Public Health Nutrition: 7(1A), 167–186 DOI: 10.1079/PHN2003587

Diet, nutrition and the prevention of hypertension and cardiovascular diseases

K Srinath Reddy[1,*] and Martijn B Katan[2]
[1]Department of Cardiology, Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi, India:
[2]Division of Human Nutrition and Epidemiology, Wageningen University, Wageningen, The Netherlands

Abstract

Cardiovascular diseases (CVD) are growing contributors to global disease burdens, with epidemics of CVD advancing across many regions of the world which are experiencing a rapid health transition. Diet and nutrition have been extensively investigated as risk factors for major cardiovascular diseases like coronary heart disease (CHD) and stroke and are also linked to other cardiovascular risk factors like diabetes, high blood pressure and obesity. The interpretation of evidence needs to involve a critical appraisal of methodological issues related to measurement of exposures, nature of outcome variables, types of research design and careful separation of cause, consequence and confounding as the basis for observed associations.

Adequate evidence is available, from studies conducted within and across populations, to link several nutrients, minerals, food groups and dietary patterns with an increased or decreased risk of CVD. Dietary fats associated with an increased risk of CHD include *trans*-fats and saturated fats, while polyunsaturated fats are known to be protective. Dietary sodium is associated with elevation of blood pressure, while dietary potassium lowers the risk of hypertension and stroke. Regular frequent intake of fruits and vegetables is protective against hypertension, CHD and stroke. Composite diets (such as DASH diets, Mediterranean diet, 'prudent' diet) have been demonstrated to reduce the risk of hypertension and CHD. Sufficient knowledge exists to recommend nutritional interventions, at both population and individual levels, to reduce cardiovascular risk. That knowledge should now be translated into policies which promote healthy diets and discourage unhealthy diets. This requires coordinated action at the level of governments, international organizations, civil society and responsible sections of the food industry.

Keywords
Dietary fats
Cardiovascular diseases
Sodium
Fruits and vegetables

The second half of the 20th century witnessed major health transitions in the world, propelled by socio-economic and technological changes that profoundly altered life expectancy and ways of living, while creating an unprecedented human capacity to use science to prolong and enhance life. The most globally pervasive change among these health transitions has been the rising burden of non-communicable diseases (NCDs). Epidemics of NCDs are presently emerging, or accelerating, in most developing countries[1]. Cardiovascular diseases (CVD), cancers, diabetes, neuropsychiatric ailments and other chronic diseases are becoming major contributors to the burden of disease, even as infections and nutritional deficiencies are receding as leading contributors to death and disability.

Global dimensions of the CVD epidemic

CVD is a major contributor to the global burden of disease among the NCDs. Coronary heart disease (CHD) is likely to be the most common cause of DALY loss in 2020 as compared with its fifth position in 1991. The World Health Organization attributes 30% of all global deaths (i.e. 15.3 million) as well as 10.3% of the total DALYs lost in 1998 to CVD[2]. The low- and middle-income countries, because of their much larger population, accounted for 78% of all deaths and 86.3% of DALYs lost—attributable to CVD—world-wide in 1998.

According to the Global Burden of Disease Study, a 55% rise would occur in DALY loss attributable to CVD between 1990 and 2020 in the developing countries[3]. This would be in contrast to a 14.3% reduction in the proportion of DALY loss attributable to CVD during the same period in the developed countries. Thus, the increasing burden of CVD would be borne mostly by the developing countries in the next two decades (Fig. 1).

The global burden of CVD affects all sections of the society. Cardiovascular deaths in 1998 contributed to 34% of global mortality in women and 28.2% of all deaths in

**Corresponding author:* Email ksreddy@ccdcindia.org

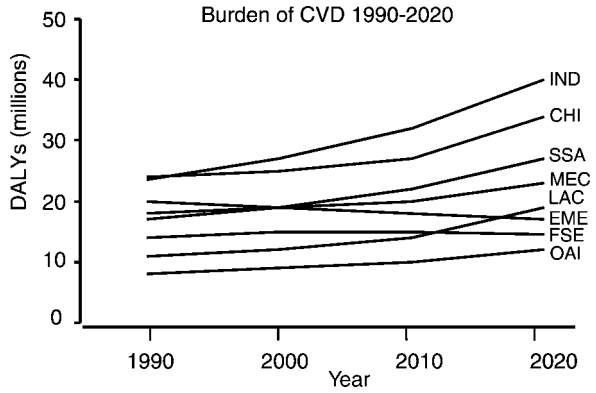

Fig. 1 Burden of CVD, 1990–2020 (IND, India; CH, China; SSA, sub-Saharan Africa; MEC, Middle Eastern crescent; LAC, Latin America; EME, established market economies; FSE, former Socialist economies; OAI, other Asia and islands). Source: Murray and Lopez[3].

men[2]. Such a scenario also exists within the developing countries, where women are increasingly affected by hypertension, stroke and CHD. In developing countries, where epidemiological transition has advanced, there is evidence of a progressive reversal of the social gradient, with the poor becoming the most vulnerable victims[4]. This parallels the pattern of the cardiovascular epidemics in the developed countries. Risk behaviours, risk factors and disease burdens in the developed countries were initially higher in the 'early adopters' (the higher social classes). However, these factors later become a mass phenomenon as the mediators of risk were abundantly produced for mass consumption and ultimately imposed the highest burdens of disease on the 'late adopters' (lower social classes), as the early adopters reduced their risk in response to new knowledge and new technologies. Evidence of such a reversal of social gradient is available from recent studies in several developing countries[5,6].

In addition to the increasing incidence of CVD, the early age at which it manifests in these populations is also contributing to the high CVD burden. Thus in 1990, 46.7% of CVD-related deaths in developing countries occurred below the age of 70 years, in contrast to only 22.8% in the high-income industrial countries[4]. The Global Burden of Disease Study projected that 6.4 million deaths would occur due to CVD in the developing countries in 2020, in the age group of 30–69 years[3].

Diet and CVD: methodological issues in the study of causal associations

Issues related to study design

Studies investigating the influence of diet on CVD or cardiovascular risk factors have employed a wide variety of study designs—ecological studies within and across populations, cross-sectional surveys, case–control studies (*de novo* or nested), cohort studies, community based demonstration projects randomised clinical trials and before–after type of metabolic studies. These differ widely in terms of their ability to (a) identify, avoid and adjust for confounding, (b) establish a temporal relationship of cause preceding the effect, (c) minimise bias, (d) provide a wide range of exposure, (e) ascertain composite end-points, including fatal outcomes, (f) evaluate population attributable risk and (g) yield generalisable results.

While ecological studies are highly vulnerable to the effects of multiple confounders, they do confer the advantage of enabling comparisons of populations across time and habitat. Cross-sectional surveys and case–control studies are mostly unsuited to study the temporal sequence and usually suffer from a 'survival bias' resulting from an inability to study fatal outcomes. They do, however, offer an early opportunity to examine associations and identify potential avenues for intervention related research. Observational cohort studies have the advantage of being able to evaluate long-term effects of dietary exposures and often provide a wide range of exposure, but are vulnerable to unknown confounders which cannot be adjusted for as well as possible measurement errors in dietary ascertainment. Effects of changes in dietary exposures occurring during the long period of observation are also difficult to evaluate. Demonstration projects provide a population laboratory to evaluate dietary interventions in real life settings but face methodological challenges from limited sample size, contamination and confounding. Clinical trials, if well designed, provide the best framework for studying associations, as free from the effects of bias and confounding as possible. However, they often evaluate interventions which are relatively short-term and introduced late in the natural history of disease and may not replicate the effects of long-term dietary exposures. Genetics now offers a possible alternative to clinical trials through 'Mendelian randomisation'. This approach takes into account that genotypic differences in the metabolism of food ingredients may cause lifelong differences in exposure to food components and their metabolites or to purported risk factors. It is a powerful way to establish causality without the need for prolonged follow-up[7].

These issues related to study design become relevant when interpreting the results of reported studies on diet and CVD and assessing their public health implications. Frequently, conclusions from studies employing weak designs are negated by the results emerging from methodologically stronger studies. Public policy and clinical practice must both be judiciously guided by credible evidence provided by scientifically stronger studies and not be misled by controversial results emerging from feeble study designs.

A related issue is the use of experimental animals. Although these are often referred to as 'animal models' their validity in predicting outcomes in humans is unclear. Lipid metabolism especially is species-specific, as exemplified by the inefficacy of cholesterol-lowering statin drugs in many animal species including monkeys[8]. Experiments in

animals are, therefore, best reserved for elucidating mechanisms, and cannot be used to argue that a particular food will have a particular effect on CVD in humans.

Issues involving outcome variables

Ideally, disease related endpoints are preferable since they clearly demonstrate the benefits or risks of dietary exposures. In an exposure such as diet, effects may extend beyond cardiovascular outcomes. The need to evaluate impact of diet on total mortality and major co-morbidities, therefore, becomes an imperative. It must also be recognised that dietary exposures which influence thrombotic pathways may have different effects on the risk of haemorrhagic stroke and thrombotic stroke, often in opposite directions. The need to differentiate the types of stroke in outcome evaluation is, therefore, clear and has important implications for populations, which differ in their stroke profiles. Similarly, selective benefits limited only to non-fatal outcomes, as in the case of CHAOS study which reported a benefit of vitamin E administration on non-fatal myocardial infarction[9], strain scientific credulity, are seldom replicated and cannot influence either public health policy or clinical practice.

The ascertainment of disease related endpoints, as the primary outcome, has most often been attempted in large and long-term cohort studies, or in clinical trials conducted in population groups in whom high event rates were anticipated in a short or medium time frame. Thus, observational cohort studies investigating the long-term impact of diet on primary prevention of CVD frequently compete with secondary prevention trials. If the results are discordant, it is difficult to interpret whether the differences are due to methodological reasons of confounding or due to the fact that exposures occurred at different times and for variable periods in the natural history of the disease. It must, however, be recognised that pathological processes such as endothelial dysfunction, plaque instability, thrombosis and cardiac arrhythmias can be influenced even by short-term exposures.

Intermediate variables have been frequently utilised in studies evaluating the association of dietary constituents or dietary patterns to CVD. Most often, these are risk factors like blood pressure or plasma lipids. While the effects of diet on blood pressure constitute an acceptable basis for estimating potential impact on future cardiovascular events[10], such an extrapolation may not be equally valid in the case of a variable like total plasma cholesterol. Similar changes in total plasma cholesterol may be associated with variable effects on levels of LDL and HDL cholesterol and on the ratio of total to HDL cholesterol. The impact on risk of atherosclerotic CVD may thus vary. The 25-year follow-up experience of the Seven Countries Study revealed that while the increase in relative risk of CHD for comparable levels of plasma cholesterol elevation was similar across diverse populations, the absolute risk of CHD varied widely at the same level of plasma cholesterol, possibly due to other dietary influences[11]. Even the effect on LDL cholesterol level may not suffice to confidently project the downstream impact on CVD. Dietary changes may influence LDL particle size differentially, as also the level of plasma triglycerides, with variable net effects on the atherogenicity of the plasma lipid pool. Simple extrapolations to benefits on coronary artery disease may not be possible in the complex area of diet related plasma and tissue lipid changes. Plasma lipids, as intermediate variables, could not also explain the degree of cardiovascular protection conferred by the Mediterranean diet in the Lyon Diet Heart Study[14]. While studies of intermediate variables are useful in identifying mechanistic pathways of dietary harm or benefit and plasma cholesterol has served well so far to explain much of the coronary risk associated with certain diets, there is a need for methodologically strong studies which relate dietary patterns or dietary interventions to hard end points such as total mortality, cardiovascular mortality and combined fatal and non-fatal cardiovascular events.

Issues involving the exposure variables

The types of dietary exposure assessed for associations with CVD, have varied from specific nutrients (such as saturated fat) to dietary items (such as fish) to food groups (such as fruits and vegetables) to dietary patterns (such as 'Mediterranean' diet or 'Adventist' diet) and composite dietary interventions (e.g. the DASH diet). The scientific method often emphasises a reductionist approach to investigations of causality. Such an approach has inherent limitations in the area of diet, because multiple interactions among many nutrients are likely to determine the physiological effects and pathological outcomes much more than the individual effects of an isolated nutrient. The failure of anti-oxidants, when administered as pills, to favourably influence cardiovascular outcomes in clinical trials does not negate a protective role for their primary food sources, as suggested by ecological and observational studies. On the other hand, identification of active components is often the way to extrapolate from one particular study and population to another, since the definition and pattern of 'vegetable' intake may vary from one country to another.

