Review Article

Replacement of saturated and *trans*-fatty acids in the diet *v.* CVD risk in the light of the most recent studies

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Abstract

Objective: To present and discuss results of the most recent studies pertaining to the effects of consumption of different types of fatty acids on the risk of CVD. The aim was also an attempt to answer the question of whether a revision of the current recommendations is necessary.

Design: A review of prospective cohort studies, systematic reviews and meta-analyses published in 2014–2017 on the effects of SFA and *trans*-fatty acid (TFA) intakes as well as various models of their replacement in the diet on CVD risk.

Results: Results of the new large prospective cohort studies pertaining to the effect of SFA consumption on CVD risk are contradictory. Similarly, the recent meta-analyses of clinical trials related to the effects of SFA substitution on CVD risk provided extremely different results, which is related to the application of different inclusion and exclusion criteria. Differences in results of randomised controlled trials may be caused by different methodologies of dietary parameter changes, varying duration of studies, as well as the time at which they were carried out.

Conclusions: It is extremely difficult to extrapolate results of recent studies to contemporary recommendations. It seems that there is a need for properly randomised studies on large groups, with good control of dietary and non-dietary parameters, which account for not only the sum of SFA and TFA, but also their source. Only such studies will allow for full evaluation of an effect of substituting SFA and TFA on cardiovascular risk.

Over the course of many years, numerous studies have reported that intakes of SFA and *trans*-fatty acids (TFA) are related to lipidic risk factors for CVD. In the case of SFA intake, the strength of this association is estimated to be as follows: every 1% increase of energy coming from SFA causes an increase in LDL cholesterol (LDL-C) concentration by 12·7–17·4 mg/l and in HDL cholesterol (HDL-C) concentration by 4·3–5 mg/l[1]. This was confirmed in a systematic review and regression analysis prepared for the WHO in 2016, which covered seventy-four randomised studies. At the same time, it has been demonstrated that replacement of SFA with *cis*-MUFA or *cis*-PUFA normalises the lipid profile more effectively than replacing them with a mixture of carbohydrates. The decrease in total cholesterol (TC), LDL-C and TAG concentrations was greatest when *cis*-PUFA were used[2]. Regarding TFA, their adverse influence on lipid parameters is also well documented.

Beginning in the 1990s, a number of studies have been published indicating that, compared with the same amount of energy from *cis*-unsaturated fatty acids or SFA, intake of TFA increases LDL-C level, decreases HDL-C level and increases TC:HDL-C[3–6]. Compared with other fatty acids, the concentration of TAG and lipoproteins also increases[1,7]. In a meta-analysis of numerous studies, Mozaffarian and Clarke concluded that intake of 1% of energy from TFA in place of other fats increases TC:HDL-C by 0·022 if SFA are replaced; by 0·051 if MUFA are replaced; and by 0·057 if PUFA are replaced[8].

Many studies have demonstrated the effectiveness of replacing SFA and TFA with other macronutrients, especially unsaturated fatty acids, in improving the lipid profile[1]. This formed a basis for developing population-based recommendations in which reduction of SFA and TFA intakes is one of the basic dietary targets aimed at

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decreasing CVD risk. The current recommendations for SFA intake, by the WHO as well as European and American scientific societies, suggest that in order to decrease the risk of myocardial infarction and stroke, SFA intake should be reduced to below 10 % of total dietary energy (5–6 % in persons who would benefit from decreasing LDL-C concentration), and in the case of TFA, their intake should be decreased to below 1 % of total dietary energy[9–12]. Still, SFA remain a significant source of energy in developed countries, fluctuating around 12 % of total dietary energy[13,14]. As for TFA, however, some countries have managed to achieve a marked reduction in their consumption.

Recently, doubts have also arisen about whether the current recommendations to reduce SFA and TFA intakes, in addition to benefits resulting from their impact on risk factors, translate into a notable effect on health in the form of CVD risk reduction. The results of studies published in 2017 pertaining to the effects of consumption of different types of fatty acids on the risk of CVD are being widely discussed and raise the question of whether a revision of the current recommendations is necessary. The present paper is a review of the most recent studies, reviews and meta-analyses on the effects of SFA and TFA intakes, as well as various models for replacing them in the diet, on CVD risk.

Literature searches (prospective cohort studies, systematic reviews and meta-analyses) were conducted in two databases, MEDLINE® (PubMed) and Scopus®. Searches spanned the period from January 2014 to August 2017. Results from these two searches were combined and filtered for human studies published in the English language.

SFA and models of their replacement in the diet

In recent years, studies have emerged on SFA and models of their replacement with regard to cardiovascular risk. Major meta-analyses, systematic reviews and results of large prospective cohort studies are shown in Table 1. They include studies that cast doubt on the effectiveness of the recommendations made to date focused on decreasing SFA intake.

In 2015, de Souza et al. published a systematic analysis of studies which described the relationship between SFA, unsaturated fatty acids with the trans configuration and all-cause mortality, CHD mortality, ischaemic stroke and type 2 diabetes[15]. The authors failed to find any clear relationship between high SFA intake and all-cause mortality, CHD mortality, IHD, ischaemic stroke or type 2 diabetes. At the same time, they demonstrated that intake of trans-unsaturated fatty acids was associated with a 34 % increase in all-cause mortality and a 28 % increase in CHD mortality as well as a 21 % increase in CHD risk[15]. However, no significant relationship was observed between high trans-fat intake and ischaemic stroke or type 2 diabetes.

