



HEART UK
THE CHOLESTEROL CHARITY



Familial Hypercholesterolaemia

An educational booklet for people
with familial hypercholesterolaemia

HEART UK – The Cholesterol Charity
providing expert support, guidance and education

PART 1: Familial Hypercholesterolaemia

What is familial hypercholesterolaemia (FH)?

Familial hypercholesterolaemia is an inherited condition, where an altered gene causes high blood cholesterol. It is usually referred to as FH.

Familial means that it runs in families and is passed from a parent to their child. Usually it is possible to trace FH over several generations.

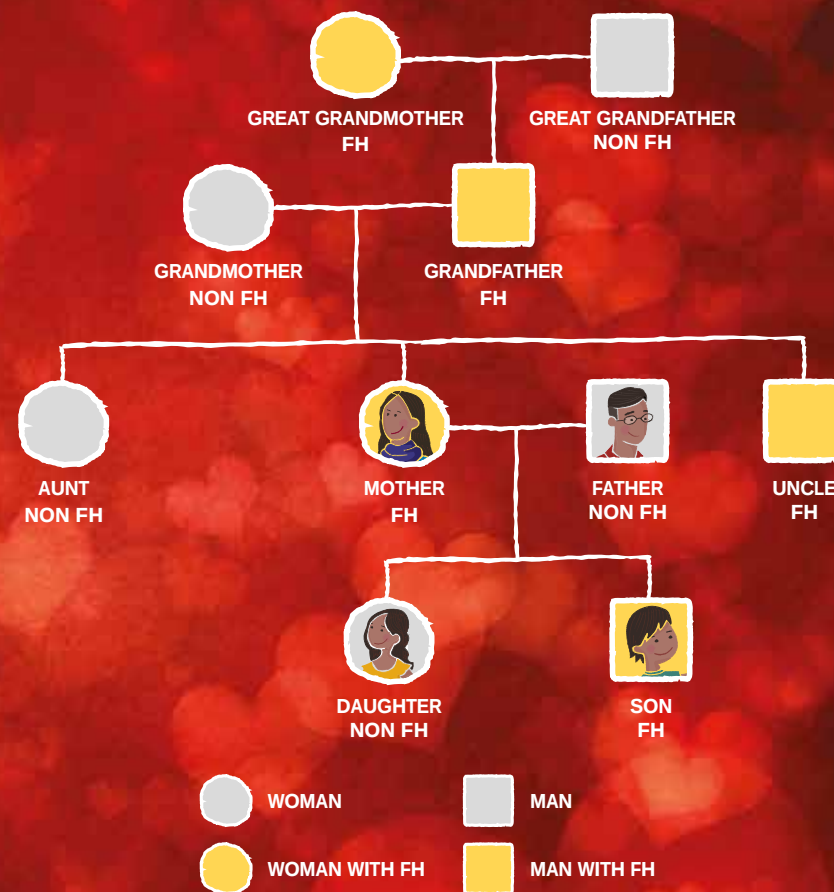
Hypercholesterolaemia means high blood cholesterol. The type of cholesterol that is specifically increased in FH is Low Density Lipoprotein-cholesterol (LDL-cholesterol). LDL-cholesterol floats in the blood stream and transports cholesterol around your body to the cells that need it. We talk a lot about LDL-cholesterol throughout this booklet.

FH is one of the most common inherited conditions. At least 1 in 500 people in the UK have an altered gene that causes FH. In some parts of the world it might be even more common. If one parent has FH, there is a 1 in 2 chance that their son or daughter will also have it.

FH is linked to an increased risk of very early cardiovascular disease. The risk from FH varies from family to family and from person to person within the family. It is influenced by cholesterol level, other inherited factors, diet, smoking, level of physical activity, and whether you are male or female. Women who have FH are affected by cardiovascular disease approximately 5–10 years later than men with the same condition and similar risk factors. With early and appropriate treatment the risk of cardiovascular disease can be reduced considerably.

The family tree

FH is an inherited condition which can usually be traced over several generations



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Because FH is inherited it runs in families. It causes high blood cholesterol, specifically LDL-cholesterol, and an increased risk of cardiovascular disease in early life.

What is LDL and LDL-cholesterol?



