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Review

Has the association between saturated fatty acids, serum cholesterol and coronary heart disease been over emphasized?

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ABSTRACT

Despite 50 years of research and public health messages, coronary heart disease is still the major cause of death in developed countries. This review outlines the elaboration of risk factors for coronary heart disease with emphasis on total and LDL cholesterol levels and discusses the dynamic and heterogeneous nature of serum lipoproteins. The role of saturated fatty acids in hypercholesterolemia is examined and it is concluded that those acids that increase levels concomitantly increase antiatherogenic HDL cholesterol and decrease proatherogenic lipoprotein[a] and small dense LDL particles such that they could be atherogenically neutral. Evidence from epidemiological studies does not supply convincing evidence for an association between saturated fatty acids and coronary heart disease. The surprisingly few randomised controlled trials that examined isocaloric substitution of saturated fatty acids for vegetable-derived fats mostly fail to show a benefit for reduction in saturated fatty acid intake on coronary heart disease risk. The contention that the benefits accruing from the potent hypocholesterolemic action of statin drugs ends the cholesterol controversy is disputed.

Contents

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1. Introduction

During the past 50 years the nutritional image of milk and dairy products, particularly those with a high fat content, has suffered because of their content of saturated fatty acids, which is associated with elevated serum cholesterol levels, a risk factor for coronary heart disease (CHD). The link between dietary fat, saturated fatty acids (SFAs), serum cholesterol and CHD has been referred to as the diet-heart or lipid hypothesis and since the hypothesis was not universally accepted the term "cholesterol controversy" emerged (Steinberg, 2006). Public health organisations worldwide have produced dietary guidelines to help reduce the risk of CHD. The National Cholesterol Education Program (NCEP) Step-One diet (Expert Panel, 1988) is typical and recommends, in part, that total fat should not exceed 30% of total calories, intake of SFAs is less than 10% of calories and a dietary cholesterol intake is less than 300 mg per day.

However, despite a half century of intensive research, dietary advice, mainly to reduce saturated fat in order to reduce serum cholesterol levels, and the production of "healthy" food items by the food industry, CHD is still the leading cause of death in developed countries. This review examines initially the early studies that established the CHD risk factors, on which dietary recommendations are now based; the strength of the relationships between SFA intake and the levels of serum cholesterol and other pro- and antiatherogenic lipoproteins; the epidemiological associations between SFA intake and risk of CHD; clinical intervention studies with SFA and the associations between serum lipids and CHD.

2. Serum cholesterol, other lipoproteins and the risk of coronary heart disease

By the end of World War II infectious diseases, formerly the major cause of morbidity and mortality, were under control and life expectancy had increased. However, an alarming rise in the incidence of coronary heart disease (CHD) became evident. At this time the cause or causes of CHD were unknown. During 1948–1950 under the direction of the then National Heart Institute, 5127 men and women aged 30–59 years from the town of Framingham in Massachusetts were recruited for the first ever-longitudinal study to determine the risk factors for CHD (Dawber et al., 1951). A report of the first 6 years of follow-up appeared in 1961. Three risk factors were reported, elevated serum cholesterol levels, hypertension and an electrocardiographic pattern of left ventricular hypertrophy (Kannel et al., 1961).

Subsequently, many other epidemiological studies, including several large, well-known prospective studies conducted in different countries found a positive association between serum cholesterol levels and the risk of CHD. They include the Framingham Study (Anderson et al., 1987; Kannel et al., 1979), the Stockholm Prospective Study (Carlson and Bottiger, 1985), the Multiple Risk Factor Intervention Trial (MRFIT) (Neaton and Wentworth, 1992; Stamler et al., 1986), the Lipid Research Clinics Program Prevalence Study (Pekkanen et al., 1990), the Whitehall Study (Davey Smith et al., 1992), and the much-cited Seven Countries Study (Verschuren et al., 1995). In MRFIT (Neaton and Wentworth, 1992), age-adjusted death rates increased 6-fold between serum cholesterol levels of 3.4 to 8.4 mmol L^{-1}. However, at any level of serum cholesterol the risk of CHD varies widely depending on the presence of other risk factors.

In these early studies cholesterol content was measured as the total contained in serum, plasma or blood. Cholesterol and other blood lipids are sparingly soluble in aqueous solution and are transported in blood attached to proteins (apoproteins). The resulting lipoproteins are an extremely heterogeneous mixture with different chemical compositions, physical properties and metabolic functions. Lipoproteins are classified on the basis of their density as determined by ultracentrifugation. There are five main serum lipoproteins classes. In order of increasing density they are chylomycrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). As the density of the particles increases their percentage of triglycerides decreases whereas protein increases (Gurr et al., 2002).

At the 11th biennial cardiovascular examination in the Framingham Study during 1969–1971, measurement of VLDL, LDL- and HDL cholesterol was added to the routine testing protocol (Gordon et al., 1977). Follow-up data from this 1969–1971 cohort and from other prospective studies of this era show that like total cholesterol, high levels of VLDL- and LDL cholesterol are positively associated

with the risk of CHD while high levels of HDL cholesterol are negatively associated with CHD risk (Gordon and Rifkind, 1989; Miller and Miller, 1975; Pekkanen et al., 1990; Stampfer et al., 1991). Elevated serum triglycerides levels (Rubins et al., 1995; Sarwar et al., 2007) and high levels of lipoprotein[a] (Lp[a]) (Danesh et al., 2000) are further lipid risk factors for CHD. Obesity, physical inactivity, hypertension, diabetes, psychosocial issues, and elevated serum homocysteine levels are other important risk factors (Braunwald, 1997; Schaefer, 2002).

The importance of CHD risk factors other than serum cholesterol can be judged, to some extent, with data from Framingham and MRFIT. In the Framingham Study the risk of cardiovascular disease (CVD), expressed as 8-year probability per 1000, for the highest level of serum cholesterol was 3.9. The addition of glucose intolerance and high systolic blood pressure (BP) increased risk to 23.2, and increased further to 34.6 with inclusion of cigarette smoking, the presence of left ventricular hypertrophy increased risk to 60.2 (Kannel et al., 1979). In MRFIT smokers with levels of serum cholesterol and systolic BP in the highest quintile, the age-adjusted death rate was 20.2-times greater than for non-smoking men with serum cholesterol and systolic BP in the lowest quintile (Neaton and Wentworth, 1992). The strength of the associations between serum cholesterol and other risk factors with CHD decreased with age (Anderson et al., 1987; Kannel et al., 1979; Neaton and Wentworth, 1992).

Twenty five-year follow-up data from the much-cited Seven Countries Study (Verschuren et al., 1995) showed that serum cholesterol was linearly related to CHD mortality in all participating countries. However, the absolute levels of CHD mortality were strikingly different. At serum cholesterol level of 5.2 mmol L^{-1} there was a 5-fold greater mortality rate in Northern Europe than in Japan. These differences in mortality risk applied after adjusting for age, smoking and systolic BP. These studies suggest that there are other powerful, yet to be determined, risk factors for CHD in industrialized communities.

2.1. Lipoprotein particle size and CHD

Both LDL- and HDL cholesterol determined currently for clinical purposes contain particles that are heterogeneous in size, density and composition (Krauss, 2005; Miller, 1987). LDL size varies greatly among individuals and is genetically influenced, with a heritability ranging from 40% to 60%, and variation is independent of total LDL cholesterol levels (Krauss, 2005). It is believed that compared with larger, more buoyant LDL particles, small dense particles are more easily taken up by the arterial wall, bind more tightly to arterial wall proteoglycans (complex glycoproteins containing highly negatively charged carbohydrate chains), have greater oxidative susceptibility and reduced LDL receptor affinity (Griffin, 1999; Krauss, 2005). For a given LDL cholesterol level an increase in small dense LDL particles is associated with increased atherogenicity. Rizzo and Berneis (2006) list 33 case–control studies 26 of which show a positive association between elevated small dense LDL particles and risk of CHD. Seventeen prospective studies are listed of which only two failed to show a positive association for small dense LDL particles. Twelve of these studies conducted multivariate analyses, but only four studies remained statistically significant after adjustment for other confounding variables, in particular serum triglycerides and HDL cholesterol concentrations. The number of LDL particles rather than their density may be a stronger determinant of CHD risk and Rizzo and Berneis (2006) list four prospective studies that determined the association between LDL number or concentration and risk of CHD. In all four studies the number of total and smaller LDL particles was a significant and independent predictor of CHD risk, even after multivariate adjustment for lipid variables.

HDL also represents a heterogeneous class of lipoprotein. It is metabolically dynamic with a number of major and minor subspecies that differ in apolipoprotein and lipid composition, size and density and can possess different physiological functions (Miller, 1987; Silverman et al., 1993). Numerous studies have shown that the large HDL_2 sub-fraction is more atheroprotective than the smaller dense HDL_3 sub-fraction, but other studies have not confirmed this effect, which may result from the dynamic state of HDL and that sub-fractions are themselves heterogeneous (Miller, 1987; Morgan et al., 2004; Silverman et al., 1993).

2.2. Apolipoproteins and CHD

The protein components of lipoproteins are known as apoproteins or apolipoproteins. There are nine major species identified by the letters A, B, C, D and E with Roman numerals used for subspecies. Apolipoproteins have characteristic amino acid sequences, chain lengths and possess different physiological and biochemical properties and are responsible for the structural integrity of the lipoproteins. Lipoprotein classes have a distinctive apolipoprotein profile (Gurr et al., 2002).

Apolipoprotein B (apo B) is found on the surface of chylomycrons, VLDL, IDL, LDL and Lp[a] and each of these particles contains one apo B molecule. Because the cholesterol content of these particles varies, apo B reflects more exactly the number of atherogenic particles, although all particles may not be equally atherogenic. Circulating levels of apo B have been shown to be superior to LDL cholesterol and non-HDL cholesterol as an independent risk factor for CHD in most studies (Pischon et al., 2005; Sacks, 2006; Thompson and Danesh, 2006; Walldius et al., 2001). Some patients have high concentrations of serum apo B in the presence of normal serum cholesterol levels. There were approximately 2.5-times more heart disease patients in the 95th percentile of apo B frequency distribution than in the 95th percentile of serum LDL cholesterol distribution (Sniderman and Silberberg, 1990). Positively charged regions on apo B interact with matrix proteins including negatively charged proteoglycans within the artery wall (Khalil et al., 2004), an initiating event in atherosclerosis (Tabas et al., 2007).

Apo A-1 is present on all HDL particles and is inversely related to the risk of CHD (Sacks, 2006; Walldius et al., 2001). The ratio of apo B:apo A is the most important indicator of risk for CHD (Walldius et al., 2001; Yusuf et al., 2004). Apo C-III is also an independent risk factor for CHD especially when it is a component of apo B lipoproteins (Lee et al., 2003; Sacks et al., 2000a). The superior ability of apolipoprotein levels over LDL cholesterol levels for prediction of CHD risk is not surprising because the apoproteins, unlike cholesterol, determine the metabolic fate of the lipoproteins to which they are attached. For instance, apo B binds to proteoglycans both on endothelial cells and in the matrix of atherosclerotic plaques where they are retained (Sacks, 2006; Tabas et al., 2007). The adhesion of human monocytic cells to vascular endothelial cells, an early event in atherosclerosis, is enhanced by apo C-III. Excessive apo C-III inhibits lipoprotein lipase activity that delays lipolysis of apo B-containing lipoproteins and their clearance from the circulation. Apo C-III also impairs apo B lipoproteins (VLDL, IDL and LDL) binding to receptors in the liver. Apo C-III has been shown to activate nuclear factor κB, which is a key regulator for inflammation in atherosclerosis (Kawakami et al., 2006).

It is often stated that the majority of CHD victims have normal or near normal serum cholesterol levels (Genest et al., 1991; Ridker et al., 2002; Rubins et al., 1995; Sacks et al., 1994). Results from the Framingham Study over 16 years of follow-up show extensive

overlap in distribution curves of total cholesterol levels for men with and without CHD (Kannel et al., 1979). Similar distribution is noted for LDL cholesterol levels (Genest et al., 1992a; Sniderman and Silberberg, 1990). However, CHD patients with serum total cholesterol levels in the normal range mostly have other significant dyslipidemia. A study from Tufts University of men under 60 years of age with angiographically confirmed CHD found more than half had a familial lipoprotein disorder (Genest et al., 1992b). The most frequent dyslipidemias were low HDL cholesterol alone 19%, high Lp(a) 15.8% and elevated LDL cholesterol alone 12.1%. Overall, however, the prevalence of HDL cholesterol and triglycerides abnormalities accounted for more than 50% of the lipoprotein abnormalities. Stepwise discriminant analysis indicated, in decreasing order of importance, that smoking, hypertension, decreased apo A-1, increased apo B, increased Lp(a) and diabetes distinguished patients with CHD from normal subjects (Genest et al., 1992a).

In summary, this section demonstrates that the etiology of CHD is complex, there are a number of important risk factors, and lipoprotein disorders other than elevated serum total and LDL cholesterol play an important role.

3. Influence of dietary saturated fatty acids on serum lipoprotein levels

Soon after the commencement of the Framingham Study, a number of groups investigated the influence of diet, especially fat, on serum cholesterol levels in man. Results from the early studies were conflicting, but a well-conducted study carried out in a metabolic ward by Ahrens et al. (1954) showed that when plant fats were substituted isocalorically for animal fats there was a significant reduction in serum cholesterol levels. Later, this group demonstrated that the lowest serum cholesterol levels were seen when corn oil, safflower seed oil or cottonseed oil constituted the sole dietary fat. Increased cholesterol levels were found with all other sole dietary fats with coconut oil and butterfat providing the highest levels (Ahrens et al., 1957).

Based on a series of experiments that investigated the effect of different fats on serum cholesterol levels Keys et al. (1957) produced a regression equation:

$$\Delta\text{Chol} = 2.74\Delta S - 1.31\Delta P$$

The equation showed that saturated fatty acids (SFAs; S) had about twice the effect in raising serum cholesterol levels (ΔChol) as polyunsaturated fatty acids (PUFAs; P) had in depressing it.

Improved prediction equations that accounted for the influence of dietary cholesterol on serum cholesterol levels were presented by Keys et al. (1965a) and Hegsted et al. (1965). Further refinements using up-dated literature data from well-controlled trials on the effect of diet on serum cholesterol levels, including LDL cholesterol, HDL cholesterol and serum triglycerides were reported by Mensink and Katan (1992), Derr et al. (1993) and Hegsted et al. (1993). Nevertheless, it is important to realize that prediction equations apply only to large groups and not to individuals. Numerous studies demonstrate wide inter-individual variation in serum cholesterol response to controlled changes in fatty acid intake, particularly SFAs (Ahrens et al., 1957; Grundy and Vega, 1988; Jacobs et al., 1983; Katan et al., 1988; Keys et al., 1965b).

Not all SFAs possess identical hypercholesterolemic potency. The shorter chain fatty acids C4:0, C6:0, C8:0, C10:0 and a portion of C12:0, present in milk fat, after absorption enter the portal circulation and pass to the liver where they are rapidly oxidised. They are not incorporated into chylomycrons and have no serum cholesterol-raising effect (Bloom et al., 1951). It is difficult to determine accurately the relative cholesterol-raising effect of C12:0, C14:0 and C16:0 using diets containing natural triglycerides because of their co-existence and some conflict does exist. However, data from both regression analyses and dietary studies suggest that C12:0 is more potent than C14:0, which is more potent than C16:0 in raising total and LDL cholesterol levels. C18:0, like monounsaturated fatty acids (MUFAs) does not appear to influence serum cholesterol levels (Denke and Grundy, 1992; Derr et al., 1993; Mensink et al., 2003; Temme et al., 1996; Zock et al., 1994).

