Module 20.1

The Place of Nutrition in the Prevention of Cardio-Vascular Diseases (CVDs)

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Learning Objectives

- To demonstrate the importance of cardio-vascular diseases (CVD) in morbidity and mortality in the world;
- To review the major risk factors for CVD;
- To give an overview on the importance of lifestyle components, particularly diet, in the modification of different risk factors, and in the prevention of CVD;
- To review the mechanisms through which nutrition may affect CVD;
- To provide global and specific recommendations on healthy diets.

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**Key Messages**

- CVD has become the major cause of mortality and morbidity worldwide;
- CVD burden could be substantially reduced by early diagnosis and appropriate measures, since atherosclerotic lesions may be substantially improved in response to measures taken;
- CVD results from a combination of genetic and environmental factors; some factors vary between different ethnic groups;
- Plasma lipid profile is an important, but certainly not the only, risk factor for CVD;
- Prevention includes healthy lifestyle: no smoking, weight control, physical activity, and healthy dietary intake; control of blood pressure, plasma glucose, and inflammation is important;
- The Mediterranean diet is a good example of healthy dietary patterns;
- Components of the Mediterranean diet may be adapted to nutritional habits of different countries, taking into account differences of taste and culture;
- The benefits of a healthy lifestyle exceed, but are additive to, those of medical treatment.
1. Rationale for prevention of CVD
CVDs, including coronary heart disease (CHD) and stroke, currently represent the major causes of mortality and morbidity all over the world. In Europe, CVDs are responsible for 43% of deaths in men and 55% in women and for 30% of all deaths before the age of 65 years (1). In 2000, CVDs also accounted for 22% of all disability adjusted life years (DALY’s) lost in Europe.

![Figure 1. Mortality from CVD in Europe (1980 – 1995)](image)

Eighty percent of CV accidents could probably be avoided by lifestyle adjustment (weight control, smoking abstinence, physical activity, and a healthy diet), together with proper management of clinical and biological risk factors. Figure 1 represents the evolution of cardiovascular mortality in several European countries.

In developed countries, there is clearly a decreasing trend as a reflection of appropriate measures. However, in countries with a more recent access to a Westernized way of life, the tendency is towards an increase. This corresponds to the trend observed all over the world. In developing countries, there is a sharp contrast between a high CVD incidence in cities in relation to urbanisation, and a lower CV mortality rate in the rural areas.

The projection for the major causes of deaths all over the world in 2020 suggests a further rise in CVD mortality and morbidity, mainly in developing countries (2). In addition, the epidemics of obesity and the frequently associated metabolic syndrome raise major concerns for the immediate and mid-term future, even in developed countries (3) Grundy SM, 2008.

2. The atherosclerotic lesion
The major typical feature of CVD is the atherosclerotic plaque, an inflammatory lesion which develops insidiously around cholesterol deposits in the intima of the arterial wall over many (20-30) years. This is due to the fact that particles carrying cholesterol in plasma may cross the endothelium (inner unicellular layer of the vessel) and enter the intimal space of the arterial wall; while low density lipoproteins (LDL) may in some conditions be endocytosed by intimal macrophages and deposit cholesterol in the intima. This is associated with further recruitment, in the intima, of macrophages and lymphocytes, and increased production of inflammatory mediators. Another important factor in the initial phase of the process is a dysfunction of the endothelium induced by
atherogenic lipoproteins and hypertension; the endothelium loses its capacity to produce nitric oxide (which induces vasodilatation, but also protects against arterial remodelling and platelet aggregation) and secretes free radicals and inflammatory mediators. The inflammation may thicken the arterial wall locally and reduce the lumen (creating a stenosis), but may also erode the lesion; interaction between blood platelets, lipids, and different mediators quickly induce thrombus formation at the site of erosion. In fact, coronary artery occlusion is much more often caused by a thrombus after rupture of a fragile lesion than by progressive stenosis.

Cholesterol deposition and development of inflammatory lesions are prevented by high density lipoproteins (HDL) which ensure a reverse cholesterol transport to the liver (and glands producing steroid-derived hormones) and reduce inflammatory and peroxidative reactions.

It is important to understand that endothelial dysfunction and inflammatory reactions may be corrected by appropriate lifestyle and therapeutic measures, causing the atherosclerotic lesion to be reversed, modified or stabilized. As a corollary, the vast majority of CVD accidents can and should be prevented.

3. Risk factors for cardiovascular disease events

Plasma cholesterol concentration has long been considered as the major (if not the sole) risk factor for CVDs. Indeed, Figure 2 is often used to confirm the strong correlation between total cholesterol concentration and coronary heart disease.