Low Density Lipoprotein (LDL) is a particle that floats in the blood and acts as a clever transport system for blood fats. It carries cholesterol around your body to the cells that need it. Cholesterol is an essential fatty substance that is needed by your body to build cells, make some hormones and to produce bile acids that are needed for digestion. We refer to the cholesterol that is carried on LDLs as LDL-cholesterol.

Too much LDL-cholesterol in your blood is not good for you; excess cholesterol can become embedded in the walls of blood vessels making them much narrower, a process called atherosclerosis. Atherosclerosis can lead to cardiovascular disease. Find out more about this process on pages 17–19.



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LDL transports cholesterol in your blood to your cells. Cholesterol is needed to build new cells, make hormones and bile acids. If there is too much LDL-cholesterol it can get stuck inside the walls of your blood vessels and cause narrowing. This process is called atherosclerosis.

What are the causes of FH?



Cell



Cell nucleus



Chromosome

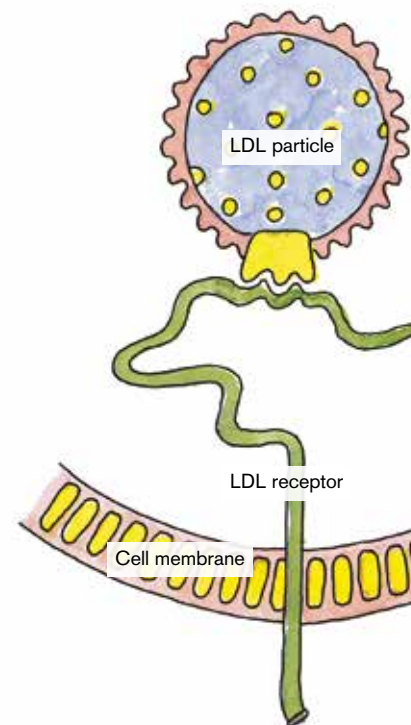


DNA

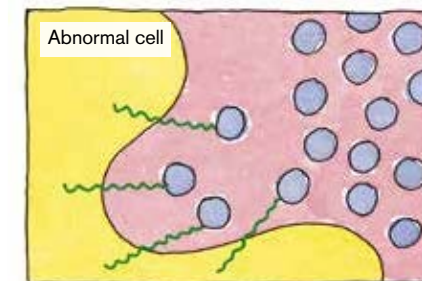
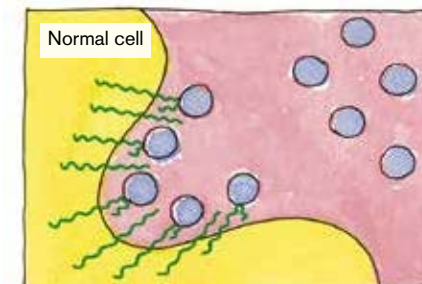
DNA, our genetic code is arranged in genes that sit on chromosomes. Chromosomes are packed into the cell nucleus, which is inside each of our cells.

The characteristics that we inherit from our parents are decided by the information carried on DNA. DNA is organised into 23 pairs of chromosomes that are found in the nuclei of cells. DNA consists of approximately 3 billion building blocks which are arranged in combinations to make around 25,000 genes. Genes provide the code for proteins that decide characteristics, such as eye and hair colour, but also how our bodies work. A change in just one of the building blocks within a specific gene can result in a medical problem. In FH there is a change in one of three genes, all of which code for proteins involved in the removal of LDL-cholesterol from the blood.

To transport cholesterol into cells, LDL particles have a specific protein on their surface called Apo-lipoprotein or ApoB. ApoB acts as a bridge between the LDL particle and the cells in your body. LDL receptors on the surface of cells attach to ApoB, allowing the LDL particle to move into the cell. Inside the cell another protein (PCSK9) is responsible for breaking down LDL receptors. If there is a problem with the LDL receptor, ApoB protein, or too many LDL receptors are broken down, the level of cholesterol in your blood will be higher than normal. This is the case in FH. Most people with FH have an altered LDL receptor gene. Only a few people in the UK have FH because of a problem with the ApoB gene or the PCSK9 gene.



The LDL receptor is attached at one end to the cell membrane. The other end binds to the LDL-cholesterol particles.



LDL receptors on the surface of cells help remove LDL particles from the blood.

Most people with FH (as seen here in the abnormal cell) have fewer LDL receptors.

