The Aetiology and Epidemiology of Cardiovascular Disease

1.1 Introduction

The British Nutrition Foundation Task Force on Cardiovascular Disease: Diet, Nutrition and Emerging Risk Factors first reported in 2005 (Stanner 2005). That report has proved to be very popular and has attracted much interest but the field has moved on. This encouraged the British Nutrition Foundation to reconvene the Task Force to produce an updated report on the field.

In the intervening years, many things have changed. Interest in antioxidant vitamin supplementation has decreased with the publication of several trials reporting negative, or adverse, outcomes. At the same time, the scientific
understanding of antioxidant mechanisms has progressed, so these failed trials can be seen in perspective. The importance of physical activity in protection against cardiovascular disease (CVD) has been emphasised, along with an understanding that its opposites, physical inactivity and sedentary behaviour, have detrimental effects. There has been an explosion of interest in, and understanding of, the importance of colonic microorganisms—sometimes called the microbiome—to human health and disease, and this report includes a new chapter on that topic (Chapter 11).

The epidemiology of CVD has changed subtly. The global burden of CVD has continued to increase, particularly reflecting the increased age and obesity of populations in many countries. A divergence has opened up in CVD mortality rates, which are lower in Japan and the Mediterranean countries such as France, Spain, Portugal, and Italy, and highest in Eastern European countries, such as Russia and Ukraine. Mortality from CVD, including coronary heart disease (CHD) and stroke, has continued to decrease worldwide, probably because of improvements in primary and secondary prevention and improved medical care. However, concern has been expressed that improved survival after myocardial infarction (MI) or stroke may outweigh falling incidence of new events, leading to an increase in disease prevalence and, therefore, a greater population burden of serious morbidity and increased treatment need.

The intervening years have also seen some controversies over diet and CVD. The widespread acceptance in 2005 of an adverse role for dietary saturated fat has been challenged, and this controversy continues—in this report we will review what evidence is available (see Section 13.4.3). In the previous edition of this report we discussed the value of low-fat diets in CVD prevention. In the time since, there has also been great interest in low-carbohydrate diets, which have been popularly promoted in the media as a means of weight loss, including by a number of celebrities. The UK’s Scientific Advisory Committee on Nutrition (SACN) reported on Carbohydrates and Health in 2015 (Scientific Advisory Committee on Nutrition 2015). The report found that ‘the hypothesis that diets higher in total carbohydrate cause weight gain is not supported by the evidence from randomised controlled trials’, but did emphasise a potentially adverse role for ‘sugars and sugars-sweetened foods and beverages’, especially in relation to risk of type 2 diabetes (see Section 13.4.4).

1.2 Aims

The aims of this chapter are:

- To introduce and explain the topic of CVD and its components, CHD, cerebrovascular disease and peripheral vascular disease.
- To introduce approaches used to investigate the relationship between risk factors and disease.
- To distinguish classic, or established, risk factors from emerging risk factors.
- To explain genetic factors and how they modify CVD risk and its relationship to diet/nutrition.
- To review the worldwide epidemiology of CVD and its components.
- To introduce the Task Force’s report on Diet, Nutrition and Emerging Risk Factors for CVD.

1.3 Definitions

This report is concerned with factors that relate to the risk of developing CVD and how these may be influenced by diet. CVD includes arterial disease affecting the blood supply to the heart or to the brain, or to the peripheral regions of the body. The term CVD refers to a number of individual diseases affecting the cardiovascular system. In some cases, in this report, we will use the term ‘cardiovascular diseases’ when we wish to make this clear. Cardiovascular diseases account for over half of all deaths in middle age and one-third of all deaths in old age in most developed countries. Globally CVDs account for 30% of all deaths.

There are many links between CVD and metabolic derangements, especially type 2 diabetes and obesity-related traits. For that reason, the term ‘cardiometabolic risk’ is often used to cover the combined risk of both CVD and metabolic disease, and will be used in this way throughout this report.

Research over the last decade has led to a greater understanding of the independent contribution of several factors identified in the initial report to cardiovascular risk. Although we have continued to use the term ‘emerging risk factors’ throughout this report to distinguish them from the classical risk factors, many are now established in terms of their ability to predict CVD risk.
1.3.1 Coronary Heart Disease

CHD is a condition in which the walls of the arteries supplying blood to the heart muscle (coronary arteries) become thickened. This thickening, caused by the development of lesions in the arterial wall, is called atherosclerosis; the lesions are called plaques. Atherosclerosis can restrict the supply of blood to the heart muscle (the myocardium) and may manifest to the patient as chest pain on exertion (angina) or breathlessness on exertion. If the cap covering the plaque ruptures, exposing the contents to the circulation, the blood may clot and obstruct the flow completely, resulting in a MI or heart attack. CHD is also known as ischaemic heart disease.

The term acute coronary syndromes is used to denote a hospitalisation for unstable angina (angina without an obvious trigger), or thrombolysis (treatment to dissolve clots) for suspected MI or an emergency revascularisation procedure for relief of ischaemic chest pain at rest.

There are several causes of sudden death, but most are related to CHD or cerebrovascular disease (see Section 1.3.2). Sudden cardiac death may be due to MI or to cardiac arrhythmia. Cardiac arrhythmias are situations where the heart rate becomes irregular, and/or too rapid or too slow. Arrhythmias may be provoked by intercurrent stress or illness but are more common, and more frequently fatal, in hearts previously damaged by ischaemic heart disease or any other cause of cardiac dysfunction, such as raised blood pressure (hypertension – usually considered to be 140/90 mm Hg or higher) or excess alcohol consumption. The main risk factors for arrhythmias and sudden cardiac death are thus very similar to those for CHD.

CHD is not the only form of heart disease. There are congenital abnormalities of the heart, some with a genetic cause, and acquired abnormalities. Among the latter is a grouping of changes which include impaired ability of the heart to pump, impaired ability to relax in diastole, and remodelling of the ventricles, especially thickening of the walls of the left ventricle, often with dilatation of the left ventricle observed as left ventricular hypertrophy. Ultimately these changes may lead to heart failure.

Underlying these changes may be cardiomyopathy – diseases of the heart muscle. Cardiomyopathy is a natural consequence of a MI, which results in death of some of the heart muscle and its replacement with fibrotic scar tissue. But cardiomyopathy can be unrelated to coronary and ischaemic disease. Continued deterioration of myocardial function may lead to heart failure. This is characterised by failure of the heart to pump sufficiently to perfuse organs such as the kidney. The kidney will respond to this by signalling, via the renin-angiotensin system, to increase blood pressure, placing further strain on the heart. Heart failure is manifest by fluid accumulation (hence swelling of legs, in particular), shortness of breath, and tiredness.

There is a special form of cardiomyopathy that occurs in diabetes – diabetic cardiomyopathy, which is characterised by diastolic dysfunction (poor relaxation of the heart muscle in diastole). As diabetes is particularly associated with small vessel damage, which can lead to ischaemia, this condition can be difficult to manage.

These deleterious changes in heart function unrelated directly to CHD are not strictly within the remit of this report. The primary aetiology is not related to impaired blood flow to the myocardium (true CHD), unless these are responses to MI. However, the most common factors underlying heart failure are CHD, hypertension, and diabetes. Thus, there may be much overlap with CHD in risk factors and natural history, depending on the origin of heart failure.

1.3.2 Cerebrovascular Disease

Cerebrovascular disease involves interruption of the blood supply to part of the brain and may result in a stroke or a transient ischaemic attack. There are two main types of stroke: ischaemic stroke and haemorrhagic stroke. Globally, in 2010, these accounted for 68% and 32% of incident strokes, respectively (Krishnamurthi et al. 2013). However, the contribution of ischaemic stroke is greater in Western countries, with estimates exceeding 80% in many studies (Heuschmann et al. 2009).

Ischaemic stroke involves a blockage in the blood supply to the brain. The loss of blood supply to part of the brain may lead to irreversible damage to brain tissue. The blockage most commonly arises from the process of thromboembolism, in which a blood clot formed somewhere else (e.g. in the heart or in the carotid
artery) becomes dislodged and then occludes an artery within the brain (cerebral arteries). Narrowing of the intracerebral arteries with atherosclerotic plaque may increase the risk, and may also lead to local formation of a blood clot. The aetiology is similar to that of CHD. In haemorrhagic stroke, there is rupture of a blood vessel supplying the brain, with release of blood into the brain (haemorrhagic stroke). High blood pressure (hypertension) is a major risk factor for haemorrhagic stroke, but otherwise the aetiology is different and will not be considered in detail in this report.

1.3.3 Peripheral Vascular Disease

Peripheral vascular disease (PVD) involves atherosclerotic plaques narrowing the arteries supplying regions other than the myocardium and brain. A common form involves narrowing of the arteries supplying blood to the legs. The result may be pain on exercise (claudication). In more severe cases, impaired blood supply leads to death of leg tissues, which require amputation (Baumgartner et al. 2005; Sontheimer 2006).

1.4 Pathogenesis

CVDs, whether affecting the coronary, cerebral, or peripheral arteries, share a common pathophysiology involving atherosclerosis and thrombosis (or clotting). The causes of CVD and why it affects some individuals and not others, or why it more severely affects one region rather than another, are discussed later in this chapter and elsewhere in this report.

