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Dietary fat composition: replacement of saturated fatty acids with PUFA as a public health strategy, with an emphasis on α-linolenic acid

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SFA intakes have decreased in recent years, both in Ireland and across other European countries; however a large proportion of the population are still not meeting the SFA recommendation of <10 % of total energy (TE). High SFA intakes have been associated with increased CVD and type-2 diabetes (T2D) risk, due to alterations in cholesterol homoeostasis and adipose tissue inflammation. PUFA, in particular EPA and DHA, have been associated with health benefits, including anti-inflammatory effects. It is well established that dietary fat composition plays an important role in biological processes. A recent review of evidence suggests that replacement of SFA with PUFA has potential to reduce risk of CVD and T2D. The public health and molecular impact of EPA and DHA have been well-characterised, while less is known of effects of α-linolenic acid (ALA). The current dietary guideline for ALA is 0·5 % TE; however evidence from supplementation trials suggests that benefit is observed at levels greater than 2 g/d (0·6–1 % TE). This review highlights the gap in the evidence base relating to effects of the replacement of SFA with ALA, identifying the need for randomised controlled trials to determine the optimal dose of ALA substitution to define the efficacy of dietary fat modification with ALA.

Dietary fat intakes: SFA: PUFA: α-Linolenic acid: Public health strategy

The UK Scientific Advisory Committee on Nutrition (SACN) recently released their draft report on the impact of SFA on health. This important qualitative review included forty-six studies of randomised controlled trials (RCT) and prospective cohort studies. In brief, the working group identified adequate evidence from RCT to support both a reduction of SFA intakes and replacement of SFA with PUFA, to reduce CVD event risk and improve glycaemic control[1]. This is in consensus with the WHO and the 2015–2020 Dietary Guidelines for Americans which recommended replacement of SFA with unsaturated fatty acids[2,3]. The timing of this report is pertinent, due to mixed public health messages following a number of controversial studies that contradicted the role of SFA in disease[4,5].

Furthermore, the current obesity epidemic is a global issue. The prevalence of obesity has risen in recent years, and the WHO estimate that 39 % of adults are overweight, of which 13 % are obese[6]. These figures are estimated to rise substantially by 2030[7]. CVD and type-2 diabetes (T2D) are two common obesity related comorbidities. CVD is the leading cause of global mortality and is responsible for 17·3 million deaths annually, a rate that is expected to increase to 23·6 million by 2030[8]. Similarly, T2D incidence has increased dramatically, it is estimated that 415 million individuals are

Abbreviations: ALA, α-linolenic acid; HFD, high-fat diet; HOMA-IR, homoeostatic model assessment-insulin resistance; HR, hazard ratio; LA, linoleic acid; LC, long chain; RCT, randomised controlled trials; RR, relative risk; SACN, UK Scientific Advisory Committee on Nutrition; TLR4, Toll-like receptor 4; TC, total cholesterol; TE, total energy; T2D, type-2 diabetes.

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currently living with diabetes, in comparison with 30 million in 1964, and an estimated 642 million by 2040[9]. Thus, obesity is associated with a significant economic burden, with global costs estimated to exceed 2 trillion US dollars annually[10]. Thus, effective public health strategies are required to reduce disease risk, therefore replacement of SFA with PUFA is a promising initiative to improve dietary quality without affecting habitual dietary patterns.

SFA intakes have been associated with increased risk of CVD, due to their LDL-cholesterol raising properties[11]. SFA probably have also been associated with adverse effects upon key biological processes including insulin sensitivity, inflammation and lipid metabolism[12]. However, a large proportion of the population are exceeding the WHO recommendation of ≤10 % of total energy (TE) from SFA[13]. One such strategy to reduce SFA intakes is replacement with PUFA[1,2]. The evidence to date typically includes total PUFA, therefore further research is required to decipher if there is a difference between the PUFA subtypes. The health benefits of EPA and DHA are widely reported[14]; however the effects of α-linolenic acid (ALA) are not as well-characterised. Therefore, the aim of this review is to discuss the public health and physiological impact of replacing SFA with PUFA, with an emphasis on ALA. We provide an overview of current dietary fat intakes, the evidence from RCT and cohort studies relating to replacement of SFA with PUFA and the associated mechanism of action.

Dietary fatty acids

Nomenclature and health impacts

Fat consists of fatty acids and glycerol or other lipids on a carbon skeleton, connected by either single or double bonds. SFA contain solely single bonds, with chain lengths ranging from one to thirty carbon atoms. These SFA can be further characterised into short-chain (<6 : 0), medium-chain (6 : 0–12 : 0) and long-chain (LC) (12 : 0–30 : 0)[15]. Dietary guidelines typically recommend reducing SFA intakes. However, not all SFA exhibit the same biological effects due to their divergent impact on serum lipids, with lauric (12 : 0), myristic (14 : 0) and palmitic (16 : 0) acids typically associated with adverse effects. A RCT by Dreon *et al.* identified an association between high SFA intake (46 % TE) and increased concentrations of LDL-cholesterol, which is a known risk factor for CVD. More specifically, myristic acid (14 : 0) and palmitic acid (16 : 0) intakes correlated with increased LDL particle size, with no significant association observed with stearic acid (18 : 0) and LDL[16]. Cohort studies have reported similar observations. A meta-analysis of RCT and prospective cohort studies by Micha *et al.* suggested that lauric acid (12 : 0), myristic acid (14 : 0) and palmitic acid (16 : 0) were associated with adverse effects on total cholesterol (TC) and LDL-cholesterol concentrations, with no observed impact of stearic acid. In addition, the TC:HDL ratio was decreased significantly by lauric acid (12 : 0), but not by myristic (14 : 0) and palmitic acid (16 : 0)[17]. This is in agreement with previous findings from the Nurses' Health Study that identified increased risk of CHD with LC SFA (12 : 0–18 : 0) but not with the shorter-chain SFA (4 : 0–10 : 0)[18]. It is difficult to fully elucidate the impact of individual fatty acids on disease risk, as we don't consume individual fatty acids but rather we consume foods that contain a variety of different SFA in combination. Moreover, the majority of studies have examined SFA as a collective group rather than investigating the effects of individual fatty acids. However, based on the existing evidence, instead of classifying SFA as an entire entity, reformulation strategies, in line with the recent SACN and WHO guidelines[1,2], should consider replacement of individual fatty acids, in particular myristic (14 : 0) and palmitic acid (16 : 0), with PUFA.