The strengths and limitations of various methods of collecting accurate food consumption data are well recognised[12]. Questionnaire methods of ascertaining information related to habitual food intake pose problems of validity and reproducibility even within well defined populations but these problems are likely to be magnified when such instruments are applied across different cultures. Even if the nutrient composition of self-reported diets is accurately estimated, different cooking methods may alter the final bioavailability of those nutrients as actually consumed. The need for valid and reproducible biomarkers is, therefore, important when studies of

specific nutrients are proposed. For example, adipose tissue fatty acid composition is a suitable biomarker for habitual type of dietary fat intake[13]. There may, however, be technical and financial constraints which limit the use of such biomarkers in large epidemiological studies.

A casual enquiry needs to recognise the lag time effect, wherein a long period of exposure to dietary variables is required before effect is evident on outcome variables (especially disease related end points of atherosclerotic vascular disorders). Short-term studies may be incapable of identifying true effects even when they exist. This is clearly illustrated by trials evaluating the effect of sodium restriction on blood pressure, where benefit was demonstrated only in trials in which the duration of exposure was at least 5 weeks[14]. The dose of exposure is another critical variable in an area like diet, where many of the nutrients are physiological requirements at a certain level but may pose risk of cardiovascular dysfunction and disease at other levels. The relationships may vary from linear to J-shaped or threshold, for different variables. Ascertainment of dose-related effects is essential, whether the exposure is salt, alcohol or fish.

Issues related to diet as an independent variable

Unhealthy dietary behaviours often occur in association with other unhealthy behaviours such as physical inactivity and smoking. Furthermore, unhealthy dietary practices such as high consumption of saturated fats, salt and refined carbohydrates as well as low consumption of fruit and vegetables tend to cluster together. In contrast, persons who habitually adopt one healthy dietary practice are more likely to adopt other healthy dietary habits as well as practice regular physical activity and abstinence from smoking. Dietary behaviours may also reflect patterns influenced by social class and may be influenced by stress levels. Dissociating the specific effects of individual dietary components from other dietary components, physical activity levels and other behaviours becomes difficult outside the setting of a carefully controlled clinical trial. In observational studies, the question arises whether some dietary practices are merely a surrogate for other dietary practices or for a composite of multiple health behaviours. Whether diet should be considered in dissociation from physical activity or should preferably be studied in combination is also an issue for observational research.

The effects of diet on multiple cardiovascular risk factors, ranging from body weight to blood lipids and blood pressure to thrombotic mechanisms, also poses the question of when and how far to adjust for these variables in evaluating the relationship of diet to CVD. Since many of these are intermediate variables linking diet to CVD, adjustment to exclude their effect would underestimate the effect of diet. However, such variables are also influenced by factors other than diet. In such cases, the decisions related to adjustment should be carefully considered.

Nutrients and CVD

Dietary fats

The relationship between dietary fats and CVD, especially CHD has been extensively investigated, with strong and consistent associations emerging from a wide body of evidence accrued from animal experiments, as well as observational studies, clinical trials and metabolic studies conducted in diverse human populations. This relationship was initially considered to be mediated mainly through the atherogenic effects of plasma lipids (total cholesterol, lipoprotein fractions and triglycerides). The effects of dietary fats on thrombosis and endothelial function as well as the relationship of plasma and tissue lipids to the pathways of inflammation have been more recently understood[13]. Similarly, the effects of dietary fats on blood pressure have also become more evident through observational and experimental research.

The association of plasma total cholesterol and its low-density lipoprotein sub fraction (LDL cholesterol) has been consistently demonstrated across several populations, with the Seven Countries Study offering strong evidence through within-population cohort experience and inter-population ecological comparisons[14]. The protective association of high-density lipoprotein (HDL) fraction of plasma cholesterol has also been well identified and the ratio of total to HDL cholesterol has emerged as a strong predictor of the risk of CHD. Plasma triglycerides too have been directly associated with the risk of atherosclerotic vascular disease and thrombotic events. The effect of various dietary fats on these plasma lipids has constituted the key link in the causal pathway that connects diet to CVD[15].

Cholesterol in the blood and tissues is derived from two sources: diet and endogenous synthesis. Dairy fat and meat are major sources. Egg yolk is particularly rich in cholesterol but unlike dairy and meat does not provide saturated fatty acids (SFAs). Dietary cholesterol raises plasma cholesterol levels[16]. Although both HDL and LDL increase, the effect on the total/HDL ratio is still unfavourable[17], but small. Observational evidence on an association of dietary cholesterol intake with CVD is contradictory[10,11]. The upper limit for dietary cholesterol intake has been prescribed, in most guidelines, to be 300 mg/d. However, there is no requirement for dietary cholesterol and it is advisable to keep the intake as low as possible. If intake of dairy fat and meat are controlled then there needs to be no severe restriction of egg yolk intake, although some limitation remains prudent.

Fatty acids are grouped into three classes—SFAs, monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). While such a classification is useful in providing a structural grouping, it tends to oversimplify the effects of dietary fats. Individual fatty acids, within each group, are now known to have differing effects on lipids, lipoproteins and platelet-vascular

homeostasis. SFA and MUFA can be synthesised in the body and hence are not dietary essentials. PUFA can be subdivided into *n*-6 and *n*-3 PUFA, derived from linoleic acid (LA) and α-linolenic acid (ALNA), respectively. These are essential fatty acids, since they cannot be synthesised in the body[18,19].

Saturated fatty acids

SFAs as a group raise total and LDL cholesterol, but individual SFAs have different effects. Myristic and lauric acids have greater effect than palmitic acid, but the latter is more abundant in food supply. The plasma cholesterol raising effects of these three SFAs is higher when combined with high cholesterol diets. Stearic acid has not been shown to elevate blood cholesterol and is rapidly converted to oleic acid (OA) *in vivo*. Metabolic (feeding) studies demonstrate a marked elevation of both HDL and LDL cholesterol induced by SFA diets[18–20]. Replacement of saturated fatty acids by polyunsaturated fat reduces the total to HDL cholesterol ratio but replacement by carbohydrates does not. Also, tropical fats rich in lauric acid (C12) raise total cholesterol strongly, but because of their specific effect on HDL, the ratio of total to HDL cholesterol falls. Thus, effects on blood lipids can be variable, depending on which blood lipids are studied, and we need data on actual outcomes to determine the true effects of fats on CHD. The relationship of dietary saturated fat to plasma cholesterol levels and to CHD was graphically demonstrated by the Seven Countries Study involving 16 cohorts, in which saturated fat intake explained 73% of the total variance in CHD across these cohorts[14]. In the Nurses Health Study[19], the effect of saturated fatty acids was much more modest, especially if saturates were replaced by carbohydrates. The most effective replacement for saturated fatty acids in terms of CHD outcome is by PUFAs, i.e. LA. This agrees with the outcome of large randomised clinical trials, in which replacement of saturated and *trans* fats by polyunsaturated vegetable oils effectively lowered CHD risk[20–22].

Trans-*fatty acids (t-FAs)*

t-FAs are geometrical isomers of unsaturated fatty acids that assume a saturated fatty acid-like configuration. Partial hydrogenation, the process used to create *t*-FA, also removes essential fatty acids such as LA and ALNA. Metabolic studies have demonstrated that *t*-FAs render the plasma lipid profile even more atherogenic than SFA, by not only elevating LDL cholesterol to similar levels but also decreasing HDL cholesterol[23,24]. As a result, the ratio of LDL cholesterol to HDL cholesterol is significantly higher with a *t*-FA diet (2.58) than with a SFA diet (2.34) or an OA diet (2.02). This greatly enhances the risk of CHD (Fig. 2). Evidence that intake of *t*-FA increases the risk of CHD initially became available from large population based cohort studies in US[25,26] and has recently been corroborated in an elderly Dutch population[27]. Levels of *t*-FA in a

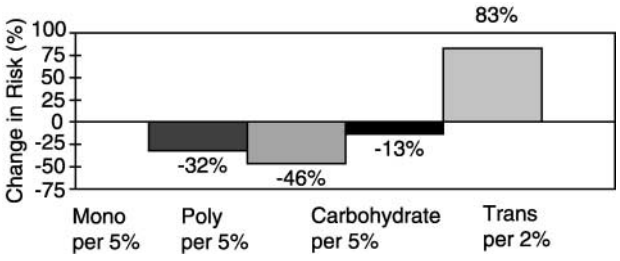

Fig. 2 Change in CHD risk associated with replacement of saturates by other fats: Nurses Health Study[19]

biochemical analysis of replicated baseline food composites correlated with the risk of coronary death in the cohorts of the Seven Countries Study. Most *t*-FAs are contributed by industrially hardened oils, but the dairy and meat fats of ruminants are also a source. Whether these two sources have the same effect on CHD risk is unclear, but reductions in ruminant fats are already advisable for other reasons. Eliminating *t*-FAs from the diet would be an important public health strategy to prevent CVD. Since these are commercially introduced agents into the diet, policy measures related to the food industry would be required along with public education. *t*-FAs have been eliminated from retail fats and spreads in a large part of the world, but deep-fat fried fast foods and baked goods are a major and increasing source[28].

Monounsaturated fatty acids

The only nutritionally important MUFA is OA, which is abundant in olive and canola oils and also in nuts. The epidemiological evidence related to MUFA and CHD is derived from studies on the Mediterranean diet, as well as from the Nurses Health Study and other similar studies, which investigated the association and control of confounding factors[29]. MUFAs have been shown to lower blood glucose and triglycerides in type II diabetics and may decrease susceptibility of LDL to oxidative modification.

Polyunsaturated fatty acids

PUFAs are derived from Dietary LA (*n*-6 PUFAs) and dietary ALNA (*n*-3 PUFAs). The important *n*-6 PUFAs are arachidonic acid (AA) and dihomogammalinolenic acid (DHGLA), while the important *n*-3 PUFAs are eicosapentaenoic acid (EPA) and docasahexaenoic acid (DHA). Eicasanoids derived from AA have opposing metabolic properties to those derived from DHA. A balanced intake of *n*-6 and *n*-3 PUFAs is, therefore, essential for health.

The biological effects of *n*-3 PUFAs are wide ranging involving lipids and lipoproteins, blood pressure, cardiac function, arterial compliance, endothelial function, vascular reactivity and cardiac electrophysiology as well as potent anti-platelet and anti-inflammatory effects including reduced neutrophil and monocyte cytokine production[13,30]. Recent data have also shown that EPA and DHA have differential effects on many of these. DHA

appears to be more responsible for the beneficial effects of fish and fish oils on lipids and lipoproteins, blood pressure, heart rate variability, glycaemic control, in comparison to EPA, while a mixture of DHA and EPA significantly reduced platelet aggregation in comparison to ALNA *in vitro*[13,31]. The very-long chain *n*-3 PUFAs powerfully lower serum triglycerides, but they raise LDL cholesterol[32]. Therefore, their effect on CHD is probably mediated through pathways other than cholesterol.

Much of the epidemiological evidence related to *n*-3 PUFAs is derived from the study of fish consumption in populations or interventions involving fish diets in clinical trials. Fish oils were, however, used in the GISSI study of 11,300 survivors of myocardial infarction[33]. In this factorial design, fish oil (1 g/d) and vitamin E (300 mg/d) were compared, alone and in combination, to placebo. After 3.5 years of follow-up, the fish oil group had a statistically significant 20% reduction in total mortality, 30% reduction in cardiovascular death and 45% decrease in sudden death. While most published studies do not indicate that dietary *n*-3 PUFA prevent restenosis after percutaneous coronary angioplasty or induce regression of coronary atherosclerosis, one study reported that occlusion of aortocoronary venous bypass grafts was reduced after 1 year by daily ingestion of 4 g fish oil concentrate[34].

