Both epidemiological studies and intervention trials support an important role of diet in reducing the risk of a variety of chronic diseases, including cardiovascular disease, and overall mortality. We discuss available evidence indicating that the generation of a pro-inflammatory milieu might be one mechanism through which unhealthy diets are linked to metabolic and cardiovascular diseases. In practical terms, fully understanding the link between diet and inflammation holds the premise to elucidate the mechanisms by which dietary patterns improve cardiovascular health.

Modern society has brought with it profound changes in lifestyle and an increased incidence of atherosclerotic vascular disease. Body weights are on the rise, diets are becoming less healthy, and people are becoming increasingly sedentary, resulting in metabolic alterations that increase atherothrombotic risk. Not surprisingly, obesity, the metabolic syndrome, and type 2 diabetes mellitus are becoming a public health problem of epidemic proportions. Nearly 70% of type 2 diabetes risk in the US is attributable to overweight and obesity.

In the past two decades, understanding of the nutrients and foods likely to promote cardiac health has grown substantially owing to studies of the molecular mechanisms of atherosclerosis and the metabolic effects of various nutrients and foods. Dietary patterns that emphasize whole grain foods and legumes, and vegetables and fruits, and that limit red meat, full-fat dairy products, and food and beverages high in added sugars are associated with decreased risk of a variety of chronic disease. In a more general sense, adherence to healthy lifestyle practices, which of course also include healthy diets, has been found to be associated with an 83% reduction in the rate of coronary disease, a 91% reduction in diabetes in women, and a 71% reduction in colon cancer in men. Despite this mounting evidence, ‘Western’ diets have shifted unfavourably. Vegetable and fruit consumption of both adults and youth continues to be below recommended levels: only 24.5% of adults and 21.4% of youth consume at least five servings each day, whereas consumption of refined grains and food high in added sugars are on the rise. Low consumption of fruit and vegetables, together with physical inactivity, are now among the top 10 causes of mortality in developed countries.

We review available evidence indicating that the generation of a pro-inflammatory milieu might be one mechanism through which unhealthy diets are linked to metabolic and cardiovascular diseases. Relevant peer-reviewed publications pertinent to the topic covered by the present review were identified by content experts; priority was given to the English language, epidemiological and clinical trials, time and venue of publication, and relevance to clinicians.

Post-prandial state

Much attention has been paid to the evidence that abnormalities of the post-prandial state are important contributing factors to the development of atherosclerosis. Post-prandial hypertriglyceridaemia has been shown to be a risk factor for cardiovascular disease in non-diabetic subjects and may be a predictor of carotid intima-media thickness in type 2 diabetic patients. Moreover, clinical data also suggest that post-prandial hyperglycaemia is a risk factor for cardiovascular disease. Meal absorption is a complex phenomenon, and post-prandial hyperlipidaemia and hyperglycaemia are simultaneously present in the post-absorptive phase, particularly in diabetic patients or in subjects with impaired glucose tolerance. Both post-prandial hyperglycaemia and hypertriglyceridaemia may cause endothelial dysfunction, which is considered an early marker of atherosclerosis. Evaluating the effect of different isocaloric meals on endothelial function in both normal subjects and type 2 diabetic patients...
patients, we have shown that the level of triglycerides after a high-fat (saturated) meal is inversely associated with endothelial function, with maximal impairment occurring at the time of the simultaneous presence of post-prandial hyperglycaemia and hypertriglyceridaemia.\footnote{16} Similar conclusions were reached by other studies investigating the effect of liquid meals rich in carbohydrates or saturated fats.\footnote{9,10} Moreover, endothelial dysfunction induced by a high-fat meal in type 2 diabetic patients\footnote{11} or associated with fasting hypertriglyceridaemia in young men\footnote{12} is also associated with increased plasma concentrations of asymmetric dimethylarginine, an endogenous nitric oxide synthase inhibitor suggested as a novel cardiovascular risk factor.\footnote{13}

Not all macronutrients are the same and some of them may show opposite effects. For instance, consumption of a high-fat meal together with vegetable foods rich in natural antioxidants largely prevents the negative effects on endothelial function.\footnote{14} In particular, endothelial dysfunction acutely triggered by the consumption of a high-fat meal rich in saturated fatty acids is reduced by the simultaneous consumption of a vegetable serving including pepper (100 g), tomatoes (100 g), and carrots (200 g).

