difficult to fully understand and implement recommendations based on nutrients intake, whereas it would be easier for them to rely on a guidance based on food groups.[3–5]

Against this background, the aim of this article is to review and update evidence on the relationship between diet and atherosclerosis by highlighting the associations between food choices and coronary heart disease (CHD) and cardiovascular diseases (CVDs)—the most common and severe clinical manifestations of atherosclerosis—taking into consideration data from prospective studies and RCTs—when available—with CVD end points.

2. Research methods

We have carried out a review of the literature on the association between individual foods/food groups and CHD/CVD incidence and/or mortality published up to 31 August 2020. Foods have been grouped on the basis of their origin (whether animal—meats, eggs, fish, dairy—or vegetal—cereals, legumes, vegetables, fruits, nuts); in addition, the literature on dietary fats and beverages consumption has also been reviewed. For each food group/item a systematic search for meta-analyses of prospective cohort studies with CHD/CVD incidence and/or mortality as end points has been performed independently by two reviewers (I.C. and A.G.). The reasons to focus on prospective studies is that this study design allows a more successful control for confounding factors; moreover, in nutritional epidemiology they often represent the best source of evidence since RCTs are not always available. The utilization of meta-analyses allows a comprehensive and balanced summary of the available evidence; in this respect, we have included in our evaluation all the available meta-analyses on the relationships between a specific food group and atherosclerotic cardiovascular events. The reproducibility of the outcomes of different meta-analyses together with the magnitude of the relative risk and its confidence interval have been considered as measures of the consistency and the strength of the association. The research has been carried out utilizing the electronic database PubMed and using as key words the food items of interest along with the terms related to the outcomes, i.e. CHD incidence or CHD mortality or CVD incidence or CVD mortality or CHD or ischaemic heart disease or coronary artery disease or acute myocardial infarction (MI). A subsequent search has been performed for recent cohort studies not included in the meta-analyses (up to August 2020) as well as for RCTs evaluating the association of specific foods/nutrients with CHD or CVD endpoints.

Exclusion criteria are meta-analyses including retrospective and/or case–control studies or studies conducted on populations with specific dietary habits (i.e. vegetarians and vegans) or with chronic diseases requiring specific dietary treatment (i.e. diabetes, dyslipidaemia, hypertension etc.).

The relative risks and their confidence intervals have been extracted, as well as the heterogeneity assessment through I^2 statistics method, and are summarized in Supplementary material online, *Tables S1–S7*. Foods consumption and their association with outcomes have been quantified by comparing the highest with the lowest consumption of the single food group. When available, data from dose–response analyses have been used in order to identify the serving sizes of foods with the strongest association with the outcomes, or representing the threshold of intake above or below which the relationship curve departs from linearity. This is particularly useful in order to provide dietary recommendations to the general population.

3. Associations between food choices and CHD

3.1 Foods of animal origin (*Table 1*)

3.1.1 Meat

The relation of meat consumption with CHD has been explored by two meta-analyses of observational prospective studies, both of which indicate an excess of CHD risk (fatal and non-fatal) associated with regular meat consumption. For each additional 100 g/day of meat intake, a 25% increase in CHD incidence is reported; similarly, a significantly increased risk is shown for the incidence of CVD. Conversely, the associations with CHD and CVD mortality do not reach the conventional level of statistical significance. All meta-analyses present a very high heterogeneity among the studies (Supplementary material online, *Table S1*).

A relevant source of heterogeneity resides in the fact that meats are broadly classified into red (i.e. beef, pork and lamb) or white (i.e. chicken, turkey and rabbit) types, with different contents of fat, cholesterol and iron; furthermore, meats can be consumed fresh or processed with the addition of salt and chemicals. These important nutritional differences may impact on health outcomes and, therefore, the associations with the atherosclerosis risk must be evaluated separately for the various meat types.

With regard to processed meat (i.e. bacon, sausages and salami), a strong positive association with CHD end points is shown in two out of three available meta-analyses of observational prospective studies in which a daily serving of 50 g/day of processed meat is associated with a 27% and a 44% increase in CHD incidence. No significant association with fatal or non-fatal CHD is reported in a third meta-analysis which, however, shows a significantly increased CVD mortality in high vs. low consumers; this is in line with three other meta-analyses with CVD end points showing a hazard ratio for CVD mortality that ranges between 1.02 and 1.24 for high vs. low consumption (Supplementary material online, *Table S1*).

The evidence on the relationship between unprocessed red meat consumption (i.e. beef, pork and lamb) and CHD is less concordant. Among the three published meta-analyses on observational prospective studies, only one reports a statistically significant 27% increase in the incidence of CHD for a daily consumption of 100 g of red meat, while the other two show no relationship. However, looking at CVD mortality, the three available meta-analyses consistently show an excess of CVD mortality associated with a regular consumption of 100 g/day of unprocessed red meat and a reduced CVD mortality associated with a three servings/week lower consumption of unprocessed red meat (Supplementary material online, *Table S1*). In this respect, it is also worth underlining that studies in which replacement of proteins from unprocessed red meat with plant proteins is investigated, consistently show that reducing red meat consumption is associated with a lower CVD mortality.[6,7]

In relation to white meat, the only available meta-analysis of observational prospective studies explores the relationship with CHD mortality and does not show any statistically significant association. Large prospective cohort studies with CHD and CVD end points subsequently published have been recently meta-analysed by our group, together with prior studies, and the results confirm the lack of association between white meat intake and incidence of CHD or CVD, either fatal or non-fatal; there is, however, a large heterogeneity among the included studies that cannot be easily explained (Supplementary material online, *Table S1*). Biologically plausible mechanisms may mediate the different relationships of processed and red meat or white meat with CV outcomes. Poultry, as compared with beef, lamb, or pork is characterized by a lower fat content, a more favourable fatty acid profile (i.e. a higher saturated/unsaturated fatty acid ratio) and a lower content of heme iron—both saturated fatty acids (SFAs) and heme iron are associated with an higher risk of atherosclerosis; in addition, preservatives, such as sodium and nitrates—largely used in the preparation of processed meat—increase the risk of hypertension, insulin resistance, and endothelial dysfunction, all of which are established CV risk factors.[8,9]

In summary, based on the consistent evidence of a markedly increased risk of CHD/CVD associated with processed meat intake (*Table 1*), this

Table 1 Association between consumption of foods of animal origin and risk of atherosclerosis

Food item	Risk of atherosclerosis		Consistency of the evidence
	CHD Incidence/mortality	CVD Incidence/mortality	
Meat	↑↑	↑	+
Processed meat	↑↑	↑↑	++
Unprocessed red meat	↑↑	↑↑	+
White meat	↔	↔	++
Eggs	↔	↔	++
Fish	↓	↓	++
Dairy products	↔	↔	++
Full fat dairy	↔	↔	+
Low fat dairy	↔	↔	+
Milk	↔	↔	+
Yogurt	↔	↓	+
Cheese	↓	↓	+

The risk of atherosclerosis associated with a higher vs. lower consumption of each food item is indicated with arrows (up: increase; down: decrease; flat: neutral). Single arrows indicate a statistically significant increase/decrease of RR up to 10%; double arrows indicate a statistically significant increase/decrease of RR >10%.
The consistency of the evidence is indicated as follows: ± insufficient/controversial; + moderate; ++ high.

food item should be consumed only occasionally. For unprocessed red meat data are less coherent (*Table 1*), but the overall evidence indicates that its consumption should also be limited, although to a lesser extent (i.e. two servings of 100 g per week), unless this is contraindicated for medical reasons. More stringent limitations may not be feasible in most western countries where red meat is consumed almost on a daily basis. White meat can be consumed in moderate amounts (up to three servings of 100 g per week), based on its neutral association with atherosclerosis risk (*Table 1*), and may represent a healthier and more eco-sustainable alternative to red meat, together with plant-based protein sources (*Figure 1*). However, these considerations are based on the features of the meat products available today on the market; it might be speculated that variations of the genetic background and modifications of the feeding modalities of pigs and cows could change the impact of red meat on cardiovascular health.

