Epidemiological studies of CHD and the evolution of preventive cardiology

Nathan D. Wong

Abstract | Cardiovascular diseases (CVDs) cause nearly one-third of all deaths worldwide. Coronary heart disease (CHD) accounts for the greatest proportion of CVDs, and risk factors such as hypertension, cigarette smoking, diabetes mellitus or elevated glucose level, elevated cholesterol levels, and obesity or being overweight are the top six causes of death globally. Ecological and population-based longitudinal studies, conducted globally or within individual countries, have established the role of traditional and novel risk factors and measures of subclinical disease in the prediction of CHD. Risk assessment with short-term or long-term risk prediction algorithms can help to identify individuals who would benefit most from risk-factor interventions. Evaluation of novel risk factors and screening for subclinical atherosclerosis can also help to identify individuals at highest cardiovascular risk. Prevention of CHD focuses on identifying and managing risk factors at both the population and individual levels through primordial, primary, and secondary prevention. Epidemiological studies have provided the hypotheses for subsequent clinical trials that have documented the efficacy of risk-factor interventions, which are the basis of preventive cardiology. Future research efforts will determine the screening and intervention strategies that have the greatest effect on CHD prevention.

Introduction

Cardiovascular diseases (CVDs) account for >17 million deaths globally each year (30% of all deaths), 80% of which occur in low-income and middle-income countries, and this figure is expected to grow to 23.6 million by 2030.[1] Ischaemic heart disease alone caused 7 million deaths worldwide in 2010, an increase of 35% since 1990.[2] Commencing in 1980, the Global Burden of Disease Study has provided the most-comprehensive estimates of disease burden for 235 causes of death[2] and the disease burden attributable to 67 different risk factors in 21 regions of the world.[3] Noncommunicable diseases, of which CVDs are the most prevalent, cause the greatest morbidity and mortality worldwide. Eliminating obesity, unhealthy diets, and physical inactivity could prevent up to 80% of heart disease, stroke, and diabetes mellitus.[1]

Coronary heart disease (CHD) is the largest contributor to CVD; its incidence and the prevalence of important risk factors varies greatly according to geographical region, sex, and ethnic background. For example, CHD death rates (per 100,000 population) vary 20-fold in men (ranging from 35 in South Korea to >733 in the Ukraine) and nearly 30-fold in women (ranging from 11 in France to nearly 313 in the Ukraine).[4] Multiple longitudinal, epidemiological studies have provided valuable insights into the natural history and risk factors associated with the development and prognosis of CHD, and have provided the foundation for intervention studies and clinical trials aimed at primordial, primary, or

secondary prevention of CHD. Primordial prevention is aimed at the prevention of CVD risk factors, such as hypertension, obesity, and dyslipidaemia. Primary prevention focuses on the modification of these and other known risk factors, and is aimed at preventing the clinical manifestations of CVD, such as myocardial infarction (MI) and stroke. Secondary prevention focuses on individuals who already have manifestations of CVD, but where aggressive control of risk factors can have a major effect on preventing recurrences of disease. Randomized clinical trials have demonstrated the value of managing several important risk factors, for both the primary and secondary prevention of CHD.

In this Review, I discuss the evolution of the epidemiology of CHD, and the contributions that major population studies have made in establishing the contribution of important risk factors to the assessment of cardiovascular risk and in laying the foundation for practice in preventive cardiology. This Review is intended to highlight key cardiovascular epidemiological studies and the messages they have provided in the evolution of the field of preventive cardiology. However, a discussion of other studies conducted in specific populations are beyond the scope of this Review.

Definitions and incidence

CVDs are comprised principally of CHD (including stable and unstable angina, nonfatal MI, and coronary death), heart failure, cardiac arrest, ventricular arrhythmias and sudden cardiac death, rheumatic heart disease, transient ischaemic attack, ischaemic stroke, subarachnoid and

Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine, C240 Medical Sciences, University of California, Irvine, CA 92697, USA. ndwong@uci.edu

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Key points

- Ecological and population-based longitudinal studies, globally or within countries, have established the role of risk factors and subclinical disease measures in the prediction of coronary heart disease (CHD) events
- CHD risk assessment, using short-term or long-term risk prediction algorithms, can help to identify individuals who would most benefit from interventions to control risk factors
- Evaluation and screening of novel risk factors or for subclinical atherosclerosis can also help to identify individuals at high risk of CHD
- Prevention of CHD focuses on identifying and managing important risk factors at both the population and individual levels through efforts aimed at primordial, primary, and secondary prevention
- Data from epidemiological studies have provided the hypotheses for subsequent clinical trials, which have documented the efficacy of risk factor interventions that are the basis of preventive cardiology
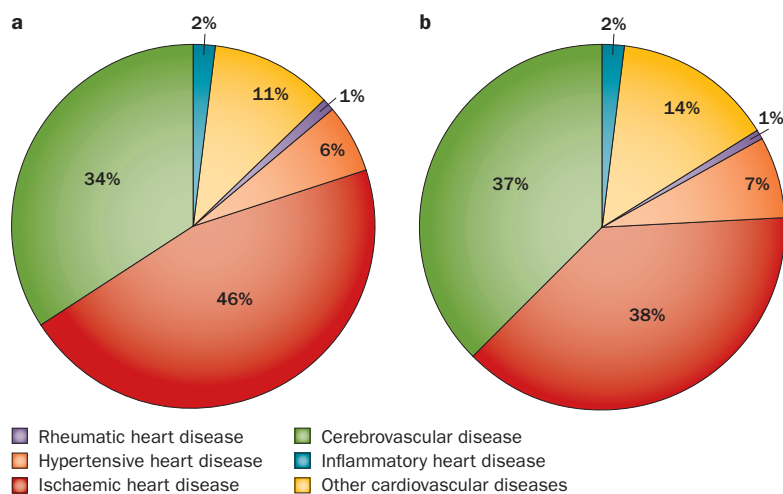

Figure 1 | The proportions of cardiovascular deaths caused by ischaemic heart disease, cerebrovascular disease, inflammatory heart disease, rheumatic heart disease, hypertensive heart disease, and other cardiovascular diseases in 2011. **a** | Men. **b** | Women. Reproduced, with the permission of the publisher, from Mendis, S., Puska, P. & Norrving, B. (Eds) *Global Atlas on Cardiovascular Disease Prevention and Control*. Geneva, World Health Organization, 2011 (Figures 4 & 5, Page 4 http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf?ua=1, accessed 24 February 2014).

intracerebral haemorrhage, abdominal aortic aneurysm, peripheral artery disease, and congenital heart disease. Ischaemic heart disease, which consists principally of CHD, is the predominant manifestation of CVD, and causes 46% of cardiovascular deaths in men and 38% in women.[1] Cerebrovascular disease is the form of CVD with the second-highest mortality—34% of cardiovascular deaths in men and 37% in women (Figure 1).[1] Although the burden of CHD was highest in Western countries during much of the 20th century, the greatest burden of CHD now occurs in particular Asian and Middle-Eastern regions (Figure 2).[1]

MI, angina pectoris, and sudden coronary death are the major clinical manifestations of CHD. The initial presentation of CHD is sudden coronary death in approximately one-third of cases. CHD can also be defined by the procedures performed as a result of documented, clinically relevant atherosclerosis, such as CABG surgery or percutaneous coronary intervention (PCI; including angioplasty and stenting). Nonfatal or fatal MI or sudden coronary death are typically included as 'hard' CHD end points in clinical trials, whereas 'total' CHD might additionally include angina requiring hospitalization as well as CABG surgery or PCI.

