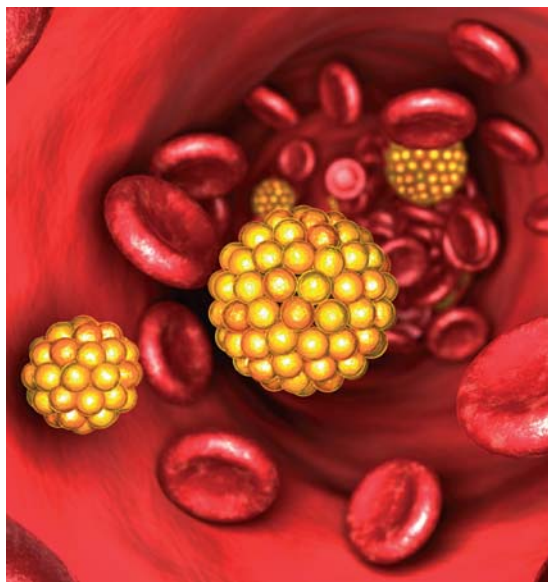


Dyslipidaemia

— the condition and non-drug management

By Zoë Gross, BPharm, MRPharmS, and George E. Reese, BSc, MBBS

Dyslipidaemia is a term used to describe the disordered metabolism of lipids. This article gives an overview of the epidemiology and aetiology of the condition and sets out details about lipid transport and metabolism and the non-drug management of dyslipidaemia



Concentrations of LDL cholesterol (shown in yellow) in the blood may be increased in patients with dyslipidaemia

Dyslipidaemia is a term used to describe disordered lipid metabolism. It encompasses changes in blood cholesterol levels such as elevated serum low-density lipoprotein (LDL) cholesterol, raised total cholesterol (TC), raised serum triglycerides and low levels of high-density lipoprotein (HDL) cholesterol. It is a broader term than hyperlipidaemia, which refers to raised serum levels of one or more of TC, LDL cholesterol, triglycerides, or both TC and triglycerides (combined hyperlipidaemia), but does not include low levels of HDL cholesterol.

Dyslipidaemia is one of the major risk factors for developing coronary heart disease (CHD), the most common cause of death in the UK, accounting for more than one in five deaths in men and one in six in women.¹ Over 50 per cent of CHD in developed countries is due to blood cholesterol levels in excess of 3.8mmol/L¹ and, overall, cholesterol causes more than 4 million premature deaths a year worldwide.² The risk of developing CHD is directly related to blood cholesterol levels.¹

In Western populations, a relationship is well established both between TC (at concentrations above 5mmol/L) and CHD and between LDL cholesterol (at concentrations above 3mmol/L) and CHD.³ Having high serum concentrations of TC and LDL cholesterol has been shown to increase the risk of an individual developing CHD, whereas HDL cholesterol confers protection, with the risk of CHD decreasing as HDL cholesterol increases.³ Low levels of HDL cholesterol (<1.0mmol/L) are strongly associated with an increased risk of developing CHD and a worse prognosis after a heart attack.^{1,4}

This article gives an overview of the epidemiology and aetiology of dyslipidaemia, normal lipid transport and lipoprotein metabolism, risk assessment tools for CHD and non-drug management of dyslipidaemia.

— Epidemiology

Target levels of serum lipids for people at high risk of CHD are shown in Panel 1 (p170). The UK population has one of the highest average serum cholesterol levels in the world⁵ with two-thirds of people having a raised serum TC level of 5mmol/L or over.¹ In England, the mean blood cholesterol level in men is about 5.5mmol/L and in women is 5.6mmol/L, with the prevalence

of raised cholesterol increasing with age in both men and women.¹ Figures from the Health Survey for England 2003, commissioned by the Department of Health, show that the prevalence of raised cholesterol in men more than doubled from around 27 per cent of men aged 16 to 24 years to around 60 per cent of those aged 25 to 34 years, peaking in the 45 to 54 year age group (81 per cent) and decreasing in older age groups. For women, the pattern was similar, but with cholesterol levels increasing up to those aged 55 to 64 years and then declining in the older age groups to a lesser extent than in men.⁴