3.1.2 Eggs

Several meta-analyses of prospective cohort studies consistently report the absence of any significant association between moderate egg consumption (up to one egg/day) and fatal or non-fatal CHD. This finding is coherent with data on CVD incidence and mortality (*Table 1* and Supplementary material online, *Table S1*). However, the data indicate a non-linear dose/response relationship and, therefore, the risk may increase for a larger consumption.

In the past, more caution on egg consumption was motivated by their high cholesterol content, which may contribute to rise the plasma cholesterol levels. However, response to dietary cholesterol is variable, and partly under genetic control:[10] 'hyper responders' present an impaired inhibition of endogenous cholesterol synthesis during a cholesterol rich diet, often associated to lower plasma levels of apolipoprotein E and increased levels of apolipoprotein C-III.[11] Moreover, other features of the diet (i.e. a high saturated fat and/or a low fibre content) can amplify the plasma cholesterol response to a cholesterol rich diet. In the majority of the population ('normal responders'), the plasma cholesterol increase elicited by a dietary cholesterol content of 300– 600 mg/day—which corresponds to three servings of two eggs per week—is small.

Therefore, on the basis of the available evidence, a moderate consumption of eggs (up to three servings of two eggs per week, or one egg per day) can be permitted (*Figure 1*). This may not apply to people with hyperlipidaemia or diabetes for whom more caution is appropriate. A similar caution would be suitable in populations with a western dietary pattern rich in foods with a high content of SFAs; in this case, it may be wise not to exceed a weekly consumption of three eggs.[12]

3.1.3 Fish

The results of seven meta-analyses of observational prospective studies are concordant in indicating that moderate fish consumption is significantly associated with a reduced CHD incidence and mortality (*Table 1* and Supplementary material online, *Table S1*). However, in some of them, there is a significant heterogeneity among the included studies; this suggests that the relationship with CVD may vary in relation to the different fish categories and/or cooking procedures that are utilized in different countries. As for quantities, a dose–response meta-analysis of 15 cohort studies reports a 12% reduction in the incidence of CHD for 4 servings of fish weekly (100 g/day); other meta-analyses indicate that even smaller fish intakes (100–150 g/week) are associated with a lower, yet statistically significant, benefit: 4–7% CHD reduction. For a consumption exceeding 3–4 servings/week, the relation with CHD (both fatal and non-fatal) is less clear. There are some indications that the relationship may shift towards a neutral or even an inverse association in a meta-analysis by Jayedi, in which a U-shaped dose–response relationship between fish consumption and non-fatal MI has been reported.[13] A subsequent dose–response meta-analysis including 19 studies, shows that provided that fish consumption is above 40 g/day, CHD incidence is linearly and inversely correlated with the intake; however, the same article reports that for what concerns CHD mortality, the relationship is not linear and the greatest reduction is observed for a fish consumption around three servings weekly remaining, nevertheless, stable for higher intakes.[14]

The benefits of moderate fish consumption in relation to atherosclerosis prevention are generally attributed to the high content of long-chain omega-3 polyunsaturated fats (PUFAs), which contribute to

Figure 1 Suggested food consumption according to the available evidence on the association between food choices and risk of atherosclerosis. The red colour indicates the association with a higher risk of atherosclerosis; the yellow colour indicates a neutral relationship with risk of atherosclerosis for a moderate consumption; the green colour indicates the association with a lower risk of atherosclerosis. [1]Canned fruits should not be used in substitution of fresh fruits. [2]The amount can vary in relation to the energy needs.

control plasma triglycerides, improve membrane fluidity, and exert an anti-inflammatory and anti-thrombotic activity. However, the contribution of other nutrients cannot be ruled out.[15]

In summary, current evidence is consistent with a fish consumption between two and four servings of 150 g per week as a means to contribute to atherosclerosis prevention (*Figure 1*); for higher intakes, some inconsistencies about the association with CHD outcomes have emerged among the available studies. Further investigation is required to explore the impact of gender and geographical location on this relationship as well as that of the specific types of fish consumed. The relevant ecological impact of fish consumption represents a further motivation to keep its consumption between two and four servings per week, since higher quantities would be probably unsustainable.[16]

3.1.4 Dairy products

This is a large food group which includes food items with several differences in their nutritional features; among others, fat and salt content, as well as processing methodologies and fermentation, may impact on cardiovascular health outcomes.

The consumption of dairy products globally is not associated with CHD, as consistently shown in six meta-analyses of observational prospective studies. Furthermore, among four of these meta-analyses reporting also CVD outcomes, one shows a significant inverse association with CVD incidence while the others do not report any significant relationship (*Table 1* and Supplementary material online, *Table S2*).

When full fat and low fat dairy foods are evaluated separately, the data are concordant in showing a neutral association with CHD for both these subtypes of dairies up to a global consumption of 200 g per day—including milk (*Table 1* and Supplementary material online, *Table S2*). However, no reliable information is available for higher intakes.

As for specific dairy foods, the consumption of a serving of ~200 g/day of milk is not associated with CHD incidence in 4 out of 5 meta-analyses. With regard to CVD, Soedamah-Muthu et al.[17] report a significant risk reduction (<10%) associated with the same amount of milk consumption, but this result has not been confirmed by two subsequent meta-analyses showing no statistically significant relationship (*Table 1* and Supplementary material online, *Table S2*).

The possible role of dairy fermentation in relation to the risk of atherosclerosis has also been evaluated. Two meta-analyses report a significant inverse relationship of fermented dairy foods (including yogurt and cheese) with CVD incidence, but not with CHD (Supplementary material online, *Table S2*). In particular, Guo et al.[18] summarizing the results of eight cohort studies—mostly from Europe—have shown a significant 17% reduction in the incidence of CVD for high vs. low intake of fermented dairies. More recently, Zhang et al.[19] have reported a significant 18% reduction in the incidence of MI associated with the habitual consumption of fermented cheese. These findings are coherent with a significant inverse association between fermented dairy and CHD or MI reported in some recently published studies not included in the available meta-analyses.[20,21]

With regard specifically to cheese, several meta-analyses have reported an inverse association with CHD and CVD incidence (*Table 1* and Supplementary material online, *Table S2*). In particular, two meta-analyses, in which the dose–response relationship has been evaluated, have shown a statistically significant reduction (average 12%) of CHD incidence for an intake of 50 g/day of cheese. As for yogurt consumption, no significant relationship has been shown in studies with CHD as the endpoint, probably due to a small number of events. Conversely, a significant inverse association with CVD incidence and mortality has been

reported in the more recent meta-analyses, in contrast with the older ones. The apparent inconsistency may be due to the insufficient amount of yogurt utilized by the high consumers in some of the old studies. In fact, a significant protective association with CVD has been reported only for a daily amount of yogurt of at least 200 g per day (*Table 1* and Supplementary material online, *Table S2*).

