Proceedings of the Nutrition Society, Page 1 of 7 doi:10.1017/S0029665119000685

The Nutrition Society Winter Meeting was held at the Royal Society of Medicine, London on 4–5 December 2018

Conference on 'Optimal diet and lifestyle strategies for the management of cardio-metabolic risk'
Symposium 4: Lifestyle factors

Are current dietary guidelines relevant to subjects on cholesterol-lowering drugs?

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The present paper reviews the evidence as to whether patients on lipid-lowering drugs should restrict dietary SFA intake. Premature mortality from atherosclerotic CVD has fallen dramatically in many high-income countries. This appears to be due to a combination of improved treatment following a cardiovascular event and reduced risk factors, including LDL-cholesterol. Whether this reduction is due to changes in dietary habits, or the increasing availability of highly potent cholesterol-reducing drugs remains to be firmly established. While reducing dietary SFA intake has been the cornerstone of public health nutrition policy for several decades, the efficacy of such dietary changes has been challenged in recent years. While there remains a lack of consensus in the literature, there is an emerging view that dietary advice should be specifically modified to emphasise replacing SFA with PUFA in the diet rather than carbohydrate. The advice to moderate dietary SFA intake given to the general population is usually also given to those individuals at high risk of CVD who are prescribed lipid-lowering drugs. There is limited evidence to suggest that any potential benefit of such a diet on LDL-cholesterol may be offset by a concurrent decrease in HDL-cholesterol. However, as diets rich in SFA are frequently energy-dense, and rich in red and processed meat (potential risk factors for CVD in themselves), it would seem prudent to continue to advise patients on lipid-lowering drugs to maintain a low-fat diet.

Cholesterol: Drugs: Dietary fat: CVD

Atherosclerotic CVD, including stroke and CHD, are major causes of morbidity and mortality across the world. In 2015, it was estimated that there were 422·7 million cases of CVD which resulted in 17·92 million deaths[1]. Between 1990 and 2015, there was a dramatic decline in CVD in countries with very high socioeconomic indices, but much lower reductions (or no change/increases) in poorer countries[1] In the UK, between 2002 and 2010, age-adjusted mortality from acute myocardial infarction fell by approximately half[2]. In men, 57 % of this reduction was due to a drop in the number of events, while the other 43 % were due to improved case-mortality rates, with equivalent figures for women of 52 and 48 %, respectively. Over a similar period (1999–2008), the incidence of stroke fell by approximately 30 %, and mortality in the first 56 d following a stroke fell from 21 to 12 %[3]. One of the major reasons for decline in mortality is improvement in post-event care and treatment. A major development in the treatment of patients, post-myocardial infarction, has been the use of percutaneous coronary interventions (stents) to open and maintain the blood flow in the affected artery. In the UK, between 1991 and 2013, there was an almost 10-fold increase in such treatment, rising from 9933 to 92 589 procedures[4].

The other major reason for the decline in CVD in more affluent countries is changes in risk factors leading

Abbreviations: PCSK-9, proprotein convertase subtilisin–kexin type 9; TFA, *trans* fatty acids.

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to a decrease in incidence. Tobacco smoking, hypertension and plasma cholesterol (raised LDL and/or decreased HDL) represent the three major modifiable risk factors for CVD. The most dramatic decline in these risk factors has been in smoking. Between 1974 and 2017, in the UK, the number of adults over the age of 16 years who smoked, dropped from 45·6 % (males 51·4 %, females 40·7 %) to 16·8 % (males 18·7 %, females 15·0 %)[5] with the biggest fall in adults over the age of 50 years. While similar trends have been seen in most high-income countries, it is not true for all regions, with smoking in African and the Eastern Mediterranean region rising rapidly[6]. In the UK, improvements have also been seen in the proportion of adults with hypertension. The Health Survey for England reports a modest fall in the number of adults with hypertension from 31 % of the population in 2002 to 27 % in 2017[7]. However, much more significant is the decline in the proportion with uncontrolled or untreated hypertension, from 25 to 16 %, over the same period. However, it is important to note that uncontrolled/untreated hypertension continues to rise in many developing parts of the world and represents a major public health problem[8]. Similar regional differences have been seen in changes in plasma cholesterol. Globally, there was little change in the mean plasma cholesterol between 1980 and 2008[9]. However, underlying this were declines in high-income regions, including Australasia, North America and Western Europe, but increases in other parts of the world such as East and South East Asia and the Pacific. The relative impact of dietary changes and drug therapy on plasma cholesterol in more affluent countries remains to be fully established and is discussed in the following sections.