Most people with FH have inherited one altered LDL-receptor gene from one of their parents, and one normal LDL-receptor gene from the other parent. As a result, they only have half of the normal number of working LDL receptors on the surface of cells. This means that there is always more

LDL-cholesterol circulating in the blood than is needed. The problem is that excess LDL-cholesterol can become trapped in walls of blood vessels. Over time, unless treated, this can lead to early cardiovascular disease. We talk more about this on pages 17–19.



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FH is caused by a change in one of three genes which code for proteins that help remove LDL-cholesterol from the circulation. The most common alteration is on the LDL receptor gene. As a result the defective LDL receptor cannot take up LDL-cholesterol from the blood into the cell.

When should FH be suspected?

Your doctor will ask you questions about your family history, arrange for you to have a blood test called a lipid (blood fat) profile, and do a physical examination. He or she may arrange for you to have a genetic test.

A lipid profile is needed to assess the levels of various lipids and lipoproteins in your blood such as total cholesterol, LDL-cholesterol, HDL-cholesterol, non-HDL cholesterol and triglycerides. We talk more about lipoproteins on page 20.

FH diagnosis at a young age is important. Treatment is more effective when started early and before the high levels of cholesterol can cause damage to your blood vessels.



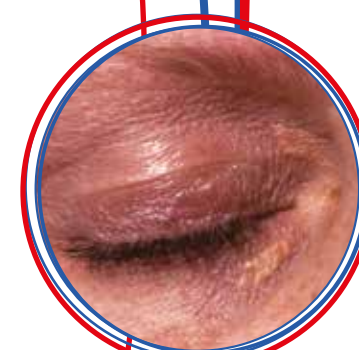
Your doctor may suspect you have FH if:

- there is a history of early cardiovascular disease in close family members
- you are man and have a heart attack before the age of 50, or 60 in a woman
- your cholesterol is very high
- other family members have been diagnosed with FH
- you have any physical signs of high cholesterol (see below)

Signs of FH

Some people with FH have physical signs on the outside of their body. These include swollen tendons on the heels and knuckles of the hands (tendon xanthoma) or yellowish patches around the eyes (xanthelasma). A white deposit of cholesterol in the shape of an arc (corneal arcus) may also be seen at the edge of the coloured part of the eye. Tendon xanthoma only occur in people with FH. Corneal arcus and xanthelasmas may happen for other reasons.

Visible physical signs of high cholesterol include swollen tendons on the back of the heel and yellow deposits in the skin around the eyes.



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FH is suspected in people who have early cardiovascular disease and high cholesterol levels and in close relatives of these people. Brothers, sisters and children of people already diagnosed with FH should all be assessed.

How is FH diagnosed?

FH is relatively easy to diagnose. In the UK most doctors diagnose FH clinically using the Simon Broome criteria. It is possible to confirm the diagnosis by using genetic testing, although this is not available everywhere. A blood sample is taken to provide DNA. FH is diagnosed by finding a “disease causing” alteration in the LDL receptor, ApoB or PCSK9 genes. People who have inherited an altered gene will have FH. Their close relatives (parents, brothers, sisters, children) will have a 1 in 2 risk of having inherited FH. Testing family members is crucial for early detection of the condition; doctors refer to this as cascade testing.

How early can FH be diagnosed?

People who have FH usually have a high total cholesterol and a high LDL-cholesterol from birth. It is recommended that parents with FH allow their children to be tested for FH, ideally after the age of 2 and before

What are the benefits of genetic testing

FH cannot skip a generation. However sometimes a person with the altered gene will not show the typical pattern of raised cholesterol we would expect of someone with FH. This may be because background genetic factors and a healthy diet and lifestyle mask the condition. However because they have the altered gene they can still go on to have a child with FH. This is why experts prefer to be able to confirm a diagnosis with genetic testing and why genetic testing is so helpful as it allows you to track FH through the family.

their 10th birthday. A confirmed diagnosis at a young age is important, as early changes in diet and eating habits can help reduce the impact of FH in later life.



IMPORTANT

FH is diagnosed by reference to specific criteria (Simon Broome criteria) and where possible through genetic testing. Genetic testing is not available everywhere.



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In families where FH has been diagnosed, children should be tested for FH ideally before they reach ten years of age. All children, but especially children diagnosed with FH, should be encouraged to eat healthily from an early age.

PART 2: Treatment

How can LDL-cholesterol be reduced?

