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16.13.2 Coronary heart disease: Epidemiology and prevention

Goodarz Danaei and Kazem Rahimi

ESSENTIALS Coronary heart disease (CHD) is now the leading cause of death and disability globally. Despite recent declines in age-adjusted death rates from CHD, the number of CHD deaths have been increasing due to a combination of growth in population numbers and their longevity. In addition, manifestation and outcome of CHD varies substantially between and within countries. Unlike many other common medical conditions that disable and kill and remain unpreventable, CHD is to a large extent preventable. There are strong, unconfounded relationships between several risk factors and CHD mortality and nonfatal myocardial infarction. The most important risk factors for CHD are smoking, high blood pressure, dyslipidaemia, diabetes, physical inactivity, unhealthy diet, and obesity. Controlling these risk factors, even in middle-aged individuals, through lifestyle changes, medical treatment, or public health interventions, may reduce CHD incidence by almost one-half. Despite the apparent triumph in risk prediction and control, the search for new biomarkers, both phenotypic and genotypic, remains a major focus of cardiovascular research. Several novel markers of risk (e.g. B-type natriuretic peptide) have already been identified and many more are likely to emerge during the next few years. However, the causal significance of these biomarkers, or their contribution to risk prediction, awaits further clarification.

Introduction Coronary heart disease (CHD) is a group of diseases characterized by insufficient circulation in coronary arteries potentially leading to angina pectoris, myocardial infarction, heart failure and (sudden) coronary death. The underlying pathophysiology is most often coronary atherosclerosis, which is discussed in detail in Chapter 16.13.1. The process of atherosclerosis may begin in utero, but the manifestation of CHD is largely preventable by controlling the common risk factors of atherosclerosis. In this chapter, we present the current evidence on the global distribution of CHD and its determinants, focusing on risk factors for atherosclerosis. Other, less common and nonatherosclerotic variants of CHD include those caused by vasoconstriction such as Prinzmetal's angina, paradoxical embolism, Kawasaki syndrome leading to coronary aneurysms and stenosis, chest trauma, irradiation, spontaneous coronary dissection, and cardiac syndrome X. These collectively constitute a small proportion of the global CHD burden, hence here we use CHD and ischaemic heart disease (IHD) interchangeably.

Global perspective Coronary disease was a rare condition at the beginning of the 20th century—a time

when deaths from CHD were greatly outnumbered

section 16 Cardiovascular disorders 3604 by those due to infectious diseases. CHD is now the leading cause of death and disability in almost all regions of the world, causing an estimated 9 million deaths in 2015 (out of 56 million). Despite a 25% decline in the age-standardized mortality rates from CHD since 1990, the number of deaths from CHD have increased by 50% due to growth in population numbers and their longevity (age-standardized mortality rates are adjusted for differences in the age structure of the population and therefore take into account that populations have aged over time). Since 1980, age-standardized CHD mortality rates have declined in most high-income and many middle-income countries in the world, but rates of premature CHD (i.e. events occurring before the age of 70) may have increased in countries in central and eastern Europe; central, south, and southeast Asia, Oceania, and sub-Saharan Africa. There are also substantial regional differences. In 2015, countries in eastern Europe and Central Asia had the highest CHD mortality rates at more than 600 per 100 000, whereas those in eastern sub-Saharan Africa had the lowest rates at less than 100 (see Fig. 16.13.2.1). There are vast disparities in age at death from CHD. Deaths occur at much younger ages in Central Asia, North Africa, the Middle East, and sub-Saharan Africa. The differences in death rates and age at presentation across nations point to the largely preventable nature of CHD. In fact, half the decline in CHD mortality in high-income countries in the recent decades is thought to be due to improvements in treatment, with the remainder due to modification of CHD risk factors. Substantial disparities in CHD within countries and across social and racial/ethnic subgroups have also been identified. The increased risk in African Americans compared with the white population in the United States of America, and increased risk in the Asian population in the United Kingdom, are largely explained by higher levels of well-known risk factors such as high blood pressure, smoking, and diabetes. The importance of modifiable risk factors is emphasized by the fact that individuals who migrate from low-risk populations to high-risk ones tend to adopt the cardiovascular risk of their adopted country. Individuals with lower education, social status, or in lower income groups in Europe and America also exhibit much higher rates of CHD due to a combination of worse risk factor profiles and lower access to, and quality of, healthcare. A substantial body of epidemiological knowledge has been generated in the past seven decades and the collective evidence from cross-country comparison studies, prospective epidemiological studies, and randomized clinical trials has helped us understand the determinants of CHD and design clinical and public health interventions to reduce CHD burden worldwide. Next, we summarize the key risk factors and the corresponding evidence that substantiates their effect on CHD.

100.00 52.73 150.00 200.00 250.00 300.00 350.00 Rate per 100 000 (a) 400.00 450.00 500.00 550.00 600.00 623.52 Fig. 16.13.2.1 Map of age-standardized ischaemic heart disease mortality rate per 100 000 in 2015 in men (a) and women (b): the Global Burden of Disease 2015 Study. From Global Burden of Disease Study 2015 (GBD 2015) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2016. Available from <http://ghdx.healthdata.org/gbd-results-tool>