Although the C12:0, C14:0 and C16:0 acids increase serum total and LDL cholesterol levels when substituted for carbohydrate or oleic acid, they concomitantly increase the level of antiatherogenic HDL cholesterol. The acids that increase LDL cholesterol the most likewise produce the greatest increase in HDL cholesterol (Denke and Grundy, 1992; Temme et al., 1996; Tholstrup et al., 1994; Zock et al., 1994). Regression models from the meta-analysis of 60 controlled dietary trials (Mensink et al., 2003) showed that C12:0 greatly increased total cholesterol, but most of its effect was on HDL cholesterol such that there was a decrease in the ratio of total to HDL cholesterol. The ratio of total to HDL cholesterol is a more powerful predictor of CHD risk than either total or LDL cholesterol levels (Stampfer et al., 1991). C14:0 and C16:0 acids had little effect on the ratio and C18:0 reduced the ratio slightly. On the other hand, the ratio decreased if SFAs or carbohydrates were replaced by *cis*-unsaturated MUFAs. Although all fatty acids elevate HDL cholesterol when substituted for carbohydrate the effect is diminished with increasing unsaturation of the fat (Mensink and Katan, 1992). Replacement of carbohydrate by fat lowers serum triglyceride levels that is independent of the type of fat (Mensink and Katan, 1992; Mensink et al., 2003).

3.1. Dietary fat and LDL particle size

In addition to a beneficial or null effect on the total to HDL cholesterol ratio, SFA intake is associated with a larger, buoyant LDL particle profile. Data from the Framingham Offspring Study show that low saturated fat and cholesterol intakes were significantly associated with smaller dense LDL particles (Campos et al., 1992). Another cross-sectional study did not find a strong relationship between reported intake of SFAs and small dense LDL levels, however, individual fatty acids typically found in milk fat (C4:0–C10:0 and C14:0) and C15:0 and C17:0 in serum phospholipids were negatively associated with the level of small dense LDL particles (Sjogren et al., 2004). In healthy men, Dreon et al. (1998) found that intake of total SFAs as well as C14:0 and C16:0 was associated with increases in larger LDL particles and decreases in smaller LDL particles.

For many years public health bodies, nutritionists and dieticians have recommended a high carbohydrate, low-fat diet as a preventative measure for CHD. Whereas these diets may reduce serum LDL cholesterol levels, they may also decrease HDL cholesterol and increase serum triglycerides levels (Abbasi et al., 2000; Dreon et al., 1999; Sacks and Katan, 2002). Low serum HDL cholesterol accompanied by elevated triglycerides levels is a powerful risk factor for CHD (Genest et al., 1992a; Rubins et al., 1995; Stampfer et al., 1996). In addition, a dietary intervention study showed that in men with a preponderance of large buoyant LDL particles who consumed a low-fat, high-carbohydrate diet shifted their phenotype towards one with a preponderance of small dense LDL particles (Dreon et al., 1999).

3.2. Dietary fat and HDL particle size

A number of studies demonstrate that decreased total and saturated fat with an associated increase in carbohydrate intake results in a proportionally greater reduction in the less dense more

antiatherogenic HDL_2 particles than in the more dense less antiatherogenic HDL_3 particles. These studies employed specially designed diets (Clevidence et al., 1992; Dreon et al., 1998; Williams et al., 1995) or a comparison of an average American diet with NCEP Step 1 or Step 2 type diets (Berglund et al., 1999; Schaefer et al., 1995). Other studies suggest that a low P:S ratio (Fumeron et al., 1991; Schonfeld et al., 1982) and cholesterol supplementation (Kestin et al., 1989; Schonfeld et al., 1982) favour an increased HDL_2:HDL_3 ratio. A diet high in C16:0 produced a higher HDL_2:HDL_3 ratio than a similar diet but high in 16:0 (Tholstrup et al., 1994).

3.3. Dietary fat and lipoprotein[a] levels

Recent studies show that the amount and type of dietary fat can influence the level of lipoprotein[a] (Lp[a]). Shin et al. (2007) found that Lp[a] levels were significantly higher with a low-fat, high-carbohydrate diet containing 4.9% SFAs than with a high-fat, low-carbohydrate diet containing 13% SFAs. Lp[a] concentration was significantly increased by 7% and 9%, respectively, when the SFA intake decreased from 28 g to 20 g and 19 g per day, respectively, and the intake of PUFAs increased from 11 g to 13 g and to 19 g per day, respectively (Silaste et al., 2004).

Ginsberg et al. (1998) found that with diets where the intake of MUFAs, PUFAs and cholesterol was constant, decreasing the level of SFAs resulted in a stepwise increase in Lp[a] levels. An SFA diet (C12:0 + C14:0 + C16:0) representing 16.7% of energy significantly lowered Lp[a] levels compared with a diet with comparable levels of oleic acid (Clevidence et al., 1997). Lp[a] levels were significantly increased when a high C18:0 diet was compared with a baseline diet where the fat was mainly butterfat (Aro et al., 1997). Almendingen et al. (1995) found that diets where the fat was largely partially hydrogenated soybean oil or partially hydrogenated fish oil significantly increased Lp[a] levels compared with a diet where the fat was largely butterfat.

Mensink et al. (1992) noted that oleic acid increased plasma Lp[a] concentrations compared with an equivalent level of SFAs. Diets high in C18:0 gave significantly higher levels of Lp[a] than diets high in C16:0 and in C12:0 + C14:0 (Tholstrup et al., 1995). These results suggest that a low-fat, high-carbohydrate diet has an adverse effect on Lp[a] levels, whereas the hypercholesterolemic SFAs like those found in milk fat appear to have a beneficial effect.

3.4. Dietary fat and apolipoprotein levels

Dietary fat influences apoprotein concentrations in a manner similar to that of the lipoproteins to which they are attached, but not always to the same extent. When a high-fat, high-SFA, low-carbohydrate diet is substituted by a low-fat, low-SFA, high-carbohydrate diet apo A and apo B generally decrease, but the variation is such that there is mostly a detrimental increase in the ratio of apo B:apo A (Dreon et al., 1998; Ginsberg et al., 1998; Schaefer et al., 1995; Shin et al., 2007). This type of dietary change also significantly increased the concentration of total and non-HDL-apo C-III and decreased the concentration of HDL-apo C-III (Shin et al., 2007). The meta-analysis of Mensink et al. (2003) showed that replacement of carbohydrates with SFAs did not change apo B concentrations. The *cis*-unsaturated fatty acids, however, decreased apo B, an effect that was slightly stronger for PUFAs.

The studies outlined in this section strongly suggest that the effect of dietary SFAs on the overall serum lipoprotein profile could be less atherogenic than when total and LDL cholesterol are considered in isolation. Even so, measurement of lipoprotein profile cannot be used to determine if SFA intake is a casual factor in CHD. For this, data from well-conducted epidemiological studies and randomised controlled trials must be considered.

4. The association between saturated fatty acids and CHD: epidemiological evidence

4.1. Ecological studies

The earliest epidemiological investigations into the relationship between SFA intake and CHD risk employed the ecological or correlation format. With this technique the apparent per capita intake of SFAs, or other items, is correlated with the CHD death rate for a number of countries or regions. Nearly all of the reported ecological studies found strong positive correlations between saturated, animal, dairy and total fat intake and CHD death rate using univariate analysis. However, it was demonstrated that bias often existed in the selection of countries from the available data pool and that selection of different groups of countries or use of the total data produced correlations of a lesser value (Wood, 1981; Yerushalmy and Hilleboe, 1957).

Studies that included other items in their analysis often found equally robust correlation coefficients. For example, sugar, eggs, protein and total calories (Stamler, 1978). Yudkin (1957) found the best correlations with CHD mortality were with the number of radio and TV licences. There was nearly as good a correlation with the number of registered motor vehicles. Whereas Masironi (1970) found strong positive correlations between consumption of total fat, saturated fat and sucrose and CHD incidence, equally good correlations were found for national per capita income and national per capita energy consumption – indices of living standards and technological progress.

The ecological study format suffers from many weaknesses. The use of national fat disappearance data is only indirectly related to intake and tells nothing about the diet of those who developed CHD and those who did not. Types and availability of food items, physical activity, lifestyle, genetic and ethnic factors, standard of medical care and adherence to CHD death classification all vary considerably between countries. For these reasons ecological studies cannot be used to ascribe a causal relationship between SFA intake and risk of CHD. Unfortunately, learned lectures and reviews still use this type of data to support the lipid hypothesis of CHD (Schaefer, 2002).

Many of the adverse aspects of the ecological format can be avoided by conducting within-population studies. The characteristics of participants are more homogeneous and adjustment can be made for other factors that influence CHD risk. The favoured formats are case–control studies and prospective or cohort studies.

4.2. Case–control studies

The case–control study provides a simple, rapid, low cost design for the determination of differences in previous dietary exposure in individuals with CHD and those free of the disease. Surprisingly, case–control studies that investigated the association between SFA intake and the risk of CHD are few and only seven studies were identified. Early studies from North Dakota (Zukel et al., 1959), Ireland (Finegan et al., 1968), Japanese and Hawaiian cohorts in Hawaii (Bassett et al., 1969) and the Scottish Heart Health cohort (Bolton-Smith et al., 1992) did not find a difference in the % calorie intake of SFAs between cases and control subjects. Later studies employed multiple logistic regression analyses to measure risk. A Greek study found the relative risk (RR) for CHD associated with the highest quintile of SFA intake compared with the lowest quintile of intake was 1.02 with a 95% confidence interval (CI) of 0.41–2.54 (Tzonou et al., 1993). An RR of 1.00 (95% CI, 0.81–1.25) was found in a study of Korean men (Suh et al., 2001). A study of men and women from Costa Rica (Kabagambe et al., 2003) was the only instance of a case–control study finding a statistically significant

Table 1
Comparison of daily intake of energy, total fat, saturated fat and polyunsaturated fat in individuals with coronary heart disease (CHD) and those free of disease in 15 cohort studies.

Study[a]		Cohort size	CHD	End point[b]	Age (y)	Follow-up (y)	Energy intake (kcal)	Saturated fatty acids[c]		Polyunsaturated fatty acids[c]		Total fat[c]	
								Level (g d^{-1})	Energy (%)	Level (g d^{-1})	Energy (%)	Level (g d^{-1})	Energy (%)
Positive associations													
Yano et al. (1978)		7705	179	B	45–68	6	2125/2290*	31/32	13/12*	16/15	7/6*	85/86	35/33*
McGee et al. (1984)		7088	456	B	45–68	10	2229/2309*	31.7/31.9	12.7/12.3*	15.7/15.4	6.3/6.0*	86.4/86.3	34.7/33.2*
Kushi et al. (1985)		1001	110	A	30–69	20	3208/3355	62/63	17.4/16.9†	9.3/10.1	2.6/2.7	–	39.4/38.5
Negative associations													
Farchi et al. (1989)		1536	58	A	45–64	15	2697/2900*	23.8/28.9*	8.0/9.0*	9.2/11.5*	3.2/3.7	76.9/90.8	26.0/28.5
Fehily et al. (1993)		2423	148	B	45–59	5	2179/2313*	72.1/76.1[d]	29.7/29.5	–	–	98.7/102	40.9/40.1
Null associations													
Paul et al. (1963)		1989	88	B	40–55	4.5	3082/3174	59/59	17.2/16.7	13.2/13.9	3.9/4.0	148/152	–
Medalie et al. (1973)		9764	427	B	40–60+	5	–	NS	NS	NS	NS	NS	–
Morris et al. (1977)		337	45	B	30–67	10–20	–	–	NS	–	NS	–	–
Garcia-Palmieri et al. (1980)	Urban	5798	213	B	45–64	6	2305/2413	36/37	13.6/13.5	17/16	6.7/5.9*	98/99	38.0/36.6*
	Rural	2420	73	B	45–64	6	2241/2353	33/33	13.1/12.6	10/11	3.9/3.9	81/86	32.3/32.2
Gordon et al. (1981)		859	79	B	45–64	6	2488/2622	43/44	15.3/14.9	16/16	5.8/5.4	112/114	–
Shekelle et al. (1981)		1900	–	A	40–55	19	–	NS	–	↓*	–	–	–
Kromhout et al. (1984)		857	30	A	40–59	10	2792/3065*	54.6/59.8	17.7/17.6	18.3/20.1	5.9/5.9	–	–
Khaw and Barrett-Connor (1987)	Men	356	42	A	50–79	12	1997/2076	30.2/31.7	13.6/13.7	14.8/15.1	6.7/6.5	–	82.6/85.8
	Women	503	23	A	50–79	12	1479/1589	21.6/24.4	13.1/13.8	11.9/12.2	7.2/6.9	–	59.5/66.5
Posner et al. (1991)	Age range 1	420	99	B	45–55	16	–/–	NS	NS	NS	NS	↑*	↑*
	Age range 2	393	114	B	56–65	16	–/–	NS	NS	NS	NS	NS	NS
Goldbourt et al. (1993)		10,059	1098	A	40+	23	–	–	↓	–	↓	–	–

[a] Positive, negative and null refer to associations with saturated fatty acids.
[b] End points are: A, CHD death; B, total CHD events.
[c] Values given are CHD/free. Asterisk denotes statistically significant; †, $p = 0.05$ after full adjustment; NS = not statistically significant; ↓, inverse association; ↑, positive association.
[d] Animal fat.

positive association between SFA intake and the risk of CHD (RR 3.00, 1.54–5.84).

Case–control studies are sensitive to bias. Bias can result from failure of control subjects to truly reflect the population under study, error in recall of past diet, CHD patients deliberately misreporting intake of a dietary item if they know it influences CHD risk, and failure to include an analysis of CHD victims who die at the time of or subsequent to the heart attack.

4.3. Prospective (cohort) studies

Prospective or cohort studies provide the most reliable format for determining the association between dietary items and disease risk. These studies largely overcome the biases introduced in case–control studies, thus diet is assessed before disease is diagnosed and at a more etiologically relevant time, while cases and control subjects are from the same cohort. Negative aspects include high cost associated with the large number of participants required to ensure adequate CHD events. A large cohort can make it difficult to obtain accurate information on diet and potential confounding factors. Because of the length of time the study runs, it may be advisable to identify individuals who changed their dietary pattern due to awareness of health risks. Irrespective of format, the accuracy of epidemiological studies is dependent on the quality of dietary assessment and the nutrient database.

4.3.1. Saturated fatty acids

Twenty-four reports of cohort studies that investigated the association between SFA intake and the risk of CHD were identified. Five of these reports were extended follow-up of previously reported studies. Some studies recorded results by sex, age group, area (rural and urban) and different CHD end points that led to 33 data sets. A comparison of daily intake for energy, total fat, SFAs and PUFAs in individuals with CHD and in those free of the disease in 15 reports from 11 cohorts is presented in Table 1. Later studies that reported CHD RR, odds ratio (OR) or hazard ratio (HR) with 95% CIs for the highest compared with the lowest reported intake level of total, saturated, monounsaturated and polyunsaturated fat from nine reports from eight cohorts are given in Table 2. In all cases the recorded data are for the fully adjusted multivariate model.