![Figure 2. Relationship between coronary death rates and mean serum cholesterol in 19 European countries and Japan (4).](image)

However, one should also consider the huge differences in the rate of CVD mortality between countries with similar average cholesterol levels (e.g., ~220-230 mg/dl or 5.5-5.6 mmol/l). This supports the role of other factors. Indeed, the initiation and development of the atherosclerotic lesion are related to a combination of several independent risk factors.

Some factors (genetic background, familial and personal history, gender) may not be modifiable while others may be corrected or improved (Table 1).
Table 1. Risk factors for cardiovascular disease

<table>
<thead>
<tr>
<th>Modifiable factors:</th>
<th>Clinical parameters</th>
<th>Biological parameters</th>
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<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
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<td>Western diet</td>
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<td>Tobacco smoking</td>
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<td>Weight gain/obesity</td>
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<td>Sedentary life</td>
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<td>Psychological stress</td>
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<td>Air pollution</td>
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<td><strong>Clinical parameters</strong></td>
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<td>High blood pressure</td>
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<td>High waist circumference</td>
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<td>Insulin resistance</td>
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<td>Diabetes</td>
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<td>Metabolic syndrome</td>
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<td>Renal insufficiency</td>
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<tr>
<td><strong>Biological parameters</strong></td>
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<td>High plasma cholesterol conc.</td>
<td>High LDL cholesterol conc.</td>
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<td>Low HDL cholesterol conc.</td>
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<td>High triglyceride conc.</td>
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<td>Markers of chronic inflammation</td>
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<td>Thrombogenic factors</td>
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<td>Markers of lipid peroxidation</td>
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<td>Markers of endothelial dysfunction</td>
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<td><strong>Non-modifiable factors:</strong></td>
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<td>Age</td>
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<td>Gender</td>
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<td>Family history of premature CVD</td>
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<td>Personal history of CVD</td>
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<td>Genetically predisposed ethnic groups</td>
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3.1 Serum Lipids

Since cholesterol deposition in the arterial wall is a key and early step in the initiation of the atherosclerotic process, decreasing the number of LDL particles (and/or avoiding their retention in the intimal space) has been a primary target.

Table 2. Serum Lipid Fractions (adapted from 4)

<table>
<thead>
<tr>
<th>Lipid Fraction</th>
<th>Description</th>
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<tbody>
<tr>
<td>LDL cholesterol</td>
<td>Total cholesterol &gt; 5.0 mmol/L and LDL cholesterol &gt;3.0 mmol/L are related to CVD risk and are the primary focus of management. Reduction of total and LDL cholesterol unequivocally diminishes CVD risk, including stroke.</td>
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<tr>
<td>Triglycerides (Triacylglycerols)</td>
<td>Moderately raised triglycerides (&gt;1.7 mmol/L, ~150 mg/dl) are related to risk; associations with abdominal obesity and blood sugar inverse association with HDL cholesterol;</td>
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<tr>
<td>HDL cholesterol</td>
<td>HDL cholesterol relates inversely to CVD risk. HDL cholesterol concentration &lt;1 mmol/l (~40 mg/dl) in men and &lt;1.2 mmol/l (~45 mg/dl) in women indicates increased risk. HDL is involved in reverse cholesterol transport; it is antiatherogenic, anti-inflammatory and anti-thrombotic particle.</td>
</tr>
<tr>
<td>Total cholesterol/HDL ratio</td>
<td>Total cholesterol/HDL ratio relates to risk but better risk estimation may be possible if they are considered separately.</td>
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<tr>
<td>Apo B/A1 ratio</td>
<td>Apo B/A1 ratio relates strongly to risk but it is not known if it should be a treatment goal.</td>
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<tr>
<td>Lp(a)</td>
<td>Lp(a) relates to risk, is genetically determined, but resistant to modification.</td>
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This is achieved by improving the number and activity of LDL receptors largely located in the liver; drugs such as statins efficiently stimulate LDL removal, but nutrition may also activate or impede receptor activity. Also, evidence that some LDL (modified by peroxidation, glycation, addition of adducts, or presence of additional apoprotein (a))
have a markedly increased atherogenic potential has drawn attention to the role of LDL size and composition, as well as to the impact of associated pathologies such as diabetes mellitus, chronic renal failure, chronic inflammatory diseases. Tobacco smoking is a major risk factor and air pollution has also been implicated; again, nutrition may affect LDL atherogenicity.

Attention is currently paid not only to decreasing LDL-cholesterol, but also to increasing the number of HDL particles; this can be achieved by lifestyle adjustments: weight control, physical activity, non-smoking and proper nutrition (5). A high concentration of plasma triglycerides is recognised as a direct risk factor (increased coagulation, impaired endothelial function, ...) but may also have indirect effects by decreasing HDL level and increasing LDL atherogenicity via formation of atherogenic small dense (sd) LDL.

