Dietary Fats and Oils

March 2015

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EXECUTIVE SUMMARY

Dietary fat includes all the lipids in plant and animal tissues that are eaten as food, and is present mostly in the form of triglycerides with three fatty acids attached to a backbone. The most common dietary fatty acids are subdivided into three broad classes according to the degree of unsaturation: saturated fatty acids (SFA) with no double bonds; monounsaturated fatty acids (MUFA) with one double bond; and polyunsaturated fatty acids (PUFA) with two or more double bonds. The function and properties of the different fatty acids, including their health properties, are determined by the varying chain length, and number and position of double bonds.

Dietary fats play an important role as a source of energy, as structural components and as carriers of other dietary components including fat-soluble vitamins. However, the role of different dietary fats and oils in human nutrition is one of the most complex and controversial areas of investigations in nutrition science.

Experts agree evidence does not suggest total fat intake has significant effects on risk of coronary heart disease (CHD) or cancers. The primary concern and importance is the potential relationship between total dietary fats and body weight, as overweight and obesity are risk factors for both cardiovascular disease (CVD) and cancer. As it is currently not possible to determine at a probable or convincing level the causal relationship of excess percent of energy (%E) from fat and unhealthy weight gain, maintaining current World Health Organization (WHO) recommendations (30-35%E total fat) seems prudent.

Currently the most debated type of fats are SFA, with some recent publications suggesting there is no association between SFA intake and CVD. Several experts have raised their concerns about the quality of these recent reviews, in particular the failure to investigate what SFA is replaced with as this has been found to play an important role in the association between SFA and CVD. Replacing SFA with PUFA (both *n*-3 and *n*-6 PUFA) is associated with improved blood lipid parameters and a lower risk of CHD, whereas replacing SFA with largely refined carbohydrates does not seem to provide a benefit and may even increase risk. A challenge remains that although SFA are grouped together, there is evidence to suggest that individual SFA have different physiological effects, but in terms of practical dietary recommendations it is not feasible to separate different types of SFA because foods contain a combination of several SFA. There is also evidence to support the idea that the total matrix of a food is more important than just its fatty acid content when predicting the effect of a food on CHD risk.

Although MUFA have a beneficial effect on blood lipid parameters, evidence from cohort studies and some experimental animal data does not suggest that MUFA are associated with a lower risk of CHD. This may be at least partly explained by the origin of MUFA in the respective studies, as many of the main sources of MUFA in Western dietary patterns are also major sources of SFA.

In contrast to MUFA and SFA, which the human body can produce, the dietary *n*-6 PUFA linoleic acid (LA) and the *n*-3 PUFA alpha-linolenic acid (ALA) are indispensable as they cannot be synthesised by humans. Recommendations of PUFA intakes are generally higher than the levels required to avoid deficiency, which is due to their purported beneficial effects for cardiovascular health. There is convincing evidence from observational studies that replacing some SFA with PUFA (*n*-3 and *n*-6 PUFA) decreases the risk of CHD. However, recently the recommendation to increase PUFA intake, both *n*-6 and *n*-3 PUFA, while reducing SFA intake has also been challenged. It has been argued that replacing SFA with *n*-6 PUFA may be detrimental to health. Proponents of this hypothesis used intervention studies with very high *n*-6 PUFA intakes to back their argument that increasing *n*-6 PUFA without also increasing *n*-3 PUFA is detrimental for health. The findings of these studies are not in contrast to current recommendations, which suggest limiting PUFA intake to no more than 11%E as it is well established that very high intakes may be detrimental to health due to risk of lipid peroxidation. Evidence does not suggest that increasing *n*-6 PUFA alongside *n*-3 PUFA is detrimental for health, but

in contrast the increase is beneficial for cardiovascular health, which is in line with the general recommendation to replace some SFA with PUFA (both *n*-3 and *n*-6). Current intakes of PUFA in New Zealand are below 5%E, and it is unlikely that the 11%E upper level would be surpassed on a population level if some SFA was replaced with PUFA.

Observational studies provide convincing evidence that fish and long-chain *n*-3 PUFA consumption is associated with a lower risk of heart disease. This is generally supported by data from Randomised Controlled Trials (RCTs), although more recent RCTs have found no beneficial effects which may be at least partly due to a higher use of statins and other modern treatments of CHD.

There is convincing evidence that *trans* fatty acid (TFA) consumption is associated with adverse effects on blood lipids and an increased risk of CHD. Evidence from observational studies does not support an adverse effect of ruminant TFA (in contrast to industrial TFA) on risk of CHD. In New Zealand TFA has largely been removed from many products.