There was a statistically significant positive association between SFA intake and the risk of CHD in only four cohorts. The Honolulu Heart Study (McGee et al., 1984; Yano et al., 1978) and the Ireland–Boston Diet Heart Study (Kushi et al., 1985) both found a positive association between % energy from SFAs, but not from absolute intake. A small Canadian Study (52 events) found an increasing energy intake from saturated fat was a risk for CHD mortality in 30 to 59-year-old men and women (RR 1.11, 1.04–1.18), but not for those aged 60–79 years (RR 0.96, 0.88–1.05) (Esrey et al., 1996). The other positive study, a small British cohort with only 57 events, found a 100 g per week increase in saturated fat intake corresponded to an RR of 1.40 (1.09–1.79) in women. No evidence was found for a corresponding relationship in men (Boniface and Tefft, 2002).

In contrast, the largest three cohort studies, the Nurses' Health Study with 78,778 participants and 1766 events (Oh et al., 2005), the Health Professionals Follow-up Study with 43,757 participants and 734 events (Ascherio et al., 1996) and the Alpha Tocopherol, Beta Carotene Cancer Prevention Study with 21,930 participants and 1339 events (Pietinen et al., 1997) did not find a positive association between saturated fat intake and CHD risk in fully adjusted models. In the Health Professionals Follow-up Study although the RR for high saturated fat intake and fatal CHD was 1.72 (1.01–2.90), statistical significance was not attained ($p = 0.09$).

On the other hand, two cohort studies found a statistically significant negative association between SFA intake and the risk of CHD. With data from two Italian cohorts of the Seven Countries Study, Farchi et al. (1989) found that both the absolute and % energy intake of SFAs were statistically higher in control subjects than in

Table 2
Relative risk and 95% confidence intervals for CHD for the highest versus the lowest reported intake levels of total, saturated, monounsaturated and polyunsaturated fat from eight cohort studies.

Study[a]	Cohort size	CHD events	End point[b]	Age (y)	Follow-up (y)	Saturated fat[c]	Monounsaturated[c]	Polyunsaturated[c]	Total fat[c]
Positive associations									
Esrey et al. (1996)	3925	52	A	30–59	12	1.11 (1.04–1.18)*	1.08 (1.01–1.16)	0.99 (0.90–1.08)	1.04 (1.01–1.08)*
Boniface and Tefft (2002)	1451[d]	57	A	40–75	16	1.40 (1.09–1.79)*	–	–	1.19 (1.03–1.37)*
Negative associations									
Pietinen et al. (1997)	21,930	581	A	50–69	6.1	0.73 (0.56–0.95)*	0.77 (0.59–1.00)	1.27 (1.00–1.61)*	0.85 (0.65–1.12)
Null associations									
Ascherio et al. (1996)	43,757	734	B	40–75	6	0.96 (0.73–1.27)	–	1.04 (0.82–1.33)[f]	1.02 (0.78–1.34)
	43,757	229	A	40–75	6	1.72 (1.01–2.90)	–	1.28 (0.83–1.98)[f]	1.22 (0.75–2.0)
Esrey et al. (1996)	621	40	A	60–79	12	0.96 (0.88–1.03)	1.00 (0.91–1.08)	1.00 (0.90–1.10)	0.99 (0.95–1.03)
Hu et al. (1997)	80,082	939	B	34–59	14	1.07 (0.77–1.48)	0.95 (0.64–1.39)	0.68 (0.53–0.88)*	1.04 (0.83–1.28)
Pietinen et al. (1997)	21,930	1339	B	50–69	6.1	0.87 (0.73–1.03)	0.82 (0.69–0.99)	1.11 (0.94–1.31)	0.87 (0.73–1.05)
	21,930	581	A	50–69	6.1	0.73 (0.56–0.95)*	0.77 (0.59–1.00)	1.27 (1.00–1.61)*	0.85 (0.65–1.12)
Boniface and Tefft (2002)	1225[e]	98	A	40–75	16	1.00 (0.86–1.18)	–	–	1.01 (0.93–1.10)
Jakobsen et al. (2004)	3686[d,e]	228[e]	B	30–71	16	1.03 (0.78–1.37)[g]	0.95 (0.65–1.40)[g]	0.80 (0.55–1.15)[g]	0.98 (0.87–1.10)[g]
		98[d]	B	30–71	16	1.36 (0.98–1.88)[g]	1.01 (0.56–1.83)g	0.89 (0.05–1.57)[g]	1.12 (0.93–1.36)[g]
Oh et al. (2005)	78,778[d]	1766	B	30–59	20	0.97 (0.73–1.27)	0.82 (0.62–1.10)	0.75 (0.60–0.92)*	0.92 (0.77–1.09)
Leosdottir et al. (2005)	11,063[e]	242	A	45–73	6.6	0.94 (0.58–1.53)	0.61 (0.36–1.03)	0.99 (0.65–1.53)	0.65 (0.45–0.94)*
	17,035[d]	97	A	45–73	6.6	0.55 (0.26–1.17)	1.53 (0.65–3.64)	0.63 (0.33–1.22)	0.74 (0.40–1.36)
Tucker et al. (2005)	501	71	A	34–80	18	1.04 (0.99–1.08)	–	–	–

[a] Positive, negative and null refer to associations with saturated fatty acids.
[b] End points are: A, CHD death; B, total CHD events.
[c] Values are given as relative risk (RR), odds ratio (OR) or hazard ratio (HR) with 95% confidence intervals in parentheses. Data are for the fully adjusted multivariate model. Asterisk denotes statistically significant.
[d] Women.
[e] Men.
[f] Linoleic acid only.
[g] Risk associated with a 5% higher level of energy of the type of fat.

cases. In the Alpha Tocopherol, Beta Carotene Cancer Prevention Study the RR of major CHD events and CHD death for the highest quintile of SFA intake compared with the lowest was 0.87 (0.73–1.03) and 0.73 (0.56–0.95), respectively (Pietinen et al., 1997). In this study the so-called hypercholesterolemic fatty acids C12:0 to C16:0, which represented 62% of total SFA intake, were investigated separately. The RRs were 0.88 (0.74–1.04) and 0.74 (0.57–0.96) for total CHD events and CHD deaths, respectively. Hu et al. (1999) with data from the Nurses' Health Study also determined associations between groups of SFAs and CHD risk, but no significant associations were found. For the highest vs. lowest quintiles of C4:0 to C10:0 the RR was 1.00 (0.82–1.21); for C12:0 to C14:0 RR 1.05 (0.83–1.32); for C16:0 RR 1.03 (0.71–1.50); for C18:0 RR 1.16 (0.81–1.66) and for the sum of C12:0 to C18:0 the RR was 1.04 (0.72–1.48).

4.3.2. Unsaturated fatty acids

A corollary of the CHD lipid hypothesis would suggest that since PUFAs lower serum cholesterol levels they should protect against CHD. Evidence from the cohort studies, however, does not support this assumption. A statistically significant positive association between energy % intakes of PUFAs and CHD was found in the Honolulu Heart Study at 6-year (Yano et al., 1978) and 10-year follow-ups (McGee et al., 1984) and in the Puerto Rico Heart Health Program for urban but not rural participants (Garcia-Palmieri et al., 1980). The only statistically significant negative association for PUFA intake and CHD was in the Nurses' Health Study at both 14-year (Hu et al., 1997) and 20-year follow-ups (Oh et al., 2005), with RRs of 0.68 (0.53–0.88) and 0.75 (0.60–0.92), respectively. The other studies produced null associations.

In the Nurses' Health Study (Hu et al., 1997) it was estimated that isocaloric substitution of 5% of energy from SFAs by carbohydrate would reduce the risk of CHD by 17%. On the other hand, substitution by unsaturated fat would reduce risk by 42%. In this study the P:S ratio was inversely associated with risk of CHD (Hu et al., 1999).

MUFA intake was positively associated with CHD mortality in 30 to 59-year-old men, but not in the 60–79 year age group in the Lipid Research Clinics Prevalence Follow-up Study (Esrey et al., 1996). There was also a positive association between the incidence of CHD and the proportion of dietary energy from MUFAs in the younger (45–55 year), but not older (55–65 year) cohort from the Framingham Study (Posner et al., 1991).

4.3.3. Total fat

Total fat consumption as a percentage of energy intake was significantly higher in CHD victims in the Honolulu Heart Study (McGee et al., 1984; Yano et al., 1978), the urban cohort of the Puerto Rico Heart Health Program (Garcia-Palmieri et al., 1980) and in the 45–55 year age group in the Framingham Study (Posner et al., 1991). A comparison of the highest with the lowest intake of total fat produced an RR of 1.04 (1.01–1.08) for 30–59 year olds in the Lipid Research Clinics Prevalence Follow-up Study (Esrey et al., 1996). In the British study the RR was 1.19 (1.03–1.37) for women (Boniface and Tefft, 2002). The only negative association was in the Malmo Diet and Cancer Study with an RR of 0.65 (0.45–0.94) for women (Leosdottir et al., 2005). All other data sets provided null associations.

4.3.4. Energy intake

It is interesting to note in Table 1 that in all 12 cohorts those participants free of CHD had a higher energy intake (five statistically significant) than those who developed the disease. A possible explanation is that a higher energy intake was a surrogate measure of increased physical activity, which is negatively associated with the risk of CHD. Increased energy intake may also be associated with alcohol consumption (Gordon et al., 1981) that is also negatively associated with CHD (Rimm, 1996).

4.3.5. Fibre intake

The protective effect of fibre was a consistent observation in the cohort studies listed in Tables 1 and 2. Liu et al. (2002) list RRs from published studies on fibre intake and risk of CHD and conducted a pooled analysis that produced an RR of 0.83 (0.78–0.89). The large

Nurses' Health Study (Hu et al., 1999) and Health Professionals Follow-up Study (Ascherio et al., 1996) both found that fibre intake was inversely associated with SFA intake. In the later study the age-adjusted RR for total CHD events for intake of saturated fat was 1.44 ($p = 0.002$), after multivariate adjustment for non-dietary risk factors the RR was weakened to 1.22 ($p = 0.14$). RR was further attenuated to 0.96 ($p = 0.69$) after adjustment for fibre intake. Intake of fibre was more strongly related to the risk of CHD than the intake of SFAs.

4.4. Comment

There is no compelling evidence from well conducted epidemiological studies that SFA intake is associated with the risk of CHD, nor is there persuasive evidence that unsaturated fatty acids exert a protective effect. Even so, epidemiological associations cannot be used to ascribe causality, for this well conducted randomised placebo-controlled trials are required.

4.5. Autopsy studies

Two studies were identified that related previous diet with the extent of atherosclerosis in the coronary arteries and aortas determined at autopsy. Moore et al. (1976) studying 253-deceased New Orleans men found that the extent of raised lesion involvement in the three coronary arteries measured at autopsy was not associated with their previous intake of animal or saturated fat either in absolute terms or as a nutrient-to-calorie ratio. Autopsy data from 258 men who participated in the Honolulu Heart Program (Reed et al., 1987) did not show a relationship between SFA intake and atherosclerosis scores in the coronary arteries and aortas.

5. Randomised controlled trials

The protocol for a clinical randomised controlled trial (RCT) to establish if dietary SFAs are causally related to CHD requires these acids to be substituted by unsaturated fatty acids isocalorically. Total fat, other dietary items and lifestyle factors associated with CHD must be similar for intervention and control subjects and along with dietary changes remain in operation for many years. In practise these conditions are extremely difficult to accomplish and it may be truly said that a randomised control trial of adequate design to establish the role of SFAs in CHD has never been conducted. Nevertheless, a few studies have examined the effect of replacing a substantial portion of animal fat in a usual diet with vegetable oils as the only variant, and without undue difference in energy intake from fat for test and habitual diet.

5.1. The Minnesota Coronary Survey

The Minnesota Coronary Survey was conducted with 9057 institutionalised men and women and is the only example of a satisfactory primary prevention trial to test the saturated fat concept (Frantz et al., 1989). The study compared a normal diet (39% fat calories, 18% SFA, 16% MUFA, 5% PUFA) with a treatment diet (38% fat calories, 9% SFA, 14% MUFA, 15% PUFA). Serum cholesterol levels fell by 14% during the intervention period of a little over 1 year. For the study population no differences between treatment and control groups were observed for cardiovascular (CV) events, CV deaths, or total mortality.

5.2. The Finnish Mental Hospitals Study

The Finnish Mental Hospitals Study (Turpeinen et al., 1979) is often cited as providing strong support for the lipid-heart disease hypothesis. It was a primary prevention study, conducted with middle-aged men in two mental hospitals. One of the hospitals received a serum cholesterol-lowering diet by replacing butter with PUFA margarine and whole milk with soybean oil filled milk. The other hospital served its normal diet. After 6 years intervention the diets at the two hospitals were reversed and the trial was continued for another 6 years. The intervention diet decreased serum cholesterol levels by about 15%. Overall, there was a suggestion of a benefit with the cholesterol-lowering diet, not for mortality, but for intermediate end points determined by electrocardiography.

However, as a randomised control trial this study was seriously flawed. The institutions were randomised not the individuals and thus was a cluster randomised trial with only two clusters; the inmates in the institutions changed during the trial and there were differences between groups in BP, cigarette smoking and use of psychotropic drugs. A characteristic of the cholesterol-lowering diet was the removal of "common margarine", which during the time of this study would have contained considerable quantities of *trans* fatty acids that are now known to be more atherogenic than SFAs (Ascherio, 1999). Thus reduction in CHD events was probably in part due to reduction in *trans* fat.

5.3. The Los Angeles Veterans Administration Study

In the Los Angeles Study (Dayton et al., 1969) 846 veterans with and without previously diagnosed CHD were randomised to a conventional diet, which contained 40% of energy mainly from animal fat, or a test diet where about two-thirds of the animal fat were replaced by vegetable oils. After about 8 years of intervention serum cholesterol levels were reduced by about 13% in the treatment group. But there was no statistically significant difference in the primary end point of the study – sudden death or (myocardial infarction (MI)) – between the groups. However, when these data were pooled with that for cerebral infarction and other secondary end points significance was obtained. Deaths due to non-atherosclerotic causes were higher in the intervention group so that overall total mortality was similar in both groups.

5.4. The Oslo Diet-Heart Study

The Oslo Diet-Heart Study (Leren, 1966) was the most successful intervention trial; it was conducted with 412 men aged 30–64 years. They were randomised 1–2 years after a first myocardial infarction to a control group who consumed their normal diet or an intervention group consuming 39% of total calories from fat with 8.5% from SFA, 20.7% from PUFA and 10.2% from MUFA to give a P/S ratio of 2.4. After 5 years of intervention serum cholesterol was 14% lower in the treatment group and there were significantly fewer major CHD relapses, but fatal MI, CV mortality and total mortality while lower than in the control group did not attain statistical significance. Intervention was more successful in patients under age 60 years and in this study CHD mortality was correlated with age, cholesterol levels, BP, body weight, smoking habits and a combination of these risk factors.

5.5. London Hospitals Study

The London Hospitals Study (Rose et al., 1965) was a small trial of 80 patients of average age 55 years with CHD who were randomised to either their normal diet (control) or to two treatment

groups with a restriction of animal fat and supplementation of about 60 g per day of either olive or corn oil. After 2 years of intervention serum cholesterol levels fell significantly in the corn oil group but not in the olive oil group. Both vegetable oil groups fared worse than the control group with the percentage of patients remaining alive being 75%, 57% and 52% for the control, olive and corn oil groups, respectively.