1.4.1 Atherosclerosis

The term atherosclerosis comes from the Greek athere, meaning porridge or gruel and referring to the soft consistency of the core of the plaque

---

**Box 1.1 Terminology Used in the Report**

**Saturates, Polyunsaturates, Monounsaturates**

Most dietary fat is in the form of triglycerides. Fats are grouped according to the predominant type of fatty acid that they contain. As saturated fats are referred to as saturates on food labels, this term will be used throughout this report. Similarly, polyunsaturates and monounsaturates will be used to denote polyunsaturated and monounsaturated fats, respectively. The abbreviations SFA, MUFA, and PUFA are also in common usage and have been used in some tables to denote saturated, monounsaturated, and polyunsaturated fatty acids, respectively.

Although fatty acids are generally grouped according to the degree of unsaturation (number of double bonds), it should be noted that their chemical and biochemical properties are also dependent upon chain length, and position and geometric configuration of double bonds (see Section 4.3.1). The position of the double bonds is normally referred to the terminal (or omega) carbon atom in the chain. This gives rise to families of unsaturated fatty acids known commonly as omega-6 and omega-3; in this report we will refer to these as n-6 and n-3 polyunsaturates, respectively. Most double bonds in dietary fatty acids are in the cis geometrical configuration and, unless otherwise stated, this should be assumed to be the case. However, some fatty acids have double bonds in the trans configuration: these are usually the result either of hydrogenation in ruminant animals (so are found in dairy products, for instance) or of catalytic hydrogenation (hardening) of unsaturated vegetable oils. Fats containing such trans unsaturated fatty acids are generally referred to as trans fats.

The effects of these different types of fats will be discussed in subsequent chapters (see overview in Chapters 4 and 13). For common food sources of the different types of fatty acids, see Table 4.1.

**Triglycerides**

The traditionally used term triglycerides will be used throughout this report, but a more biochemically accurate term is triacylglycerols (often abbreviated to TAG).

For more information on dietary fats and fatty acid structures, see Gurr et al. (2016).
The lipid of the atherosclerotic plaque is mainly cholesterol from low-density lipoprotein (LDL) particles that have left the circulation. Current understanding is that the LDL particles must be chemically modified in some way before they are taken up by the so-called scavenger receptors of macrophages (white blood cells that have become resident in the arterial wall). This chemical modification may involve lipid peroxidation (see Section 9.8), which leads in turn to peroxidation of the large protein known as apolipoprotein-B100 that is associated with each LDL particle. While uptake of cholesterol by cells is normally tightly controlled so that cellular cholesterol levels do not become excessive, lipid uptake by the scavenger receptor pathway is not subject to such regulation. Therefore, the macrophages may engulf large amounts of lipid, giving them a foamy appearance under the microscope. These so-called foam cells are characteristic of the atherosclerotic plaque.

Accumulation of foam cells in the arterial wall leads to the first visible stage in atherosclerosis, formation of a yellowish, minimally raised spot (the spots later merging into streaks) in the arterial wall. These are known as fatty streaks. The process at this stage must be largely reversible since more than 40% of infants coming to post-mortem examination during the first year of life have fatty streaks in their aortas (Woolf 1990).

These macrophages send chemical signals that trigger further events associated with atherosclerosis. Blood monocytes and T-lymphocytes (other types of white blood cells) adhere to the cellular lining of an artery, the endothelium. The monocytes migrate into the subendothelial space where they differentiate into further macrophages and engulf further lipid. Development of the atherosclerotic plaque involves proliferation of smooth muscle cells of the arterial wall and the elaboration of a connective tissue matrix, forming a fibrous cap to the lesion (Fig. 1.1). These processes may be seen as reparative, and this has led to the description of these events as the ‘response to injury’ hypothesis of atherosclerosis.

Within the lesion there may be breakdown of dead macrophages and release of their contents, with the formation of a semi-liquid pool of extracellular lipid. At the same time, calcification of the arterial wall leads to hardening (lack of elasticity). The lid of the lesion may remain firm, in which case the lesion may protrude into the arterial lumen.
arterial lumen, obstructing flow but not causing acute damage. Some plaque caps, however, become unstable and are damaged, exposing the contents of the plaque. This results in the normal response to vessel wall damage – thrombus formation (blood clotting).

1.4.2 Blood Clotting

The process of blood clotting will be described fully in Chapter 8, but, briefly, it begins when the endothelial lining of a blood vessel is damaged, exposing cells, and surfaces that are normally covered by the endothelium (Fig. 1.2). This may happen at the site of an atherosclerotic plaque, especially following rupture of the plaque cap. Proteins thus exposed activate the clotting pathway. Formation of a clot depends upon a cascade of proteolytic reactions, with enzymes initially in an inactive, precursor (or ‘zymogen’) form becoming activated sequentially. Because of the cascade nature of this process, there is amplification, each enzyme catalysing the production of many of its product enzymes. In the course of this activation process, blood platelets are drawn to the site of injury where they aggregate and form a primary plug. Upon this is built a mesh of fibrils of the protein fibrin, formed by cleavage of the circulating precursor protein fibrinogen. If the coagulation process is brought about by bleeding outside the blood vessel, then the product is known as a clot. If it is brought about by damage to the endothelium, as, for instance, at the site of an atherosclerotic plaque, then the product is known as a thrombus. Part of the thrombus may become loose and then be carried to other sites where it can lodge and obstruct flow, the process of thromboembolism (e.g. in ischaemic stroke).

Not surprisingly, there is also a pathway for the dissolution of clots or thrombi, the fibrinolytic pathway (also known as fibrinolysis); the process of coagulation is a balance between the activities of the coagulation and fibrinolytic pathways. As will be described later, components of both these pathways may be risk markers for CVD.

1.4.3 Raised Blood Pressure/Hypertension

Blood is pumped around the body by the left ventricle of the heart. The pressure resulting from this process is opposed by the resistance of the vessels through which the blood flows, and the balance of these two opposing forces is known as blood pressure. Blood pressure is conventionally recorded as systolic (highest) over diastolic (lowest) pressure and needs to be sufficiently high to ensure adequate blood flow to the brain and
Elevated blood pressure is strongly related to death from CHD or stroke, and indeed to death from all forms of disease involving blood vessels (Prospective Studies Collaboration 2002). Systolic blood pressure is slightly more closely related to risk than diastolic blood pressure. The strength of the association is seen more clearly when blood pressure is measured on repeated occasions rather than a single measurement – the phenomenon known as regression dilution (Clarke et al. 1999, 2002). The effect of blood pressure on CVD mortality is seen even at low levels of hypertension, sometimes called prehypertension (Huang et al. 2014). Randomised trials of blood pressure-lowering treatments have confirmed that there is a significant reduction in major cardiovascular events (MI and stroke) but they have not shown a reduction in mortality from CVD (Lv et al. 2012).

There are many causes of hypertension, including defined hormonal and genetic syndromes, renal disease, and multifactorial racial and familial factors. In most cases where the mechanism of hypertension is understood, the hypertension can be ascribed to one or more of the key factors listed in Table 1.1. In addition, there are other less common causes, such as hypercalcaemia, raised intracranial pressure, hormonal diseases such as phaeochromocytoma, structural arterial abnormalities (e.g. congenital coarctation of the aorta), and inflammatory conditions of the blood vessels such as polyarteritis nodosa.

Several diet and lifestyle-related risk factors (some of these are covered in other chapters) contribute to hypertension (Table 1.1), although as many of these factors co-segregate, it is not entirely clear to what extent they are acting independently. However, it is clear that removing these factors will often reduce hypertension.

### 1.4.4 Relationship of Risk Factors to the Pathological Processes

The nature of the processes described above provides a framework for understanding how certain factors may predispose to atherosclerosis. The role of plasma lipids explains why elevated serum total cholesterol level has long been recognised as a predisposing factor to atherosclerosis. However, evidence has accumulated over the past few decades that has highlighted the importance of other processes, including an impairment of endothelial function, the tendency to oxidation in the subendothelial space, the inflammatory processes involved in formation of a plaque, and blood clotting. In this report, the evidence for emerging risk factors for CVD relating to these processes is considered in some detail.

### 1.4.5 Genetic Risk Factors for Cardiovascular Disease

There is a strong genetic background to CVD risk and to many of the risk factors considered in this report. In other words, there is an inherited component of risk, although there is also an environmental component: two people with the
same genetic background may not show the same risk because of differences in diet, lifestyle, socioeconomic status, etc. This section is intended to provide a brief background to genetic factors that will be relevant to all sections of this report.

The human genetic material (genome), which is present in most cells, codes for about 20,000 genes (estimates of total protein- and RNA-coding genes range up to 30,000). Each gene contains the code for the amino acid structure of a single protein. All the genes are encoded within DNA, which itself is made up of a series of deoxynucleotides. The enormous DNA molecules (and their attached supporting framework) are called chromosomes, and each human has 23 pairs of chromosomes, one of each pair coming from each parent; thus, there are potentially two alternative codes (alleles) for each gene on the chromosome. These 20,000 or so genes may also produce ‘splice variants’ whereby different sections of the gene product are joined at the messenger RNA (mRNA) level; this may increase the number of protein variants to about 100,000. The structure and function of all these proteins and splice variants depend upon the genetic code within an individual’s DNA.