16.13.2 Coronary heart disease: Epidemiology and prevention 3605 Modifiable and nonmodifiable risk factors Overview of risk factors The most important risk factors for CHD are smoking, high blood pressure, dyslipidaemia, diabetes, physical inactivity, unhealthy diet, and obesity. The Global Burden of Disease project estimated that in 2015, 55% of the CHD burden (as measured by disability-adjusted life years) was attributable to nonoptimal blood pressure, 48% to high serum total cholesterol, 28% to air pollution and about 20–25% separately to each of the following risk

factors: smoking, high fasting plasma glucose, and high body mass index, diet low in nuts and seeds, whole grains, sea- food omega-3 fatty acids, vegetables and diet high in sodium (Table 16.13.2.1). The sum of these proportions far exceeds 100% because one CHD case can be attributable to more than one risk factor (i.e. could have been prevented by controlling any of several risk factors). It is also worth noting that the ranking of the risk factors in the Table depends on both their relative risk for CHD and prevalence of each risk factor at the global level. A risk factor with a larger relative risk such as tobacco smoking may therefore appear below a risk factor with a smaller relative risk but higher prevalence, such as high blood pressure (here defined as systolic blood pressure of ≥ 110 –115 mm Hg). Lifelong exposure to these risk factors collectively explains about 70–80% of the incidence of CHD, and over 75% of patients presenting with CHD will have at least one of these risk factors. Controlling these risk factors, even in middle-aged individuals, may reduce CHD incidence by almost one-half. Tobacco smoking, second-hand smoke, and other forms of tobacco use Tobacco smoking is a major driver of CHD worldwide. Strong evidence from many prospective epidemiological studies and laboratory experiments clearly indicate the harmful effects of tobacco on CHD through its impact on reducing oxygen-carrying capacity, increasing blood pressure, damaging the endothelial cells, increasing inflammation, thrombosis, and oxidation of low-density lipoprotein (LDL) particles. There is a strong dose-response relationship between the duration and intensity of smoking and risk of CHD, and heavy smokers may have up to five times higher risk of CHD than never smokers. The relative risks of tobacco smoking and CHD decline with age and are at least as large among women as among men. The 20th century has aptly been named the ‘tobacco century’ to signify the substantial rise in tobacco consumption initially in the high-income nations and subsequently its export into developing countries. After the publication of the first report of the Royal College of Physicians in the United Kingdom in 1962 and the Surgeon General’s report of 1964 in the United States of America, various public health interventions and policies including educational campaigns and raising taxes and banning advertising have led to lower tobacco smoking in many high-income countries which may have contributed substantially to reductions in CHD rates. For example, in the United States 12% of the decline in the CHD rates between 1980 and 2000 has been attributed to reductions in smoking prevalence. Smoking cessation is the most effective preventive measure for CHD. The harmful impact of smoking on CHD takes up to 10 years to revert to normal after quitting smoking, but the impact is large (Fig. 16.13.2.2). (b) Fig. 16.13.2.1 Continued

section 16 Cardiovascular disorders 3606 Cessation programmes including nicotine patches and gums, behavioural counselling and group therapy programmes, and the use of antidepressants (in particular bupropion and nortriptyline) may increase quitting success rates, but preventing uptake of smoking remains the key challenge. Bans on sales of tobacco products to minors, bans on advertising, and increasing taxes are among the most cost-effective ways to reduce CHD burden, and 179 countries have signed a global treaty, the Framework Convention on Tobacco Control, adopted in 2003, to implement these policies. Other forms of tobacco smoking (cigar, pipe, hookah) increase risk for CHD to a similar extent to cigarettes. Passive (second-hand) smoking A significant component of the global impact of smoking on the incidence of CHD is related to passive smoking. Although the relative risk of CHD due to passive smoking is much lower than for active smoking, a substantially larger number of individuals are exposed to this harmful effect, raising the importance of banning smoking in public places. Table 16.13.2.1 Proportion of ischaemic heart disease burden (measured in disability-adjusted life years in 2015) attributable to individual risk factors, worldwide along with the corresponding relative risks, Global Burden of Disease Study

results 2015 Risk factors Proportion of IHD burden attributable (95% CI) Relative risk for IHD mortality At age 60–64 Unit or comparison for relative risk Physiological and behavioural risk factors High blood pressure 55% (47, 62) 1.41 10 mm Hg High total cholesterol 48% (40, 56) 1.40 mmol/litre Tobacco smoking, including second-hand smoke 24% (21, 28) 2.4 Men 3.0 Women 1.25 Smoker versus nonsmoker Second-hand smoke High fasting plasma glucose 20% (14, 28) 1.18 mmol/litre High body mass index 20% (14, 27) 1.41 Per 5 kg/m² above 25 kg/m² Physical inactivity and low physical activity 10% (7, 14) 1.41 1.25 1.13 Inactive Insufficiently active Sufficient but not highly active Dietary risk factors Diet low in nuts and seeds 25% (16, 35) 1.06 4 g/day Diet low in whole grains 23% (13, 32) 1.1 50 g/day Diet low in seafood omega-3 fatty acids 19% (8, 30) 1.12 100 mg/day Diet high in sodium 19% (10, 31) 1.09 g/day Diet low in vegetables 18% (7, 30) 1.07 100 g/day Diet low in fruits 14% (5, 24) 1.10 100 g/day Diet high in trans fatty acids 7 (3, 12) 1.28 2% energy/day Diet low in fibre 5% (2, 8) 1.30 20 g/day Diet low in polyunsaturated fatty acids 5% (2, 8) 1.08 5% energy/day Diet high in processed meat 5% (0, 10) 1.44 50 g/day Environmental risk factors Air pollution 28% (24, 32) From 1.12 (for 10 microg/m³) to 1.71 (for 600 microg/m³) Household air pollution Lead exposure 3% (1, 4) 1.02 Per 10 µg/g Global Burden of Disease Study results 2015 Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2016. Available from <http://ghdx.healthdata.org/gbd-results-tool> 2.5 0.0 0 10 20 Time since cessation (years) Cardiovascular mortality relative risk 30 40 50 0.5 1.0 1.5 2.0 Male Female Fig. 16.13.2.2 Relative risk of cardiovascular mortality by time since cessation of smoking. From Ezzati M, Lopez AD, Rodgers A, Murray CJL. Smoking and oral tobacco use. Comparative quantification of health risks: Global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization; 2004. pp. 883–957.