There are two main steps that help to reduce cholesterol:

Step 1: A heart healthy diet

Step 2: Medication

A change in diet is the first step in reducing cholesterol levels but if this does not reduce cholesterol enough, appropriate medication must be started as well. This is true for all people with FH. A change in diet may reduce high cholesterol by 10–15%, but this will depend upon the individual and how many changes they can make to their diet. The aim of treatment (diet and medication) is to reduce the LDL-cholesterol level by half. For those who already have cardiovascular disease, the aim may be to lower cholesterol even further.

Very, very occasionally (about 1 in a million births) someone inherits an altered gene from both parents. This results in very, very high cholesterol levels and a very severe form of FH. In most of these cases drug treatment and dietary change are insufficient to reduce the extremely high cholesterol levels. In these people, LDL-cholesterol can be lowered mechanically by removing it from the blood using a dialysis-like cleansing technique called LDL apheresis.



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Dietary changes may lower LDL-Cholesterol by 10-15%. For most people with FH, this will not be enough and a change in diet should be combined with medication. For severe forms of FH an additional dialysis-like cleansing treatment (LDL apheresis) may be required.

Step 1: A heart healthy diet

What is a heart healthy diet?

A heart healthy diet is an important step in helping to lower your cholesterol and safeguarding your long term health. The aim is to gradually reduce the intake of saturated fat, while, at the same time, focusing on eating more unsaturated fats, whole grains, fruit, vegetables and pulses. There are some key foods that have a role in lowering cholesterol such as nuts, soluble fibre, plant sterol and stanol fortified foods and vegetable proteins such as soy.

Changing your diet takes time and effort and requires regular help, support and advice from a dietitian and from your doctor. What you eat on a regular basis is what matters; the occasional deviation from a healthy diet is unlikely to result in increased blood cholesterol.

For children with FH, dietary management should be supported by a change in diet for the whole family. It is important that healthy food habits are established early.

Heart healthy fats

All fat in food is a mixture of saturated and unsaturated fat. Saturated fats are mainly found in animal foods such as butter, lard, ghee, suet, full fat milk, cheese, yoghurt, fatty meats, meat products, hard margarines, palm oil, coconut oil and in most cakes, biscuits, pastries, pies, "fast food" and confectionary. These saturated fats increase cholesterol, while unsaturated fat from cereals, seeds, nuts and fish reduce or have a neutral effect on LDL-cholesterol. All people with FH should restrict their intake of saturated fat and replace some or all of this saturated fat with unsaturated fats.

Oily fish such as salmon, herring, sardines and mackerel are rich in omega 3 fatty acids, which may have a beneficial effect on circulation and heart rhythm. Omega 3 also help reduce triglyceride levels. To ensure a good intake of omega 3 fats, eating fish at the main meal at least twice a week, one portion of which should be oily is recommended. Vegetarian sources of omega 3 include dark green leafy vegetables, nuts (walnuts, almonds, peanuts), linseeds, soya products (tofu, soyabeans) and rapeseed, soya and walnut oils.

Do I need to limit cholesterol in food?

Some people with FH may be advised to limit their intake of cholesterol containing foods too, but you should discuss this with your doctor or dietitian. Dietary cholesterol is found in egg yolk, offal, meat, full fat milk, cream, cheese and butter. If you are cutting back on saturated fat you will already be limiting many of these foods too.

Soluble fibre from oats and barley, beans, peas, fruit, berries and vegetables, has a beneficial effect on cholesterol. Soluble fibres can bind cholesterol in the gut. This means more is excreted via faeces and so helps to reduce blood cholesterol levels. Foods high in fibre are also an important source of vitamins, minerals and antioxidants.

Do I need to buy foods fortified with plant sterols and stanols?

If eaten in the right amounts every day these may lower your cholesterol level by around 7–10%. They work by reducing the absorption of cholesterol rich bile acids from the gut. This means more cholesterol is lost via the faeces and results in more cholesterol being broken down to replace the lost bile acids.

You can find out more about cholesterol lowering diets on the HEART UK website including HEART UK's own Ultimate Cholesterol Lowering Plan (UCLP®).



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Five important guidelines for a heart-friendly diet:

1. Replace saturated fats with unsaturated fats
2. Eat more whole grains, nuts, pulses, vegetables and fruit every day



3. Choose meat free meals (fish, nuts, pulses, soya, quorn) more often
4. Limit food and drinks high in sugar or alcohol
5. Cook more meals from scratch, and limit takeaway and processed foods

Step 2: Using medication

How does medication affect LDL-cholesterol?