5.6. Medical Research Council Soybean Oil Study

In the Soybean Oil Study (Research Committee to the Medical Research Council, 1968) 393 men aged under 60 years recovering from a first MI were randomly allocated to their normal diet or a diet that was low in saturated fat and contained about 80 g soybean oil daily. Participants were in the trial for 2 to nearly 7 years and the test diet lowered serum cholesterol levels by a mean of 22%. Fatal CHD events and major first relapses were the same in both groups, but non-major relapses were non-significantly lower in the soybean group. Relapses were not related to initial serum cholesterol levels.

5.7. Sydney Diet-Heart Study

This study consisted of a control group of 237 men with average age around 49 years recovering from CHD who consumed a diet that contributed 13.5% of total calories as SFA and 9.5% as PUFA. A similarly matched intervention group substituted PUFA margarine for butter resulting in a dietary intake of 9.8% of calories from SFA and 15.1% as PUFA. After 5 years of intervention 16.7% of the PUFA group had died compared with only 11.8% in the control group. During follow-up serum cholesterol had no predictive value for outcome and dietary factors were not significantly related to survival (Woodhill et al., 1978).

5.8. MRC Low-Fat diet trial

This low-fat diet trial (Research Committee to the Medical Research Council, 1965) involved 252 men less than 65 years of age who were recovering from a first MI. They were randomised to receive their normal diet, which contained from 110 g to 130 g of fat per day or a low-fat diet with the same type of fats as the controls but at a level of about 45 g per day. Despite a lowering of serum cholesterol levels and greater loss of body weight in the treatment group there was not a significant difference in reinfarction and death in the two groups.

5.9. Comment

These trials provide no convincing evidence that removal of SFA from the diet will help prevent CHD. There was only one primary prevention study and that lasted for 1 year only. The others were secondary prevention studies conducted with men recovering from premature CHD, which does not reflect the total population. There was a trend to a more successful outcome in men of a younger age and a higher baseline serum cholesterol level. It can be argued that the numbers in the trials were too small to have the power to determine certain CHD outcomes, that intervention times were too short and that atherosclerosis was too far advanced to respond to dietary intervention. Nevertheless, these trials are repeatedly cited to justify the lipid-heart hypothesis and to make dietary recommendations for the general population.

6. Multifactor dietary intervention studies

A number of studies investigated the effect on CHD of a diet with reduced SFA and increased PUFA content while endeavouring to reduce total fat intake as well as modifying other risk factors like hypertension, overweight and cigarette smoking.

6.1. The Oslo Study

The Oslo Study (Hjermann et al., 1981) involved 1232 healthy men aged 40–49 years with high serum cholesterol levels (7.5–9.8 mmol L^{-1}) and at high risk for CHD. Subjects were randomised to an intervention group that was counselled to stop smoking and partake of a diet that reduced fat from 44% of calories to 28% and SFAs from 18% to 8% of calories. The advised diet was significantly higher in fibre than the control diet. No changes were made to the diet or lifestyle of the control subjects. After 5 years of intervention serum cholesterol fell by 13% in the intervention group and total coronary events, but not total mortality, were significantly lower than in controls. There were significantly more cigarettes smoked in the control group. Cigarette smoking was the most important single contributor to CHD in the Nurses' Health Study (RR 5.48, 4.67–6.42) where the RR for dietary score was 1.90 (1.55–2.34) (Stampfer et al., 2000). The authors of the Oslo Study report admit that without modification to smoking habit the outcome would not have attained statistical significance.

6.2. Multiple Risk Factor Intervention Trial (MRFIT)

MRFIT (MRFIT Research Group, 1982) was a large, well-conducted trial to test multifactor intervention on CHD mortality. Participants were 12,866 men aged 35–57 years at high risk for CHD, who were randomised to an intervention program to lower BP, reduce smoking, normalise body weight and a serum cholesterol-lowering diet that reduced total fat, SFAs and cholesterol and increased PUFAs. The control group was referred to their usual source of medical care. CHD mortality was the trial end point. After about 7 years of follow-up there was no significant difference between groups for CHD, CVD or all cause mortality. However, during the intervention period there were also substantial decreases in risk factors for the control group.

6.3. Multifactor Primary Prevention Trial in Goteborg, Sweden

This Swedish study (Wilhelmsen et al., 1986) of men aged 47–55 years at high risk for CHD was similar to MRFIT. Here there were 10,000 men in the intervention group that received treatment for hypertension, dietary advice to reduce serum cholesterol levels and advice to stop smoking. After 10 years of intervention the risk factors decreased markedly, but there were also decreases in the control group. Total mortality, CHD and stroke incidence did not differ between groups.

6.4. Diet and Reinfarction Trial (DART)

DART (Burr et al., 1989) had 2033 male participants who had recovered from MI. They were randomised to three treatment arms, each with a control group; reduction in total fat and SFAs, but an increase in PUFAs; an increase in fatty fish intake; an increase in cereal fibre intake. After 2 years of intervention there was no significant difference in non-fatal MI, total CHD events, CHD deaths or total mortality for the fat advice and fibre advice groups. For the fish advice group there was a significant decrease in total and CHD deaths, although there was no change in serum cholesterol levels.

6.5. The Indian Diet Heart study

The Indian Diet Heart study (Singh et al., 1992) consisted of 505 MI patients who were randomised into two groups within 2 days of infarction. One group were advised to follow a fat reduced diet (control group), the other group was additionally advised to eat more fruit, vegetables, nuts and grain products. After 1 year the vegetable group received a significantly higher percentage of energy from (I) vegetable protein, (II) complex carbohydrate, (III) PUFAs, (IV) fibre in the form of fruit, vegetables, and nuts, (V) fish, (VI) soybean, sunflower and ground nut oils. Antioxidant vitamins and minerals were significantly higher in the vegetable group, but differences in SFA and PUFA intake as a percentage of energy between groups were not great, 7.2% vs. 10.8% and 8.6% vs. 7.0%, respectively. Serum cholesterol levels were on average 0.42 mmol L^{-1} lower and weight loss was greater in the vegetable group after 1 year of intervention. The outcome was a statistically significant decrease in total CV events and mortality in the cardioprotective group compared with the control group.

Another Indian study (Singh et al., 2002) with 2000 CHD patients randomised to an Indo-Mediterranean diet or a local NCEP prudent diet produced a similar result after 2 years of intervention.

6.6. The Lyon Diet Heart Study

The Lyon Diet Heart Study (De Lorgeril et al., 1994) was a successful secondary prevention study involving 605 men who survived an MI. They were randomised to a control group that consumed a usual post-infarct prudent diet or an experimental group advised to adopt a Mediterranean-type diet with (I) more bread, (II) more root and green vegetables, (III) more fish, (IV) beef, lamb and pork to be replaced with poultry, (V) no day without fruit, (VI) butter and cream to be replaced with margarine. The difference between control and experimental groups for energy from SFAs and the P/S ratio was not great, 11.7% vs. 8.3% and 0.69 vs. 0.65, respectively. After an average follow-up of 27 months there were significantly fewer major primary CV events, CV deaths and total mortality in the experimental group. It is interesting to note that these benefits occurred without any differences throughout the duration of the study in total, LDL and HDL cholesterol levels, BP and body mass.

6.7. The Women's Health Initiative Randomised Controlled Dietary Modification Trial

The Women's Health Initiative Randomised Controlled Dietary Modification Trial (Howard et al., 2006) was a large US study where 48,835 post-menopausal women were randomised to an intervention group (40%) or a comparison group (60%). The aim with the intervention group was to reduce total fat intake to 20% of calories with SFAs contributing no more than 7%, and increased intakes of vegetables and fruits to 5 servings per day and grains to 6 servings per day. To accomplish these changes, intervention subjects underwent an intensive behavioural modification program involving 18 group sessions in the first year and quarterly maintenance sessions thereafter. The comparison group received diet-related educational material, but had no contact with nutrition interventionists.

After a mean follow-up of 8.1 years there were no significant differences in the incidence of CHD, CVD and stroke between the two groups. Despite the intensive nutritional counselling the intervention group achieved only an 8.2% decrease in energy intake from fat and 2.9% from SFAs, and there was only a modest increase in fruit and vegetable consumption. At year 3 LDL cholesterol levels were only 0.09 mmol L^{-1} lower in the intervention group than in the comparison group.

6.8. Comment

Because multiple dietary, lifestyle and medication changes were made in these multifactor intervention studies they cannot be used to establish a role for SFAs and serum cholesterol levels in the aetiology of CHD. Overall the results from the multifactor trials are disappointing, especially in those where a benefit for CHD events was not accompanied by a benefit for total mortality. The short term Indian Diet Heart Studies (Singh et al., 1992, 2002) and the Lyon Diet Heart Study (De Lorgeril et al., 1994) were the most successful and offer some hope for intervention, but it is interesting to note that these successes occurred in spite of little change in serum cholesterol levels.

In Singh et al. (1992) serum cholesterol decreased by 12.7% in the treatment group and by 9.4% in the control group at first year. In the Lyon Diet Heart Study (De Lorgeril et al., 1994) benefits occurred without any differences throughout the duration of the study in total, LDL and HDL cholesterol levels for treatment and control subjects. The failure of the larger and longer running Women's Health Initiative Randomised Controlled Dietary Modification Trial (Howard et al., 2006) illustrates the difficulty of sustaining dietary changes over an extended period of time.

For most of the trials there was bias towards the intervention group because they received more attention and advice from health professionals than control subjects. This attention could result in an increased psychological expectation of benefit in these patients inducing a placebo effect (Kaptchuk, 2002). Thus, in the Coronary Drug Project (Coronary Drug Project Research Group, 1980), 5-year mortality for CHD patients treated with clofibrate was 20.0% compared with 20.9% in those given a placebo. Post hoc sub-group analysis showed mortality for good adherers to clofibrate was 15.0% and 24.6% for poor adherers. However, similar findings were noted in the placebo group, 15.1% mortality for good adherers and 28.3% for poor adherers.

7. Assessment of randomised control trial results

In addition to RCTs based on dietary modification there have been multiple RCTs that used hypocholesterolemic drugs, either alone or in combination with modification of diet and other lifestyle risk factors, to lower serum cholesterol and thus influence CHD incidence. Many systematic reviews and meta-analyses that analysed the results of these trials together with those relating to diet have been published. These analyses that used different inclusion and exclusion criteria as well as end points reached mixed conclusions on the effect of lipid lowering on CHD mortality (Katerndahl and Lawler, 1999).

Only one meta-analysis addressed the effect of SFA reduction and that study used total mortality as the end point (Iestra et al., 2005). The pooled effect estimate for four studies (Burr et al., 1989; Leren, 1966; Research Committee to the Medical Research Council, 1968; Woodhill et al., 1978) was a non-significant 0.98 (0.81–1.18). Examples from other systematic reviews that analysed dietary trials are provided in Studer et al. (2005) who analysed 18 dietary trials, some of which included drug use. There was an average serum total cholesterol reduction of 10% (range 1–24%). Risk ratios for cardiac mortality and overall mortality were 0.91 (0.82–1.02) and 0.97 (0.91–1.04), respectively. This systematic review also gives risk ratios for primary and secondary intervention trials using first generation hypolipidemic drugs (fibrates, resins, niacin), the statins and ω-3 fatty acids.

A Cochrane systematic review by Hooper et al. (2001) included 27 RCTs that investigated reduced or modified fat or cholesterol intake. Pooled rate ratios for total mortality were 0.98 (0.86–1.12) and for CV mortality 0.91 (0.77–1.07). The rate ratio for combined CV events was 0.84 (0.72–0.99), which was attenuated to 0.86 (0.72–1.03) after a sensitivity analysis. Trials with at least 2 years follow-up provided stronger evidence of protection from CV events. An early meta-analysis by Davey Smith et al. (1993) found that although there seemed to be some benefit associated with lowering serum cholesterol for high-risk groups, this was not true in intermediate and lower risk groups. However, it is only with the statin drugs that statistically significant reductions in CHD incidence are found (Cholesterol Treatment Trialists, 2005; Studer et al., 2005; Thavendiranathan et al., 2006).

8. The statins, serum cholesterol and CHD

The statin drugs are the most powerful class of hypolipidemic drugs currently available. Depending on the class of statin and an individual's variability in response they lower serum total cholesterol by 22–42%, LDL cholesterol by 27–55%, and triglycerides by 10–35% and increase HDL cholesterol by 4–8% (Maron et al., 2000). Statins competitively inhibit 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase, the enzyme that catalyses the conversion of HMG-CoA to mevalonate, the rate limiting step in cholesterol biosynthesis. Reduction in hepatic cholesterol levels results in an increased expression of LDL receptors to increase the uptake of serum LDL to maintain cholesterol homeostasis, which in turn lowers serum LDL cholesterol levels (Maron et al., 2000; Ray and Cannon, 2004).

Many CHD primary and secondary clinical prevention studies have been conducted with statins and it is enthusiastically claimed that they reduce the risk of major coronary events by about 30% (O'Keefe et al., 2004; Sacks et al., 1996; Scandinavian Simvastatin Survival Study Group, 1994; Shepherd et al., 1995). The large reductions in serum total and LDL cholesterol levels with attendant CHD risk benefits are claimed to have settled the so-called cholesterol controversy and justified the diet-heart hypothesis (Steinberg, 2006).

Recently, Cholesterol Treatment Trialist's Collaborators (2005) conducted a meta-analysis of data from 90,056 participants in 14 randomised trials of statins. The mean duration of follow-up among survivors was 4.7 years. At 1 year the weighed average difference in LDL cholesterol between controls and those on statins therapy was 1.09 mmol L^{-1}. The RR for a 1.0 mmol L^{-1} LDL cholesterol reduction on non-fatal MI, CHD death and total mortality was 0.74 (0.70–0.79), 0.81 (0.75–0.87) and 0.88 (0.84–0.91), respectively. During the trial period 6.2% of the control group suffered a non-fatal MI against 4.4% in the statin group. This translated to a 29% proportional reduction per mmol L^{-1} LDL cholesterol reduction. For CHD deaths and all cause mortality the corresponding figures are 4.4%, 3.4% and 23%, and 9.7%, 8.5% and 12.4%, respectively. However, the results show that the absolute risk reduction is small and in the order of 2% or less. It is generally accepted that the reduction in LDL cholesterol by the statins is the major, if not only, mechanism for their beneficial effect in preventing CHD. However, there are a number of lines of evidence to suggest that this may not be the case and statins may possess cholesterol-independent properties.

9. Clinical events that suggest a cholesterol-independent benefit for statins

In the first instance it is important to remember that statins also reduce serum triglyceride levels and increase levels of HDL cholesterol (Maron et al., 2000), to some extent reduce homocysteine levels (Jankowski and Kawecka-Jaszez, 2004), and depending on class may also increase LDL particle size (Rizzo and Berneis, 2006). There is also evidence that statins reduce BP (Glorioso et al., 1999), reduce the risk of developing diabetes (Freeman et al., 2001) and improve left ventricular function (Node et al., 2003). A systematic review of 13 studies showed that statins reduced the concentration of C-reactive protein (CRP) by 13–50% compared with placebo. The reduction was independent of their effect on serum lipid levels (Balk et al., 2003). CRP is a highly sensitive marker of systemic inflammation and is considered a stronger independent predictor of CHD than the LDL cholesterol level (Ridker et al., 2002). Post hoc analyses of some of the large statin trials provide insight into possible cholesterol-independent effects of statins. In the Scandinavian Simvastatin Survival Study (4S) the beneficial effect of simvastatin was found to be determined mainly by the magnitude of change in LDL cholesterol, but the relative reduction in risk of major coronary events was independent of baseline levels of total, LDL and HDL cholesterol (Pedersen et al., 1998). Sacks et al. (2000b) reported that the benefits of pravastatin were also independent of baseline LDL cholesterol, HDL cholesterol and triglyceride levels in three large trials and this has also been noted in trials with other statins (Liao, 2005).

