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The confusion about dietary fatty acids recommendations for CHD prevention

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Abstract

A recent meta-analysis of prospective cohort studies has not found an association between dietary saturated fat intake and CHD incidence. This funnelled the discussion about the importance of the recommendation to lower the intake of saturated fat for the prevention of CHD. At the same time a document of the European Food Safety Authority has suggested that specific quantitative recommendations are not needed for individual fatty acids but that more general statements can suffice. In this review, we discuss methodological aspects of the absence of association between SFA intake and CHD incidence in prospective cohort studies. We also summarise the results of the controlled dietary experiments on blood lipids and on CHD incidence in which saturated fat was replaced by either *cis*-unsaturated fat or carbohydrates. Finally, we propose a nutritionally adequate diet with an optimal fatty acid composition for the prevention of CHD in the context of dietary patterns. Such diets are characterised by a low intake of saturated fat, and as low as possible intake of *trans*-fat and fulfil the requirements for the intake of *n*-6 and *n*-3 fatty acids. No recommendation is needed for the intake of *cis*-MUFA.

Key words: Dietary fatty acids: Saturated fat: Polyunsaturated fat: Serum cholesterol: CHD

The recommendation to lower saturated fat in the diet for the prevention of CHD has recently been challenged[1]. In their meta-analysis of prospective cohort studies, Siri-Tarino *et al.*[2] found that dietary SFA were not associated with an increased risk of CHD. The same authors[2] argued that substitution of saturated fat by carbohydrates, especially refined carbohydrates, may actually increase the risk of CHD. They attributed this to differential effects of dietary saturated fats and carbohydrates on concentrations of larger and smaller LDL particles and concluded that replacement of saturated fats by carbohydrates may increase CHD risk through atherogenic dyslipidemia[2].

Besides the discussion on the controversial role of dietary saturated fat, the optimal amount of total fat and individual fatty acids for CHD prevention is also debated in the scientific community. Do we need specific quantitative recommendations for total fat and individual fatty acids, or do quantitative recommendations for some fatty acids and general statements for others suffice? The latter approach was taken in the Dietary Reference Values for fats of the European Food Safety Authority (EFSA)[3]. Examples of the EFSA recommendations are 'the lower the better' for saturated fat, no recommendation for *cis*-MUFA and 'at least 250 mg/d' for the *n*-3 fatty acids EPA and DHA.

In this review, we challenge the interpretation of Siri-Tarino *et al.* about the absence of association between saturated fat and risk of CHD in prospective cohort studies, discuss the effect on CHD incidence of replacement of saturated fat by *cis*-unsaturated fat *v.* carbohydrates in controlled dietary experiments, and provide recommendations for fatty acids and dietary patterns for CHD prevention.

Lack of association between dietary saturated fat and CHD risk

The recently published meta-analysis of sixteen prospective cohort studies by Siri-Tarino *et al.*[1] has not provided evidence that a high intake of saturated fat is associated with an increased risk of CHD. This meta-analysis included 214 182 subjects who were followed up for 5–23 years and developed 8644 cases of CHD. The median or mean of saturated fat intake in these studies varied between 12 and

Abbreviations: ALA, α-linolenic acid; EFSA, European Food Safety Authority; P:S, polyunsaturated:saturated.

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20 % of energy. The pooled relative risk comparing extreme quantiles of saturated fat was 1·07 (95 % CI 0·96, 1·19; $P=0·22$) for CHD. This finding is discordant with the classic diet–heart hypothesis that a high saturated fat intake increases the risk of CHD, mediated by raised serum cholesterol.

In his editorial accompanying the article by Siri-Tarino *et al.*, Stamler[4] argues that the diet–heart hypothesis is supported by a vast array of concordant evidence from multidisciplinary research. A major issue in this context is the accuracy of dietary data in epidemiological studies on saturated fat and CHD. Balogh *et al.*[5] had already shown many years ago that twenty-two randomly collected 24-h dietary recalls are required to estimate the true individual mean intake within ±20 %, while most studies have only one recall or a food frequency measure of saturated fat intake available. Therefore, the weak associations found may be explained by unreliability of this aspect of dietary information in observational studies. We discuss in more detail the methodological aspects related to dietary saturated fat, serum cholesterol and CHD.