Dairy products represent one of the most heterogeneous food groups. Full fat dairy products have been traditionally assumed to be a high and unnecessary source of saturated fat. However, despite their high content of SFAs—mostly long-chain SFAs, some of which are also present in meat (lauric acid, myristic acid, palmitic acid, and stearic acid)—they are an important source of potentially beneficial compounds, such as the medium-chain and odd-chain saturated fats, naturally occurring trans-fatty acids (TFAs), branched-chain amino acids, vitamin K1 and K2, and calcium.[22] These nutritional characteristics could explain why the epidemiological evidence does not support a pro-atherogenic role of milk and dairy foods, even if full fat. Obviously, this applies to the healthy population in the context of a balanced diet, since the impact of these foods on the atherosclerosis risk might be detrimental in people at high CVD risk in the light of the hypercholesterolemic effect of a high saturated fat diet. With respect to fermentation, a number of epidemiological observations support the beneficial role of fermented dairy in relation to the risk of atherosclerosis, possibly due to their probiotic activity. The intake of probiotics plays an important role in improving the intestinal flora, favouring the growth of beneficial bacteria and reducing the risk of chronic illnesses, such as CVDs. In particular, probiotics have antioxidative, anti-platelet aggregation, and anti-inflammatory properties and may lower the level of cholesterol and blood pressure.[23]

In summary, current evidence endorses recommendations to utilize milk and cheese with moderation (one cup daily and, respectively, three small servings of 50 g per week), and to include a serving of 200 g yogurt in the daily diet (*Figure 1*).

3.2 Plant-based foods (*Table 2*)

3.2.1 Legumes

An inverse relationship between legume consumption and incidence of CHD has been reported in two recent meta-analyses of observational prospective studies; the largest risk reduction (-14%) has been observed for a consumption of 400 g per week. These results have been confirmed in subsequent meta-analyses in which high (at least 250 g/week) vs. low (0 g/week) intakes have been compared. The findings are qualitatively similar when CVD outcomes are considered; conversely, no significant relationship has been reported for fatal events (*Table 2* and Supplementary material online, *Table S3*). A reduction of CHD and CVD mortality is associated with the consumption of soy products in some meta-analyses, but the results are not fully concordant; however, a beneficial association seems to be present with fermented soy foods like *natto* and *miso*. No data are available on the dose–response relationship (Supplementary material online, *Table S3*).

Besides the high protein content, legumes are a good source of viscous fibre, which have a well-documented beneficial effect on plasma lipids and on post-prandial glucose and insulin responses; moreover, they are rich in multiple bioactive constituents—including folate and phytochemicals—that can improve the cardiometabolic health.[24] However, it is possible that the metabolic benefits of legume consumption are partly due to the fact that legumes are often consumed as an alternative to meat, high glycemic index (GI) cereals, starchy foods, and sugar rich foods.[6,7]

In summary, a regular consumption of legumes, up to four servings of 180 g (fresh or frozen) per week, represents one of the most evidence-based dietary means to reduce the risk of atherosclerosis (*Figure 1*).

3.2.2 Nuts

The evidence of an inverse relationship between the habitual nut consumption and the risk of CHD incidence and mortality is very consistent. As for quantities, four dose–response meta-analyses have reported an average 25% reduction in the incidence of CHD for a daily consumption of 28 g of nuts. Data on CVD risk are concordant with these findings (*Table 2* and Supplementary material online, *Table S3*). Nuts are rich in fibre, and are also a source of linoleic acid, which has been shown to be inversely associated with the incidence of CHD and CVD (Supplementary material online, *Table S5*).

Therefore, in agreement with dose–response analyses, a daily consumption of a serving of nuts (a handful: around 30 g) is recommended (*Figure 1*).

3.2.3 Vegetables and fruits

Five out of six meta-analyses of observational prospective studies on the association between vegetable consumption and CHD have reported a significant inverse association; an 8–18% lower incidence of CHD events has been found in people consuming large amounts of vegetables, with a maximal reduction (nearly 18–21%) associated with a daily consumption of 400 g (i.e. two servings per day); for this amount, the reduction of CHD mortality has been reported to be 34% (Supplementary material online, *Table S3*). As for vegetable types, high compared to low consumptions of green leafy vegetables and tomatoes are associated with a significant 17% and 10% reduction in the incidence of CHD, respectively. The data are generally concordant with that on CVD outcomes (*Table 2* and Supplementary material online, *Table S3*).

Fruit consumption is inversely associated with CHD incidence and mortality in several meta-analyses; however, some of them present a significant heterogeneity, thus suggesting that the relationship with the events may vary in relation to the fruit type. The most recent and comprehensive dose–response meta-analysis indicates that a daily consumption of 400 g of fruit is associated with reduction of CHD incidence (-10%) and mortality (-18%); this amount of fruit is associated also with a significant reduction of CVD incidence (-21%) and mortality (-32%) (*Table 2* and Supplementary material online, *Table S3*). This significant inverse relationship is shared by fruit juices (containing 100% fruit). Conversely, tinned fruit is associated with a significantly higher risk of CVD (Supplementary material online, *Table S3*).

As for mechanisms, the high fibre content, both soluble and insoluble, of fruits and vegetables can play a relevant role. Dietary fibre can modulate major risk factors for atherosclerosis (i.e. plasma lipids, blood glucose and insulin sensitivity) in the fasting and post-prandial state.[25] Polyphenols are also very important constituents of plant foods with antioxidant properties and relevant metabolic benefits. They interact selectively with intestinal microbiota and facilitate the growth of bacterial strains with a beneficial metabolic activity. Moreover, they can be absorbed in the intestine and reach the liver where they modulate glucose and lipid metabolism. There is evidence that diets rich in polyphenols improve glucose and insulin metabolism as well as the plasma lipid profile and reduce the systemic inflammatory status.[26,27]

The available evidence consistently supports a large consumption of fruit and vegetables—at least two servings of 200 g per day for each of them—in the habitual diet (*Figure 1*).

Table 2 Association between consumption of plant-based foods and risk of atherosclerosis

Food item	Risk of atherosclerosis		Consistency of the evidence
	CHD Incidence/mortality	CVD Incidence/mortality	
Legumes	↓	↓	++
Nuts	↓↓	↓↓	++
Vegetables	↓↓	↓↓	++
Fruits	↓↓	↓↓	++
100% fruit juices	↓	±	±
Canned fruits	±	↑↑	±
Whole-grain cereals	↓↓	↓↓	++
Refined cereals	↑	↔	±
Refined cereals and other starchy foods with high glycemic index	↑↑	±	+

The risk of atherosclerosis associated with a higher vs. lower consumption of each food item is indicated with arrows (up: increase; down: decrease; flat: neutral). Single arrows indicate a statistically significant increase/decrease of RR up to 10%; double arrows indicate a statistically significant increase/decrease of RR >10%; ± indicates insufficient/controversial data.
The consistency of the evidence is indicated as follows: ± insufficient/controversial; + moderate; ++ high.

3.2.4 Cereals

They represent the major constituent of the habitual diet almost in every country and embody a large and heterogeneous group of food items with different nutritional properties. Within this group, three major categories can be identified: refined carbohydrates with high GI (i.e. white rice and white bread); refined cereals with low GI (i.e. pasta, parboiled rice, and corn tortilla), and whole-grain cereal foods.

As for the overall consumption of refined cereals, only one over three meta-analyses of observational prospective studies reports an association with an increased CHD risk. Less information is available on the relationship with CVD and it does not indicate a significant association (*Table 2* and Supplementary material online, *Table S4*).