Some of the risk factors in this report are ‘emerging’ because of secular or temporal trends in which progressive changes in an environment affect a population; for example, the progressive increase in adiposity in Western society (see Section 1.6.7). However, within a population at a given time, it is often genetic variations that determine which individuals will be most affected. Genetic factors can mean that one individual will be more obese than another, whatever environment they share; or, for a given degree of obesity, more or less at risk of CVD. Thus, the study of newly emerging risk factors may involve both understanding changes in the environment as well as the genes that determine which individuals are likely to be most affected. This process is referred to as gene–environment interaction.

Susceptibilities to CVD and regulation of metabolic events in relation to food intake have been shown to be genetically regulated. The inter-individual variability is likely to depend on differences in the genetic code between people. The genome is variable and within almost every gene a certain degree of genetic variability can be detected. If this is a rare change, normally defined as an allele frequency of less than 1/100 (i.e. found in less than 1 in 50 people since each person has two copies of the gene), it is called a mutation. The overwhelming majority of rare mutations are recessive, which means that carriers of one copy of a mutated allele are unaffected and the disease is only precipitated if two mutated alleles are carried. This is the case for most ‘inborn errors of metabolism’. Inborn error of metabolism is a term used to describe the condition that arises from an inherited mutation in a gene that affects the activity of the protein that it encodes (usually rendering it inactive). The protein concerned may be, for instance, an enzyme, a carrier protein or a transporter, a receptor, or a transcription factor. Because the term is used to refer to single-gene mutations (‘monogenic’ conditions), these conditions are inherited in a Mendelian fashion. They are catalogued in the freely available resource: Online Mendelian Inheritance in Man (OMIM) (© Johns Hopkins University) and referred to by their OMIM catalogue number.

Most differences between people’s DNA sequences, however, are due to more commonly occurring single nucleotide polymorphisms (SNPs), although deletions and insertions of deoxynucleotides are also seen. In an SNP, one single base-pair in the DNA is different from the most common. When SNPs occur within the coding region of a gene, this may lead to an amino acid exchange in the gene product with an impact on function. However, because more than one codon (sequence of three bases in DNA) codes for a given amino acid, the SNP may be ‘silent’, i.e. the protein produced is identical. In addition, SNPs in the non-coding region may affect the transcription of the gene and thus alter gene function.

Alterations in genes that are linked to disease may be found in different ways. For Mendelian conditions, often there is a relatively small number of cases, and DNA from these people and their families is compared with DNA from non-affected people to find a region that is different: this can then be narrowed down until the affected gene is identified. This can lead to new discoveries in biology. There are several examples in lipid metabolism; for instance, the cholesterol transporter ABC-A1 (gene ABCA1) was identified through searching for the gene affected in Tangier disease (OMIM catalogue
no. 205400), a condition in which high-density lipoprotein (HDL)-cholesterol concentrations are abnormally low (see Section 4.14). ABC-A1 is now under investigation as a possible drug target. The gene alterations responsible may be traced through knowledge of the physiological or pathophysiological pathway or process involved (known as ‘candidate genes’). This ‘candidate gene approach’ can be helpful to understand some aspects of gene function, but it has also become clear that most disease-causing genes have not been detected by this approach.

Most conditions with an inherited component involve alterations in many genes (‘polygenic’ conditions). They are not inherited in a simple Mendelian fashion. This is true, for instance, for most cases of elevated cholesterol levels, for most obesity and for most type 2 diabetes: no single gene is the cause. In such conditions, genome-wide scans (generally known as genome-wide association studies, GWAS) have been employed to detect genes involved in disease processes. This may involve a large collection of big families or even larger collections of affected sibling pairs, or more commonly now large collections of individuals in whom physiological or metabolic variables have been measured [e.g. cholesterol level, body mass index (BMI)], known as ‘quantitative traits’. In essence, after defining the phenotype in every individual, the likelihood of shared gene markers and phenotype is analysed to ring-fence certain areas in the genome. These areas are later searched for disease genes.

Diet and nutritional effects on CVD can largely be seen in the context of gene–environment interactions. Metabolic stress, such as obesity or an unbalanced diet, may reveal dysfunction in a susceptible gene which contains variants with different functional properties. For example, the genetic defects causing familial hypercholesterolaemia have minimal clinical impact in environments with low-fat diets such as rural China. Other examples of this are given throughout this report. Such interactions are known as diet–gene interactions. A well-known example is the common polymorphism in the gene apoE coding for apolipoprotein E, a constituent of lipoproteins carrying cholesterol. There are three common alleles of the apoE gene and they determine how an individual will respond to changes in dietary fat and cholesterol. This is discussed in more detail in Section 4.14.

Genetics are also relevant to the CVD risk factors discussed in this report as a means of testing hypotheses. Sometimes there is a clear association of a biochemical measure with CVD risk. C-reactive protein (CRP), a marker of inflammation, is an example. It is not clear from this association, however, whether CRP is causal in the CVD pathway or whether it is simply a marker. Sometimes it is possible to intervene, for example with drugs, to alter the biochemical measure and look for effects on CVD outcomes. Lowering of serum cholesterol with statin drugs is an example. The fact that statin drugs reduce CVD deaths is almost universally taken to mean that cholesterol is part of the pathway to CVD. But in other cases, no such intervention is available. There may, however, be gene alterations (typically, common polymorphisms) that are known primarily to affect the biochemical variable. This is the case with CRP; a number of gene variants are associated with variations in CRP level. That provides a means of testing whether ‘primary’ variations in CRP level affect CVD risk. The case of CRP is discussed further in Section 5.6.1. A similar process has been applied to the sulphur-containing amino acid homocysteine, which is also a marker for CVD risk (see Section 10.3). This technique has become known as Mendelian randomisation.

Beyond alterations in the sequence of the bases in DNA, there are changes that affect the functioning of the DNA. The bases in the DNA may be chemically altered (typically by methylation of cytosine), or the proteins that wrap the DNA up into chromosomes, the histones, may be altered, and such changes will affect the expression of genes (i.e. their transcription – the reading off into mRNA). This is the field of epigenetics. It has many implications for the topics discussed in this report. First, the methylation process itself involves a biochemical pathway of ‘one-carbon metabolism’ that seems to be closely linked to CVD risk, with the component homocysteine having attracted most attention: this is discussed in more detail in Section 10.3. In addition, epigenetic mechanisms provide a means by which alterations in gene expression, perhaps with implications for CVD risk, can be present throughout life, and even potentially passed between generations, without alteration of the sequence of bases in the DNA. This topic is fully discussed in Section 2.10.
1.5 Epidemiology of Cardiovascular Disease

1.5.1 The Burden of Cardiovascular Disease

CVD is the leading cause of death worldwide, accounting for around 17.3 million deaths each year (31% of all deaths globally). In 2012, it was responsible for the largest proportion of non-communicable disease deaths under the age of 70 (37%) (World Health Organization 2014b). Of these deaths, an estimated 7.4 million were due to CHD and 6.7 million were due to stroke (World Health Organization 2014b). Low- and middle-income countries account for around 82% of the global CVD death rate (World Health Organization 2014b). CVD mortality rates vary considerably between higher income countries, being lower in Japan and the Mediterranean countries such as France, Spain, Portugal, and Italy, and highest in Eastern European countries, such as Russia and Ukraine (Townsend et al. 2012) (Fig. 1.4).

CVD is the major cause of death in the US, causing nearly 800,000 deaths per year (one in three deaths) (Centers for Disease Control and Prevention 2015) and it is a leading cause of mortality (along with cancer and dementia) in the UK; in 2014, it was responsible for 27% of all deaths (around 155,000 deaths), including a quarter of premature deaths (before 75 years) in men and 17% in women (Fig. 1.5) (Townsend et al. 2015). CHD by itself is a common cause of death in the UK, with 15% of men and 10% of women dying from the disease in 2014, with stroke accounting for a further 6% and 8% of deaths, respectively (Townsend et al. 2015).

CVD is also a major cause of ill health and disability. It has been estimated that there are 1 million men and nearly 500,000 women in the UK who have survived a heart attack, nearly 600,000 men and 600,000 women who have had a stroke, and over 1.6 million men and 1 million women have angina (Townsend et al. 2012). A report by the Centre for Economics and Business Research, published in 2014, estimated the healthcare costs of CVD in the UK to be £11.3 billion, with costs from lost work days from mortality and morbidity to be £3.9 billion and £151.6 million, respectively. This resulted in total estimated costs of CVD in the UK of £15.2 billion (Centre for Economic and Business Research 2014). The estimated cost to the EU economy is almost 196 billion Euros per year (European Heart Network et al. 2012).

1.5.2 Temporal Trends

Globally, the number of deaths due to CVD increased by 41% between 1990 and 2013, climbing from 12.3 million deaths to 17.3 million deaths (despite a 39% decrease in age-specific death rates) (Roth et al. 2015). More than 80% of these deaths occurred in low- and middle-income countries (World Health Organization 2014b). It is envisaged that the global prevalence will continue to increase and is expected to be responsible for more than 23.6 million deaths by 2030 (Smith et al. 2012), a figure that is largely attributable to today’s dramatic demographic changes with increasing proportions of ageing and obese groups.