Evolution of CHD epidemiology

The first major organized efforts involving epidemiological approaches to cardiovascular disease began in the 1940s. However, the lack of reliable data on heart disease was noted as early as the 1880s[5] and, in 1934, a conference of the International Society of Geographical Pathology on the subject of cardiovascular diseases described data on the frequency of atherosclerotic lesions across countries and by social class and occupation.[6] In 1946, before the field of cardiovascular epidemiology existed, the first prospective studies of CHD in professional men were launched in Minnesota, USA.[7] The methods involved in the Minnesota studies led to the development of the renowned Seven Countries Study,[8] which formally started in Yugoslavia in 1958, although hypotheses on the relationship between serum cholesterol and geographical differences in the frequency of CHD were first proposed in 1953.[9] The Seven Countries Study[8] culminated in the participation of 12,763 men aged 40–59 years, across 16 cohorts in seven countries. Much of our current knowledge on the relationships between lifestyle, diet, CHD, and stroke in different parts of the world was derived from this study.[10,11] Importantly, the Seven Countries Study[10] showed, at both the population and individual levels, that the rates of heart attack and stroke were directly related to the level of total cholesterol, and that this relationship was consistent across different cultures. The first symposium on CVD epidemiology took place in 1954 in Washington, DC, USA in conjunction with the World Congress of Cardiology.[9]

Planning for the Framingham Heart Study (FHS),[12] considered by many to be the seminal epidemiological study of CHD, was begun in 1947 by the newly formed National Heart Institute (the predecessor of today's National Heart, Lung, and Blood Institute; NHLBI). Recruitment of the original cohort of 5,209 participants aged 30–62 years began in 1948, and involved biennial physical examinations, risk-factor assessments, and surveillance for CHD and CVD events. The initial design of the FHS[13] was published in 1951. In 1957, age-related and sex-related differences in CHD were first reported, as well as findings on the clinical relevance of elevated blood pressure and cholesterol levels, and being overweight, in predicting CHD.[14] The FHS was instrumental in the identification of many of the factors that are associated with an increased risk of CHD. In 1961, study director William B. Kannel coined the term 'risk factors' that is widely utilized in many fields of medicine today.[15] Landmark papers documenting the roles of serum cholesterol,[16] cigarette smoking,[17] and hypertension[18] as predictors of CHD were published during the first 2 decades of the study. The increased awareness of major risk factors for CHD initially identified in the FHS and by other researchers provided the impetus for important public health initiatives against smoking in the 1960s,
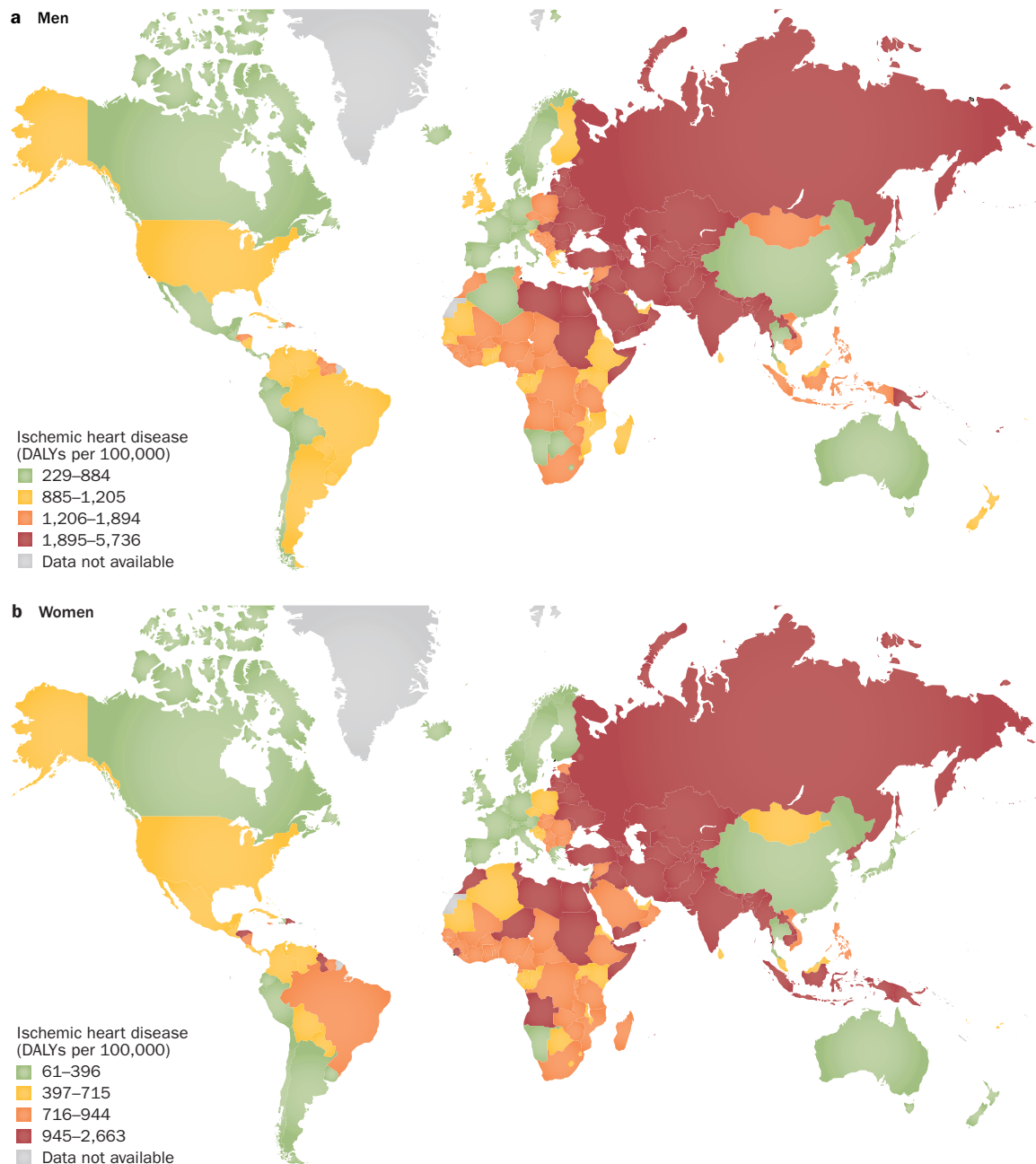
a Men

Ischemic heart disease
(DALYs per 100,000)

- 229–884
- 885–1,205
- 1,206–1,894
- 1,895–5,736
- Data not available

b Women

Ischemic heart disease
(DALYs per 100,000)