In terms of LDL cholesterol, which makes up 60 to 70 per cent of total serum cholesterol, no clear age-related variation was found in men. However, for women, slightly more of a difference was evident between different age groups for mean LDL cholesterol and raised LDL cholesterol was higher among those women aged 55 and over.⁴ For HDL cholesterol, which makes up 20 to 30 per cent of total serum cholesterol, the prevalence of low levels varies to some extent with age.^{1,4} Figures for 2003 show no clear age-related pattern for men, but for women, the proportion with low HDL cholesterol was higher among those aged 16 to 44 than among those aged 45 and over.⁴ Mean HDL cholesterol was also slightly

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Panel 1: Recommended levels of serum lipids for people at high risk of CHD

Type of lipid	Optimum target levels of serum lipids	Current treatment practice audit standard
Total cholesterol	<4.0mmol/L or reduced by 25 per cent (whichever is greater)	<5.0mmol/L or reduced by 25 per cent (whichever is greater)
LDL cholesterol	<2.0mmol/L or by 30 per cent (whichever is greater)	<3.0mmol/L or by 30 per cent (whichever is greater)
HDL cholesterol	≥1.0mmol/L	≥1.0mmol/L
Triglycerides	<2.3mmol/L	<2.3mmol/L

"CHD" is coronary heart disease, "LDL" is low-density lipoprotein and "HDL" is high-density lipoprotein. Figures are those cited in reference 12

higher in women (1.6mmol/L) than in men (1.4mmol/L).⁴

As well as age and sex variations, lipid and lipoprotein concentrations also vary among different populations. Countries where a Western diet is consumed generally have higher TC and LDL cholesterol levels than

those where a diet low in saturated fat is regularly consumed.³ Nearly 8 per cent of all disease burden in developed countries is caused by raised blood cholesterol, compared with around 2 per cent in low mortality developing countries.^{1,2} Mean total cholesterol and the prevalence of raised blood cholesterol

levels are marginally lower in all ethnic minority groups than in the general population.¹ However, there are significant variations in the prevalence of low HDL cholesterol — for example, 45.3 per cent of men of Pakistani origin have low HDL cholesterol, compared with 10.3 per cent of the general population.

— Transport and metabolism

An overview of normal lipid transport and plasma lipoprotein metabolism is set out in Figure 1. Essentially, cholesterol, triglycerides and phospholipids are transported in the plasma in the form of lipoproteins, of which there are six main classes:

- Chylomicrons
- Chylomicron remnants
- Very low-density lipoprotein cholesterol
- Intermediate-density lipoprotein cholesterol
- Low-density lipoprotein cholesterol
- High-density lipoprotein cholesterol

