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Review Article

Annals of Nutrition & Metabolism

Ann Nutr Metab 2016;68:249–257
DOI: 10.1159/000446865

Received: May 12, 2016
Accepted: May 14, 2016
Published online: June 3, 2016

Dietary Fatty Acids: Is it Time to Change the Recommendations?

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Key Words
Fatty acids · Dietary recommendations · Saturated fatty acids · Dietary fat and CHD risk

Abstract
Limiting the saturated fatty acid (SAFA) consumption forms the basis of dietary fat recommendations for heart health, despite several meta-analyses demonstrating no link between dietary SAFA and the risk of cardiovascular disease (CVD). Three experts on dietary fat and health discussed the evidence of reducing SAFA intake at a symposium of the Federation of European Nutrition Societies in Berlin, Germany, October 23, 2015. Ronald P. Mensink, Maastricht University, the Netherlands, discussed the evidence linking dietary fatty acids and CVD risk. He emphasized the importance of the replacement nutrient(s) when SAFA intake is reduced. Julie Lovegrove, University of Reading, UK, addressed the question of whether higher intakes of unsaturated fatty acids are beneficial. She discussed the replacement of SAFA by polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA), noting the reduction in CVD risk with PUFA replacement and in CVD risk markers with MUFA replacement of SAFA. Ursula Schwab, University of Eastern Finland, Kuopio, Finland, discussed the importance of dietary patterns in achieving reduced risk of CVD, observing that several dietary patterns following the principles of a health-promoting diet and adapted to local customs, food preferences and seasonality are effective in reducing the risk of CVD, type 2 diabetes and other chronic diseases. This paper summarizes the symposium presentations.

Restricting the consumption of saturated fatty acids (SAFA) to reduce the risk of cardiovascular disease (CVD) forms the basis of recent dietary fat recommendations [1, 2], in spite of the disagreement about the link between dietary SAFA and CVD [3–6]. Several systematic reviews, meta-analyses [7, 8] and prospective cohort studies [9] have questioned the link between SAFA and CVD risk. Recent systematic reviews, however, highlight the importance of partial replacement of SAFA by polyunsaturated fatty acids (PUFA) in decreasing the risk of CVD [1, 10, 11]. At the Federation of European Nutrition Societies meeting in Berlin, Germany, October 20–23, 2015 three experts on dietary fat and health discussed several aspects of current recommendations for fatty acid consumption to reduce the CVD risk. The symposium was hosted by the International Expert Movement to Improve Dietary Fat Quality [12], an initiative of the International Union

Report of a Meeting of the Federation of European Nutrition Societies FENS, Berlin, October 23, 2015.

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of Nutritional Sciences, funded by an unrestricted education grant from Unilever NV. This paper summarizes the presentations of the symposium.

Should Saturated Fat Intakes Be Reduced?

Media attention to recent studies questioning the link between the intake of SAFA and the risk of CVD has increased the confusion among consumers about consuming SAFA-rich foods [13, 14]. Addressing the question of whether SAFA intakes should be reduced, Ronald P. Mensink, Maastricht University, the Netherlands, explained that the formulation of dietary recommendations mainly relies on risk biomarkers, which are causally related to CVD. Although studies examining relationships between SAFA intake and risk of coronary heart disease (CHD) are conflicting, SAFA increases low-density lipoprotein-cholesterol (LDL-C) levels compared with *cis*-unsaturated fatty acids. Increased LDL-C is causally related to an increased CHD risk. Hence, dietary guidelines recommend limiting SAFA intake. The 3-way relationship among SAFA, LDL-C and CHD is the cause of consumer confusion.

Questions about the link between dietary SAFA and CVD arose from the work of Siri-Tarino et al. [9] whose meta-analysis of 21 prospective cohort studies concluded that the evidence did not support an association between SAFA consumption per se and an increased risk of CVD or CHD. In another systematic review and meta-analysis of 12 prospective cohort studies, de Souza et al. [7] found neither significant association between SAFA consumption and all-cause CVD and CHD mortality nor risk of ischemic stroke or type 2 diabetes. Mensink pointed out that the key question is the effect of nutrients that replace SAFA. Thus, Jakobsen et al. [15] reported that replacement of 5% energy (En) from SAFA with PUFA was associated with a significantly reduced risk of coronary events and death (hazard ratio, HR 0.87, 95% CI 0.77–0.97; and HR 0.74, 95% CI 0.61–0.89, respectively), whereas replacement with carbohydrates was associated with a modestly higher risk of coronary events (HR 1.07, 95% CI 1.01–1.14). Evidence pooled from 2 large prospective cohort studies suggested that isocaloric replacement of 5% SAFA with PUFA or monounsaturated fatty acids (MUFA) was associated with a significant 25 or 15% reduction in CHD risk, respectively, between the highest and lowest quintiles of consumption [16]. Others have also reported that PUFA intake is associated with a lower risk of CHD when it replaces SAFA, *trans* fats or carbohydrates [17, 18].