Evidence on the effect of specific sources of dietary fats is more limited. Palm oil is a commonly used alternative to partially hydrogenated fat, but is one of the few plant fats with a high SFA content. Although evidence suggests that palm oil is less favourable compared to other vegetable oils in terms of the effect on total:HDL cholesterol, palm oil still has a more beneficial effect than TFA found in partially hydrogenated fats. Coconut oil is another plant fat high in SFA, yet is often heralded to be a healthy fat in popular media. Evidence seems to suggest that despite its high SFA content coconut oil has a more favourable effect on blood lipids compared to carbohydrates and other fats high in SFA, but has a less favourable effect compared to dietary fats high in PUFA. Olive oil has also been heralded as a particularly beneficial oil, mainly due to its prominence in the Mediterranean diet, which is associated with a lower risk of CVD. However, there is a lack of association between consumption of olive oil, a rich source of MUFA, and CHD in line with a lack of association between MUFA and CHD (see MUFA section for details). It is likely the health protective effect of the Mediterranean diet is due to the overall healthy profile of this dietary pattern, which is high in fruits, vegetables, legumes and unrefined grains, rather than one single component.

Dairy products are a major contributor to SFA intakes in Western countries. However, evidence from observational studies does not support the hypothesis that dairy, including high-fat dairy foods, is linked to an increase cardiovascular risk. Dairy products are typically nutrient-dense foods rich in minerals and vitamins, which can exert beneficial effects on CVD. It has also been suggested that bioactive fatty acids present in dairy may also play a role in counteracting negative effects of SFA, although more evidence is needed to support this.

Overall, the recommendation to reduce intakes of SFA in the diet still holds. .New Zealanders have average intakes clearly above the recommended 12%E from SFA. Both mean and median SFA intake in New Zealand (NZ) is around 13%E, which means more than half of NZ adults have intakes above the recommended level. Also more than half of the NZ adult population has PUFA intakes below the minimum recommended level. In particular the intakes of omega-3 are low and more education would be beneficial on the recommended ratios of omega-6 to omega-3. However, there may be a need to be more specific in dietary recommendations on the relationship between SFA and CVD. Replacing SFA with rapidly digested carbohydrates does not lead to a cardiovascular benefit, and may potentially be detrimental to health.

Simply telling consumers to lower their intake of SFA may give the impression SFA *per se* is bad for health and that it does not matter what they replace SFA with, as long as they lower their intakes overall. Consumer demands for products low in SFA (and total fat) as well as pressure from governmental and non-governmental organisations has led to reformulation of products where in an effort to reduce total fat and SFA levels they may be replaced with rapidly digested carbohydrates, unlikely to lead to a benefit. The vehicle in which macronutrients including SFA are delivered also

seems to play a role in its association with health, and there may be a need to consider this in recommendations. The challenging positions by several health experts, in particular regarding SFA and its role in cardiovascular health, may be an opportunity to rethink how scientific evidence is translated into recommendations, and also government and industry efforts around reformulation, that truly benefit the consumer.

DEFINITIONS AND CLASSIFICATIONS

Fats, oils and lipids consist of a large number of organic compounds, including fatty acids (FA), monoacylglycerols (MG), diacylglycerols (DG), triacylglycerols (TG), phospholipids (PL), eicosanoids, resolvins, sterols, sterol esters and others. Dietary fat includes all the lipids in plant and animal tissues that are eaten as food. The most common fats (solid) or oils (liquid) are glycerolipids, which are essentially composed of TG, accompanied by minor amounts of PL, MG, DG and sterols/sterol esters. Each TG has three fatty acids attached by ester linkages to a glycerol backbone. Fatty acids are strings of carbon atoms with a methyl group at one end and a carboxyl group at the other end. They provide a source of energy and are required for metabolic and structural activities (FAO 2010; Sanders 2010).

The most common dietary fatty acids are subdivided into three broad classes according to the degree of unsaturation: saturated fatty acids (SFA) with no double bonds; monounsaturated fatty acids (MUFA) with one double bond; and polyunsaturated fatty acids (PUFA) with two or more double bonds. Double bonds can be of *cis* configuration, which is the most common configuration, or of *trans* configuration. The configuration of the double bond can be altered from *cis* to *trans* during food processing, particularly during partial hydrogenation. Fatty acids are also of varying chain length (see Table 1). PUFA are further defined by the position of the double bond of the fatty acid closest to the methyl end of the molecule (FAO 2010). The most common PUFA families have the bond three carbons (*n*-3) or six carbons (*n*-6) away from the methyl group. Animals are able to insert double-bonds further away from the methyl end of a fatty acid, but not between the methyl group and the *n*-6 position. This makes *n*-3 and *n*-6 fatty acids, derived from linoleic acid (LA; 18:2*n*-6) and α-linolenic acid (ALA; 18:3*n*-3), essential as these cannot be produced in the human body but have to come from dietary sources (see Figure 1 for nomenclature of fatty acids). The parent essential fatty acids LA and ALA can be converted to longer chains of PUFA in the body. LA is converted mainly to arachidonic acid (AA) but can also be converted to docosapentaenoic acid (DPA), and ALA is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are major components of animal cell membrane (Sanders 2010). However this conversion in humans is inefficient and these fatty acids could be easily increased by consuming fish or omega-3 supplements of good quality.