Parallel to the lack of association between saturated fat intake and CHD risk, as shown in the meta-analysis, is the lack of association between dietary saturated fat and serum cholesterol in cross-sectional analyses of the Framingham, Tecumseh and Zutphen studies[6–8]. Keys[9] explained the lack of an association between dietary saturated fat and serum cholesterol in cross-sectional studies by the large day-to-day variation within individuals in both saturated fat intake and serum cholesterol. He showed that the intra-individual variance of the SFA palmitic acid was more than twice as large as the inter-individual variance, based on two measurements. He also found that in healthy adults on an ostensibly constant diet, the average intra-individual standard deviation of serum cholesterol was approximately 200 mg/l (20 mg/dl), about half the total standard deviation[9].

The mathematical aspects of the zero or low-level correlation between dietary saturated fat and serum cholesterol were dealt with in a paper by Jacobs *et al.*[10]. Even with a fixed diet, serum cholesterol will vary due to differences in blood sampling, chemical analysis and variation in cholesterol levels unrelated to diet. Besides the variability in serum cholesterol there is also substantial variability in estimating dietary fatty acids. Jacobs *et al.* described the following sources of variation: (1) errors in identifying foods in food tables, (2) discrepancy between food table values and the true composition in foods eaten, (3) errors in estimating quantities of food eaten, (4) errors in remembering what was eaten and (5) differences in the food pattern of the observation period and that of the previous 2–4 weeks. These sources of error in both the dietary exposure and the effect measure will attenuate the correlation between dietary saturated fat and serum cholesterol. The attenuation of the true correlation is determined by the ratio of the variance between intra- and inter-individual variations. The larger the intra-individual variation, the larger the error term and the smaller the observed correlation.

It is therefore not a surprise that zero correlations were observed between dietary saturated fat and serum cholesterol in cross-sectional analyses. Jacobs *et al.*[10] stated in their article 'A corollary of the mathematical model here presented is that a correlation close to zero would likely be observed between diet e.g. dietary saturated fat and coronary heart disease incidence.' The results of the meta-analysis by Siri-Tarino *et al.*[1] are an illustration of their prophecy. Jacobs *et al.*[10] concluded their article by saying that 'An appropriate design for demonstrating or refuting diet and coronary heart disease incidence is a dietary experiment.'

Effect of different SFA on total and HDL-cholesterol

The classical controlled dietary experiments carried out before 1970 showed that replacing saturated fat, generally by starch or sucrose, decreased serum cholesterol, while replacing starch or sucrose by polyunsaturated fat also decreased serum cholesterol[11,12]. The serum cholesterol-raising effect of saturated fat was twice as strong as the decreasing effect of polyunsaturated fat. Controlled dietary experiments carried out after 1970 showed a somewhat smaller serum cholesterol-raising effect when carbohydrate was replaced by saturated fat and only half of the serum cholesterol-decreasing effect after replacement of carbohydrate by polyunsaturated fat[13]. This was recently confirmed by the large multi-centre Reading University, Imperial College London, Surrey University, MRC Human Nutrition Research Cambridge and King's College London (RISCK) trial[14].

A recent meta-analysis of controlled feeding experiments showed that SFA with twelve, fourteen and sixteen carbon atoms in contrast to the one with eighteen carbon atoms increased LDL-cholesterol when they isoenergetically replaced carbohydrate[15]. All four SFA raised HDL-cholesterol, but the HDL-cholesterol-raising effect was greater as the chain length decreased. Overall, the total:HDL cholesterol ratio is not affected by the SFA with fourteen, sixteen and eighteen carbon atoms, but is significantly reduced when the SFA with twelve carbon atoms replaces carbohydrate. However, replacement of SFA with 12–18 carbon atoms by *cis*-MUFA- and -PUFA leads to lowering of total and LDL-cholesterol, while only slightly lowering HDL-cholesterol, and thus improving the total:HDL cholesterol ratio and CHD risk[16].