These lipoproteins have a protein component, known as apoproteins, examples of

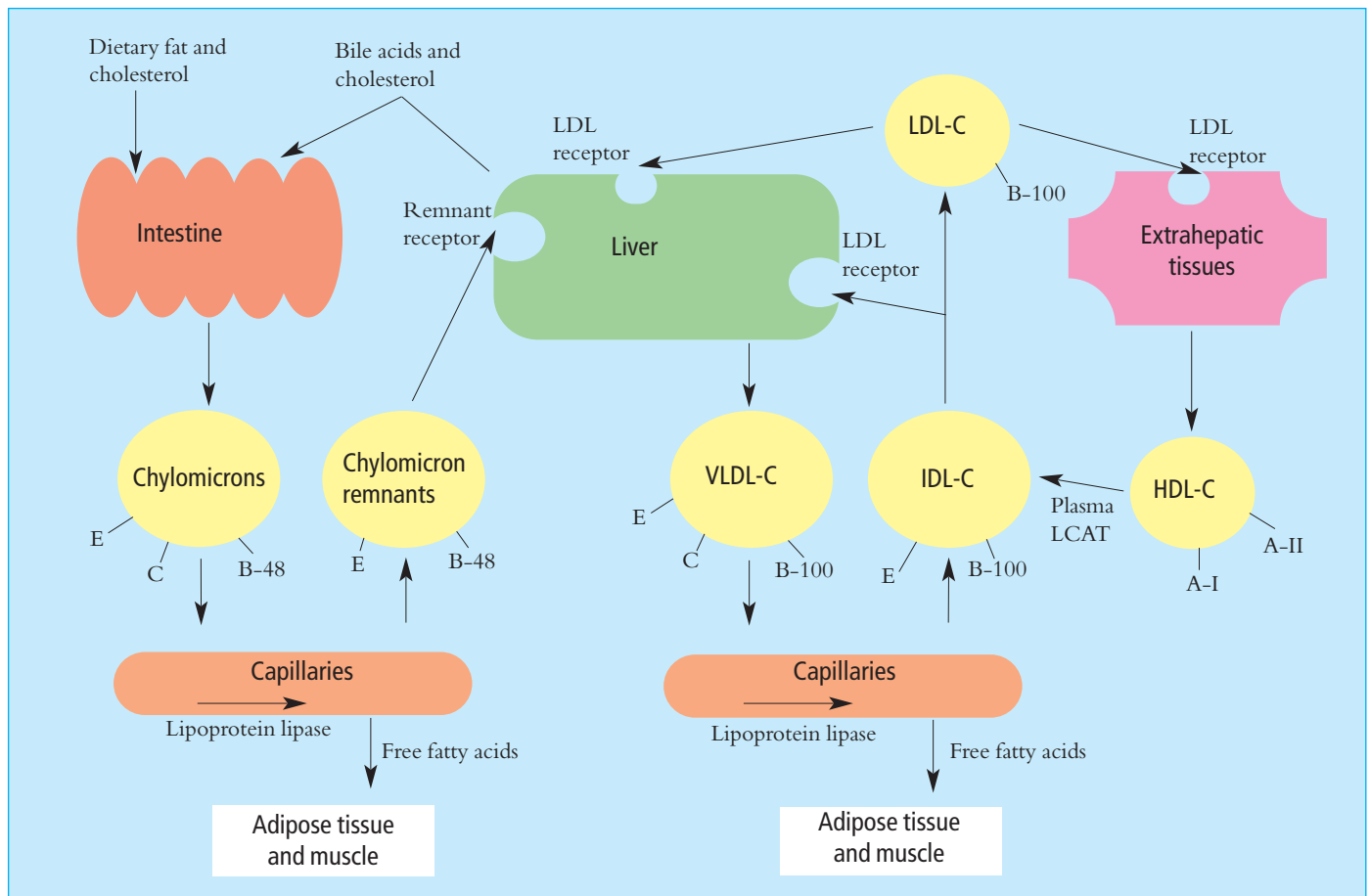


Figure 1: Schematic representation of lipoprotein metabolism in plasma. "VLDL-C" means very low-density lipoprotein cholesterol, "IDL-C" means intermediate-density lipoprotein cholesterol, "HDL-C" means high-density lipoprotein cholesterol. "A-I", "A-II", "B-48", "B-100", "C" and "E" are apoproteins. "LCAT" means lecithin-cholesterol acyltransferase. VLDL-C is formed in the liver and contains high concentrations of triglycerides and moderate concentrations of cholesterol and phospholipids. It is a precursor of IDL-C, which is formed from VLDL-C by the removal of a large

amount of triglycerides, resulting in the relative concentrations of cholesterol and phospholipids being increased. LDL-C is made from IDL-C by removing almost all triglycerides. HDL-C is formed in the liver and also synthesized in the intestinal epithelium — it contains a high concentration of protein, but smaller concentrations of cholesterol and phospholipids. Adapted from Walker R. Dyslipidaemia. In Walker R and Edwards C. Clinical pharmacy and therapeutics. 3rd edition. Edinburgh: Churchill Livingstone; 2003. pp355.

which include apoproteins A-I, A-II, E, C, B-48 and B-100.

Dietary cholesterol and triglycerides are absorbed from the intestine and transported in intestinal lymph vessels as chylomicrons. These chylomicrons enter the plasma and are transported in the circulation. Most of the chylomicrons are removed from the circulation as they pass through the capillaries of adipose tissue and skeletal muscle. The endothelial cells of adipose tissue and skeletal muscle contain large quantities of the enzyme lipoprotein lipase. This enzyme is activated by apoprotein C-II, a component of apoprotein C found on chylomicrons, and catalyses the breakdown of triglycerides in chylomicrons to free fatty acids and glycerol. The fatty acids and glycerol then diffuse freely into the fat cells of adipose tissue and muscle cells. The chylomicron remnants are taken up by the liver.³