The function and properties of the different fatty acids, including their health properties, are determined by the varying chain length, and number and position of double bonds.

Abbreviations:

AA	*arachidonic acid*
ALA	*α-linolenic acid*
CHD	*coronary heart disease*
CI	*confidence interval*
CVD	*cardiovascular disease*
DG	*diacylglycerols*
DHA	*docosahexaenoic acid*
DPA	*docosapentaenoic acid*
EPA	*eicosapentaenoic acid*
FA	*fatty acids*
HDL	*high density lipoprotein*
HR	*hazard ratio*
LA	*linoleic acid*
LCPUFA	*long-chain polyunsaturated fatty acids*
LDL	*low density lipoprotein*
MG	*monoacylglycerols*
MI	*myocardial infarction*
MUFA	*monounsaturated fatty acids*
n-	*omega-*
OA	*oleic acid*
OR	*odds ratio*
PL	*phospholipids*
PUFA	*polyunsaturated fatty acids*
RCT	*randomised controlled trial*
RR	*relative risk*
SFA	*saturated fatty acids*
TG	*triacylglycerols*
TFA	*trans fatty acids*

Table 1: Categories of fatty acids, chain length and dietary sources.

Fatty acids	Chain length	Dietary sources
Saturated fatty acids	Short-chain: 3-7 carbon atoms Medium-chain: 8-13 carbon atoms. Long-chain: 14-20 carbon atoms. Very-long-chain: ≥21 carbon atoms.	Mainly animal and especially ruminant dairy fats; some tropical oils, especially palm oil and coconut oil
Monounsaturated fatty acids	Short-chain: ≤19 carbon atoms. Long-chain: 20-24 carbon atoms. Very-long-chain: ≥25 carbon atoms.	Oleic acid (OA) is the most common MUFA and it is present in considerable quantities in both animal and plant sources
Polyunsaturated fatty acids		Linoleic acid (LA) and α-linolenic acid (ALA) occur in all dietary fats, with largest proportions found in vegetable oils Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are mainly present in oily fish

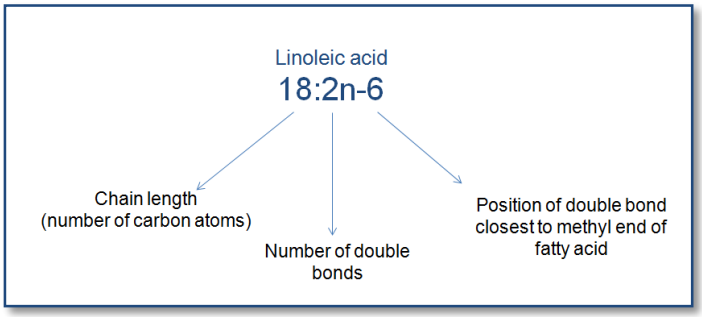

Figure 1: Nomenclature of fatty acids explained (example linoleic acid)

Most dietary fat sources contain a mixture of SFA, MUFA and PUFA at varying amounts. Most vegetable oils are particularly rich in unsaturated fatty acids, whereas animal fats and also coconut and palm oil are rich in SFA. See Figure 2 for the fatty acid profile of selected food sources.