Besides the effect of the chain length there may also be an effect of the source (e.g. animal *v.* plant origin and natural *v.* interesterified) of saturated fat on total and HDL-cholesterol. This was reviewed by Hayes & Pronczuk[17]. They noted that typical diets provide 2–4 % of energy as stearic acid (18 : 0) from natural fats. When a hardened fat is needed (replacing food applications that until recently used *trans*-fats), an unmodified saturated fat, for example from a palm or coconut product, was seen as preferable to interesterified fat[17]. At 2–4 % interesterified 18 : 0, effects on total and HDL-cholesterol and on glucose and insulin metabolism, immune function and liver enzymes are small. Detection of adverse effects starts at only approximately 7–8 % of energy or higher, although, similar to *trans*-fat, adverse effects of lower levels of interesterified fatty acids on other body systems could not be ruled out[17]. We agree with Hayes & Pronczuk[17] that interesterified fatty acids should be used sparingly until more evidence about their health effects has become available.

Replacement of saturated fat by *cis*-unsaturated fat or carbohydrates and CHD risk in controlled dietary experiments

Different strategies are available for replacing the energy lost when lowering saturated fat intake. Among these strategies, saturated fat can be replaced by either *cis*-unsaturated fatty acids or carbohydrates. In most controlled dietary experiments of CHD risk, saturated fats were replaced by polyunsaturated vegetable oils[18]. The PUFA studied were mainly *n*-6 fatty acids (linoleic acid) and small amounts of the *n*-3 fatty acid α-linolenic acid (ALA) in some cases, e.g. when soyabean oil was used. Meta-analyses of short-term controlled dietary experiments lasting generally 4–6 weeks showed that these PUFA favourably influence the LDL:HDL cholesterol ratio[13,16]. This ratio is a better predictor of CHD risk than total cholesterol or the individual lipoprotein fractions[13].

Between 1968 and 1992 eight controlled dietary experiments of more than 1-year duration with hard coronary end points were reported[19]. In these trials, control diets were characterised by both a high total fat (35–45 % of energy) and a high saturated fat content (approximately 20 % of energy). The average polyunsaturated fat consumption was 15 % of energy in the intervention groups and 5 % of energy in the control groups. Replacement of saturated by polyunsaturated fat changed the polyunsaturated:saturated (P:S) ratio from approximately 0·2 to 2. The overall pooled risk reduction in CHD incidence was 19 % corresponding to 10 % reduced risk per 5 % energy of increased polyunsaturated fat intake. Study duration was an independent determinant of risk reduction, with studies of longer duration showing greater benefits[19].

Ramsden *et al.*[20] concluded from the meta-analysis by Mozaffarian *et al.*[19] that the effect of replacement of SFA by PUFA on CHD incidence could not be exclusively ascribed to an effect of *n*-6 PUFA. After an extensive literature search and dietary data extraction they concluded that in only three of the eight trials saturated fat was solely replaced by *n*-6 polyunsaturated fat and in the other five by a mixture of *n*-6 and *n*-3 fatty acids. In the latter trials, the CHD incidence was reduced by 22 % when saturated fat was replaced by a mixture of *n*-6 and *n*-3 PUFA. No effect was observed in the other three trials, but the number of studies was too small to draw conclusions. We agree with Ramsden *et al.*[20] that the effect of replacement of saturated fat by polyunsaturated fat on CHD incidence in the meta-analysis by Mozaffarian *et al.*[19] should be ascribed to the combined effects of *n*-6 and *n*-3 PUFA. However, as Mozaffarian *et al.*[19] showed, the effect on CHD incidence is in accord with the effect of the change in fatty acids on the total:HDL cholesterol ratio. Taking the results of these two meta-analyses together, we conclude that the effect of replacement of saturated fat by a mixture of *n*-6 and *n*-3 polyunsaturated fat can be ascribed to an effect of blood lipids and to that of *n*-3 PUFA independent of blood lipids, e.g. through prevention of ventricular arrhythmias[21].