3.2 Hypertension

Increases the entry of LDL particles into the intima and impedes their return into the circulation; it also raises peroxidative damage, inducing endothelial dysfunction and LDL modifications; dietary manipulation may help reducing blood pressure eg by reducing weight and salt intake.

3.3 Inflammatory processes

In different organs and at distant sites from atherosclerotic lesions, inflammation is now recognised as an aggravating factor, since it increases free radical production, induces LDL modifications and increases LDL retention in the intima, but also causes macrophage activation and stimulation of LDL uptake into the intima; again, adequate nutrition may help to modulate inflammation (6).

3.4. High homocystein concentration

A high homocystein level in plasma is another risk factor, via a toxic effect on the endothelium and induction of peroxidative damage. Apart from pathological conditions (e.g., chronic renal failure), a low folic acid status is often present in subjects with impaired homocystein metabolism (7); this is generally related to genetic polymorphisms of enzymes involved in homocystein metabolism. Supplementation with folic acid, sometimes combined with supplementation of vitamin B6 (pyridoxine) and vitamin B12 may lower homocystein levels (8); however, the efficacy of these supplementation on clinical outcome has not been demonstrated.

3.5 Obesity

Is associated with an increased risk of coronary heart disease and stroke (9). The distribution of fat in different areas of the body is important since accumulation of fat within the abdominal cavity (as observed in truncal or android obesity) represents a much more severe cardiovascular risk than accumulation in subcutaneous adipose tissues (i.e. gynoid obesity). This explains why waist circumference measurements, and to some extent waist-to-hip ratio, is a more relevant index of coronary disease risk than BMI values (10). The relation between obesity and cardiovascular risk is via an effect on lipid and lipoprotein profile, on blood pressure, on insulin-resistance, on inflammation, on endothelial function, and on thrombus formation. This, together with epidemiological observations, has led to the concept of the metabolic syndrome.

**The metabolic syndrome** represents the clustering of anthropometric, clinical, and biological cardiovascular risk factors. It is defined as the simultaneous presence of (at least) three among the following risk factors: high waist circumference (> 94 cm in men and 80 cm in women), high blood pressure (> 135/85 Hg cm), high plasma triglycerides
 (> 150 mg/dL or 1.69 mmol/L), low plasma HDL-cholesterol (< 40 mg/dL or 1 mmol/L in men and 50 mg/dL or 1.25 mmol/L in women), and high plasma glucose concentration (> 100 mg/dL). It should be noted that cut off values for parameters of the metabolic syndrome may vary between guidelines from different associations. However, a common concern is that the worldwide epidemic of obesity may stop or reverse the decline of cardiovascular disease burden in Western countries and raise it in developing countries. Importantly, lifestyle and dietary patterns have a strong influence on most components of the metabolic syndrome.

3.6 Smoking

There is overwhelming evidence for an adverse effect of smoking on health (11). In long-term smokers, smoking is considered to be responsible for 50% of all avoidable deaths, half of which are a consequence of cardiovascular disease (12, 13). Although "only" 20% of US inhabitants are smokers, cigarettes account for 435,000 deaths every year (13). Tobacco smoking increases the risk of atherosclerotic disease via several mechanisms (some of which are not fully understood yet): smoking increases peroxidative damage, alters endothelial functions, enhances both the development of atherosclerosis, the occurrence of thrombosis, and activates platelets and leukocytes. The impact of smoking on atherosclerosis progression is greater for subjects with diabetes and hypertension.

3.7 Air pollution

It has become evident that air pollution may severely increase cardiovascular burden. Recent studies suggest that, within a given city, the rate of cardiovascular events may be doubled in some areas, with a direct relationship to traffic, particularly diesel exhaust fumes. Among the different components of air pollution, long- and short-term exposures to fine particulate matter < 2.5 micron (PM 2.5) are generally considered to be responsible for increased cardiovascular morbidity and mortality (14), as well as for inducing deep vein thrombosis. However, accumulation of ultrafine particles may also play a role in favouring cardiac events. Air pollution appears to increase risks particularly in non-smokers and in subjects with the metabolic syndrome. Exposure to PM increase cardiovascular problems (myocardial ischaemia and infarction, heart failure, hypertension, arrhythmias, strokes) via different pathways: systemic inflammation and oxidative stress, alterations in autonomic balance, and direct action of PM constituents on vasculature with endothelial dysfunction.

3.8 Combination of risk factors

The combination of several factors, e.g. hypertension plus high cholesterol and smoking markedly enhances the risk of CV accidents. In order to better assess the risk for development of CVD, different multifactorial risk models have been proposed. The Guidelines of the European Society of Cardiology recommend a new model for total risk estimation based on the SCORE (Systematic COronary Risk Evaluation) system. The risk is defined on the basis of age, gender, systolic blood pressure, total cholesterol and smoking status and is expressed in terms of absolute 10 year probability of developing a fatal cardiovascular event for populations living either in low risk regions (Belgium, France, Greece, Italy, Luxemburg, Spain, Switzerland and Portugal) and in high risk regions of Europe. A previous event, the presence of diabetes or a familial history of severe cardiovascular accidents at an early age markedly raise risks.
Thus, the etiology of CVDs is multifactorial and most of the time involves a combination of genetic and behavioural factors.