16.13.2 Coronary heart disease: Epidemiology and prevention 3607 E-cigarettes Since 2004, electronic cigarettes (or e-cigarettes) have been launched as a smoke-free and implicitly harm-free nicotine delivery device. A recent review of chemical and toxicological studies found that aerosols are contaminated by toxic substances including nitrosamines, aldehydes, metals, and volatile organic compounds. The amount of nicotine delivered by e-cigarettes easily surpasses the threshold limit values used in occupational health investigations for nicotine. Whether e-cigarettes are good or bad for public health has been much debated. Concerns have been raised that uptake of e-cigarettes among nonsmokers may lead to habitual smoking. However, a recent Cochrane Review found that they can help people to quit smoking and reduce their cigarette consumption, and consequently regarded e-cigarettes as a positive public health opportunity, while agreeing that continued vigilance and research was needed in this area. Public Health England has stated that e-cigarettes are less harmful to health than normal cigarettes, and that when supported by a smoking-cessation service help smokers to quit tobacco altogether. Recent (2017) US data has shown that e-cigarette use is associated with higher smoking cessation rate at both individual and population levels. Blood pressure The invention of the sphygmomanometer in the last decade of the 19th century made the measurement of blood pressure at the bedside possible, and the landmark description of the sounds and their relationship with pulse waves by Korotkoff in 1905 made the measurements more precise and standardized. As early as the first or second decade of the 20th century, the relationship between very high blood pressure and mortality was known and had led to the designation of ‘malignant hypertension’. However, the dominant view in the first half of the past century was that blood pressure lower than 210/110 mm Hg was ‘benign’ and did not need to be treated. A vivid example of such views can be seen in the last years of the life of American president Franklin Delano Roosevelt, who died from a stroke in 1945 and had a systolic

blood pressure of 300/190 mm Hg on the day of his death. He had a recorded blood pressure of 186/108 one year earlier, but his personal physicians had considered it 'normal for a man of his age'. Despite a correct diagnosis of hypertension, hypertensive heart disease, and heart failure made by his cardiologist several months later, the understanding of high blood pressure as a risk factor and options for treatment were limited at that time. In 1948, three years after Roosevelt's death, his successor Harry Truman signed the National Heart Act which stated that 'the Nation's health is seriously threatened by diseases of the heart and circulation, including high blood pressure'. Early evidence from analyses of life insurance records indicated that even presumably 'normal' levels of blood pressure are associated with higher mortality. This view was further strengthened with large prospective studies conducted in the 1950s and onwards. It is now clear, based on evidence from more than 100 prospective cohort studies and many randomized trials, that both systolic and diastolic blood pressure increase CHD risk in a continuum and that blood pressure levels even within the clinically 'normal' range may lead to higher risk of CHD (Fig. 16.13.2.3). These studies collectively indicate that in people without any known vascular disease the optimal level of systolic blood pressure may be as low as 110 mm Hg. Fig. 16.13.2.3 Relative risks of mortality from CHD in 61 cohort studies by age and separately for systolic and diastolic measurements. Reprinted from *The Lancet*, Vol. 360, Lewington S, et al., Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies, 1903–13, Copyright 2002, with permission from Elsevier.

section 16 Cardiovascular disorders 3608 Hg. However, the debate on the optimal blood pressure level continues because of insufficient evidence for the safety and efficacy of antihypertensive drugs at very low levels of blood pressure, and inconsistent evidence from observational studies in patients with known cardiovascular disease. Among various measures of blood pressure, systolic blood pressure measured via the brachial artery has been shown to be most strongly associated with CHD risk. Other measures such as diastolic blood pressure, pulse pressure, ankle-brachial blood pressure index, and blood pressure measured at the wrist have also been used in epidemiological studies, but are weaker determinants of CHD risk. Mean systolic blood pressure levels have been declining since mid-1970s in high-income countries by as much as 3 mm Hg per decade, possibly due to better diagnosis and treatment of cases as well as reduced smoking prevalence and intensity. By contrast, during the past four decades blood pressure levels have remained stable in many developing countries and may have increased in south and southeast Asia, Oceania, and sub-Saharan Africa. In 2015, global age-standardized prevalence of hypertension (defined as systolic blood pressure of 140 mm Hg or more, diastolic blood pressure of 90 or more or being on antihypertensive drugs) was 24% in men and 20% in women, leading to an estimated 1.1 billion hypertensive patients worldwide. Fig. 16.13.2.4 shows prevalence of hypertension by country and gender in 2015. Analyses of data from more than 100 prospective observational studies show similar relative risks from different cohorts in Western and Asian populations as well as similar relative risks by gender. However, it is clear that relative risks decline by age, possibly due to higher competing risks by other causes of death or higher baseline CHD risks. Nonetheless, because of high absolute risk of CHD in older people, lowering blood pressure levels in older age groups is expected to have preventive effects similar to those in younger individuals. Pooled analysis of many large prospective studies indicates a 41% higher risk of CHD for each 10 mm Hg higher systolic blood pressure level among individuals 60 to 64 years old. Age-standardised adult prevalence of raised blood pressure Raised blood pressure, men 2015 55% (a)

45% 35% 25% 15% 5% Age-standardised adult prevalence of raised blood pressure Raised blood pressure, Women 2015 55% (b) 45% 35% 25% 15% 5% Fig. 16.13.2.4 Age-standardized prevalence of hypertension by country and gender in 2015 in men (a) and women (b). Reprinted from The Lancet, Vol 389, NCD Risk Factor Collaboration (NCD-RisC), Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants.

16.13.2 Coronary heart disease: Epidemiology and prevention 3609 Evidence from these observational prospective studies is corroborated by many randomized clinical trials of antihypertensive treatment, starting from trials of the Veteran's Affairs healthcare system in the United States in the 1960s. Clinical trials of antihypertensive drugs have also shown that proportional effects are rather similar in different studied patient groups and using different classes of drug. See Chapter 16.17.2 for more details on diagnosis and management of hypertension.