In contrast to the 4S study the Cholesterol and Recurrent Events (CARE) trial found absolute or percentage reduction in LDL cholesterol had little relationship to coronary events (Sacks et al., 1998). Associations between on-study serum lipid levels and CHD events were weaker in the group assigned to pravastatin compared with placebo in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial (Simes et al., 2002). The West of Scotland Coronary Prevention Study Group (1998) also found that the fall in LDL cholesterol did not correlate with CHD risk reduction and patients on pravastatin had fewer coronary events than those on placebo who had similar LDL cholesterol levels. In addition, benefit from statin therapy is an early event and takes place before any effect on plaque regression could occur (Schwartz et al., 2001; Plenge et al., 2002), and improvement in endothelial function can occur within 24 hours and before serum cholesterol and CRP levels decrease (Laufs et al., 2001). Quantitative angiographic studies show that minor changes in plaque size cannot explain reductions in CV events (Archbold and Timmis, 1999).

Patients treated with either ezetimibe, a novel cholesterol absorption inhibitor, or simvastatin had their cholesterol levels lowered by around 15.5%, but only those taking simvastatin exhibited improved endothelium-dependent vasodilation (Landmesser et al., 2005). In animals, monkeys treated with pravastatin had improved endothelial function and lesion characteristics associated with greater plaque stability that were independent of serum lipoprotein concentrations (Williams et al., 1998). Simvastatin decreased aortic cholesterol accumulation and anti-inflammatory activity (Sparrow et al., 2001) and induced plaque stability in atherosclerotic lesions (Bea et al., 2002) in apo E deficient mice, which was independent of serum lipid levels. The above observations provide strong evidence for a cholesterol-independent action of statin drugs.

9.1. Cholesterol-independent mechanisms of statins

The statins as inhibitors of HMG-CoA reductase prevent the synthesis of mevalonate, the key step in a pathway that leads to the synthesis of squalene and eventually cholesterol. In this mevalonate pathway, mevalonate is converted into two activated isoprenes that condense to form geranyl pyrophosphate and farnesyl pyrophosphate. These non-steroid isoprenoids play an important role in signal transduction pathways by their attachment (prenylation) to regulatory proteins, such as the G proteins Ras, Rho

and Rab. Several of the cholesterol-independent effects of statins on CHD events, the so-called pleiotropic effects, have been traced to prenylation of these proteins (Ray and Cannon, 2004; Schonbeck and Libby, 2004).

The pleiotropic effects of statins are the subjects of many reviews (e.g., Bellosta et al., 2000; Davignon, 2004; Palinski and Tsimikas, 2002; Schonbeck and Libby, 2004; Takemoto and Liao, 2001). Beneficial effects include improvement in endothelial function, stabilization of the atherosclerotic plaque, antithrombic effects and anti-inflammatory properties. Macrophage-rich areas in human atherosclerotic lesions over-express HMG-CoA reductase, which may explain, in part, the beneficial effects of statins in CHD (Tuomisto et al., 2003).

Vascular endothelial dysfunction is a strong and independent predictor of CVD. Statins improve endothelial dysfunction by increasing endothelial-dependent vasodilation, most likely by increasing nitric oxide bioavailability and reducing oxidative stress. Statins also enhance the production and recruitment of endothelial progenitor cells for replacement of damaged cells in the arterial wall.

Damage to endothelial cells on the surface of the artery wall, an initiating event in atherosclerosis, results in an inflammatory response that leads initially to secretion of leukocyte and vascular cell adhesion molecules that allow recruitment of circulating leukocytes like monocytes to the endothelial cells where they migrate into the intima and differentiate into macrophages. The macrophages express scavenger receptors that take up oxidised LDL to become lipid-laden foam cells. These events, and subsequent development of the complex plaque, are driven by an array of inflammatory factors derived from inflammatory cells and from vascular cells that include cytokines, chemokines, growth factors, enzymes and proteins (Libby, 2006; Packard and Libby, 2008; Ross, 1999). There is substantial experimental and clinical evidence that statins inhibit a range of inflammatory mechanisms associated with atherosclerosis. They reduce adhesion molecules and chemokines, reduce the migration of cells and diminish the expression and function of proatherogenic cytokines like IL-1, 1L-6, IFN-γ and TNF-α (Ray and Cannon, 2004; Schonbeck and Libby, 2004).

The inflammatory cytokine IL-6 produced in the arterial plaque travels in the circulation to the liver where it elicits an acute phase response that results in the release of CRP (Packard and Libby, 2008). Multiple prospective epidemiological studies have shown that CRP is an independent predictor of CVD in men and women irrespective of age and in those with and without a prior history of CVD. CRP is a stronger predictor of CVD risk than LDL cholesterol and CRP levels are poorly correlated with LDL cholesterol with only about 3% of variance in CRP ascribed to LDL cholesterol (Ridker, 2003; Ridker et al., 2002). Follow-up data from the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study suggest that reduction in CRP levels conferred a similar protection for CHD events as reduction in LDL cholesterol levels (Ridker et al., 2005).

Some interesting animal studies also support LDL cholesterol-independent role for statins in atherosclerosis. Diomede et al. (2001) compared the action of common statins with squalestatin, a novel squalene synthase inhibitor that prevents the post-mevalonate synthesis of squalene the penultimate step in cholesterol synthesis. The common statins, but not squalestatin, inhibited leukocyte recruitment together with cytokine and chemokine production, which suggests that biosynthesis of non-sterol compounds arising from mevalonate is critical for the anti-inflammatory effects of statins. Statins inhibited leukocyte function antigen-1, which has an important role in the pathophysiology of inflammation, in a manner independent of HMG-CoA reductase inhibition (Weitz-Schmidt et al., 2001). Using an in vitro model Yoshida et al. (2001) showed that a statin reduced monocytes adhesion to vascular endothelium, one of the earliest events in atherosclerosis.

Critics of the pleiotropic effect hypothesis argue that the CV benefits of statins are mostly due to their ability to lower LDL cholesterol levels. Regression lines for a number of statin and non-statin cholesterol-lowering trials suggest that the risk of CHD events is closely correlated with on-trial levels of LDL cholesterol or percentage reduction in LDL cholesterol (O'Keefe et al., 2004; Davidson, 2005). On the other hand, Liao (2005) pointed out that this type of analysis does not take into account the time factor. He demonstrated that the regression line for percentage change in CHD risk fitted statin trials, a trial with the bile acid resin colestyramine and a trial that utilised partial ileal bypass. However, when the regression analysis was repeated using outcome at 4.5 years, the non-statin trials, which take many years to show a benefit, no longer fitted the regression line and showed less benefit than the statins.

The cumulative evidence suggests there are cholesterol-lowering independent effects for statins in the prevention of CVD, but the relative contribution of the two pathways is yet to be determined. Nevertheless the proposition that the large cholesterol-lowering effect of statins justifies the diet-heart hypothesis and finally puts to rest the cholesterol controversy (Steinberg, 2006) is not justified. After all, may not the lowering of serum cholesterol by statin drugs be a surrogate measure of their efficiency as inhibitors of HMG-CoA reductase and the metabolic consequences of this event?

10. Discussion

It is widely believed that SFAs are hypercholesterolemic and that elevated total and LDL cholesterol levels are a major risk factor for CHD. This review examines the evidence that shows the major cholesterol-raising SFAs, C12:0, C14:0 and C16:0 concomitantly elevate antiatherogenic HDL cholesterol levels and compared with a low-fat, low-SFA, high-carbohydrate diet have a beneficial effect on atherogenic Lp[a] and small dense LDL particles. Overall, the effect of SFAs on serum lipoproteins suggests that they may be atherogenically neutral.

The 33 data sets provided by prospective cohort studies (Tables 1 and 2) provide no convincing evidence for a consistent association between SFA intake and risk of CHD. These data also fail to provide strong support in favour of a protective role for PUFAs. Finally, the surprisingly few RCTs that examined isocaloric substitution of SFAs for vegetable-derived fats mostly fail to show a benefit for reduction in SFA intake.

Nutritional reductionism may be useful in determining risk factors for a disease, but SFAs are consumed as components of a food item along with MUFAs, PUFAs and other antiatherogenic agents like fibre and antioxidants. Milk and milk-derived products are large contributors of SFAs to the diet, and Elwood et al. (2004) found that the pooled estimate of risk from 10 cohort studies of ischemic heart disease in subjects with the highest intake of milk relative to subjects with a low milk intake was 0.87 (0.74–1.03).

There is accumulating evidence that milk and its products ameliorate a number of important non-lipoprotein CHD risk factors. Dietary calcium that is largely supplied by dairy products and dairy products independently lower BP (McCarron et al., 1984; Ruidavets et al., 2006). Milk electrolytes and small digestion-resistant peptides encrypted in milk proteins can affect BP beneficially (Jauhiainen and Korpela, 2007). Dietary calcium, especially from dairy products may have a positive effect on body weight and adiposity (Major et al., 2008). Milk proteins are insulinotropic

(Major et al., 2008). A meta-analysis of four prospective studies on dairy product consumption and incident type 2 diabetes produced an RR of 0.91 (0.86–0.96) for the highest intake of dairy products (Elwood et al., 2008). Hypertension, type 2 diabetes and obesity are important components of the metabolic syndrome, which has a 20–30% incidence in most countries, and those with the syndrome have a 2-fold increased risk of CVD than those without the syndrome (Grundy, 2008). A meta-analysis of four studies that investigated the association between dairy consumption and the metabolic syndrome by Elwood et al. (2008) found a statistically significant RR of 0.74 (0.64–0.84) for the highest intake compared with the lowest.

Controversy still exists regarding the mechanisms by which high LDL levels actually instigate atherosclerosis (Libby et al., 2000; Packard and Libby, 2008). Over the years several hypotheses have been proposed to explain the initiation of atherosclerosis. The response-to-retention model is currently favoured (Tabas et al., 2007; Williams and Tabas, 1995). This model realises that apo B lipoproteins continually penetrate the arterial wall by upregulated transcytosis and pass to the intimal subendothelial space. Some of these particles adhere to subendothelial matrix molecules, mainly a range of proteoglycans synthesized by endothelial cells and macrophages. Accessory molecules like lipoprotein lipase, phospholipase A2 and sphingomyelinase facilitate retention of apo B-containing lipoproteins. Sphingomyelinase, which is secreted by endothelial cells and macrophages for instance, can cleave sphingomyelin on the surface of lipoproteins leading to fusion and aggregation of lipoprotein particles. Aggregation leads to an increase in size that prohibits their exit from the artery wall compared with monomeric lipoproteins. Biological response to retained apo B containing lipoprotein is considered an initiating event in atherosclerosis. Prolonged retention of lipoprotein complexes can result in chemical modification especially oxidation (Tabas et al., 2007).

There is a low rate of uptake of native LDL by macrophages, which is not considered atherogenic. However, oxidised LDL components, apo B and lipid moieties like the phospholipids contain epitopes that are immunogenic and proinflammatory. Oxidised LDL does not bind to the LDL receptor, but binds avidly to scavenger receptors on macrophages leading to foam cell formation and secretion of an array of proinflammatory cytokines that drive the atherosclerotic process (Glass and Witztum, 2001; Witztum and Steinberg, 2001).

Cholesterol has been implicated in atherosclerosis for more than a century due to its accumulation in atherosclerotic plaques. Because this cholesterol originates from the major circulating lipoprotein LDL, total and LDL cholesterol are considered major risk factors for CHD. However, it is well cited that individuals with normal or low serum LDL cholesterol levels, as currently defined by national guidelines, can succumb to CHD, whereas some individuals with high LDL cholesterol can manage a normal life-span. In addition, major statin trials show substantial lowering of LDL cholesterol by statin drugs does not prevent most events in patients at risk of CHD.

Obviously, other important risk factors must be involved. It is interesting to note that LDL is a ligand for other atherogenic molecules such as homocysteine and CRP. Olszewski and McCully (1991) found that the homocysteine level was 4.1-times higher per gram of protein in LDL from hypercholesterolemic men than from normocholesterolemic men. CRP binds to oxidized LDL through its phospholipids, but not native LDL (Chang et al., 2002). Is LDL cholesterol a causative factor for CHD or is it a correlate or consequence of the disease? To what extent is elevated LDL cholesterol related to dysfunction in one or more of the myriad of processes involved in lipoprotein processing and metabolism? What are the dysfunctional processes within the arterial wall that lead to aggregation and retention of apo B containing lipoproteins and their subsequent oxidation that leads to cholesterol-enriched foam cell formation? Much is still to be learnt.

Even so, the evidence outlined in this review suggests the demonization of SFAs is unwarranted and the role of serum cholesterol in CHD is overstated. The reason for the latter is perhaps explained in terms of the historical development of risk factor profiles, resistance to change associated to new developments and commercial interests. Public health messages, although well meaning, have not always been correct. For instance, in the 1960s and 1970s dietary advice was to replace butter with margarine. However, most margarine during that era contained considerable quantities of trans fatty acids, now known to be more atherogenic than SFAs. Indeed, a report from the Framingham Study found that margarine but not butter intake was positively associated with the risk of CHD (Gillman et al., 1997). More recent advice to consume low-fat, high-carbohydrate diets to reduce serum LDL cholesterol levels can also result in reduced HDL levels and increased levels of triglycerides, small dense LDL and insulin, which have been shown to increase the risk of CHD (Krauss, 2001). A quantitative coronary angiography study by Mozaffarian et al. (2004) showed that at least in post-menopausal women with established CHD who consumed a low-fat diet, a greater intake of SFAs was associated with less progression of coronary atherosclerosis whereas carbohydrate intake was associated with greater progression.

In 1951, before the first report from the Framingham Study on risk factors for CHD, Barr et al. (1951) reported a protective effect for alpha lipoproteins, now known as HDL, on CHD. The ramifications of this observation were largely ignored until it was revisited by Miller and Miller (1975) and results of the multicentre Cooperative Lipoprotein Phenotyping Study showed that the inverse association between HDL cholesterol level and CHD prevalence was more uniform than the positive associations between total and LDL cholesterol and triglycerides levels and CHD (Castelli et al., 1977). In a history of the diet-heart issue, Tavia Gordon, a pioneer Framingham investigator, refers to the reluctance to accept the negative relationship between HDL cholesterol and risk of CHD. The reluctance no doubt resulted from the conceptual difficulty in accepting a fraction of the lipoproteins (LDL) could be detrimental while another fraction (HDL) could be protective. After spending 20 or more years researching total and LDL cholesterol as a risk factor for CHD, conservatism and human propensity for status no doubt also contributed (Gordon, 1988).

It is interesting to speculate what would have happened if the observation of Barr et al. (1951) that HDL cholesterol was cardioprotective was pursued with the same vigour as the negative impact of LDL. Perhaps today public health messages would exhort us to increase the content of SFAs in our diet to elevate HDL levels to help prevent heart disease!

References

Abbasi, F., McLaughlin, T., Lamendola, C., Kim, H.S., Tanaka, A., Wang, T., Nakajima, K., Reaven, G.M., 2000. High carbohydrate diets, triglycerides-rich lipoproteins, and coronary heart disease risk. American Journal of Cardiology 85, 45–48.

Ahrens, E.H., Blankenhorn, D.H., Tsaltas, T.T., 1954. Effect on human serum lipids of substituting plant for animal fat in diet. Proceedings of the Society for Experimental and Biological Medicine 86, 872–878.