The main link between dietary fatty acids and CHD risk is observed from their effects on plasma or serum LDL-C levels. A fatty acid is considered hypercholesterolemic when an isoenergetic exchange of carbohydrates in the diet for the fatty acid causes an increase in the serum total cholesterol (TC) concentrations. Carbohydrates have arbitrarily been called 'neutral'. Replacement of *trans* fatty acids or SAFA with PUFA leads to a significant decrease in LDL-C concentrations, with the substitution of *trans*-MUFA by PUFA being the most favorable.

Subsequently, Mensink questioned the best lipid biomarker or combination of lipid biomarkers to predict the risk of CHD: LDL-C, apolipoprotein B, apolipoprotein CIII, small dense LDL, high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1, triacylglycerols, TC:HDL-C, postprandial metabolism, or Lp(a)? When fat is replaced by carbohydrate, one result is an increase in the prevalence of small dense LDLs, which are associated with higher CVD risk [19, 20]. Increasing carbohydrate at the expense of SAFA may not improve the serum lipoprotein profile as HDL-C may be reduced and triacylglycerol increased [6]. Further, the carbohydrate type may affect the lipid response, with refined starches and sugars being associated with a comparable risk of CHD as SAFA, but those from whole grains associated with a significantly lower CHD risk [16, 21].

Consumption of SAFA may affect other atherogenic pathways unrelated to lipoproteins. Examples include systemic inflammation, blood pressure, endothelial function, hemostatic function, insulin resistance, postprandial metabolism and weight gain. However, the effects of dietary SAFA on these parameters yielded mixed results.

Various SAFA behave differently, metabolically speaking, which raises the question of whether to discriminate among them for CVD risk. Although food fats contain mixtures of SAFA, the predominant ones in Western diets are palmitic (C16:0) and stearic (C18:0) acids. Dairy products are relatively rich in short- and medium-chain SAFA (C4:0-C10:0), while coconut and palm kernel oil each have relatively large amounts of lauric (C12:0) and myristic (C14:0) acids. The potency of individual longer-chain SAFA (≥C12) in raising LDL-C levels compared to carbohydrate diminishes from lauric acid with increasing chain length up to stearic acid, which generally has a neutral effect on lipid and lipoprotein levels [6].

Interestingly, the effects of various SAFA on markers of inflammation may differ from the pattern observed on plasma lipids. For example, when carbohydrate was replaced by 8% stearic acid in controlled diets consumed by healthy men, plasma fibrinogen and interleukin-6 levels

were significantly increased, while the C-reactive protein did not increase significantly [22]. Although others have reported contrasting results with dietary stearic acid compared with unsaturated FA and *trans* MUFA [23], these studies emphasize that knowledge on the effects of individual SAFA on CHD risk markers other than serum lipids is limited.

The contribution of SAFA-related food matrix to the risk of CVD and its associated biomarkers is sometimes overlooked. A recent systematic review and meta-analysis of the effect of cheese consumption on blood lipids, for example, concluded that the consumption of hard cheese lowers LDL-C and HDL-C when compared to butter, but both had comparable effects on fasting triacylglycerol concentrations [24]. Others have also reported differences in CVD risk or plasma lipid levels depending on the food source of SAFA [25–27].

In brief, Mensink noted that prospective cohort studies and randomized controlled trials can be complementary or contradictory [28], as illustrated by studies on antioxidants [29], folic acid [30] and possibly SAFA [31]. He emphasized the importance of discussing the replacement nutrient(s) when SAFA intake is reduced, and observed that a food pattern or food is more than a single nutrient. Although individual SAFA are metabolized differently, whether they affect the health differently is uncertain. Resolving current issues will require studies with integrated end points or, preferably, hard end points.

Unsaturated Fats: Are Higher Intakes Beneficial?