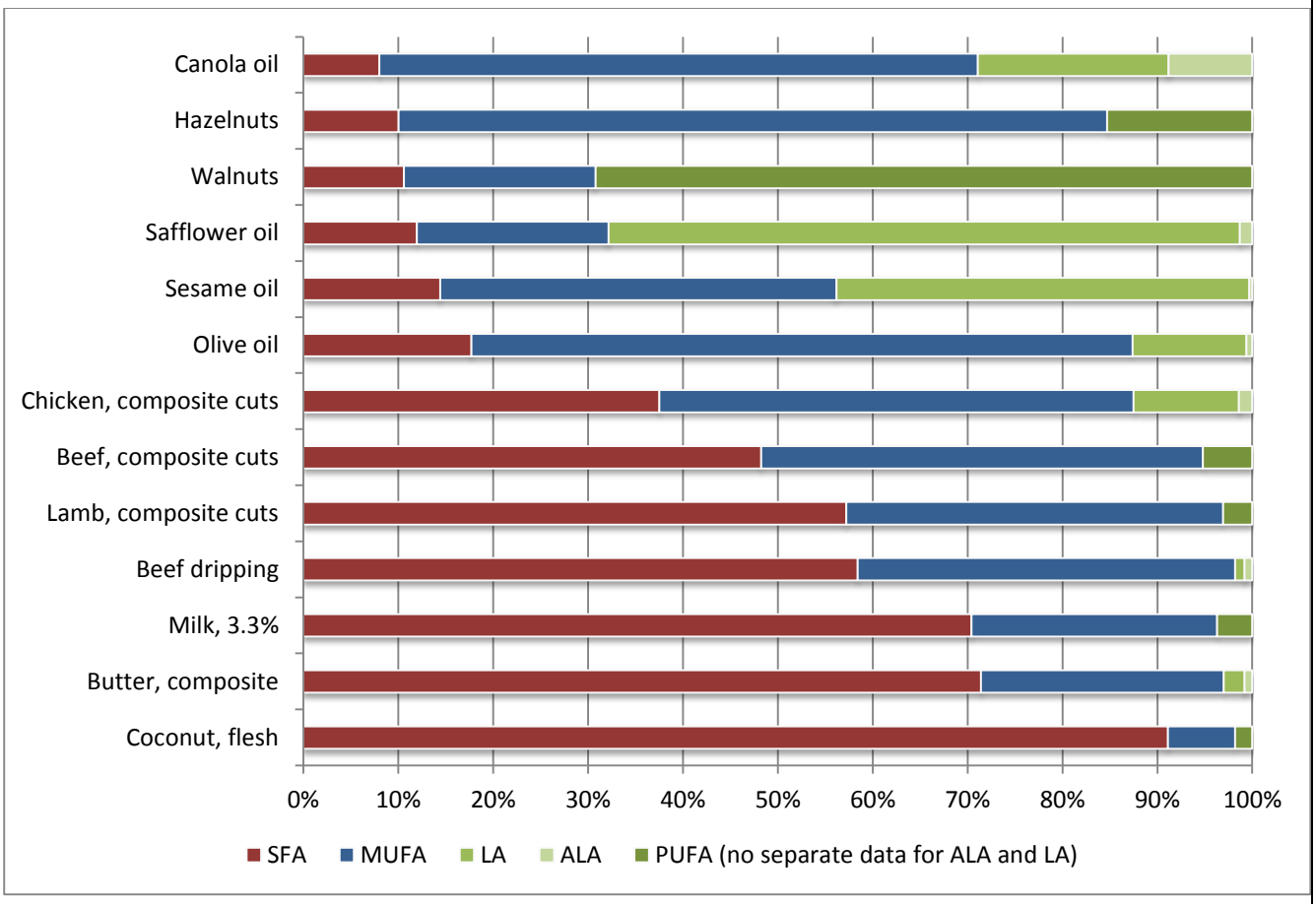

Figure 2: Fatty acid profile of dietary fat present in selected foods.
SFA saturated fatty acids; MUFA monounsaturated fatty acids; LA linoleic acid; ALA α-linolenic acid; PUFA polyunsaturated fatty acids; where separate data for ALA and LA was available it was used, otherwise total PUFA was used. Source: Sivakumaran et al. 2012

DIETARY FATS AND HEALTH

The role of dietary fats and oils in human nutrition is one of the most complex and controversial areas of investigation in nutrition science (Nishida & Uauy 2009). This section will summarise the latest evidence around the different types of fats and their association with health, taking into account and discussing the different views among researchers. Those aspects of dietary fats that are most controversial are discussed in more detail.

Dietary fats are important as a source of energy, as structural components and as carriers of other dietary components including fat-soluble vitamins. The composition of the fat in our diet has implications for our health. As mentioned above, fatty acids are usually grouped by the number of double-bonds into SFA, MUFA and PUFA, and the latter are further sub-categorised by the position of the double bonds. However, an Expert Consultation convened by the Food and Agriculture Organization of the United Nations (FAO) recognised that individual fatty acids within each broad classification may have unique biological properties and health effects, which has relevance in making recommendations. In spite of these limitations, the scientific community and the general population continues to use the groupings based on chemical structure, which would make abandoning the groupings difficult. In addition, few countries have food composition databases that enable dietary assessment of individual fatty acids (FAO 2010).

TOTAL FAT

Experts agree evidence does not suggest that total fat intake has significant effects on risk of coronary heart disease or cancers (WHO 2003, FAO 2010). The primary concern and importance is the potential relationship between total dietary fats and body weight, as overweight and obesity are risk factors for both CVD and cancer (WHO 2003; WCRF/AICR 2007).