The Lyon Heart Study incorporated an *n*-3 fatty acid (ALNA) into a diet altered to develop a 'Mediterranean diet' intervention[9]. In the experimental group, plasma ALNA and EPA increased significantly and the trial reported a 70% reduction in cardiovascular mortality at 5 years in its initial report. Total and LDL cholesterol were identical in the experimental and control groups, suggesting that thrombotic and perhaps arrhythmic events may have been favourably influenced by *n*-3 PUFA. Since the diet altered many other variables, such as fibre and anti-oxidants (by increasing fruit and vegetable consumption), direct attribution of benefits to *n*-3 PUFA becomes difficult to establish.

The effect of different fatty acids on cardiac arrhythmias has been an area of great interest. Diets rich in saturated fatty acids increase the risk of ventricular fibrillation and sudden cardiac death in primates. A recent population based case–control study, using biomarkers, revealed a modest association of *t*-FAs in general and a strong association of *trans* isomers of LA in particular, with primary cardiac arrest in humans[35]. Several studies in different animal models, primate and rodent, have shown that *n*-3 PUFA are protective against cardiac arrhythmias, especially ventricular fibrillation[36]. It has been suggested that the fall in CHD mortality in USA and Australia, since 1967, is probably attributable to an increase in poly-unsaturated fat consumption in both countries since 1960[37]. The decline in CHD mortality in the Zutphen cohort has similarly been attributed to a decreased consumption, over time, of *t*-FAs[27].

The proportions of SFA, MUFA and PFA as constituents of total fat intake and total energy consumption have engaged active attention, in view of the strong relationship of these fatty acids to the risk of CVD, especially CHD. The reduction of SFA in the diet has been widely recommended, but its replacement remains an area of debate as to whether the place of reduced SFAs should be taken by MUFA, PUFA or carbohydrate. Both MUFA and PUFA improve the lipoproteins profile, although PUFAs are somewhat more effective. In view of this, recent US dietary recommendations, suggested that SFA should be reduced to 7–8%, MUFA should be increased to 13–15% and PUFA raised to 7–10% of daily energy, with the total fat contributing to no more than 30% of all calories consumed[29,38]. These may need to be adjusted for populations who consume less quantities of total fat, so as to ensure an adequate intake of MUFA and PUFA even under those circumstances.

The total quantity of fat consumed, as a proportion of daily energy intake, has not shown a relation to CVD that is independent of the SFA content. It has now generally been agreed that the type of fats consumed in diet is more important than the total amount of fat consumed[39]. The compatibility of high-fat Mediterranean diets (with total fat contributing $>30\%$ of calories) with coronary protection has been cited as supportive evidence. While the emphasis on the type of fat is well placed, it must be recognised that high-fat diets are also high in energy. Whether this contributes substantially to overweight is a subject of much debate[40]. While the emphasis in dietary recommendations should be on using the healthier fats in preference to unhealthier fats, the total fat may be restricted to $<30\%$ of all energy in most populations and individuals. However, individuals who regularly undertake vigorous physical activity may consume higher levels of fat in their daily diets (up to 35%).

Enhancing the nutritional quality of dietary fat consumption, to provide greater cardiovascular protection, may be attempted by decreasing the sources of saturated fats and eliminating *t*-FAs in the diet, increasing the consumption of foods containing unsaturated fatty acids (both MUFA and PUFA) and decreasing dietary cholesterol consumption. Modification of cooking oils either through appropriate admixture of different oils[41] or through genetic modification of oilseed crops[42] may provide methods for improving the quality of dietary fat consumed through edible oils.

Carbohydrates

The relationship of dietary carbohydrates to CVD appears to be mediated through indirect mechanisms: contribution to total energy and its effect on overweight and obesity; influence on central obesity; effects on plasma lipids, especially triglycerides and effects on glycaemic control. The balance between carbohydrates and fat as sources of energy as well as the fibre component of the diet are also

areas of interest while considering this relationship. In feeding experiments, an increase in dietary energy from carbohydrates is usually associated with a moderate increase in fasting plasma triglyceride levels in the first few weeks but these return to near original levels in the first few weeks. Epidemiologically, high-carbohydrate intakes are associated with low plasma cholesterol and variable plasma triglyceride concentrations[43].

The effect of a high-carbohydrate diet on HDL cholesterol and thereby on the total to HDL cholesterol ratio as well as on the particle size of LDL are matters of interest while considering the influence on vascular function and risk of CVD. High-carbohydrate diets appear to reduce HDL cholesterol levels and increase the fraction of small dense LDL, both of which may impact adversely on vascular disease. This dyslipidemic pattern is consistent with the elevation of plasma triglycerides. There is as yet no clear evidence that the risk of CVD is altered independently by the carbohydrate levels in the diet. The glycaemic index of foods might also be a determinant of the extent to which carbohydrates can influence the glycaemic status. Carbohydrate diets with high-glycaemic index might adversely impact on glucose control, with associated changes in plasma lipids[44,45].

Dietary fibre

Dietary fibre is a heterogenous mixture of polysaccharides and lignin that cannot be degraded by the endogenous enzymes of vertebrate animals[46]. Water-soluble fibres include pectins, gums, mucilages and some hemicelluloses. Insoluble fibres include cellulose and other hemicelluloses. Most soluble fibres reduce plasma total and LDL cholesterol concentrations, as reported by several trials[47]. Pectins, psyllium, gums, mucilages, algal polysaccharides and some hemicelluloses lower total and LDL cholesterol levels without affecting HDL cholesterol, the reductions in total cholesterol being usually in the range of 5–10%. Human experiments have clearly shown that oat fibre tends to lower plasma total and LDL cholesterol but wheat fibre does not. Rice bran and barley may also lower cholesterol[48]. Fibre consumption predicted insulin levels, weight gain and cardiovascular risk factors like blood pressure, plasma triglycerides, LDL and HDL cholesterol and fibrinogen more strongly than other dietary components in the CARDIA cohort study of young adults[49]. However, fibre intake may be confounded with many other determinants of cardiovascular health.

Between 1996 and 2001, five very large cohort studies in the USA, Finland and Norway have all reported that subjects consuming relatively large amounts of whole grain cereals have significantly lower rates of CHD[48,50]. High intake of fibre from cereal sources was associated with a reduced risk of CHD in the Nurses Health Study[50] and was inversely associated with the risk of hypertension in the Health Professionals Follow-up Study[51]. Available evidence supports a recommendation for consumption of about 15 g/1000 kcal of fibre[47]. Since some of the reported benefits may have risen from other dietary components occurring in association with fibre in natural foods, dietary consumption of high-fibre rather than isolated fibre foods should be recommended. Addition of wheat or cereal bran may be considered, where necessary, to supplement natural foods in order to attain the recommended dietary intake.

Anti-oxidants

The oxidation of LDL by oxygen free radicals results in the unregulated uptake of modified LDL by macrophages in arterial walls, accelerating the atherosclerotic process. Anti-oxidant nutrients, which can directly scavenge free radicals, include α-tocopherol (vitamin E isomer) and ascorbic acid (vitamin C), which have shown anti-oxidant activity both *in vitro* and *in vivo*, as well as β-carotene (a provitamin A carotenoid) which has displayed anti-oxidant activity *in vitro*[52]. These mechanisms suggested that increased dietary intake or supplementation of these nutrients would be protective against atherosclerotic vascular disorders. This was supported by evidence from observational studies for vitamin E and β-carotene, but results of clinical trials employing supplements have been disappointing.

Observational cohort data suggest a protective role for carotenoids. In a meta-analysis, the pooled relative risk reduction for cardiovascular death, in those who ate diets rich in β-carotene, was 31% (95% CI: 41–20%), when dietary and blood carotene levels were measured to compare high and low consumers. The randomised trials, in contrast, reported a moderate adverse effect of β-carotene supplementation, with a relative increase in the risk of cardiovascular death of 12% in a meta-analysis of four trials[53]. Cancer risk was also increased.

Several large cohort studies showed significant reductions in the incidence of cardiac events in men and women taking high-dose vitamin E supplements[52]. However, The HOPE trial, a definitive clinical trial relating vitamin E supplementation to cardiovascular outcomes, revealed no effect of vitamin E supplementation (at 400 IU/d, for a mean follow-up of 4.5 years) on MI, stroke or death from cardiovascular causes in men or women[54]. Other trials too failed to demonstrate a cardioprotective effect of vitamin E supplements[55].

The conflict between diet based observational studies and clinical trials employing supplements may arise because of one or more explanatory factors: confounding, interactions/synergistic activity (among anti-oxidants; with other nutrients), isomers with differing activity in food compared to supplements, other associated protective elements in natural foods (e.g. flavonoids, phytoestrogens) and/or temporal dissociation of anti-oxidant blood levels from fat intake in meals, when administered as once a day pills. While the failure of pill supplementation does

not necessarily exclude protective effects of dietary anti-oxidants, current evidence does not support supplementation of any of these anti-oxidant vitamins for prevention of CHD. However, intake of their primary food resources, especially fruit and vegetables, may be encouraged.

Folate

The relationship of folate to CVD has been mostly explored through its effect on homocysteine, which has been incriminated as an independent risk factor for CHD and probably stroke[56–59]. Folic acid is required for the methylation of homocysteine to methionine. Reduced plasma folate has been strongly associated with plasma elevated plasma homocysteine levels and folate supplementation has been demonstrated to decrease those levels[60]. However, the role of homocysteine as an independent risk factor for CVD has been subject to debate, in view of the data from several prospective studies which did not find this association to be independent of other risk factors[61]. It has also been suggested that elevation of plasma homocysteine is a consequence and not a cause of atherosclerosis, wherein impaired renal function due to atherosclerosis raises plasma homocysteine levels[62].

Whether homocysteinaemia is the cause or consequence of atherosclerosis, its role in promoting thrombosis makes an intervention with folate appear attractive. There is also recent evidence that suggests that homocysteinaemia results in endothelial dysfunction, an effect that is reversed by oral folate supplementation[63,64]. An independent anti-oxidant role for folate has also been postulated[82]. Data from the Nurses' Health Study showed that folate and vitamin B6, from diet and supplements, conferred protection against CHD (fatal and non-fatal events combined) and suggested a role for their increased intake as an intervention for primary prevention of CHD[65]. Food grain fortification with folate and cyancobalamin has also been recommended as a cost-effective measure for CHD prevention[66].

Recommendations related to folate supplementation must, however, await the results of ongoing clinical trials. Dietary intake of folate through natural food sources may be encouraged in the meanwhile, especially in individuals at a high risk of arterial or venous thrombosis and elevated plasma homocysteine levels[67].

Flavonoids and other phytochemicals

Flavonoids are polyphenolic anti-oxidants which occur in a variety of foods of vegetable origin, such as tea, onions and apples. Data from several prospective studies indicate an inverse association of dietary flavonoids with CHD[68]. A benefit on stroke risk has also been reported[69]. However, confounding may be a major problem and may explain conflicting results of observational studies on flavonoids and CHD. Fruits and vegetables also contain other phytochemicals that may have protective properties, including isothiocyanates and indoles (found in cruciferous vegetables), sulphides (found in onions and garlic), terpenes (found in citrus oils) and phytoestrogens[47]. While their role in relation to CVD risk is not clearly established and trial evidence related to garlic supplements is generally not supportive, their consumption in the natural food form may have benefits, which need to be evaluated.

Minerals: blood pressure and CVD

Sodium

High blood pressure (HBP) is a major risk factor for CHD and both forms of stroke (ischaemic and haemorrhagic). The relative risk of CVD for both systolic and diastolic blood pressures, operates in a continuum of increasing risk for rising pressure but the absolute risk of CVD is considerably modified by co-existing risk factors[70].

Of the many risk factors associated with HBP, the dietary exposure most investigated has been daily sodium consumption. It has been studied extensively in animal experimental models, in epidemiological studies, controlled clinical trials and in population studies on restricted sodium intake[70]. Salt or sodium intake has been directly correlated with mean blood pressure levels and prevalence of hypertension in many populations. Comprehensive epidemiological evidence was provided by the INTERSALT Study[71,72] which investigated the relationship of 24 hr urinary electrolyte excretion to blood pressure in 52 population groups across 32 countries, using standardised methodology to provide comparable data. In adults aged 20–59 years, there was a significant positive relationship between urinary sodium excretion and blood pressure across the 52 population samples. Further, it was also observed that in four of these populations in whom the mean 24 hr urinary sodium excretion was lower than 100 mmol/d, systolic blood pressure did not rise with age[73].