- 61–396
- 397–715
- 716–944
- 945–2,663
- Data not available

Figure 2 | The global distribution of ischaemic heart disease burden, in DALYs, in 2011. **a** | Men. **b** | Women. Data are age-standardized per 100,000 of the population. Abbreviation: DALYs, disability-adjusted life years. Reproduced, with the permission of the publisher, from Mendis, S., Puska, P. & Norrving, B. (Eds) *Global Atlas on Cardiovascular Disease Prevention and Control*. Geneva, World Health Organization, 2011 (Figures 19 & 20, Page 12 http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf?ua=1, accessed 24 February 2014).

hypertension in the 1970s, and hypercholesterolaemia in the 1980s. The FHS later showed the inverse relationship between HDL cholesterol and CHD risk, regardless of total-cholesterol level (Figure 3),[19] and the important connection between diabetes and CHD, including the higher risk of CHD and CVD associated with diabetes in women than in men.[20,21] Moreover, the FHS has provided important contributions in genetic epidemiology, such as the genomic determinants of hypertension,[22,23] and in the epidemiology of stroke[24] and heart failure.[25] In addition,

the FHS demonstrated that risk factors are often clustered, and that the number of risk factors present and their co-occurrence is directly related to the incidence of CHD (Figure 4).[15,26] Importantly, the concept of multivariable or global risk assessment for CHD was first introduced in the FHS.[26] Among its other contributions to the field of preventive cardiology, the FHS[27] corrected clinical misconceptions, revealed the effect of overt and subclinical CVD, enhanced mortality statistics with population-based incidence of nonfatal cardiovascular events, and
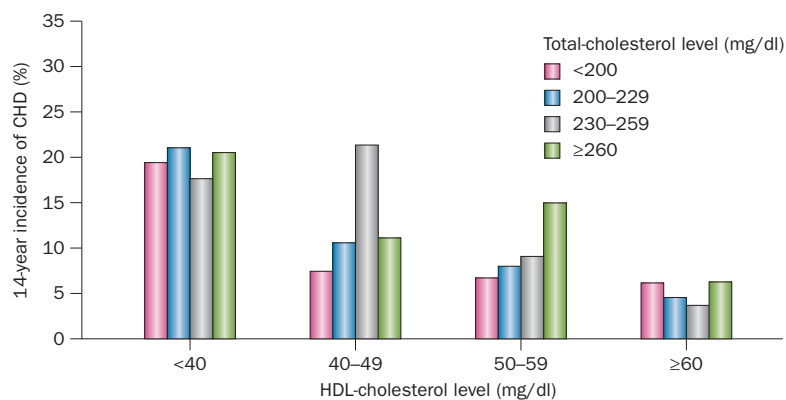
Figure 3 | Association between HDL-cholesterol levels and CHD risk according to levels of total cholesterol.[19] Abbreviation: CHD, coronary heart disease.

developed multivariable cardiovascular risk assessment profiles (the Framingham Risk Score). Table 1 shows the pivotal epidemiological studies on CHD that have been performed globally or in individual countries. These studies are discussed individually below.

Global studies of CHD epidemiology

Critical to our understanding of the global distribution of CVD are the multinational studies into the incidence of, and risk factors for, CHD and CVD across various cultures.

The MONICA project

The largest and one of the most-important studies on the international incidence of CHD and CVD was the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project,[28] which was developed by the WHO to measure the incidence and determinants of

	A	B	C	D
Blood pressure (mmHg)	120/80	140/90	140/90	140/90
Total-cholesterol level (mg/dl)	200	240	240	240
HDL-cholesterol level (mg/dl)	50	50	40	40
Diabetes mellitus	No	No	Yes	Yes
Cigarette smoking	No	No	No	Yes

Figure 4 | Estimated 10-year CHD risk in adults aged 55 years in the Framingham Heart Study[26] according to levels of various risk factors. Abbreviation: CHD, coronary heart disease.

fatal and nonfatal CHD and stroke in various populations over a 10-year period. Beginning in 1979, the programme focused on evaluating these trends in a total population of ~15 million men and women aged 25–64 years. Three major publications from the MONICA project focused on trends in survival and coronary event rates,[29] the contribution of changes in classic risk factors to these trends in coronary event rates,[30] and the contribution of changes in coronary care to survival, event rates, and CHD mortality.[31] Another report from this study recorded trends in risk factors over the 10-year period among 38 populations in 21 countries, showing that the rate of smoking generally decreased in men, but increased in women, the rate of systolic blood pressure and cholesterol levels decreased in both sexes, but that BMI increased significantly in over half of the populations studied.[32,33] Figure 5 shows the important association between serum cholesterol and rates of CHD observed in the MONICA study.
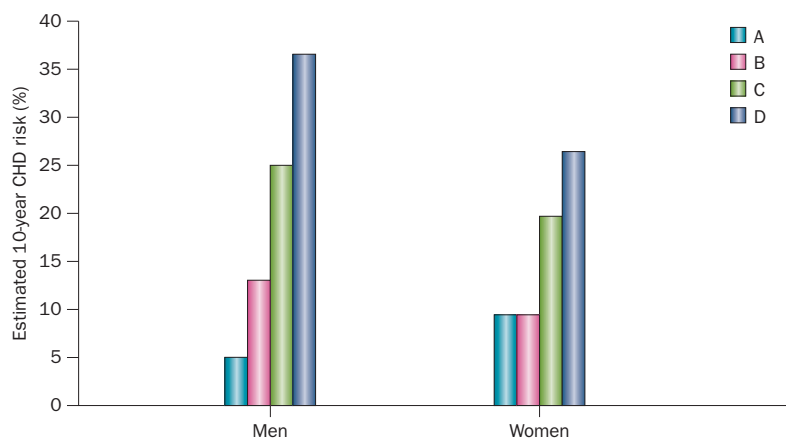
The INTERHEART study

A further important contribution to our understanding of the variation in CHD aetiology between populations was the Canadian-led INTERHEART study,[34] a global case–control study of risk factors for acute MI. This study was intended to explore the associations between a wide array of risk factors and acute MI within different ethnic or geographical populations spanning 52 countries throughout Africa, Asia, Australia, Europe, the Middle East, and North and South America, and to assess the relative importance of these risk factors across populations. Among 12,461 patients with acute MI and 9,459 age-matched and sex-matched controls without heart disease, nine risk factors (apolipoprotein B, apolipoprotein A-I, current smoking, the presence of diabetes, hypertension, or abdominal obesity, psychosocial index, lack of exercise, and excessive alcohol intake) were associated with acute MI, with risks consistent across all regions, ethnic groups, and men and women worldwide.[34,35]

The PURE study

Building upon the experience of the INTERHEART study, in 2002 the same investigators embarked on the Prospective Urban Rural Epidemiology (PURE) study,[36] in which they aimed to examine societal influences on lifestyle behaviours, cardiovascular risk factors, and incidence of chronic noncommunicable diseases. By March 2009, 139,506 individuals were enrolled across 600 communities in 17 low-income, middle-income, and high-income countries. Reports from the PURE study describe a widespread low prevalence of healthy lifestyle behaviours across countries of all levels of income, with a particularly low prevalence of these behaviours,[37] and a very low rate of cardioprotective drug use in secondary prevention, in low-income countries.[38]