The FAO Expert Consultation concluded there was convincing evidence energy balance is critical to maintaining healthy body weight and ensuring optimal nutrient intakes, regardless of macronutrient distribution of energy as % total fat and % total carbohydrates (FAO 2010). Although some older intervention studies from industrialised countries suggest diets with a lower % of energy (%E) from fat tend to be hypocaloric and therefore are associated with weight loss, more recent RCTs in predominantly overweight populations from industrialised countries comparing isocaloric diets with different levels of total fat have shown that a higher %E from fat can lead to greater weight loss than observed with low-fat diets. However, differences in the intake of other macronutrients such as amount and type of carbohydrates and the relatively high drop-out rate in some studies limit the strength of evidence and the generalisation of the results. Ecological data from developing and transitional countries suggest that shifting from lower to higher %E from fat has been associated with weight gain, whereas the opposite has been observed in industrialised countries where %E from fat has decreased while obesity has increased (FAO 2010).

Recommended fat intakes for adults

- *Total fat: 30-33% E*
- *SFA plus TFA: ≤12%E*
- *PUFA: 6-10%E*
- *MUFA: 10-20%E*

Source: Ministry of Health 2003

A recent systematic review and meta-analysis that compared the effects of low-fat vs. high-fat diets in RCTs in overweight and obese people found that decreases in total cholesterol and LDL cholesterol were significantly more pronounced with low-fat diets, whereas rises in HDL cholesterol and reduction in triglyceride levels were more distinct in the high-fat diet groups. Including only hypocaloric diets, the effects of low-fat vs. high-fat diets on total cholesterol and LDL cholesterol levels were abolished (Schwingshackl & Hoffmann 2013).

The Expert Consultation of the FAO suggested it was not possible to determine at a probable or convincing level the causal relationship of excess %E from fat and unhealthy weight gain and that maintaining current World Health Organization (WHO) recommendations is prudent (FAO 2010). The WHO recommends that 30-35% of energy come from dietary fat (WHO 2003), which is similar to the recommendation of 30-33%E from fat by the New Zealand Ministry of Health (Ministry of Health 2003).

SATURATED FATTY ACIDS

Healthy eating guidelines generally recommend limiting consumption of SFA and/or major SFA food sources to reduce the risk of heart disease. The Ministry of Health in New Zealand recommends that SFA (together with *trans* fatty acids) contributes no more than 12%E (Ministry of Health 2003), while the World Health Organization (WHO) recommends limiting the intake of SFA to no more than 10%E (WHO 2003). Recommendations on SFA intakes are generally based on their association with cardiovascular disease (CVD), in particular heart disease.

The first key evidence that contributed to recommendations to reduce SFA intakes came from the Seven Countries study, an ecological study that compared differences in coronary heart disease (CHD) rates between mean intakes of fatty acids in different populations. Based on data from almost 13,000

middle-aged men, Keys and colleagues demonstrated strong associations between mean intakes of SFA and mean levels of serum total cholesterol (Keys 1980), and a positive association between dietary intake of SFA and CHD (Keys *et al.* 1986). A large number of epidemiological and clinical studies followed, adding to the evidence base for current dietary recommendations (see FAO 2010; Skeaff & Miller 2009).

More recently, the paradigm that SFA is associated with a higher risk of CVD has been challenged by various health professionals and researchers (Malhotra 2013; DiNicolantonio 2014; Ravnskov *et al.* 2014), and is probably currently one of the most debated areas in human nutrition, adding to confusion among consumers and health professionals. In particular two large systematic reviews and meta-analyses have cast doubt over the independent association of SFA with CVD. A meta-analysis of data from 21 prospective cohort studies including almost 350,000 subjects followed over 5-23 years, resulting in 11,000 cases of CHD or stroke, found a non-significant positive association between SFA intake and CHD (RR 1.07; 95%CI 0.96, 1.19), a non-significant inverse association with stroke (RR 0.81; 95%CI 0.62, 1.05) and no association with total CVD (RR1.00; 95%CI 0.89, 1.11). The authors concluded there was no significant evidence dietary SFA is associated with risk of CHD or CVD (Siri-Tarino *et al.* 2010a). A recently published systematic review and meta-analysis of prospective observational studies and randomised controlled trials (RCTs) came to similar conclusions. Meta-analysis of data from 32 prospective cohort studies including 530,525 subjects followed for 5-23 years, with almost 16,000 incident coronary outcomes, resulted in no significant association between SFA intake and risk of coronary disease (RR 1.02; 95%CI 0.97, 1.07). The review also found no significant association between SFA biomarkers and risk of coronary outcomes (RR 1.06; 95%CI 0.97, 1.17) (Chowdhury *et al.* 2014).