Figure 3. The multiplicative effect of risk factors (6)

4. Genetic factors: polymorphisms and epigenetic

As indicated above, a family history of CVD in a first degree relative aged <55 (men) or 65 (women) years carries an independent relative risk of 1.5-1.7 (15, 16).

Genetic background is involved in the presence of different risk factors. Among these, abnormal lipid phenotypes are associated with 40-60% heritability, and even of >90% in the case of lipoprotein or Lp(a) (17).

The prevalence of familial hypercholesterolaemia (FH) is very low (1/10^6) for the homozygotous form, but not uncommon (1/500) for the heterozygotous form. Of note, at similar concentrations of cholesterol and LDL-cholesterol, FH is associated with a more severe disease than non-FH.

More recently, the presence of a high proportion of small dense (sd) LDL or B phenotype in subjects with excess weight gain and a sedentary life style is largely associated with a dominant genotype.

The heritability of diabetes is also well known. Multiple polymorphisms with small but cumulative effects on risk are under investigation. The information on genetic factors is important for identifying patients at high risk of developing CHD (18), in order to provide an opportunity, at an earlier stage, for aggressive therapeutic intervention together with lifestyle and dietary guidance.

It is also important to understand how genetic polymorphisms may affect the response to a given diet or to specific supplementation (nutrigenetic) and how much specific nutrients may modify the expression of a number of genes (epigenomic), some of these modifications being transmitted to the next generation.

5. Relationship between nutrition and CVD risk

5.1 Impact of dietary habits on CVD burden

As indicated in Fig. 2, CVD burden may vary substantially between different countries and areas of the world. While many Western countries appear to be at high risk, original
observations of a very low prevalence of CVDs disease were made in countries such as Japan and Crete. That such differences in CVD burden are not primarily due to different genetic background is confirmed by observations that Japanese migrants moving to Hawai and the USA show increased CVD rates, in relation to their adoption of Western dietary habits and the related rise in serum cholesterol concentrations. Similarly, African populations, living according to original primitive habits, appear protected from CVD while their counterparts in contact with Western “civilization” develop atherosclerotic lesions. Of interest, marked differences of CVD prevalence may exist between different areas within a given country, as shown by a much lower CVD incidence in Southern vs. Northern part of France. In Europe, populations surrounding the Mediterranean sea appear particularly protected, which led to the concept of a Mediterranean diet with its potential to prevent chronic diseases, such as CVD diabetes, and cancer.

5.2 The Mediterranean diet

May vary substantially from one region to another; it is mainly based on:
- a high consumption of fruits, vegetables, whole bread and other cereals, beans, nuts and seeds;
- a large consumption of olive oil which represents an important source of monounsaturated fats;
- the regular consumption of fish and poultry, and of selected dairy products (cheese and yogurt);
- a low consumption of red meat;
- consumption of wine in low to moderate amounts.

Figure 4. The Mediterranean diet

In a recent survey(19), dietary pattern was determined in a large sample of 22,043 adults, aged from 20 to 86 years of the Greek population, which was then followed up for 44 months. Those who continued to adhere strictly to the Mediterranean diet showed a 50% lower mortality rate than those who switched to a westernized diet; this observation held true for both genders.
This study confirms the potential for nutrition in disease prevention and highlights the concept of feeding patterns i.e. preferential intake of groups of foods; indeed, with the notable exception of oily fish, no single “protective” nutrient could be identified in the Mediterranean diet.

Of interest, the Mediterranean diet concept is not limited to a small number of foods, but can be enlarged and adapted to other areas and to populations with very different tastes and cultural habits. This was highlighted by a study of secondary CVD prevention conducted in Lyon, France (20). After a myocardial infarct, 605 patients were randomly assigned to receive a regular (step 1 American Heart Association) prudent diet together
with standard care and encouragement to take regular physical exercise (control group),
or to similar measures plus an experimental translation of the Cretan diet.
As shown from the survival rates in Fig 5, adding an adapted type of Mediterranean diet
was associated with improved outcome (with lower rates of morbidity and mortality)
which was evident from the very first months and persisted throughout the 5 year follow
up.

5.3 Evidence that Lifestyle and proper nutrition may reduce CVD
burden
Several models of healthy diets may be considered, allowing greater acceptability among
people of differing nationality and cultural traditions. When other protective aspects of
lifestyle (no smoking, weight control, and regular physical exercise) are also integrated,
the reduction in CVD mortality may reach ~50%, and to this may be added the benefit
provided by pharmacological treatment of hyperlipidaemia and arterial hypertension.
The effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum
lipids and C-Reactive Protein were investigated by D.J.A. Jenkins et al, JAMA, 2003(21).