A mild pro-oxidative state accompanies meal ingestion, which results in raised circulating biomarkers of inflammation, adhesion, and endothelial dysfunction, all of which are factors in the development of cardiovascular disease.\footnote{15} The effect of hyperglycaemia, hypertriglyceridaemia, and raised free fatty acids (FFA) levels, both fasting and post-prandial, on endothelial function may be mediated through the generation of an oxidative stress. The process is supposed to involve increased superoxide generation, which in turn inactivates nitric oxide. Superoxide and nitric oxide combine to produce peroxynitrite, a potent and long-lived oxidant that is cytotoxic, initiates lipid peroxidation, and nitrates amino acids such as tyrosine, which affects many signal transduction pathways. The production of the peroxynitrite anion can be indirectly inferred by the presence of nitrotyrosine (NT). An increase in plasma NT levels has been reported in association with raised plasma concentrations of IL-6 and TNF-\(\alpha\).\footnote{8} Moreover, the same high-fat meal\footnote{20} may increase the circulating levels of IL-18, a pro-inflammatory cytokine supposed to be involved in plaque destabilization, associated with the simultaneous decrease of circulating adiponectin, an adipocyte-derived protein with insulin sensitizing, anti-inflammatory, and antiatherogenic properties.\footnote{21}

**From dietary inflammation to insulin resistance**

Ingestion of particular macronutrients causes a shift towards oxidative stress and inflammation, which in turn may reduce insulin sensitivity. Metabolic abnormalities found in diabetes, obesity, and the metabolic syndrome include, among others, increases in the circulating levels of metabolites, such as FFA and triglycerides, and cytokines, such as TNF-\(\alpha\) and IL-6. Both FFA and inflammatory markers have been shown to predict type 2 diabetes independent of known risk factors.\footnote{22,23} Both FFA and TNF-\(\alpha\) have also been shown to activate inhibitor K kinase \(\beta\) (IKK\(\beta\)) in adipocytes and hepatocytes, which can then increase the serine phosphorylation of insulin receptor substrate 1 (IRS-1), with subsequent reduction in insulin-dependent tyrosine phosphorylation of IRS-1, and ultimately glucose transport.\footnote{24} IKK\(\beta\) is a serine kinase that controls the activation of NF-\(\kappa\)B, a transcription factor associated with inflammation. IRS-1 may be directly phosphorylated by IKK\(\beta\) at serine residues, representing a novel class of substrates for IKK\(\beta\).\footnote{25} Convincing evidence for this has come from a recent study,\footnote{26} in which hepatic expression of the IkappaBalpha super-repressor, which reduces IKK\(\beta\) activity, reversed the phenotype of wild-type mice fed a high-fat diet, indicating that lipid accumulation in the liver leads to subacute hepatic ‘inflammation’ through NF-\(\kappa\)B activation and downstream cytokine production. This causes insulin resistance both locally in liver and systemically.

IL-6 circulates in plasma at high concentrations and is associated with insulin resistance in men and in obese or hyperandrogenic women.\footnote{27} Circulating IL-6 levels and insulin sensitivity relationships seem to occur in parallel to increases in plasma FFA. In contrast to IL-6 and TNF-\(\alpha\), adiponectin mRNA is reduced in adipose tissue from patients with type 2 diabetes.\footnote{21} Although the precise mechanism by which a low adiponectin production contributes to insulin
resistance has not been fully elucidated, there is evidence that adiponectin decreases circulating FFA levels by increasing fatty acid oxidation by skeletal muscle. An unbalance between inflammatory and anti-inflammatory cytokines may contribute to the enhancement of the endogenous pro-inflammatory potential in the post-prandial phase, particularly following the ingestion of ‘ Western ’ dietary patterns. Part of this effect may be mediated through modification of circulating FFA levels.

Resistance to the anti-inflammatory actions of insulin might also play a role. At physiologically relevant concentrations, insulin causes a suppression of NF-κB, thus reducing the production of some of its transcripts, namely IL-6 and TNF-α. This effect has been related to the ability of insulin to induce the release of nitric oxide and to enhance the expression of constitutive nitric oxide synthase.

Specific dietary patterns may reduce inflammation

The raised flux of nutrients in the post-prandial state is associated with an increase in circulating levels of pro-inflammatory cytokines, recruitment of neutrophils, and oxidative stress. As stated before, the generation of ROS may be a common ground for all these findings and may help understanding current dietetic recommendations emphasizing increased consumption of fruits, vegetables, and fibre, which contain a myriad of natural antioxidants that help fighting the oxidative wall of meals. Moreover, reducing trans- saturated fatty acids intake and increasing the consumption of omega-3 fatty acids are also considered important strategies to reduce coronary heart disease (CHD) risk. It is interesting to note that these two strategies are also associated with a reduced inflammatory status. For instance, levels of C-reactive protein and markers of endothelial dysfunction are 73% higher in the highest quintile of trans-fatty acids intake in the Nurses’ Health Study, compared with the lowest quintile, and low-cholesterol/low-saturated fat diets are associated with mitigation of low-grade systemic inflammation which correlated with reduction of plasma C-reactive protein levels. Moreover, another cross-sectional study from the Nurses’ Health Study I cohort demonstrated lower concentrations of many markers of inflammation and endothelial activation, including C-reactive protein, IL-6, and E-selectin, among those in the highest quintile of omega-3 fatty acids, when compared with the lowest quintile.