Serum lipids Dyslipidaemias are a major risk factor for CHD and are themselves affected by unhealthy diet, alcohol use, physical inactivity, and genetic factors. Early studies of familial hypercholesterolemia and studies by Ansel Keys and others in the 1950s on cross-country comparison of CHD rates pointed to the potential role of serum cholesterol in CHD. Subsequently, analysis of data from the Framingham Heart Study and other prospective epidemiological studies indicated that high serum cholesterol was indeed positively associated with CHD risk. Separation of subfractions of serum lipids based on their density led to the identification of LDL and high-density lipoprotein (HDL) particles with opposite associations with CHD risk. In the past three decades, serum total and LDL cholesterol levels have declined in high-income countries, which back in the 1980s had some of the highest levels observed worldwide. In contrast, serum cholesterol levels have increased in many developing countries, especially in southeast Asia, creating a global convergence in serum total cholesterol levels. Unfortunately, information on trends on LDL is not available in many low- and middle-income countries. As with high blood pressure, evidence from observational studies indicates a continuous increase in CHD risk with serum total cholesterol levels with no threshold at the commonly used clinical cut-off of 200 or 240 mg/dl (5–6 mmol/litre). The risk of CHD continues to decline with lower LDL cholesterol levels (about 80 mg/dl or 2 mmol/litre). Pooled analysis of multinational studies shows similar relative risks for dyslipidaemia across different populations, and even in very low-risk populations such as the Chinese. Although the relationship between cholesterol and risk is not strong in elderly people it remains a major contributor because of their higher absolute risk of CHD. Many randomized primary and secondary prevention clinical trials of cholesterol lowering, initially with fibrates and then with statins, support the important role of serum cholesterol in CHD. The results clearly demonstrate the beneficial effects of these drugs, with an estimated 25% reduction in relative risks of coronary events per 1 mmol/litre reduction in LDL cholesterol, independent of the starting LDL cholesterol level. Initial fears of an increased risk of cancer with use of statins were not substantiated in later studies, but statins seem to increase the risk of diabetes mellitus slightly. Potential beneficial effects of having a higher HDL-cholesterol are well documented in epidemiological studies. However, Mendelian randomization studies are now suggesting that HDL-cholesterol may not be causally associated with CHD, and clinical trials that aimed at increasing HDL using niacin, fibrates, or cholesteryl ester transfer protein inhibitors have not been successful in reducing CHD risk. A few large-scale studies are still underway. Observational studies have also found an association between apolipoproteins (i.e. apoA1 and apoB) and lipoprotein-associated phospholipase A2 with CHD risk. There is also some evidence that levels of nonfasting serum total

cholesterol are as predictive as fasting levels for CHD risk. The current evidence on the role of serum triglycerides on CHD is mixed, with some large pooling projects reporting no association between triglycerides and CHD after adjusting for other dyslipidaemias. Obesity Excess body fat (adiposity) has been linked to higher mortality since the first decades of the 20th century. Since then, various measures of adiposity have been used in clinical and epidemiological studies including relative body weight, body mass index (BMI), waist circumference, waist-to-hip ratio, weight in water, and measurements of body fat using imaging modalities such as computed tomography (CT) scans. Among these measures, BMI, which 'standardizes' body weight to height (by dividing weight in kilograms by the square of height in metres) is most commonly used in epidemiological studies because of its ease of measurement and strong relationship with CHD and other health outcomes. However, it is well known that BMI does not measure fat mass and is a poor measure of adiposity in athletes and in elderly people. Furthermore, BMI does not reflect the distribution of fat in the body, which determines the biological impact of adiposity. For example, abdominal fat may be much more biologically active and therefore harmful than subcutaneous fat, and measures of abdominal obesity such as waist circumference and waist-to-hip ratio appear to be better predictors of cardiovascular diseases. The main determinants of adiposity are increased caloric intake and lower physical activity. Less important are changes in body metabolism and genetic factors. Almost half of the impact of obesity on CHD is mediated by hypertension, dyslipidaemia, and diabetes. Other factors including low-grade chronic inflammation and increased coagulability are less important mediators. Globally, the number of obese adults has doubled in the past 30 years and obesity, defined as BMI greater than 30 kg/m², is on the rise in almost all regions of the world with a global prevalence of about 11% in men and 15% in women (see <https://www.ncdrisc.org>). Childhood obesity is rising even faster than adult obesity: in 2015, prevalence of obesity was 5.6% in girls and 7.5% in boys aged 5 to 19 years. Observational epidemiological studies clearly indicate a continuous relationship between BMI and CHD at levels above 25 kg/m² and, in a similar manner to blood pressure and serum cholesterol, there seems to be no threshold value to define obesity. The optimal levels of adiposity are the current focus of interest in many studies: some have shown risk reduction for CHD to levels as low as 21 kg/m²; others have shown that the nadir may be higher, at around 23–25 kg/m². Epidemiological evidence on the impact of weight change on CHD (especially weight loss) is mixed, partly due to analytical challenges in separating any beneficial effect of weight loss from the harmful impact of undiagnosed diseases in which weight loss is a feature. Nonrandomized studies of bariatric surgery in morbidly obese patients show rapid reversal of physiological changes after surgery, especially diabetes, but these observations may be due to hormonal changes rather than weight loss per se. There is little evidence from randomized clinical trials on the beneficial effect of weight loss in CHD. Clinical trials of diet have often managed to induce weight loss in the first year, but this has not

section 16 Cardiovascular disorders 3610 been maintained for a sufficient period to detect a potential benefit. However, weight loss trials do show improvements in metabolic profiles such as reduced blood pressure and serum cholesterol and improved glucose tolerance, which should in principle lead to future reductions in CHD risk. Such lack of evidence for benefits of weight loss increases the importance of preventing weight gain, starting in childhood or early adolescence. Diabetes mellitus Diabetes is a major risk factor for CHD. There has been a substantial increase in the number of patients with diabetes in almost all regions of the world, with a global prevalence of about 10% in adults in 2015. This rise has been partly fuelled by increases in obesity, and hence is expected to continue in the coming decades if current trends in unhealthy diet, urbanization, and