The EPIC-NL (European Prospective Investigation into Cancer and Nutrition–Netherlands) cohort study also revealed surprising results. A low risk of CHD was observed in persons with high SFA intake (the mean follow-up time was 12 years). It had been demonstrated that replacement of SFA with animal protein, cis-MUFA or even cis-PUFA or carbohydrates was associated with a significantly higher risk of IHD (hazard ratio per 5 % of energy = 1·27–1·37)[16]. However, the authors of the study noted the specific sources of SFA among the participants (mostly dairy products) as well as the distribution of individual fatty acids in the SFA pool, a large proportion of which comprised short- and medium-chain acids[16]. This observation seems to confirm the results of the MESA (Multi-Ethnic Study of Atherosclerosis), in which high intake of SFA coming from dairy products was associated with a lower risk of IHD, while high intake of SFA coming from meat was associated with a higher CVD risk. The follow-up was carried out for 10 years[17]. The authors of both papers, however, pointed out that further studies are required in populations with a greater variety of SFA sources, as well as the need to assess the negative role of TFA in cases in which SFA are replaced with plant sources of fatty acids. The results of these studies seem to confirm meta-analyses on the effect of dairy product consumption on the risk of CVD. A meta-analysis by Alexander et al. covering thirty-one prospective cohort studies revealed a possible link between dairy product consumption and decreased risk of CVD[18]. Similar observations were demonstrated in an earlier meta-analysis by Qin et al.[19], which covered twenty-two prospective cohort studies. The authors observed that dairy product consumption has a negative correlation with the risk of CVD and stroke. They also concluded that consumption of dairy products with decreased fat content leads to decreased incidence of stroke, while consumption of cheese may reduce the incidence of both stroke and CHD[19]. It was shown in a large multicentre study by Brassard et al. that SFA from cheese or butter do not have a significant effect on non-lipid cardiometabolic risk factors, such as inflammation markers, arterial blood pressure and homeostatic model assessment of insulin resistance, which can partly explain why observational studies have not shown a link between consumption of cheese and an increased risk of coronary artery disease[20]. Other meta-analyses indicated beneficial effects of dairy product consumption in terms of the risk of both type 2 diabetes[21] and obesity[22]. It seems therefore that elimination of dairy products as the source of SFA may be detrimental to health.

Results of some large prospective studies have been published recently. In 2016, Wang et al. and Zong et al. published results from American prospective studies, the Nurses' Health Study and the Health Professionals Follow-up Study, which indicated that larger intake of SFA contributes to a slight increase in total mortality (no link to CVD mortality) and risk of CHD[23,24]. Completely different data were provided by the PURE (Prospective Urban Rural Epidemiology) study, whose findings were published in 2017. This was a large, prospective study which included a

Table 1 SFA and models of their replacement in regard to cardiovascular risk: meta-analyses, systematic reviews and prospective cohort studies published in the years 2014–2017

Study	Design	*n*	Follow-up	Objective	Principal findings
Li *et al.* (2015)[36]	Prospective, longitudinal cohort study (Nurses' Health Study, Health Professionals Follow-up Study), USA	84 628 women 42 908 men	24 years	Investigate associations of saturated fats compared with unsaturated fats and different sources of carbohydrates in relation to CHD risk	1. Replacing 5 % of energy intake from SFA with equivalent energy intake from PUFA, MUFA or carbohydrates from whole grains was associated with a 25 %, 15 % and 9 % lower risk of CHD, respectively
Zong et al. (2016)[24]	Prospective, longitudinal cohort study (Nurses' Health Study, Health Professionals Follow-up Study), USA	115 782	24 years	Analyses on associations between intake of individual SFA and risk of CHD and estimate risk of CHD when individual SFA were replaced	1. Dietary intakes of major individual SFA were positively associated with risk of CHD 2. Replacement of 1 % daily energy intake from the combined group of 12 : 0–18 : 0 by equivalent energy from polyunsaturated fat, wholegrain carbohydrate or plant proteins was associated with a 6–8 % reduced risk of CHD 3. The same replacement of 16 : 0 was associated with 10–12 % reduction in risk
Wang *et al.* (2016)[23]	Prospective, longitudinal cohort study (Nurses' Health Study, Health Professionals Follow-up Study), USA	83 349 women 42 884 men	24 years	Examine the associations of specific dietary fats with total and cause-specific mortality	1. Higher SFA intake was associated with a slight increase in total mortality, but not significantly associated with CVD mortality 2. Replacing SFA with unsaturated fatty acids was associated with substantially lower risk of total and CVD mortality
Praagman *et al.* (2016)[16]	Prospective, cohort study (European Prospective Investigation into Cancer and Nutrition–Netherlands cohort), Netherlands	35 597	12 years	Analyses on associations of SFA with IHD risk and whether associations depended on (i) the substituting macronutrient, (ii) the carbon chain length of the SFA and (iii) the SFA food source	1. Higher SFA intake was not associated with higher IHD risks 2. The inverse association between the substitution of SFA with PUFA and IHD risk was found
Dehghan *et al.* (2017)[25]	Epidemiological cohort study (Prospective Urban Rural Epidemiology (PURE) study), eighteen countries: regions included China, South Asia, North America, Europe, South America, Middle East, South-East Asia and Africa	135 335	7·4 years	Assess the association of fats (total, SFA and unsaturated fats) and carbohydrate with total mortality and CVD events Examine associations between these nutrients and myocardial infarction, stroke, CVD mortality and non-CVD mortality	1. Fats, including SFA, are not harmful and diets high in carbohydrate have adverse effects on total mortality 2. No effect of higher fat intake on cardiovascular events 3. Saturated fat had an inverse association with stroke 4. Global dietary guidelines should be reconsidered in light of these results
Farvid *et al.* (2014)[32]	Systematic review and meta-analysis of thirteen prospective cohort studies	310 602	5–30 years	Summarise the evidence regarding the relationship of dietary LA intake and CHD risk	1. Dietary LA intake is inversely associated with CHD risk in a dose–response manner
Schwingshackl and Hoffmann (2014)[29]	Systematic review of twelve RCT, meta-analysis and univariate/multivariate meta-regression	7150	>1 year	Assess the effects of reduced- and/or modified-fat diets and dietary fatty acids on all-cause mortality, cardiovascular mortality and cardiovascular events in participants with established CHD	1. Replacing SFA by PUFA showed no significant benefit in the secondary prevention of CHD