Impact of dietary fatty acids on plasma cholesterol and cardiovascular risk

A link between raised plasma cholesterol and the development of atherosclerosis has been recognised for over a century. In 1948, Morrison *et al.*[10] published one of the first studies showing that individuals with premature (age under 60 years) coronary thrombosis were more likely to have elevated cholesterol. In the 1950s, the development of techniques to separate lipoproteins led to the discovery that it was cholesterol carried by LDL that was specifically associated with atherosclerosis[11]. Subsequently the protective effects of HDL began to emerge and were confirmed in two major prospective studies: the Tromso Heart Study[12] and the Framingham Population Study[13]. Such findings inevitably led to the question of what causes the variation in lipoprotein concentrations within populations. While in a small number of individuals this could be attributed to specific genetic mutations, or polymorphisms, it was clear that other factors must also be involved. While in most animals species, feeding excess cholesterol is required to initiate the development of atherosclerosis, it became increasingly clear that the amount and type of fat fed could also impact on the rate of development[14]. The now infamous Seven Countries Studies, published by Keys *et al.*[15] was one of the first to demonstrate a relationship between dietary SFA intake, plasma cholesterol and cardiovascular risk in human subjects. The design, presentation and interpretation of the results of this study are still hotly debated. However, it is perhaps the carefully controlled human feeding studies performed by Keys *et al.*[16], and independently by Hegsted *et al.*[17], that most clearly demonstrated a clear quantitative relationship between the amount and type of fatty acids consumed and the level of plasma cholesterol. Both groups clearly showed that SFA increased plasma cholesterol, while PUFA reduced it. Furthermore, both agreed that the impact of SFA was more potent than that of PUFA. Subsequent studies have refined this relationship indicating effects on both LDL- and HDL-cholesterol and identifying that the chain length of the SFA plays an important role, with lauric (C12:0), palmitic (C14:0) and palmitic (C16:0) have the greatest impact on LDL-cholesterol[18,19]. Further work also highlighted the potent effect of *trans* fatty acids (TFA), particularly those associated with partially hydrogenated oils, on LDL-cholesterol[18,19]. Such findings have underpinned the dietary recommendations for reduction of CVD across the world. In the UK, the Committee on Medical Aspects of Food Policy[20,21] set specific guidelines such that the average contribution of total fat to dietary energy in the population should be reduced to 35 % and SFA and TFA should be reduced to 10 and 2 %, respectively. However, they recommended that *n*-6 PUFA should not increase further and no specific recommendations were made for MUFA. These, and similar recommendations around the world, have remained a cornerstone of public health policy to reduce CVD for the past 30 years.

Recent years have seen considerable debate, in both the scientific and popular press as to whether such dietary policies were warranted, or whether they have had any positive impact on CVD outcomes. The National Diet and Nutrition Survey[22,23] showed that intake of SFA and TFA, as a proportion of dietary energy, dropped markedly, from 16 to 13·6 %, between 1986/87 and 2000/01. However, in recent years, there has been little further change in SFA intake which, in the 2014/15–2015/16 survey[24], was still standing at 11·9 % (although TFA had fallen further to only 0·5 % of total energy intake). When these data are compared with those for plasma cholesterol, over a similar period there was a steady drop in mean plasma cholesterol, in adults, between 1985 and 2005 (from 6·2 to 5·4 mM), which has remained stable in more recent years[25]. While it is tempting to link the drop in SFA intake with that in cholesterol, and indeed CVD mortality, this should be done with caution due to both the increasing use of cholesterol-lowering drugs (mentioned later) and changes in other potential risk factors already discussed.

While reducing SFA intake has remained a major goal in many countries for the past 30 years, there has been increasing debate over the actual relationship between fat intake and cardiovascular mortality/morbidity. This has largely been fuelled by the mixed results of a series

of systematic reviews and meta-analyses of both cohort and intervention studies, some of which are summarised in Table 1. Some of these have challenged any link of SFA with CVD morbidity/mortality[26–28] while others have specifically emphasised the value of replacing SFA with *n*-6 PUFA in the diet[29–33]. Of the latter, perhaps the most compelling is the Cochrane Review of Hooper *et al.*[33] who, having reviewed fifteen randomly controlled trials (including 59 000 participants) of various strategies for reducing SFA intake, concluded that replacing SFA with PUFA is a useful strategy to reduce CVD risk, while replacing with carbohydrate appears to be of little value. Due to the limited evidence available relating to replacing SFA with MUFA, they felt unable to reach a conclusion as to the potential benefit.