Ahrens, E.H., Hirst, J., Insull, W., Tsaltas, T.T., Blomstrand, R., Peterson, M.L., 1957. The influence of dietary fats on serum-lipid levels in man. Lancet 272 (6976), 943–953.

Almendingen, K., Jordal, O., Kierulf, P., Sandstad, B., Pedersen, J.I., 1995. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and Lp[a] in men. Journal of Lipid Research 36, 1370–1384.

Anderson, K.M., Castelli, W.P., Levy, D., 1987. Cholesterol and mortality. 30 years of follow-up from the Framingham Study. Journal of the American Medical Association 257, 2176–2180.

Archbold, R.A., Timmis, A.D., 1999. Modification of coronary artery disease progression by cholesterol-lowering therapy: the angiographic studies. Current Opinion in Lipidology 10, 527–534.

Aro, A., Jauhiainen, M., Partanen, R., Salminen, I., Mutanen, M., 1997. Stearic acid, trans fatty acids, and dietary fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects. The American Journal of Clinical Nutrition 65, 1419–1426.

Ascherio, A., 1999. Trans fatty acids and coronary heart disease. The New England Journal of Medicine 340, 1994–1998.

Ascherio, A., Rimm, E.B., Giovannucci, E.L., Spiegelman, D., Stampfer, M., Willett, W.C., 1996. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. British Medical Journal 313, 84–90.

Balk, E.M., Lau, J., Goudas, L.C., Jordan, H.S., Kupelnick, B., Kim, L.U., Karas, R.H., 2003. Effect of statins on nonlipid serum markers associated with cardiovascular disease. Annals of Internal Medicine 139, 670–682.

Barr, D.P., Russ, E.M., Elder, H.A., 1951. Protein–lipid relationship in human plasma. II. In atherosclerosis and related conditions. American Journal of Medicine 11, 480–493.

Bassett, D.R., Abel, M., Moellering, R.C., Rosenblatt, G., Stokes, J., 1969. Coronary heart disease in Hawaii: dietary intake, depot fat, "stress", smoking, and energy balance in Hawaiian and Japanese men. The American Journal of Clinical Nutrition 22, 1483–1503.

Bea, F., Blessing, E., Bennett, B., Levitz, M., Wallace, E.P., Rosenfeld, M.E., 2002. Simvastatin promotes atherosclerotic plaque stability in apoE-deficient mice independently of lipid lowering. Arteriosclerosis, Thrombosis, and Vascular Biology 22, 1832–1837.

Bellosta, S., Ferri, N., Bernini, F., Paoletti, R., Corsini, A., 2000. Non-lipid-related effects of statins. Annals of Medicine 32, 164–176.

Berglund, L., Oliver, E.H., Fontanez, N., Holleran, S., Matthews, K., Roheim, P.S., Ginsberg, H.N., Ramakrishnan, R., Lefevre, M., 1999. HDL-subpopulation patterns in response to reductions in dietary total and saturated fat intakes in healthy subjects. The American Journal of Clinical Nutrition 70, 992–1000.

Bloom, B., Chaikoff, I.L., Reinhardt, W.O., 1951. Intestinal lymph as pathway for transport of absorbed fatty acids of different chain lengths. American Journal of Physiology 166, 451–455.

Bolton-Smith, C., Woodward, M., Tunstall-Pedoe, H., 1992. The Scottish Heart Health Study. Dietary intake by food frequency questionnaire and odds ratios for coronary heart disease risk. I. The macronutrients. European Journal of Clinical Nutrition 46, 75–84.

Boniface, D.R., Tefft, M.E., 2002. Dietary fats and 16-year coronary heart disease mortality in a cohort of men and women in Great Britain. European Journal of Clinical Nutrition 56, 786–792.

Braunwald, E., 1997. Shattuck lecture – cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. The New England Journal of Medicine 337, 1360–1369.

Burr, M.L., Fehiy, A.M., Gilbert, J.F., Rogers, S., Holliday, R.M., Sweetnam, P.M., Elwood, P.C., Deadman, N.M., 1989. Effect of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). Lancet 2 (8666), 757–761.

Campos, H., Blijlevens, E., McNamara, J.R., Ordovas, J.M., Posner, B.M., Wilson, P.W.F., Castelli, W.P., Schaefer, E.J., 1992. LDL particle size distribution. Results from the Framingham Offspring Study. Arteriosclerosis and Thrombosis 12, 1410–1419.

Carlson, L.A., Bottiger, L.E., 1985. Risk factors for ischaemic heart disease in men and women. Acta Medica Scandinavica 218, 207–211.

Castelli, W.P., Doyle, J.T., Gordon, T., Hames, C.G., Hjortland, M.C., Hulley, S.B., Kagan, A., Zukel, W.J., 1977. HDL cholesterol and other lipids in coronary heart disease. The Cooperative Lipoprotein Phenotyping Study. Circulation 55, 767–772.

Chang, M.-K., Binder, C.J., Torzewski, M., Witztum, J.L., 2002. C-reactive protein binds to both oxidised LDL and apoptotic cells through recognition of a common ligand: phosphorylcholine of oxidized phospholipids. Proceedings of the National Academy of Sciences of the United States of America 99, 13043–13048.

Cholesterol Treatment Trialists' (CTT) Collaborators, 2005. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 366, 1267–1278.

Clevidence, B.A., Judd, J.T., Schaefer, E.J., Jenner, J.L., Lichtenstein, A.H., Muesing, R.A., Wittes, J., Sunkin, M.E., 1997. Plasma lipoprotein(a) levels in men and women consuming diets enriched in saturated, *cis*-, or *trans*-monounsaturated fatty acids. Arteriosclerosis, Thrombosis, and Vascular Biology 17, 1657–1661.

Clevidence, B.A., Judd, J.T., Schatzkin, A., Muesing, R.A., Campbell, W.S., Brown, C.C., Taylor, P.R., 1992. Plasma lipid and lipoprotein concentrations of men consuming a low-fat, high-fiber diet. The American Journal of Clinical Nutrition 55, 689–694.

Coronary Drug Project Research Group, 1980. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. The New England Journal of Medicine 303, 1038–1041.

Danesh, J., Collins, R., Peto, R., 2000. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. Circulation 102, 1082–1085.

Davey Smith, G., Shipley, M.J., Marmot, M.G., Rose, G., 1992. Plasma cholesterol concentration and mortality. Journal of the American Medical Association 267, 70–76.

Davey Smith, G., Song, F., Sheldon, T.A., 1993. Cholesterol lowering and mortality: the importance of considering initial level of risk. British Medical Journal 306, 1367–1373.

Davidson, M.H., 2005. Clinical significance of statin pleiotropic effects. Circulation 111, 2280–2281.

Davignon, J., 2004. Beneficial cardiovascular pleiotropic effects of statins. Circulation 109 (Suppl. III), III-39–III-43.

Dawber, T.R., Meadors, G.F., Moore, F.E., 1951. Epidemiological approaches to heart disease: The Framingham Study. American Journal of Public Health 41, 279–286.

Dayton, S., Pearce, M.L., Hashimoto, S., Dixon, W.J., Tomiyasu, U., 1969. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation 40 (Suppl. II), II-1–II-63.

De Lorgeril, M., Renaud, S., Mamelle, N., Salen, P., Martin, J.-L., Monjaud, I., Guidollet, J., Touboul, P., Delaye, J., 1994. Mediterranean alpha-linolenic acid rich diet in secondary prevention of coronary heart disease. Lancet 343, 1454–1459.

Denke, M.A., Grundy, S.M., 1992. Comparison of effects of lauric acid and palmitic acid on plasma lipids and lipoproteins. The American Journal of Clinical Nutrition 56, 895–898.

Derr, J., Kris-Etherton, P.M., Pearson, T.A., Seligson, F.H., 1993. The role of fatty acid saturation on plasma lipids, lipoproteins, and apolipoproteins: II. The plasma total and low-density lipoprotein cholesterol response of individual fatty acids. Metabolism 42, 130–134.

Diomede, L., Albani, D., Sottocorno, M., Donati, M.B., Bianchi, M., Fruscella, P., Salmona, M., 2001. In vivo anti-inflammatory effect of statins is mediated by nonsterol mevalonate products. Arteriosclerosis ,Thrombosis, and Vascular Biology 21, 1327–1332.

Dreon, D.M., Fernstrom, H.A., Campos, H., Blanche, P., Williams, P.T., Krauss, R.M., 1998. Change in dietary saturated fat intake is correlated with change in mass of large low-density-lipoprotein particles in men. The American Journal of Clinical Nutrition 67, 828–836.

Dreon, D.M., Fernstrom, H.A., Williams, P.T., Krauss, R.M., 1999. A very-low-fat diet is not associated with improved lipoprotein profiles in men with a predominance of large, low-density lipoproteins. The American Journal of Clinical Nutrition 69, 411–418.

Elwood, P.C., Givens, D.I., Beswick, A.D., Fehily, A.M., Pickering, J.E., Gallacher, J., 2008. The survival advantage of milk and dairy consumption: an overview of evidence from cohort studies of vascular diseases, diabetes and cancer. Journal of the American College of Nutrition 27, 723S–734S.

Elwood, P.C., Pickering, J.E., Hughes, J., Fehily, A.M., Ness, A.R., 2004. Milk drinking, ischaemic heart disease and ischaemic stroke II. Evidence from cohort studies. European Journal of Clinical Nutrition 58, 718–724.

Esrey, K.L., Joseph, L., Grover, S.A., 1996. Relationship between dietary intake and coronary heart disease mortality: Lipid Research Clinics Prevalence Follow-up Study. Journal of Clinical Epidemiology 49, 211–216.

Expert Panel, 1988. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. Archives of Internal Medicine 148, 36–69.

Farchi, G., Mariotti, S., Menotti, A., Seccareccia, F., Torsello, S., Fidanza, F., 1989. Diet and 20-y mortality in two rural population groups of middle-aged men in Italy. The American Journal of Clinical Nutrition 50, 1095–1103.

Fehily, A.M., Yarnell, J.W.G., Sweetnam, P.M., Elwood, P.C., 1993. Diet and incident ischemic heart disease: The Caerphilly Study. British Journal of Nutrition 69, 303–314.

Finegan, A., Hickey, N., Maurer, B., Mulcahy, R., 1968. Diet and coronary heart disease: dietary analysis on 100 male patients. The American Journal of Clinical Nutrition 21, 143–148.

Frantz, I.D., Dawson, E.A., Ashman, P.L., Gatewood, L.C., Bartsch, G.E., Kuba, K., Brewer, E.R., 1989. Test of effect of lipid lowering by diet on cardiovascular risk. Arteriosclerosis 9, 129–135.

Freeman, D.J., Norrie, J., Sattar, N., Neely, D.G., Cobbe, S.M., Ford, I., Isles, C., Lorimer, R., Macfarlane, P.W., McKillop, J.H., Packard, C.J., Shepherd, J., Gaw, A., 2001. Pravastatin and the development of diabetes mellitus. Circulation 103, 357–362.

Fumeron, F., Brigant, L., Parra, H.-J., Bard, J.-M., Fruchart, J.-C., Apfelbaum, M., 1991. Lowering of HDL_2-cholesterol and lipoprotein A-I particle levels by increasing the ratio of polyunsaturated to saturated fatty acids. The American Journal of Clinical Nutrition 53, 655–659.

Garcia-Palmieri, M.R., Sorlie, P., Tillotson, J., Costas, R., Cordero, E., Rodriguez, M., 1980. Relationship of dietary intake to subsequent coronary heart disease incidence: The Puerto Rico Heart Health Program. The American Journal of Clinical Nutrition 33, 1818–1827.

Genest, J., McNamara, J.R., Ordovas, J.M., Jenner, J.L., Silberman, S.R., Anderson, K.M., Wilson, P.W.F., Salem, D.N., Schaefer, E.J., 1992a. Lipoprotein cholesterol, apolipoprotein A-1 and B and lipoprotein(a) abnormalities in men with premature coronary heart disease. Journal of the American College of Cardiology 19, 792–802.

Genest, J.J., Martin-Munley, S.S., McNamara, J.R., Ordovas, J.M., Jenner, J.L., Meyers, R.H., Silberman, S.R., Wilson, P.W.F., Salem, D.N., Schaefer, E.J., 1992b. Familial lipoprotein disorders in patients with premature coronary artery disease. Circulation 85, 2025–2033.

Genest, J.J., McNamara, J.R., Salem, D.N., Schaefer, E.J., 1991. Prevalence of risk factors in men with premature coronary artery disease. American Journal of Cardiology 67, 1185–1189.

Gillman, M.W., Cupples, L.A., Gagnon, D., Millen, B.E., Ellison, R.C., Castelli, W.P., 1997. Margarine intake and subsequent coronary heart disease in men. Epidemiology 8, 144–149.

Ginsberg, H.N., Kris-Etherton, P., Dennis, B., Elmer, P.J., Ershow, A., Lefevre, M., Pearson, T., Roheim, P., Ramakrishnan, R., Reed, R., Stewart, K., Stewart, P., Phillips, K., Anderson, N., 1998. Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects. Arteriosclerosis, Thrombosis, and Vascular Biology 18, 441–449.

Glass, C.K., Witztum, J.L., 2001. Atherosclerosis: the road ahead. Cell 104, 503–516.

Glorioso, N., Troffa, C., Filigheddu, F., Dettori, F., Soro, A., Parpaglia, P.P., Collatina, S., Pahor, M., 1999. Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia. Hypertension 34, 1281–1286.

Goldbourt, U., Yaari, S., Medalie, J.H., 1993. Factors predictive of long-term coronary heart disease mortality among 10,059 male Israeli civil servants and municipal employees. Cardiology 82, 100–121.

Gordon, T., 1988. The diet-heart idea. American Journal of Epidemiology 127, 220–225.

Gordon, D.J., Rifkind, B.M., 1989. High-density lipoprotein – the clinical implications of recent studies. The New England Journal of Medicine 321, 1311–1316.

Gordon, T., Castelli, W.P., Hjortland, M.C., Kannel, W.B., Dawber, T.R., 1977. High density lipoprotein as a protective factor against coronary heart disease. American Journal of Medicine 62, 707–714.

Gordon, T., Kagan, A., Garcia-Palmieri, M., Kannel, W.B., Zukel, W.J., Tillotson, J., Sorlie, P., Hjortland, M., 1981. Diet and its relation to coronary heart disease and death in three populations. Circulation 63, 500–515.

Griffin, B.A., 1999. Lipoprotein atherogenicity: an overview of current mechanisms. The Proceedings of the Nutrition Society 58, 163–169.

Grundy, S.M., 2008. Metabolic syndrome pandemic. Atherosclerosis, Thrombosis, and Vascular Biology 28, 629–636.

Grundy, S.M., Vega, G.L., 1988. Plasma cholesterol responsiveness to saturated fatty acids. The American Journal of Clinical Nutrition 47, 822–824.

Gurr, M.I., Harwood, L.L., Frayn, K.N., 2002. Lipid Biochemistry, fifth ed. Blackwell Science, Oxford, UK.

Hegsted, D.M., Ausman, L.M., Johnson, J.A., Dallal, G.E., 1993. Dietary fat and serum lipids: an evaluation of the experimental data. The American Journal of Clinical Nutrition 57, 875–883.

Hegsted, D.M., McGrandy, R.B., Myers, M.L., Stare, F.J., 1965. Quantitative effects of dietary fat on serum cholesterol in man. The American Journal of Clinical Nutrition 17, 281–295.