Statins are the most effective medicine for lowering your LDL-cholesterol. They work by increasing the number of working LDL receptors. This enables better uptake of LDL-cholesterol from your blood.

In some cases a statin may not lower your LDL-cholesterol enough and adding Ezetimibe, a cholesterol absorption inhibitor, may help. In a small number of people other treatments, such as resins or fibrates may be considered, but these are usually only prescribed by a lipid specialist.



PART 3: Cardiovascular disease and lipoproteins

What is cardiovascular disease?

Cardiovascular disease refers to diseases of the heart and blood vessels caused by atherosclerosis. Atherosclerosis involves a build up of cholesterol rich fatty plaques inside your blood vessels which cause them to narrow leading to reduced blood flow.

How does it happen?

Atherosclerosis is a slow process, but it can begin very early in life. The speed at which it progresses depends upon the number of risk factors that you have. It starts when cholesterol-filled cells become trapped in the inner wall of damaged blood vessels (see illustration on page 18–19). This causes inflammation, the invasion of more cells, further deposits of cholesterol, the formation of scar tissue and hardening, resulting in the formation of “plaque”. Plaques can narrow the blood vessels and reduce the flow of blood to the heart and other organs. In the heart, reduced blood supply can cause pain or discomfort, particularly after exercise. This is called angina. Plaques can burst resulting in damage to the inside of the blood vessel, and the formation

of a blood clot, which can severely restrict or block the blood supply. This causes an immediate lack of oxygen to the part of the organ supplied by the blood vessel and will result in damage (major or minor). When this happens in the heart it is called a myocardial infarction, MI or heart attack.

It is important to restore blood flow as quickly as possible after a heart attack to limit any damage. This can be achieved with blood clot-dissolving drug treatment, a direct mechanical removal of the blood clot using a catheter (a small tube designed to go into blood vessels) and by increasing the size of the blood vessel with a small balloon that is expanded inside the vessel, followed by insertion of metal netting in the blood vessel (stenting). These methods are often combined.



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Drug treatments include statins, resins, cholesterol absorption inhibitors and fibrates. Your doctor might prescribe one or more of these types of medicines. Your medication, a healthy lifestyle, and a heart friendly diet need to be continued throughout life.

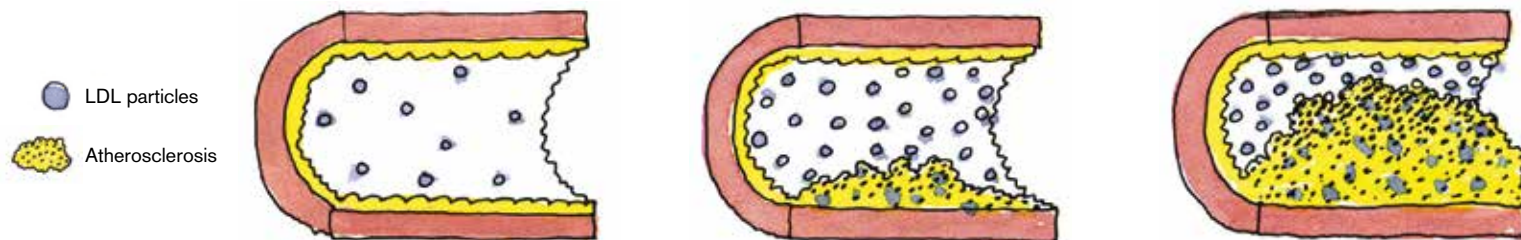


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Heart attack and stroke are the end result of atherosclerosis. Atherosclerosis is a hardening and narrowing of the blood vessels caused by a build up of cholesterol and inflammation to form plaque. Plaque decreases the size of the inside of a blood vessel. A damaged plaque can cause a blood clot, with very rapid narrowing or blockage of the blood vessel.

What are cardiovascular risk factors?

Cross-section of blood vessels in three stages showing the build up of cholesterol and the development of atherosclerosis.



Risk factors are characteristics that increase the likelihood of a person developing a condition such as atherosclerosis and cardiovascular disease. In a group of people with certain risk factors, more people will develop cardiovascular disease over a period of time, compared to a similar group of people without the risk factors. One of the most important risk factors for cardiovascular disease is a high level of LDL-cholesterol.