The Ni–Hon–San study

Although not as large as the three studies mentioned above, the Nippon–Honolulu–San Francisco (Ni–Hon–San) study[39] was an important 'natural experiment' in CHD epidemiology. This investigation conducted in the

Table 1 | Major global and national epidemiological studies of cardiovascular disease*

Study	Year commenced	Location	Population studied
The Minnesota Businessmen study[6]	1946	Minnesota, USA	281 men aged <55 years
The Seven Countries study[7–10]	1958	Global	12,763 men aged 40–59 years
Framingham Heart Study[11–26]	1948	Massachusetts, USA	5,209 men and women aged 30–62 years
MONICA[27–32]	1979	Global	15 million men and women aged 25–64 years
INTERHEART[33,34]	1999	Global	15,152 patients with MI and 14,820 age-matched and sex-matched control individuals
The PURE study[35–37]	2002	17 countries	153,996 adults aged 35–70 years
The Ni–Hon–San study[38,39]	1965	Japan; Hawaii, USA; San Francisco, CA, USA	20,000 Japanese men aged 45–69 years
The Whitehall and Whitehall II studies[40–47]	1967 and 1985	UK	18,403 male civil servants aged 40–64 years, and 10,314 male and female civil servants aged 35–55 years
The Rejkavik study and AGES[48–50]	1968 and 2003	Iceland	9,141 and 2,499 men aged 34–79 years
The PROCAM study[51–53]	1979	Germany	4,043 men and 1,333 women aged 50–65 years
The CARDIA study[54–58]	1984	Four communities in the USA	5,115 African American and white men and women aged 18–30 years
ARIC[59–63]	1987	Four communities in the USA	15,792 African American and white men and women aged 45–64 years
The Strong Heart study[64–66]	1989	13 American Indian tribes in the USA	4,549 Native American men and women aged 45–75 years
The Cardiovascular Health study[67–70]	1989	Four communities in the USA	5,888 African American and white men and women aged 65–102 years
The Jackson Heart study[71,72]	2000	Jackson, MS, USA	5,302 African American men and women aged 21–94 years
MESA[73–79]	2000	Six communities in the USA	6,814 African American, Chinese, Hispanic, and white men and women aged 45–80 years
The Hispanic Community Health study/Study of Latinos[80,81]	2006	Four communities in the USA	15,079 Hispanic men and women aged 18–72 years

*All studies are discussed in this Review. Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Determinants in Young Adults; MESA, Multiethnic Study of Atherosclerosis; MI, myocardial infarction; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; Ni–Hon–San, Nippon–Honolulu–San Francisco; PROCAM, Prospective Cardiovascular Munster; PURE, Prospective Urban Rural Epidemiology.

1960s involved a cross-sectional evaluation of CHD in migrant Japanese men aged 45–69 years in Hawaii and California, and Japanese men of this age in Japan. The Ni–Hon–San study[39,40] showed that lifestyle changes associated with acculturation can potentially explain important changes in CVD risk. Japanese Americans had higher cholesterol levels and higher CHD mortality than men who remained in Japan, resulting from the adoption of a US lifestyle.[39,40]

National studies of CHD epidemiology
The success of the FHS no doubt led to the development of, and motivated the funding for, other important prospective, national, epidemiological studies during the past 50 years. Many of these studies incorporated elements of the FHS design, including the use of repeated examinations over time to follow the progression of risk factors and disease, the use of multivariable analytical approaches to decipher the independent contributions of multiple risk factors, and the use of standardized protocols for measurement of risk factors and cardiovascular outcomes. Most of these studies still accrue follow-up to the present day, and have helped to fill many of the gaps

in our knowledge on the determinants and prognosis of CHD risk factors in multiethnic populations, as well as the role of subclinical atherosclerosis in modifying CHD risk. Epidemiological studies involving specific or small populations not discussed in this Review that have made important contributions towards advancing the field of preventive cardiology are shown in Box 1.

The Whitehall studies
The Whitehall study, in which 18,403 British male civil servants aged 40–64 years were enrolled, started in 1967 and provided early data on cardiovascular risk factors, myocardial ischaemia, and CHD death,[41] as well as the prognostic relevance of respiratory symptoms[42] and cholesterol levels.[43] Between 1985 and 1988, an additional 10,314 male or female civil servants were enrolled in a new phase of this study (Whitehall II[44]), which provided valuable information on social determinants of health inequalities, including an inverse association between employment grade and angina prevalence, ischaemia, bronchitis, and health risk behaviours. Additional reports from this study have shown inverse associations between fair and respectful treatment at work and CHD,[45] and job
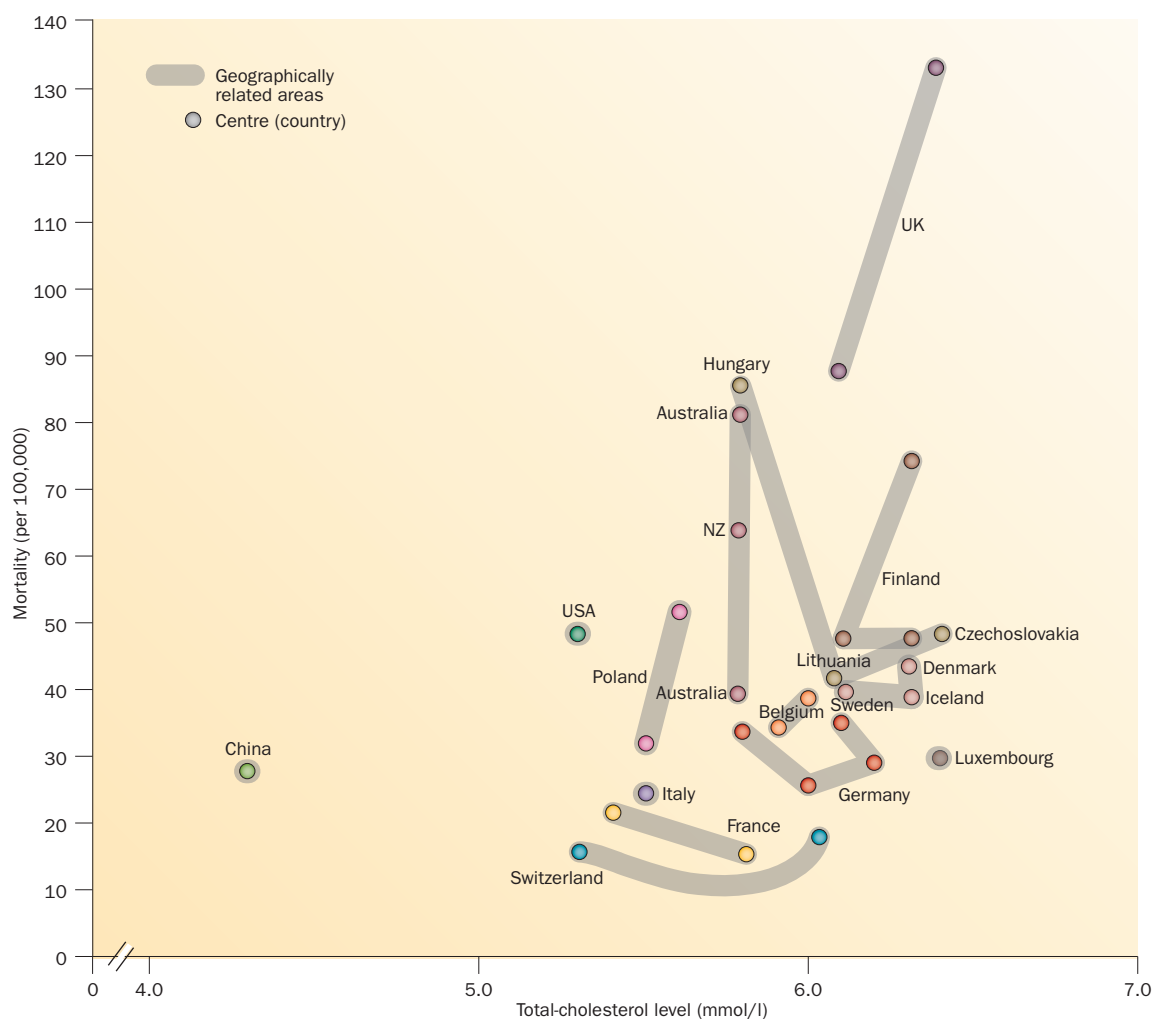
Figure 5 | Age-standardized ischaemic heart disease mortality in men aged 35–64 years (per 100,000 of the population) in relation to mean cholesterol levels at centres participating in the MONICA project.[32] The graph shows the association between total cholesterol and total mortality within a country, or region within the country. Each point represents a single centre. Encircling in grey shows regions of similar geographical area, but with variation in mortality according to total-cholesterol level. Abbreviation: NZ, New Zealand.