Table 3. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin
on serum lipids and C-Reactive Protein

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>diet very low in sat fats &amp; rich in whole cereals</td>
</tr>
<tr>
<td>B</td>
<td>same diet + Lovastatin 20 mg</td>
</tr>
<tr>
<td>C</td>
<td>diet high in plant sterols (1.0 g/1000 kcal)</td>
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<tr>
<td></td>
<td>soy proteins (21.4 g/1000 kcal)</td>
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<tr>
<td></td>
<td>viscous fibers (9.8 g/1000 kcal)</td>
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<tr>
<td></td>
<td>almonds (14 g/1000 kcal)</td>
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The study included 46 volunteers – healthy adults with mild hyperlipidaemia undergoing 4 week dietary intervention vs. drug on the basis of a prudent diet. This study showed that a dietary manipulation over 4 weeks, combining several nutrients with a (weak) hypolipidaemic effect, can reduce LDL-C and CRP as efficiently as a first generation statin. The remaining challenge is to design attractive menus with palatablel nutrients and similar properties.

Another study, showing the importance of Mediterranean diet, was conducted in Sweden on Women with mild hyperlipidaemia and a metabolic syndrome (22). the Mediterranean diet showed the potential to reduce not only serum TG (by 17%) but also total cholesterol (by 13 %) and LDL cholesterol (by 23 %) as well as apo B (by 17%) in otherwise healthy Swedish subjects with the metabolic syndrome; in contrast, omega-3 supplementation only affects plasma TG.

There are, therefore, several possible ways of achieving a healthy diet, allowing cultural factors and personal taste to be taken into account.

**Figure 8. Healthy Swedish Women with mild hyperlipidaemia and a metabolic syndrome Adjunctive effect of a Mediterranean (vs. Swedish) diet plus physical exercise**

### 6. Influence of nutrition on CVD risk factors: Dietary Fats?

While this paragraph provides evidence for a protective effect of diet on CVD risk, it must be emphasized that the evolution of dietary habits in most areas of the world, particularly developing countries, is going in the opposite direction iey with a switch from an originally healthy diet to a more Western pattern. The resulting rise in CVD burden is a cause for concern.

As mentioned above, dietary habits may have a potent effect on CVD risk; this is not achieved via the regulation of one single risk factor (e.g. lowering plasma cholesterol level), but via the modulation of several parameters eg cell signalling and metabolism, and on intercellular communication.

**6.1 Dietary Fats**

Although the primary focus of the Lyon Heart Study was to provide an adaptation of the Mediterranean diet, a special effort was made to increase the intake of n-3 fatty acids, namely α-Linolenic acid (ALA). A parallel can be made with previous observations of a low incidence of CVD mortality in Greenland Eskimos (by comparison with the Danish population living in the continental part of the country) and to studies using...
supplementation of fish oils or n-3 long-chain fatty acids from marine sources, as discussed later.

![Nutrition and Cardiovascular Diseases Diagram](image)

**Figure 9. Mechanisms through which nutrition influences CVD risk (23)**

Dietary fat induces changes in cholesterol and lipid metabolism, and modulates insulin effects/cellular response. These changes indirectly affect membrane composition, formation of eicosanoid derivatives and activation of sterol regulatory element-binding protein (SREBP).

![Dietary Fat Influence Diagram](image)

**Figure 10. Dietary fat influences**

Among the nutrients present in various foods, fat and cholesterol have received a lot of attention from health professionals and the media. In addition to their effect on plasma total and LDL-cholesterol, dietary fatty acids have an important impact on the fatty acid composition of cell membrane phospholipids, and therefore on cell metabolism. For a number of years, the high fat intake prevailing in most Western countries has been considered as «the enemy» responsible for the high rate of CVDs. This is particularly due to the high content of saturated fats in the typical Western diet. Indeed, different fatty acids may variably affect plasma cholesterol and its distribution in lipoproteins. Equations have been proposed to predict the effect of dietary saturated and unsaturated fatty acids on plasma total and LDL cholesterol (LDL-C). However, these equations were developed for Western populations and it is likely they do not apply to all ethnic groups.
6.2 Saturated fatty acids

Saturated fats (no double bonds) raise total serum cholesterol levels and LDL-C levels. These fatty acids (FA) also increase the rigidity of cell membranes and alter the function of LDL receptors, and possibly raise cholesterol production in the liver. Specific fatty acids, i.e. myristic (C14:0) and lauric (C12:0) acids present in butterfat and in tropical (coconut and palm kernel) oils, increase plasma cholesterol more than palmitic acid (C16:0), the most prevalent fatty acid in the food supply (24); in contrast, stearic acid (C18:0), also very common in foods, is rapidly converted to oleic acid (C18:1n-9), and does not elevate blood cholesterol. Of interest, saturated fatty acids may also raise CVD risk by stimulating platelet aggregability and activating some coagulation factors; this may explain why many CV accidents occur during the post-prandially.