Table 1 *Continued*

Study	Design	n	Follow-up	Objective	Principal findings
Al-Khudairy et al. (2015)[31]	Systematic review of four RCT	660	>0·5 year	Determine the effectiveness of increasing n-6 intake in place of saturated or monounsaturated fats or carbohydrates for the primary prevention of CVD	1. No statistically significant effects of either increased or decreased n-6 intake on CVD risk factors
Hooper et al. (2015)[33]	Systematic review of fifteen RCT	59 000	>2 years	Assess the effect of reducing saturated fat intake and replacing it with carbohydrate, PUFA, MUFA and/or protein on mortality and cardiovascular morbidity	1. Reducing dietary SFA reduced the risk of cardiovascular events by 17 % 2. Reduction in cardiovascular events was seen in studies that primarily replaced SFA with PUFA, and no effects were seen in studies replacing SFA with carbohydrate or protein 3. Effects of replacement with MUFA were unclear due to inclusion of only one small trial
de Souza et al. (2015)[15]	Systematic review and meta-analysis of fifteen cohort studies	99 859	Seven studies, <15 years Eight studies, ≥15 years	Review associations between intake of saturated fat and all-cause mortality, CVD and associated mortality, CHD and associated mortality, ischaemic stroke and type 2 diabetes	1. SFA intake was not associated with all-cause mortality, CVD mortality, total CHD, ischaemic stroke or type 2 diabetes
Harcombe et al. (2016)[30]	Systematic review and meta-analysis of ten RCT	62 421	>1 year	Re-examine dietary guidelines for total fats and SFA, to assess their evidence base against the RCT evidence currently available	1. No significant difference in all-cause mortality or CHD mortality, resulting from the dietary fat interventions 2. RCT evidence currently available does not support the current dietary fat guidelines
Sacks et al. (2017)[45]	Meta-analysis of four core RCT (American Heart Association Presidential Advisory)	2870	>4 years	Review and discuss the scientific evidence, including the most recent studies, on the effects of dietary saturated fat intake and its replacement by other types of fats and carbohydrates on CVD	1. Polyunsaturated fat from vegetable oils (mainly n-6, LA) reduces CVD somewhat more than monounsaturated fat (mainly oleic acid) when replacing saturated fat
Hamley (2017)[46]	Meta-analysis of eleven RCT	17 072	>1 year	Account for the major confounding variables in the diet–heart disease trials, and emphasise the results from those trials that most accurately test the effect of replacing SFA with mostly n-6 PUFA	1. Replacing SFA with mostly n-6 PUFA is unlikely to reduce CHD events, CHD mortality or total mortality 2. The suggestion of benefits reported in earlier meta-analyses is due to the inclusion of inadequately controlled trials

RCT, randomised controlled trial; LA, linoleic acid.

population of over 135 000 adults aged 35–70 years from eighteen countries of Asia, Europe, North and South America and the Middle East, lasting an average of 7·4 years. Consumption of total fat and other types of fatty acids, including SFA, was not linked to the risk of CVD, myocardial infarction or mortality caused by CVD. It was the first so-broad study to describe the relationship between low intake of SFA (e.g. <7 % of energy) and total mortality and CVD. A reverse correlation was observed between intake of SFA and the risk of stroke. The authors claimed that the available data do not justify the recommendation for reducing consumption of SFA to less than 10 % of total energy and that their very low intake (i.e. below about 7 % of energy) can even be harmful[25]. However, it should be noted that the PURE study has numerous limitations such as use of the FFQ only at baseline, huge economic variation within the cohorts and limited data collection.

Studies on models of replacement of SFA in the diet with other macronutrients have also given inconsistent results. The paradigm of benefits stemming from the replacement of SFA with PUFA (i.e. linoleic acid (LA)) was called into question by the authors of a repeated analysis of the MCE (Minnesota Coronary Experiment) results[26]. Ramsden *et al.* confirmed the effectiveness of replacing SFA with LA in decreasing cholesterol concentrations: in the intervention group, a significant decrease in serum cholesterol concentrations was achieved compared with the control group (mean change from baseline = −13·8 % *v.* −1·0 %, $P < 0.001$). However, the expected benefits to health associated with this fact in the intervention group were not achieved in terms of decreased incidence of coronary artery atherosclerosis or myocardial infarction. Importantly, the mean dietary intervention period was 1063 d, i.e. just under 3 years[26]. In 2013, the same authors published a similar article involving a repeated analysis of medical data of SDHS (Sydney Diet Heart Study) participants[27]. This revealed that patients receiving a diet of decreased SFA content and increased LA content (*n* 221) had a higher mortality rate than patients in the control group (*n* 237; all causes of death, 17·6 % *v.* 11·8 %; CVD, 17·2 % *v.* 11·0 %; CHD, 16·3 % *v.* 10·1 %). The follow-up was carried out for 12 months. The dietary intervention in the SDHS led to an increase in PUFA intake to as much as about 15 % of total dietary energy (mostly LA) as well as a decrease in SFA intake to less than 10 % of total dietary energy and a decrease of food cholesterol intake to below 300 mg daily[27]. On the other hand, the MCE study revealed an increase in LA to 13·2 % of total dietary energy and a decrease in SFA intake to 9·2 %[26]. Both studies involved decreasing the amount of SFA through reduction of their rich sources, such as butter, and replacing them with fats rich in LA in the form of corn oil or safflower oil, or margarines with a high content thereof[26,27]. Thus, the intervention focused on fat substitution while disregarding other important aspects of diet, for instance dietary fibre or