There is a concern that a high intake of omega-6 fatty acids may reduce the known beneficial effects of omega-3 fatty acids on CHD risk; however, recent epidemiological evidence indicates that this fear may be unjustified, as combination of both types of fatty acids is associated with the lowest level of inflammation.

As oxidative processes are supposed to play a key role in the development of atherosclerosis, antioxidant–vitamin supplementation has been proposed for the treatment and prevention of chronic diseases, including coronary disease. The encouraging results of short-term trials in participants with coronary atherosclerosis were not confirmed in large-size intervention trials. More recently, Miller et al. reported the results of a carefully conducted meta-analysis of clinical trials of vitamin E supplementation concluding that high doses of this agent increase the risk for death. Their meta-analysis involved data from 19 randomized trials, which recorded 12,504 deaths. Overall, being randomly assigned to receive vitamin E had no effect, either positive or negative. However, the data suggested a decreased risk for death associated with vitamin E in trials that used lower doses (<400 IU) and showed a statistically significant trend towards increased risk at doses of 400 IU and above. Thus, it may be wrong to focus on a single element of the diet; guidelines from some professional or governmental panels recommend attempting to obtain vitamins and minerals from food sources rather than from supplements.

Diet and cardiovascular health

Recent epidemiological data support an important role of diet in reducing overall mortality. In particular, Knoops et al. (Colleagues from the Netherlands, France, Spain, and Italy) have shown that in European men and women aged 70–90, adherence to a Mediterranean-style diet, which represents a solid example of a healthy dietary pattern, moderate alcohol consumption, non-smoking status, and physical activity, was associated with a lower rate of all-cause mortality. Taken together, the combination was associated with a mortality rate of about one-third that of those with none or only one of these protective factors. In a large prospective survey involving about 22,000 adults from Greece (the Greek cohort of the EPIC study), it has been shown an inverse correlation between a greater adherence to a Mediterranean-style diet and death. In particular, approximately a 2/9 increment in the Mediterranean diet score was associated with a 25% reduction in total mortality and a 33% reduction in CHD mortality.

The two main intervention trials using the whole diet approach so far produced are also in line with this epidemiological evidence. In the Lyon Diet Heart Study, 605 patients who had had a myocardial infarction were randomly assigned to a ' Mediterranean-style ' diet or a control diet resembling the American Heart Association Step I diet. The Mediterranean diet model supplied 30% of energy from fats and <10% of energy from saturated fatty acids, whereas the intake of 18:3(n-3) (α-linolenic acid) provided >0.6% of energy. After a mean follow-up of 27 months, the risk of new acute myocardial infarction and episodes of unstable angina was reduced by ~70% by the Mediterranean diet. Moreover, total mortality was also reduced by 70%. Singh et al. tested an ‘ Indo-Mediterranean diet ’ in 1000 patients in India with existing coronary disease or at high risk for coronary disease. When compared with the control diet, the intervention diet—characterized by increased intake of mustard or soyabean oil, nuts, vegetables, fruits, and whole grains—reduced the rate of fatal myocardial infarction by one-third and the rate of sudden death from cardiac causes by two-thirds.

Esposito et al. explored possible mechanisms underlying a whole dietary approach in patients at increased cardiac risk. The authors randomized 180 patients (99 men, 81 women) with the metabolic syndrome to a Mediterranean-style diet (instructions about increasing daily consumption of whole grains, vegetables, fruits, nuts, and olive oil) vs. a cardiac-prudent diet with fat intake <30%. Physical activity increased equally in both groups. After 2 years,
patients on the Mediterranean diet showed greater weight loss, had lower C-reactive protein and pro-inflammatory cytokine levels, had less insulin resistance, had lower total cholesterol and triglyceride and higher HDL-cholesterol levels, and had a decreased prevalence of the metabolic syndrome, which was reduced approximately by one-half. These results suggest possible mechanisms for the beneficial effects of a Mediterranean-style diet.

The clustering atherogenic and diabetogenic abnormalities of the metabolic syndrome are highly prevalent in our affluent, sedentary populations.27 The shift towards energy-dense, refined diet, which has been adopted by an increasing proportion of people, may have led to the development of a positive energy balance, weight gain, and obesity. Adipose tissue excess, particularly in the visceral compartment, is widely acknowledged as an endocrine organ secreting an increasing number of mediators, including pro-inflammatory cytokines.42 As visceral obesity is a key promoter of low-grade systemic inflammation43–45 and is characterized by the most severe metabolic abnormalities,46,47 it is possible that persons with abdominal adiposity are particularly prone to the pro-inflammatory effects of unhealthy diets. Although the evidence is still lacking, the Quebec Family Study has shown that a decrease in the consumption of fat-foods or an increase in consumption of whole foods predicted a lower increase in body weight and adiposity indicators over a 6-year follow-up.48 However, no specific dietary recommendations have been advocated by health agencies for the treatment of insulin resistance or the metabolic syndrome. Given that the metabolic syndrome is an identifiable and potentially modifiable risk state for both type 2 diabetes and cardiovascular disease, adopting a dietary pattern as that used in the study of Esposito et al.41 may reduce the potential risk of these diseases.