Among various nutritional properties, cereal foods may largely differ for the rate of carbohydrate digestion and absorption, which modulates the post-prandial glucose response. This is measured by the GI, generally considered a marker of the overall metabolic impact of these foods.[28] The amount of carbohydrates consumed multiplied by the GI of the food is expressed by the glycemic load. In the last decades, six meta-analyses have evaluated the relationship between the GI of the diet and CHD in longitudinal studies and they are concordant in showing an increased atherosclerosis risk in individuals consuming high GI diets (*Table 2* and Supplementary material online, *Table S4*). The relative risks for the high vs. the low GI diets range between 1.06 and 1.25 and reach statistical significance in four out of six meta-analyses. When the dose–response relationship is explored, a daily consumption of 98 g of carbohydrate consumed as high GI cereal foods (i.e. 80 g of white bread plus 50 g of rice) is significantly associated with a 66% higher CHD risk. Similarly, CHD risk is 44% higher for each 65 g/day of glycemic load.[29] The relationship with CVD has been explored in one meta-analysis of eight cohort studies with mortality endpoints, which has not found any significant association; no data are available for non-fatal events.

The diverging relationships with the atherosclerosis risk of high or low GI refined cereals are largely due to their different impact on post-prandial blood glucose, which is the consequence of physical-chemical properties of the food matrix within which the available (glycemic) carbohydrates are embedded. These properties modulate the rate of digestion, absorption, and metabolism of carbohydrates and, thus, the rate of glucose appearance in the blood stream, which in turn, influences other metabolic pathways relevant for the atherosclerosis risk, like insulin sensitivity, plasma insulin, lipids, blood pressure, subclinical systemic inflammation, and the oxidative stress.[30]

As for whole-grain foods (i.e. bread, rice, oat, and barley), a strong and consistent inverse relationship with CHD risk has been found in several meta-analyses of longitudinal cohort studies; the risk reduction associated with the habitual consumption of these food items ranges from 25% to 34% (Supplementary material online, *Table S4*). However, some meta-analyses report a significant heterogeneity among the included studies; this might indicate that various cereal types (or the technologies employed for their preparation) might have different relationships with the outcomes. The dose–response analysis indicates that for each additional intake of 30 g/day of whole-grain cereal foods a reduction of 8% in CHD mortality is observed. The risk estimates for CVD incidence and mortality are similar (*Table 2* and Supplementary material online, *Table S4*).

The benefits of habitual whole-grain consumption are mediated by the improvement of multiple risk factors for atherosclerosis, such as insulin resistance, dyslipidaemia, subclinical inflammation, and oxidative stress. Whole grains are also a great source of insoluble dietary fibre and, therefore, they are bulky and have a low-energy density; this can promote satiety and prevent weight gain. Insoluble dietary fibre from whole grain is not digested and absorbed in the small intestine but passes to the colon, where it undergoes bacterial degradation. This is an anaerobic process producing short chain fatty acids—acetate, propionate, and butyrate—as end-products; these have important effects on satiety and on glucose and lipid metabolism.[31]

In summary, in view of the rather consistent evidence that high GI refined cereals (and other starchy foods like potatoes) are associated with an elevated atherosclerosis risk, it seems appropriate to recommend to reduce their use, limiting their consumption to no more than two servings per week (*Figure 1*). A more stringent restriction might be appropriate, but it seems presently not feasible on a general scale, since in most countries these items represent staple foods. Replacement of high GI refined cereals could be achieved with both low GI refined cereal foods and whole grain. For both of them a dose–response relationship with atherosclerotic cardiovascular events has been reported; according to

the available information, a relevant decline in the events could be achieved already for a daily consumption of one or two daily servings—the size depends on the specific item—of both low GI and whole-grain cereal foods in substitution of high GI refined cereals (*Figure 1*).

3.3 Dietary fats (*Table 3*)

There is very consistent evidence indicating that consumption of foods containing TFAs is associated with a higher risk of CVD and sudden death; this relationship is stronger than for any other dietary fat. In fact, a meta-analysis of four prospective cohort studies has shown that a 2% increase in energy intake from TFAs is associated with a 23% higher incidence of CHD (Supplementary material online, *Table S5*).

In relation to butter, two meta-analyses of observational prospective studies have been published on the relationship with CHD incidence and both report the lack of a statistically significant association. Similarly, the only available meta-analysis with CVD endpoints does not show any significant relationship with butter consumption (*Table 3* and Supplementary material online, *Table S5*). It is, however, of note that these meta-analyses are based on few studies (3–5) and in one of them—the largest one with 120 852 participants—an increased ischaemic heart disease mortality is associated with butter and dairy fat intake in women.[32] Moreover, the usual butter intake in the meta-analysed studies is moderate (i.e. 9 g/day on average and 25 g/day in the high consumers group) and, therefore, no information can be gained from these studies on higher intakes, which are common in many populations.

In relation to non-tropical vegetable oils, the available evidence must be considered separately for olive oil, rich in monounsaturated fats (MUFAs), and other vegetable oils rich in linoleic acid. As for olive oil, there are three meta-analyses of observational prospective studies on the relationship with CHD incidence and all of them report a trend towards a lower risk for an increased olive oil consumption; however, only in one of them the conventional level of statistical significance is reached. The relationship with CVD incidence is more reproducible, since three meta-analyses of prospective studies with this endpoint consistently show a significant risk reduction in the highest categories of olive oil consumption (*Table 3* and Supplementary material online, *Table S5*). In a dose–response evaluation, a 5 g increase in olive oil consumption is associated with significant reduction of CHD incidence (-7%), CVD incidence (-4%), and CVD mortality (-8%). Furthermore, a recent intervention trial, the PREDIMED, has shown that the incidence of major cardiovascular events is reduced by 31% in those participants assigned to a Mediterranean diet supplemented with extra-virgin olive oil in comparison to those assigned to a reduced-fat diet.[33]

As for the relationship between consumption of vegetable oils rich in linoleic acid (i.e. safflower, sunflower, corn, and soybean oils) and the risk of atherosclerotic events, the evidence from meta-analyses of observational prospective studies was rather weak until some years ago; however, two very recent meta-analyses with a much larger number of cases than the previous ones (50 786 and 15 198, respectively) report a very clear association between higher intakes of linoleic acid rich oils (evaluated by a reliable biomarker of intakes, such as the fatty acid spectrum of plasma lipids) and a reduced CVD mortality (-13%) or total CVD incidence and CVD mortality (-7% and -22%, respectively)[34,35] (*Table 3* and Supplementary material online, *Table S5*).

However, in order to get a better insight into the potential impact of different dietary fats on the risk of atherosclerosis, it is relevant to look also at the extensive literature of longitudinal cohort studies and RCTs evaluating the risk of events associated with substitution of SFAs—the major type of fat present in butter, animal fat, and tropical oils—with different nutrient sources (Supplementary material online, *Table S6*). Notably, in the context of the overall diet, when the energy intake is kept constant, eating less of one macronutrient implies necessarily eating more of others. The quality of the replacement can influence the observed effect. In fact, consistent evidence from prospective studies indicates that if SFAs reduction is obtained through the replacement with refined carbohydrate foods, the risk of atherosclerotic events not only does not decrease, but it can even rise, in parallel with an increase of the rate of obesity and type 2 diabetes.[1,5] Conversely, the substitution of 5% energy from SFAs with an isoenergetic amount of omega-6 PUFAs is consistently associated with a significant reduction of CHD incidence—between 9% and 25%—in five available meta-analyses, and with a reduction of CHD mortality (between 13% and 26%) in two meta-analyses.