antioxidants. There was also no information regarding the patients' diet after completion of follow-up, so we do not know whether the changes introduced in the study were continued. Critics of this intervention also point to the fact that the provided plant fats had the form of hydrogenated oil or margarines rich in TFA[28]. Inclusion of new data from the SDHS in a meta-analysis of dietary interventions performed by the same research team, in which SFA were replaced with LA, did not reveal any benefits associated with all-cause mortality and mortality due to CVD resulting from such a dietary change[27]. These findings are consistent with those of the meta-analysis of thirteen randomised controlled trials conducted by Schwingshackl and Hoffmann, which showed that an increase in consumption of PUFA in place of SFA does not benefit secondary prevention of CHD[29]. In their meta-analysis concerning the effectiveness of dietary interventions in prophylaxis, Harcomb *et al.* also did not find reduced intake of SFA to have a beneficial effect on total mortality or mortality due to CHD[30]. The conclusions from a Cochrane systematic review performed by Al-Khudairy *et al.* on the potential of using *n*-6 acids in primary prevention also undermined any benefits associated with their use. The analysis following application of the inclusion criteria included only four European controlled clinical trials (the oldest one from 1998) involving 660 participants. More than 140 clinical trials were excluded from the analysis because of a lack of randomisation, too short duration or too small groups. The Cochrane systematic review failed to demonstrate any relationship between PUFA intake and decreased or increased CVD risk. According to the authors, there is a need for randomised studies assessing cardiovascular events as well as the presence of cardiovascular risk factors with larger study groups[31].

Different results came from a meta-analysis by Farvid *et al.*, which included thirteen published and unpublished cohort studies involving a total of 310 602 persons and 12 479 cardiovascular events, including 5882 CHD deaths. It was demonstrated that a 5 % increase in energy coming from LA, substituted for energy from SFA, was associated with a 9 % lower risk of cardiovascular events (relative risk = 0·91; 95 % CI 0·87, 0·96) and a 13 % lower risk of death due to CHD (relative risk = 0·87; 95 % CI 0·82, 0·94)[32].

Hooper *et al.* performed an analysis of fifteen randomised controlled trials with 59 000 participants. The analysis included only those studies carried out for more than 24 months. The results revealed a 17 % decrease in the risk of cardiovascular events resulting from reduced intake of SFA, which did not, however, translate into a decrease in all-cause mortality or mortality due to CVD. The authors said that better effects are achieved when SFA are replaced with PUFA. Significantly worse effects are achieved through replacement of SFA with carbohydrates, while the effect of using MUFA remains unclear,

probably due to the low number of studies meeting the inclusion criteria[33].

The results of that analysis are in line with those of a previous meta-analysis by Jacobsen et al., in which it was concluded that replacement of SFA with n-6 PUFA decreases the risk of cardiovascular events by 13 % and of cardiovascular death by 26 %[34]. Regarding the possibility of using MUFA to replace SFA in the diet, most authors of meta-analyses point to the decidedly lower number of cohort studies and clinical studies as well as meta-analyses and systematic reviews than for those concerning n-6 PUFA, which means that no definite conclusions can be drawn[35]. Despite this fact, when considering the effectiveness of SFA replacement, one must not forget the updated Nurses' Health Study, covering 30 years of follow-up of 84 628 American women, and the Health Professionals Follow-up Study, covering 34 years of follow-up of 42 908 American men. In both studies, replacement of 5 % of energy from SFA with an equivalent amount of cis-MUFA led to a 15 % decrease in CHD risk (95 % CI 3, 26 %)[36]. Another study excluded from the analysis by Hooper et al. (due to lack of a clearly defined target regarding the overall level of fat intake), which utilised nutrition models with a high MUFA content, is the PRE-DIMED trial involving 7447 patients who were put on a Mediterranean diet and additional intake of 1 litre of olive oil per week or one portion of 30 g of nuts per day. Both study groups showed a good level of patient compliance and a significant reduction in the number cardiovascular events compared with the control group that used a standard low-fat diet. However, the proportion of individual fatty acid groups in the diet of the study groups was not specified[37].

In their analysis of studies on the possibility of using MUFA in primary and secondary CVD prevention which were published in the years 2013–2015, Joris and Mensink concluded that the results of the most recent studies confirm the previously suggested beneficial effects of these acids, comparable with those of LA and α-linoleic acid. At the same time, they indicated the necessity of further properly prepared clinical trials with cardiovascular events as end points[38].