Lipid metabolism and atherosclerosis are closely linked with cholesterol, particularly LDL cholesterol, which plays an important role in atherogenesis. Atherogenesis progresses as LDL cholesterol accumulates in the arterial intima (inner wall). Monocytes and T cells are attracted to the affected area of intima where intrainitimal monocytes ingest LDL cholesterol and become foam cells. Clusters of foam cells join together to form fatty streaks and smooth muscle cells are stimulated to migrate to the intima where they proliferate and synthesise proteins to form fibrous plaque caps. Fibrous plaques cause cardiovascular disease (CHD and stroke) by increasing in volume and interfering with blood flow through the affected artery, thus leading to chronic symptoms such as stable angina. Injury to a plaque cap leads to thrombosis and can cause episodes of unstable angina, myocardial infarction or sudden death. Atrophy of the arterial media beneath the plaque is common and, if severe enough, may lead to aneurysm formation.⁶

— Aetiology

Dyslipidaemia may be expressed in the form of familial syndromes, known as primary dyslipidaemias. Of the familial syndromes, heterozygous familial hypercholesterolaemia affects approximately 1 in 500 of the UK population and familial combined hyperlipidaemia affects 1 in 200 people. Around 60 per cent of variability in serum fasting lipids may be genetically determined. Other dyslipidaemias, accounting for up to 40 per cent of all dyslipidaemias, may be secondary to disorders such as diabetes mellitus, chronic renal failure and hypothyroidism, or to certain drugs, and are referred to as secondary dyslipidaemias. However, it is the interaction between genetic abnormalities and environmental factors, most importantly diet, that is likely to be the most common cause of dyslipidaemia.^{3,6}

Panel 2: Fredrickson/WHO classification of hyperlipidaemias and examples of their primary and secondary causes

Type	Lipoprotein raised	Primary causes	Secondary causes
I	Chylomicrons	Lipoprotein lipase deficiency, apoprotein C-II deficiency	Systemic lupus (rare)
IIa	LDL cholesterol	Familial hypercholesterolaemia	Hypothyroidism, nephrotic syndrome
IIb	LDL cholesterol and VLDL cholesterol	Familial combined hyperlipidaemia	Nephrotic syndrome, diabetes, anorexia nervosa
III	Chylomicron remnants and IDL cholesterol	Familial type III hyperlipidaemia	Nephrotic syndrome, diabetes, obesity
IV	VLDL cholesterol	Familial combined hyperlipidaemia, familial hypertriglyceridaemia	Diabetes, chronic renal disease
V	Chylomicrons and VLDL cholesterol	Familial combined hyperlipidaemia, apoprotein C-II deficiency	Alcohol, beta-blockers, diuretics, oral contraceptives

“WHO” means world health organization, “VLDL” means very low-density lipoprotein, “IDL” means intermediate-density lipoprotein. Information is taken from reference 6.

Dyslipidaemias, as mentioned above, encompass hyperlipidaemias, which can be classified according to the Fredrickson/World Health Organization classification (see Panel 2). In the classification, there are five phenotypes, one of which is subdivided, which are defined according to which lipoprotein is raised. It should be noted that the Fredrickson/WHO classification is not a diagnostic classification. It is a way of reporting which serum lipoproteins are raised in concentration and this often changes as treatment with diet and drug therapy is introduced.⁸

— Risk assessment

CHD risk can be estimated using tools such as the Joint British Societies' cardiac risk assessor computer program or coronary risk prediction chart (found in the British National Formulary), the revised Sheffield table and the New Zealand guidelines. For individuals who have not been diagnosed with CHD, these tools provide an aid to making clinical decisions, for example, about lipid modifying therapy. Calculating CHD risk using these tools takes into account the following common risk factors: hypertension, smoking, TC:HDL cholesterol ratio, diabetes, age and sex. All three risk assessment tools use the Framingham risk equation to determine the risk of an event.⁹

— Non-drug management

As well as drugs having a positive effect on lipid profile, lifestyle changes have been shown to play an important part in managing dyslipidaemia and reducing both blood TC levels and LDL cholesterol concentration and hence atherogenesis. Such changes in lifestyle include dietary modifications, in particular a reduction in the consumption of saturated fat, undertaking more physical exercise, reducing body weight and smoking cessation. A combination of complete smoking cessation, setting all individuals' body mass index to no more than 22 and a simulated mean cholesterol level of 2.3mmol/L, has been estimated to halve the 12-year risk of CHD in men and women.² Weight loss, smoking cessation, a diet moderate in unsaturated fat and moderate alcohol consumption have all been found to increase HDL cholesterol.⁴