Recent reports on the global risks for disease mortality and disability-adjusted life years (DALYs), that is, the years lost due to premature mortality and disability, identified diet as the predominant contributor to mortality and disability from predominantly CVD, but also diabetes and neoplasms [32]. Expressed in numbers, modifiable dietary risks accounted for 11.3 million deaths and 241.1 million DALYs worldwide in 2013. These data suggest opportunities for effective dietary prevention policies. The question of whether higher intake of unsaturated fats is beneficial to these dietary risks was addressed by Julie Lovegrove, University of Reading, UK.

There is consistent evidence that partial replacement of dietary SAFA with PUFA significantly reduces the risk of CHD events and mortality [10, 11, 16, 18], although inconsistent or contradictory data have been reported in some secondary prevention trials [33, 34]. In contrast, too few data exist to ascertain the effect of MUFA substitution on CVD mortality [11, 35]. Furthermore, dietary MUFA are derived from both plant (such as olive and rapeseed oils, nuts and seeds) and animal sources (including meat and poultry). The food source may have an impact on the association between MUFA intake and disease incidence or mortality. A recent meta-analysis of 32 cohort studies comparing the top vs. the bottom third intakes of total MUFA reported significant risk reductions ranging from 9 to 17% for all-cause and cardiovascular mortality, cardiovascular events and stroke [36]. However, in sub-group analysis of MUFA of mixed origin, only higher intakes of olive oil were associated with a reduced risk of all-cause mortality, cardiovascular events and stroke.

There are 2 distinct families of PUFA, namely, omega-6 PUFA found in vegetables and vegetable oils and omega-3 PUFA, which include alpha-linolenic acid (ALA) found only in plants and eicosapentaenoic and docosahexaenoic acids (EPA and DHA), respectively, found mainly in fish and shellfish. Evidence suggests that higher dietary ALA and EPA/DHA consumption is associated with significantly reduced risk of CVD and CHD mortalities [37–39], although inconsistent and contradictory data have been reported [34, 40]. The proposed mechanisms of action of EPA/DHA are varied and include anti-arrhythmic, anti-thrombotic and triacylglycerol-lowering effects, which may be observed within weeks [41–43], while changes in heart rate and blood pressure may take months [44, 45] to be visible.

In a study on the relationship between circulating levels of linoleic acid (LA), the major n-6 PUFA in food and plasma, and risk of total and cause-specific mortality, LA was associated with a 13% lower risk of total mortality and a 22% lower risk of CVD mortality, comparing the top and bottom quintiles [46]. The investigators also reported a 49% lower risk of non-arrhythmic CHD mortality across quintiles of LA, but no significant association with arrhythmic CHD mortality. With stratification of the participants on both LA and n-3 PUFA, those with the highest circulating levels of both types of fatty acids had a 54% lower risk of CVD death compared to those with the lowest levels. These data support the benefits of PUFA and CVD risk reduction.

There is scientific consensus that high intakes of industrially produced *trans* unsaturated fatty acids, mainly *trans*-elaidic acid (18:1*t*9), are detrimental to heart health [7, 47]. It is less clear whether the *trans* fatty acids produced in ruminants via the bacterial metabolism of unsaturated fatty acids, as found in dairy products and meats, are also harmful. The main *trans* fatty acid found

in ruminant fats is vaccenic acid (18:1*t*11), although lesser amounts of *trans* palmitoleic (C16:1*t*9) are also present. The latter is increasingly recognized as a biomarker of dairy intake, as humans are only able to endogenously synthesize this from vaccenic acid, which originates in dairy fats [48]. Systematic reviews and studies have reported that ruminant *trans* fatty acids are not associated with CHD [7, 49] or CVD risk markers [50], but other published reports suggested that both ruminant and industrial *trans* produced from partially hydrogenated oils are associated with an increased CVD risk [51–53].

Recent investigations on *trans*-palmitoleic acid reported relations between circulating levels and higher LDL-C, but significantly lower triacylglycerols, incident diabetes and atherogenic dyslipidemia [54, 55]. Of interest are findings from a German cohort of patients scheduled for coronary angiography in which total *trans* and *trans*-palmitoleic acids in erythrocyte membranes were inversely associated with the risk of cardiovascular mortality and sudden cardiac death [56]. However, it is of particular interest that the concentrations of *trans* fatty acids in this cohort were low compared with values in US populations for the same time period (0.96 ± 0.3 vs. 2.68 ± 0.8%). Further clarity is required to establish the specific impact of ruminant *trans* on disease risk.