Table 3 Association between consumption of dietary fats, salt, beverages, and chocolate and risk of atherosclerosis

Food item	Risk of atherosclerosis		Consistency of the evidence
	CHD Incidence/mortality	CVD Incidence/mortality	
Butter[a]	↔↑	↔↑	+
Olive oil[b]	↓	↓↓	++
Vegetable oils (rich in linoleic acid)[b]	↓↓	↓↓	++
Salt	↑↑	↑↑	+
Sugar-sweetened beverages	↑↑	↑↑	++
Low-calories sweetened beverages	↑	↑	+
Alcoholic beverages[c]	↓↓	↓↓	++
Coffee[c]	↓	↓↓	+
Tea[c]	↓	↓	+
Chocolate[c]	↓	↓↓	++

The risk of atherosclerosis associated with a higher vs. lower consumption of each food item is indicated with arrows (up: increase; down: decrease; flat: neutral). Single arrows indicate a statistically significant increase/decrease of RR up to 10%; double arrows indicate a statistically significant increase/decrease of RR >10%.
The consistency of the evidence is indicated as follows: ± insufficient/controversial; + moderate; ++ high.
[a]Depending on the replacing food.
[b]The evaluation includes observational studies and RCTs taking into account the replacing food or macronutrient (Supplementary material online, *Tables S5 and S6*).
[c]Moderate consumption.

A further meta-analysis exploring the substitution of 1% energy from SFAs with omega-6 PUFAs shows a statistically significant 8% reduction of CHD incidence. In relation to CVD incidence, only one meta-analysis is available and reports a 25% reduction of the incidence associated with a 5% energy substitution of omega-6 PUFAs for SFAs (Supplementary material online, *Table S6*).

These findings are consistent with those of a meta-analysis of RCTs showing that replacement of SFAs with omega-6 PUFAs induces a statistically significant reduction of CHD incidence (-24%).[36] However, this meta-analysis includes mostly patients with pre-existing CVD and therefore the results may not be fully reproducible in the healthy population; nevertheless, when the data were evaluated by subgroup analysis, people who were currently healthy appeared to benefit by this intervention as much as those at increased risk of heart disease or stroke (people with high blood pressure, high serum cholesterol, or diabetes), and people who have already had heart disease or stroke events.[36] Another meta-analysis including a larger number of studies has shown a significant 10% reduction in CHD incidence for substituting omega-6 PUFAs to SFAs.[37] In contrast, no effect of this substitution on CHD incidence and mortality has been shown in another meta-analysis of RCTs;[38] this article, however, has been criticized because of the flawed design of some meta-analysed trials: mixed dietary intervention, insufficient study duration, low adherence, and inadequate statistical power. Limiting the meta-analysis to the adequate controlled trials, the results show that lowering saturated fat and replacing it with vegetable oils rich in PUFA reduces CHD by 29%.[39]

The results of meta-analyses of longitudinal cohort studies on the association between replacement of SFAs with an isoenergetic quantity of MUFAs are less concordant since in only one of the four available meta-analyses this substitution is associated with a statistically significant CHD reduction (-15%) (Supplementary material online, *Table S6*). These inconsistencies are probably due to the fact that in North American cohorts a large part of dietary MUFAs is not of vegetable origin and might have a different impact from that of MUFAs from olive oil. In this regard, it is of note that the only meta-analysis which shows statistically significant results specifically evaluates the effect of MUFAs from olive oil.[40] The findings of a large European cohort from the PREDIMED study, evaluated in an observational perspective, are coherent with this interpretation; in fact, participants in the upper energy-adjusted tertile of olive oil consumption compared to the bottom tertile show a 35% lower risk of CVD.[41] These results confirm the outcomes of the PREDIMED trial in which the intervention consisted of a Mediterranean type of diet supplemented with olive oil.[33]

The pro-atherogenic role of foods high in saturated fat has been elucidated by the results of RCTs on atherosclerosis risk factors. They have clearly shown a reduction in LDL-cholesterol—a major risk factor for atherosclerosis—when SFAs are replaced by MUFAs or PUFAs.[42] Moreover, the substitution of butter with olive oil or other oils rich in unsaturated fatty acids has been reported to decrease blood pressure, improve insulin sensitivity, reduce subclinical inflammation, and control the haemostatic process.[43,44]

In summary, olive, soybean, sunflower, safflower, and corn oil are healthier choices than butter as well as other animal fats or tropical oils rich in saturated fat; these should be sparely utilized in the habitual diet, being, instead, replaced by unsaturated fats (*Figure 1*). Among the healthier sources of unsaturated fats special emphasis in the context of the primary prevention of atherosclerosis should be given to extra-virgin olive oil, in view of the results of the PREDIMED study; in addition, this oil is a relevant source of micronutrients that have been shown to have a beneficial impact on cardiometabolic risk factors.[26,27,45] The average daily consumption of non-tropical vegetable oils should be between 25 and 40 g depending on the energy needs.

3.4 Salt, beverages, and chocolate (*Table 3*)

3.4.1 Salt

Salt has received considerable attention as a potential risk factor for CVD. However, evidence on the dose–response association between dietary sodium intake and CVD risk is not always coherent and in many meta-analyses is characterized by high heterogeneity among the included studies (*Table 3* and Supplementary material online, *Table S7*). Discrepancies might be partly explained by methodological errors common in observational studies, including reverse causality, systematic and random errors in sodium intake assessment, interindividual differences in salt sensitivity, and residual confounders.[46] A recent comprehensive meta-analysis of 24 cohort studies shows that compared with individuals with a low sodium intake, those with a high sodium intake have a higher adjusted risk of CVD (rate ratio 1.19, 95% confidence interval 1.08–1.30) and that the risk of CVD increases up to 6% for every 1 g increase in dietary sodium intake.[47] These data are only partially coherent with prior meta-analyses (*Table 3* and Supplementary material online, *Table S7*).

High sodium intake has been shown to have a strong impact on pathophysiological mechanisms of CVD. Besides the documented effects on blood pressure—a well-established risk factor for atherosclerosis—high salt intake has unfavourable effects on left ventricular mass, arterial stiffness, renal function, cardiac output, and alterations in sympathetic outflow. Common underlying mechanisms include excess inflammation and oxidative stress.[48] Furthermore, the long-term follow-up observation of two lifestyle intervention trials on the prevention of hypertension, has demonstrated that people assigned to a sodium restriction intervention experience a 25–30% lower risk of cardiovascular outcomes 10–15 years after the end of the trial.[49] Currently, an average intake below 5 g of salt per day (equivalent to ~2.3 g sodium) is recommended to healthy adult people, but this quantity is largely exceeded in most populations (*Table 4*). In western countries, around 80% of salt ingested is hidden in processed and canned foods, such as processed meats, bread and other bakery products, canned legumes, or fish. Besides avoiding added salt, effective reduction of salt intake can be achieved only if reduced salt products are made widely available and their use is promoted.[50]

3.4.2 Soft drinks

Four meta-analyses of observational prospective studies have shown that a daily consumption of one serving/day (250 mL) of sugar-sweetened beverages (SSBs) is associated with a 15–22% higher incidence of CHD; qualitatively similar results are available for CHD mortality and for CVD incidence and mortality (*Table 3* and Supplementary material online, *Table S7*). As for low-calories sweetened beverages (LCSBs), they contain low-energy sweeteners, such as acesulfame-K, aspartame, and sucralose, and are consumed as an alternative to SSBs, due to the comparable sweet taste and the very low-energy content. Recent meta-analyses have reported a marginal, but statistically significant increase in the incidence of CHD incidence as well as of CVD incidence and mortality associated with the regular consumption (1 serving/day) of LCSBs (*Table 3* and Supplementary material online, *Table S7*).