Hjermann, I., Velve Byre, K., Holme, I., Leren, P., 1981. The effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. Lancet 2 (8259), 1303–1310.

Hooper, L., Summerbell, C.D., Higgins, J.P.T., Thompson, R.L., Capps, N.E., Davey Smith, G., Riemersma, R.A., Ebrahim, S., 2001. Dietary fat intake and prevention of cardiovascular disease: systematic review. British Medical Journal 322, 757–763.

Howard, B.V., Van Horn, L., Hsia, J., Manson, J.E., Stefanick, M.L., Wassertheil-Smoller, S., Kuller, L.H., LaCroix, A.Z., Langer, R.D., Lasser, N.L., Lewis, C.E., Limacher, M.C., Margolis, K.L., Mysiw, W.J., Ockene, J.K., Parker, L.M., Perri, M.G., Phillips, L., Prentice, R.L., Robbins, J., Rossouw, J.E., Sarto, G.E., Schatz, I.J., Snetselaar, L.G., Stevens, V.J., Tinker, L.F., Trevisan, M., Vitolins, M.Z., Anderson, G.L., Assaf, A.R., Bassford, T., Beresford, S.A.A., Black, H.R., Brunner, R.L., Brzyski, R.G., Caan, B., Chlebowski, R.T., Gass, M., Granek, I., Greenland, P., Hays, J., Heber, D., Heiss, G., Hendrix, S.L., Hubbell, A., Johnson, K.C., Kotchen, J.M., 2006. Low fat dietary pattern and risk of cardiovascular disease. Journal of the American Medical Association 295, 655–666.

Hu, F.B., Stampfer, M.J., Manson, J.E., Ascherio, A., Colditz, G.A., Speizer, F.E., Hennekens, C.H., Willett, W.C., 1999. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. The American Journal of Clinical Nutrition 70, 1001–1008.

Hu, F.B., Stampfer, M.J., Manson, J.E., Rimm, E., Colditz, G.A., Rosner, B.A., Hennekens, C.H., Willett, W.C., 1997. Dietary fat intake and the risk of coronary heart disease in women. The New England Journal of Medicine 337, 1491–1499.

Iestra, J.A., Kromhout, D., van der Schouw, Y.T., Grobbee, D.E., Boshuizen, H.C., van Staveren, W.A., 2005. Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary heart disease patients. Circulation 112, 924–934.

Jacobs, D.R., Anderson, J.T., Hannan, P., Keys, A., Blackburn, H., 1983. Variability in individual serum cholesterol response to change in diet. Arteriosclerosis 3, 349–356.

Jakobsen, M.U., Overvad, K., Dyerberg, J., Schroll, M., Heitmann, B.L., 2004. Dietary fat and risk of coronary heart disease: possible effect modification by gender and age. American Journal of Epidemiology 160, 141–149.

Jankowski, P., Kawecka-Jaszez, K., 2004. Lipid-lowering drugs and homocysteine a comparison between statins and other lipid lowering drugs. Atherosclerosis 172, 191–194.

Jauhiainen, T., Korpela, R., 2007. Milk peptides and blood pressure. Journal of Nutrition 137, 825S–829S.

Kabagambe, E.K., Baylin, A., Siles, X., Campos, H., 2003. Individual saturated fatty acids and nonfatal acute myocardial infarction in Costa Rica. European Journal of Clinical Nutrition 57, 1447–1457.

Kannel, W.B., Castelli, W.P., Gordon, T., 1979. Cholesterol in the prediction of atherosclerotic disease. Annals of Internal Medicine 90, 85–91.

Kannel, W.B., Dawber, T.R., Kagan, A., Revotskie, N., Stokes, J., 1961. Factors of risk in the development of coronary heart disease. Annals of Internal Medicine 55, 33–50.

Kaptchuk, T.J., 2002. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Annals of Internal Medicine 136, 817–825.

Katan, M.B., Berns, M.A.M., Glatz, J.F.C., Knuiman, J.T., Nobels, A., de Vries, J.H.M., 1988. Congruence of individual responsiveness to dietary cholesterol and to saturated fat in humans. Journal of Lipid Research 29, 883–892.

Katerndahl, D.A., Lawler, W.R., 1999. Variability in meta-analytic results concerning the value of cholesterol reduction in coronary heart disease: a meta-meta-analysis. American Journal of Epidemiology 149, 429–441.

Kawakami, A., Aikawa, M., Libby, P., Alcaide, P., Luscinakas, F.W., Sacks, F.M., 2006. Apolipoprotein CIII in apolipoprotein B lipoproteins enhances the adhesion of human monocytic cells to endothelial cells. Circulation 113, 691–700.

Kestin, M., Clifton, P.M., Rouse, I.L., Nestel, P.J., 1989. Effect of dietary cholesterol in normolipidemic subjects is not modified by nature and amount of dietary fat. The American Journal of Clinical Nutrition 50, 528–532.

Keys, A., Anderson, J.T., Grande, F., 1957. Prediction of serum-cholesterol response of man to changes in fats in the diet. Lancet 273 (7003), 959–966.

Keys, A., Anderson, J.T., Grande, F., 1965a. Serum cholesterol response to changes in the diet. IV. Particular saturated fatty acids in the diet. Metabolism 14, 776–787.

Keys, A., Anderson, J.T., Grande, F., 1965b. Serum cholesterol response to changes in the diet. III. Differences among individuals. Metabolism 14, 766–775.

Khalil, M.F., Wagner, W.D., Goldberg, I.J., 2004. Molecular interactions leading to lipoprotein retention and the initiation of atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology 24, 2211–2218.

Khaw, K.-T., Barrett-Connor, E., 1987. Dietary fiber and reduced ischemic heart disease mortality rates in men and women: a 12-year prospective study. American Journal of Epidemiology 126, 1093–1102.

Krauss, R.M., 2001. Dietary and genetic effects on low-density lipoprotein heterogeneity. Annual Review of Nutrition 21, 283–295.

Krauss, R.M., 2005. Dietary and genetic probes of atherogenic dyslipidemia. Arteriosclerosis, Thrombosis, and Vascular Biology 25, 2265–2272.

Kromhout, D., de L. Coulander, C., 1984. Diet, prevalence and 10-year mortality from coronary heart disease in 871 middle-aged men. American Journal of Epidemiology 119, 733–741.

Kushi, L.H., Lew, R.A., Stare, F.J., Ellison, C.R., el Lozy, M., Bourke, G., Daly, L., Graham, I., Hickey, N., Mulcahy, R., Kevaney, J., 1985. Diet and 20-year mortality from coronary heart disease. The New England Journal of Medicine 312, 811–818.

Landmesser, U., Bahlmann, F., Mueller, M., Spiekermann, S., Kirchhoff, N., Schulz, S., Manes, C., Fischer, D., de Groot, K., Flisher, D., Fauler, G., Marz, W., Drexler, H., 2005. Simvastatin versus ezetimibe. Pleiotropic and lipid-lowering effects on endothelial function in humans. Circulation 111, 2356–2363.

Laufs, U., Wassmann, S., Hilgers, S., Ribaudo, N., Bohm, M., Nickening, G., 2001. Rapid effects on vascular function after initiation and withdrawal of atorvastatin in healthy, normocholesterolemic men. American Journal of Cardiology 88, 1306–1307.

Lee, S.-J., Campos, H., Moye, L.A., Sacks, F.M., 2003. LDL containing apolipoprotein CIII is an independent risk factor for coronary events in diabetic patients. Arteriosclerosis, Thrombosis, and Vascular Biology 23, 853–858.

Leosdottir, M., Nilsson, P.M., Nilsson, J.-A., Mansson, H., Berglund, G., 2005. Dietary fat intake and early mortality patterns – data from the Malmo Diet and Cancer Study. Journal of Internal Medicine 258, 153–165.

Leren, P., 1966. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. Acta Medica Scandinavica, Supplement 466, 1–92.

Liao, J.K., 2005. Clinical implications for statin pleiotropy. Current Opinion in Lipidology 16, 624–629.

Libby, P., 2006. Inflammation and cardiovascular disease mechanisms. The American Journal of Clinical Nutrition 83, 456s–460s.

Libby, P., Aikawa, M., Schonbeck, U., 2000. Cholesterol and atherosclerosis. Biochimica et Biophysica Acta 1529, 299–309.

Liu, S., Buring, J.E., Sesso, H.D., Rimm, E.B., Willett, W.C., Manson, J.E., 2002. A prospective study of dietary fiber intake and risk of cardiovascular disease among women. Journal of the American College of Cardiology 39, 49–56.

Major, G.C., Chaput, J.-P., Ledoux, M., St-Pierre, S., Anderson, G.H., Zemel, M.B., Tremblay, A., 2008. Recent developments in calcium-related obesity research. Obesity Reviews 9, 428–445.

Maron, D.J., Fazio, S., Linton, M.F., 2000. Current perspectives on statins. Circulation 101, 207–213.

Masironi, R., 1970. Dietary factors and coronary heart disease. Bulletin of the World Health Organisation 42, 103–114.

McCarron, D.A., Morris, C.D., Henry, H.J., Stanton, J.L., 1984. Blood pressure and nutrient intake in the United States. Science 224, 1392–1398.

McGee, D.L., Reed, D.W., Yano, K., Kagan, A., Tillotson, J., 1984. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. American Journal of Epidemiology 119, 667–676.

Medalie, J.H., Kahn, H.A., Neufeld, H.N., Riss, E., Goldbourt, U., 1973. Five-year myocardial infarction incidence – II. Association of single variables to age and birthplace. Journal of Chronic Diseases 26, 329–349.

Mensink, R.P., Katan, M.B., 1992. Effect of dietary fatty acids on serum lipids and lipoproteins. Arteriosclerosis and Thrombosis 12, 911–919.

Mensink, R.P., Zock, P.L., Katan, M.B., Hornstra, G., 1992. Effect of dietary *cis* and *trans* fatty acids on serum lipoprotein[a] levels in humans. Journal of Lipid Research 33, 1493–1501.

Mensink, R.P., Zock, P.L., Kester, A.D.M., Katan, M.B., 2003. Effects of dietary fatty aids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. The American Journal of Clinical Nutrition 77, 1146–1155.

Miller, G.J., Miller, N.E., 1975. Plasma-high-density-lipoprotein concentration and development of ischaemic heart disease. Lancet 1 (7879), 16–19.