physical inactivity continue. Early studies mostly focused on microvascular complications of diabetes and the threshold levels above which the risk of these complications sharply increased. These thresholds were then used to set clinical cut-offs to diagnose diabetes. Recent studies indicate that—similar to blood pressure, serum cholesterol, and adiposity—the relative risks for different cardiovascular outcomes (when shown on a doubling scale) are linearly associated with various measures of blood glucose such as fasting plasma glucose, even down to levels below the conventional thresholds used to define diabetes (down to 4.9–5.3 mmol/litre) (Fig. 16.13.2.5). The landmark UKPDS study identified a quintet of modifiable risk factors for CHD in non-insulin-dependent diabetes mellitus, comprising HDL and LDL cholesterol, haemoglobin A1C, systolic blood pressure, and smoking. Of these the relative risks were highest for LDL cholesterol and blood pressure. CHD risk in patients with diabetes may be further refined by the detection of microalbuminuria as a reflection of early endothelial and microvascular damage. The optimal levels of blood glucose for CHD risk are still under debate, partly because several large randomized clinical trials of intensive glucose control among diabetic patients failed to show consistent reduction in risk. Early trials of intensive treatment were not powered to detect a small reduction in CHD risk, and more recent trials showed mixed results: some studies indicated increased risk, possibly due to higher age at enrolment or side effects of drugs, including hypoglycaemia, and others did not find an effect, possibly due to use of other preventive drugs in the control groups that reduced the power to detect any change in the outcomes. Several large randomized trials have shown that modification of lifestyle (such as quitting smoking, weight loss, and a healthy diet) and medical intervention may substantially reduce the risk of diabetes among high-risk patients (i.e. obese individuals or those who have borderline high blood glucose). A particular focus of interest in diabetes prevention and control is improving the quality of dietary carbohydrates to include less processed carbohydrates and more whole grains. Another potential preventive intervention is reducing sugar-sweetened beverage intake, which is associated with higher risk of obesity. Diet quality The evidence on diet quality and CHD has grown substantially in the last few decades and the focus of this line of research has changed from analysis of specific nutrients to foods and dietary patterns. Early epidemiological data identified the Mediterranean diet, which is high in olive oil, cereals, nuts, fruits, and vegetables, and low in animal fat, as protective against cardiovascular disease, and a recent large randomized trial has corroborated this finding. Next, we summarize the main evidence on CHD prevention by improving diet quality. Salt Our perception of salt (sodium chloride) has changed from being a common food preservative to becoming one of the main causes of high blood pressure, which is itself the leading risk factor for CHD. Many observational studies have reported a positive association between salt intake and risk of CHD, but some studies have also Fig. 16.13.2.5 Relative risk of stroke and CHD by fasting glucose levels. From Lawes CM, et al. (2004). Blood glucose and risk of cardiovascular disease in the Asia Pacific region. *Diabetes Care*, 27(12), 2836–42.

16.13.2 Coronary heart disease: Epidemiology and prevention 3611 reported a lower intake of salt to be associated with higher risk of mortality. This observation may be due to the presence or severity of an underlying chronic disease (e.g. patients with advanced chronic kidney disease or congestive heart failure, which have high mortality, may have a low salt intake). Several dozen randomized clinical trials of salt reduction have shown reduction in blood pressure following short-term feeding interventions that reduce salt intake. In meta-analyses of these trials, each 2.3 g/day lower salt intake has been associated with 4–7 mm Hg reduction in systolic blood pressure, and the effects are larger in older or hypertensive individuals or individuals from particular racial/ethnic

groups (e.g. African Americans). Although a reduction in blood pressure is expected to reduce the risk of CHD and stroke, only the long-term follow-up of one of the larger salt reduction trials has shown some reduction in CHD risk. Future large-scale trials are expected to provide a more definitive answer to the question of the effect of salt reduction on CHD in a range of populations and levels of baseline salt consumption. Salt intake has been stable in the past 20 years in many countries. However, the average global intake (c.10 g/day) is almost double the level recommended by the World Health Organization (WHO), with some regions such as East and Central Asia, and eastern Europe, having much higher intake levels. The optimal level of salt intake is still highly debated and the most recent recommendations from national guidelines in the United States of America and the United Kingdom suggest 5.8 g/day. There is some evidence that current efforts to reduce salt intake in the United Kingdom may have been responsible for further reductions in CHD risk at the population level, and WHO recommends salt reduction programmes as one of the most cost-effective ways to prevent CHD.

Fat composition

The relationship between dietary fat composition and CHD has been one of the major sources of controversy in the field of nutritional epidemiology. There is now a consensus that trans fats from hydrogenated oils increase the risk of CHD by increasing LDL cholesterol, and there is strong evidence that substituting saturated fats with polyunsaturated fats reduces CHD risk. The recommendation for a low-fat diet in the 1970s, which was used as a marketing technique by many food manufacturers, was based mostly on ecological studies in the 1960s that had shown a positive correlation between average saturated fat intake and CHD mortality across countries, and short-term feeding studies and animal studies that had shown a rise in serum total cholesterol with higher saturated fat intake. However, more recent reanalyses of the feeding studies and results of prospective studies of diet and CHD showed no increased risk of CHD if saturated fat was substituted by carbohydrates, which could partly be explained by increases in both LDL- and HDL-cholesterol. The importance of polyunsaturated fats (in particular those high in n-3 and n-6 fatty acids) was proposed following observational studies in the 1970s that suggested a low incidence of CHD in Greenland and Alaskan Eskimos consuming a diet based on oily cold-water fish. The beneficial effects could be mediated by the impact of polyunsaturated fats on coagulation, platelet and endothelial function, and serum LDL, and HDL composition and levels. The effect of higher intake of polyunsaturated fatty acids in reducing CHD risk is consistent with recent evidence from a large randomized trial which showed lower CHD risk among individuals who received a serving (about 30 g) of nuts every day for 5 years compared with a usual Mediterranean diet. The impact of n-3 polyunsaturated fatty acids on CHD prevention has also been widely studied. Meta-analyses of observational studies show a protective effect of higher n-3 intake, with beneficial effects for an intake of up to 250 mg/day. However, the most recent meta-analysis of randomized trials of n-3 supplementation did not find any reduction in mortality or risk of myocardial infarction. A recent global analysis of nutritional surveys indicated that between 1990 and 2010 intakes of trans and saturated fatty acids remained stable, while those of n-6 and n-3 fatty acids increased. However, the current trends in developing countries toward higher intake of animal meat and processed foods which contain high saturated and trans fatty acids may well lead to a more harmful impact of fat composition on CHD.