PUFA are intricate fatty acids containing a minimum of two double bonds with the configuration of the fatty acid contributing to its role in metabolic processes. PUFA are further characterised as an *n*-3 or *n*-6 PUFA by the location of first double bond, which is either on the third or sixth carbon atom, respectively[15]. As with SFA, PUFA can be further characterised based on their carbon chain length, wherein PUFA with greater than twenty carbon atoms are referred to as LC PUFA. There is conflicting evidence relating to the inflammatory status of *n*-6 PUFA[19], nevertheless evidence suggests that intakes of linoleic acid (LA) are associated with reduced adiposity[20], CHD[21] and mortality[22] and improved glycaemic control[23]. The anti-inflammatory effects of the LC *n*-3 PUFA, EPA and DHA are well recognised[14,24,25]. In brief, mechanisms include attenuation of the pro-inflammatory NF-κB pathway, activation of pro-inflammatory PPARγ and production of the anti-inflammatory mediators, resolvins, protectins and eicosanoids. However, the impact of the *n*-3 PUFA, ALA is not as well recognised and will be detailed in the current review.

Sources of dietary fatty acids

When evaluating the impact of SFA on markers of health, it is important to consider fat quality as not all dietary SFA exert the same effects. Primary dietary sources of SFA include dairy, meat and vegetable oils[26]. Data from eleven European countries have identified that 17–30 % of dietary SFA intake comes from dairy products and 15–30 % from meat products[27]. This is similar to reported intakes in the USA, wherein dairy contributes to 13 % and meat to 15 % of SFA intakes[28]. Palmitic acid (16 : 0) is the most abundant dietary SFA as it is derived from animal lipids and plant seed oils. Stearic acid (18 : 0) is the next most abundant and is found in animal and vegetable lipids, while dairy fats typically comprise the odd-chain SFA, including pentadecanoic acid (15 : 0) and heptadecanoic acid (17 : 0)[26]. Data from the US Health Professionals Follow-Up Study and the Nurses' Health Study (*n* 222 234) reported that dairy fat intake was not significantly associated with risk of stroke (relative risk (RR) 0·99; 95% CI 0·93, 1·05), CHD (RR: 1·03; 95% CI 0·98, 1·09) or CVD (RR: 1·02; 95% CI 0·98, 10·5) in males

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and females[29]. Furthermore, evidence from the Multi-Ethnic Study of Atherosclerosis prospective cohort study reported that SFA of dairy origin are cardio-protective (hazard ratio (HR): 0·79; 95 % CI 0·68, 0·92) compared with meat-derived SFA (i.e. palmitic acid (16 : 0) and stearic acid (18 : 0)) which were associated with increased CVD risk (HR: 1·26; 95 % CI 1·02, 1·54; $P < 0·05$)[26]. A similar effect was observed in the EPIC cohort, whereby high dairy derived SFA intakes were associated with reduced risk of IHD, however no adverse association between meat-derived SFA was observed in this Dutch cohort[30]. This was previously reported by Sjogren *et al.* who identified that milk-derived fatty acids were favourably associated with reduced LDL particles, and consequently CHD risk[31]. The food matrix in which the lipids are contained has been shown to have a central role in their health effects. For example, dairy fat within a cheese matrix was associated with significant improvements in total and LDL-cholesterol ($P < 0·05$) in overweight adults, compared with alternate dairy matrices, including butter[32]. This is in agreement with previous evidence wherein butter increased total and LDL-cholesterol[33]. The differences in SFA composition may partly explain this association as cheese contains lower levels of lauric acid (12 : 0) and higher levels of palmitic acid (16 : 0) and stearic acid (18 : 0) than butter[34]. Lauric acid (12 : 0) has been associated with increased LDL-cholesterol, therefore the reduced levels in cheese may be beneficial for health[35]. However, further research is required as cheese also contains higher levels of protein and calcium, which may be contributing to the positive effects on lipid profiles[32]. The primary dietary sources of the LC *n*-3 PUFA, EPA and DHA are oily fish, additionally they can be synthesised endogenously from ALA[36]. ALA, however, is an essential fatty acid, wherein it cannot be synthesised endogenously and needs to be obtained from dietary sources. Sources of ALA include green leafy vegetables, certain nuts e.g. walnuts, flaxseed, rapeseed and the respective oil counterparts[37].