The alternative to replace energy from saturated fat with carbohydrates is much more complex, because 'carbohydrates' actually encompass a huge range of foods varying from high to low in micronutrients, phytochemicals and fibre (fruits, vegetables, whole grains *v.* sugar and refined grain). These two replacement strategies within the context of 'carbohydrates' are not likely to have the same effect on long-term risk. Only one controlled dietary experiment of long-term CHD risk has been carried out using this strategy[22]. Therefore, we also report here the recently published results of a Danish cohort study in which SFA in the statistical model were substituted for carbohydrates with low glycaemic index values (a marker of healthy carbohydrate-containing foods). This was associated with a lower risk of myocardial infarction[23]. However, replacing SFA with carbohydrates with high glycaemic index values (a marker of unhealthy carbohydrate-containing foods) was associated with a higher risk[23]. In a large long-term controlled dietary experiment carried out in 48 835 women aged 50–79 years, energy from fat decreased by 8 % and carbohydrates increased by the same percentage[22]. This trial population had a low habitual fibre intake (15 g/d) and the difference in fibre intake between the high- and low-carbohydrate groups was 2·4 g/d. Over 8 years of follow-up, there was no effect of diet on the total:HDL cholesterol ratio and CHD incidence[22]. More favourable results may be expected for low-fat diets with a P:S ratio of at least 1 and a high fibre content (>50 g/d), which would be rich in micronutrients and phytochemicals. However, controlled trials that tested the effect of this type of diet on CHD end points have not been carried out.

Given the paucity of controlled dietary experiments of CHD risk using the carbohydrate replacement strategy, the influence of low-fat, high-carbohydrate diets on lowering serum cholesterol is also of interest in this context. In a classic experiment reported in 1981, Lewis *et al.*[24] compared diets low in fat (27 % of energy with a P:S ratio of 1) and high in carbohydrates (59 % of energy) that were either low (20 g/d) or high (55 g/d) in fibre. The fibre-enriched diet contained more fruit and vegetables and substituted whole-wheat bread for white bread. The low-fat, high-fibre diet reduced LDL-cholesterol by 35 % and HDL-cholesterol by 11 % while the low-fat, low-fibre diet decreased LDL-cholesterol by 27 % and HDL-cholesterol by 12 %. These results suggest that the LDL:HDL cholesterol ratio is more favourably influenced by the low-fat, high-fibre diet than by the low-fat, low-fibre diet[24]. These results were confirmed in a controlled dietary experiment using a dietary portfolio of cholesterol-lowering plant foods[25]. The diet contained 29 % of energy from fat with a P:S ratio of 1·6 and 77 g fibre/d.

A food-based dietary experiment carried out in a sub-study of the Spanish PREvención con DIeta MEDiterránea (PREDIMED) Study is of further interest concerning fibre-rich diets, not necessarily in a low total fat context[26]. For this study, subjects with at least two CHD risk factors were randomised into three groups. The reference group was assigned to a low-fat diet and the other two groups were allocated to a recommended Mediterranean-style diet to which either 1 litre of extra virgin olive oil per week or 30 g nuts/d was added. Both the olive oil and the nut supplements were supplied to the participants by the investigators. Both olive oil and nuts are rich in MUFA and tree nuts also in *n*-6 and *n*-3 polyunsaturated fat. The diets

Table 1. Summary of the results of prospective cohort studies and trials on fatty acids and CHD risk

	CHD risk reduction	
Fatty acid change	Cohort studies (%)	Trials (%)
5 % of energy of SFA replaced by PUFA	−13[27]	−10[19]
2 % of energy decrease in *trans*-MUFA	−24[28]	NA
Increase in EPA–DHA from 0 to 250 mg/d	−36[33]*	−36[33]*

NA, not available.
* Based on both cohort studies and trials.

with extra olive oil or nuts decreased LDL-cholesterol by −39 and −34 mg/l (− 3·9 and − 3·4 mg/dl), and increased HDL-cholesterol by 29 and 16 mg/l (2·9 and 1·6 mg/dl)[26]. These results were comparable to those obtained in controlled dietary experiments[13,16].