However, examination of CVD mortality trends across countries reveals considerable
variability in changes in prevalence rates since the 1950s. Increased death rates from CVD have been noted in developing countries undergoing the ‘epidemiological transition’, where control of infectious, parasitic, and nutritional diseases allows most of the population to reach the ages at which CVD manifests itself. Accompanying changes in diet and lifestyle are also leading to a growing epidemic of overweight/obesity and type 2 diabetes in these countries, which are major risk factors for CVD (see Section 1.6.7).

In fact, by the mid-1990s, CVD had become the leading cause of death in developing as well as developed countries (Pearson 1999). The former socialist economies in Central and Eastern Europe also saw steep increases in CHD mortality until the beginning of the twenty-first century (European Heart Network et al. 2012). Since 2000–2005, however, rates appear to have been declining in the majority of Eastern and Central European countries.

The former socialist economies in Central and Eastern Europe also saw steep increases in CHD mortality until the beginning of the twenty-first century (European Heart Network et al. 2012). Since 2000–2005, however, rates appear to have been declining in the majority of Eastern and Central European countries.

In contrast, CHD mortality rates have remained relatively low in Japan and several European Mediterranean countries (Beaglehole 1999; Mirzaei et al. 2009) but have been declining since the 1960 or 1970s in most European countries, North America, and Australia/New Zealand (Sarti et al. 2000; Tunstall-Pedoe et al. 2000; Townsend et al. 2012). The UK has also experienced declines, with mortality from CHD falling at one of the fastest rates in Europe (Fig. 1.6) (Townsend et al. 2012). Between 1974 and 2013, UK age-standardised CHD death rates declined by 81% for those dying before age 75 years (Townsend et al. 2015).

However, in recent years, CHD death rates have been falling relatively slowly in the younger age groups and fastest in those aged 55 years and over. For example, between 2000 and 2010, there was a 43% fall in the CHD mortality rate in men aged 55–64 years compared with a 21% fall in men aged 35–44 years (Townsend et al. 2012).

Stroke mortality has also fallen in most European countries. The combined mortality rate in 27 European countries fell by over 40% for both men and women between 1986 and 2006 (Scarborough et al. 2009). However, death rates from stroke vary considerably within those areas of Europe where comparable data are available, with mortality rates being higher in Central Europe, than in Northern, Southern, and Western Europe (Fig. 1.7). In the UK, death rates from haemorrhagic stroke have been falling over the twentieth century, while secular trends in deaths from ischaemic stroke have
Cardiovascular Disease

paralleled those of CHD mortality (i.e. fallen from a peak in the 1970s) (Lawlor et al. 2002). Overall stroke rates decreased by 78% between 1968 and 2013 across the UK (Townsend et al. 2015), and mortality rates from stroke in those aged under 75 years fell by 85% during this period (Fig. 1.8) (Townsend et al. 2015).

The decline in CVD mortality experienced by most Westernised countries has been attributed to improvements in primary and secondary prevention and improved medical care, although the specific impact of each is debated. Morbidity data are less reliable than mortality data so trends are harder to discern. In the 1990s, the WHO MONICA project identified the decline in CHD events as the most significant contributor to the decline in mortality but this did not infer decreased overall CVD prevalence (Tunstall-Pedoe et al. 1999). However, concern has been expressed that improved survival after MI or stroke may actually outweigh falling incidence of new events, leading to an increase in disease prevalence and, therefore, a greater population burden of serious morbidity and increased treatment need. Davies and colleagues, for example, reviewed the changing trends in CHD prevalence and associated

Fig. 1.5 Deaths by cause in men and women aged under 75 years in the UK, 2010. Source: Townsend et al. (2015).
The Aetiology and Epidemiology of Cardiovascular Disease

Fig. 1.6  Percentage change in coronary heart disease death rates, by sex, in selected countries, 1998–2008. Source: Townsend et al. (2012).

Fig. 1.7  Death rates from stroke, men, and women of all ages, latest available data, Europe. Source: Scarborough et al. (2009).
mortality in the UK from 1996 to 2005 and concluded that the most significant contributor to increased prevalence was due to increased survival combined with an ageing population (Davies et al. 2007). Evidence from several countries has suggested that a substantial proportion of the observed reductions in CVD mortality has been due to reductions in both incidence and case fatality rates (Nichols et al. 2013). Hospital discharge data can be used as an indicator of morbidity. The WHO European Region’s Health for All Database reported an annual rate of hospital discharges for CVD in Europe in 2010 of just over 2500 per 100,000 population, although up-to-date data are not available for all countries. In 2000, the rate was lower at 2234 per 100,000 population (World Health Organization 2014a).

In the UK, national surveys (e.g., the Health Survey for England and the General Household Survey) suggest that, while mortality from CVD is falling rapidly in the UK, morbidity has not been falling to the same extent. The Health Survey for England (2006) found an increase in the prevalence of CVD from 7.1% to 8.1% in men and 5.2%
to 5.6% in women between 1994 and 2006. These increases were found in the majority of age groups but the most consistent increases have been seen in the oldest age group (75 years and over) (NHS Digital 2008). The General Household Survey also suggests that the overall prevalence of CVD rose in Great Britain from 1988 with a peak in 2006, with rates declining slightly in recent years (Townsend et al. 2015) (Fig. 1.9). A study examining trends in the epidemiology of stroke in the UK between 1999 and 2008 reported stroke incidence to have fallen by 30% over this period but also demonstrated substantial improvements in survival after stroke (56-day mortality nearly halved over the 10-year period) and suggested that improved drug treatment in primary care is likely to be the major contributor to this (Lee et al. 2011b). Quality & Outcomes Framework data have indicated slight increases in prevalence of stroke in recent years (2005/2006–2013/2014) (Townsend et al. 2015). Unfortunately, there is little evidence of significant improvements in some CVD risk factors acting at the primary prevention level (preventing onset of disease) among the adult UK population (see Section 1.6.7).

1.5.3 Variation in Cardiovascular Disease in the UK

CVD (predominantly CHD) is significantly higher among males than females, although the difference in risk varies widely between countries. In the UK, a man is more than twice as likely to die from premature CHD than a woman (Townsend et al. 2015). Although men and women share most of the major risk factors for heart disease (see Section 1.4), it has been speculated that before the menopause, endogenous oestrogens may confer some protection against CHD in women. Although hormonal factors may be important contributors to lower CHD rates among women, secular and geographical trends indicate that environmental factors (i.e. diet and lifestyle) are also likely to play a part (Lawlor et al. 2001). Rates of CHD among women increase around the fifth to sixth decade of life, indicating that any protective effect is lost after this time. This may be linked to changes in fat distribution as longitudinal data support an increase in central body fatness occurring during the menopausal transition (Guthrie et al. 2003).

There are also marked regional, social, and ethnic differences in risk of CVD within the UK. Mortality and morbidity from CVD are highest in Scotland and the north-west of England and lowest in the south of England (Townsend et al. 2012). For example, in 2011/2013, premature deaths rates from CVD were nearly 60% higher in Scotland compared with the South-east of England (95/100 000 vs 60/100 000) (Townsend et al. 2015). Within those areas of high CVD mortality, the highest death rates are concentrated...
in certain urban areas such as inner-city areas of Glasgow, Manchester, Liverpool, Leeds, Birmingham, Sheffield, Edinburgh, and Belfast (Townsend et al. 2012). CHD and cerebrovascular disease patterns within the UK and other countries have consistently shown that CVD is more common among those in less-privileged socioeconomic groups. For example, in the UK death rates from CVD are highest in the lowest socioeconomic group and lowest in the highest socioeconomic group, with the gradient across social groups being more pronounced in women. In 2001/2003, the death rate in female workers with routine jobs was five times higher than those with managerial or professional jobs (Townsend et al. 2012). There is also evidence that the socioeconomic gradient in CVD mortality appears to be widening. In the 1970s, the difference between men in social classes V and I in risk of dying of a heart attack was twofold, but by the 1990s this had risen to threefold. More recent data show no narrowing of the relative difference between the most deprived and the least deprived, particularly in women (Fig. 1.10).

While some of the social class differences in CVD mortality and morbidity can be attributed to a higher proportion of smokers among men and women in lower socioeconomic groups, there is also evidence of variation in diet-related risk factors (see Section 1.6 for a description of these factors). While the social or regional variations cannot be explained by differences in the consumption of fat or saturates, or in blood cholesterol levels, there has been a social class gradient for obesity and blood pressure, as well as for fruit and vegetable intake, throughout the past decade (NHS Digital 2008, 2012). There is also evidence of geographical differences in fruit and vegetable consumption, with the north of England and Scotland having lower intakes (Department for Environment Food and Rural Affairs 2013). Other proposed explanations for the social class differences include early life factors (see Chapter 2), psychological factors, and access to health care (Kamphuis et al. 2012).

Significant differences in premature CVD incidence and prevalence also exist for some ethnic populations living in the UK compared with the indigenous population. For example, men born in South Asia and living in the UK (Indians, Bangladeshis, Pakistanis, Sri Lankans) have higher premature death rates from CHD and stroke than the national UK average (Fig. 1.11) (Scarborough et al. 2010). The difference in the death rates between South Asian men and the rest of the population is also increasing because the death rate from CVD is not falling as fast in South Asians as it is in the rest of the population.