The speed at which your arteries narrow depends partly on how high your LDL-cholesterol level is, and how long you have lived with high cholesterol.

Other factors include diabetes and high blood pressure, which can be influenced by lifestyle factors such as being overweight, a low intake of fruit and vegetables, eating too much salt and limited physical activity. Smoking is one of the most important risk factors. Some risk factors cannot be changed such as your age, gender and having FH.

Is it possible to reduce the risk of cardiovascular disease in FH?

YES! Studies have shown that reducing high LDL-cholesterol reduces the risk of cardiovascular disease. By lowering LDL-cholesterol levels, individuals with early signs of cardiovascular disease can reduce their risk of further cardiovascular disease. However it is important to start reducing your LDL-cholesterol as soon as possible, and to reduce any other risk factors you might have. Stopping smoking is crucial for reducing the risk of cardiovascular disease.



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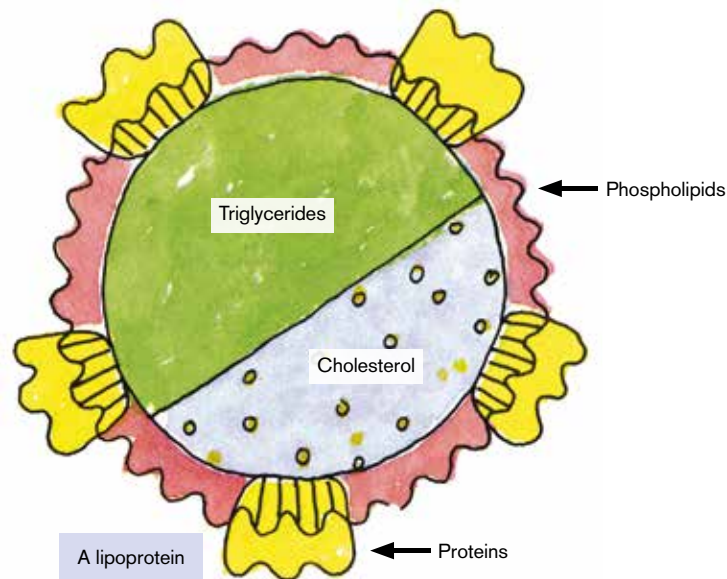
Risk factors such as high LDL-cholesterol, smoking, high blood pressure and diabetes increase the risk of developing atherosclerosis and heart disease. You can reduce these risk factors by eating a healthy diet, being more active and by taking the medicines your doctor prescribes.



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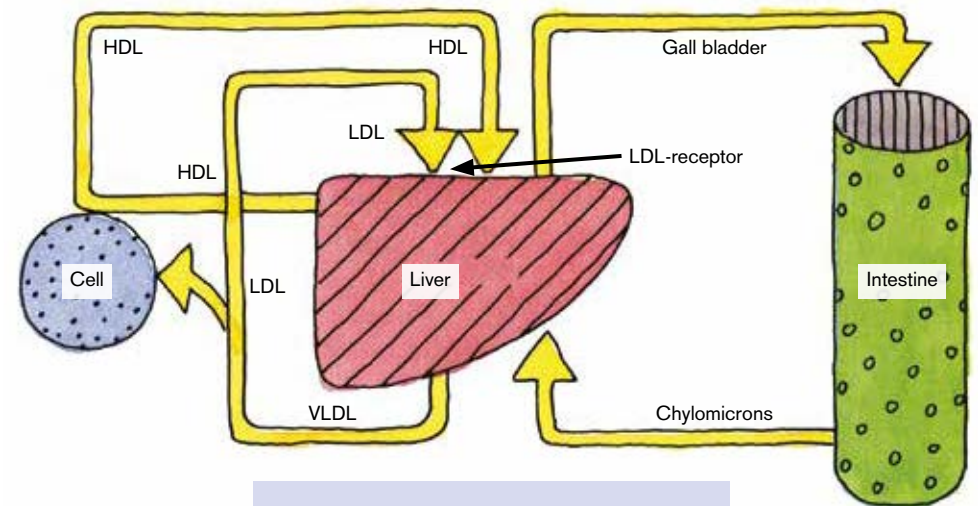
Lowering LDL-cholesterol in FH is important as this reduces hardening and narrowing of the blood vessels and decreases the risk of cardiovascular disease. Stopping smoking is crucial.