Typical fatty acid intakes

The SACN[1] and the WHO[2] recommend that SFA intakes are 10 % less of TE intake, while the European Food Safety Authority recommends that SFA intakes should be as low as possible[38]. Nevertheless, population intakes typically exceed these recommendations. Mean SFA intakes are between 8·9 and 15·5 % in Europe[27], 11 % in the USA[39], and 13·3 % in Ireland[40] and 12·7 % in the UK[41]. It is estimated that reduction of SFA intakes to 10 % TE, by replacing 3 % with PUFA would infer a 10 % reduction in CVD risk[42]. The WHO recommends that total PUFA intakes are greater than 6 % TE[13]. In a global review of dietary intakes, twenty out of the forty studies included met the aforementioned PUFA recommendation, with intakes ranging from 2·8 to 11·3 %[43], with over half of EU countries adhering to the >6 % TE recommendation[27]. Many studies report PUFA intakes cumulatively, however the FAO/WHO and European Food Safety Authority recommend that intakes of ALA are >0·5 % TE[13,38]. Alas, population ALA intakes are not always reported, however, data from the latest Irish food survey suggest 100 % adherence to the ALA recommendation, at the population level, with a mean daily intake of 0·65 % TE (1·4 g)[40], which is similar to other EU counties for which an intake of 0·4–0·8 % TE (0·7–2·3 g) is reported[38] and the USA (1·5 g)[44]. Of note, a recent review of the evidence relating to ALA and CVD risk suggests that this recommendation should be reviewed as evidence suggests that intakes of greater than 2 g/d (0·6–1·1 % TE) would be more beneficial for reducing CVD risk[45], in agreement with a previous recommendation[46].

Health impact of dietary fatty acids

SFA have been associated with increased risk of heart disease since the seven countries study by Ancel Keys in 1958 up to the current draft SACN report on saturated fats and health, which identified improved total and LDL-cholesterol, and reduced CHD risk following reduction in SFA intakes[1]. Due to the complex nature of the hypothesis and the complexity of dietary intakes it is difficult to extend the direct impact of SFA intakes on CVD risk.

The robust SACN report included a Cochrane review of fifteen RCT, which included long-term trials (minimum of 24 months). This analysis demonstrated that a reduction in SFA intake was associated with a 17 % reduced risk of CVD events (RR: 0·83; 95% CI 0·72, 0·96), following sensitivity analyses[47]. This review also identified a 27 % reduction in CVD risk (RR: 0·73; 95% CI 0·58, 0·92) following substitution of 10 % SFA with PUFA[47]. This is in agreement with previous meta-analyses. For example, a meta-analysis including eight RCT (*n* 13 614) demonstrated that a 5 % replacement of SFA with PUFA resulted in a 10 % decrease in CHD risk (RR: 0·90; 95% CI 0·83, 0·97)[48]. Similarly, Mensink *et al.* identified a reduction in TC and HDL-cholesterol, and an improvement in the TC: HDL-cholesterol ratio with the substitution of 1 % SFA with PUFA[35]. Thus, even slight replacement of SFA is capable of exerting health benefits. Recent evidence from a large prospective cohort study of men and women (*n* 126 233) from the Health Professionals Follow-up Study and the Nurses' Health study reported an 8 % increased risk (95 % CI 1·03, 1·14, $P < 0·001$) of total mortality with the highest SFA consumption (17·9 % TE) after a follow-up period of approximately 30 years[49]. However, the SACN report concludes that the length of follow-up in studies was not sufficient to derive a relationship between a reduction in SFA or the replacement of SFA with PUFA on overall mortality[1].

It is well established that SFA exert their adverse effects on CVD risk by increasing serum LDL-cholesterol, which directly correlates to increased CVD risk[11]. Despite this, a number of meta-analyses of observational studies have recently challenged this concept by reporting that dietary SFA was not associated with increased risk of CVD or total mortality[4,50]. Chowdhury and colleagues concluded that their findings did not support altering the public health guidelines to reduce SFA and increase

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PUFA for CVD prevention. Similarly, De Souza *et al.* concluded that SFA are not associated with increased risk of mortality, heart disease or diabetes. However, the results of these studies need to be interpreted with caution due to study limitations. First, it is important to note that cause and effect of disease cannot be derived from observational studies. Moreover, these studies presented study selection bias, heterogeneity and residual confounding which are factors that may have influenced CVD risk, while carbon chain length and replacement SFA macronutrient also varied between studies[51].

Whilst recent results from the controversial PURE study, an observational study encompassing eighteen countries, reported that total fat and SFA were inversely associated with reduced total mortality risk[5]. It is important to note that there are a number of study limitations that also must be acknowledged, including the undefined carbohydrate sources, as similar to fat, different carbohydrates have been associated with divergent health effects[52]. Furthermore, a number of countries were of low socio-economic status, hence the unusually high carbohydrate (>60 %) intakes, furthermore, the main source of SFA was meat and dairy, which may have been corrected for micronutrients deficiencies in countries with poor dietary quality. Conversely, findings from the same cohort also identified an association between intakes of SFA and increased total and LDL-cholesterol[53]. Nonetheless, it is important to consider the macronutrient of replacement for SFA, as PUFA, and to a lesser extent MUFA, have been associated with beneficial effects, while there is inconsistent evidence relating to carbohydrate substitution[1].

Replacement of SFA with PUFA

The replacement of SFA with an alternate macronutrient to reduce risk of disease has been a controversial topic in recent years. Prospective cohort studies and RCT have presented inconsistent results, which can be partly explained by differing populations, intervention durations, doses and the nominated replacement macronutrient. One of the most important confounding factors is body weight, wherein reducing SFA may occur in conjunction with weight loss, and concomitant weight changes would also affect physiological outcomes[54]. Nevertheless the SACN concluded that there was adequate evidence from RCT to suggest that replacement of SFA with PUFA reduces total and LDL-cholesterol, decreases CHD and CVD event risk and improves glycaemic control. They also identified a beneficial effect of MUFA replacement on blood lipids and T2D risk[1] (Fig. 1).