In the Government's White Paper on public health, “Saving lives: our healthier nation”, one of the national targets to be achieved by 2010 is a reduction in the death rate from CHD and stroke, and related diseases, by at least two fifths in people under the age of 75.¹⁰ The National Service Framework for Coronary Heart Disease recommends that to reduce CHD, in primary care, in high-risk patients with diagnosed CHD or other occlusive arterial disease, patients should receive dietary advice and statins to lower serum cholesterol either to

less than 5mmol/L (LDL cholesterol to below 3mmol/L) or by 30 per cent, whichever is greater, unless contraindicated.¹¹ However, more recent guidelines published by the British Hypertension Society, in 2004, recommend optimal therapeutic cholesterol lowering targets which are lower than the levels stated in the NSF (see Panel 1, p170).¹² Recommendations for the management of low HDL cholesterol were published in 2002 by a group of international experts on HDL cholesterol. For patients with or without cardiovascular disease, but at high risk of developing it, an HDL cholesterol concentration of 1.0mmol/L or more is recommended.⁴

The following five lifestyle changes that can help reduce cholesterol levels are covered in more detail below:

- Dietary modification
- Weight loss
- Smoking
- Physical exercise
- Alcohol

— Dietary modification

Dietary modification can significantly improve dyslipidaemia and is an essential part of the management of lipid disorders. In patients taking lipid-modifying drugs, it achieves additional lipid-lowering that enhances the therapeutic effects of drug therapy.¹³ Researchers have also found that intensive dietary therapy to reduce cholesterol levels may be just as effective as certain statins.¹⁴ Intensive dietary intervention may decrease blood cholesterol and LDL-cholesterol by around 30 per cent.¹⁴ A sustained reduction in blood TC concentration of 1 per cent can lower the risk of CHD by 2 per cent.¹⁵

The aim of dietary advice for lowering cholesterol is to decrease saturated fat intake, increase polyunsaturated fat and reduce dietary cholesterol. Reducing dietary intake of saturated fat and cholesterol and increasing polyunsaturated fat intake have been shown to contribute to decreasing mortality from CHD.^{16,17} Dietary fats, cholesterol, plant sterols and stanols, fish oils and soluble fibres can all have an effect on lipid profiles. Particular elements of a lipid-lowering diet are briefly discussed below:

Fats Fat in the diet is one of the most important determinants of blood cholesterol levels. Current thinking is that it is the type of fat in the diet that is important, rather than the amount of fat.¹⁸ Dietary fats may be considered to be either “good” or “bad” fats. Monounsaturated and polyunsaturated fats are good fats because they lower LDL and raise HDL cholesterol levels, whereas saturated fat, found mainly in red meat and full-fat dairy products, raises both LDL and HDL cholesterol and trans fats raise LDL

cholesterol.¹⁸ Substituting saturated fat in the diet with monounsaturated fat, polyunsaturated fat or carbohydrates may result in nearly an 80 per cent lowering of LDL cholesterol.¹³ Those who consume a Mediterranean diet, which is low in saturated fat and rich in foods such as fruit, vegetables, nuts and seeds, have been found to have a lower incidence of CHD than those who do not.³ However, in patients where HDL cholesterol needs to be raised an increase in dietary fat may be necessary with the caveat that it should be low in saturated fat.¹³

Cholesterol Reducing dietary intake of cholesterol to <200mg per day can improve LDL cholesterol levels by 1–3 per cent.¹³ Dietary cholesterol is found in animal products and examples of cholesterol-rich foods include offal and egg yolk.

Plant sterols and stanols Plant sterols and stanols reduce serum concentrations of cholesterol by decreasing absorption of cholesterol from the gut. Adding 2g per day of stanols or sterol esters to an average daily portion of margarine has been shown to reduce serum LDL cholesterol by about 10 per cent. By doing this for two years, a reduction in the risk of heart disease of about 25 per cent may be achieved.¹⁹

Omega-3 fatty acids Oily fish, such as salmon, mackerel and sardines, contain omega-3 fatty acids, a type of polyunsaturated fat. Eating 6–12g per day of omega-3 fatty acids has been shown to reduce serum triglyceride levels by between 40 and 80 per cent.¹³