These overall conclusions are generally reflected in the recently updated draft reports from both the World Health Organisation[34] and the UK Scientific Advisory Committee on Nutrition[35] which continue to support reducing SFA intake but with more emphasis on replacement with *n*-6 PUFA.

The National Institute for Health and Care Excellence (NICE) provides specific advice about dietary fat intakes for patients with elevated plasma cholesterol, who are at increased risk of developing (or who already have) CVD. Their recommendations suggest such patients should be encouraged to reduce their intake of SFA to <7 % of total energy intake[36].

Statins, plasma cholesterol and cardiovascular risk

Until the late 1980s, pharmaceutical interventions for reducing plasma cholesterol were limited. The most widely used treatment was administration of bile acid binding agents, such as cholestyramine or colestipol, which act by binding to bile acids in the intestine, increasing their excretion and requiring the liver to synthesise more from cholesterol[37]. The resulting decrease in hepatic cholesterol leads to an increase in LDL receptor expression, thus increasing removal of LDL particles from the circulation. However, the beneficial effects are partly offset by an increase in cholesterol synthesis in the liver[37]. In 1987, the first statin was approved for human use[38]. Statins are competitive inhibitors of the enzyme HMGCoA reductase, the rate-limiting step in cholesterol synthesis, which leads to an up-regulation of LDL receptors in the liver. By 1994 evidence emerged that statins not only decrease LDL-cholesterol but also reduce cardiovascular events[39]. This has now been confirmed in numerous studies, with a recent meta-analysis of twenty-eight trials (including 186 854 participants) indicating that a 1 mM drop in LDL-cholesterol was associated with a 21 % drop in major vascular events[40]. Beneficial effects were seen across all age groups and statin therapy had no effect on non-vascular mortality, cancer death or cancer incidence. Despite the apparent efficacy of statin treatment, adherence to treatment has long been a problem due to perceived adverse effects. This was largely fuelled by the removal of one form of the drug, cerivastatin, from the market in 2001 due to fifty-two deaths associated with rhabdomyolysis leading to kidney failure[41]. In subsequent years, statin use has frequently been claimed to be associated with a high incidence of side-effects, including myopathy, new-onset diabetes mellitus and haemorrhagic stroke. Amid increasing concern that such fears were limiting the potential benefit of statin therapy, a recent review estimated that treatment of 10 000 patients for 5 years with an effective dose of statin would only result in five cases of myopathy, 50–100 new cases of diabetes and 5–10 haemorrhagic strokes[42]. This was set against an estimated prevention of between 500 (primary prevention) and 1000 (secondary prevention) vascular events. The authors concluded that most of the cases of symptomatic adverse events (such as muscle pain or weakness) were not actually caused by the drug itself. It thus appears that unjustified concerns about such side-effects are reducing adherence to statin treatment and increasing risk of cardiovascular events. In the UK, NICE recommend that statin therapy should be considered for treatment of all subjects with a >10 % risk of developing CVD in the next 10 years[43]. Such treatment should be in addition to continuing advice relating to lifestyle risk factors including a reduction in SFA intake to <7 % of total energy intake. It has been suggested that this could potentially include 11·8 million people in England including all males and females between the ages of 75 and 84 years[44]. Actually, statin prescriptions increased dramatically between the years of 2000 and 2010 and now appear to be levelling off with 128 prescriptions per 1000 people in the UK in 2013[45].

New cholesterol-lowering therapies

Since the widespread introduction of statins for the treatment of elevated plasma cholesterol, two further therapies have emerged. In 2002, ezetimibe was shown to inhibit cholesterol absorption from the intestine and, thereby reduce plasma total LDL-cholesterol in human subjects[46]. It was subsequently shown to bind to Niemann–Pick C1-like protein and thereby preventing conformational changes that are necessary for the translocation of cholesterol across the membrane into the enterocyte[47]. Ezetimibe is now prescribed as an alternative treatment for those in whom statins are contra-indicated, or as a complementary treatment in patients (often suffering from heterozygous familial hypercholesterolaemia) who fail to achieve adequate reductions in plasma cholesterol on statins alone[43]. A recent meta-analysis of seven trials (including 31 048 patients) concluded that compared to statin treatment alone, the addition of ezetimibe reduces the risk of myocardial infarction and stroke, but without any effect on all-cause and cardiovascular mortality[48].