In summary, replacement of saturated fat by polyunsaturated fat decreases the LDL:HDL cholesterol ratio and reduces the incidence of CHD. Replacement of saturated fat by *cis*-MUFA decreases the LDL:HDL cholesterol ratio. Low-fat diets high in carbohydrates but low in fibre do not change the LDL:HDL cholesterol ratio. In contrast, low-fat diets with a P:S ratio of at least 1 and high-fibre content do decrease the LDL:HDL cholesterol ratio. Diets high in *cis*-MUFA and low in fat with a P:S ratio of at least 1 and high fibre content may reduce CHD risk, although this has not been proven experimentally. This leads to the conclusion that different diets could be designed to prevent CHD. This potential diversity is crucial in engaging the diverse cultures and tastes worldwide in cardiovascular prevention[18].

Optimal fatty acid composition and dietary patterns for CHD prevention

The ultimate question to be answered is what the optimal fatty acid composition of diets for CHD risk reduction could be? Based on eight carefully controlled studies, Sacks & Katan[18] concluded that *trans*-fatty acids had the worst effect on blood lipids of all dietary fatty acids. *cis*-MUFA and *n*-6 PUFA reduce the total:HDL cholesterol ratio, whereas carbohydrates have a negligible effect on the ratio[16]. However, if low-fat, high-carbohydrate diets with a P:S ratio of at least 1 also had a high amount of fibre, a similar total:HDL cholesterol ratio was obtained when saturated fat was replaced by polyunsaturated fat[24,25]. This suggests that for optimal CHD risk reduction not only the fatty acid composition but also the fibre content, probably indicating a composite of micronutrients and phytochemicals, is of importance.

Both saturated and *trans*-fatty acids not only have a detrimental effect on blood lipids but also increase CHD risk. This was observed in controlled dietary experiments in which saturated fat was replaced by vegetable oils rich in mostly *n*-6 PUFA. These diets reduced CHD incidence and the stronger the saturated fat reduction, the lower the CHD incidence[19]. When 5% of energy from saturated fat was replaced by a similar amount of mostly *n*-6 polyunsaturated fat, CHD risk was reduced by 10% (Table 1). Similar results were obtained in a meta-analysis of pooled data of eleven prospective cohort studies[27]. *Trans*-fats increase the risk of CHD even more strongly than saturated fats. These fatty acids were introduced industrially in only a few products and tend to have relatively low within-person variance in observational data. For *trans*-fatty acids data from only prospective cohort studies are available. A meta-analysis of four studies showed that a reduction in *trans*-fatty acid intake of 2% of energy is associated with a 24% lower CHD risk (Table 1)[28].

n-3 Fatty acids also contribute to an optimal fatty acid composition of the diet. The mother compound of these fatty acids is ALA, a PUFA with eighteen carbon atoms and three double bonds arising in plant oils, e.g. soyabean and linseed oil. A meta-analysis of prospective cohort studies showed that a high ALA intake compared to a low ALA intake was associated with a lower, though not statistically significant, risk of CHD mortality (relative risk 0·79; 95% CI 0·60, 1·04)[29]. Fish is an important source of the *n*-3 fatty acids EPA and DHA. Meta-analyses showed that persons who eat fish at least once a week have an approximately 15% lower risk of fatal CHD[30]. Meta-analyses of randomised trials showed that an additional amount of EPA–DHA reduced the risk of both fatal CHD and sudden cardiac death[31,32]. In a meta-analysis of both prospective cohort studies and trials, Mozaffarian & Rimm[33] showed that an increase from 0 to 250 mg EPA and DHA per d was associated with a 36% lower CHD mortality risk (Table 1).