The major food sources of saturated fats are animal fats such as red meats and whole milk dairy products but also some vegetable oils such as palm oil which is increasingly used in many products and preparations; the labelling as vegetable oil may be particularly misleading to the public. In contrast, meat from chicken and turkey contain less saturated fat, especially if skinless.

With a notable exception of conjugated linoleic acids present in milk, most natural unsaturated FAs have a cis configuration, which induces an angle in the chain at the site of the double bond. A higher number of double bonds is related to lower freezing temperatures typical of oils rich in polyunsaturated FAs.
6.3 Trans fatty acids
These are geometrical isomers of cis-unsaturated fatty acids with a saturated-like configuration; they are generally produced by industry to increase fusion temperature and give a more solid texture to vegetable oils. Frying food may also increase trans FA content and consumption. However, these trans FAs have a very negative impact on plasma lipid profile, increasing of LDL-C, decreasing HDL-C levels, and raising lipoprotein concentrations. They are considered more atherogenic than saturated fats (26) and may also increase CVD risk(27) This property is not shared by natural trans fatty acids present in dairy fats.
There is a consensus to recommend a sharp decline in the consumption of trans fatty acids produced by hydrogenation. However, they are too often replaced by semi-solid fractions of palm oil.

6.4 Monounsaturated FA (MUFA)
The major food sources of monounsaturated fats (a single double bond) are vegetable and nuts oils: from 72 % in almond and olive oils, avocado, to peanut (51 %) oils. The only nutritionally important MUFA is oleic. Replacement of saturated and trans FAs with monounsaturated or polyunsaturated fats of vegetable origins decreases LDL-cholesterol(28).

6.5 Polyunsaturated fatty acids (PUFA)
Polyunsaturated FAs have different chemical composition providing two main groups: n-6 and n-3 PUFA's. Linoleic acid is the main representative of the n-6 group, made up of 18 carbon atoms and two double bonds Fig.12. The n-6 group fatty acids mainly originate from walnut, soyabean, maize oils.
α-Linolenic acid (ALA) is the precursor in the n-3 group (18 carbon atoms and three double bonds). ALA is an essential fatty acid. The main food sources are certain vegetable oils: soybean, sunflower and linen oils. In prospective epidemiological studies, a high intake of ALA is associated with a reduction in fatal cardiovascular events(29, 30). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two important representatives of the n-3 group, derived mainly from fish oils and fats.
The consumption of PUFA’s instead of saturated FA’s or trans FA’s is inversely correlated to risk of CVD as shown in prospective epidemiological investigations (26). The intake of PUFA’s reduces plasma LDL cholesterol and, to a lesser extent, HDL cholesterol as compared to saturated FA’s. This was shown by several randomized clinical trials in which saturated fats were replaced by vegetable oils (rich in n-6 PUFAs). PUFAs and to a lesser extent MUFAs may slightly reduce HDL-cholesterol, but the ratio of total to HDL-cholesterol remains markedly improved. It is recognized that the consumption of n-6 fatty acids has become excessive, raising inflammatory reactions. Therefore, the emphasis is on increasing intake of n-3 PUFA. Systematic review of randomised studies of high monounsaturated or high polyunsaturated diets suggests no significant differences in total, LDL or HDL cholesterol with these two types of fat.
Triglyceride levels were reduced by 0.14 (95% CI 0.00-0.29) mmol/l on the diets high in PUFA’s especially by omega-3 FA’s. There is much evidence suggesting that consumption of EPA and DHA are beneficial for triglycerides, blood pressure, haemostatic balance and heart rhythm (31).
Table 4. Influence of n-3 Fatty Acids on Lipid Metabolism, serum lipids and Lipoproteins.