control with future CHD risk.[46] A subsequent report demonstrates the roles of genetic and nongenetic factors in the prediction of type 2 diabetes in the Whitehall II chort.[47]

The Reykjavik Heart Study

The Reykjavik Heart Study[48] also began in 1967, and was a population-based study of >30,000 men and women born in the greater Reykjavik area in Iceland between 1907 and 1935. In this study, risk factors for CHD were evaluated, and trends in the type and prevalence of CHD between 1968 and 1986 were examined.[48] The incidence, prevalence, characteristics, and prognosis associated with unrecognized MI were also investigated. One-third of those with unrecognized MI had a history of angina, and those with unrecognized MI had similar survival to those with recognized MI.[49] A new phase of this study called the AGES (Age, Gene, Environment, Susceptibility) study[50] began in 2003 as a 7-year collaboration between the Icelandic Heart Association and the NIH in the USA, and is one of the most-detailed and extensive studies of

ageing ever to be performed. In the AGES study,[50] which has 5,764 participants, genetic and other 'new' indicators of cardiovascular disease (such as retinal photographs of arterial damage, arterial tonometry, and MRI) are being examined, as well as gene–environment interactions and molecular markers of oxidative stress, immunological, and endocrine indicators. Some important cardiovascular findings from this study include the observation that individuals with a high coronary artery calcium score were more likely to have dementia than those with a low score, although this association was attenuated after adjustment for brain lesions and volumes.[51] In another report, those with diabetes who were receiving statins had a 50% lower cardiovascular mortality than those not taking statins.[52]

The PROCAM study

The Prospective Cardiovascular Munster (PROCAM) study[53] started in 1979, with the primary objectives of determining the prevalence of CHD risk factors and their

outcomes in the German population and improving the prediction and early detection of CHD. Initial reports focused on the prevalence and prognosis associated with important CHD risk factors.[53,54] However, probably the most-important contribution of the PROCAM study[55] was the development of a risk prediction score for CHD. Of interest, when the Framingham score was applied to this cohort, the risk of CHD was overestimated twofold.[56]

The CARDIA study
The Coronary Artery Risk Determinants in Young Adults (CARDIA) study[57] started in 1984, with the aim of examining lifestyle and other factors that affect the risk of CHD during young adulthood. A total of 5,116 participants aged 18–30 years were enrolled, half of whom were African American and half of whom were white.[57] This study was instrumental in examining the development and evolution of cardiometabolic risk factors and subclinical atherosclerosis, and their association with CHD events in young adults. The CARDIA study[57] and the Cardiovascular Health Study[58] (discussed below) were the first large cohort studies to include echocardiography to assess subclinical disease that included measures of left ventricular mass, wall thicknesses, and systolic function. In 2000, this study and the Multiethnic Study of Atherosclerosis (MESA; discussed below)[59] were the first in which the measurement of coronary calcium was used in young adults, and CARDIA[60] was the first to include reporting of on ethnic differences of this marker in young adults. Among other important findings from the CARDIA study were the relationship between weight change above the age of 15 years and changes in CHD risk factors,[61] and the ethnic differences in the incidence of heart failure among young adults.[62]

The ARIC study
The Atherosclerosis Risk in Communities Study (ARIC) study,[63] which commenced in 1987, is the single largest prospective US study of CVD, with 15,792 participants aged 45–64 years, half of whom are white and half African American. This study was the first major epidemiological investigation in which subclinical measures of atherosclerosis, notably carotid intima–media thickness, were used, as well as apolipoprotein levels, and coagulation and platelet assays. Reports from the ARIC study initially described risk-factor associations with carotid atherosclerosis,[64] and subsequently the additive value of carotid atherosclerosis and presence or absence of plaque over standard risk-factor assessment in the prediction of cardiovascular events.[65] With the interest in genetic contributions to CHD and CVD risk, the ARIC investigators also examined the effects of the 9p21 genetic variant on carotid intima–media thickness.[66] A further contribution of the ARIC study was to show the direct relationship between good cardiovascular health behaviours and low future CVD event risk.[67]

The Strong Heart Study
In response to the concern that insufficient information was available on CHD and CVD in Native Americans, the NHLBI began the Strong Heart Study[68] in 1988, involving 13 Native American tribes and communities in three geographical areas. The study included a survey to determine CVD mortality from 1984 to 1994, as well as clinical examination and morbidity and mortality surveillance of 4,500 tribal members who met the inclusion criteria. The study later expanded to include genetic epidemiology by investigating the heritability of CVD in these populations.[68] Among the important findings of the Strong Heart Study was the variation in incidence and predictors of diabetes across the different tribal areas studied,[69] and the associations between insulin resistance, metabolic syndrome, and CVD.[70]

The Cardiovascular Health Study
The Cardiovascular Health Study (CHS)[71] began in 1989 and involved a cohort of individuals aged 65–101 years at baseline. Initially, 5,201 participants, the majority of whom were white, were recruited, followed by an additional 587 African American individuals after 5 years. This investigation was the first major epidemiological study specifically focused on the elderly population, and included several measures of subclinical disease—carotid ultrasonography, ankle–brachial index and, for the first time (along with the CARDIA study) in a large cohort study, cardiac echocardiography.[58] Among many important contributions to our knowledge of the epidemiology of CHD, the CHS investigators reported on age-related trends in cardiovascular morbidity and physical functioning,[72] risk factors associated with mortality in elderly adults,[73] and associations between blood-pressure patterns (such as isolated systolic hypertension) and subclinical CVD.[74]