The most recent treatment for elevated LDL-cholesterol is the use of monoclonal antibodies raised against proprotein convertase subtilisin–kexin type 9 (PCSK-9). PCSK-9 is a protein that binds to LDL receptors in the liver and prevents them from being recycled to the cell membrane, thus reducing the rate of removal of LDL from the circulation[49]. The importance of PCSK-9 in regulating plasma

Table 1. Recent systematic reviews on the impact of dietary SFA on CVD

Authors	Type of studies	Conclusions and key findings
Jakobsen *et al.*[29]	Cohort	To reduce risk of CHD, SFA should be replaced with PUFA rather than MUFA or carbohydrate Significant inverse association between PUFA intake and risk of coronary events (hazard ratio 0·87 (95 % CI 0·77, 0·97)
Skeaff and Miller[30]	Cohort and RCT	Probably no relationship between SFA and CHD. PUFA decreases risk Relative risk of CHD event 0·84 (95 % CI 0·70, 1·00) per 5 % energy increase in PUFA
Mozaffarian *et al.*[31]	RCT	Consuming PUFA in place of SFA reduces CHD events Relative risk of CHD event 0·90 (95 % CI 0·83, 0·97) per 5 % energy increase in PUFA
Siri-Tarino *et al.*[26]	Cohort	Insufficient evidence that SFA is associated with CHD or stroke Relative risk between extreme quantiles of SFA intake for CVD events 1·00 (95 % CI 0·89, 1·11)
Chowdhury *et al.*[27]	Cohort	Evidence does not support the benefit of low SFA/high PUFA diet Relative risks for coronary outcomes were 1·03 (95 % CI 0·98, 1·07) for SFA and 0·98 (0·90, 1·06) for *n*-6 PUFA
Harcombe *et al.*[28]	RCT	Evidence of RCT before 1983 did not support the introduction of dietary guidelines Relative risk for CHD death between intervention and control 0·989 (95 % CI 0·784, 1·247)
De Souza *et al.*[32]	Cohort	SFA not associated with any negative health outcomes but replacing SFA with PUFA reduced risk of CHD Relative risk of total CHD for SFA 1·04 (95 % CI 0·95, 1·17)
Hooper *et al.*[33]	RCT	Replacing SFA with PUFA significantly reduced the risk of CVD Relative risk of reducing SFA on CVD 0·83 (95 % CI 0·72, 0·96)

RCT, randomly controlled trials.

LDL-cholesterol levels became evident in studies looking at the impact of specific mutations in its genes. In individuals in whom such mutations led to a 'loss of function' of the protein, LDL-cholesterol was found to be significantly reduced (15–28 %) and this was associated with a 47–88 % reduction in CHD[50]. By contrast, other mutations leading to a 'gain of function' of PCSK-9 have been shown to be associated with a hypercholesterolaemic phenotype and a marked increase in cardiovascular risk[51]. This led to the development of PCSK-9 monoclonal antibodies for administration to patients to inhibit the activity of the protein. Initial human trials demonstrated a robust lowering of LDL-cholesterol by as much as 50–70 %[52]. In a recent double-blinded trial, one such antibody (evolcumab) was given to a group of patients already being treated with statins and resulted in a fall in LDL-cholesterol from 2·4 to 0·78 mM[53]. This was associated with a significant reduction in the primary clinical endpoint of the study (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation). The high cost of such treatment (repeated injections of antibodies) remains a major factor as to how such therapies might be applied and, at present, NICE only recommend their use in patients at high risk of CVD, with primary hypercholesterolaemia (or mixed dyslipidaemia), in whom LDL-cholesterol cannot be sufficiently lowered with maximum lipid-lowering therapies[43]. Table 2 compares the outcome of some recent systematic reviews[54–56] looking at the effects of statins alone or in combination with ezetimibe or PCSK9 inhibitors.

Is diet important in patients treated with cholesterol-lowering drugs?

As reviewed earlier, patients judged to be at high risk of CVD (or who have suffered a CVD event), with elevated LDL-cholesterol, are highly likely to be recommended to undertake statin therapy. Should this prove to be ineffective, they may be offered combined therapy with ezetimibe or even PCSK9 monoclonal antibodies. However, whatever drug regimen they are taking, they are also likely to be advised to follow a diet low in SFA[43]. This is based on a supposition that the impact of such a diet is likely to be, at least, additive in reducing LDL-cholesterol. As previously described, statins act by inhibiting the action of HMGCoA reductase, thereby reducing hepatic cholesterol concentration and up-regulating LDL receptors. Animal studies have clearly demonstrated that high SFA diets reduce LDL receptor activity[57] which is associated with a dose-dependent down-regulation of LDL receptor gene expression[58]. While the exact mechanism by which SFA exert this effect has not been fully elucidated, it appears to be through regulating the storage of cholesterol ester within the cell and thereby modulating the amount of free cholesterol available to regulate LDL receptor expression[59]. Thus, conversely, if the amount of SFA in the diet is reduced, then hepatic LDL receptor activity should increase and more LDL particles should be removed from the circulation. As statins and reduction in dietary SFA are impacting on LDL receptor activity by independent mechanisms, it might appear logical to assume that they will indeed be additive in their effects. However, in human subjects, there is very little published evidence to confirm this. An early study performed by Hunninghake *et al.*[60] looked at the impact of Lovastatin on plasma lipoproteins in patients who were either on a low- or high-fat diet. The low-fat diet reduced LDL by 5 %, while Lovastatin reduced it by 27 %. The combined effect was indeed found to be additive. However, they also found that when patients were on the low-fat diet, HDL-cholesterol was also significantly lowered. As a result, there was no additional beneficial change in the LDL:HDL ratio when drug-treated patients undertook the low-fat diet. A similar result was