<table>
<thead>
<tr>
<th>n-3 Fatty Acids and Lipid Metabolism</th>
<th>n-3 Fatty Acids and Plasma Lipoproteins</th>
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<tbody>
<tr>
<td>• Inhibition of FA release from fat stores</td>
<td>• ↓ plasma triglycerides</td>
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<tr>
<td>• Inhibition of hepatic lipogenesis</td>
<td>• ↓ plasma VLDL-TG and VLDL-cholesterol</td>
</tr>
<tr>
<td>• Inhibition of TAG synthesis</td>
<td>• ↑ or → HDL-cholesterol, but → apo A-1</td>
</tr>
<tr>
<td>• Inhibition of apo B net production</td>
<td>• ↑ LDL-cholesterol (generally slight)</td>
</tr>
<tr>
<td>• ↑ fat oxidation</td>
<td>• ↓ fraction of small dense LDL</td>
</tr>
<tr>
<td>• ↓ ectopic fat storage</td>
<td>(phenotype B subjects)</td>
</tr>
<tr>
<td>• ↓ hepatic production of VLDL</td>
<td>• ↑ VLDL → LDL conversion</td>
</tr>
<tr>
<td>• ↑ VLDL → LDL conversion</td>
<td></td>
</tr>
</tbody>
</table>

Of interest n-3 PUFAs have only a mild effect on raising HDL-cholesterol levels, but no effect on LDL-cholesterol. However, at high dose, they may markedly reduce plasma triglycerides and free fatty acids, both in fasting and postprandial conditions.

Of potential importance, high dietary intake of PUFA may increase the sensitivity of LDL particles to oxidative damage, which in turn may profoundly raise their atherogenicity. In contrast, oleic acid (probably with other components of olive oil) reduces LDL susceptibility to oxidation. In addition, high dietary intake of n-6 PUFA appears to stimulate the development of inflammatory reactions, an effect which is largely inhibited by n-3 PUFA. In general, the evidence for the benefits of fish oil is stronger in secondary than in primary prevention(32).

The supplementation of the diet with 850 mg -f EPA/DHA (fish oil) in subjects who had heart attacks, was found (GISSI study)(33) to be associated with 21% reduction in total mortality, a 30% reduction in CV death and a 45% decrease in sudden death during the 3.5 year follow-up period. [RR for total mortality 0.59 (95% CI 0.36–0.97), n=11 323].

![Graph showing effect of Omega-3 PUFAs on all-cause mortality](image)

Figure 13. GISSI-Prevenzione Trial: Secondary Endpoint Results: Early Effect of Omega-3 PUFAs on All-Cause Mortality.

Mode of action of n-3 PUFAs varies:
- Components of cell membranes
• Formation of eicosanoids
• Formation of second messengers involved in cell signalling pathways
• Gene regulation

n-3 PUFAs affect cell responses by regulation of gene expression and subsequent downstream events. n-3 PUFAs control transcription factors such as peroxisome proliferator-activated receptors (PPARs) and sterol-regulatory-element binding proteins (34).

FAs effects on cellular responses vary from changes in surface adhesion molecule expression to altered cytokine production.

n-3 PUFAs posses an important effect on Transcriptional activity of certain genes:
• Decrease inflammation: ↑ PPAR’s ↓ NFkB (35)
• Decrease fat synthesis (TG>chol): ↓ SREBP (34)
• Increase fat oxidation: ↑ PPAR’s
• Improve i.c. antioxidant defences: ↓ NFkB
• Decrease cachexia: ↓ NFkB

Efforts at reducing total fat intake have led to increasing carbohydrate calories. However, if high carbohydrate diets effectively reduce LDL-cholesterol, they also markedly raise plasma triglycerides (in genetically predisposed individuals), the fraction of atherogenic small dense LDL, and reduce the fraction of protective e HDL particles. In that respect, while views on the role of polyunsaturated fats have evolved over the past 30 years, a strict limitation in the intake of saturated fats (< 8-10% of calorie intake) remains a strong and consensual recommendation.

Thus, instead of advising high or low carbohydrate diets, it would be meaningful to mention the type of carbohydrates and fats included. Such healthy diets reduce CVD risk via several mechanisms including their effects on lipids, weight reduction, lowering of blood pressure, oxidative stress, control of glucose and endothelial function, reduction of inflammatory and thrombotic reactions.

6.6 Dietary cholesterol intake

The response to low cholesterol diet is extremely heterogeneous among subjects and individual susceptibilities, suggesting that some patients might benefit substantially from low cholesterol diet (36). Generally reduction of cholesterol intake has relatively small effects on serum lipids: reduction of 100 mg dietary cholesterol per day appears to reduce total serum cholesterol by only 0.06 or 0.07 mmol/l (roughly 1%)(37, 38). Indeed, certain subjects may need professional advice on food and food choices to select a diet associated with a reduction of CVD risk.

Recent progress in the understanding of cholesterol absorption by the intestine and the finding of genetic polymorphisms leading to increased absorption of cholesterol suggest that a high dietary cholesterol intake impacts on plasma cholesterol in ~ 20% of the population referred to as “high absorbers”. Of note, these subjects also absorb a significant proportion of plant sterols; since plant sterols may be found in atherosclerotic lesions, caution may be advised regarding the use of plant sterol preparations to lower plasma cholesterol.