What are lipoproteins?



Lipoproteins are particles that transport fat around in the blood (see above illustration). Fatty substances called triglycerides and cholesterol cannot be dissolved in the blood and depend on a transport system that takes them from the organs that absorb or produce them (the gut and liver) to the cells.

The two most important lipoproteins in this transport system are called Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL). The cholesterol carried on these lipoproteins is referred to as LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C). Chylomicrons and VLDL are two other lipoproteins.



HDL-cholesterol and LDL-cholesterol work together to keep cholesterol in the blood at a "healthy" level.

The cholesterol transported in HDL is often called "good" cholesterol. One of the important functions of HDL is to transport excess cholesterol from the cells and tissues back to the liver. So having a high HDL-cholesterol is good. HDL may also

be able to remove some cholesterol from the walls of blood vessels. Doctors can distinguish the two types of cholesterol (LDL-cholesterol and HDL-cholesterol) in blood tests. It is important to achieve a "healthy" balance between the two.



IMPORTANT

The cholesterol transported in LDL is often described as "bad" cholesterol. This is because excess LDL-cholesterol can become trapped in blood vessels causing them to harden and narrow.



IMPORTANT

People with low LDL-cholesterol (and high HDL-cholesterol) are at lower risk of developing atherosclerosis. Being active, not smoking and having a healthy diet can increase your HDL-cholesterol.

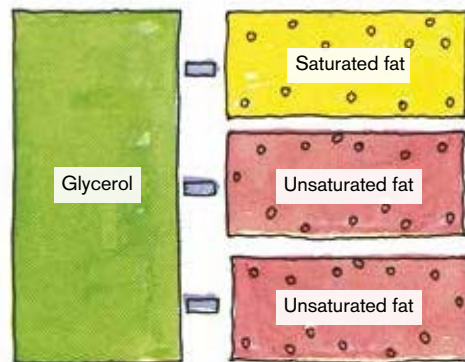
What are lipids, cholesterol and triglycerides?

Lipids are the name given to fatty substances, such as cholesterol and triglycerides, in the body. Your doctor can find out your levels of cholesterol and triglycerides by doing a blood test.

Cholesterol is an essential fatty substance used to build cell walls. It is also needed to make hormones, vitamin D and bile acids. All cells can produce cholesterol but most cholesterol is made in your liver and gut. The liver is also the main organ for breaking down cholesterol by converting it to bile acids. If your body makes excess cholesterol, absorbs too much, or cholesterol is broken down too slowly there will be excess cholesterol in your blood.

Saturated fats – these are mainly found in animal foods such as butter, ghee, lard, suet, meat and full fat dairy foods and foods made from these such as cakes, biscuits, pies, pastries, puddings and confectionary. Coconut oil and palm oil are also saturated fats.

Trans fats – these are made when unsaturated fats are hardened for food manufacture. They increase LDL-cholesterol and lower HDL-cholesterol. It is best to



Triglycerides are made from glycerol and fatty acids.

avoid them – you can do this by eating less processed and takeaway foods.

Triglycerides – this is another name for fat. Most of the fat in our food is in the form of triglycerides. Triglycerides also circulate in the blood, especially after a meal. They are made of glycerol and three (hence the tri in triglycerides) fatty acids (see image above). The fatty acids attached to each glycerol molecule can be saturated, or unsaturated, or a mixture of both.

Unsaturated fats – these are mainly found in vegetable sources such as nuts, seeds and vegetable, nut and seed oils, fish and avocado.

Important lifestyle questions



If you are an adult with FH it is OK to have a moderate amount of alcohol. This means not exceeding 3–4 units a day for a man and 2–3 units a day for a woman. Alcohol should be consumed with caution if your blood triglyceride level is high.



For adults at least 150 minutes of activity (or 75 minutes of very vigorous activity) is recommended each week. Children should be active for at least an hour a day.



On average smokers die 15 years earlier than non-smokers. People with FH who smoke are at very high risk of cardiovascular disease.



IMPORTANT

Cut down on foods that contain saturated fat and eat more foods that are rich in unsaturated fats.



IMPORTANT

On average smokers die 15 years earlier than non-smokers. People with FH who smoke are at very high risk of cardiovascular disease.