![Fig. 1.10 Trends in coronary heart disease death rates per 100,000 population in women, by deprivation quintile, Great Britain, 1994–2008. Source: Townsend et al. (2012).](image-url)
Studies have suggested that these high rates of CHD, as well as concomitant high rates of type 2 diabetes, are most easily explained by the existence of metabolic syndrome, prevalent in South Asian populations and associated with a pronounced tendency to central obesity in this group (see Section 3.3) (Misra and Khurana 2011). In contrast, premature death rates from CHD for Caribbeans and West Africans living in the UK are lower than average. However, individuals of African-Caribbean descent have an increased risk of stroke, hypertension, and diabetes (Scarborough et al. 2010). The reasons for this are not fully understood, but differences in genetic predisposition, lifestyle factors, or other novel stroke risk factors could play a role (Leung and Stanner 2011).

1.6 Risk Factors for Cardiovascular Disease

1.6.1 Definition of Risk Factors

The term ‘risk factor’ describes those characteristics found to be related to the subsequent occurrence of CVD. This term includes modifiable lifestyle, biochemical, and physiological characteristics, as well as unmodifiable personal characteristics such as age, sex, and family history of CVD.

In any given study, it is necessary to consider whether the relationship between a risk factor and CVD is likely to be causal (i.e. whether modification of this factor will lead to a change in CVD risk). Such a judgement must be made in the context of all the available evidence and as such must be re-evaluated with new findings. Criteria that aid in the judgement of causality include the strength of the association, the biological credibility of the hypothesis, the consistency of the findings, as well as other information concerning the temporal sequence and the presence of a dose–response relationship (Bradford Hill 1965). Inferences on causality can also be derived from genetic associations if the gene associated with a particular characteristic is associated with disease (referred to as Mendelian randomisation; see Section 1.4.5).

Risk factors may be related to one another. Family history may involve elevated LDL-cholesterol, for instance, and male gender is associated with lower HDL-cholesterol. If a risk factor is not related to other known risk factors, it is said to be independent. In this report, we will attempt to distinguish which risk factors have independent status.

The term ‘risk marker’ is sometimes preferred to risk factor, to avoid the implication that cause and effect are known. For instance, church attendance is associated with lower risk of CVD (Kawachi et al. 1996), but most would argue that...
a causal relationship is less likely than the fact that this reflects some other aspect of lifestyle that has a bearing on CVD. In this report we will generally use the term risk factor, but recognising that cause and effect may not have been demonstrated unequivocally.

1.6.2 Approaches Used to Investigate the Relationship Between Risk Factors and Disease

The observational epidemiological evidence in support of particular risk factors for CVD varies according to the study design. Cross-sectional studies (where the measurement of risk factors and occurrence of disease are recorded at one point in time) compare the distribution of risk factors and of the presence, or severity, of disease in individuals, and examine relationships between these. Cross-sectional studies may give spurious results if two risk factors (A and B) are highly correlated and B is related to disease but A is not. Failure to take account of the relationship between A and B may inappropriately lead to the conclusion that A is related to disease. This is known as confounding. To illustrate this, a cross-sectional study may report a higher mortality among people taking cholesterol-lowering drugs. This may imply that the drugs cause death from CHD, whereas the true explanation is that people using such medication have had prior elevated levels of cholesterol, which gives them a higher risk of death from CHD.

In a case-control study, people with the disease (in this case CHD) are compared with people without it and matched for relevant factors, such as age and sex. A limitation of the case-control study is the inability to distinguish whether the disease may cause some biochemical abnormality rather than vice versa (referred to as reverse causality). Case-control studies cannot demonstrate cause and effect, although this may be inferred from a knowledge of the pathological processes involved (thus, it seems more likely that a high serum cholesterol concentration causes CHD than the reverse).

In prospective (or cohort) studies, healthy people are investigated and followed up for several years to record the onset of disease. At the end of a particular follow-up period, the characteristics of people who developed (or died from) the disease are compared with people who did not. However, while prospective studies can demonstrate an association or relationship between disease and some factor, whether or not this is causal is often uncertain. It is possible that the association may be mediated through some other factor to which both are related (i.e. confounding).

The most convincing evidence in support of causality for a particular risk factor comes from an intervention study in which that factor is modified and the effects on subsequent disease are studied. Thus, intervention trials with cholesterol-lowering drugs consistently show reductions in mortality from CHD and have led to acceptance of the 'lipid hypothesis' (that a high blood lipid level is causally related to development of CHD). In this report we shall distinguish between levels of evidence for each of the risk factors discussed. Clearly, for the emerging risk factors, the evidence for causality is still incomplete.

1.6.3 Interpretation of the Association

The magnitude of the association between a risk factor and a disease is often expressed as a relative risk (RR) or risk ratio. This indicates the likelihood of developing a disease in those exposed to a risk factor (or treatment) relative to those who are not exposed, and is defined as the ratio of the incidence of the disease in the exposed group divided by the corresponding incidence of the disease in the non-exposed group. A relative risk of 1.0 indicates that the rates of disease are the same in the exposed and unexposed groups. A value greater than 1.0 indicates a positive association or an increased risk among those exposed to a risk factor. A value below 1.0 indicates a reduction in risk among those exposed to a risk factor.

Epidemiological studies also commonly use the term attributable risk (AR). AR measures the excess risk accounted for by exposure to a particular factor and is defined as the disease rate in the exposed group minus that in the unexposed group. If the attributable risk of an exposure is greater than zero, this indicates an increase in the risk of disease; if it is negative (e.g. if the exposure is a treatment), this demonstrates a beneficial effect. AR is the measure of association that is most relevant when making decisions for individuals, because it relates to
their risk of developing a disease. If a condition is common, such as CHD, the importance of reducing an individual’s risk is much greater than if the condition is rare.

The population attributable risk (also known as attributable fraction) measures the reduction in disease in the whole population that might be achieved by eliminating a risk factor. It is calculated by multiplying the attributable risk by the prevalence of exposure to a risk factor in a population. This may be expressed as a percentage and is the most useful measure for public health purposes. A particular risk factor may substantially increase the risk of CVD (i.e. have a high RR), but if exposure to this risk factor is relatively rare, its influence on the rates of CVD in a particular population may be limited. The converse is also true; if a risk factor is common, it may exert a substantial influence on the occurrence of a disease in a population even if it exerts a comparatively small increase in risk for an individual. For example, people who are physically active have a lower risk of CHD. In 2015, estimates from the Health Survey for England suggested that 35% of men and 42% of women were not meeting the current guidelines suggested by the government of at least 150 minutes of moderate aerobic activity every week (NHS Digital 2017a) and, as a consequence, a large number of deaths from CHD have been attributed to physical inactivity. The Department of Health estimates that between 20% and 35% of CVDs could be prevented if more people became active throughout the life course (Department of Health 2011) (see Chapter 12). Research from the World Health Organization attributes 30% of the burden of CHD in developed countries to physical inactivity (World Health Organization 2010).

1.6.4 Conventional Risk Factors for Coronary Heart Disease

The aetiology of CHD began to be unravelled seriously in the 1950s. The American nutritionist Ancel Keys was interested in the low rates of CHD that he observed in countries bordering the Mediterranean. He established the Seven Countries Study to compare CHD rates and diet in different countries. An early finding from this study was that there was a strong relationship, when comparing one country with another, between the incidence of CHD and the dietary intake of saturates compared with polyunsaturates (a high ratio of dietary saturates to polyunsaturates was associated with a high rate of CHD). It was then found that the average level of serum cholesterol, comparing one country with another, correlated positively both with the incidence of CHD and with the average ratio of saturates to polyunsaturates ingested. This relationship was later shown to exist even within a country. Thus, an elevated serum cholesterol concentration became the first well-documented risk factor for the development of CHD. Now the strong relationship between total serum cholesterol and CHD is well established from multiple prospective trials (Fig. 1.12).

Until perhaps 20 years ago, there were a small number of factors that were recognised to mark a predisposition to CHD. These are the so-called classical, or conventional, risk factors (Table 1.2).
| Risk factor                     | Direction of association       | Modifiable by dietary factors? | Relevance to CVD                                                                                                                                                                                                 |
|--------------------------------|-------------------------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------- Eve rful                                                                                                                                     |
| Age                            | Increases with age            | No                            | Increased prevalence as population ages                                                                                                                                                                  |
| Gender                         | Males at higher risk          | No                            | Risk in men and women is equalised after the menopause, possibly due to protection by oestrogens in younger women or to increases in male pattern (central) obesity among postmenopausal women |
| Socioeconomic status           | Lower socioeconomic status increases risk | Some dietary changes may help to reduce the higher risk in lower socioeconomic groups | Highly related to other factors (e.g. diet, smoking, physical inactivity)                                                                                                                                   |
| Ethnic group                   | People from the Indian subcontinent are at particularly high risk of CHD | No                            | May reflect abdominal obesity and insulin resistance (see Chapter 3)                                                                                                                                      |
|                                | People of African-Caribbean descent in the UK are at greater risk of stroke |                                | Possibly reflects genetic predisposition to hypertension. Rates are falling as a result of better detection and treatment of hypertension                                                                 |
| Smoking                        | Smoking increases risk        | No                            | Increases oxidative stress (see Chapter 9) and impairs endothelial function (see Chapter 7)                                                                                                                   |
| Serum total cholesterol concentration | Higher blood cholesterol level increases risk | Yes                           | Uptake of cholesterol by macrophages is the origin of the core of the atherosclerotic plaque                                                                                                             |
| Serum LDL-cholesterol concentration | Higher LDL-cholesterol level increases risk | Yes                           | LDL particles carry cholesterol that may be deposited in arterial walls                                                                                                                                  |
| Serum HDL-cholesterol concentration | Lower HDL-cholesterol increases risk, particularly among women | Yes                           | HDL may transport excess cholesterol to the liver for excretion                                                                                                                                           |
| Serum triglyceride concentration | Higher triglyceride level increases risk | Yes                           | Strongly inversely related to HDL-cholesterol although serum triglyceride is also an independent risk factor, perhaps reflecting more subtle alterations in lipid metabolism (see Chapter 4). |
| Blood pressure                 | Higher blood pressure increases risk | Yes                           | Hypertension increases the risk of haemorrhagic/ischaemic stroke, induces endothelial dysfunction, exacerbates the atherosclerotic process and contributes to the instability of the atherosclerotic plaque |
| Diabetes                       | Diabetes increases risk        | Somewhat                      | See Chapter 3                                                                                                                                                                                                |
| Physical inactivity/ sedentary lifestyle | Being inactive increases risk; fitness reduces risk | No                            | See Chapter 12                                                                                                                                                                                              |
| Obesity                        | Overweight and obesity increase risk partly via other CHD risk factors (e.g. blood pressure, diabetes, blood cholesterol) | Yes                            | See Chapter 3                                                                                                                                                                                                |