What is remarkable about the aforementioned literature on the replacement of SFA with other macronutrients is the ambiguity of results pertaining to replacement of SFA with PUFA. There are several possible causes of this. In some studies, n-6 fatty acid intake exceeded 10 %, which – as shown in experimental studies – may be associated with pro-inflammatory activity. The authors of the SDHS pointed out a potential mechanism of increasing cardiovascular risk by LA, which is thought to contribute to increased production of bioactive oxidised LA metabolites (e.g. 9- and 13-hydroperoxyoctadecadienoic acid as well as 9- and 13-hydroxyoctadecadienoic acid), which play a role in atherosclerotic plaque formation[27]. The fact that participants in certain studies smoked tobacco and drank alcohol (a common occurrence in the case of interventions taking place in the 1960s and 1970s) may also be of importance, since this may enhance oxidative stress and oxidation processes, thereby increasing the cardiovascular risk[39,40]. A factor of high importance may be the type of substitution used, especially whether TFA and SFA have been replaced with cis n-6 PUFA alone, a mixture of cis and trans n-6 PUFA (which may have been the case in studies conducted in the 1960s) or with a mixture of cis n-6 and n-3 PUFA.

A meta-analysis performed by Ramsden et al. demonstrated that mixtures of n-3/n-6 PUFA and a mixture of n-6 PUFA alone affect the risk of non-fatal myocardial infarction and death due to CHD in different ways. The authors claimed that substitution of a n-3/n-6 PUFA mixture for TFA and SFA causes a decreased CHD risk, while n-6 PUFA substitution demonstrates a tendency towards increased risk coronary artery disease[41]. However, due to a small number of studies included in this analysis, especially those concerning the use of a n-3/n-6 mixture, and inclusion of results from the SDHS and the MCE in evaluation of the efficacy of a mixture of n-6, these findings should be treated with caution. Some doubts have been raised concerning the clinical usefulness of the proportion between n-3 and n-6 fatty acids consumed. Some authors claim that this ratio serves no purpose and is confusing, and since it is believed that both PUFA types have beneficial effects, it should be omitted in modern recommendations[42]. However, Hammad et al. indicated that the results of studies in which SFA and TFA are replaced with increased intake of n-6 and n-3 PUFA should not be interpreted as demonstrating the effect of n-6 PUFA, since their outcome was affected both by the presence of n-3 fatty acids and the decreased proportion of TFA. They believe that preventive measures should be aimed at the elimination of TFA from the diet, reducing SFA and n-6 PUFA to less than 7 % and 10 % of energy, respectively, and achievement of a ratio of n-6 to n-3 fatty acids which is as close as possible to 1:1 with a sufficient amount of essential unsaturated fatty acids[43]. This seems important in the light of a study by Ninomiya et al., which demonstrated that a lower ratio of EPA to arachidonic acid in serum is linked to a higher risk of CVD, especially CHD, in people with a higher level of high-sensitivity C-reactive protein in the general population of Japan[44].

Controversies concerning the findings and methodology of the meta-analyses of studies on an effect of substitution of SFA with PUFA have been widely discussed in papers published in 2017: the American Heart Association Presidential Advisory and Hamley's meta-analysis[45,46]. The authors of the American Heart Association position statement claimed that studies whose methodology is questioned because of their short duration, small study groups and use of margarines potentially containing TFA should be excluded from analyses of an effect on CHD risk (e.g. MCE, SDHS). After taking these factors into account,

only four studies were included in the final meta-analysis; this was reflected in the conclusion, which confirmed that polyunsaturated fat from vegetable oils reduces risk of CVD a little more than monounsaturated fats in the substitution of saturated fats[45]. On the other hand, Hamley adopted as the main exclusion criterion the absence of a simultaneously decreasing intake of SFA and increasing intake of PUFA by at least 20 % in the intervention group compared with the control group. Additionally, the author categorised the studies into properly controlled and improperly controlled, i.e. those with too many dietary and/or non-dietary differences between groups to regard a test of substituting SFA by *n*-6 PUFA as valid. In effect, following application of such inclusion and exclusion criteria, only one study included in the American Heart Association meta-analysis was among the five studies included in the group of properly controlled ones in Hamley's meta-analysis. Due to debate over high TFA intake in the SDHS experimental group, this trial was also excluded in a sensitivity analysis of the adequately controlled trials. In consequence, completely different results were obtained, indicating that substituting SFA with PUFA does not reduce the risk of CHD, death due to CHD or total mortality[46].

Trans-fatty acids and their impact on CVD risk

Unsaturated TFA isomers in the diet originate from two sources: as natural ingredients of products coming from ruminants (beef, lamb and dairy products) and as industrial products of the process of vegetable oil hydrogenation, during which 30–50 % of double bonds change their configuration from *cis* to *trans*[47]. TFA from both sources contain the same isomers, but in different proportions. Elaidic acid isomers (C18 : 1D10*t* and D9*t*) are found in larger quantities in industrially produced fat, while vaccenic acid (C18 : 1D11*t*) is usually the main component of the TFA pool coming from ruminants[48]. In a systematic review for the WHO, Bouwer pointed out that replacement of the total amount of TFA (the sum of industrial TFA (iTFA) and ruminant TFA) with *cis*-MUFA, *cis*-PUFA and carbohydrates leads to increased HDL-C concentrations and decreased concentrations of TC and LDL-C, as well as to a decrease in the ratios TC:LDL-C and TC:HDL-C. At the same time, the strongest effects are observed when TFA are replaced with *cis*-PUFA. Only substitution of *cis*-MUFA and *cis*-PUFA demonstrated a significant decrease in TAG concentrations, which was not observed in the case of carbohydrates[49].

In their meta-analysis of twenty-eight cohort studies, Skeaff and Miller demonstrated a strong link between TFA intake and CHD incidence and mortality[50]. This was confirmed in a study by Mozzafarian *et al.*, which made it possible to determine the effect of TFA intake level on CVD: a 2 % increase in TFA intake is associated with a 23 % increase in the number of cardiovascular events[51].