Glossary

Apo B: The LDL particle has a specific protein attached to it named Apolipoprotein B or ApoB. ApoB acts as a bridge between the LDL particle and the cells in your body that carry the LDL-receptor.

Bile acids: The liver produces bile acids from cholesterol. Bile acids are excreted into the gut when we eat. This helps fats in the gut enter the blood.

Cell: Cells are the building blocks of the body and can be compared to building bricks. The body is made up of approximately 100,000,000,000,000 (100 billion) cells.

Cholesterol: Cholesterol is an essential fatty substance. Most of our cholesterol is made by our bodies. We can also get cholesterol from foods that come from animals. Large amounts of cholesterol can be stored in the liver.

Chromosomes: The hereditary material present in the nucleus of each cell.

Chylomicrons: Large lipoprotein particles that transport lipids from the gut to cells.

Dietitian: A health professional who is an expert in diet and health. He or she will have undergone 4–5 years of university study.

DNA: A string of molecules that build our genes in our chromosomes.

Familial hypercholesterolaemia (FH): This is a hereditary condition caused by inheriting an altered gene. It results in high blood cholesterol.

Gall bladder: A kind of bag attached to the liver that stores bile.

Gene: A section of DNA that codes for a certain protein.

HDL-cholesterol: Also referred to as “good cholesterol”. It is OK to have a lot of this in your blood.

Trans fat/hydrogenated fat/hardened fat: These are all different names for a type of fat found in food products. This fat begins as an unsaturated fat and is then turned into a saturated fat. Conversion of unsaturated fat into saturated fat is quite common because saturated fat has a longer shelf life.

LDL-cholesterol: Otherwise referred to as “bad” cholesterol. It is best to only have a small amount of LDL-cholesterol in the blood.

Lipids: Blood fats.

Lipoproteins: Lipoproteins are small transport packages made up of cholesterol, triglycerides and proteins which circulate in the blood. There are various kinds of lipoproteins, the most important being HDL and LDL.

Myocardial infarction (MI): A heart attack. Usually this happens suddenly when the blood supply to the heart is blocked. Causes of myocardial infarction include high cholesterol and smoking.

Receptors: Receptors are located on the outside of the cells. They catch substances in the blood needed by cells. There are special receptors for lipoproteins. People with Familial Hypercholesterolaemia (FH) often have too few working receptors for LDL-lipoproteins. This means that the cholesterol from LDL remains in the blood. Excess circulating cholesterol can then become trapped in the walls of blood

vessels, eventually forming plaques, which cause narrowing.

Saturated fat: Found mainly in animal foods such as butter, ghee, lard, suet, meat and full fat dairy foods and foods made from these such as cakes, biscuits, pies, pastries, puddings and confectionary. Coconut oil and palm oil are also saturated fats. Eating too much saturated fat results in an increase in blood cholesterol.

Unsaturated fat: Found in vegetable sources such as nuts, seeds and vegetable, nut and seed oils, fish and avocado. We should replace saturated fats with these.

Triglycerides: Another word for fats. They are found in foods and in the blood. It is good to have low levels of triglycerides in the blood.

VLDL: When fat from the gut reaches the liver it is packed into large, fat rich particles, which are called VLDL (very low density lipoprotein).



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HEART UK – The Cholesterol Charity – provides expert support, guidance and education for people with FH and their families. Please call our Cholesterol Helpline or visit our website.

T: 0345 450 5988 E: ask@heartuk.org.uk W: www.heartuk.org.uk

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Dr. Leiv Ose, has worked with patients affected by lipid disorders since 1970. He has been involved in scientific activities related to that field; his main interests are preventative cardiology and genetic hyperlipidaemias such as Familial Hypercholesterolaemia (FH). He has been the head of the Lipid Clinic at Oslo University Hospital, Norway, since 1984.

HEART UK – The Cholesterol Charity

We hope you have learnt more about familial hypercholesterolaemia (FH), an inherited condition that runs in families and is caused by an altered gene.

HEART UK is the only charity in the UK dedicated to providing expert support, guidance and education for people with FH.

You can find out more about FH, how it might affect your family and things you can do to lower your risk by visiting the HEART UK website. You can also email, or call, our confidential Cholesterol Helpline, or visit our on-line patient community.

Cholesterol Helpline

T: 0345 450 5988

E: ask@heartuk.org.uk

Website

W: ask@heartuk.org.uk

Patient Community

W: www.healthunlocked.com/heartuk

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