Other dietary risk factors

Fruit and vegetables

Low intake of fruits and vegetables has been linked to higher CHD risk in several prospective observational studies, leading to recommendations of at least five daily servings of fruits and vegetables. In the absence of randomized trials that directly evaluate this effect, there is still potential for such associations to be due to confounding by other lifestyle factors. The mechanisms and pathways for such potential effects are not clear, but could include the effects of fruits on increasing potassium intake and

therefore lowering blood pressure and the potential benefits of fibre, antioxidants, micronutrients, and folate. Red and processed meat The controversy about the effect of fresh red meat intake on CHD continues, but there is ample evidence from observational studies on the harmful effects of processed meat on CHD (which could partly be due to the increased risk of diabetes): each 50 g per day higher intake of processed meat is associated with 44% higher risk of CHD. Folate, B12, and homocysteine There is strong evidence from observational studies that higher serum homocysteine levels are associated with CHD risk. However, randomized clinical trials of folate and vitamin B12 supplementation that reduce serum homocysteine have found mixed results. A large study that used the methylene tetrahydrofolate reductase (MTHFR) gene to examine the effect of lower homocysteine on cardiovascular disease suggested that the observed association is unlikely to be causal. Dietary cholesterol The strong epidemiological data relating serum cholesterol to CHD summarized just now, along with early animal feeding studies, led to many researchers and clinicians recommending lowering dietary cholesterol in patients at risk of CHD. However, the correlation between dietary cholesterol and serum cholesterol is quite weak and there is insufficient evidence on the impact of dietary cholesterol on serum cholesterol levels and risk of CHD.

section 16 Cardiovascular disorders 3612 Dairy products There is no evidence that higher dairy intake is associated with CHD risk, possibly due to beneficial effects through blood pressure reduction being balanced by harmful effects through increased risk of arterial calcification. Similarly, there is no evidence that intake of whole-fat dairy would increase the risk of CHD. Exercise, fitness, and sedentary lifestyle Physical inactivity is associated with higher risk of CHD. Early studies in the 1960s on London bus conductors and longshoremen in San Francisco (California) found a clear gradient of CHD risk across levels of physical activity. Since then, several dozen observational studies have found a dose-response relationship with 30–35% risk reduction for CHD in the most active individuals compared with the least active. This effect is believed to be partly mediated through weight loss as well as reductions in blood pressure and better metabolic and lipid profiles. The current prevention guidelines recommend at least half an hour of moderate or vigorous activity at least 5 days a week. Vigorous physical activity can also be a trigger for acute myocardial infarction and the overall risk should be balanced when encouraging patients to increase their physical activity. Cardiorespiratory fitness can be considered the consequence of physical activity and is often measured by exercise tolerance testing. A recent meta-analysis of observational studies reported that each 1 km/h higher speed of running or jogging is associated with a 15% reduction in risk of CHD. Finally, a new line of research has identified sedentary lifestyle as a risk factor for CHD above and beyond physical inactivity. Each additional 2 hours of screen time is linked to 5% higher risk of cardiovascular events. The associations were weaker but still significant for overall sitting time. Reducing television watching time in children is one of the few interventions that have proved beneficial in controlling childhood obesity. Alcohol More than 30 observational studies have found beneficial effects of regular and moderate alcohol drinking on CHD risk, and all types of alcohol beverages seem to confer this benefit similarly, the potential mechanism perhaps being by reducing platelet adhesion. Heavy and binge drinking will offset these beneficial effects: higher alcohol intake increases blood pressure and risk of cardiac arrhythmias, and directly damages myocardial cells. In 2015, just over 40% of adults worldwide drank alcohol, with about one-sixth of drinkers drinking large amounts and therefore not benefiting from potential CHD risk reduction. Massive and rapid changes in alcohol intake were responsible for the largest observed increase in CHD mortality in modern times, which happened in Russia in

the 1990s. Illicit drugs Among various illicit drugs, cocaine abuse has been clearly identified as a trigger for acute myocardial events. Intake of marijuana also has the biological potential to increase the risk of atherosclerosis and act as a trigger of acute events. There is recent evidence from a large observational study in Iran that opium use may also increase CHD mortality. Sleep duration and quality Insufficient sleep is associated with higher risk of CHD, possibly through its effect on blood pressure as well as systemic inflammation, oxidative stress, and endothelial dysfunction. An extreme example is obstructive sleep apnoea, which is linked to a potential doubling of CHD risk. Psychosocial factors Major depression has been associated with higher CHD risk in observational studies, with the risk increasing by 80% in patients with a history of major depression episode. However, randomized trials of antidepressant treatment among CHD patients have provided mixed results. The role of stress in CHD was initially investigated by identifying 'character types' in the Framingham Heart Study in the 1950s. Chronic stress is a clear cause of high blood pressure and acute stress can trigger myocardial events. Evidence from studies conducted in the 1960s and 1970s also indicate that chronic stress can increase the risk of death following an acute myocardial infarction. More recently, 'relaxation response' has been shown to reduce blood pressure. Various types of psychosocial stress are associated with higher CHD risk. These include acute and chronic stressors and anxiety as well as a sense of deprivation and inequality, social isolation, and poor social support. The landmark Whitehall studies of British civil servants have provided strong evidence that socioeconomic position of an individual is a strong determinant of their CHD risk, possibly through changes in established cardiovascular risk factors such as smoking, hypertension, diabetes, and dyslipidaemia. See Chapter 2.14 for further discussion. Environmental factors The harmful effect of outdoor and indoor air pollution on CHD has been shown in observational studies. Higher concentrations of smaller particles (PM 2.5) is more strongly associated with risk of CHD than larger particles (PM 10). Globally in 2015, 28% of the burden of disease from CHD was attributed to air pollution. In rural areas and developing countries, similar harmful effects have been observed due to burning solid fuels indoors for cooking or heating. See Chapter 10.3.1 for further discussion. Recent evidence has also linked high road traffic noise levels to CHD, possibly through increasing blood pressure. Chronic lead exposure through inhalation (dust or fumes) and ingestion (water, food, cigarettes) has been associated with higher blood pressure, which could itself lead to higher CHD risk. Harmful effects have also been reported for cadmium exposure and high doses of arsenic. HIV and other infections With more successful and accessible HIV treatments, the interaction between HIV and its treatment with CHD and other cardiovascular diseases has become a novel area of research. It is well known that some antiretroviral drugs increase serum cholesterol levels, the pathophysiology of HIV infection may itself lead to dyslipidaemia, and there is some evidence that effective HIV treatment may lead to weight gain. However, the overall impact of long-term HIV infection and antiretroviral treatment on CHD remains unknown.