CVD risk factors include both modifiable and nonmodifiable components, with diet and lifestyle contributing to modifiable factors, such as LDL-C, blood pressure, elevated triacylglycerols, vascular function, inflammation, obesity and diabetes [57]. Diet modification focused on improving blood lipids by the partial replacement of SAFA intakes with unsaturated fatty acids. An early review of metabolic ward studies demonstrated that isocaloric replacement of 5% of calories from SAFA with PUFA or MUFA reduced the total blood cholesterol by 0.39 and 0.24 mmol/l, respectively, with the main reduction occurring in LDL-C [58]. There is consistent evidence from randomized controlled trials that replacement of SAFA with unsaturated fatty acid reduces lipid risk biomarkers [10].

Jebb et al. [59] reported that replacement of SAFA with MUFA or carbohydrate resulted in a significantly lower TC and LDL-C, but only MUFA replacement was associated with a significantly lower TC:HDL-C ratio, a clinically recognized biomarker of CVD [59, 60]. Replacing 9.5%En from SAFA with MUFA or n-6 PUFA resulted in a significantly lower TC and LDL-C and TC:HDL-C ratio after 4 months [61]. Several studies concluded that partial replacement of dietary SAFA with PUFA results in the greatest reduction in the risk of CVD, events and risk factors [11, 16, 62]. In their review of substituting increasing levels of %En from carbohydrates with different fatty acids, Micha and Mozaffarian [62] reported that MUFA and PUFA reduced the ratio of TC:HDL-C to the greatest extent, *trans* fatty acids increased the ratio significantly, but SAFA had no significant effect.

Lovegrove discussed factors other than blood lipids that contribute to the risk of CVD mortality, particularly high blood pressure. In a parallel-group study of diets rich in SAFA, MUFA or PUFA, consumed for 16 weeks by men and women with moderate CVD risk, consumption of MUFA-rich diet attenuated a significant increase in night systolic blood pressure (SBP) observed with SAFA [61]. In a meta-analysis of 12 randomized controlled trials on diets high (>12%En) or low (≤12%En) in MUFA and risk factors for obesity and CVD, Schwingshackl et al. [63] reported significant reductions in systolic and diastolic blood pressures with diets containing >12%En from MUFA and significantly lower fat mass.

Arterial stiffness, an independent predictor of CVD, is affected by dietary fatty acid consumption [64]. In a study of men aged 45–59 years, who were followed for a mean of 17.8 years, higher consumption of PUFA at baseline was associated with significantly lower systolic and diastolic blood pressures and pulse wave velocity, a measure of arterial stiffness, compared with men having a higher intake of SAFA [65]. Additional confirmation is, however, required.

Dietary fat may also affect insulin sensitivity in healthy adults. Vessby et al. [66] reported that with diets having >37%En from fat, the quality of fat did not affect insulin sensitivity; however, in diets with <37%En from fat, the substitution of MUFA for SAFA significantly improved insulin sensitivity in healthy volunteers. However, in the RISCK study, volunteers with symptoms of metabolic syndrome who consumed diets in which SAFA were replaced with MUFA or carbohydrates with high or low glycemic index showed no improvement in insulin sensitivity with any of the replacement diets [59]. A similar lack of effect of SAFA substitution with MUFA or carbohydrate on insulin sensitivity was observed in LIPGENE, another large randomized controlled trial performed in a pan-European population with metabolic syndrome [67]. While others also found no evidence for the effect of dietary SAFA on insulin resistance or type 2 diabetes [68], a recent review of MUFA vs. SAFA on insulin sensitivity concluded that the strength of the evidence favoring MUFA over SAFA was probable because of the small number of participants, although neither the RISCK nor LIPGENE data were included in this analysis [10].

Liver and visceral fat are contributing factors to cardiometabolic risk and insulin resistance that can be modified through diet. Excess energy intake leads to fat accumulation in liver and pancreas, which results in insulin resistance, beta-cell dysfunction, hyperglycemia, dyslipidemia and vascular dysfunction [69]. Compared with the consumption of PUFA, high-SAFA intakes, mainly from palm oil, increased the accumulation of liver fat and visceral adipose tissue in young, normal-weight, overfed adults, while high PUFA intakes resulted in a nearly 3-fold increase in lean tissue compared with SAFA [70]. Similar findings for liver fat were reported in abdominally obese participants who consumed either SAFA-rich (mainly butter) or n-6 PUFA-rich diets for 10 weeks [71]. In addition, those who consumed the n-6 PUFA-rich diet showed a modest improvement in serum lipids and insulin levels without signs of inflammation or oxidative stress.