Although these findings do not seem to support an independent association between SFA and CVD, both reviews, and in particular the authors' conclusions, have been criticised by several nutrition experts for several reasons. Firstly, it has been suggested that the method of looking at SFA (as well as MUFA or PUFA) as separate entities is flawed because the health effect of a macronutrient that delivers a substantial amount of daily energy depends on which other macronutrient(s) are replaced (Katan *et al.* 2010; Geleijnse *et al.* 2014; Lartey *et al.* 2014). Evidence generally shows that the effect of reducing SFA on cardiovascular risk depends on what SFA in the diet is replaced with, which is something that was not taken into account by the above reviews. There is good evidence that replacing SFA with PUFA is beneficial for cardiovascular health, whereas such benefit has not been found when SFA was replaced with carbohydrates (Baum *et al.* 2012; Astrup *et al.* 2011). Secondly, it has been argued that in about half of the studies included by Siri-Tarino and colleagues (2010a) dietary intakes were assessed using 1-day dietary assessments or other unvalidated methods to assess SFA intake. As food intake varies from day to day, 1-day records provide poor estimation of the usual dietary intake of an individual, which cannot reliably rank individuals by their long-term intake. This leads to so called regression dilution bias, which can consequently lead to a lack of significant associations (Katan *et al.* 2010; Skeaff & Miller 2009). Regression dilution bias, together with confounding of one nutrient by another, has also been argued by Skeaff and Miller (2009) to be a main reason for the lack of association between SFA and CHD in their own meta-analysis (Skeaff & Miller 2009). A third limitation of the review by Siri-Tarino and colleagues (2010a), highlighted by Scarborough *et al.* (2010), was that many of the included cohort studies had adjusted for serum cholesterol levels, which is a pathway of the effect of SFA on cardiovascular risk and therefore not a confounder. Adjusting for blood cholesterol levels has been suggested to bias the estimates of effect of SFA intake toward the null hypothesis (Scarborough *et al.* 2010). However, subsequent meta-analysis by Siri-Tarino only including data that was not adjusted for blood cholesterol levels led to a slightly stronger, yet still statistically non-significant association between SFA intake and CHD risk (RR 1.13; 95%CI, 0.96, 1.33), but did not change the association with risk of stroke (RR 0.84; 95%CI 0.63, 1.10) or total CVD (1.02; 95%CI, 0.96, 1.19) (Siri-Tarino *et al.* 2010b). In response to the findings by Chowdhury *et al.* (2014) that biomarkers for SFA intake are not associated with coronary outcomes, it

was argued that two of the 8 included studies only looked at SFA from milk-fat rather than total SFA, both of which resulted in a negative association. Excluding these two trials from the meta-analysis resulted in a significant positive association between total SFA blood levels and coronary outcomes (RR 1.21; 95%CI 1.04, 1.40) (Dawczynski *et al.* 2014), which contradicts the findings by Chowdhury and colleagues.

A pooled analysis by Jakobsen *et al.*, published in 2009, addressed several of the above mentioned issues. In this analysis of data from 11 cohort studies, only studies using dietary assessment methods that cover a longer period of time (food frequency questionnaire, diet history) and that underwent validation or repeatability studies were included, therefore reducing the risk of measurement error and subsequently regression dilution bias. Studies with follow-up periods of more than 10 years were truncated to reduce possible effect modification by time. Pooled analysis of data from almost 350,000 subjects followed over a period of four-ten years, during which 5,249 coronary events and 2,155 coronary deaths occurred, showed a significant 13% reduction of coronary events (HR 0.87; 95%CI 0.77, 0.97) and a significant 26% reduction in coronary deaths (HR 0.74; 95%CI 0.61, 0.89) when 5% of energy from SFA was replaced by PUFA. In contrast, there was a significant 7% higher risk of coronary events (HR 1.07; 95%CI 1.01, 1.14) and no significant effect on risk of coronary deaths (HR 0.96; 95%CI 0.82, 1.13) when 5% of energy from SFA was replaced with carbohydrates. When SFA was substituted with MUFA there was also a borderline significant 19% increased risk of coronary events (HR 1.19; 95%CI 1.00, 1.42) but no association with risk of coronary deaths (HR 1.01; 95%CI 0.73, 1.41) (Jakobsen *et al.* 2009). The findings of this pooled analysis suggest that replacing SFA with PUFA reduces the risk of cardiovascular events and deaths, whereas replacing SFA with carbohydrates (or MUFA) has no beneficial effect, although this may depend on the quality of carbohydrates.