16.13.2 Coronary heart disease: Epidemiology and prevention 3613 Other viral or bacterial infections such as *Chlamydia pneumoniae*, *Helicobacter pylori*, Cytomegalovirus (CMV) have also been associated with higher CHD risk, but there is currently no strong evidence that such associations are independent of other well-known risk factors. Chronic kidney disease There is strong evidence from observational studies that chronic kidney disease increases the risk of CHD, and cardiac disease is the leading cause of death among patients with end stage renal disease. Even minor impairment of renal function (chronic kidney disease stage 3, eGFR 30–60 ml/min) has been linked to slightly higher risk of CHD and points to the need for more aggressive management

of classic risk factors in these patients. The potential mechanisms are through higher blood pressure levels, dyslipidaemia, anaemia, and increased systemic inflammation. Novel biomarkers Several inflammatory, haemostatic, and coagulation markers have been associated with higher CHD risk. Among these C-reactive protein, fibrinogen, and interleukin-6 are the most well-known. However, there is still insufficient evidence on the exact role of these biomarkers, and hence it is not clear how they may be used to design preventive interventions, but of particular interest is their use in improving risk prediction models and discovery of new therapeutic targets.

Gender and genetic influences Gender Despite a lower incidence of myocardial infarction in women compared to men, CHD is the most common cause of death in women in most developed countries, and the rate of decline in death from coronary disease has been less for women than for men. The difference in incidence of coronary disease between men and women is not explained by conventional risk factors alone. Although there is no distinct inflection in the incidence of coronary disease in women around the menopause, the difference in incidence of CHD has been attributed to the impact of hormonal changes. This concept was supported by theoretical considerations on the impact of oestrogens and progesterone on the vasculature and thrombogenesis, and a meta-analysis of observational studies suggesting that hormone replacement therapy (HRT) might be protective. The Women's Health Initiative trial of HRT strongly refuted this hypothesis, finding an increased risk of events (odds ratio 1.29) among women randomized to HRT.

Genetic influences Several studies have demonstrated the independent association of family history with the risk of cardiovascular disease, but the observed associations tend to add very little to risk discrimination when risk prediction models include other traditional risk factors. Nonetheless, twin and family studies suggest that about half of the susceptibility to CHD is heritable; an effect that is most evident among younger individuals. This observation has sparked numerous studies to unravel the genetic basis of CHD. Multiple genome-wide association studies investigating tens of thousands of common single nucleotide polymorphisms (SNPs) have been reported. These studies have identified about 60 common SNPs that are associated with CHD risk, mainly among individuals from European and South Asian ancestry. This has led to a better understanding of the genetic architecture of CHD and has demonstrated that CHD largely derives from the effect of multiple common SNPs of small effect size, rather than rare variants with large effects. However, the identified SNPs together explain only about 10% of the genetic variance of CHD, partly because many of them contribute to risk through traditional risk factors, such as blood pressure and lipid metabolism. Despite this, the identified SNPs have revealed novel promising drug targets within established risk factor pathways and have identified a few novel pathways such as inflammation that may contribute to the pathogenesis of CHD. However, the relevance of many other genes to CHD remains unknown and subject to ongoing studies. The availability of large-scale genotyping studies has also facilitated the development of Mendelian randomization studies as a method of assessing causality between a risk factor and an outcome, and these have (for instance) refuted the causal role of HDL-cholesterol, homocysteine, and CRP. Although genetic markers, in particular those that show potential new causal pathways, are highly valuable for identification of new molecular targets for prevention and management of CHD, the anticipated clinical utility of genotyping for risk prediction has not (thus far) materialized. This is because conventional risk prediction scores are already relatively good at predicting CHD, questioning the incremental value of costly genotyping. It has been argued that more precise classification of subtypes of CHD is needed to better understand the impact of different mutations on the biology and pathophysiology of CHD. Supporting evidence for this line of thinking comes from a study that showed different SNPs to be associated with different manifestations of CHD, with some increasing

the risk of coronary atherosclerosis while others are associated with the risk of plaque rupture and acute myocardial infarction. In addition to pathophysiological pathways, the impact of genetic variants may differ by presence or absence of comorbid conditions. In one large-scale study, the same SNP was associated with a significantly higher risk of CHD among patients with diabetes, but no significant difference in risk of CHD among patients without diabetes was observed.