In relation to the strong evidence supporting the association between SSBs and atherosclerosis, their high content of fructose could certainly play a relevant role. Several studies have shown a detrimental effect of fructose intake on plasma lipids and insulin sensitivity. Fructose is

Table 4 Acceptable consumption of salt, beverages, and chocolate according to the available evidence on the association between their consumption and risk of atherosclerosis

Daily	Occasionally (less than once/week)
At least 2 L of water	Soft drinks
Up to three cups of coffee or tea	
Up to 1–2 glasses of wine or one can of beer	
Up to 5 g of salt (equivalent to about 2.3 g of sodium)[a]	
Up to 10 g of chocolate	

[a]To make the dishes more pleasant spices, vinegar, and aromatic herbs can be used. Canned foods (i.e. tuna and legumes) or salt preserved foods (i.e. processed meats and olives) should be limited due to their high salt content; alternatively, canned legumes and olives should be washed before their utilization.

metabolized in the intestine and the liver and promotes the synthesis of triglycerides, thus contributing to the development of dyslipidaemia, visceral adiposity, and insulin resistance;[51] moreover, in a prospective study of 42 883 participants, SSB consumption has been found to be associated with higher levels of C-reactive protein, and inflammatory cytokines.[52] SSB consumption has also been suggested to increase serum uric acid concentrations which, in turn, reduces endothelial nitric oxide activity thus impairing skeletal muscle blood flow.[53] These mechanisms can also explain why SSBs increase the risk of hypertension. Furthermore, the habitual consumption of low-energy sweeteners may educate the taste towards a sweet preference, thus leading to a high consumption of sugar-sweetened foods and drinks.[54]

Within this context, despite the fact that the consumption of LCSBs in replacement of SSBs may seem a healthier choice, their regular use is not beneficial in the long term. Therefore, in the light of the available evidence, it is appropriate to limit drastically the consumption of all soft drinks and to replace them with water (*Table 4*).

3.4.3 Alcoholic beverages

In the absence of contraindications and in the context of a healthy eating and lifestyle, there is evidence that low-to-moderate alcohol consumption is associated with a reduced cardiovascular risk in the adult population (*Table 3* and Supplementary material online, *Table S7*). In particular, a meta-analysis with total CVD as the endpoint, shows that 24 g per day of alcohol (i.e. two glasses of wine) is associated with the maximal risk reduction (32%) and that higher intakes are associated with a progressive increase of the risk.[55] This meta-analysis also shows that moderate beer consumption (one can per day) is associated with a 20% lower risk of CVD as compared with abstainers, in agreement with previous data derived from the analysis of high vs. low beer consumption.

The complex relationship emerging from the dose–response analysis has been interpreted as a J-shaped curve, since by increasing amounts of alcohol the dose–response curve, after an initial decrease, reverts towards a positive trend. It is of note that data on all-cause death suggest a smaller intake of alcohol (10 g per day) to obtain the maximal risk decrease.[55]

The benefits of moderate alcohol intake are due to its effect on lipid and glucose/insulin metabolism as well as on systemic subclinical inflammation and coagulation.[56] However, in higher intakes its effects are deleterious; in fact, it increases blood pressure, induces fatty liver disease, impairs insulin sensitivity and contributes to rise plasma glucose and triglyceride levels.[57]

In summary, moderate alcohol consumption can be allowed to people already utilizing alcoholic beverages, since consumption of up to two glasses of wine per day in men and one glass in women or one can of beer is associated with a significantly lower risk of atherosclerosis in comparison to abstainers or to those consuming higher amounts of alcohol (*Table 4*).

3.4.4 Coffee and tea

Four meta-analyses with only few cohorts have reported no association between the consumption of coffee and CHD outcomes. Two more recent meta-analyses including also new studies have shown that the consumption of three cups of coffee per day is inversely and significantly associated with a 10% and 16% reduction, respectively, of the risk of CHD incidence and mortality. The dose–response analysis on CVD incidence indicates that the protective association disappears for a consumption higher than five cups daily (*Table 3* and Supplementary material online, *Table S7*).

The non-linear U-shaped relationship between coffee consumption and CVD risk may be explained by some biological mechanisms. Coffee is a complex chemical mixture with many active compounds, including the phenolic ones like chlorogenic acid, as well as caffeine, minerals like potassium and magnesium, niacin and its precursor trigonelline, and lignans. Coffee consumption is associated with higher insulin sensitivity, a lower risk of type 2 diabetes, and lower concentrations of inflammatory markers, such as C-reactive protein and E-selectin.[58] Conversely, heavy coffee consumption is associated with a slightly elevated risk of hypertension[59] and higher levels of plasma homocysteine in the long term.[60,61] In addition, cafestol a major component of unfiltered coffee, increases serum total cholesterol concentrations;[62] this can explain why in older studies, in which the use of unfiltered coffee was more widespread, the outcomes are usually less beneficial. In summary, the U-shaped relationship between coffee consumption and risk of CVD might be due to a balance between beneficial and detrimental effects: for moderate coffee consumption (three cups per day), the beneficial effects may prevail and vice versa. This could not apply to people with conditions that can make them particularly sensitive to the detrimental effects of coffee (i.e. arrhythmias, hypertension etc.).

Tea consumption is associated with lower CHD incidence and mortality in three meta-analyses. The risk reduction is >20% for three cups of tea per day (*Table 3* and Supplementary material online, *Table S7*).

The consumption of tea, especially green tea, may be beneficial for atherosclerosis prevention due to its high catechin content. It is known that this compound has antioxidative properties useful to prevent the oxidation of low-density lipoproteins *in vitro* and *in vivo*, and that it contributes to favourably modulate the plasma lipid profile and the vascular reactivity and to reduce vascular inflammation, atherogenesis, and thrombogenesis.[63]

In summary, in consideration of the available evidence, consumption of up to three cups of coffee or tea per day may be permitted, if not contraindicated for specific health reasons (*Table 4*).

3.4.5 Chocolate

A marginal, but statistically significant, decrease in the incidence of CHD (5% on average) has been reported by four dose–response meta-analyses for a moderate chocolate consumption (*Table 3* and Supplementary material online, *Table S7*). Notably, the most recent one,[64] including eight

studies, shows no further risk reduction for a consumption exceeding 20 g/day. As for CVD, a non-linear relationship was found between chocolate consumption and CVD incidence by Ren et al.;[65] they identified a checkmark-shaped curve, with the greater risk reduction associated with 45 g of chocolate daily. Thus, the optimal dose of chocolate to consume may vary in relation to the cardiovascular outcome (i.e. CHD or CVD) and also to the type of chocolate: dark chocolate contains more cocoa—and its bioactive substances—than milk chocolate, which, conversely is richer in saturated fats and added sugars. Unfortunately most existing studies do not distinguish between dark and milk chocolate and this may be relevant to reliably evaluate the dose–response relationship between different cocoa sources and CVDs. Polyphenols, including flavanols, such as catechin, are present in chocolate in higher amounts than in other dietary sources, such as red wine or tea; moreover, cocoa is also a source of polymeric proanthocyanidinis. These compounds may contribute to atherosclerosis prevention through the reduction of oxidative stress and lipid peroxidation, as well as platelet activation.[26,27] In this line, a meta-analysis of randomized controlled trials has shown that cocoa flavanol intake is associated to a decrease in serum triglycerides and C-reactive protein, and to an increase in high-density lipoprotein.[66] The available evidence allows up to 10 g per day of dark chocolate within a dietary approach to prevent atherosclerosis, since for this amount of consumption the beneficial effects exceed the risk of weight gain and its related harmful consequences on cardiovascular health (*Table 4*).