The consequences of increased sodium consumption accompanying urbanization, on blood pressure levels, was demonstrated in the Kenyan Luo Migration Study wherein rural farmers who traditionally consumed a low salt diet were observed to have an elevation of blood pressure when they migrated to an urban environment. These migrants exhibited blood pressure levels higher than rural controls and comparable to levels observed in western populations[74]. This rise in blood pressure was related to an increase in salt consumption and a reduced dietary intake of potassium. An overview of observational data in populations suggested that a difference in sodium intake of 100 mmol/d could be associated with average differences in systolic blood pressure of 5 mmHg at age 15–19 years and 10 mmHg at age 60–69 years[75]. Diastolic blood pressures are reduced by about half as much, but the association increases with age and the magnitude of the initial blood pressure. It was estimated that a universal reduction in dietary intake of salt by 50 mmol/d would

lead to a 50% reduction in the number of people requiring anti-hypertensive therapy, a 22% reduction in number of deaths due to strokes and a 16% reduction in number of deaths from CHD[75].

A recently reported cohort study in Finland prospectively followed up 1173 men and 1263 women aged 25–64 years, with complete data on 24 hr urinary sodium excretion and cardiovascular risk factors[76]. The hazard ratios for CHD, CVD and all cause mortality, associated with a 100 mmol increase in 24 urinary sodium excretion, were 1.51 (95% CI 1.14–2.00), 1.45 (1.14–1.84) and 1.26 (1.06–1.50), respectively, in both men and women. The frequency of acute coronary events, but not acute stroke events, rose significantly with increasing sodium excretion. Disaggregated analyses revealed significant risk ratios in men only and revealed that sodium predicted mortality in men who were overweight. Despite the limitations of such subgroup analyses, the overall association of increasing sodium excretion with CVD and all cause mortality further support the evidence linking increased sodium intake to adverse cardiovascular health outcomes.

Several clinical intervention trials, conducted to evaluate the effects of dietary salt reduction on blood pressure levels in hypertensive and normotensive individuals, have been systematically reviewed[14,77]. Many of the earlier trials were of limited size, short duration and deficient in statistical power. Based on an overview of 32 methodologically adequate trials (22 in hypertensive subjects and 12 in normotensive persons), Cutler *et al.*[14] concluded that a daily reduction in intake of sodium by 70–80 mmol was associated with a lowering of blood pressure both in hypertensive and normotensive individuals, with systolic and diastolic blood pressure reductions of 4.8/1.9 mmHg in the former and 2.5/1.1 mmHg in the latter. Clinical trials have also demonstrated the sustained blood pressure lowering effects of sodium restriction in infancy[78], as well as in the elderly in whom it provides a useful non-pharmacologic therapy[79].

The results of low sodium—DASH diet trial[80] further strengthen the conclusion that reduction of daily sodium intake, through salt restricted diets, lowers blood pressure effectively and is additive to the benefits conferred by the DASH diet. This trial revealed that low sodium diets, with 24 hr sodium excretion levels around 70 mmol/d, are effective and safe. Sodium consumption has also been linked to the presence of left ventricular hypertrophy[81,82] and restricted sodium intake has been demonstrated to result in regression of this important indicator of cardiovascular risk[81,82].

Of three population studies on restriction of salt, two (the Portuguese Salt Trial and the Tianjin trial in China) revealed significant reductions in blood pressure in the intervention group, while the third (the Belgian Salt Intervention Trial) did not reveal success because of difficulties in reducing salt consumption[83–85]. Animal models as well as ecological associations derived from the INTERSALT suggest a direct relationship between sodium consumption and the risk of stroke, though the methodology employed in these studies is not strong[86,87].

Based on the observational and trial data so far available, it would be justified to recommend a daily salt intake of less than 5 g/d[80]. Such an advice would be appropriate even in tropical climates, as sodium homeostasis regulates sodium excretion in sweat and urine without adverse effects under such conditions.

Potassium

Cardioprotective effects of dietary potassium have been hypothesised as the basis for low CVD rates in populations consuming 'primitive' diets and in vegetarians in industrialised cultures[88]. The INTERSALT study provided evidence of an inverse association between urinary potassium excretion and blood pressure levels, across diverse populations[71]. Migrant studies too revealed a rise in blood pressure when diets changed to a lower potassium and higher sodium intake[74].

A protective effect of potassium on blood pressure was suggested by clinical studies reporting that severe short-term potassium restriction induces salt sensitivity in normotensive humans[89], well as the blood pressure lowering effect of potassium supplements to the diet (ranging from 24 to 104 mmol/d) in hypertensive subjects[88]. Whelton *et al.* concluded, from a meta-analysis of randomised controlled trials, that potassium supplements reduced mean blood pressures (systolic/diastolic) by 1.8/1.0 mmHg in normotensive subjects and 4.4/2.5 mmHg in hypertensive subjects[90]. An increase in dietary intake of potassium, from approximately 60–80 mmol/d was shown to be inversely and significantly related to the incidence of stroke mortality in women[91].

While dietary potassium has been shown to have protective effects on blood pressure and CVD, there is no evidence to suggest that long-term potassium supplements should be administered for cardiovascular protection. The beneficial effects of fruit and vegetables recommend their regular use in daily diets at a level that should assure an adequate intake of dietary potassium.

Calcium and magnesium

A meta-analysis of studies involving calcium supplements reveal modest effects on blood pressure. The estimated blood pressure reduction was 2.1 mmHg for systolic blood pressure and 1.1 mmHg for diastolic blood pressure[92]. A review of 29 studies of magnesium was inconclusive due to methodological problems but suggested that there was no negative association of blood pressure with magnesium[93]. There is presently no evidence to recommend public health or clinical interventions involving the use of these minerals for cardiovascular protection in populations or individuals, other than in the form of a balanced diet providing an adequate daily intake.

Food items and food groups

Fruits and vegetables

While the consumption of fruit and vegetables has been widely believed to promote good health, evidence related to their protective effect has only been presented in recent years[94–96]. A systematic review reported that nine of ten ecological studies, two of three case–control studies and six of sixteen cohort studies found a significant protective association for CHD with consumption of fruit and vegetables or surrogate nutrients[96]. For stroke, three of five ecological studies and six of eight cohort studies found a significant protective association[96].

A 5-year follow-up study of 39,876 female health professionals[97], observed a significant inverse association between fruit and vegetable intake and CVD risk. For increasing quintiles of total fruit and vegetable intake, the relative risks were 1.0, 0.78, 0.72, 0.68 and 0.68. After excluding participants with a self-reported history of diabetes, hypertension or high cholesterol at baseline, the multi-variate adjusted relative risk was 0.45 when extreme quintiles were compared (95% CI: 0.22, 0.91). In a 12-year follow-up of 15,220 male physicians in United States[98], men who consumed at least 2.5 servings of vegetables per day were observed to have an adjusted relative risk of 0.77 for CHD, compared with men in the lowest category (<1 serving per day).

Combining analyses of data from two large prospective cohort studies of women and men, respectively, Joshipura *et al.*[6] reported that overall fruit and vegetable consumption were inversely related to the risk of ischaemic stroke after adjusting for confounders[99]. Assessed as a continuous trend, an increment of 1 serving per day was associated with 6% lower risk of ischaemic stroke among men and women combined. When analysed separately for the type of fruit and vegetables, the lowest risks were observed for high consumption of cruciferous vegetables such as Brussels sprouts, cabbage and cauliflower, green leafy vegetables, citrus fruits, vitamin C-rich fruits and vegetables.

The effects of increased fruit and vegetable consumption on blood pressure alone or in combination with a low-fat diet, were assessed in the DASH trial[100]. While the combination diet was more effective in lowering blood pressure, the fruit and vegetable diet too lowered the blood pressure in comparison to the control diet (2.8 mmHg systolic and 1.1 mmHg diastolic). Such reductions, while seeming modest at the individual level, would result in a substantial reduction in population wide risk of CVD by shifting the blood pressure distribution.

Fish

Most, but not all, population studies have shown that fish consumption in populations is associated with a reduced risk of CHD[101–103]. A systematic review concluded that the discrepancy in the studies may be due to differences in the populations studied, with only high-risk individuals benefiting from increasing their fish consumption[103]. It was estimated that, in high-risk populations, an optimum fish intake estimated at 40–60 g/d would lead to approximately a 50% reduction in death from CHD. In the diet and reinfarction trial, 2 year mortality was reduced by 29% in survivors of a first myocardial infarction in persons receiving advice to consume fatty fish at least twice a week[104]. While the protective effects of fish on CHD are principally mediated by *n*-3 PUFA, the contribution of other constituents of fish cannot be ruled out. The effect of dietary fish on the risk of stroke has been investigated in cohort studies, with conflicting results on the risk of ischaemic stroke[105,106]. A recent study reported that fish consumption is associated with a reduced risk of death from all causes as well as CHD and stroke mortality, using data from 36 countries[107].

Nuts

Five large epidemiological studies have, thus far, demonstrated that frequent consumption of nuts was associated with decreased risk of CHD, the best known among them being the Adventist Health Study[108–111]. The relative risk ranged from 0.43 to 0.82 for subjects who consumed nuts more than 5 times/week compared to those who never consumed nuts. An inverse dose–response relationship was demonstrated between the frequency of nut consumption and the risk of CHD, in men as well as in women. Most of these studies considered nuts as a group, combining many types of nuts.

The effect of specific nuts on lipid and lipoprotein endpoints were evaluated in several clinical studies. The nuts studied to date include walnuts, almonds, legume peanuts, macadamia nuts, pecans and pistachio nuts[108]. Collectively, these clinical studies indicate that inclusion of nuts in a lipid-lowering diet has favourable effects, but do not provide unequivocal evidence of an additive effect of nuts to the effects of a low saturated fat diet *per se*. The fatty acid profile of nuts (high in unsaturated fatty acids and low in saturated fatty acids) contributes to cholesterol lowering by altering the fatty acid composition of the diet as a whole. Nuts are also a rich source of dietary fibre. It must, however, be recognised that the high-fat content of nuts makes them high in calorie content and advice to include nuts in the diet must be tempered in accordance with the desired energy balance. While further research is needed to characterise the independent protective effects of nuts against CVD and identify the mechanisms of such protection, available evidence suggests that nuts should be recommended as part of an energy appropriate healthy diet which is intended to reduce the risk of CHD.

Soy

Several trials indicate that intake of soy has a beneficial effect on plasma lipids[112,113]. A composite analysis of 38 clinical trials found that an average consumption of 47 g of soy protein a day led to a 9% decline in total cholesterol

and a 13% decline in LDL cholesterol in subjects free of CHD[112]. The benefit of soy consumption was associated with baseline cholesterol levels, such that those with the highest cholesterol levels derived the maximum benefit (subjects with total cholesterol >335 mg/dL showed a 19% reduction in total and 24% reduction in LDL cholesterol). Cholesterol lowering of this magnitude could potentially reduce the risk for CAD by 20–40%.

Soy is rich in isoflavones, compounds that are structurally and functionally similar to estrogen. Several animal experiments suggest that intake of these isoflavones may provide protection against CHD[114], but human data on efficacy and safety are still awaited. Naturally occurring isoflavones, isolated with soy protein, reduced the plasma concentrations of total and LDL cholesterol without affecting the concentrations of triglycerides or HDL cholesterol in mildly hypercholesterolemic individuals, in a casein-controlled clinical trial[115].

Dairy products

Milk and milk products are important contributors to dietary fat and can be high in saturated fat and cholesterol. They are also sources of minerals like potassium, magnesium and calcium. Milk protein has been implicated in a study reporting elevated levels of antibodies to milk protein in patients of myocardial infarction in comparison with healthy controls[116]. Dairy consumption has been correlated positively, in an ecological study, with blood cholesterol as well as coronary mortality. Milk consumption correlates positively with coronary mortality rates in 43 countries and with myocardial mortality in 19 regions of Europe[117,118]. In contrast, a population based study in men of Japanese ancestry in Honolulu reported a reduced risk of ischaemic stroke in older middle-aged men, which could not be explained by the intake of dietary calcium[119].