It is perhaps naive to expect any single nutrient to have a major effect in preventing CVD. In the past decade nutrition research has moved from the study of micronutrients and macronutrients cardioprotective properties to focus on evaluating food-based approaches to prevent cardiovascular diseases(39). In observational studies, specific dietary patterns have been identified that are associated with increased or decreased incidence of cardiovascular events.
7. Recommendations for Management of risk in clinical practice

The new European guidelines on cardiovascular disease prevention in clinical practice have been prepared to manage the risk of CVD in clinical practice and contain strategies for preventing CVD.

The new European guidelines were developed in cooperation with a number of other European medical and clinical organizations: ESC, represented by its European Association of Prevention and Rehabilitation and Working Group on Cardiovascular Nursing; European Society of Atherosclerosis; European Society of Hypertension (ESH); European Heart Network; Family Practice (World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians - WONCA); International Society of Behavioral Medicine; European Association for the Study of Diabetes (EASD)/International Diabetes Federation Europe; and European Stroke Initiative.

7.1 Strategies for promoting CVD prevention

Multimodal interventions: The primary prevention strategy is promotion of a healthy lifestyle including a proper low-calorie nutrition combined with increased physical activity. Most studies demonstrate that physically active people have significantly lower mortality from cardiovascular disease, compared with sedentary people. There is a clear relationship between physical activity and lipid profile, indicating a reduction in plasma triglycerides and an increase in HDL-cholesterol in individuals who exercise regularly.

Change and management of behavioural risk factors:

- Dietary changes,
- Prevention and management of smoking,
- Management of physical activity,
- Control of arterial hypertension,
- Management of dyslipidemia,
- Prevention of risk of CVD in diabetes,
- Prevention in subjects with the metabolic syndrome.

The subjects at low risk for CVD should be helped to maintain this state lifelong, and those at increased CVD risk should be helped to reduce their risk. Nutrition is an integral part of this strategy. Patients with cardiovascular disease and individuals at high risk should be given recommendations on their food and dietary options combined with increased physical activity.

- No smoking;
- Healthy food choices (5 portions of fruit and vegetables per day);
- Physical activity: Walk 3 km daily, or 30 minutes of any moderate activity;
- BMI < 25 kg/m² and avoidance of central obesity;
- Blood pressure < 140 mm Hg systolic blood pressure (SBP);
- Total cholesterol < 5 mmol/L (~190 mg/dL);
- Low-density lipoprotein (LDL) cholesterol < 2.5 mmol/L (~100 mg/dL);
- Blood glucose < 6 mmol/L (~110 mg/dL).

The guidelines appropriately give highest priority to the highest risk subjects because these people gain most from risk modification. This includes patients with established atherosclerotic CVD, asymptomatic individuals who have multiple risk factors, Type 2 or
type 1 diabetics with microalbuminuria, those with markedly increased single risk factors, or close relatives of subjects with premature atherosclerotic CVD. The goals of CVD prevention in these high-risk individuals are:

- Blood pressure < 130/80 mm Hg if feasible;
- Total cholesterol < 4.5 mmol/L (~175 mg/dL) with an option of < 4 mmol/L (~155 mg/dL) if feasible;
- LDL cholesterol < 2.5 mmol/L (~100 mg/dL) with an option of < 2 mmol/L (~80 mg/dL) if feasible;
- Fasting blood glucose < 5 mmol/L (~80 mg/dL) and glycated hemoglobin (HbA1c) < 6.5% if feasible.

The prevention paradox is that high risk individuals gain most from preventive measures—but most CVD deaths come from apparently low risk subjects because they are so numerous.

The three strategies aimed at (1) the general population, (2) primary prevention in high risk individuals, and (3) secondary prevention in those with established CVD, should be complementary, but not competitive.

8. Summary

CVDs, including coronary heart disease (CHD) and stroke, currently represent the major causes of mortality and morbidity all over the world. In Europe, CVDs are responsible for 43% of deaths in men and 55% in women and for 30% of all deaths before the age of 65 years. CVD burden could be substantially reduced by early diagnosis and appropriate measures, since atherosclerotic lesions may be substantially improved in response to measures taken. CVD results from a combination of genetic and environmental factors; some factors vary between different ethnic groups. Plasma lipid profile is an important, but certainly not the only, risk factor for CVD.

Prevention includes healthy lifestyle: no smoking, weight control, physical activity, and healthy dietary intake; control of blood pressure, plasma glucose, and inflammation is important; The Mediterranean diet is a good example of healthy dietary pattern. Components of the Mediterranean diet may be adapted to nutritional habits of different countries, taking into account differences of taste and culture. The benefits of a healthy lifestyle exceed, but are additive to, those of medical treatment.
9. References

1 European Society of Cardiology-www.escardio.org
2 Thomas A. Gaziano, MD, MSc Cardiovascular Disease in the Developing World and Its Cost-Effective Management, Circulation. 2005;112:3547-3553