**Slow foods vs. fast foods**

Increased consumption of high-density and low-quality foods, such as those rich in refined starches, sugar, and unhealthy lipids (saturated and trans-fatty acids) and poor in natural antioxidants and fibre, may cause an activation of the innate immune system, most likely by an excessive production of pro-inflammatory cytokines associated with a reduced production of anti-inflammatory cytokines (Figure 1). This imbalance may favour the generation of a pro-inflammatory milieu, which in turn may produce insulin resistance in the peripheral tissues and endothelial dysfunction at the vascular level, and ultimately predispose susceptible people to an increased incidence of the metabolic syndrome and diabetes. The change in dietary patterns that occurred in recent years has introduced the consumption of a larger amount of foods that seem faster in preparation and in producing health damage. The recent findings from the prospective US CARDIA (Coronary Artery Risk Development in Young Adults) study show that frequent fast-food consumption is associated with weight gain and risk of insulin resistance over 15 years.49 In practical terms, fully understanding the link between diet and inflammation holds the premise to elucidate the mechanisms by which dietary patterns improve cardiovascular health.

Inflammatory mechanisms appear to be important for mediating both metabolic insulin resistance and impaired insulin action in vascular endothelium that contribute to the relationship between metabolic and cardiovascular disorders. This has implications for novel therapeutic strategies because drugs that reduce inflammation would be predicted to improve both metabolic and endothelial functions. Indeed, recent clinical studies have demonstrated additive beneficial endothelial and metabolic effects of combining statins with angiotensin II type 1 receptor blockers in patients with type 2 diabetes.10 Moreover, reduction of post-prandial hyperglycaemia in type 2 diabetic patients has been shown to reduce the inflammatory milieu in association with regression of carotid atherosclerosis.7 However, these promising results cannot let us forget that appropriate dietary patterns, as those associated with the eating model of Mediterranean-type diets, represent rediscovered therapeutic strategies to reduce inflammation and the associated metabolic and

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/27/1/15/608091)
cardiovascular risks. Fast-food habits seem to warm up inflammation, whereas slow-food habits cool it down.

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Tricuspid valve endocarditis and septic pulmonary emboli illustrated by ECG-gated multi-slice CT of the chest

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A 27-year-old man, an intravenous drug addict, was referred to our institution for treatment of a tricuspid valve endocarditis. Clinical examination revealed a normal cardiopulmonary auscultation and multiple sites of drug injection on both arms. A chest radiograph on admission showed bilateral multiple nodules. Blood culture revealed Staphylococcus aureus, oxacillin-resistant. Septic arthritis of the knee was discovered during clinical work-up.

A retrospective ECG-gated 16-slice computer tomography (CT) (Philips Medical systems, Cleveland, OH, USA) of the entire chest was performed with 16 × 1.5 mm collimation. The entire chest was imaged in one breath-hold during 20 s, after injection of the contrast medium. Frontal reformatted images of the entire chest (Panel A) demonstrated multiple nodules of various sizes, some with necrotic centres and feeding vessels in the peripheral areas and suggestive of septic emboli. CT images reconstructed retrospectively at systolic (Panel B) and diastolic phase (Panel C) revealed an elongated hypodense masse measuring 13 mm long axis, implanted on the tricuspid valve and confirmed by transoesophageal echocardiography (Panel D).

In the present case, ECG-gated multi-slice CT of the chest led to a combined diagnosis of tricuspid valve endocarditis and septic pulmonary embolism on the same imaging modality. The patient was treated successfully with appropriate antibiotic therapy and aspiration of the infected bone joint.

Panel A. Thin slab (10 mm), maximal intensity projection and lung window setting image of the entire chest acquired with retrospective ECG-gating demonstrating lung nodules consistent with septic emboli.

Panel B. CT long axis view of the heart reconstructed at systolic phase (12.5% of the R-R interval) revealing a vegetation (straight arrow) implanted on the tricuspid valve (curved arrow).

Panel C. CT long axis view of the heart reconstructed at diastolic phase (75% of the R-R interval) revealing a vegetation (straight arrow) implanted on the tricuspid valve (curved arrow).

Panel D. Transoesophageal echocardiography photographed during systole confirmed the presence of a vegetation (straight arrow) attached to the tricuspid valve (curved arrow).