On the basis of presently available evidence, reduced intake of high-fat dairy foods should be recommended for cardiovascular protection. Whether milk or milk products modified to substantially lower the content of saturated fat are associated with an increase or decrease in cardiovascular risk cannot be commented upon at present. They formed a component of the DASH diet which significantly lowered blood pressure and may be considered as part of a composite dietary advice.

Alcohol

The relationship of alcohol to overall mortality and cardiovascular mortality has generally been J-shaped, when studied in western populations in whom the rates of atherothrombotic vascular disorders are high[120–124]. The protective effect of moderate ethanol consumption is primarily mediated through its effect on the risk of CHD, as supported by more than 60 prospective studies[121]. A consistent coronary protective effect has been observed for consumption of 1–2 drinks per day of an alcohol containing beverage but heavy drinkers have higher total mortality than moderate drinkers or abstainers, as do binge drinkers. Moderate alcohol consumption (upto two drinks per day) has also been associated with a reduced risk of ischaemic stroke in men and women[125]. Long-term heavy alcohol consumption (>60 g/d) increases an individual's risk for all stroke subtypes.

Several mechanisms for the cardioprotective effects of alcohol have been proposed: increase in plasma HDL cholesterol; reduced platelet aggregation or clotting; enhanced fibrinolysis; phenolic constituents of some alcoholic beverages acting as anti-oxidants or platelet inhibitors[126]. Genetic variations which slow alcohol metabolism have been shown to increase HDL cholesterol and reduce the risk of myocardial infarction[3]. Based on current evidence, the benefit of moderate alcohol consumption seems to be a generic effect regardless of the type of beverage[127]. While the specific advantages of red wine over other alcoholic beverages is unproven, the claimed beneficial effects of flavonoids on lipoprotein oxidation are available from grape juice as from wine[128].

The possible beneficial effects of moderate ethanol consumption must be weighed against the deleterious effects of high intake, including increased risk of hypertension, cardiomyopathy and hemorrhagic stroke. Alcohol consumption, in excess of three drinks per day, is associated with a rise in blood pressure and plasma triglyceride levels. Reduction or cessation of alcohol consumption is a widely recommended measure for non-pharmacologic therapy of hypertension, in many international guidelines. The recommendations related to alcohol should be made in accordance with the cultural practices of the populations and the clinical profile of individuals, with advice to avoid excess in all cases. The optimal intake, for cardiovascular protection, depends on age, gender, presence of other risk factors or associated diseases and on the intake of folic acid. However, it is generally recommended to be about two drinks a day for men and one a day for women.

Eggs

They are unique because of their high-cholesterol content. Major effects on atherosclerosis are observed in experimental animals but extrapolation to humans is doubtful. A large observational study suggested that there was no increase in the risk of CHD up to one egg per day (except in a diabetic subgroup), in the US population[129]. In terms of global recommendations, it may still be prudent to limit the intake to 3–4 eggs per week.

Dietary patterns and composite dietary interventions

The Mediterranean diet

The traditional Mediterranean diet has been described to have eight components: (i) high monounsaturated-to-saturated fat ratio, (ii) moderate ethanol consumption,

(iii) high consumption of legumes, (iv) high consumption of cereals (including bread), (v) high consumption of fruits, (vi) high consumption of vegetables, (vii) low consumption of meat and meat products and (viii) moderate consumption of milk and dairy products[130]. Most of these are found in many diets. The characteristic component is olive oil, and many equate a Mediterranean diet with consumption of olive oil.

Based on ecological comparisons, Keys *et al.*[131] hypothesised that traditional Mediterranean diet conferred protection against CVD and several other disorders, principally because of a low saturated fat content. Three prospective population studies in Greece, Denmark and Australia provided supportive evidence of protective effects on overall mortality[132]. However, this traditional form of 'Mediterranean diet' has not been tested in controlled clinical trials.

A secondary prevention trial of dietary intervention in survivors of a first recent myocardial infarction, which aimed to study the cardioprotective effects of a 'Mediterranean type' of diet, actually left out its most characteristic component, olive oil[133]. This diet was designed to supply $<35\%$ of energy as fat, $<10\%$ of energy as saturated fat, $<4\%$ of the energy as LA (*n*-6) and $>0.6\%$ of energy as ALNA (*n*-3). The main fat source was rapeseed oil. Vegetables and fruits were also increased in the diet. Two major biological factors were modified by the intervention: plasma levels of α-tocopherol and ascorbic acid were elevated and plasma *n*-3 fatty acids increased along with a decrease in *n*-6 fatty acids. Other biological mediators of altered risk, like flavonoids, folate and minerals like potassium were probably altered but not measured. While the initial publication reported a 70% reduction in recurrence of myocardial infarction and cardiac death, the 4-year follow-up study reported a 72% reduction in cardiac death and non-fatal myocardial infarction. The risk of overall mortality was lowered by 56%[11].

Vegetarian diets

A reduced risk of CVD has been reported in populations of vegetarians living in affluent countries[134–136] and in case–control comparisons in developing countries[137]. Reduced consumption of animal fat and increased consumption of fruit, vegetables, nuts and cereals may underlie such a protective effect. However, vegetarian diets *per se* need not be healthful[136]. If not well planned, they can contain a large amount of refined carbohydrates and *t*-FAs while being deficient in the levels of vegetable and fruit consumption. The composition of the vegetarian diet should, therefore, be defined in terms of its cardio protective constituents rather than use or endorse the 'vegetarian' label as an omnibus category.

'Prudent' vs. 'western' patterns

Using factor analysis on a 131-item food frequency questionnaire, Hu *et al.* identified two major dietary patterns at baseline in 44,875 men followed up for 8 years in the Health Professionals Follow-up Study[138]. The 'prudent' pattern was characterised by higher intake of vegetables, fruit, legumes, whole grains, fish and poultry whereas the 'western' pattern was characterised by higher intake of red meat, processed meat, refined grains, sweets and dessert, French fries and high-fat dairy products. After adjustment for age and other coronary risk factors, relative risks, from the lowest to the highest quintiles of the prudent pattern score, were 1.0, 0.87, 0.79, 0.75 and 0.70. In contrast, the relative risks, across increasing quintiles of the western pattern, were 1.0, 1.21, 1.36, 1.40 and 1.64. These associations persisted in subgroup analyses according to cigarette smoking, body mass index and parental history of myocardial infarction.

DASH Diets

The effects of composite dietary interventions on blood pressure levels, in 'normotensive' and 'hypertensive' individuals, were studied in well designed clinical trials[80,100]. The initial dietary intervention, used in the dietary approaches to stop hypertension (DASH) trial involved a diet that emphasised fruits, vegetables and low-fat dairy products and included whole grains, poultry, fish and nuts while reducing the amounts of red meat, sweets and sugar containing beverages. Two variants of the intervention diet were used: a fruit and vegetables (F–V) diet and a low-fat F–V (DASH) diet. The latter was designed to lower the intake of total and saturated fat as well as dietary cholesterol. In comparison with a 'typical' diet in the United States, both intervention diets lowered blood pressure but the DASH diet was more effective in substantially reducing systolic and diastolic blood pressures, both in people with hypertension and in those without hypertension[80]. The DASH diet was also demonstrated to be effective as first-line therapy in individuals with stage I isolated systolic hypertension (i.e. with a systolic blood pressure of 140–159 mmHg and a diastolic blood pressure below 90 mmHg), with 78% of the persons on the DASH diet reducing their systolic blood pressure to <140 mmHg, in comparison to 24% in the control group[139]. The DASH diet resulted in lowering plasma levels of total cholesterol and LDL cholesterol but these changes were also accompanied by a reduction in HDL cholesterol levels[140]. While the Framingham risk score improved as a result of the impact on total and LDL cholesterol as well as blood pressure, the impact of the associated reduction in HDL cholesterol needs to be assessed.

The DASH trial was followed by a well designed factorial trial combining the DASH diet with high, intermediate and low levels of sodium consumption and measuring the effects on blood pressure, in comparison to a control diet typical of the United States, administered with similar graded variations in the sodium content[100]. Within each assigned group (DASH vs.

typical), participants ate foods with high intermediate and low levels of sodium for 30 consecutive days each, in random order. Reduction in sodium intake, at each level, resulted in significant lowering of systolic and diastolic blood pressures in both DASH and control groups. The fall was, however, maximal when the DASH diet was modified to reduce the sodium content. As compared with the control diet with a high sodium level, the DASH diet with a low sodium level led to a mean systolic blood pressure that was 7.1 mmHg lower in participants without hypertension and 11.5 mmHg lower in participants with hypertension. There was also a −4.5 mmHg difference in the mean diastolic pressure level, between the low sodium-DASH diet phase and the high sodium-control diet phase of the trial.

The effects of the low sodium-DASH diet have a great potential for application in both population based and individual focused strategies for prevention and control of HBP and associated CVD. Adoption of the low sodium-DASH diet, by populations at large, is likely to be safe and beneficial in shifting the population distributions of blood pressure (and plasma cholesterol) towards lower levels of cumulative risk of CVD in those populations. Similarly, this diet will also provide an effective non-pharmacological therapeutic intervention in the clinical management of individuals identified to be at an increased risk of CVD because of HBP and associated risk factors.

Japanese diet

The traditional Japanese diet has attracted much attention because of the highest life expectancy and low CHD mortality rates among the Japanese[141, 142]. This diet is low in fat and sugar and includes soy, seaweeds, raw fish and a predominant use of rice. It has been high in salt, but salt consumption has recently been declining in response to Japanese Health Ministry guidelines. There is also recent trend towards increased fat consumption and plasma cholesterol levels have risen, and their effects on CHD and CVD mortality rates need to be watched.

Implications for policy

The rising global burden of CVD requires a rapid response that integrates policies and programmes which enable effective prevention and control in diverse geographical and resource settings. Diet and nutrition play a critical role in the causation of major CVDs and, along with physical activity, influence many of the biologic variables that mediate the risk of those diseases. There is, therefore, an opportunity to alter the direction and dimensions of the global CVD epidemic through policy interventions (at the local, national and global levels), which promote the availability, affordability and acceptability of health promoting diets and restrain the marketing and consumption of unhealthy foods.

Currently available evidence strongly indicates that cardiovascular health is strongly influenced by the quality of dietary fat and the quantity of fruits and vegetables as well as salt consumed daily. While several other food items also contribute to enhanced or decreased risk of CVD, these remain the principal determinants of diet related CVD risk. Whether the evidence is derived from demonstration projects, controlled clinical trials or an ecological study of reasons for sharp decrease in coronary mortality in Poland since 1991, the evidence suggests that dietary changes can substantially alter the risk of CVD[143]. Policies must, therefore, address these directly and decisively.

These measures must encompass a wide range of educational as well as regulatory measures, acting through price and non-price mechanisms. That success in reducing CVD risk factor levels as well as CVD mortality is achievable through such measures that influence usual diet patterns is clear from the experience of developed countries[144]. Developing countries like Mauritius too have shown that population levels of CVD risk factors can be altered by a combination of community education and regulatory interventions related to the price of edible oils[145]. Measures to influence the quality of dietary fat (as well as the total quantity) consumed must address the elimination of *trans*-fats and reduction of saturated fats from the daily diet. Governments must work with the food industry to influence production, processing, pricing and labelling of food products so that these goals can be met. Consumer education must be enhanced so that informed choices can be made, even as the availability of healthier foods is promoted through such measures. As market economy becomes a globally pervasive economic model, it must be recognised that markets are not autonomous entities and should be moulded, for public good, by consumer consciousness as well as enlightened regulatory measures.

Edible oil production and pricing is a case where such policy measures are strongly indicated. Global nutrition transition is being propelled by the increasing availability and utilisation of vegetable oils in developing countries[146]. The production of oils for mass consumption, with respect to SFA, MFA and PUFA content as well as preferential pricing of low-SFA oils are areas of policy which need early attention and action. Mixture of edible oils for marketing and genetic modification of crops, for attainting optimal fatty acid ratios are options to consider[42,147]. The production, preservation, processing, distribution and pricing of fresh fruits and vegetables (especially green leafy vegetables) require agricultural and trade policies that ensure their availability for universal consumption in adequate quantities. The ambit of policy change has to encompass and integrate a variety of local and global responses, from community based programmes for increasing local production and self-sufficiency to national programmes that usher in a

'rainbow revolution' to global trade policies that do not promote polarised consumption of these essential foods only in some countries.