The findings by Jakobsen *et al.* (2009) are also supported by experimental data. This was shown in a meta-analysis of 8 RCTs that randomised adults to increased total PUFA or *n*-6 PUFA consumption (but not mainly *n*-3 PUFA) for at least 1 year and reported risk estimates for 'hard' CHD events (myocardial infarction [MI], CHD death, and/or sudden death), with a total of 13,614 participants and 1,042 CHD events. Increasing PUFA consumption in place of SFA (on average by 9.9% of energy) resulted in a significant 19% reduction of occurrence of CHD events (RR 0.81; 95%CI 0.70, 0.95), which corresponds to a risk reduction for each 5%E greater PUFA consumption of 10% (RR 0.90; 95%CI 0.83, 0.97) (Mozaffarian *et al.* 2010). The quality of the included studies was medium to low with all studies either scoring 2 or 3 out of 5 points, somewhat limiting the strength of the findings. Further supporting evidence comes from trials showing that replacing SFA with PUFA decreases total and LDL cholesterol levels, but that there is a lack of benefit in replacing SFA with refined carbohydrates as while this lowers LDL cholesterol levels, it also lowers HDL cholesterol levels and LDL particle size, and increases triglyceride levels (Mensink *et al.* 2003; FAO 2010; Astrup *et al.* 2011; Baum *et al.* 2012) [although it has been suggested international epidemiologic data cast doubt as to the generalisability of 'carbohydrate-induced dyslipidemia'; see Stamler 2010].

Another recent publication also questioned the benefits of replacing SFA with PUFA, in particular n-6 PUFA, suggesting that recommendations to increase n-6 PUFA in the diet may in fact increase the risk of CVD, leading to more confusion among health professionals and consumers (Ramsden *et al.* 2013). See a detailed critical discussion on this in the PUFA section below.

The overall consensus among most experts is still that replacing SFA with PUFA (both *n*-3 and *n*-6 PUFA) is associated with improved blood lipid parameters and a lower risk of CHD, whereas replacing SFA for largely refined carbohydrates does not seem to provide a benefit or may even increase risk (FAO 2010; Astrup *et al.* 2011; Baum *et al.* 2012). The Expert Consultation convened by the FAO concluded that there is insufficient evidence relating to the effect on the risk of CHD in replacing SFA with either MUFA or largely whole grain carbohydrates; however, based on indirect lines of evidence this could result in a reduced risk of CHD (FAO 2010). Another challenge remains that although SFA

are grouped together, there is evidence to suggest that individual SFA have different physiological effects, but in terms of practical dietary recommendations it is not feasible to separate different types of SFA because foods contain a combination of several SFA (FAO 2010; Astrup *et al.* 2011). It has also been argued that there is increasing evidence to support that the total matrix of a food is more important than just its fatty acid content when predicting the effect of a food on CHD risk, e.g. the effect of SFA from cheese on blood lipids and CHD may be counterbalanced by the content of protein, calcium, or other components in cheese.

The Expert Consultation convened by the FAO concluded there is insufficient evidence for establishing any relationship of SFA consumption with cancer (FAO 2010).

MONOUNSATURATED FATTY ACIDS (MUFA)

International recommendations on MUFA intakes vary significantly between 12-25%E, or are not provided at all, including by prestigious authorities and organisations such as the US National Institute of Medicine, the European Food Safety Authority or the US Department of Agriculture (see Schwingshackl & Hoffmann 2012). The WHO recommends that MUFA should provide the difference of total fat minus SFA, PUFA and *trans* fatty acids (TFA) (WHO 2003). The New Zealand Ministry or Health (2003) recommends MUFA intakes should be between 10-20%E.

A high intake of MUFA has long been suggested to be a major contributor to the cardioprotective effects of the Mediterranean diet, which is characterised by a heavy reliance on olive oil. The beneficial effects may well arise from quality extra virgin olive oil with low oxidation levels and high levels of polyphenols, absent in most traded cheap olive oil. However, this paradigm does not seem to be supported by evidence from observational studies (Baum *et al.* 2012). This is despite data from experimental studies providing convincing evidence that replacing carbohydrates with MUFA increases HDL cholesterol concentrations, and that replacing SFA with MUFA reduces LDL cholesterol concentration and total/HDL cholesterol ratio (FAO 2010; Baum *et al.* 2012), suggesting increasing MUFA intake should reduce the risk of cardiovascular events. However, meta-analysis of data from cohort studies by Jakobsen *et al.* (2009; see details of review in SFA section) resulted in a borderline significant higher risk of coronary events when substituting 5% of SFA with MUFA (HR 1.19; 95%CI 1.00, 1.42), but found no association with risk of coronary deaths (HR 1.01; 95%CI 0.73, 1.41). Also Chowdhury *et al.* (2014) found no association between MUFA and risk of coronary disease (RR 0.99; 95%CI 0.89, 1.09) in a meta-analysis of prospective cohort studies, although concerns have been raised about the validity of this meta-analysis (see SFA section above). A lack of association between MUFA intake and CHD mortality and events was also found in a meta-analysis by Skeaff & Miller (2009). The Expert Consultation convened by the FAO concluded there is insufficient evidence for a relationship of MUFA consumption with chronic disease end points such as CHD (or cancer) (FAO 2010).