Lovegrove concluded that the replacement of SAFA by PUFA is associated with a reduction in CVD (risk and mortality); replacement by PUFA or MUFA is associated with reduced lipid markers of cardiovascular risk; replacement by MUFA is associated with a reduction in other risk markers, such as SBP; and minimization of *trans* fatty acid consumption benefits cardiovascular health. For dietary policy, it is important to use the totality of evidence and multiple validated risk factors for mortality, and to translate nutrient intakes to foods and diets.

Translating Dietary Recommendations to Food-Based Guidelines

Recent dietary guidelines have shifted their focus from single nutrients to foods and dietary patterns, partly to make recommendations more relevant to consumers, and partly from increased awareness of nutrient and food matrix interactions. Overall, healthy dietary patterns have been associated with a lower risk of most chronic diseases, although different approaches have been used to evaluate various food patterns [72]. Discussing food-based dietary guidelines, Ursula Schwab, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland, explained that nutrient-based guidelines have been difficult to interpret by various users – the general population, food services, industry – and that people eat foods, not nutrients in isolation. It is also thought that it will be easier for people to adhere to a healthy food pattern rather than nutrient-based recommendations as indicated by recent studies [73].

Food patterns have been studied in whole diet trials, such as those involving the Mediterranean [74, 75], Dietary Approaches to Stop Hypertension (DASH) [76], and healthy Nordic diets [77], and epidemiological studies [72] and systematic reviews [74, 75]. Whole diet trials have yielded similar and consistent conclusions on weight loss, reduction in CVD risk factors and improved longevity [78]. Epidemiological studies have shown that dietary patterns rich in vegetables, fruits, nuts, whole grain cereals, fish, low-fat dairy products and vegetable oils, but low in refined cereals and sugar-rich products, red and processed meats are associated with a lower risk of most chronic diseases [57, 79]. Systematic reviews have also found consistent benefits for similar diet patterns and lower risks of incident or fatal CHD, breast cancer, all-cause mortality, CVD, cancer and neurodegenerative diseases [31, 74, 80]. Several studies have reported inverse association between various healthful dietary patterns or scores and risk of type 2 diabetes [81–83].

The DASH diet, described in 1997 [84], was the first to combine several dietary modifications – increased fruits and vegetables, fat-free and low-fat dairy products, whole grain foods, poultry, fish, nuts and unsaturated fat – with reductions in dietary saturated fat, red meat, sweets, sugar-sweetened beverages and salt. This diet resulted in significant reductions in systolic and diastolic blood pressures in hypertensive and normotensive participants over 8 weeks compared with those consuming a controlled diet or a diet rich in fruits and vegetables only.

In a review of 20 randomized controlled trials, Shirani et al. [85] reported that a 16-week DASH diet significantly reduced the fasting insulin concentration in patients with metabolic syndrome or dyslipidemia. The diet did not affect fasting glucose concentrations.

Most studies of the Mediterranean diet in the context of type 2 diabetes and CVD have shown favorable effects on glycemic control and CVD risks, although there is some controversy about obesity [86, 87]. A recent 4-year prospective cohort study examined the relationship between the Mediterranean diet and mortality in individuals with type 2 diabetes. The traditional Mediterranean diet was associated with a reduced risk of total and CVD mortality, independent of disease severity [88]. Principal factor analysis suggested that the main contributors to the effect of diet were moderate alcohol, high intake of cereals, fruits and nuts and lower consumption of dairy and meat products. In an intervention study of the primary prevention of CVD in 418 high-risk individuals (PREDIMED), 2 variations of the Mediterranean diet,

supplementation with either virgin olive oil or nuts, were compared with a controlled diet of about similar fat content (41%En) [89]. After 4 years, the incidence of type 2 diabetes was significantly lower in the 2 Mediterranean diet groups, 10.1 and 11.0%, respectively compared with 17.9% in the control group (40%En from fat). When the 2 diet groups were pooled, the risk of type 2 diabetes was reduced by 52% compared with the control group. These changes occurred with no change in body weight or physical activity. In the full cohort of 7,447 participants, the HRs for incident type 2 diabetes were 0.60 (95% CI 0.43–0.85) and 0.82 (95% CI 0.61–1.10) for olive oil and nut-supplemented diets, respectively [90]. The HRs for CVD events, including myocardial infarction, stroke or CVD death, were 0.70 (95% CI 0.53–0.91) and 0.70 (95% CI 0.53–0.94) for the 2 diet groups compared with the control group. Several classical and emerging risk factors for CVD were also favorably affected.