Perspectives from cohort studies

A limitation of cohort studies that have investigated the replacement of SFA with PUFA is that they typically do not differentiate between *n*-3 and *n*-6 PUFA. Nevertheless, the SACN committee concluded that there was adequate evidence from prospective cohort

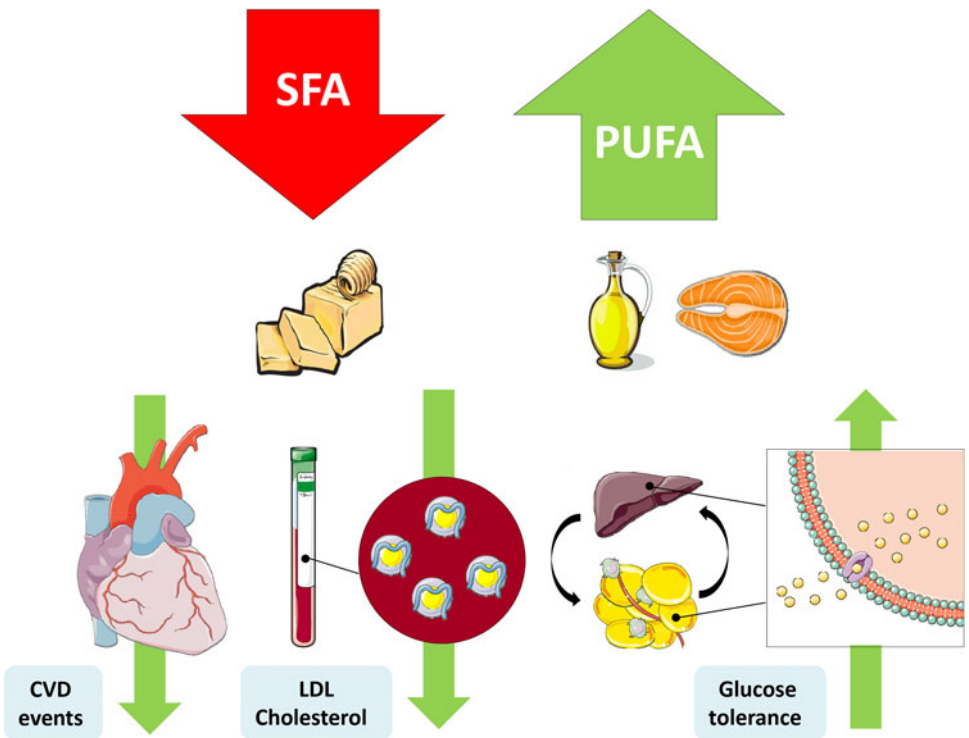

Fig. 1. (Colour online) Replacement of SFA with PUFA reduces the risk of CVD events, improves the blood lipoprotein profile to reduce LDL-cholesterol and increases glycaemic control. This figure was prepared using the SMART Servier Medical Art website (https://smart.servier.com).

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studies to support a reduced risk of CHD events and mortality with replacement of SFA with PUFA but insufficient evidence to derive an association with improved blood lipids[1].

A modelling approach using data from the US Nurses' Health Study (*n* 73 147) and the Health Professionals Follow-up Study (*n* 426 354) suggested that isoenergetic replacement of 1 % SFA with PUFA could reduce CHD risk by 8 % (HR: 0·92; 95% CI 0·89, 0·96)[55]. This complements previous results from Li *et al.* that identified a 25 % reduction in CHD risk (HR: 0·75; 95% CI 0·67, 0·84) when 5 % of dietary SFA was replaced with PUFA after a minimum of 24 years of follow-up in this US cohort[56]. Similarly, Chen *et al.* also modelled the impact of replacing dairy fat with PUFA, and reported that 5 % substitution would reduce CVD risk by 24 % (RR: 0·76; 95% CI 0·71, 0·81)[29]. Furthermore, outcomes from the PREDIMED study showed that isoenergetic replacement of SFA with PUFA was associated with reduced CVD risk[57]. In addition to the cardio-protective impact, complementary results from the US Nurses' Health Study (*n* 83 349) and the Health Professionals Follow-up Study (*n* 42 884) found that replacing 5 % of SFA with PUFA resulted in a 27 % reduced risk of total mortality (HR: 0·73; 95% CI 0·70, 0·77)[49]. These studies are in agreement with previous analyses using data from prospective cohort studies that reported improvements in CVD risk following substitution of SFA with PUFA[35,58–60]. Whilst evidence relating to the direct substitution of SFA with ALA is limited, a continuous (1-SD increase) analysis of nineteen cohort studies reported that plasma ALA was associated with a 9 % reduced risk of fatal CHD (RR: 0·91; 95% CI 0·84, 0·98)[61]. Equivalently, Chowdhury *et al.* reported decrease in CHD risk following supplementation with ALA (<2 g/d) in a meta-analysis of observational studies[50]. In agreement with a previous analysis which reported that dietary ALA intake was associated with reduced CVD risk (RR: 0·90; 95% CI 0·81, 0·99), results from the pooled dietary analysis suggesting that each 1 g increment of ALA was associated with a 10 % reduced risk of CHD mortality[62]. It has been established that replacement of PUFA is a promising future health strategy, however, as with SFA, the types of PUFA should be also considered. The health benefits of EPA and DHA are well recognised, however, evidence from prospective studies suggest that ALA is also a plausible replacement for SFA. Substantial research, including RCT, is required to elucidate the optimal dose of ALA required to attain a health benefit.