The goals of cardiovascular health need to be reconciled with other public health objectives, as in the case of salt. Reduced salt consumption must be promoted through a combination of community education, altered production practices in food manufacturing and labelling of marketed food products for their salt content. At the same time, it must be recognised that salt is now being widely used and advocated as a vehicle for iodine delivery through diet. There is a clear need for ensuring that these two public health programmes do not collide in their intent and operations, perhaps by increasing the iodine concentration in salt or choosing alternate modes of iodine delivery.

Globalisation offers a formidable challenge to the implementation of nutritional policies at the national level, as relevant to the needs of cardiovascular health. From documented evidence of the extensive diversion of fruits from domestic to export markets[148] to the recent UNEP caution on the consequences of selling fishing rights[149], it is a matter of concern that developing countries are increasingly losing nutrient rich food resources, which adversely affect local consumption. At the same time, the growth of the global fast food industry and the rapid penetration of high-salt, high-SFA, high-energy processed foods into developing country markets is promoting the consumption of foods detrimental to cardiovascular health. Global and national policies, in agriculture and trade, must speedily address these concerns and find sustainable solutions.

Even in clinical practice, the role of diet as an effective instrument of primary and secondary prevention of CVD must be emphasised. National and international guidelines must accord this component due prominence and provide clarity of content. In terms of implementation of these guidelines, health professionals must be trained to comprehend and communicate dietary advice through counselling contacts with individuals and groups. Dietary advice must not be regarded merely as a 'politically correct' adjunct to a pharmacologic prescription but must be treated as an effective pathway to risk reduction. Food-based dietary guidelines too need to be developed, as appropriate to local, regional or national context to enable people, patients, professionals and policy makers to clearly identify the practical dietary measures required to promote cardiovascular health.

Such proactive policy and programme initiatives to promote and protect global cardiovascular health through diet and nutrition need to be brought onto the national and global health agenda through multi-institutional collaboration and implemented through inter-sectoral coordination. It would require wide ranging public–private partnerships as well as a strong participation by the voluntary sector to advance this agenda. WHO and FAO are best positioned to inform and invigorate such global and national action, through their Member States and partners.

Diet and CVD: summary of evidence and recommendations

Based on the experimental and observational evidence reviewed in the foregoing sections, the risk associations of dietary constituents with CVD (CHD/HBP/stroke/arrhythmias) may be summarised as follows (Table 1).

Dietary recommendations

Fats

Dietary intake of fats, especially the qualitative composition of fats in the diet, strongly influences the risk of CVDs like CHD and stroke, through effects on blood

Table 1 Evidence for diet and risk of CVD

	Increase in risk	Decrease in risk	No relation
Convincing	Myristic and palmitic acids *t*-FAs High sodium intake Overweight High alcohol intake (for stroke)	LA Fruits, berries and vegetables Fish and fish oils (EPA and DHA) Potassium Physical activity Low to moderate alcohol intake (for CHD)	Vitamin E supplements
Probable	Dietary cholesterol Unfiltered boiled coffee β-Carotene supplements	ALNA OA Non-starch polysaccharides (fibre) Whole grain cereals Nuts (unsalted) Folate Plant sterols	Stearic acid
Possible	Fats rich in lauric acid Impaired fetal nutrition	Flavenoids Soy products	

Insufficient evidence: carbohydrates, iron, calcium, magnesium, vitamin C

lipids, thrombosis, blood pressure, arterial (endothelial) function, arrhythmogenesis and inflammation.

For promoting cardiovascular health, diets should provide:

- A low intake of SFAs: less than 7% of daily energy intake (within these limits, intake of foods rich in myristic and palmitic acids should be especially reduced).
- A very low intake of *t*-FAs (hydrogenated oils and fats): less than 1% of daily energy intake.
- Adequate intake of PUFAs: 6–10% of daily energy intake, with an optimal balance of *n*-6 and *n*-3 PUFA at 5–8% and 1–2% levels of daily energy intake, respectively.
- Intake of MUFA to make up the rest of daily energy intake from fats, with daily total fat intake ranging between 15 and 30% of daily energy intake (this may be based on current levels of population consumption in different regions and modified in accordance with age, activity and goals of body weight).
- While there is no evidence that links the quantity of dietary fat to CVD, independent of the effects of fat composition and unhealthy weight gain, there are concerns over potential excess energy consumption associated with an unrestricted fat intake. These support a recommendation that fat intake should not exceed 30% of daily energy intake. However, in very active groups with healthy dietary practices and stable healthy weight, fat intake may go up to 35% of energy.
- Dietary cholesterol consumption should be restricted to less than 300 mg/d, mainly through the restriction of dairy fats.
- These dietary goals can be met by limiting the intake of fat from dairy and meat sources, avoiding the use of hydrogenated oils and fats in cooking and manufacture of food products, using appropriate edible vegetable oils in moderation, regular intake of fish (1–2 times per week) and/or plant sources of ALNA. Practices of food preparation should preferentially employ non-frying methods.

Fruits and vegetables

Fruits and vegetables contribute to cardiovascular health through a variety of phyto-nutrients, potassium and fibre. Daily intake of fresh fruit and vegetables (including berries, green leafy and cruciferous vegetables and legumes), in an adequate quantity (400–500 g/d) is recommended to reduce the risk of CHD, stroke and HBP.

Sodium

Dietary intake of sodium, from all sources, influences blood pressure levels in populations and should be limited so as to reduce the risk of CHD and both forms of stroke. Current evidence suggests that an intake of 70 mmol or 1.7 g of sodium per day (equivalent to a daily sodium chloride intake of 4 g/d) is beneficial in reducing blood pressure and is not associated with adverse effects.

Limitation of dietary sodium intake to meet these goals should be achieved by:

- Restricting daily salt (sodium chloride) intake to less than 5 g/d. This will enable many populations to move towards the goal of around 4 g/d, from their current high intakes. This should take into account total sodium intake from all dietary sources.
- Minimising other forms of sodium consumption such as through food additives or preservatives, such as monosodium glutamate (MSG).

Potassium

Dietary intake of potassium lowers blood pressure and is protective against stroke and cardiac arrhythmias. Potassium intake should be at a level which will keep the sodium:potassium ratio close to 1, i.e. at daily potassium intake levels of 70–80 mmol/d. This may be achieved through adequate daily consumption of fruits and vegetables. Such a balance may also be obtained through use of potassium enriched low sodium salt substitutes.

Non-starch polysaccharides (commonly referred to as fibre)

Fibre is protective against CHD and has also been used in blood pressure lowering diets. Adequate intake may be achieved through fruits, vegetables and whole grain cereals.

Fish

Regular fish consumption, as consumed on a weekly basis, is protective against CHD and ischaemic stroke and is recommended for persons whose cultural beliefs do no prohibit the consumption of fish. The consumption of fish and other marine foods should provide over 200 mg/d of DHA and EPA.

Alcohol

While regular low to moderate consumption of alcohol is protective against CHD, concerns about other cardiovascular and health risks associated with alcohol consumption (including stroke, hypertension and some cancers) do not favour a general recommendation for its use.

Research recommendations

i. Clinical trials using composite dietary interventions (such as the low sodium-DASH diet or a low sodium-Lyon diet) to evaluate the impact on:

- comprehensive (absolute) cardiovascular risk profile, incorporating multiple cardiovascular risk factors

- cardiovascular events (fatal and non-fatal MI, stroke and sudden cardiac death)
- total mortality.

ii. Clinical trials to evaluate the impact of ALNA, as a sole dietary intervention, on cardiovascular end-points and total mortality.

iii. Demonstration projects, in developing countries, to evaluate the impact of culturally appropriate interventions incorporating principles of healthy diets and regular physical activity on cardiovascular risk factors distributions in populations. This should also incorporate research into the factors that determine and influence change in health behaviours related to dietary intake and physical activity.

iv. Policy research to evaluate the impact of current agricultural and trade practices on dietary patterns in different national/regional settings.

Recommendations to national governments

i. Develop and implement food and agriculture policies, which will enable adequate production and domestic supply of fruits, vegetables and whole grain cereals, at affordable prices to all segments of the population.

ii. Develop and implement policies related to edible oil production and domestic supply, which will enable consumers to exercise healthier choices, in accordance with the nutrient recommendations made in this report.

iii. Employ regulatory measures to restrict the hydrogenation of oils and fats intended for dietary consumption or manufacture of food products.

iv. Enact and enforce measures for labelling of food products, with respect to their sodium and fatty acid content, with clear codes, which will enable consumers to readily identify products with high sodium and/or fatty acid content.

v. Develop and implement policies, which will enable adequate sustainable supply of fish in domestic markets.

vi. Facilitate the development of national food based dietary guidelines through consultation with nutrition experts and community representatives.

vii. Develop and implement policies involving urban planning and transport to create facilities for supporting regular physical activity by all people of all ages.

viii. Develop national standards for manufacture and marketing of fats and oils.

ix. Utilise mass communication channels to promote national and community-based nutrition education.

Recommendations to UN/bilateral agencies

i. Facilitate the development of global trade policies which will ensure adequate supply of health promoting foods to all population groups of the world, through appropriate measures related to production subsidies, pricing and transnational movement (WTO, WHO, FAO).

ii. Facilitate the development of national food based dietary guidelines, in collaboration with national agencies (WHO, FAO).

iii. Assist in developing and testing models of community empowerment, involving local production, nutrition education and enhanced consumer consciousness (WHO, UNDP, UNICEF).

iv. Support research for developing and testing culture-specific interventions for promoting population-wide changes in dietary preferences and practices as well as regular physical activity (WHO, FAO, Bilateral Agencies).

v. Undertake country case-studies of the effects of agricultural and trade practices on nutrition and health (WHO, FAO).

Recommendations to industry

i. Make low sodium and low fat foods widely available in the market, through appropriate manufacturing practices and lower the sodium content of regularly consumed foods like breads and cereals.

ii. Implement effective food labelling practices that will help consumers exercise informed choice with respect to sodium and fatty acid content of purchased foods.

Acknowledgements

An earlier version of this paper was prepared as a background paper for the Joint WHO/FAO Expert Consultation on diet, nutrition and the prevention of chronic diseases (Geneva, 28 January–1 February 2002). The authors wish to thank Dr Ghafoorunissa, National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India, Professor A. Stewart Truswell, Human Nutrition Unit, University of Sydney, Sydney, Australia, and Dr Salim Yusuf, McMaster University, Hamilton, Canada, for the valuable comments they provided on the earlier manuscript.

References

1 Reddy KS. Cardiovascular diseases in the developing countries: dimensions, determinants, dynamics and directions for public health action. *Public Health Nutrition* 2002; **5**: 231–7.

2 *The World Health Report 1999: making a difference*. Geneva: World Health Organization, 1999.

3 Murray CJL, Lopez AD. *Global Health Statistics. Global Burden of Disease and Injury Series*. Boston, MA: Harvard School of Public Health, 1996.

4 Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998; **97**: 569–601.

5 Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases. Part I: general considerations, the epidemiological transition, risk factors, and impact of urbanization. *Circulation* 2001; **104**: 2746.

6 Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases. Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. *Circulation* 2001; **104**: 2855.

7 Clayton D, McKeigue PM. Epidemiological methods for studying genes and environmental factors in complex diseases. *Lancet* 2001; **358**(9290): 1356–60.

8 Krause BR, Princen HMG. Lack of predictability of classical animal models for hypolipidemic activity: a good time for mice? *Atherosclerosis* 1998; **140**: 15–24.

9 Stephens NG, Parsons A, Schofield PM, *et al*. Randomized controlled trial of Vitamin E in patients with coronary disease; Cambridge Heart Anti-oxidant Study (CHAOS). *Lancet* 1996; **347**: 781–6.

10 Verschuren WMM, Jacobs DR, Bloemberg BPM, *et al*. Serum total cholesterol and long-term coronary heart disease mortality in different cultures: twenty-five year follow-up of the Seven Country Study. *Journal of the American Medical Association* 1995; **274**: 131–6.

11 De Lorgeril M, Salen P, Martin JL, *et al*. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of Lyon Diet Heart Study. *Circulation* 1999; **99**: 779–85.