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
As well as the ‘unmodifiable’ risk factors (e.g. age, sex, genetic predisposition), and the regional, social and ethnic differences described in Section 1.5.3, these include smoking, raised blood cholesterol, raised blood pressure, physical inactivity, and obesity. Overweight and obesity, for example, are estimated to account for 23% of the ischaemic heart disease burden in England (Public Health England 2015a), and are closely linked with other CVD risk factors (see Section 3.3.3). This has been demonstrated across the life course. For example, children who have a higher BMI have higher levels of risk markers for CVD, including blood pressure, serum lipids, impaired glucose tolerance, and insulin resistance (Herouvi et al. 2013). It has also been shown that the onset of fatty streaks and fibrous plaques begins during childhood and higher BMI and higher levels of these risk markers are associated with increased atherosclerotic changes in the coronary vessels (Herouvi et al. 2013). People with type 2 diabetes also have a two- to fourfold greater risk of death from CVD than non-diabetic individuals (see Section 3.7.1). These ‘classical’ risk factors have been reviewed in a previous British Nutrition Foundation report (Ashwell 1997). Some of the newer insights into the relationship between diet and these risk factors will be discussed in Chapter 13. Inevitably, however, the definition of what is conventional and what is novel, or emerging, is somewhat subjective. In 2005, the British Nutrition Foundation published a Task Force report reviewing more novel, or emerging, risk factors which were being widely researched at that time for their link with CVD (Ashwell 1997). Some of the newer insights into the relationship between diet and these risk factors will be discussed in Chapter 13. Inevitably, however, the definition of what is conventional and what is novel, or emerging, is somewhat subjective. In 2005, the British Nutrition Foundation published a Task Force report reviewing more novel, or emerging, risk factors which were being widely researched at that time for their link with CVD (Stanner 2005). Since this time a considerable amount of research has helped to clarify the importance of some of these risk factors and led to the emergence of additional factors that may be worthy of consideration and an update of the report seemed timely. The risk factors that are considered in detail in this edition are listed in Table 1.3.

1.6.5 Conventional Risk Factors for Cerebrovascular Disease

The most important modifiable risk factor for cerebrovascular disease is hypertension (see Section 1.4.3); higher systolic and diastolic blood pressure has been associated with an increased incidence of ischaemic and haemorrhagic stroke (MacMahon 1996). Historically, salt (sodium) is viewed as the most important dietary determinant of blood pressure, in part influencing the rise in blood pressure with age. Sodium is the principal cation in the extracellular fluid and plays a key role in maintaining water balance in the body. There is an upper limit to the rate at which excretion of excess sodium can occur, causing an increase in body sodium content and water retention. If this situation persists, one important manifestation may be the development of raised blood pressure. In 1994, the Committee on Medical Aspects of Food Policy (COMA) recommended a reduction in average salt intake (to 6 g/day for the adult population) (Committee on Medical Aspects of Food and Nutrition Policy 1994) (see Sections 1.7 and 13.9.8), and this was supported by a subsequent review by the UK government’s SACN (Scientific Advisory Committee on Nutrition 2003), which also set targets for children. Several recent systematic reviews have also concluded that lower sodium intake reduces blood pressure and is associated with a reduced risk of stroke and fatal CHD in adults (Aduro et al. 2013b). The strongest evidence comes from the Dietary Approaches to Stop Hypertension (DASH) Sodium Trial, in which stepwise reductions in blood pressure were demonstrated in response to a lowering of dietary salt levels (Sacks et al. 2001). In this study, the greatest reductions were observed when a decrease in dietary salt was combined with a diet rich in fruit and vegetables and low-fat dairy products, indicating that a whole diet approach is likely to be the most effective population-based method of lowering blood pressure (see Section 13.5).

Observational studies also support an association of other lifestyle-related risk factors with increasing risk of stroke (e.g. lack of exercise, alcohol consumption, diabetes, obesity, smoking). The role of fat intake as a risk factor for stroke remains uncertain, although the use of cholesterol-lowering drugs reduces stroke risk (Castilla-Guerra et al. 2016). Research has also investigated links with other risk factors, such as hyperhomocysteinaemia, micronutrients (e.g. vitamins C and E, carotenoids, selenium), fibrinogen, and clotting factors, which will be discussed further in this report (see Chapters 8–10, 13).
Cardiovascular Disease

1.6.6 Smoking and Peripheral Vascular Disease

The risk factors that contribute to peripheral vascular disease (PVD) are similar to those associated with CHD and cerebrovascular disease (e.g. diabetes, hypercholesterolaemia, high blood pressure, physical inactivity, low levels of HDL-cholesterol, a high BMI, hyperhomocysteinaemia). However, data from the Framingham Study (Murabito et al. 2002) and other population studies indicate that cigarette smoking has a particularly strong association with PVD and is one of the most important risk factors for the condition. A possible explanation for this relation is that smoking induces a wide variety of physiological responses, some of which appear likely to be involved in development of atherosclerosis or increased probability of thrombosis. These responses include modified lipid levels, decreased fibrinolysis, increased fibrinogen levels, and changes in endothelial and platelet functions, which are themselves either known risk factors for, or early features of, atherosclerosis. The rapid amelioration of the risk of CVD after cessation of smoking suggests that these processes are readily reversible.

Table 1.3 Emerging risk factors for cardiovascular disease covered in this report.

<table>
<thead>
<tr>
<th>Individual factors</th>
<th>Chapter reference</th>
<th>Relevance to CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid-related factors (other than cholesterol concentration)</td>
<td>4</td>
<td>Relates to development of atherosclerotic plaque and possibly thrombosis. Factors other than LDL-cholesterol may play a role in atherosclerosis</td>
</tr>
<tr>
<td>Inflammation-related factors</td>
<td>5</td>
<td>May reflect atherosclerosis as an inflammatory process</td>
</tr>
<tr>
<td>Adipose tissue-derived factors</td>
<td>6</td>
<td>Not clear but may act through lipid factors, inflammation, endothelial dysfunction, and coagulation</td>
</tr>
<tr>
<td>Vascular (endothelial) dysfunction</td>
<td>7</td>
<td>Impaired endothelial function may allow entry of monocytes and LDL particles to subendothelial space, and/or may reflect injury to endothelium. Mechanical stress on blood vessels because of high blood pressure is likely to be an important factor in endothelial dysfunction.</td>
</tr>
<tr>
<td>Coagulation-related factors</td>
<td>8</td>
<td>Thrombus formation leads to MI or stroke</td>
</tr>
<tr>
<td>Markers of oxidative stress</td>
<td>9</td>
<td>Oxidation of LDL-cholesterol may be involved in atherosclerosis</td>
</tr>
<tr>
<td>Blood homocysteine concentration</td>
<td>10</td>
<td>Not clear</td>
</tr>
<tr>
<td>Vitamin intake/status (e.g. B vitamins, vitamins D, antioxidant nutrients)</td>
<td>10</td>
<td>Not clear</td>
</tr>
<tr>
<td>Influences of the human gut microbiome</td>
<td>11</td>
<td>Gut organisms may reduce cholesterol levels Possible effects on inflammation (e.g. C-reactive protein) Possible link with obesity and insulin resistance but causality yet to be established</td>
</tr>
</tbody>
</table>

Common mechanisms

| Obesity, especially abdominal | 3, 9, 11 | Related to insulin resistance and metabolic syndrome |
| Metabolic syndrome | 3 | Involves dyslipidaemia, pro-coagulant state and endothelial dysfunction |
| Maternal and/or fetal undernutrition | 2 | May relate to insulin resistance and hypertension |

CVD, cardiovascular disease; LDL, low-density lipoprotein; MI, myocardial infarction.
1.6.7 Trends in the Classic Cardiovascular Risk Factors

1.6.7.1 Trends in the US

Data from the National Health and Nutrition Examinations Survey have shown a decreasing trend in the proportion of adults in the US with at least one of three classical risk factors for CVD (high blood pressure, high blood cholesterol, and smoking) between 1999 and 2010; this fell from 57.8% in 1999–2000 to 46.5% in 2009–2010 (Fryar et al. 2012). There was a 7.6% decline in uncontrolled high blood pressure and a 9.3% decline in uncontrolled high LDL-cholesterol during this period, although smoking prevalence did not decline significantly. In 2009/2010, among adults aged 20 years or over, 25% were current smokers, 23% had uncontrolled high LDL-cholesterol and 12% had uncontrolled high blood pressure. However, rates of overweight and obesity have continued to rise; from 56% in 1988–1994 to 70.4% in 2013/2014 (Centers for Disease Control and Prevention 2016; National Center for Health Statistics 2016).