According to an assessment by the US Centers for Disease Control and Prevention, elimination of total TFA intake in the USA would decrease the number of coronary events by 20 000 each year and the number of cardiac deaths by 7000[52].

The beneficial effect of TFA intake reduction on the risk of CVD may also be explained by studies on LDL-P (LDL particle number), a new risk factor with a high potential for use in prevention. People with higher LDL-P levels may have a two- to threefold higher risk of CVD, irrespective of LDL fraction concentrations[53]. A study by Garshick *et al.* demonstrated that a decrease in TFA intake of nearly 1 % over the course of a year resulted in significant decrease in LDL-P, irrespective of other factors and covariates. This suggests that a decrease in LDL-P may be one of the mechanisms by which a decrease in dietary TFA content lowers cardiovascular risk[54].

Certain studies seem to prove that the assessment of the role of TFA in the development of CVD should take account of their source of origin as well as specific fatty acids from the TFA pool. As early as in 2008, the TRANSFACT (Trans Fatty Acids Collaboration) study revealed that TFA coming from natural products and industrially hardened oils have different effects on CVD risk factors, such as LDL-C and HDL-C concentrations as well as apoA and apoB1. The low number of subjects in this study and the visible difference in results depending on participant sex did not, however, make it possible to draw conclusions for the entire population[55]. A systematic review and meta-analysis of observational studies performed by de Souza *et al.* demonstrated that, overall, the intake of TFA was associated with increased all-cause mortality, CHD mortality as well as with development of CHD. No relationship, however, was demonstrated with ischaemic stroke and type 2 diabetes. An analysis of the sources of TFA confirmed that intake of industrially produced isomers increases CHD mortality, but it failed to confirm such effects for TFA coming from ruminants. Interestingly, intake of *trans*-palmitoleic acid was inversely related to the incidence of type 2 diabetes (relative risk = 0·58, 95 % CI 0·46, 0·74)[15]. In the Cardiovascular Health Study covering 2742 adult patients aged over 65 years, concentrations of *t/t*-18 : 2 were most adversely related to all-cause mortality, mainly due to increased CVD risk. Concentrations of *t/c*-18 : 2 were also positively related to all-cause mortality and CHD, but only after accounting for the effects of other TFA[56].

The Ludwigshafen Risk and Cardiovascular Health Study demonstrated that overall TFA content in erythrocyte cell membranes in the studied population was associated with a lower risk of cardiovascular risk in this population[57]. However, the study population was composed of people qualified for coronary angiography in Germany, a country in which the overall intake of TFA, especially iTFA, is relatively low, and the majority of TFA consumed comprise those from dairy products[48]. This

study also led to a conclusion that high TFA concentrations in erythrocyte cell membranes are correlated with a favourable metabolic profile characterised by lower TAG concentrations, lower blood pressure and lower fasting glucose concentrations[57]. In contrast to these findings, NHANES (National Health and Nutrition Examination Survey) data showed plasma elaidic acid levels to be associated with higher risks of all-cause and CVD-related mortality[58].

Liska *et al.* noted that drawing any conclusions regarding the effect of TFA intake on cholesterol concentrations is very difficult. The authors noted that many studies fail to describe the methodology of iTFA production and hence may be misleading in their description of food products used, for example margarines. Another problematic task is determination of TFA intake, which is described by some authors in grams per day and by some as a percentage of total dietary energy or the proportion of total fat. It is also difficult to assess the isolated effect of increasing iTFA intake on lipid parameters, since in most studies this is associated with reduced intake of *cis*-PUFA and/or *cis*-MUFA. There is also an insufficient number of studies assessing the impact of low intake of iTFA, especially those coming from partially hydrogenated oils, on CHD risk[59]. In the majority of available studies, the level of iTFA intake <1% (which corresponds to its present average intake in the USA) is classified as the control group for study groups consuming 1–2% of energy as iTFA or more than 2% of energy as iTFA[59]. Therefore, further studies are necessary, especially as the literature provides greater proof of varied atherogenic effect of TFA exerted through various mechanisms, such as increasing the inflammatory condition or oxidative stress[60]. Moreover, a study conducted by Nakamoto *et al.* indicated that increased intake of TFA, reflected in an elevated level of elaidic acid in plasma, can increase instability of atherosclerotic plaque *in vivo*[61].

Summary

Conclusions arising from studies published in 2014–2017 concerning replacement of SFA and TFA in the diet as an element of CVD prevention require a high level of caution in interpretation. The observed inconsistencies, especially in clinical trials of SFA substitution and their meta-analyses, may stem from different methodologies of dietary parameter changes (supplementation, replacement of selected food products with other products, change of the entire nutrition model), varying duration of studies, as well as the time at which they were carried out. One should take account of the fact that the risk of CVD is affected not only by fatty acids, but also by a number of other dietary and non-dietary elements of lifestyle. Therefore, these might have also influenced the results of individual studies, especially when the controlled replacement pertained only to fat. This also points to the differences

in follow-up duration and timing of observation of the pre-specified end points. The results also seem to be affected by the population in which the dietary intervention was performed, as well as the baseline nutrition model, which – especially in the 1960s and 1970s – was different from now. It is extremely difficult to extrapolate such studies to contemporary recommendations. It seems that there is a need for properly randomised studies on large groups, with good control of dietary and non-dietary parameters, which account for not only the sum of SFA and TFA, but also their source: dairy products and meat for SFA, ruminant-derived and industrial products for TFA. Only such studies will allow for full evaluation of an effect of substituting SFA and TFA on cardiovascular risk.