Perspectives from randomised controlled trials

Prospective cohort studies provide a platform to derive associations between dietary fat intakes and disease. However, cohort studies are seriously challenged by virtue of the inherent limitations of dietary assessment methodologies, wherein fatty acid, macronutrient and energy intake is often significantly under-reported. Therefore RCT are required in order to determine the causal effect of replacing SFA with PUFA on health parameters. In terms of insulin sensitivity, a recent systematic review and meta-analysis of 102 RCT investigated the impact of PUFA replacement on glucose-insulin homoeostasis using findings. In agreement with the beneficial effects on CVD risk, 5 % substitution with PUFA significantly improved fasting glucose concentrations (−0·04 mmol/l), fasting insulin (−1·6 pmol), haemoglobin A1c (−0·15 %), C-peptide (+0·03 nmol/l), homoeostatic model assessment-insulin resistance (HOMA-IR; −4·1 %) and insulin secretion capacity[63]. Although many studies fail to differentiate between the types of PUFA, a recent review of the evidence suggests that replacement of SFA with *n*-6 PUFA is a feasible public health initiative to reduce CVD risk[64]. In terms of the impact of substituting SFA with *n*-3 PUFA, Ramsden *et al.* demonstrated a 21 % reduced risk of CVD mortality (RR: 0·79; 95% CI 0·63, 0·99) with a combination of *n*-3 and *n*-6 PUFA, compared with a null effect following sole replacement with *n*-6, suggesting that *n*-3 PUFA is eliciting a greater cardio-protective effect[65]. Similarly, a RCT (*n* 79 males) that replaced SFA with 4 % fish oil for 8 weeks reported a decrease in plasma TAG and arterial blood pressure[66]. Hence, current evidence suggests that replacement of SFA with *n*-3 PUFA may have more potent beneficial effects than replacement with *n*-6 PUFA.

To the best of the authors' knowledge, no studies have investigated the impact of replacing SFA with ALA. However, a number of RCT have investigated the impact of ALA supplementation including the Alpha Omega trial in participants who had experienced previous myocardial infarction. They reported a 27 % reduction in CVD events in women following daily supplementation with 2 g ALA for 40 months, with a non-significant 9 % reduction in CVD incidence in the overall population[67]. This is similar to previous results from the Lyon Heart Study which suggested that a diet rich in ALA, obtained from consumption of margarine containing 5 % ALA, was an effective strategy for the secondary prevention of CHD, wherein there was a significantly lower rate of cardiac deaths in the intervention group (*n* 3) compared with the control (*n* 17)[68]. Evidence from a RCT suggested that diet in which two-thirds of the fat was derived from rapeseed oil (ALA) reduced TC by 12 % and LDL-cholesterol by 16 %, a similar magnitude to what was observed with the maize oil (LA)[69]. Taken together this suggests that replacement of SFA with ALA would infer a cardio-protective effect. Nonetheless, the earlier benefits were observed at intakes significantly greater than the current dietary guidelines (0·5 % TE)[38]. Therefore, further RCT are required to determine the optimal ALA dose and whether the beneficial effects of ALA are more pronounced in women. Moreover, increased ALA intakes may also improve LC *n*-3 PUFA status, which would consequently infer cardiovascular health benefits[70].

Whilst evidence suggests that replacement of SFA with PUFA has the potential to reduce CVD and T2D risk in a number of populations; the impact of inter-individual variation should also be considered. It has been established that individuals respond differently to dietary interventions depending on their baseline dietary and

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metabolic health status, as well as other parameters which may include genetic background and ethnicity. An example of this was observed in the LIPGENE study; a randomised dietary intervention trial intended to determine the most effective dietary approach to reduce dietary SFA in individuals with the metabolic syndrome (*n* 417) encompassing eight European countries. The participants were randomly assigned to one of four isoenergetic diets for 12 weeks: a high-fat, SFA-rich, high-fat MUFA enriched, low-fat with high-complex carbohydrate, or low-fat with high-complex carbohydrate with 1·2 g/LC *n*-3 PUFA[71]. In this study, reducing SFA intakes in a weight-stable context in obese individuals had no effect on insulin sensitivity, cholesterol, blood pressure or inflammatory status[71]. Of note, replacement of SFA with the low-fat, high-complex carbohydrate LC *n*-3 PUFA diet did significantly improve plasma TAG and NEFA concentrations in males[71]. Further analysis of this cohort stratified participants by insulin sensitivity (HOMA-IR). Participants with the greatest HOMA-IR, higher BMI and the most adverse metabolic phenotype, responded better to dietary replacement of SFA with MUFA and PUFA. In this adverse phenotype group, fasting insulin and HOMA-IR were significantly reduced, following the dietary replacement of SFA within the dietary intervention[72]. In contrast, individuals with the lowest HOMA-IR status, increased HOMA-IR in response to the SFA diet, wherein fasting insulin and HOMA-IR concentrations were significantly increased[72]. Thus, incorporation of personalised nutrition into future public health strategies may improve population health by providing a tool to predict which dietary interventions are most likely to improve health. However, a recent review by Ordovas *et al.* on personalised nutrition and health concluded that a large body of the current evidence supporting personalised nutrition is derived from observational studies, not RCT, therefore substantial research and regulation will be required before personalised nutrition can be implemented[73].