Fibre Eating a diet high in fibre may help reduce the amount of cholesterol absorbed from the intestine into the blood.²⁰ Oat bran, grapefruit pectin and psyllium — water soluble fibres — have been found to reduce LDL cholesterol.¹³ A 7 per cent reduction, approximately, in serum LDL cholesterol may be achieved by adding 3–6g per day of soluble fibre from oat products or psyllium.¹⁴

Soy protein Dietary soy protein reduces serum TC, LDL cholesterol and triglycerides and increases serum HDL cholesterol.¹⁴

Examples of the types of food to eat, as well as those to avoid, to help improve lipid profile are set out in Panel 3 (p176). Although ward-based studies have shown that, by eating a healthy diet, it is possible to reduce TC by 10–15 per cent,¹⁵ community-based studies have shown TC to be reduced by only 3–6 per cent.³ Nevertheless, changes in dietary habits should always be encouraged in a patient with dyslipidaemia, although it should be noted that dietary intervention is rarely successful alone in significantly improving lipid profiles.³

— Weight loss

The lipid-lowering effect achieved by dietary changes alone can be doubled by a 2.3kg loss in body weight.¹³ Weight loss reduces the production rate of VLDL by the liver which in turn reduces LDL cholesterol.¹³ Reducing body weight can also reduce triglyceride levels and lead to a slight increase in HDL cholesterol levels.¹⁴ Individuals with hyperlipidaemia who are overweight or obese should reduce their weight to a body mass index of 25 or less, unless contraindicated.¹⁴ High fibre, high carbohydrate and low saturated fat and cholesterol diets promote weight loss.

— Smoking

Increasing levels of plasma cholesterol concentration have been shown to be associated with increasing numbers of cigarettes smoked per day. In men aged 18 to 60 years, the average plasma cholesterol has been found to be increased by 0.0085mmol/L for each cigarette smoked. In women aged 31 to 50 years, average plasma cholesterol has been shown to be increased by 0.0124mmol/L for each cigarette smoked per day. This association, however, has not been observed in men and women over the age of 60.²¹

— Physical activity

HDL cholesterol levels have been shown to increase with increases in physical activity. Greater increases in activity result in greater rises in HDL.¹³ Aerobic exercise, for example, brisk walking, cycling, jogging and swimming, for 30 minutes, three to five times a week, has a desirable effect on lipid profile.³

— Alcohol

Alcohol consumption has a linear relationship with serum triglycerides — excess alcohol consumption worsens dyslipidaemia in patients with raised serum triglyceride levels. There is also an association between HDL cholesterol and alcohol consumption, with increased alcohol intake raising plasma HDL cholesterol. Despite this, patients with an underlying dyslipidaemia can have a low HDL cholesterol level even with a high alcohol intake.¹³

— Conclusion

Dyslipidaemia is one of the major risk factors for developing coronary heart disease, which is the most common cause of death in the UK. Although there is a genetic element to most dyslipidaemias, environmental factors, such as diet, alcohol intake and body weight, play a part in influencing lipid profiles. Patients with diabetes and

hypertension are also at particularly high risk of the complications of dyslipidaemia. The second article in this special feature will describe the pharmacological treatments available (pp177–81).

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Panel 3: Foods that can effect lipid profiles

Class	Detrimental effect	Beneficial effect
Fats	Saturated fats — found in butter, lard, ghee, full fat dairy foods, red meat, coconut oil, palm oil, ice cream, chocolate Trans fats — found in margarines, deep fried chips, partially hydrogenated vegetable oil, many fast foods, most commercial baked goods	Monounsaturated fatty acids — found in olives, olive oil, rapeseed oil, walnut oil, avocado Polyunsaturated fatty acids — found in sunflower oil, cornflower oil, soybean, oily fish
Fish	Fried fish (in batter), roe, fish pate	Oily fish (eg, herring, kippers, mackerel, sardines, salmon) at least twice weekly, white fish
Meat	Fatty meat, duck, sausages, meat pies and pastries, pork, bacon	Lean meat, poultry without skin
Fruit and vegetables	Vegetables in batter	Five portions a day
Dairy and eggs	Whole and condensed milk, cream, hard and processed cheese, cream cheese, whole eggs	Skimmed milk, low fat cheese (eg, cottage cheese), low fat yoghurt, egg white

Information (which is not exhaustive) is based on the Heart UK diet sheet and guidelines for a cardioprotective diet and on references 3, 18 and 20