3.5 Dietary micronutrient supplements

Several comprehensive meta-analyses of RCTs have investigated the impact of dietary supplements on atherosclerosis prevention.[67–69] They focus on Vitamin E, Vitamin C, Vitamin D, beta-carotene, folic acid, Vitamin B complex, multivitamins, calcium, and selenium.

In relation to multivitamin supplementation, even though a marginal reduction of the CHD risk was observed in observational studies, the results of clinical trials clearly indicate that it does not improve cardiovascular outcomes in the general population.[70]

Among the compounds with antioxidants properties (i.e. Vitamin E, beta-carotene, and Vitamin C) the most investigated is Vitamin E. Two recent meta-analyses of RCTs specifically focusing on Vitamin E supplementations have reached opposite conclusions.[67,68] Other dietary supplements with antioxidant effects, namely beta-carotene and Vitamin C, have shown no relationship with CHD incidence. Therefore, globally, the available evidence from RCTs does not support the dietary supplementation of antioxidant vitamins for atherosclerosis prevention.

As for folic acid, a beneficial effect of its supplementation in the prevention of CVD events is reported in two meta-analysis of RCTs.[68,69] However, this finding is largely driven by a Chinese multicentre trial in 20 702 hypertensive adults, which showed a 19% decreased risk of CVD due to a lower incidence of stroke.[71] It has been hypothesized that such finding may be related to the lack of folic acid fortification in China. To what extent, these results could apply to countries where folic acid fortification is already undertaken is uncertain. The supposed mechanism by which folic acid may reduce the risk of stroke is through the reduction of plasma homocysteine levels; however, the cause–effect relation between folic acid supplementation and stroke is not well established.[72] In addition, there is concern that high folic acid intake might increase the risk of cancer, as seen for prostate cancer in the long-term follow-up of the Selenium and Vitamin E Cancer Prevention Trial study.[73] For these reasons, additional evidence is required before folic acid supplementation is recognized to be part of the population strategy for atherosclerotic CVD prevention.

Vitamin D supplementation has been proposed as a potential tool for reducing the atherosclerosis risk in view of its activity on the renin–angiotensin–aldosterone system and on the endothelial function, as well as for its direct effect on calcium-dependent myocyte contractility and on inflammation.[74] A recent meta-analysis of five RCTs[67] shows a significant inverse relationship between Vitamin D supplementation alone—not combined with calcium—and the incidence of CHD and CVD, but these findings are not concordant with the previously published meta-analysis by Jenkins et al. Thus, data from RCTs on Vitamin D supplementation for the prevention of atherosclerosis is controversial.

Vitamin B complex, calcium and selenium, and other trace elements have been also explored in relation to cardiovascular prevention. All in all, the data does not show reproducible effects of these supplements on the risk of atherosclerotic events.[67–69]

A search of evidence from meta-analyses of observational studies and clinical trials on hard cardiovascular endpoints in people free of CVD was also carried out for some dietary supplements known to be especially beneficial for cardiometabolic risk factors, such as fermented red rice, pro- and prebiotics (fibre), omega-3 PUFAs, plant sterols in people without clinical manifest CVD, but it retrieved no results.

4. Current ESC and AHA recommended food choices for CVD prevention and future directions

The core message of the most recent recommendation for CVD prevention of the two leading international scientific societies of cardiology—the European Society of Cardiology (ESC)[75] and the American Heart Association (AHA)[76] is in line with the evidence here reviewed, since both documents emphasize the consumption of plant-based rather than animal-based foods, suggest reducing the salt intake and SSBs, and recommend to those who drink alcoholic beverages to use them in moderation. More in detail, in relation to plant-based foods, they underline the need to increase the consumption of fruits, vegetables, nuts, and whole grains and, for what concerns animal-based foods, they both recommend to reduce processed meat intake and to increase the consumption of fish.

However, there are some relevant differences between these two guidelines since those of the AHA provide more details on the type and quantity of recommended foods, while the European Guidelines (2016) are more nutrient-oriented and, with some exceptions, provide indications for nutrient intakes, rather than food selection. Nevertheless, the European document should be viewed in connection with the 'ESC/EAS guidelines for the management of dyslipidemias to reduce cardiovascular risk', which has a more comprehensive approach to dietary intervention and is more food-oriented[77] (*Table 5*).

Anyway, some relevant innovations in relation to the appropriate food choices for atherosclerosis prevention emerge from the evidence reviewed in this article (summarized in *Table 5*).

With regard to animal-based foods, the most recent research calls for more attention to the different types of meat, distinguishing not only between processed and unprocessed meat but also between red meat and poultry. In this context, not only processed meat should be limited to occasional utilization, but also red meat consumption should be substantially reduced in most countries where it is consumed on a daily basis. Two servings per week would represent a more health-conscious

consumption (*Figure 1*). This choice is also motivated by ecological considerations, as the production of red meat has a very strong impact on CO_2 emissions.[78] As for other sources of proteins, legumes are the recommended replacement for red meat; moderate fish consumption is also supported, though it may rise sustainability issues. Poultry may also be a suitable protein source alternative to red meat, since it has been shown to have a neutral relation with the risk of atherosclerosis in moderate amounts and its production has a lower impact on the ecosystem.[78] Another new understanding relates to dairy products. Recent evidence does not support different attitudes in the consumption of these food items based on their fat content (full fat or reduced-fat dairies). It suggests, instead, that in the context of a balanced diet, for a global daily consumption of <200 g/day—including milk—no increase of CHD risk is observed in the healthy population, and that, among the dairies, fermented products like cheese (in small amounts) and yogurt should be preferred in view of their association with a reduced risk of atherosclerotic CVDs (*Figure 1*).

In relation to plant-based foods, recent evidence supports the need to differentiate not only whole grain from refined cereals, but also low from high GI refined cereal foods. The indication to limit high GI foods consumption and to replace them with whole grain and low GI cereals is gaining increasing support from recent scientific data and needs to be clearly highlighted (*Figure 1*). As for consumption of fruits and vegetable, it seems well established that dietary guidelines should give more and more emphasis to these food items, since they are strongly associated with a lower atherosclerosis risk; accordingly, the daily consumption of fruit and vegetables should be increased up to 400 g/day for each of them in the light of the linear inverse dose–response relationship between the incidence of atherosclerotic CVD and consumption of these food items at least up to these amounts. On the basis of the evidence provided by dose–response analyses, also the desirable consumption of legumes should be higher than presently recommended, up to four servings per week (*Figure 1*).

5. Research gaps and future directions

The evidence here reviewed is fairly consistent in establishing a relationship between some food choices and atherosclerotic cardiovascular outcomes; however, for some food groups inconsistencies between meta-analyses and a significant heterogeneity among the included studies represent relevant limitations of the available evidence. This indicates that the relationship with atherosclerotic outcomes may vary in relation to the study population, the background diet, the study outcome, and the specific food item within the broad food category. Therefore, it seems appropriate to direct future epidemiological research towards the evaluation of possible sources of heterogeneity, in particular through targeted analyses on individual food items rather than on broad food groups.