Insights into the mechanism of action of altering dietary fat composition

This review seeks to present a synopsis of the biological mechanism as to how fatty acid modification affects health. A plethora of studies have investigated the *in vivo* effects of PUFA; however, it is important to consider the differences in doses of PUFA between studies, as some studies apply total replacement whereas others replace a proportion of the diet with PUFA, which is more physiologically relevant, furthermore a variety of different mouse models are used, all of which could lead to discrepancies between studies. Furthermore, while it is possible to achieve efficacy in animal studies, this does not always translate to human subjects.

Mechanism of action of SFA beyond cholesterol homoeostasis and CVD risk

The impact of SFA on metabolic health have been recently reviewed[12,74]. In brief, SFA have been associated with negatively altered insulin sensitivity, adipose tissue and pancreatic β-cell inflammation, hepatic steatosis and mitochondrial dysfunction[12]. A high-SFA diet negatively impacts *in vivo* signalling pathways, including impaired insulin signalling via downregulation of insulin receptor substrate-1 mRNA expression, which contributes to the progression of insulin resistance, and subsequently T2D. This often occurs in tandem with modulation of adipose tissue inflammation, wherein pro-inflammatory cytokine production is increased. Thus, promoting a hypertrophic adipose phenotype[75] with increased pro-inflammatory M1 macrophage polarisation and the formation of crown-like structures, whereby macrophages surround necrotic adipocytes and secrete pro-inflammatory mediators[76]. However, the majority of this mechanistic evidence is derived from cell culture and animal studies; therefore, it is difficult to elucidate the biological impact of SFA substitution in human subjects, as 100 % replacement is not a feasible dietary fat modification.

The activation of the Toll-like receptor 4 (TLR4) pathway and subsequently the NF-κB pathway has been one of the fundamental pathways thought to be involved in SFA-induced inflammation and insulin resistance[74,77]. Quite recently, this theory was challenged in a pertinent and refined publication which provided novel evidence that palmitate does not activate TLR4 but promotes inflammation by reprogramming macrophage metabolism[78]. The authors of this study suggest that SFA are not TLR4 agonists *per se* rather that TLR4-dependent priming is required and that the palmitate provides the 'second hit' to induce inflammation, coupled with alterations to macrophage metabolism and the lipidome[78]. This theory is in agreement with previous evidence demonstrating that SFA does not induce a rapid activation of c-Jun N-terminal and NF-κB compared with lipopolysaccharide[79,80] and neoseptin-3[81]. Moreover, it is within reason that circulating SFA which are in constant flux could not solely activate such a potent inflammatory response. It is important to note that this study only used palmitic acid, which had been previously associated with TLR4 activation, however, it is currently unknown if other types of SFA also induce inflammation in a TLR4-independent manner. Lancaster and colleagues also provided evidence to support SFA-induced metabolic endotoxaemia[82,83], wherein the gut microbiota is altered and promotes lipopolysaccharide secretion, which subsequently induces TLR4 activation, adipose inflammation and pro-inflammatory adipose tissue macrophage activation[78]. This new evidence changes the classical paradigm of SFA activation via the TLR4 pathway; therefore, further research is required to fully elucidate the mechanism by which SFA contribute to inflammatory effects.

Modulation of fatty acid composition: putative health impacts of α-linolenic acid

As SFA mediate a number of adverse effects, substitution with other fatty acids has been the focus of much research. MUFA and PUFA have been associated with beneficial effects, hence supporting the proposed

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replacement of SFA to modulate disease risk. The role of MUFA in ameliorating adipose tissue inflammation has been recently reviewed[12]. Briefly, oleic acid has potential to modulate the NLRP3 inflammasome to reduce IL-1β cytokine production and improve insulin sensitivity *in vivo*[75]. Moreover, oleic acid[75] and palmitoleic acid[84] activate an important metabolic hub 5′-AMP-activated protein kinase. This subsequently impedes inflammatory signalling, improves glucose metabolism, promotes mitochondrial biogenesis and fatty acid oxidation[85]. This review will focus on the *in vivo* evidence relating to ALA and metabolic health.

Evidence from *in vitro* studies suggests that ALA exerts beneficial effects through activation of PPARγ and subsequent inhibition of the NF-κB pathway[86], inactivation of the NLRP3 inflammasome[87] and ameliorating the pro-inflammatory effects of M1 macrophages[88]. Yu *et al.* recently illustrated attenuated high-fat diet (HFD)-induced insulin resistance in C57BL/6J mice by amelioration of metabolic activation of adipose tissue macrophages[89]. Mice were allocated to one of five groups; low fat diet (10 % energy fat), HFD (60 % energy fat) or HFD with 10, 20 or 30 % of fat replaced by flaxseed oil for 16 weeks. All three flaxseed groups demonstrated significant improvements in insulin sensitivity and a stepwise improvement in HOMA-IR was observed with increasing ALA replacement ($P < 0{\cdot}05$)[89]. Furthermore, adipose tissue inflammation was attenuated following substitution with flaxseed oil, with reduced secretion of TNFα, IL-6, IL-1β and monocyte chemoattractant protein-1 and increased adiponectin in adipose tissue[89]. In agreement with these findings, a previous study reported improvements in insulin sensitivity and attenuation of hepatic, adipose and skeletal muscle inflammation following replacement of 10 % of energies in a HFD with ALA, for 16 weeks, through induction of G protein-coupled receptor-120[90]. In addition, recent evidence suggests an alternate mechanism of action whereby ALA attenuates the NLRP3 inflammasome through activation of the PPARγ pathway[87]. Similar beneficial effects on HFD-induced hepatic steatosis, inflammation and lipid homoeostasis were observed following substituting of 10 % of HFD with ALA for 12 weeks[91–94]. Furthermore, ALA has been associated with improvements in CVD risk factors. A recent study showed that ALA supplementation increased peripheral vasodilation in Zucker rats[95]. These findings complement previous evidence demonstrating that a high ALA diet (7·3 % w/w) reduced plaque area by 50 % in apolipoprotein $E^{-/-}$ mice and significantly decreased plaque T-cell accumulation, vascular cell adhesion protein-1 and TNFα[96]. Therefore, there is consistent *in vivo* evidence to suggest that partial replacement of SFA with ALA improves insulin sensitivity, inflammation, hepatic steatosis and CVD risk factors (Fig. 2). Nevertheless, the dose of ALA administered in the aforementioned animal studies is physiologically greater than typical intakes, as a proportion of dietary fat composition. Thus, further