The Jackson Heart Study
The Jackson Heart Study,[75,76] is the largest prospective epidemiological study of African American individuals; 5,302 men and women aged 21–94 years from Jackson, MS, USA were enrolled. This study has provided valuable information on genetic and lifestyle determinants of metabolic syndrome and cardiovascular risk factors,[76]

and emerging data on novel biomarkers and prediction of CVD events. In one report, adiponectin was directly associated with incident stroke in women, but not in men and not with CHD in either sex, whereas leptin was not associated with either CHD or stroke.[77]

The Multiethnic Study of Atherosclerosis

Enrolment in the MESA[78] started in 2000, and people from four major US ethnic groups (African American, Chinese, Hispanic, and white individuals) were recruited. The focus of the MESA was on how the prevalence of, and outcomes associated with, subclinical athero-sclerosis differ between ethnic groups. The MESA also includes ancillary studies on air pollution, pulmonary disease, aortic calcification, and genetics. An important component of the MESA was the evaluation and prog-nostic relevance of coronary artery calcification, using a standardized protocol also used in the CARDIA study.[59] The MESA was the first major, population-based study to use cardiac MRI to assess subclinical CVD,[79] and the first to demonstrate ethnic differences in coronary artery calcium[80] and its association with CHD events.[81] Risk prediction was similar across major ethnic groups and incremental to traditional risk factors. The study was also among the first to use the new metric of clinical utility—net reclassification index—to demonstrate that coronary artery calcium scores can be used to stratify an individual's CHD risk.[82] Among MESA participants with metabolic syndrome or diabetes, the risk of CHD events varied 10-fold across levels of coronary calcium, showing that the risk of CHD is low if no calcium is present, chal-lenging the concept of diabetes as a CHD risk equivalent (a condition or combination of risk factors conferring a future risk or prognosis similar to that of a diagnosis of CHD; Figure 6).[83] A report from the MESA on the comparison between subclinical measures of athero-sclerosis and novel risk factors in the prediction of CHD events over standard risk factors was published in 2012, demonstrating that the addition of coronary artery calcium to traditional risk assessment improved risk prediction more than any other screening tool or biomarker assessed.[84]

The Hispanic Community Health Study

Starting in 2006, >15,000 men and women aged 18–74 years were enrolled in the Hispanic Community Health Study/Study of Latinos.[85] The aim of this study is to characterize the health status, disease burden, and con-sequences of immigration and acculturation in the largest minority population in the USA. In a report on the preva-lence of cardiovascular risk factors and disease, the great-est risk factor burden was recorded among Puerto Rican study participants, those of low socioeconomic status, and those with high levels of acculturation.[86]

Meta-analyses, GWAS, and consortia

Over the past 25 years, but particularly the past decade, several important consortia of both prospective epidemio-logical studies and clinical trials have developed and published reports involving meta-analyses of traditional
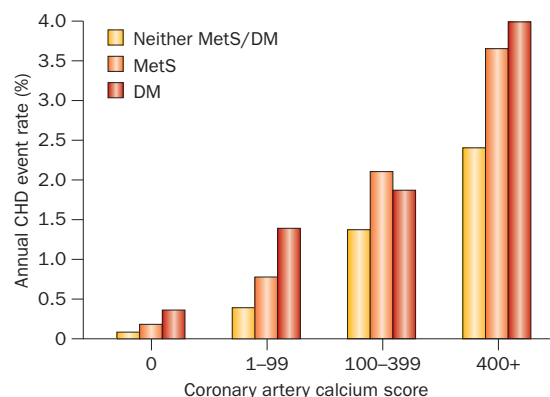

Figure 6 | Annual CHD event rates (%) by coronary artery calcium score categories in patients with DM, MetS, or neither disease. Abbreviations: CHD, coronary heart disease; DM, diabetes mellitus; MetS, metabolic syndrome. Republished with permission of the American Diabetes Association from Malik, S. *et al.* Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the Multiethnic Study of Atherosclerosis. *Diabetes Care* **34** (10), 2285–2290 (2011); permission conveyed through Copyright Clearance Center, Inc.

and emerging risk factors, genetic factors, and the role of risk-factor interventions, such as therapies to lower lipid levels and blood pressure, and dual antiplatelet therapy. The Emerging Risk Factors Collaboration incorporating 160,309 study participants (>1.3 million person years at risk) demonstrated the independent predictive value of C-reactive protein (CRP) for CHD and stroke in 54 pro-spective studies,[87] the clinical utility of CRP and fibrino-gen in CVD risk prediction,[88] and the limited role of adding the novel lipid markers apolipoprotein B, apolipo-protein A-I, lipoprotein(a), and lipoprotein-associated phospholipase A_2 to traditional lipid measures.[89] This group also demonstrated that BMI, waist circumference, and waist-to-hip ratio modestly predicted CVD across 58 cohort studies, but did not improve risk prediction beyond that determined by blood pressure, diabetes status, and lipid levels.[90] The group also showed the strong association between diabetes and deaths from vascular disease and other causes in 97 prospective studies.[91]

Consortia of genome-wide association studies (GWAS), incorporating multiple prospective studies, have made valuable contributions to our understanding of genetic factors and the role of single nucleotide polymorphisms (SNPs) in the prediction of CHD and other vascular diseases. A large meta-analysis of 22 studies showed a small, but significant, association between SNPs at locus 9p21 and CHD.[92] The FHS investigators examined SNPs related to blood pressure and arterial stiffness, although none attained genome-wide significance.[93] Large consor-tia, such as the Coronary Artery Disease Genome-Wide Replication and Meta-Analysis (CARDIoGRAM), have confirmed that important blood pressure-associated SNPs are positively associated with CHD.[94] Other large consortia, such as the Interleukin-6 Receptor Genetics Consortium and the Emerging Risk Factors Collaboration,

have examined SNPs related to IL-6 receptor-related pathways and CHD,[95] and other SNPs related to lipids, diabetes, and CHD are currently under investigation.[96]

Consortia of clinical trials have been instrumental in providing the evidence base for CHD risk-factor interventions that are the foundation of CVD prevention guidelines. Among the best known of these consortia is the Cholesterol Treatment Trialists' Collaboration, which documented the efficacy of statin treatment for CHD risk reduction according to the intensity of therapy,[97] as well as baseline CHD risk level.[98] These studies formed the basis of the 2013 ACC/AHA guidelines for cholesterol management.[99] Other collaborative meta-analyses have been published from the Blood Pressure Trialists' Collaboration, documenting the benefits both of any treatment,[100] and with various classes of antihypertensive drug.[101] In addition, the Antithrombotic Trialists' Collaboration has examined the efficacy of various antiplatelet regimens,[102] as well as aspirin,[103] in the primary and secondary prevention of vascular disease.