12 Willett WC. *Nutritional Epidemiology*. New York: Oxford University Press, 1998.

13 Kris-Etherton P, Daniels SR, Eckel RH, *et al*. for the Nutrition Committee of the American Heart Association, Summary of the Scientific Conference on Dietary Fatty Acids and Cardiovascular Health. *Circulation* 2001; **103**: 1034–9.

14 Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. *American Journal of Clinical Nutrition* 1997; **65**(Suppl. 2): 643S–51S.

15 Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). *American Journal of Cardiology* 1992; **70**: 733–7.

16 Hopkins PN. Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review. *American Journal of Clinical Nutrition* 1992; **55**: 1060–70.

17 Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. *American Journal of Clinical Nutrition* 2001; **73**: 885–91.

18 Katan MJ, Zock PL, Mensink RP. Dietary oils, serum lipoproteins and coronary heart disease. *American Journal of Clinical Nutrition* 1995; **61**(Suppl.): 1368S–73S.

19 Hu F, Stampfer MJ, Manson JE, *et al*. Dietary fat intake and the risk of coronary heart disease in women. *New England Journal of Medicine* 1994; **337**: 1491–9.

20 Kromhout D, Menotti A, Bloemberg B, *et al*. Dietary saturated and *trans* fatty acids and cholesterol and 25-year mortality from coronary heart disease: the Seven Countries Study. *Preventive Medicine* 1995; **24**: 308–15.

21 Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins—a meta-analysis of 27 trials. *Arteriosclerosis and Thrombosis* 1992; **12**: 911–9.

22 Sacks F. Dietary fats and coronary heart disease. *Journal of Cardiovascular Risk* 1994; **1**: 3–8.

23 de Roos NM, Schouten EG, Katan MB. *Trans* fatty acids, HDL-cholesterol, and cardiovascular disease. Effects of dietary changes on vascular reactivity. *European Journal of Medical Research* 2003; **8**: 355–7.

24 Judd JT, Clevidence BA, Muesing RA, *et al*. Dietary *trans* fatty acids: effects of plasma lipids and lipoproteins on healthy men and women. *American Journal of Clinical Nutrition* 1994; **59**: 861–8.

25 Willett WC, Stampfer MJ, Manson JE, *et al*. Intake of *trans* fatty acids and risk of coronary heart disease among women. *Lancet* 1993; **341**: 581–5.

26 Ascherio A, Rimm EB, Giovannucci EL, *et al*. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *British Medical Journal* 1996; **313**: 84–90.

27 Oomen CM, Ocke MC, Feskens EDM, *et al*. Association between *trans* fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population—based study. *Lancet* 2001; **357**: 746–51.

28 Katan MB. *Trans* fatty acids and plasma lipoproteins. *Nutrition Reviews* 2000; **58**: 188–91.

29 Kris-Etherton PM. Monosaturated fatty acids and risk of cardiovascular disease. *Circulation* 1999; **100**: 1253–8.

30 Mori TA, Beilin LJ. Long-chain omega 3 fatty acids, blood lipids and cardiovascular risk reduction. *Current Opinion in Lipidology* 2001; **12**: 11–7.

31 Mori TA, Bao DQ, Burke V, *et al*. Purified eicosapentaenoic acid and docosahexaenoic acid have differential effects on serum lipids and lipoproteins, LDL-particle size, glucose and insulin, in mildly hyperlipidaemic men. *American Journal of Clinical Nutrition* 2000; **71**: 1085–94.

32 Harris WS. *n*-3 Fatty acids and serum lipoproteins: human studies. *American Journal of Clinical Nutrition* 1997; **65**: 1645S–54S.

33 GISSI-Prevenzione Investigators. Dietary supplementation with *n*-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI Prevenzione Trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lancet* 1999; **354**: 447–55.

34 Von Schacky C. *n*-3 fatty acids and the prevention of coronary atherosclerosis. *American Journal of Clinical Nutrition* 2000; **71**(Suppl. 1): 224S–7S.

35 Lemaitre RN, King IB, Raghunathan TE, *et al*. Cell membrane *trans*-fatty acids and the risk of primary cardiac arrest. *Circulation* 2002; **105**: 697–701.

36 McLennan PL, Abeywardena MY, Charnock JS. Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion. *American Heart Journal* 1998; **116**: 709–17.

37 Hetzel BS, Charnock JS, Dwyer T, McLennan PL. Fall in coronary heart disease mortality in U.S.A. and Australia due to sudden death: evidence for the role of polyunsaturated fat. *Journal of Clinical Epidemiology* 1989; **42**: 885–93.

38 Grundy SM. What is the desirable ratio of saturated, polyunsaturated, and monounsaturated fatty acids in the diet? *American Journal of Clinical Nutrition* 1997; **66**(Suppl.): 988S–90S.

39 Grundy SM. The optimal ratio of fat-to-carbohydrate in the diet. *Annual Review of Nutrition* 1999; **19**: 325–41.

40 Willett WC. Dietary fat plays a major role in obesity: no. *Obesity Reviews* 2002; **3**: 59–68.

41 Mendis S, Samarajeewa U, Thattil O. Coconut fat and serum lipoproteins: effects of partial replacement with unsaturated fats. *British Journal of Nutrition* 2001; **85**: 583–9.

42 Knutzon DS, Knauf V. Manipulating seed oils for polyunsaturated fatty acid content. In: Harwood J, ed.. *Plant Lipid Biosynthesis: Fundamentals and Agricultural Applications*. Cambridge, UK: University Press, Society for Experiment Biology Seminar Series 1998; **287**: 67.

43 Truswell AS. Food carbohydrates and plasma lipids—an update. *American Journal of Clinical Nutrition* 1994; **59**(Suppl.): 710S–8S.

44 Jenkins DJA, Jenkins AL, Wolever TMS, *et al*. Low glycemic index: lente carbohydrates and physiological effects of altered food frequency. *American Journal of Clinical Nutrition* 1994; **59**(Suppl.): 706S–9S.

45 Liu S, Willet WC, Stampfer MJ, *et al*. A prospective study of dietary glycemic load, carbohydrate intake, and risk of

coronary heart disease in US women. *American Journal of Clinical Nutrition* 2000; **71**: 1455–61.
46 Marlett JA. Content and composition of dietary fiber in 117 frequently consumed foods. *Journal of the American Dietetic Association* 1992; **92**: 175–86.
47 Shikany JM, Ala B, White GL. Dietary guidelines for chronic disease prevention. *Southern Medical Journal* 2000; **93**: 1138–51.
48 Truswell AS. Cereal grains and coronary heart disease. *European Journal of Clinical Nutrition* 2002; **56**: 1–14.
49 Ludwig DS, Pereira MA, Kroenke CH, *et al*. Dietary fiber, weight gain, and cardiovascular risk factors in young adults. *Journal of the American Medical Association* 1999; **282**: 1539–46.
50 Liu S, Stampfer MJ, Hu FB, *et al*. Whole grain consumption and the risk of coronary heart disease: from the Nurses' Health Study. *American Journal of Clinical Nutrition* 1999; **70**: 412–9.
51 Rimm EB, Ascherio A, Giovannucci E, *et al*. Vegetable, fruit and cereal fiber intake and risk of coronary heart disease among men. *Journal of the American Medical Association* 1996; **275**: 447–51.
52 Rimm EB, Stampfer MJ. Antioxidants for vascular disease. *Medical Clinics of North America* 2000; **84**: 239–49.
53 Ness AR. Commentary: beyond beta-carotene—antioxidants and cardiovascular disease. *International Journal of Epidemiology* 2001; **30**: 143–4.
54 Yusuf S, Dagenais G, Pogue J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *New England Journal of Medicine* 2000; **345**: 154–60.
55 Collaborative group of the primary prevention project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *Lancet* 2001; **357**: 89–95.
56 Stampfer MJ, Malinow MR, Willett WC, *et al*. A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. *Journal of the American Medical Association* 1992; **268**: 877–81.
57 Selhub J, Jacques PF, Bostom AG, *et al*. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *New England Journal of Medicine* 1995; **332**: 286–91.
58 Stampfer MJ, Malinow MR, Willett WC, *et al*. A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. *Journal of the American Medical Association* 1992; **268**: 877–81.
59 Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *New England Journal of Medicine* 1998; **338**: 1042–50.
60 Brouwer IA, van Dusseldorp M, Thomas CM, *et al*. Low dose folic acid supplementation decreases plasma homocysteine concentrations: a randomized trial. *American Journal of Clinical Nutrition* 1999; **69**: 99–104.
61 Scott JM. Homocysteine and cardiovascular risk. *American Journal of Clinical Nutrition* 2000; **72**: 333–4.
62 Guttormsen AB, Ueland PM, Svarstad E, Refsum H. Kinetic basis of hyperhomocysteinemia in patients with chronic renal failure. *Kidney International* 1997; **52**: 495–502.
63 Celermajer DS, Sorensen K, Ryalls M, *et al*. Impaired endothelial function occurs in the systemic arteries of children with homozygous homocystinuria but not in their heterozygous parents. *Journal of the American College of Cardiology* 1993; **22**: 854–8.
64 Bellamy MF, McDowell IF, Ramsey MW, *et al*. Oral folate enhances endothelial function in hyperhomocysteinaemic subjects. *European Journal of Clinical Investigation* 1999; **29**: 659–62.
65 Rimm EB, Willett WC, Hu FB, *et al*. Folate and Vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *Journal of the American Medical Association* 1998; **279**: 359–64.
66 Tice JA, Rose E, Coxson PG, *et al*. Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease. Effect of grain fortification and beyond. *Journal of the American Medical Association* 2001; **286**: 936–43.
67 Seshadri N, Robinson K. Homocysteine, B Vitamins, and coronary artery disease. *Medical Clinics of North America* 2000; **84**: 215–37.
68 Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease. The Zutphen elderly study. *Lancet* 1993; **342**: 1007–11.
69 Keli SO, Hertog MGL, Feskens EJM, Kromhout D. Dietary flavonoids, antioxidant vitamins and incidence of stroke. *Archives of Internal Medicine* 1996; **154**: 637–42.
70 Gibbs CR, Lip GYH, Beevers DG. Salt and cardiovascular disease: clinical and epidemiological evidence. *Journal of Cardiovascular Risk* 2000; **7**: 9–13.
71 INTERSALT Cooperative Research Group. INTERSALT: an international study of electrolyte excretion and blood pressure. Results for 24 hr urinary sodium and potassium excretion. *British Medical Journal* 1988; **297**: 319–28.
72 Elliott P, Stamler J, Nicholas R, Dyer AR, Stamler R, Marmot M, *et al*. for the Intersalt Cooperative Research Group, Intersalt revisited: further analyses of 24 hr sodium excretion and blood pressure within and across populations. *British Medical Journal* 1996; **312**: 1249–55.
73 Mancilha Carvalho JJ, Baruzzi RG, Howard PF, *et al*. Blood pressure in four remote populations in the Intersalt study. *Hypertension* 1989; **14**: 238–46.
74 Poulter NK, Khaw KT, Hopwood BEC, Mugambi M, Peart WS, Rose G, *et al*. The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *British Medical Journal* 1990; **300**: 967–72.
75 Law MR, Frost MD, Wald NJ. By how much does salt reduction lower blood pressure? III. Analysis of data from trials of salt reduction. *British Medical Journal* 1991; **302**: 819–24.
76 Tuomilehto J, Jousilahti P, Rastenyte D, Moltchanov V, Tanskanen A, Pietinen P, Nissinen A. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet* 2001; **357**: 848–51.
77 Law MR, Frost CD, Wald NJ 3rd. Analysis of data from trials of salt reduction. *British Medical Journal* 1991; **302**: 819–24.
78 Geleijnse JM, Hofman A, Witteman JC, Hazebroek AA, Valkenburg HA, Grobbee DE. Long-term effects of neonatal sodium restriction on blood pressure. *Hypertension* 1997; **29**: 913–7. (Published erratum in Hypertension 1997; **29**: 1211.).
79 Whelton PK, Appel LJ, Espeland MA, *et al*. Sodium reduction and weight loss in the treatment of hypertension in older persons. *Journal of the American Medical Association* 1998; **279**: 839–46.
80 Sacks FM, Svetkey LP, Vollmer WM, *et al*. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *New England Journal of Medicine* 2001; **344**: 3–10.
81 Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD. Dietary salt intake. A determinent of cardiac involvement in essential hypertension. *Circulation* 1988; **78**: 951–6.
82 Liebson PR, Grandits GA, Dianzumba S, *et al*. Comparision of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygenic therapy in the Treatment of Mild Hypertension Study (TOHMS). *Circulation* 1995; **91**: 698–706.