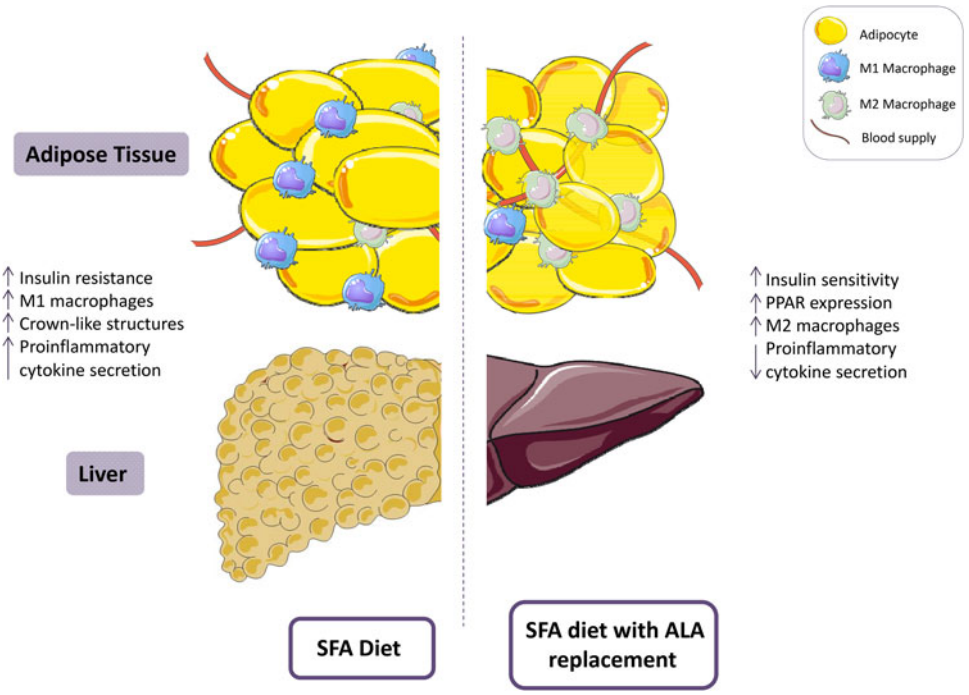

Fig. 2. (Colour online) A diet high in SFA has been associated with reduced insulin sensitivity and increased adipose tissue inflammation, including a pro-inflammatory (M1) resident macrophage population. Replacement of SFA with α-linolenic acid (ALA) ameliorates insulin sensitivity and attenuates adipose tissue inflammation. This figure was prepared using the SMART Servier Medical Art website (https://smart.servier.com).

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research is required to investigate the translation of these findings to human subjects, and to whether efficacy can be achieved using a physiologically relevant dose of ALA.

Furthermore, ALA is a precursor of the LC *n*-3 PUFA, whereby it is biosynthesised to EPA, and subsequently DHA by elongases and desaturases, with delta-6 desaturase being the rate limiting enzyme[14]. Therefore, the beneficial effects of ALA have typically been attributed to provision of a precursor for LC *n*-3 PUFA. However, in man this endogenous biosynthesis is poor, with 8–12 % converted to EPA, a mere 1 % of which is converted to DHA in males, with better rates observed in females[36]. Interestingly, a study identified a protective effect of ALA against hepatic steatosis in the delta-6 desaturase knockout mouse model, whereby the ALA group presented lower hepatic lipid accumulation and inflammation than the comparative lard group, highlighting the ability of ALA to ameliorate steatosis independent of EPA and DHA[97]. However, LA, an *n*-6 PUFA is converted to arachidonic acid by the same elongase and desaturase enzymes as ALA, therefore there is competition for the rate-limiting delta-6 desaturase between the essential PUFA[14]. However, LA is much more abundant than ALA in the Western diet, with an estimated ratio of 20 : 1, therefore conversion of LA to arachidonic acid is more prominent[98]. Therefore, it is evident that dietary ALA intakes need to be increased to modulate the LA:ALA ratio and increase the availability for LC *n*-3 fatty acid synthesis. Thus, modulation of fatty acid composition to reduce SFA and increase ALA has the potential to increase dietary ALA, and consequently ALA abundance for conversion to EPA and DHA. These LC *n*-3 PUFA mediate a range of potential anti-inflammatory mechanisms, we will not elaborate on this here as this evidence has been reviewed in detail[14,24,25].