On the other hand, interest is growing in identifying the determinants of interindividual variation in response to food intake. The overall target of this research line is the identification of appropriate markers for a personalized nutrition based on each person's profile of genes and phenotypic characteristics. Several studies have identified gene–nutrient interactions for some gene variants able to influence the metabolic response to specific dietary components;[79] however, the major drawback of this research line is the poor reproducibility. Other underlying individual characteristics besides genetic markers may be of greater help for personalized nutrition. Among them, the role of metabolomics and gut microbiota composition is gaining increasing attention since different microbiotic patterns can influence the response to nutrition and modulate the effects on health.[80]

Accordingly, future directions of nutritional research should include new methodological approaches taking into account more closely the potential of personalized markers to predict metabolic responses to dietary interventions, thus guiding the appropriate food choices at the individual level.[81] However, although current research on precision medicine is very promising, the massive and rapid worldwide increase in CVDs in recent times demonstrates that global environmental risk factors play a relevant role in the present epidemic of non-communicable diseases. Therefore, only a population strategy can help to reduce the burden on health of inadequate eating habits underpinning the epidemic we are facing.[5]

6. Conclusions

Food choices are the most important factors undermining health and well-being, accounting for as much as almost 50% of all CVD deaths. According to the Global Burden of Disease Study, more than 9.1 million premature deaths from CVD worldwide—equal to 52% of all CVD deaths—are attributable to diet-related risks.[82] Other lifestyle related factors—such as smoking and low physical activity—as well as the individual's genetic background can modify CV risk and may also modulate the impact of diet on atherosclerosis; however, to review the role of these factors remains beyond the scope of this article. While acknowledging the importance of other environmental and genetic factors, we focus here on food choices, since diet is one of the most important exogenous factors that humans are exposed to in the every-day life.

The evidence here reviewed indicates that diets with a higher intake of plant-based foods—limiting the consumption of refined cereals and starchy foods—are associated with a markedly lower cardiovascular risk in comparison with diets including predominantly animal foods.[83] Although small in magnitude, the reported reductions in relative risks, when translated at the population level, may significantly impact on the absolute cardiovascular risk, resulting in a substantial reduction of the number of events.[82]

We have focused our research mainly on evidence from observational studies, but the conclusions are also supported by some large trials: The Dietary Approaches to Stop Hypertension diet, focused on blood pressure control and other cardiovascular risk factors,[84] the Lyon Diet Heart study exploring the effect of the Mediterranean diet in people with previous CVD[85] and the PREDIMED trial for CVD reduction in people without a prior CV event.[33] The findings of these studies corroborate long-term cohort studies reporting the cardiovascular benefits of a Mediterranean-like diet and its components, including olive oil, nuts, legumes, fruits, vegetables, whole grains, fish, and wine (in moderate amount).[86–89] In the PREDIMED trial, a 30% reduction of total CVD was reported among individuals randomized to a Mediterranean diet plus extra-virgin olive oil or mixed nuts.[33]

Although future research directions need to take into account individual factors that would allow a greater personalization of the nutritional approach, for the time being, the evidence supports at the population level changes in the habitual diet that are coherent with the features of the traditional Mediterranean diet. This model not only has proven to be able to substantially contribute to the prevention of atherosclerosis, but can also facilitate dietary compliance in view of its strong links with the cultural roots of the populations from that region. It may be wise to

Table 5 Summary table of the current ESC and AHA/ACC recommended food choices for CVD prevention and recent evidence that may be considered for future dietary guidelines

Dietary component	ESC (2016)[75]	AHA/ACC (2019)[76]	Recent evidence that may be considered for the formulation of future recommendations
Vegetables and legumes	≥200 g/day (2–3 servings)	Overall: 2½ cups/day Dark green vegetables: 1½ cups/week Red/orange vegetables: 5½ cups/week Starchy vegetables: 5 cups/week Other vegetables: 4 cups/week Beans and peas: 1½ cups/week	Consumption of legumes up to 400 g/week is associated with CVD risk reduction. Therefore, legumes should be consumed in larger quantities and more frequently than currently recommended, as a partial replacement for red meat.
Fruits	≥200 g/day (2–3 servings)	2 cups/day	
Unsalted Nuts	30 g/day	5 oz eq/day of nuts, seeds, and legumes	
Cereals	Preferably from whole grain	6 oz eq/day Whole grain: 3 oz eq/day Other refined grains: 3 oz eq/day	High GI refined starchy foods are associated with an increased CHD risk in comparison with whole grain and low GI cereal foods. Therefore, it may be appropriate to drastically reduce the consumption of high GI foods and replace them with whole grain (2 servings/day) and refined low GI cereal foods (1 serving/day).
Fish	1–2 times/week, one of which to be oily fish	Preferably oily fish: 8 oz eq/week	
Dairy foods	–	Fat free or low fat: 3 cups/day	Consumption of up to 200 g/day of total dairy foods (including milk), irrespective of being full fat or low fat, is not associated with an increased CVD risk and, therefore, can be allowed in the absence of dyslipidemia. Fermented dairies should be preferred in view of a negative association with CVD (i.e. cheese: 3 servings/week, yogurt: 1 serving/day).
Lean meat, poultry	–	26 oz eq/week	White meat should be preferred to red meat given its neutral association with CVD. In contrast to red meat, white meat in moderate amounts is not associated with an increased CVD risk.
Processed meat	Processed foods: to displace	To displace	
Eggs	–	Not specified (eggs are combined with lean meat and poultry)	1 egg daily is not associated with an increased CVD risk and, therefore, can be allowed in people without diabetes and dyslipidemia.
Oils: unsaturated FAs sources	–	45 g/day	In addition to the results of previous epidemiological studies and RCTs, the evidence from the PREDIMED trial and new data on the importance of olive polyphenols as modulators of CVD risk factors support to consider extra-virgin olive oil as a preferential choice for the replacement of SFAs and industrial trans-fats sources. Other non-tropical vegetable oils can also be considered.
Alcoholic beverages	Males: 2 glasses/day (20 g/day of alcohol) Females: 1 glass/day (10 g/day of alcohol)	2 drinks/day for males 1 drink/day for females	
Sugar-sweetened soft drinks	Consumption must be discouraged	Consumption must be limited Added sugars: up to 100 Kcal/day (F)	Low-calories sweetened drinks should also be limited since their consumption is associated with an increased cardiovascular risk.

Continued

Table 5 *Continued*

Dietary component	ESC (2016)[75]	AHA/ACC (2019)[76]	Recent evidence that may be considered for the formulation of future recommendations
		up to 150 Kcal/day (M)	
Sodium	≤2000 mg/day Salt: <5 g/day	≤2300 mg/day Salt: ≤5–6 g/day	
Coffee or tea	Not mentioned	Not mentioned	Moderate consumption (up to 3 cups/day) is associated with a reduced CVD risk and, therefore, can be permitted.
Chocolate	Not mentioned	Not mentioned	Moderate consumption (10 g/day) is associated with a reduced CVD risk and, therefore, can be permitted.

ESC, European Society of Cardiology; AHA, American Heart Association; ACC, American College of Cardiology; g, grams; oz, ounce; eq, equivalent; GI, glycemic index; FAs, fatty acids; SFAs, saturated fatty acids.

make this heritage available to other people, giving them the opportunity to take advantage of a gastronomic tradition that links so well health with enjoyment. This may be extremely important for the implementation of feasible programmes for prevention of chronic non-communicable diseases. In fact, long lasting lifestyle changes are difficult to be achieved and, although health motivations may help compliance in the short term, pleasure remains an important determinant of any dietary change aimed to last. In addition, among the relevant factors influencing the intention to change food choices, the most important ones are motivation, affordability, time, access, and knowledge.[90] Therefore, a strategy based exclusively on guidelines and nutritional education will not be sufficient to change the lifestyle of the population; policy options to be considered should necessarily include initiatives to facilitate production, marketing, availability, and affordability of foods that are not only healthy but also gastronomically appealing.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Conflict of interest: G.R. is member of the scientific advisory board of the 'BCFN Foundation' and of the Barilla Health and Well-being advisory board, of the Nutrition Foundation of Italy and of 'Istituto Nutrizionale Carapelli'.

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