Table 2. Recent systematic reviews of the impact of different drugs on CVD

Authors	Type of studies	Conclusions and key findings
Chou *et al*.[54]	19 randomised clinical trials of statins *v*. placebo including 71 344 participants without prior CVD events	In adults at increased CVD risk, statin therapy is associated with reduced risk of all-cause mortality (risk ratio 0·86 (95 % CI 0·80, 0·93)) and cardiovascular mortality (0·69 (0·54, 0·88))
Zhan *et al*.[55]	26 randomly controlled trials of ezetimibe *v*. placebo or ezetimibe plus other lipid-modifying drugs including 23 499 participants	Combining ezetimibe with statins reduces major CVD events compared with statins alone (risk ratio 0·94, 95 % CI 0·90, 0·98). Little evidence of any effect on total or CVD mortality
Schmidt *et al*.[56]	20 all parallel group and factorial randomised controlled trials comparing PCSK9 inhibitors with placebo, ezitimibe or ezitimibe and stains including 67 237 participants	Compared to placebo PCSK9 decreased risk of CVD events (OR 0·86, 95 % CI 0·80, 0·92). Compared with ezetimibe and statins, PCSK9 inhibitors appeared to have a stronger protective effect (0·45, (0·27, 0·75)). PCSK9 inhibitors probably had no effect on overall mortality

found when patients taking simvastatin who replaced dietary SFA/TFA with a diet rich in MUFA and PUFA[61]. In fact, it is well established that SFA have the capacity to increase HDL as well as LDL. Thus if LDL-cholesterol is maximally reduced by drug therapy, then the main impact of reducing SFA on lipoprotein metabolism may be to reduce HDL-cholesterol which might be seen as detrimental. However, it should be remembered that diets rich in SFA are often energy-dense, potentially leading to obesity and insulin resistance, and associated with high red and processed meat intake, all of which may be associated with increased CVD risk.

It is also of interest to consider what dietary patterns patients on long-term cholesterol-lowering drug therapy are actually adopting. A review of data arising from the National Health and Nutrition Examination Survey in the USA revealed some interesting differences in time trends in dietary behaviour between statin and non-statin users[62]. Within the period 2000–2001, statin users consumed less dietary fat than non-users. However, in the subsequent decade, while intake remained unchanged in non-users, it actually increased in those taking the drugs. As a result, over this period, the mean BMI increased in those on statin, while it remained unaltered in the control population. The authors concluded that statin users may become less restrained in their dietary choices. While this may not have major impacts on plasma lipoproteins, again the potential impact on obesity and associated morbidities should be considered.

Conclusions

There are widely varying patterns in the incidence of CVD across the world, with marked decreases in early mortality from such diseases in many high-income countries. This appears to be due to a combination of improved outcome following a cardiovascular event and reductions in risk factors, including LDL-cholesterol. The relative impact of public health policies advocating a reduction in SFA intake and the dramatic increase in availability of highly effective cholesterol-lowering drugs remains to be fully established. While at the present time, most patients at high risk of developing CVD are prescribed statins, they continue to be advised to follow a low SFA diet. While existing evidence fails to confirm any major benefits of such a dual regimen on plasma lipoprotein profile, the high energy content of SFA-rich diets, often associated with high intakes of red and processed meats, suggests it is prudent to continue with such advice. Interactions between diet and other lipid-lowering therapies (ezitimibe and PCSK9 monoclonal antibodies) remain largely unexplored.

Acknowledgements

I would like to acknowledge all colleagues and students who have worked with me over the past 40 years on topics related to this area of research.

Financial Support

None.

Conflict of Interest

None.

Authorship

The author had sole responsibility for all aspects of preparation of this paper.

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