Food reformulation as a public health initiative to improve dietary quality

A substantial body of evidence supports replacement of SFA with PUFA which would reduce population SFA intakes and ultimately reduce disease risk. There are a number of strategies that could be implemented to achieve this. For example, the reformulation of dairy products to reduce fat content has proved successful in reducing population SFA intakes. A 6 % reduction in contributions of whole milk and butter to SFA intakes was observed over a 10-year period in younger Irish adults, which is potentially attributable to adherence to low-fat dairy product public health messages[40]. Consistent with this, data from the latest UK food consumption survey reported a 9 % reduction in whole milk consumption; however the overall percentage contribution of milk and milk products to dietary fat remained unchanged[41]. Future evidence from prospective cohort studies will further elucidate the benefit of low-fat dairy consumption. Interestingly, recent evidence from the UK National Diet and Nutrition Survey highlighted the efficacy of product reformulation in reducing *trans*-fat intakes, wherein following product reformulation, only 2·5 % of adults exceeded the WHO recommendation of <1 % TE, compared with 57 % pre-reformulation[99]. Therefore, this highlights the potential of improving the profile of commonly consumed foods in reducing disease risk.

Red meat is one of the primary sources of dietary SFA, along with providing many essential vitamins and minerals. Red meat, in particular processed red meat, has been associated with increased risk of CHD[100] and diabetes[101]. However, the associations were derived from observational studies; therefore it is not plausible to infer causality. No association was observed between a high processed red meat dietary pattern and markers of CVD and T2D risk, including cholesterol, in the latest adult Irish food consumption survey[102]. Nonetheless, due to the ingredient profile of processed red meat, recent modelling studies have demonstrated product reformulation as a potential strategy to reduce SFA and sodium intake and infer a health benefit[103,104].

Animal feeding practices to alter food composition

An additional reformulation strategy is modification of the fatty acid composition of beef and dairy products through ruminant grass-based feeding practices. This results in a reduction of SFA and an increase in PUFA concentrations, in particular ALA and conjugated linoleic acid[105]. A limited number of studies have investigated the health impact of consumption of grass-fed red meat or dairy products. A RCT by McAfee *et al.* identified a significant increase in plasma, platelet and dietary intakes of LC *n*-3 PUFA after replacement of habitual red meat consumption (<500 g/week) with grass-fed beef or lamb for 4 weeks[106]. The impact of modifying the ruminant diet to improve milk fat was recently reviewed and concluded that it was an effective strategy to reduce population SFA intakes but that further research is required to optimise the palatability for consumers[107]. In 2018, Benbrook and colleagues applied a dietary modelling approach to investigate the impact of grass-fed milk consumption on dietary fat intakes. Consumption of grass-fed milk was estimated to decrease LA intakes and the LA:ALA ratio, and increase intakes of ALA, which consequently improves LC *n*-3 PUFA precursor bioavailability[108]. It is evident that further research is required to fully elucidate the impact of grass-fed meat/dairy consumption on markers of health, and also to investigate if the fatty acid profile of grass-fed beef could be further enhanced with flaxseed or alternate ALA supplementation. However, the evidence to date suggests that habitual consumption of unprocessed red meat and dairy products following reformulation with grass-based feeding practices has the potential to improve dietary fat quality, within current dietary red meat guidelines of <500 g per week[109].

Health v. *food sustainability issues*

Whilst grass-fed beef consumption provides a potential strategy to reduce SFA and increase PUFA intakes without altering habitual dietary consumption it is important

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to consider the sustainability of beef. Ruminant animals currently produce one-third of the global protein, and demand is set to increase based on the growing population. A recent review by Layman *et al.* recommended implementation of strategies to optimise land use and minimise environmental impact for production of high quality protein[110]. Grass-fed beef had previously been associated with a large environmental footprint due to methane production and land use. However, a recent report suggested that both grass-fed and concentrate-fed beef elicit a similar environmental impact[111]. Therefore, consumption of lower quantities of high-quality beef protein, as part of a healthy diet, is a potential strategy to meet global protein requirements and reduce the environmental impact. Moreover, oily fish is the primary dietary source of LC *n*-3 PUFA, however due to the depletion of fish stocks and the estimated population growth, it is predicted that the fish stocks alone will not be adequate to provide sufficient LC *n*-3 PUFA intakes[37]. Hence, to sustain intakes a complementary LC *n*-3 PUFA source will be required. Alternate strategies include algal oil, GM oil seeds and biosynthesis from plant-based ALA[112].

Conclusions

Whilst modification of foods to reduce SFA and replace it with PUFA is an attainable public health strategy to reduce SFA intakes and subsequently disease risk, there are still gaps in the knowledge base as to the adequate dose of PUFA replacement. Research needs to be completed and validated in a number of populations to establish if the replacement PUFA dose varies by age, sex and habitual dietary intakes. Furthermore, the interplay from confounding dietary and non-dietary factors needs to be considered. The food industry and nutrition researchers are faced with the challenge of implementing long-term RCT, with controlled diet and lifestyle parameters, to answer this pertinent research question in order to improve overall dietary quality and optimise health outcomes. Moreover, it is apparent that not all SFA and PUFA exert the same effects, thus replacement strategies need to consider fat quality, as well as consumer palatability to ensure adherence to the public health initiative. The global obesity epidemic is greater than fat quality alone, therefore simultaneous, effective public health strategies are required to achieve a healthy diet and lifestyle, and collectively reduce disease risk.

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Conflict of Interest

None.

Authorship

Y. M. L. completed the review. B. A. M. and H. M. R. advised in relation to content, and critically evaluated the manuscript. All authors have read and approved the final manuscript.

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