1.6.7.2 Trends Across Europe

The WHO MONICA project studied trends in the classic risk factors in several populations throughout Europe over a 10-year period (within a total study period of 1979–1996). This survey demonstrated declining trends in the prevalence of smoking in men in most of the study populations but an increase in the prevalence of female smokers in several countries. Systolic blood pressure increased during this period in most centres in both sexes, while cholesterol generally showed a small downward trend. The most disturbing feature of the results was the rise in BMI, particularly among men, which occurred in three-quarters of the populations studied (Evans et al. 2001).

More recent studies suggest that these trends have continued. The prevalence of smoking among men has fallen over the last 30 years in almost all European countries for which data are available (European Heart Network et al. 2012). Although the decline has been less marked in women, most countries have seen a drop in prevalence over the same period, although the Russian Federation, Latvia, Hungary, Estonia, and Slovakia have experienced an increase in smoking in adolescent girls.

There has also been a steady decrease in levels of alcohol consumption in several Southern and Western European countries, particularly France, Italy, and Luxembourg between 2000 and 2007, although large increases in consumption have been seen in a number of countries in Eastern Europe over the same period (European Heart Network et al. 2012). Improvements in some other risk factors, such as blood cholesterol levels and blood pressure, have also been demonstrated at a population level in many areas of Europe, including the UK (World Health Organization 2011).

However, a consistent increase in average BMI has occurred in almost all countries from 1980 to 2008 (European Heart Network et al. 2012). The overall prevalence of obesity in Europe was 21.5% in men and 24.5% in women in 2014 (World Health Organization 2016a) perhaps reflecting, at least to some extent, a more sedentary lifestyle. This reflects the global trend; the world prevalence of obesity more than doubled between 1980 and 2014 (World Health Organization 2016b). In 2014, 41 million children under the age of 5 years were overweight or obese worldwide (World Health Organization 2016b). In 2014, 41 million children under the age of 5 years were overweight or obese worldwide (World Health Organization 2016b). In 2014, 41 million children under the age of 5 years were overweight or obese worldwide (World Health Organization 2016b). In 2014, 41 million children under the age of 5 years were overweight or obese worldwide (World Health Organization 2016b).

According to the COSI study by WHO, which collected data in 2007/2008 on children aged 6–9 years-old in 12 European countries, 19–49% of boys and 18–43% of girls were defined as overweight (including obese) and 6–27% of boys and 5–17% of girls were obese (Wijnhoven et al. 2013). Physical inactivity has become increasingly common across Europe. In the 2013 Eurobarometer survey, 42% of adults reported that they never participate in exercise or sport (European Commission 2014). Participation in informal physical activity was also low, with 14% reporting that they never participated in outdoor activities such as walking, cycling, or gardening. On a usual day, about two-thirds (69%) of respondents spent between 2.5 and 8.5 hours sitting, with 11% sitting for more than 8.5 hours.
1.6.7.3 Trends in the UK

Similar trends have been reported by surveys in the UK. There has been a long-term decline in smoking prevalence in men and women in Britain. Smoking among adults (>16 years) has fallen by more than half in the last 40 years (from 46% in 1974 to 19% in 2013) (Office for National Statistics 2014), with a greater decline among men than women (Townsend et al. 2015). Alcohol intake has also declined slightly in the UK in recent years. For example, in England, the proportion of men consuming more than the recommended four units of alcohol on the heaviest day’s drinking in a surveyed week showed a small decrease between 2006 (41%) and 2014 (37%) (NHS Digital 2015).

Data from the Health Survey for England show that since 1978 there has been a significant decrease in the mean total cholesterol level (of 0.5 mmol/l in both sexes) to 5.1 mmol/l in men and 5.2 mmol/l in women (NHS Digital 2012). This survey has also shown prevalence of treated hypertension to increase from 5% to 10% in men and 6% to 10% in women between 2003 and 2014, but the proportion of adults with untreated hypertension decreased in both sexes (from 20% to 17% in men and 16% to 11% in women) over the same period (NHS Digital 2015). In England, 32% of men and 27% of women have hypertension (defined as a systolic blood pressure of 140 mmHg or over, or a diastolic blood pressure of 90 mmHg or over) or are being treated for the condition (NHS Digital 2015).

Of most concern, however, is the rapid rise in the prevalence of overweight and obesity and the associated increase in the number of people suffering from type 2 diabetes. In England, the percentage of men aged 16 years and over who are obese rose from 13% in 1993 to 24% in 2014 and from 16% in 1993 to 27% over this period among women (NHS Digital 2015) (Fig. 1.13). Health Survey for England data have also demonstrated an increase in the prevalence of abdominal obesity (defined as a waist circumference of ≥94 cm in men and ≥88 cm in women) in England from 1993 to 2008; among 18–67 year-old adults, abdominal obesity rose from 19.2% to 35.7% in men, and from 23.8% to 43.9% in women (Howel 2012). Later figures from this survey have shown a high or very high waist circumference in 66% of women and 54% of men (NHS Digital 2015).

The prevalence of obesity has also risen among children; being 19% among English boys and 16% of girls aged 2–15 years in 2014 compared to 11% and 12%, respectively, in 1995 (NHS Digital 2015). In 2015/2016, in England, one in five children in reception (4–5 years) was overweight or obese and one in three children in Year 6 (10–11 years) was overweight or obese (NHS Digital 2016b). A study examining data from five UK birth cohorts reported that the probability of being overweight by age 10 years was two to three times higher in those born after the 1980s than those born before the 1980s (Johnson et al. 2015).

It has been estimated that up to 90% of type 2 diabetes is attributable to increased bodyweight.

---

**Fig. 1.13** Obesity prevalence of adults (16 years and over) in England from 1993 to 2013. Source: NHS Digital (2015).
Increasing rates of obesity are therefore leading to a rapidly rising prevalence of type 2 diabetes in the UK, particularly among people from ethnically susceptible groups, notably South Asians. Around 6% of adults currently have diagnosed diabetes (Public Health England 2014) and it is estimated that there are an additional half a million people in the UK who have undiagnosed diabetes (Diabetes UK 2016). Around 90% of these have type 2 diabetes, which is most frequently caused by obesity, insulin resistance, and low physical fitness (see Section 3.7). Of particular note is the increasing development of type 2 diabetes in children. This condition was not seen in children until the first cases were diagnosed in the year 2000 but is now rapidly increasing in incidence (Diabetes UK 2016). Children of Asian or Black origin are more likely to develop type 2 diabetes than Caucasian children. The vast majority of children with type 2 diabetes are aged 10–19 years, with slightly more of these falling into the 15–19 years bracket (Royal College of Paediatrics and Child Health 2015).

Primary prevention strategies to bring about a continued decline in CVD incidence therefore remain a major challenge (see Section 13.11).

1.6.8 The Emergence of New Risk Factors

Although a high serum cholesterol level undoubtedly increases the risk of CHD in an individual, it is nevertheless true that in surveys of people with documented CHD (e.g. those presenting with MI), the distribution of serum cholesterol levels does not clearly distinguish those with from those without the disease. This reflects partly the concept of attributable risk discussed previously (see Section 1.6.3); the number of people in the population with particularly high serum cholesterol levels is not great. But it also shows that other factors must underlie the risk of CHD in many people. In fact, although the importance of the major cardiovascular risk factors (elevated blood cholesterol, cigarette smoking and high blood pressure) have been strongly substantiated and it is likely that they account for most cases of heart disease (Magnus and Beaglehole 2001), it is also likely that other novel risk factors may account for a substantial proportion of CVD cases. This has initiated a search for alternative risk factors. In addition, new research on the mechanisms of atherosclerosis has suggested the presence of novel risk factors, such as oxidative stress, in the aetiology of CHD. Understanding of the role of lipid peroxidation in atherosclerosis has led to a search for indicators of oxidative stress that may predict development of CHD (see Chapter 9). Observations from basic science and epidemiological evidence have prompted interest in the role of antioxidants. However, nutrients with antioxidant properties may also affect cardiovascular risk by other (not directly antioxidant-type) mechanisms of action, such as effects on the immune system, markers of endothelial damage and effects on gene expression and cell signalling. This situation needs to be taken into account in the design of studies.

1.7 Role of Diet

Because of the large variation in risk of mortality from CHD and stroke, it is likely that behavioural risk factors play an important role in the aetiology of these diseases. It has been recognised for some time that diet, as well as other lifestyle factors (e.g. alcohol consumption, smoking, physical inactivity), is strongly related to several of the main risk factors for CVD.