Miller, N.E., 1987. Associations of high-density lipoprotein subclasses and apolipoproteins with ischemic heart disease and coronary atherosclerosis. American Heart Journal 113, 589–597.
Moore, M.C., Guzman, M.A., Schilling, P.E., Strong, J.P., 1976. Dietary-atherosclerosis study on deceased persons. Journal of the American Dietetic Association 68, 216–223.
Morgan, J., Carey, C., Lincoff, A., Capuzzi, D., 2004. High-density lipoprotein subfractions and risk of coronary heart disease. Current Atherosclerosis Reports 6, 359–365.
Morris, J.N., Marr, J.W., Clayton, D.G., 1977. Diet and heart: a postscript. British Medical Journal 2 (6098), 1307–1314.
Mozaffarian, D., Rimm, E.B., Herrington, D.M., 2004. Dietary fats, carbohydrate, and progression of coronary atherosclerosis in postmenopausal women. The American Journal of Clinical Nutrition 80, 1175–1184.
Multiple Risk Factor Intervention Trial Research Group, 1982. Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. Journal of the American Medical Association 248, 1465–1477.
Neaton, J.D., Wentworth, D., 1992. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Archives of Internal Medicine 152, 56–64.
Node, K., Fujita, M., Kitakaze, M., Hori, M., Liao, J.K., 2003. Short-term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. Circulation 108, 839–843.
Oh, K., Hu, F.B., Manson, J.E., Stampfer, M.J., Willett, W.C., 2005. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. American Journal of Epidemiology 161, 672–679.
O'Keefe, J.H., Cordain, L., Harris, W.H., Moe, R.M., Vogel, R., 2004. Optimal low-density lipoprotein is 50 to 70 mg/dl. Journal of the American College of Cardiology 43, 2142–2146.
Olszewski, A.J., McCully, K.S., 1991. Homocysteine content of lipoproteins in hypercholesterolemia. Atherosclerosis 88, 61–68.
Packard, R.R.S., Libby, P., 2008. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clinical Chemistry 54, 24–38.
Palinski, W., Tsimikas, S., 2002. Immunomodulatory effects of statins: mechanisms and potential impact on arteriosclerosis. Journal of the American Society of Nephrology 13, 1673–1681.
Paul, O., Lepper, M.H., Phelan, W.H., Dupertuis, G.W., MacMillan, A., McKean, H., Park, H., 1963. A longitudinal study of coronary heart disease. Circulation 28, 20–31.
Pedersen, T.R., Olsson, A.G., Faergeman, O., Kjekshus, J., Wedel, H., Berg, K., Wilhelmsen, L., Hagh,felt, T., Thorgeirsson, G., Pyorala, K., Miettinen, T., Christophersen, B., Tobert, J.A., Musliner, T.A., Cook, M.S., 1998. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 97, 1453–1460.
Pekkanen, J., Linn, S., Heiss, G., Suchindran, C.M., Leon, A., Rifkind, B.M., Tyroler, H.A., 1990. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. The New England Journal of Medicine 322, 1700–1707.
Pietinen, P., Ascherio, A., Korhonen, P., Hartman, A.M., Willett, W.C., Albanes, D., Virtamo, J., 1997. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. American Journal of Epidemiology 145, 876–887.
Pischon, T., Girman, C.J., Sacks, F.M., Rifai, N., Stampfer, M.J., Rimm, E.B., 2005. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 112, 3375–3383.
Plenge, J.K., Hernandez, T.L., Weil, K.M., Poirier, P., Grunwald, G.K., Marcovina, S.M., Eckel, R.H., 2002. Simvastatin lowers C-reactive protein within 14 days. Circulation 106, 1447–1452.
Posner, B.M., Cobb, J.L., Belanger, A.J., Cupples, A., D'Agostino, R.B., Stokes, J., 1991. Dietary lipid predictors of coronary heart disease in men. Archives of Internal Medicine 151, 1181–1187.
Ray, K.K., Cannon, C.P., 2004. Intensive statin therapy in acute coronary syndromes: clinical benefits and vascular biology. Current Opinions in Lipidology 15, 637–643.
Reed, D.M., MacLean, C.J., Hayashi, T., 1987. Predictors of atherosclerosis in the Honolulu Heart Program. American Journal of Epidemiology 126, 214–225.
Research Committee to the Medical Research Council, 1965. Low-fat diet in myocardial infarction. Lancet 2 (7411), 501–504.
Research Committee to the Medical Research Council, 1968. Controlled trial of soya-bean oil in myocardial infarction. Lancet 2 (7570), 693–700.
Ridker, P.M., 2003. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 107, 363–369.
Ridker, P.M., Cannon, C.P., Morrow, D., Rifai, N., Rose, L.M., McCabe, C.H., Pfeffer, M.A., Braunwald, E., 2005. C-reactive protein levels and outcomes after statin therapy. The New England Journal of Medicine 352, 20–28.
Ridker, P.M., Rifai, N., Rose, L., Buring, J.E., Cook, N.R., 2002. Comparison of C-reactive protein and low-density lipoprotein cholesterol in the prediction of first cardiovascular events. The New England Journal of Medicine 347, 1557–1565.
Rimm, E.B., 1996. Invited commentary – alcohol consumption and coronary heart disease: good habits may be more important than just good wine. American Journal of Epidemiology 143, 1094–1098.
Rizzo, M., Berneis, K., 2006. Low-density lipoprotein size and cardiovascular risk assessment. Quarterly Journal of Medicine 99, 1–14.
Rose, G.A., Thomson, W.B., Williams, R.T., 1965. Corn oil in treatment of ischaemic heart disease. British Medical Journal 1 (5449), 1531–1533.
Ross, R., 1999. Atherosclerosis – an inflammatory disease. The New England Journal of Medicine 340, 115–126.
Rubins, H.B., Robins, S.J., Collins, D., Iranmanesh, A., Wilt, T.J., Mann, D., Mayo-Smith, M., Faas, F.H., Elam, M.B., Rutan, G.H., Anderson, J.W., Kashyap, M.L., Schectman, G., 1995. Distribution of lipids in 8,500 men with coronary artery disease. American Journal of Cardiology 75, 1196–1201.
Ruidavets, J.-B., Bongard, V., Simon, C., Dallongeville, J., Ducimetiere, P., Arveiler, P., Amouyel, P., Bingham, A., Ferrieres, J., 2006. Independent contribution of dairy products and calcium intake to blood pressure variations at a population level. Journal of Hypertension 24, 671–681.
Sacks, F.M., 2006. The apolipoprotein story. Atherosclerosis Supplements 7, 23–27.
Sacks, F.M., Katan, M., 2002. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. American Journal of Medicine 113 (9B), 13S–24S.
Sacks, F.M., Moye, L.A., Davis, B.R., Cole, T.G., Rouleau, J.L., Nash, D.T., Pfeffer, M.A., Braunwald, E., 1998. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events Trial. Circulation 97, 1446–1452.
Sacks, F.M., Pasternak, R.C., Gibson, C.M., Rosner, B., Stone, P.H., 1994. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. Lancet 344, 1182–1186.
Sacks, F.M., Pfeffer, M.A., Moye, L.A., Rouleau, J.L., Rutherford, J.D., Cole, T.G., Brown, l., Warnica, J.W., Arnold, J.M.O., Wun, C.-C., Davis, B.R., Braunwald, E., 1996. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. The New England Journal of Medicine 335, 1001–1009.
Sacks, F.M., Alaupovic, P., Moye, L.A., Cole, T.G., Sussex, B., Stampfer, M.J., Pfeffer, M.A., Braunwald, E., 2000a. VLDL, apolipoproteins B, CIII, and E, and risk of recurrent coronary events in the Cholesterol and Recurrent Events (CARE) trial. Circulation 102, 1886–1892.
Sacks, F.M., Tonkin, A.M., Shepherd, J., Braunwald, E., Cobbe, S., Hawkins, M., Keech, A., Packard, C., Simes, J., Byington, R., Furberg, C.D., 2000b. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors. Circulation 102, 1893–1900.
Sarwar, N., Danesh, J., Eiriksdottir, G., Sigurdsson, G., Wareham, N., Bingham, S., Boekholdt, S.M., Khaw, K.-T., Gudnason, V., 2007. Triglycerides and the risk of coronary heart disease. Circulation 115, 450–458.
Scandinavian Simvastatin Survival Study Group, 1994. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 344, 1383–1389.
Schaefer, E.J., 2002. Lipoproteins, nutrition, and heart disease. The American Journal of Clinical Nutrition 75, 191–212.
Schaefer, E.J., Lichtenstein, A.H., Lamon-Fava, S., Contois, J.H., Li, Z., Rasmussen, H., McNamara, J.R., Ordovas, J.M., 1995. Efficacy of a National Cholesterol Education Program Step 2 diet in normolipidemic and hypercholesterolemic middle-aged and elderly men and women. Arteriosclerosis, Thrombosis, and Vascular Biology 15, 1079–1085.
Schonbeck, U., Libby, P., 2004. Inflammation, immunity, and HMG-CoA reductase inhibitors. Circulation 109 (Suppl. II), II-18–II-26.
Schonfeld, G., Patsch, W., Rudel, L.L., Nelson, C., Epstein, M., Olson, R.E., 1982. Effects of dietary cholesterol and fatty acids on plasma lipoproteins. Journal of Clinical Investigation 69, 1072–1080.
Schwartz, G.G., Olsson, A.G., Ezekowitz, M.D., Ganz, P., Oliver, M., Waters, D., Zeiher, A., Chaitman, B.R., Leslie, S., Stern, T., 2001. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. Journal of the American Medical Association 285, 1711–1718.
Shekelle, R.B., Shryock, A.M., Paul, O., Lepper, M., Stamler, J., liu, S., Raynor, W.J., 1981. Diet, serum cholesterol, and death from coronary heart disease. The New England Journal of Medicine 304, 65–70.
Shepherd, J., Cobbe, S.M., Ford, I., Isles, G., Lorimer, A.R., Macfarlane, P.W., McKillop, J.H., Packard, C.J., 1995. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. The New England Journal of Medicine 333, 1301–1307.
Shin, M.-J., Blanche, P.J., Rawlings, R.S., Fernstrom, H.S., Krause, R.M., 2007. Increased plasma concentrations of lipoprotein(a) during a low-fat, high-carbohydrate diet are associated with increased plasma concentrations of apolipoprotein C-III bound to apolipoprotein B-containing lipoproteins. The American Journal of Clinical Nutrition 85, 1527–1532.
Silaste, M.-L., Rantala, M., Alfthan, G., Aro, A., Witztum, J.L., Kesaniemi, Y.A., Horkko, A.K., 2004. Changes in dietary fat intake alter plasma levels of oxidized low-density lipoprotein and lipoprotein(a). Arteriosclerosis, Thrombosis, and Vascular Biology 24, 498–503.
Silverman, D.I., Ginsburg, G.S., Pasternak, R.C., 1993. High-density lipoprotein subfractions. American Journal of Medicine 94, 636–645.
Simes, J.R., Marschner, I.C., Hunt, D., Colquhoun, D., Sullivan, D., Stewart, R.A.H., Hague, W., Keech, A., Thompson, P., White, H., Shaw, J., Tonkin, A., 2002. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial. Circulation 105, 1162–1169.
Singh, R.B., Dubnov, G., Niaz, M.A., Ghosh, S., Singh, R., Rastogi, S.S., Manor, O., Pella, D., Berry, E.M., 2002. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet 360, 1455–1461.
Singh, R.B., Rastogi, S.S., Verma, R., Laxmi, B., Singh, R., Ghosh, S., Niaz, M.A., 1992. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up. British Medical Journal 304, 1015–1019.
Sjogren, P., Rosell, M., Skoglund-Andersson, C., Zdravkovic, S., Vessby, B., de Faire, U., Hamsten, A., Hellenius, M.-L., Fisher, R.M., 2004. Milk-derived fatty acids are

associated with a more favourable LDL particle size distribution in healthy men. Journal of Nutrition 134, 1729–1735.
Sniderman, A.D., Silberberg, J., 1990. Is it time to measure apolipoprotein B? Arteriosclerosis 10, 665–667.
Sparrow, C.P., Burton, C.A., Hernandez, M., Mundt, S., Hassing, H., Patel, S., Rosa, R., Hermanowski-Vosatka, A., Wang, P.-R., Zhang, D., Peterson, L., Detmers, P.A., Chao, Y.-S., Wright, S.D., 2001. Simvastatin has anti-inflammatory and anti-atherosclerotic activities independent of plasma cholesterol lowering. Arteriosclerosis, Thrombosis, and Vascular Biology 21, 115–121.
Stamler, J., 1978. Lifestyles, major risk factors, proof and public policy. Circulation 58, 3–19.
Stamler, J., Wentworth, D., Neaton, J.D., 1986. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Journal of the American Medical Association 256, 2823–2828.
Stampfer, M.J., Hu, F.B., Manson, J.E., Rimm, E.B., Willett, W.E., 2000. Primary prevention of coronary heart disease in women through diet and lifestyle. The New England Journal of Medicine 343, 16–22.
Stampfer, M.J., Krauss, R.M., Ma, J., Blanche, P.J., Holl, L.G., Sacks, F.M., Hennekens, C.H., 1996. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. Journal of the American Medical Association 276, 882–888.
Stampfer, M.J., Sacks, F.M., Salvini, S., Willett, W.C., Hennekens, C.H., 1991. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. The New England Journal of Medicine 325, 373–381.
Steinberg, D., 2006. An interpretive history of the cholesterol controversy, part V: the discovery of statins and the end of the controversy. Journal of Lipid Research 47, 1339–1351.
Studer, M., Briel, M., Leimenstoll, B., Glass, T.R., Bucher, H.C., 2005. Effect of different antilipidemic agents and diets on mortality. Archives of Internal Medicine 165, 725–730.
Suh, I., Oh, K.W., Lee, K.H., Psaty, B.M., Nam, C.M., Kim, S.I., Kang, H.G., Cho, S.Y., Shim, W.H., 2001. Moderate dietary fat consumption as a risk factor for ischemic heart disease in a population with a low fat intake: a case–control study in Korean men. The American Journal of Clinical Nutrition 73, 722–727.
Tabas, I., Williams, K.I., Boren, J., 2007. Subendothelial lipoprotein retention as the initiating process in atherosclerosis. Circulation 116, 1832–1844.
Takemoto, M., Liao, J.K., 2001. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Arteriosclerosis, Thrombosis, and Vascular Biology 21, 1712–1719.
Temme, E.H.M., Mensink, R.P., Hornstra, G., 1996. Comparison of the effects of diets enriched in lauric, palmitic, or oleic acids on serum lipids and lipoproteins in healthy women and men. The American Journal of Clinical Nutrition 63, 897–903.
Thavendiranathan, P., Bagai, A., Brookhart, M.A., Choudhry, N.K., 2006. Primary prevention of cardiovascular disease with statin therapy. Archives of Internal Medicine 166, 2307–2311.
Tholstrup, T., Marckmann, P., Jespersen, J., Vessby, B., Jart, A., Sandstrom, B., 1994. Effect on blood lipids, coagulation, and fibrinolysis of a fat high in myristic acid and a fat high in palmitic acid. The American Journal of Clinical Nutrition 60, 919–925.
Tholstrup, T., Marckmann, P., Vessby, B., Sandstrom, B., 1995. Effect of fats high in individual saturated fatty acids on plasma lipoprotein[a] levels in young healthy men. Journal of Lipid Research 36, 1447–1452.
Thompson, A., Danesh, J., 2006. Associations between apolipoprotein B, apolipoprotein A1, the apolipoprotein B/A1 ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. Journal of Internal Medicine 259, 481–492.
Tucker, K.L., Hallfrisch, J., Qiao, N., Muller, D., Andres, R., Fleg, J.L., 2005. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: The Baltimore Longitudinal Study of Aging. Journal of Nutrition 135, 556–561.
Tuomisto, T.T., Korkeela, A., Rutanen, J., Viita, H., Brasen, J.H., Riekkinen, M.S., Rissanen, T.T., Karkola, K., Kiraly, Z., Kolble, K., Yla-Herttuala, S., 2003. Gene expression in macrophage-rich inflammatory cell infiltrates in human atherosclerotic lesions as studied by laser microdissection and DNA array. Arteriosclerosis, Thrombosis, and Vascular Biology 23, 2235–2240.
Turpeinen, O., Karvonen, M.J., Pekkarinen, M., Miettinen, M., Elosuo, R., Paavilainen, E., 1979. Dietary prevention of coronary heart disease: The Finnish Mental Hospital Study. International Journal of Epidemiology 8, 99–118.
Tzonou, A., Kalandidi, A., Trichopoulou, A., Hsieh, C.-C., Toupadaki, N., Willett, W., Trichopoulos, D., 1993. Diet and coronary heart disease: a case–control study in Athens, Greece. Epidemiology 4, 511–516.
Verschuren, W.M.M., Jacobs, D.R., Bloemberg, B.P.M., Kromhout, D., Menotti, A., Aravanis, C., Blackburn, H., Buzina, R., Dontas, A.S., Fidanza, F., Karvonen, M.J., Nedeljkovic, S., Nissinen, A., Toshima, H., 1995. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Journal of the American Medical Association 274, 131–136.
Walldius, G., Jungner, I., Holme, I., Aastveit, A.H., Kolar, W., Steiner, E., 2001. High apolipoprotein B, low apolipoprotein A-1, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 358, 2026–2033.
Weitz-Schmidt, G., Welzenbach, K., Brinkmann, V., Kamata, T., Kallen, J., Bruns, C., Cottens, S., Takada, Y., Hommel, U., 2001. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nature Medicine 7, 687–692.
West of Scotland Coronary Prevention Study Group, 1998. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 97, 1440–1445.
Wilhelmsen, L., Berglund, G., Elmfeldt, D., Tibblin, G., Wedel, H., Pennert, K., Vedin, A., Wilhelmsson, C., Werko, L., 1986. The multifactor primary prevention trial in Goteborg, Sweden. European Heart Journal 7, 279–288.
Williams, K.J., Tabas, I., 1995. Retention hypothesis of early atherogenesis. Arteriosclerosis, Thrombosis, and Vascular Biology 15, 551–561.
Williams, J.K., Sukhova, G.K., Herrington, D.M., Libby, P., 1998. Pravastatin has cholesterol-lowering independent effects on the artery wall of atherosclerotic monkeys. Journal of the American College of Cardiology 31, 684–691.
Williams, P.T., Dreon, D.M., Krauss, R.M., 1995. Effects of dietary fat on high-density-lipoprotein subclasses are influenced by both apolipoprotein E isoforms and low-density-lipoprotein subclass patterns. The American Journal of Clinical Nutrition 61, 1234–1240.
Witztum, J.L., Steinberg, D., 2001. The oxidative modification hypothesis of atherosclerosis: does it hold for humans? Trends in Cardiovascular Medicine 11, 93–102.
Wood, P.D.F., 1981. A possible selection effect in medical science. The Statistician 30, 131–135.
Woodhill, J.M., Palmer, A.J., Leelarthaepin, B., McGilchrist, C., Blacket, R.B., 1978. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. Advances in Experimental Medicine and Biology 109, 317–330.
Yano, K., Rhoades, G.G., Kagan, A., Tillotson, J., 1978. Dietary intake and the risk of coronary heart disease in Japanese men living in Hawaii. The American Journal of Clinical Nutrition 31, 1270–1279.
Yerushalmy, J., Hilleboe, H.E., 1957. Fat in the diet and mortality from heart disease. New York State Journal of Medicine 57, 2343–2354.
Yoshida, M., Sawada, T., Ishii, H., Gerszten, R.E., Rosenzweig, A., Gimbrone, M.A., Yasukochi, Y., Numano, F., 2001. HMG-CoA reductase inhibitor modulates monocytes–endothelial cell interaction under physiological flow conditions in vitro. Arteriosclerosis, Thrombosis, and Vascular Biology 21, 1165–1171.
Yudkin, J., 1957. Diet and coronary thrombosis. Lancet 273, 155–162.
Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., Lisheng, L., 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. Lancet 364, 937–952.
Zock, P., de Vries, J.H.M., Katan, M.B., 1994. Impact of myristic acid versus palmitic acid on serum lipid and lipoprotein levels in healthy women and men. Arteriosclerosis and Thrombosis 14, 567–575.
Zukel, W.J., Lewis, R.H., Enterline, P.E., Painter, R.C., Ralston, L.S., Fawcett, R.M., Meredith, A.P., Peterson, B., 1959. A short-term community study of the epidemiology of coronary heart disease: a preliminary report on the North Dakota Study. American Journal of Public Health 49, 1630–1639.