83 Forte JG, Miguel JM, Miguel MJ, *et al*. Salt and blood pressure: a community trial. *Journal of Human Hypertension* 1989; **3**: 179–84.

84 Tian HG, Guo ZY, Hu G, *et al*. Changes in sodium intake and blood pressure in a community-based intervention project in China. *Journal of Human Hypertension* 1995; **9**: 959–68.

85 Staessen J, Bulpitt CJ, Fagard R, *et al*. Salt intake and blood pressure in the general population: a controlled intervention trial in two towns. *Journal of Hypertension* 1988; **6**: 965–73.

86 Tobian L, Hanlon S. High sodium chloride diets injure arteries and raise mortality without raising blood pressure. *Hypertension* 1990; **15**: 900–3.

87 Xie JX, Sasaki S, Joossens JV, Kesteloot H. The relationship between urinary cations obtained from the INTERSALT study and cerebrovascular mortality. *Journal of Human Hypertension* 1992; **6**: 17–21.

88 Young DB, Lin H, McCabe RD. Potassium's cardiovascular protective mechanisms. *American Journal of Physiology* 1995; **268**: R825–37.

89 Krishna GG, Miller E, Kapoor S. Increased blood pressure during potassium depletion in normotensive men. *New England Journal of Medicine* 1989; **320**: 1177–82.

90 Whelton PK, He J, Cutler JA, *et al*. Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *Journal of the American Medical Association* 1996; **275**: 1016–22.

91 Khaw KT, Barrett-Connor E. Dietary potassium and stroke associated mortality. *New England Journal of Medicine* 1987; **316**: 235–40.

92 Griffith LE, Guyatt GH, Cook RJ, *et al*. The influence of dietary and non-dietary calcium supplementation on blood pressure. An updated meta-analysis of randomized controlled trials. *Journal of Hypertension* 1999; **12**: 84–92.

93 Mizushima S, Cuppauccio FP, Nichols R, Elliott P. Dietary magnesium intake and blood pressure: a qualitative overview of the observational studies. *Journal of Human Hypertension* 1998; **12**: 447–53.

94 Nestle M. Animal vs. plant foods in human diets and health: is the historical record unequivocal? *Proceedings of the Nutrition Society* 1999; **58**: 211–8.

95 Law MR, Morris JK. By how much does fruit and vegetable consumption reduce the risk of ischaemic heart disease? *European Journal of Clinical Nutrition* 1998; **52**: 549–56.

96 Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. *International Journal of Epidemiology* 1997; **26**: 1–13.

97 Liu S, Manson JE, Lee I-M, *et al*. Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *American Journal of Clinical Nutrition* 2000; **72**: 922–8.

98 Liu S, Lee I-M, Ajani U, *et al*. Intake of vegetables rich in carotenoids and risk of coronary heart disease in men: The Physicians' Health Study. *International Journal of Epidemiology* 2001; **30**: 130–5.

99 Joshipura KJ, Ascherio A, Manson JF, *et al*. Fruit and vegetable intake in relation to risk of ischemic stroke. *Journal of the American Medical Association* 1999; **282**: 1233–9.

100 Appel LJ, Moore TJ, Obarzanek E, *et al*. A clinical trial of the effects of dietary patterns on blood pressure. *New England Journal of Medicine* 1998; **336**: 1117–24.

101 Kromhout D, Bosschieter Eb, de Lezenne Coulander C. The inverse relation between fish consumption and 20 year mortality from coronary heart disease. *New England Journal of Medicine* 1985; **312**: 1205–9.

102 Daviglus ML, Stamler J, Orencia AJ, *et al*. Fish consumption and the 30-year risk of fatal myocardial infarction. *New England Journal of Medicine* 1997; **336**: 1046–53.

103 Marckmann P, Gronbaek M. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. *European Journal of Clinical Nutrition* 1999; **53**: 585–90.

104 Burr ML, Fehily AM, Gilbert JF, *et al*. Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989; **2**: 757–61.

105 Gillman MW, Cupples LA, Millen BE, *et al*. Inverse association of dietary fat with development of ischaemic stroke in men. *Journal of the American Medical Association* 1997; **278**: 2145–50.

106 Orenica AJ, Daviglus ML, Dyer AR, *et al*. Fish consumption and stroke in men. *Stroke* 1996; **27**: 204–9.

107 Zhang J, Sasaki S, Amano K, Kesteloot H. Fish consumption and mortality from all causes, ischaemic heart disease and stroke: an epidemiological study. *Preventive Medicine* 1999; **28**: 520–9.

108 Kris-Etherton PM, Zhao G, Binkoski AE, *et al*. The effects of nuts on coronary heart disease risk. *Nutrition Reviews* 2001; **59**: 103–11.

109 Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Archives of Internal Medicine* 1992; **152**: 1416–24.

110 Fraser GE, Lindsted KD, Beeson WL. Effect of risk factor values on lifetime risk of and age at that first coronary event. The Adventist Health Study. *American Journal of Epidemiology* 1995; **142**: 746–58.

111 Hu FB, Stamfer MJ. Nut consumption and risk of coronary heart disease: a review of epidemiologic evidence. *Current Atherosclerosis Reports* 1999; **1**: 204–9.

112 Anderson JW, Smith BM, Washnok CS. Cardiovascular and renal benefits of dry bean and soybean intake. *American Journal of Clinical Nutrition* 1999; **70**(Suppl.): S464–74.

113 Third International Symposium on the role of soy in preventing and treating chronic disease. *Journal of Nutrition* 2000; **130**(Suppl.): S653–711

114 Anthony MS, Clarkson TB, Bullock BC. Soy protein versus soy phitoestrogens (isoflavones) in the prevention of coronary artery atherosclerosis of cyno molgus monkeys (Abstract). *Circulation* 1996; **94**(Suppl. 1): 1–265.

115 Crouse JR III, Morgan T, *et al*. Randomized trial comparing the effect of casein with that of soy protein containing varying amounts of isoflavones on plasma concentrations of lipids and lipoproteins. *Archives of Internal Medicine* 1999; **159**: 2070–6.

116 Davies DF. Cow's milk antibodies and coronary heart disease. *Lancet* 1980; **8179**: 1190–1.

117 Law MR, Wald N. An ecological study of serum cholesterol and ischaemic heart disease between 1850 and 1990. *European Journal of Clinical Nutrition* 1994; **48**(5): 305–25.

118 Seely S. Diet and coronary disease. A survey of mortality rates and food consumption statistics of 24 countries. *Medical Hypotheses* 1981; **7**: 907–18.

119 Abbott RD, Curb JD, Rodriguez BL, *et al*. Effect of dietary calcium and milk consumption on risk of thromboembolic stroke in older middle aged men. *Stroke* 1996; **27**: 813–8.

120 Gaziano JM, Buring JE, Breslow JL, *et al*. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *New England Journal of Medicine* 1993; **329**: 1829–34.

121 Rehm J, Bondy S. Alcohol and all cause mortality: an overview. *Novartis Foundation Symposium* 1998; **216**: 223–32.

122 Gaziano JM, Godfried S, Hennekens CH. Alcohol and coronary heart disease. *Trends in Cardiovascular Medicine* 1996; **329**: 1829–34.

123 Maclure M. Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. *Epidemiologic Reviews* 1993; **15**: 328–51.
124 Moore RD, Pearson T. Moderate alcohol consumption and coronary artery disease: a review. *Medicine* 1986; **65**: 242–67.
125 Sacco RL, Elkind Mm, Boden-Albala B, *et al*. The protective effect of moderate alcohol consumption on ischemic stroke. *Journal of the American Medical Association* 1999; **281**: 53–60.
126 Gaziano JM, Buring JE, Brestlow JL, Goldhaber SZ, *et al*. Moderate alcohol intake increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *New England Journal of Medicine* 1993; **329**: 1829–34.
127 Gaziano JM, Hennekens CH, Godfried SL, *et al*. Type of alcoholic beverage and risk of myocardial infarction. *American Journal of Cardiology* 1999; **83**: 52–7.
128 Miyagi Y, Miwa K, Inoue H. Inhibition of human low-density lipoprotein oxidation by flavonoids in red wine and grape juice. *American Journal of Cardiology* 1997; **80**: 1627–31.
129 Hu FB, Stampfer MJ, Rimm EB, *et al*. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *Journal of the American Medical Association* 1999; **281**(15): 1387–94.
130 Trichopoulou A, Kouris-Blazos A, Vassilakou T, *et al*. The diet and survival of elderly Greeks; a link to the past. *American Journal of Clinical Nutrition* 1995; **61**(Suppl.): 1346S–50S.
131 Keys A, Menotti A, Karvonen MJ, *et al*. The diet and 15-year death rate in the Seven Countries Study. *American Journal of Epidemiology* 1986; **124**: 903–15.
132 Trichopoulou A, Vasilopoulou E. Mediterranean diet and longevity. *British Journal of Nutrition* 2000; **84**(Suppl. 2): S205–9.
133 De Lorgeril, Renaud S, Mamelle N, *et al*. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994; **343**: 1454–9.
134 Rimm EB, Ascherio A, Giovannucci E, *et al*. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *Journal of the American Medical Association* 1996; **275**: 447.
135 Gilman MW, Cupples LA, Gagnon DJ, *et al*. Protective effect of fruits and vegetables on development of stroke in men. *Journal of the American Medical Association* 1995; **273**: 1113–7.
136 Willett WC. Convergence of philosophy and science: the Third International Congress on Vegetarian Nutrition. *American Journal of Clinical Nutrition* 1999; **70**(Suppl.): 434S–8S.
137 Pais P, Pogue J, Gerstein H, Zachariah E, *et al*. Risk factors for acute myocardial infarction in Indians: a case–control study. *Lancet* 1996; **348**: 358–63.
138 Hu FB, Rimm EB, Stampfer MJ, *et al*. Prospective study of major dietary patterns and risk of coronary heart disease in men. *American Journal of Clinical Nutrition* 2000; **72**: 912–21.
139 Moore TJ, Conlin PR, Ard J, Svetkey LP for DASH Collaborative Research Group, DASH (Dietary Approaches to Stop Hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. *Hypertension* 2001; **38**: 155–8.
140 Obarzanek E, Sacks FM, Vollmer WM, *et al*. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *American Journal of Clinical Nutrition* 2001; **74**: 80–9.
141 Shimamoto T, Komachi Y, Inada H, *et al*. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation* 1989; **79**: 503–15.
142 Truswell AS. Review of dietary intervention studies: effect on coronary events and on total mortality. *Australian and New Zealand Journal of Medicine* 1994; **24**: 98–106.
143 Zatonski WA, McMichael AJ, Powles JW. Ecological study of reasons for sharp decline in mortality for ischaemic heart disease in Poland since 1991. *British Medical Journal* 1998; **317**: 678.
144 Pietinen P, Vartianinen E, Seppanen R, *et al*. Changes in diet in Finland from 1972 to 1992: impact on coronary heart disease risk. *Preventive Medicine* 1996; **25**: 243–50.
145 Dowsen GK, Gareeboo H, George K, *et al*. Changes in population cholesterol concentrations and other cardiovascular risk factor levels after five years of non-communicable disease intervention programme in Mauritius. *British Medical Journal* 1995; **311**: 1255–9.
146 Drewnowski A, Popkin BM. The nutrition transition: new trends in the global diet. *Nutrition Reviews* 1997; **55**: 31–43.
147 Indu M, Ghafoornissa. Fatty acids in Indian diets—comparison of the effects of precursor (alpha-linolenic acid) vs product (long chain *n*-3 poly unsaturated fatty acids). *Nutrition Research* 1992; **12**: 569–82.
148 Lang T. The public health impact of globalisation of food trade. In: Shetty PS, McPherson K, eds. *Diet, Nutrition and Chronic Disease. Lessons from Contrasting Worlds*. Chichester: Wiley, 1997, 173–87.
149 United Nations Environment Programme. www.unep.ch/etu/doha/papers.htm