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References

1. Mensink RP, Zock PL, Kester ADM *et al.* (2003) Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* **77**, 1146–1155.
2. Mensink RP (2016) *Effects of Saturated Fatty Acids on Serum Lipids and Lipoproteins: A Systematic Review and Regression Analysis.* Geneva: WHO.
3. Laine DC, Snodgrass CM, Dawson EA *et al.* (1982) Lightly hydrogenated soy oil versus other vegetable oils as a lipid-lowering dietary constituent. *Am J Clin Nutr* **35**, 683–690.
4. Mensink RP & Katan MB (1990) Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *N Engl J Med* **323**, 439–445.
5. Zock PL & Katan MB (1992) Hydrogenation alternatives: effects of trans fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J Lipid Res* **33**, 399–410.
6. Judd JT, Clevidence BA, Muesing RA *et al.* (1994) Dietary trans fatty acids: effects on plasma lipids and lipoproteins of healthy men and women. *Am J Clin Nutr* **59**, 861–868.
7. Ascherio A, Katan MB, Zock PL *et al.* (1999) Trans fatty acids and coronary heart disease. *N Engl J Med* **340**, 1994–1998.
8. Mozaffarian D & Clarke R (2009) Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils. *Eur J Clin Nutr* **63**, Suppl. 2, S22–S33.
9. Lichtenstein AH (2014) Dietary trans fatty acids and cardiovascular disease risk: past and present. *Curr Atheroscler Rep* **16**, 433.

10. EFSA Panel on Dietetic Products Nutrition, and Allergies (2010) Scientific opinion on dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol. *EFSA J* **8**, 1461.

11. US Department of Agriculture & US Department of Health and Human Services (2010) *Dietary Guidelines for Americans*, 7th ed. Washington, DC: US Government Printing Office.

12. Eckel RH, Jakicic JM, Ard JD *et al.* (2014) 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* **63**, 2960–2984.

13. Wright JD, Wnag CY, Kennedy-Stephenson J *et al.* (2003) Dietary intakes of ten key nutrients for public health: 1999–2000. *Adv Data* issue 334, 1–4.

14. Bates B, Lennox A, Prentice A *et al.* (2014) National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009–2011/2012). http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310995/NDNS_Y1_to_4_UK_report.pdf (accessed March 2018).

15. de Souza RJ, Mentem A, Maroleanu A *et al.* (2015) Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ* **351**, h3978.

16. Praagman J, Beulens JW, Alssema M *et al.* (2016) The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and Nutrition–Netherlands cohort. *Am J Clin Nutr* **103**, 356–365.

17. de Oliveira Otto MC, Mozaffarian D, Kromhout D *et al.* (2012) Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr* **96**, 397–404.

18. Alexander DD, Bylsma LC, Vargas AJ *et al.* (2016) Dairy consumption and CVD: a systematic review and meta-analysis. *Br J Nutr* **115**, 737–750.

19. Qin LQ, Xu JY, Han SF *et al.* (2015) Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies. *Asia Pac J Clin Nutr* **24**, 90–100.

20. Brassard D, Tessier-Grenier M, Allaire J *et al.* (2017) Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial. *Am J Clin Nutr* **105**, 800–809.

21. Gijsbers L, Ding EL, Malik VS *et al.* (2016) Consumption of dairy foods and diabetes incidence: a dose–response meta-analysis of observational studies. *Am J Clin Nutr* **103**, 1111–1124.

22. Abargouei AS, Janghorbani M, Salehi-Marzijarani M *et al.* (2012) Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. *Int J Obes (Lond)* **36**, 1485–1493.

23. Wang DD, Li Y, Chiuve SE, Stampfer MJ *et al.* (2016) Association of specific dietary fats with total and cause-specific mortality. *JAMA Intern Med* **176**, 1134–1145.

24. Zong G, Li Y, Wanders AJ *et al.* (2016) Intake of individual saturated fatty acids and risk of coronary heart disease in US men and women: two prospective longitudinal cohort studies. *BMJ* **355**, i5796.

25. Dehghan M, Mente A, Zhang X *et al.* (2017) Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet* **390**, 2050–2062.

26. Ramsden C, Zamora D, Majchrzak-Hong S *et al.* (2016) Re-evaluation of the traditional diet–heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968–73). *BMJ* **353**, i1246.

27. Ramsden CE, Zamora D, Leelarthaepin B *et al.* (2013) Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *BMJ* **346**, e8707.

28. Michas G, Micha R & Zampelas A (2014) Dietary fats and cardiovascular disease: putting together the pieces of a complicated puzzle. *Atherosclerosis* **234**, 320–328.

29. Schwingshackl L & Hoffmann G (2014) Dietary fatty acids in the secondary prevention of coronary heart disease: a systematic review, meta-analysis and meta-regression. *BMJ Open* **4**, e004487.

30. Harcombe Z, Baker JS, DiNicolantonio JJ *et al.* (2016) Evidence from randomised controlled trials does not support current dietary fat guidelines: a systematic review and meta-analysis. *Open Heart* **3**, e000409.

31. Al-Khudairy L, Hartley L, Clar C *et al.* (2015) Omega 6 fatty acids for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* issue 11, CD011094.

32. Farvid MS, Ding M, Pan A *et al.* (2014) Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. *Circulation* **130**, 1568–1578.

33. Hooper L, Martin N, Abdelhamid A *et al.* (2015) Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev* issue 6, CD011737.

34. Jakobsen MU, O'Reilly EJ, Heitmann BL *et al.* (2009) Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr* **89**, 1425–1432.