Epidemiology and CVD risk assessment
Cardiovascular epidemiological studies conducted over the past 70 years have made important contributions to our knowledge of disease distribution and the importance of risk factors and subclinical disease in predicting cardiovascular events, and have led to the development of methods for estimating the individual's 'global' risk of CHD and CVD. This information has been used to guide the initiation and intensity of preventive therapies.[104–106]

The FHS was pivotal in establishing the concept of multivariable risk assessment, beginning with the observation that individuals with multiple risk factors were at greater risk of coronary events than those who had a single risk factor.[15] This finding led to the development of the initial 'coronary risk profiles', using categories as well as equations (Figure 4).[26,107,108] As early as 1976, the FHS investigators noted that these profiles can provide an "economic and efficient method of identifying persons at high cardiovascular risk who need preventive treatment, and persons at low risk who need not be alarmed about one moderately elevated risk characteristic".[107] This statement is among the first suggestions of how global risk assessment could be used to guide preventive management. Scoring algorithms were aligned to clinically defined categories,[26] and were also developed to estimate total CVD risk for primary-care providers.[108] Subsequently, other equations and categorical risk scoring sheets with points corresponding to various risk-factor levels were developed by groups such as PROCAM[52] and the Systematic Coronary Risk Evaluation (SCORE).[109,110] The Framingham Risk Score, recommended by the Adult Treatment Panel (ATP) III of the US National Cholesterol Education Program,[105] was derived from FHS follow-up data and is based on an individual's age, sex, systolic blood pressure (and treatment status), current smoking status, and total-cholesterol and HDL-cholesterol levels. Each factor is assigned a particular number of points according to its presence (and degree) or absence. The total score corresponds to a probability of experiencing a CHD event

in the next 10 years. If the projected 10-year risk of CHD is <10%, the individual is generally considered to be at low risk, 10–20% is classified as intermediate risk, and >20% is judged to be high risk (and a CHD risk-equivalent).[105] In the past 15 years, interest has focused on longer-term (for example, 30-year)[111] or lifetime[112,113] cardiovascular risk. Such longer-term risk algorithms might improve communication of risk, and motivate risk-factor modification efforts in patients, especially young individuals and women in whom short-term risk algorithms often underestimate risk.

In 2013, pooled cohort algorithms for prediction of 10-year risk of atherosclerotic CVD, including nonfatal and fatal MI and stroke, were described as part of the 2013 ACC/AHA cardiovascular risk assessment guidelines.[114] The algorithms were based on follow-up of the Framingham Heart and Framingham Offspring studies, and the ARIC, CARDIA, and CHS cohorts. These groups included large samples of both African American and white individuals to give greater precision than previous risk algorithms developed from single cohorts. Using the pooled cohort algorithm, statin therapy is recommended on the basis of global risk alone, using a cut-off point of a 10-year CVD risk of ≥7.5%. The ATP III guidelines for cholesterol management recommended a combination of calculated CHD risk and LDL-cholesterol levels to determine the initiation of cholesterol-lowering therapy,[105] and other statements on hypertension[115] and metabolic syndrome[116] have used cut-off points of global calculated CHD risk to determine initiation or intensity of treatment.

Important to the interpretation of the various risk scores are the end points used and the timeframe on which risk is based. For example, the 10-year CHD risk score recommended by the ATP III[105] included only 'hard' CHD events (MI and CHD death) and, therefore, does not include other CHD end points (such as angina or revascularization) or other forms of CVD such as stroke, heart failure, and peripheral artery disease, which were included in the updated 10-year Framingham Risk Score in 2008.[108] Notably, the PROCAM algorithm is limited to the 5-year risk of fatal CHD.[55] The pooled cohort algorithms published in 2013 involve calculation of nonfatal and fatal MI and stroke, but do not include other CVD end points such as percutaneous interventions, angina, heart failure, or peripheral artery disease.[114] As CHD risk-factor interventions often affect a variety of CVD end points, the ideal risk-prediction algorithm should contain the broadest range of CVD end points that are clinically relevant to patients and health-care providers. Most algorithms contain a limited number of end points, owing to the lack of consistent data across the studies used in their development.

The 2013 ACC/AHA guidelines suggest that global risk should not to be the definitive declaration of an individual's risk of CHD, but the starting point of risk assessment and an opportunity to educate a patient about their risk.[99,114] In situations where the appropriate treatment is not clear on the basis of risk assessment or traditional risk-factor levels, the ACC/AHA guidelines recommend
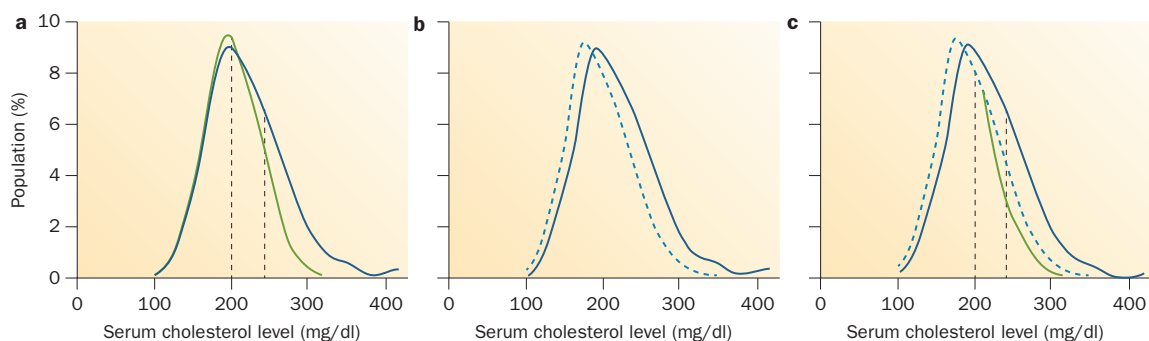
Figure 7 | Expected shifts in the cholesterol distribution. **a** | A 'high-risk approach', focusing on identifying individuals with extremely high cholesterol levels (blue line) and treating them intensively to reduce the number at risk (green line), **b** | A 'population approach' focusing on reducing serum cholesterol levels in the entire population (solid line) to lower levels of serum cholesterol (dashed line). **c** | Combined high-risk and population approaches. The curves show the downward shift in the cholesterol distribution resulting from each type of approach. Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Pearson, T. A. Public policy approaches to the prevention of heart disease and stroke. *Circulation* **124**, 2560–2571 © (2011).

that other information be considered, such as CRP level (high-sensitivity assay; hs-CRP), family history of CHD, or subclinical measures including coronary artery calcium and ankle–brachial index.[106,114] For example, a patient with an hs-CRP level ≥2 mg/dl, ankle–brachial index <0.9, or coronary artery calcium score of ≥300 in the highest quartile for age and sex would be a candidate for risk-factor modification efforts (for example, statin treatment), if the global risk based on risk scores were ambiguous.[114] The large, population-based studies described in this Review have helped to establish the independent and incremental predictive value of these subclinical measures of disease. However, no randomized clinical trials have demonstrated whether risk-factor interventions initiated as a result of such screening result in improved clinical outcomes.