Other healthy diet patterns modeled on the Mediterranean diet, such as the healthy Nordic diet [91], have been developed to include local customs, food preferences and seasonality. Compared with the Mediterranean diet, the healthy Nordic diet includes rapeseed (canola) oil in place of olive oil; seasonal fruits, berries, root vegetables, pulses and nuts; vegetables with rapeseed oil salad dressings; consumption of fatty and other fish, game, whole grains and low-fat/non-fat milk products; and avoidance of butter, fatty dairy products, salted foods and red meat. In a randomized, controlled trial of 88 hypercholesterolemic patients, those consuming the healthy Nordic diet for 18–24 weeks experienced significant reductions in plasma TC, LDL-C, HDL-C, LDL-C:HDL-C ratio and apolipoprotein B compared with those on the control diet [92]. In a different study, the healthy Nordic diet was associated with a significant reduction in obesity-related markers of inflammation, for example, hs-C-reactive protein [93]. The healthy Nordic diet was also associated with the down-regulation of genes involved in subcutaneous adipose tissue inflammation in obese individuals with the metabolic syndrome, independent of body weight change [94].

The principles of the healthy Nordic diet were incorporated into a successful lifestyle intervention program to prevent type 2 diabetes in participants with impaired glucose tolerance [95]. Reduced consumption of total fat and SAFA with increased intake of dietary fiber and the addition of more than 4 h/week of physical activity resulted in a significant reduction in the risk of developing type 2 diabetes in a median follow-up of 9 years (HR 0.61, 95% CI 0.48–0.79) compared to the control group [95]. Six key Nordic foods formed the basis of the healthy Nordic food index, which was associated with an 18% lower total mortality between the highest and lowest diet scores over 21 years in Swedish women [96]. However, the diet was not associated with CVD risk in the same cohort [97]. In a Danish cohort, greater adherence to the healthy Nordic index was associated with a 25% lower risk of type 2 diabetes over 15 years in women and a 38% lower risk in men [98].

Schwab concluded that the beneficial effects of health-promoting diets have been shown to reduce the risk of CVD, type 2 diabetes and other chronic diseases in several studies using different methods [57, 72, 99]. Taking into account the local food culture also improves dietary adherence.

In summary, symposium participants agreed that dietary guidelines should continue to recommend limiting dietary SAFA consumption, but at the same time emphasize the importance of replacing SAFA with PUFA to reduce CVD risk. Replacement of *trans*-fatty acids with PUFA has the most favorable effect on reducing LDL-C and therefore the CVD risk. Partial replacement of SAFA with MUFA may reduce some risk markers for CVD, but data are inconclusive about the effect of MUFA on the risk of CVD mortality. Participants agreed that dietary recommendations should shift their focus away from single nutrients toward more healthy foods, such as whole grains, and dietary patterns, such as the Mediterranean, DASH and healthy Nordic diets, which promote health and reduce the risk of CVD, type 2 diabetes and other chronic diseases.

In the general discussion, one audience member asked the presenters whether reducing the dairy fat intake was important if an individual was not obese. Lovegrove responded that it is recommended that dietary SAFA should be reduced to <10%En irrespective of body weight. However, despite the SAFA content, milk and dairy food consumption has been associated with lower cardiometabolic risk, possibly due to other dairy constituents, such as calcium and bioactive peptides [100, 101]. Another participant wondered whether an energy-reduced diet for overweight diabetic individuals should have more or less fat or carbohydrate. Schwab replied that the aim with such patients was not just weight loss, but also the overall improvement of the diet. The evidence suggests that diabetic patients can lose weight and improve their glycemic control with a variety of macronutrient interventions that include reduced energy intake, regular physical activity, education and support [102].

Acknowledgments

Selected material from this report was originally presented at the Federation of European Nutrition Societies meeting in Berlin, Germany, October 23, 2015. Unilever, the Netherlands, provided financial assistance for this publication and travel support for J.A.N., R.P.M., J.A.L. and U.S.

Disclosure Statement

The authors declare no conflicts of interest.

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