35. Schwingshackl L & Hoffmann G (2012) Monounsaturated fatty acids and risk of cardiovascular disease: synopsis of the evidence available from systematic reviews and meta-analyses. *Nutrients* **4**, 1989–2007.

36. Li Y, Hruby A, Bernstein AM *et al.* (2015) Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. *J Am Coll Cardiol* **66**, 1538–1548.

37. Estruch R, Ros E, Salas-Salvadó J *et al.* (2013) Primary prevention of cardiovascular disease with a Mediterranean diet. PREDIMED Study Investigators. *N Engl J Med* **368**, 1279–1290.

38. Joris P & Mensink R (2016) Role of *cis*-monounsaturated fatty acids in the prevention of coronary heart disease. *Curr Atheroscler Rep* **18**, 38.

39. Waddington EI, Croft KD, Sienuarine K *et al.* (2003) Fatty acid oxidation products in human atherosclerotic plaque: an analysis of clinical and histopathological correlates. *Atherosclerosis* **167**, 111–120.

40. Yokode M, Ueyama K, Arai NH *et al.* (1996) Modification of high- and low-density lipoproteins by cigarette smoke oxidants. *Ann N Y Acad Sci* **786**, 245–251.

41. Ramsden CE, Hibbeln JR, Majchrzak SF *et al.* (2010) *n*-6 Fatty acid-specific and mixed polyunsaturate dietary interventions have different effects on CHD risk: a meta-analysis of randomised controlled trials. *Br J Nutr* **104**, 1586–1600.

42. Willett WC (2012) Dietary fats and coronary heart disease. *J Intern Med* **272**, 13–24.

43. Hammad S, Pu S & Jones PJ (2016) Current evidence supporting the link between dietary fatty acids and cardiovascular disease. *Lipids* **51**, 507–517.

44. Ninomiya T, Nagata M, Hata J Y *et al.* (2013) Association between ratio of serum eicosapentaenoic acid to arachidonic acid and risk of cardiovascular disease: the Hisayama Study. *Atherosclerosis* **231**, 261–267.

45. Sacks FM, Lichtenstein AH, Wu JHY *et al.* (2017) Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation* **136**, e1–e23.

46. Hamley S (2017) The effect of replacing saturated fat with mostly n-6 polyunsaturated fat on coronary heart disease: a meta-analysis of randomised controlled trials. Nutr J 16, 30.

47. Baum SJ, Kris-Etherton PM, Willett WC et al. (2012) Fatty acids in cardiovascular health and disease: a comprehensive update. J Clin Lipidol 6, 216–234.

48. Hulshof KF, van Erp-Baart MA, Anttolainen M et al. (1999) Intake of fatty acids in western Europe with emphasis on trans fatty acids: the TRANSFAIR Study. Eur J Clin Nutr 53, 143–157.

49. Brouwer IA (2016) Effect of Trans-Fatty Acid intake on Blood Lipids and Lipoproteins: A Systematic Review and Meta-regression Analysis. Geneva: WHO.

50. Skeaff CM & Miller J (2009) Dietary fat and coronary heart disease: summary of evidence from prospective cohort and randomised controlled trials. Ann Nutr Metab 55, 173–201.

51. Mozaffarian D, Katan MB, Ascherio A et al. (2006) Trans fatty acids and cardiovascular disease. N Engl J Med 354, 1601–1613.

52. Brownell KD & Pomeranz JL (2014) The trans-fat ban – food regulation and long-term health. N Engl J Med 370, 1773–1775.

53. Ip S, Lichtenstein AH, Chung M et al. (2009) Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. Ann Intern Med 150, 474–484.

54. Garshick M, Mochari-Greenberger H & Mosca L (2014) Reduction in dietary trans fat intake is associated with decreased LDL particle number in a primary prevention population. Nutr Metab Cardiovasc Dis 24, 100–106.

55. Chardigny JM, Destaillats F, Malpuech-Brugère C et al. (2008) Do trans fatty acids from industrially produced sources and from natural sources have the same effect on cardiovascular disease risk factors in healthy subjects? Results of the Trans Fatty Acids Collaboration (TRANSFACT) study. Am J Clin Nutr 87, 558–566.

56. Wang Q, Imamura F, Lemaitre R et al. (2014) Plasma phospholipid trans-fatty acids levels, cardiovascular diseases, and total mortality: the Cardiovascular Health Study. J Am Heart Assoc 3, e000914.

57. Kleber ME, Delgado GE, Lorkowski S et al. (2016) Trans-fatty acids and mortality in patients referred for coronary angiography: the Ludwigshafen Risk and Cardiovascular Health Study. Eur Heart J 37, 1072–1078.

58. Li H, Zhang Q, Song J et al. (2017) Plasma trans-fatty acids levels and mortality: a cohort study based on 1999–2000 National Health and Nutrition Examination Survey (NHANES). Lipids Health Dis 16, 176.

59. Liska DJ, Cook CM & Wang DD (2016) Trans fatty acids and cholesterol levels: an evidence map of the available science. Food Chem Toxicol 98, 269–281.

60. Monguchi T, Hara T & Hasokawa M (2017) Excessive intake of trans fatty acid accelerates atherosclerosis through promoting inflammation and oxidative stress in a mouse model of hyperlipidemia. J Cardiol 70, 121–127.

61. Nagasawa Y, Shinke T & Toh R (2017) The impact of serum trans fatty acids concentration on plaque vulnerability in patients with coronary artery disease: assessment via optical coherence tomography. Atherosclerosis 265, 312–317.