The 2010 ACC/AHA guidelines[106] also include modest recommendations for measuring levels of lipoprotein-associated phospholipase A_2, glycated haemoglobin, and albumin (but not brain natriuretic peptide or other natriuretic peptides or measures of inflammation) for risk stratification in some patients at intermediate cardiovascular risk. Numerous other tests have various levels of association with CVD event risk, including assessment of endothelial function, pulse wave velocity, brachial artery reactivity, and imaging soft plaque

using CT coronary angiography. However, the evidence available for most of these tests is insufficient for them to be guideline recommended for CVD risk assessment in asymptomatic individuals.[114]

Epidemiology and CVD prevention

Epidemiological studies of CHD can provide information to guide prevention strategies at the individual and population levels. The concept that most CHD events do not occur among individuals at highest risk, but in those at moderate risk, and that the entire population of interest needs to adopt preventive measures (focusing prevention strategies only on those at highest risk would miss many future CHD events) was first proposed in 1972.[117] The high-risk approach seeks to identify and treat intensively only those individuals with the highest levels of cholesterol, whereas the population approach reduces overall risk by reducing cholesterol levels in the entire population (Figure 7).[118] Concerted efforts between governmental agencies, communities, and the private sector are required to address the continuing CVD epidemic.[119]

A wealth of clinical trials included in many of the large and sophisticated meta-analyses discussed above[98–103] have documented the efficacy of interventions both in primary and secondary prevention. Furthermore, the effects of dietary factors, such as fruit and vegetable intake,[120] and a Mediterranean diet,[121] as well as physical activity[122] have been summarized in systematic reviews. These and numerous other clinical trials and meta-analyses have provided a solid foundation for CVD prevention guidelines.[99,105,115,123]

The AHA currently promotes the concept of improving the cardiovascular health of all US citizens by 20%, while reducing mortality from heart disease and stroke by 20%, by the year 2020.[4] These goals emphasize the promotion of cardiovascular health, a more-positive and motivating message than the concept of preventing CVD. The strategy is based on 'ideal levels' of seven metrics (also known as the AHA's Life's Simple Seven™; Box 2). Fewer than 20% of adults and only ~40% of children meet five or more of these criteria for ideal cardiovascular health,

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Box 2 | The AHA's Life's Simple Seven™*

- Cigarette smoking: nonsmoking is ideal
- Physical activity: ≥150 min moderate intensity or equivalent exercise per week is ideal
- BMI: <25 kg/m² is ideal
- Healthy diet: achieving at least four of the five important dietary components, focusing on fruits and vegetables, fish, fibre, and sodium intake and sweetened beverage intake
- Total cholesterol level: <200 mg/dl is ideal in adults, <170 mg/dl is ideal in children
- Blood pressure: <120/80 mmHg is ideal
- Fasting plasma glucose level: <100 mg/dl is ideal

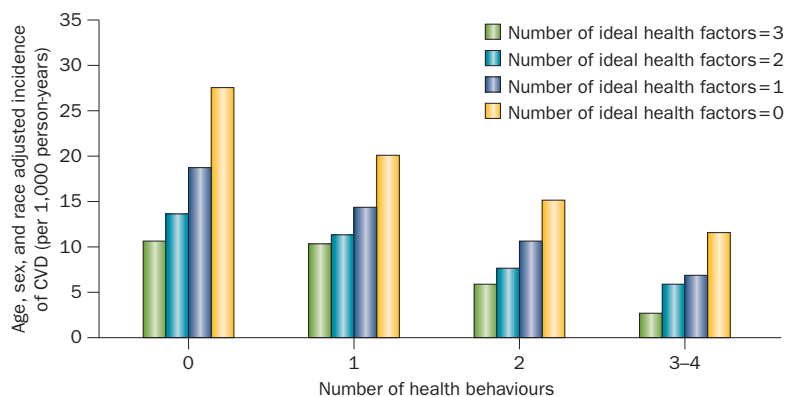*Ideal levels of metrics for cardiovascular disease prevention.

Figure 8 | The incidence of CVD according to the number of ideal health behaviours and health factors adopted. 'Health factors' include cholesterol and glucose levels and BMI, whereas 'health behaviours' relate to diet, exercise, and stress. Abbreviation, CVD, cardiovascular disease. Permission obtained from Elsevier Inc. and the American College of Cardiology © Folsom, A. R. et al. J. Am. Coll. Cardiol. **57**, 1690–1696 (2011).

and <1% of adults are at ideal levels of all seven metrics.[4] CVD incidence has been shown to vary >10-fold according to the number of cardiovascular health behaviours and risk factors that are present (Figure 8).[67]

In a Presidential Advisory issued in 2012, the presidents of the AHA, ESC, WHF, and other leading cardiac societies called to reduce deaths from noncommunicable diseases (of which nearly half are owing to CVD) by 25% by the year 2025.[124] Recommended targets included a 10% reduction in the prevalence of insufficient physical activity, a 25% reduction in the prevalence of raised blood pressure, a 30% reduction in salt or sodium intake (goal of <5 g salt or <2,000 mg sodium per day), and a 30% reduction in the prevalence of tobacco smoking. Reduction of saturated fat intake by 15%, halving the prevalence of obesity, reducing alcohol intake by 10%, reducing elevated cholesterol by 20%, increasing by 50% the number of individuals eligible to receive preventive drug therapy, and increasing the availability of basic technologies and generic essential medicines for CVD prevention, also received support in this directive.[124]

Conclusions

CVDs account for the greatest burden of morbidity and mortality worldwide, in both developed and developing countries, and CHD is the greatest contributor to CVD.[1] Cardiovascular risk factors, including hypertension, cigarette smoking, high blood glucose, physical inactivity, obesity, and elevated cholesterol levels are (in that order) the leading causes of death worldwide.[1–3]

The epidemiology of CVD and CHD is the science of, and foundation for, preventive cardiology. Classic epidemiological studies, from the Seven Countries Study, to the FHS, to more-contemporary studies, provided the rationale for and data upon which hundreds, if not thousands, of clinical trials were designed and implemented to document the efficacy of risk-factor reduction in primary and secondary cardiovascular prevention.

Future epidemiological studies of CHD should focus on elucidating the combination of biomarkers and imaging or screening tests that can best improve prediction of CHD events and, in particular, identify vulnerable patients who are at substantial short-term risk of an acute event, both in primary and secondary prevention. Moreover, such studies should address important issues in personalized medicine, including development of risk-prediction tools that aid in the identification of individuals most likely to respond to, and benefit from, preventive therapies. Concerted global efforts aimed at prevention of obesity and other major risk factors, identifying individuals with cardiovascular risk factors and targeting them with evidence-based treatments, and co-ordinating care for those with pre-existing CVD are critical for reducing CHD and CVD morbidity and mortality.

Review criteria

The references for this Review were selected from a search of the PubMed database using the following key words: "epidemiology", "prospective", "cardiovascular", as well as key study names, such as "Framingham", "PROCAM", and "INTERHEART", alone or in combination, with no date restriction. Only full-length articles published in English were selected for inclusion in this Review.

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