Clusters of risk factors: the metabolic syndrome

The concept of metabolic syndrome (syndrome X or insulin resistance syndrome) was proposed in the late 1980s to designate a constellation of risk factors for CHD and other atherosclerotic cardiovascular diseases. The idea was that co-occurrence of several risk factors may be due to common underlying pathophysiological processes and may confer a level of risk that is larger than the sum of the effect of each risk factor alone. The components of metabolic syndrome include hyperglycaemia, hypertriglyceridaemia, and low HDL levels, high blood pressure, and abdominal obesity. Some studies have found that the patients with metabolic syndrome have twice as high a CHD risk compared with individuals with no risk factor. However, others have argued based on similar analyses in different settings that the 'syndrome' may just be a co-occurrence of a subset of cardiovascular risk factors and not an entity by itself. Irrespective of these debates, many clinicians continue to use this

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term to alert others of the presence of the cluster of risk factors in an individual. Combining risk factors to predict and manage risk in individuals Successful and cost-effective prevention of CHD requires identification of high-risk individuals who would benefit more from risk reduction. One way of identifying high-risk individuals is to measure their risk factor levels and use clinical thresholds for each risk factor separately to designate a high-risk status (e.g. hypertensive or diabetic). This approach has been used in the past 50 years and is still the method commonly proposed by clinical guidelines used by clinicians. However, as just summarized, CHD is a multifactorial disease and most risk factors increase CHD even at levels well below the conventional thresholds used to define high-risk status. Generally, single risk factors are rarely accurate enough in predicting future risk for individuals. For example, for a binary risk marker to provide good discrimination between those who will suffer an event from those who will not, the odds ratio of that marker with the outcome would need to be greater than about 9, which is not the case for any single risk factor described here. Therefore, to predict an individual's risk one must combine the information on levels of the most important risk factors. A common way of doing this is to use a risk prediction score. Most risk prediction scores combine CHD and stroke to provide a predicted risk for overall cardiovascular disease (CVD). The most well-known risk score is the Framingham Risk Score, which is based on the analysis of the Framingham Heart Study cohort in Massachusetts (United States). Each risk score is a combination of a 'baseline' or average risk and a set of coefficients for different risk factors that predict how each individual deviates from that average risk based on how much their risk factor levels deviate from mean risk factor levels in the target population. To apply a risk score to a new population, the average risk and mean risk factor levels must be recalibrated to correspond to the target population; otherwise the risk score will be biased. Most risk scores use information on the major CVD risk factors such as smoking, blood pressure, serum cholesterol, and diabetes. Others include socioeconomic factors and family history of heart disease as well. Although risk prediction scores, even when based on a few simple risk factors, are usually more accurate in estimating risk than individual risk factors or a qualitative summary of several risk factors by clinicians, their performance is still far from ideal. For those individuals classified as having an intermediate level of risk, different risk scores may provide different results, hence many

researchers are focusing on identifying new risk factors or risk markers that can help improve the performance of prevailing models that are based on traditional risk factors. Several potentially useful novel risk factors are summarized earlier in the chapter, of which inflammatory markers have had the greatest potential in improving the predictive value of risk scores. In addition to the risk factors already mentioned, several other biomarkers have been evaluated. For instance, blood B-type natriuretic peptide levels or different types of vascular imaging (carotid intima-media thickness and coronary calcium scoring) have shown some promising results. Further research is underway to establish the value of such markers to subgroups of patients and healthcare systems. Most risk scores provide an approximate 10-year risk of CHD or CVD risk and clinicians can then use this information, along with current clinical guidelines, to propose a prevention strategy for each patient. Primary intervention (i.e. for patients without pre-existing diagnosis of vascular disease) is based on a threshold of risk. One example, the Globorisk chart (Fig. 16.13.2.6) uses age, gender, smoking, diabetes, systolic blood pressure, and serum total cholesterol to predict 10-year risk of fatal and nonfatal CVD for 187 countries worldwide. An office-based version estimates the same risk using BMI instead of diabetes and serum cholesterol, allowing risk prediction in resource-poor settings with limited access to a laboratory. Most national and international guidelines recommend that individuals with a 10-year risk of fatal or nonfatal CVD greater than 20% should be offered lifestyle advice and specific treatment for individual risk factors. Use of these risk charts in conjunction with guidelines for treatment of hypertension (see Chapter 16.17.2) and other modifiable risk factors will guide priorities in drug therapy. Likely future developments

Several risk factors have been shown to be significantly associated with future risk of CHD and a few of these, largely through randomized trials, are known to cause CHD. Although new research into new CHD risk factors is likely to help identify new molecular targets for its prevention and management, the shorter-term advantage that such new markers offer is an increasing accuracy in the estimation of CHD risk and treatment benefits. Large-scale observational studies investigating the utility of new biomarkers, both phenotypic and genotypic, will help improve the accuracy of existing risk scores. This, combined with randomized evidence (e.g. from large individual patient data meta-analyses), will provide more granular information about the safety and efficacy of specific interventions in specific subgroups of patients. The combination of better risk prediction and better estimation of treatment effects in subgroups of patients is expected to lead to 'personalized prevention', where those with the greatest risk and greatest potential benefit of treatment will be offered an intervention. However, the challenge of maximizing benefits of preventive therapies for individuals as well as societies will not be solved by developing better risk scores and risk management algorithms alone. Previous research suggests that cardiovascular risk prediction models are not widely used, partly because many clinicians find risk calculation too time-consuming and remain unconvinced of the predicted risk. Automated data capture systems and better techniques for risk visualization may minimize clinician burden and facilitate communication of risks and uncertainties to patients and their families. Similar tools could also make information directly accessible to patients and therefore increase their engagement, as well as that of their healthcare providers. Ultimately, a scenario could be envisaged in which there is seamless linkage between data capture, risk and benefit estimation, and clinical guidelines, resulting in the routine provision of personalized guidance for care that is both evidence-based and cost-effective. However, given that the introduction of such innovative models in complex healthcare environments can have multiple intended and unintended effects, appropriately designed studies are needed to evaluate the actual effects of such system changes before more general recommendations are made.

16.13.2 Coronary heart disease: Epidemiology and prevention 3615 Fig. 16.13.2.6 Globorisk chart: 10-year risk of fatal or nonfatal coronary heart disease or stroke in the United Kingdom, calculated using the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. Reprinted from The Lancet Diabetes and Endocrinology, Vol. 5, Ueda P, et al., Laboratory-based and office-based risk scores and charts to predict 10-year risk of cardiovascular disease in 182 countries: a pooled analysis of prospective cohorts and health surveys, pp. 196–213, Copyright 2017, with permission from Elsevier.

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