The results for the different fatty acids make clear the large potential of an optimal fatty acid composition for CHD prevention. Table 2 summarises broad recommendations for an optimal fatty acid composition in the context of nutritionally adequate diets[34,35]. For CHD prevention, a recommendation for total fat is not needed and may even be counterproductive. High-fat diets (30–45% of energy) with a P:S ratio of more than 1 reduce the LDL:HDL cholesterol levels and CHD incidence compared with diets high in saturated fat with a P:S ratio of 0·2[16,19]. Evidence is accumulating that this may also be the case for a low-fat diet with a P:S ratio of 1 and high-fibre content. However, low-fat, high-carbohydrate diets with low fibre content, have an unfavourable effect on blood lipoprotein fractions and therefore likely also on CHD risk[2]. Both SFA and, even more, *trans*-fatty acids increase CHD risk. Therefore, we see merit in the EFSA recommendation of an intake as low as possible for

Table 2. Summary of recommendations for fatty acid intake for adults*

Fatty acids	Prevents essential fatty acid deficiency	CHD prevention
Total fat		No recommendation
SFA		Low, as long as the diet is nutritionally adequate
trans-Fatty acids		As low as possible
cis-MUFA		No recommendation
Linoleic acid	>2·5% of energy	>5% of energy
α-Linolenic acid	>0·5% of energy	
EPA–DHA		>250 mg/d

* Adapted from the scientific opinion on dietary reference values for fats from the European Food Safety Authority Panel on Dietetic Products, Nutrition, and Allergies[3].

these fatty acids[3]. However, this recommendation does not mean that people must avoid all foods high in SFA, such as chocolate, cheese, palm oil and coconut. We interpret the EFSA recommendation as an incentive to consume a nutritionally adequate diet with a low saturated fat content. To our opinion, there is no minimal amount of saturated fat that should be eaten. *cis*-MUFA compared with saturated and *trans*-fatty acids have a favourable effect on the LDL:HDL cholesterol ratio and possibly on CHD risk also. They are, however, not essential and, therefore, a recommendation is not needed.

The most common *n*-6 fatty acid, linoleic acid, is essential. To prevent an essential fatty acid deficiency an intake of at least 2·5 % of energy is recommended[36]. On the basis of aggregate data from randomised trials, case–control and cohort studies, and long-term animal feeding experiments, Harris *et al.*[37] concluded that an intake of at least 5 % of energy from linoleic acid is needed to reduce CHD risk. To prevent an essential fatty acid deficiency of the *n*-3 fatty acid ALA, an intake of at least 0·5 % of energy is recommended[36]. There is some but not yet convincing evidence from prospective cohort studies that a high ALA intake is associated with a lower CHD mortality risk[29]. Upper limits for the intake of both linoleic acid and ALA are not needed for nutritionally adequate diets. Finally, there is convincing evidence from prospective cohort studies and trials that an intake of the *n*-3 fatty acids, EPA and DHA, of at least 250 mg/d is needed[33]. There is no evidence that a higher intake is needed for CHD prevention.

We propose to consume nutritionally adequate diets that are low in saturated fat and as low as possible in *trans*-fat. We raise concern about fabricated substitutes for *trans*-fat, such as interesterified fats. Nutritionally adequate diets should fulfil the requirements for the intake of *n*-6 and *n*-3 fatty acids. No recommendation is needed for the intake of *cis*-MUFA. Recommendations for fatty acid intake must be considered in the context of whole diets. Natural experiments showed that both traditional Mediterranean and Japanese diets were associated with a low risk of CHD[38,39]. The common feature of these diets was that they were both low in saturated and *trans*-fat, meat and dairy, and high in legumes, nuts and vegetables. The traditional Mediterranean diet was high in olive oil, whole grains and fruit, and moderate in fish while the traditional Japanese diet was high in fish and rice[40]. This underscores that recommendations for fat intake must be made within a food-based approach to CHD prevention[41,42].

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