1.7.1 Dietary Recommendations to Reduce Cardiovascular Disease

Epidemiological studies have shown a log-linear relationship of increasing risk of CHD with increasing levels of total cholesterol, with no threshold value below which a lower level is not associated with lower risk of CHD. Moreover, controlled clinical trials have shown the importance of pharmacological lowering of serum cholesterol levels in reducing cardiovascular mortality (and morbidity) in individuals at high-risk of CHD (Cholesterol Treatment Trialists’ Collaboration 2005, 2012). Lowering the population mean level of LDL-cholesterol is probably the most important public health strategy to prevent CHD mortality. While most dietary measures to achieve this are less effective than a statin drug, they are likely to have substantial benefit for CVD risk as they may impinge simultaneously on several of the risk markers described in this report. There is therefore considerable potential for dietary modification in the primary and secondary prevention of CHD.
As a result of the interest in blood cholesterol levels, dietary recommendations for CVD prevention have concentrated primarily on reducing fat intake. However, the focus is no longer simply on a need to reduce total fat and saturates intake. Research has identified the benefits of unsaturates, particularly polyunsaturates in helping to keep levels of blood cholesterol (and other blood lipids) down (see Section 13.4.3). The n-3 polyunsaturates, of which oil-rich fish is an important source of the longest chain length members of this group [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)], have little effect on blood cholesterol but reduce blood triglyceride levels. There is also evidence for other beneficial effects, for example with regard to blood clotting (see Chapter 8). Former concerns about the trans fatty acid content of the diet have now largely disappeared in Britain for the majority of people eating a varied diet, since manufacturers have taken steps to reduce the trans content of margarines and spreads to a minimum and average intake has fallen well below the recommended level (see Section 13.4.2).

In 1994, COMA published dietary (food and nutrient) recommendations to prevent CVD (Committee on Medical Aspects of Food and Nutrition Policy 1994) (Table 1.4). These included reducing the average contribution of total fat to dietary energy (i.e. from food and alcohol) in the population to about 35% and reducing the average contribution of saturates to dietary energy to no more than 10%. COMA recommended that average intakes of trans fatty acids should not increase but made no specific recommendations for monounsaturates. The report recommended that average intakes of n-6 polyunsaturates need not increase above current levels, and intakes of long-chain n-3 polyunsaturates (EPA and DHA) should double from 0.1 g/day to 0.2 g/day. Information about dietary sources of these fatty acids can be found in Section 13.9.2. The population was also advised to increase the proportion of dietary energy derived from carbohydrate to approximately 50% and to reduce salt intake by at least one-third from its current level of 9 g/day to 6 g/day (Committee on Medical Aspects of Food and Nutrition Policy 1994). The practical food-based advice arising from the COMA recommendations for CVD prevention is therefore to maintain a healthy bodyweight, eat five or more portions of fruit and vegetables each day, reduce intake of fat, particularly saturates, reduce salt intake and eat at least two portions of fish, of which one should be oil-rich fish, each week (see Section 13.7 for an update).

SACN has made subsequent dietary recommendations for the UK population on salt, long-chain n-3 fatty acids, energy, free sugars, and dietary fibre, which are discussed in Chapter 13. In particular, in 2015, SACN reviewed the evidence on carbohydrates and health and concluded that, based on cohort studies, there was no significant association between total daily carbohydrate intake and incidence of CVD endpoints but supported the previous recommendation that around

<table>
<thead>
<tr>
<th>Dietary factor</th>
<th>Nutrient recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat</td>
<td>Reduce population average to 35% of dietary energy</td>
</tr>
<tr>
<td>Saturates</td>
<td>Reduce to no more than 10% of dietary energy</td>
</tr>
<tr>
<td>n-6 polyunsaturates</td>
<td>No further increase in average intake of n-6 polyunsaturates</td>
</tr>
<tr>
<td>n-3 polyunsaturates</td>
<td>Increase population average consumption of long-chain n-3 polyunsaturates from 0.1 to 0.2 g/day (1.5 g/week)</td>
</tr>
<tr>
<td>Trans fatty acids</td>
<td>Trans fatty acids should not provide more than 2% of dietary energy</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>No increase in average dietary cholesterol intake (250–300 mg/day)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Increase the average proportion of dietary energy derived from carbohydrate to approximately 50%</td>
</tr>
<tr>
<td>Salt (sodium)</td>
<td>Reduce salt intake from 9 to 6 g/day</td>
</tr>
<tr>
<td>Potassium</td>
<td>Increase potassium intake to around 3.5 g/day</td>
</tr>
</tbody>
</table>

Table 1.4 Committee on Medical Aspects of Food Policy (COMA) recommendations on diet and cardiovascular disease for the UK population.

50% of total dietary energy should be derived from total carbohydrates (Scientific Advisory Committee on Nutrition 2015). Although evidence linking free sugars and cardiometabolic outcomes in adults was considered insufficient, lowering free sugars intake to 5% of total dietary energy was advised to help reduce energy intake and risk of weight gain in the UK population. A meta-analysis of cohort studies found a reduction in CVD risk with dietary fibre and an increase in the recommendation was recommended, to 30 g per day for adults (Scientific Advisory Committee on Nutrition 2015). The COMA recommendation to reduce average population intake of saturates has also been supported by a SACN review of the current evidence base (Scientific Advisory Committee on Nutrition 2018).

Recent dietary recommendations have been published elsewhere (Perk et al. 2012; Eckel et al. 2014; United States Department of Agriculture and US Department of Health and Human Services 2015) and these have incorporated some of the newer insights into the role of diet in CVD risk; for example, they have included specific recommendations to increase the ratio of monounsaturates to other fatty acids and emphasised dietary patterns over individual dietary components (see Section 13.8).

### 1.8 Structure of the Report

The Task Force was asked to review the present state of knowledge of the link between emerging aspects of CVD and diet (and related factors). Chapter 3 deals with common themes (e.g. insulin resistance, obesity) that are linked to several risk factors and are therefore consistently referred to throughout the report. Chapters 2 and 4–12 present the evidence for the role of the major emerging risk factors, providing information about methods of assessment (including the

![Fig. 1.14](image_url) A schematic diagram depicting a proposed model for research into nutrition, diet, and cardiovascular health in an 'intermediate risk population'. ABP, ambulatory blood pressure; ACS, acute coronary syndrome; BMI, body mass index; Chol, cholesterol; cIMT, carotid intima media thickness; Comp, composition; CVD, cardiovascular disease; Demog, demographic factors; DXA, dual X-ray absorptiometry; ECG, electrocardiogram; FMD, flow mediated dilatation; Inc., including; LD, laser Doppler; MI, myocardial infarction; NO, nitric oxide; PWA, pulse wave analysis; PWV, pulse wave velocity; Si, insulin sensitivity; Smo, smoking; TIA, transient ischaemic attack.
robustness of these measurements) and outlining the evidence for the potential role of diet in their modification. Neither the order of these chapters, nor their length, is intended to provide an indication of the relative strength of evidence for each individual risk factor. This information is brought together in Chapter 13 which deals with public health issues and summarises current recommendations in relation to diet and activity. Chapters 14 and 15 present the conclusions and research recommendations from each chapter and Chapter 16 summarises the key messages of the Task Force in a question and answer format. A detailed glossary is provided and a full bibliography can be found at the end of the report, but key references are also available at http://www.wiley.com/go/bnf/cardiovascular_diseases. An overview of the components of CVD risk and how they lead to disease is presented as a model for future research in Fig. 1.14.

### 1.9 Key Points

- CVD refers to disease of the arteries supplying the heart (CHD), the brain (cerebrovascular disease) and the extremities, especially the legs (peripheral vascular disease, PVD). It involves the processes of atherosclerosis (lesions in the arterial wall) and thrombosis (blood clotting), as well as changes to the function of the arterial lining.
- CVD is the leading cause of death worldwide, accounting for around 18 million deaths each year. Around 50% of these deaths are from CHD and a further 25% from stroke.
- In the UK, CVD is a leading cause of death, with more than one in three people dying from this condition. The disease is also a major cause of illness and disability, including angina and heart attacks.
- Death rates from CHD have been falling in the UK since the early 1970s, while death rates from stroke have declined throughout the latter part of the twentieth century. Both lifestyle modification and medical treatments have played an important role in this decline.
- While CHD mortality has been falling, surveys suggest that morbidity from CHD is not falling and, in older age groups, may even be rising. This reflects both the ageing of the population and the survival of those who would previously have died.
- There are major social, regional, and ethnic inequalities in CVD morbidity and mortality in the UK, which appear to be widening.
- Although there is an inherited component to CVD risk, there is also an environmental component. Interactions between an individual’s psychosocial and physical environment and their unique genetic make-up are now accepted to play an important role in nearly all CVD conditions and underlying biological processes.
- Conventional lifestyle-related risk factors for CVD include smoking, raised circulating cholesterol levels, particularly low-density lipoprotein (LDL)-cholesterol, raised blood pressure, physical inactivity, obesity, and diabetes. However, these ‘classical’ risk factors cannot fully explain the regional, gender, socioeconomic, and ethnic differences in CVD, and emerging evidence suggests that other novel risk factors may play an important role.
- This Task Force considers some of these novel or emerging risk factors for CVD and reviews the potential role of diet in their modification.