Animal studies also support the above findings in humans and shed some light on possible reasons for a lack of effect on CHD despite the positive effects on blood cholesterol levels. Data from studies in primates and mice also suggest that MUFA compared to SFA may not protect against the development of coronary artery atherosclerosis, despite favourable changes in serum lipoprotein lipids (Astrup *et al.* 2011; Baum *et al.* 2012). Studies in monkeys indicate changes in the LDL cholesterol ester fatty acid composition, or more specifically a high cholesteryl oleate composition of plasma LDL, caused by high MUFA intakes, may result in increased atherosclerotic lesions (Baum *et al.* 2012). Data from human studies to support this hypothesis are lacking.

It has also been suggested controversial findings relating to MUFA intake and cardiovascular risk may be at least partly explained by the origin of MUFA in the respective studies, as many of the main sources of MUFA in Western dietary patterns are also major sources of SFA (mostly animal fats) (Astrup *et al.* 2011; Schwingshackl & Hoffmann 2012).

POLYUNSATURATED FATTY ACIDS (PUFA)

In contrast to MUFA and SFA, which the human body can produce, the *n*-6 PUFA linoleic acid (LA) and the *n*-3 PUFA alpha-linolenic acid (ALA) are indispensable as they cannot be synthesised by humans. The minimum intake values for essential fatty acids to prevent deficiency symptoms are estimated to be 2.5% of energy for LA plus 0.5% of energy for ALA (FAO 2010). Recommendations of PUFA intakes are generally higher due to their purported beneficial effects for cardiovascular health. The WHO (2003) and the NZ Ministry of Health (2003) recommend that PUFA should contribute between 6 and 10% of energy. Separate recommendations for the long-chain *n*-3 PUFAs (*n*-3 LCPUFA) DHA and EPA are also available due to their positive effect on cardiovascular health. The FAO Expert Consultation recommends a daily intake of 250 mg EPA plus DHA, with pregnant and lactating women requiring a higher intake of 300 mg/day, 200 mg of which should be DHA (FAO 2010).

The FAO Expert Consultation confirmed in their 2010 report there is convincing evidence that replacing SFA with PUFA decreases the risk of CHD (FAO 2010). This has been confirmed by both observational studies (Jakobsen *et al.* 2009) and RCTs (Mozaffarian *et al.* 2010). For more details see SFA section.

The Expert Consultation also concluded that there is insufficient evidence for establishing any relationship between PUFA consumption and cancer (FAO 2010). A systematic review and meta-analysis of prospective cohort studies concluded intake of *n*-3 and *n*-6 PUFA does not significantly affect risk of prostate cancer (Chua *et al.* 2102). However, another systematic review and meta-analysis of data from prospective cohort studies found a higher intake ration of *n*-3:*n*-6 PUFA is associated with lower risk of breast cancer (Yang *et al.* 2014). More research on the association between PUFA and cancer is needed before any firm conclusions can be made. There are growing concerns about the adverse effects of overheated polyunsaturated oils used in contionuous deep frying. Whilst no direct link has been proven the compounds produced are potentially cytotoxic.

In the following, different types of PUFA are discussed in more detail.

n-6 PUFA

The general recommendation for reducing cardiovascular risk is to replace SFA in the diet with PUFA including *n*-3 and *n*-6 PUFA. Recently, concern has been raised by some about the purported benefits of increasing *n*-6 PUFA, and that in fact doing so may increase cardiovascular risk (e.g. Ramsden *et al.* 2010, 2013; Ravnskov *et al.* 2014; DiNicolantonio 2014)

A systematic review and meta-analysis aimed to identify whether studies that exclusively increased *n*-6 PUFA without increasing *n*-3 PUFA supported the general recommendation that increasing *n*-6 PUFA (along with *n*-3 PUFA) is beneficial for cardiovascular health. Based on three datasets from two trials, pooled analysis resulted in no effect of (almost) exclusively increasing *n*-6 PUFA on non-fatal MI (RR 1.03; 95%CI 0.74, 1.43; p=0.90), and a non-significant positive association with CHD death (RR 1.17; 95%CI 0.82, 1.68; P=0.38) and all-cause mortality (RR 1.16; 95%CI 0.95, 1.42; p=0.15) (Ramsden *et al.* 2010). Ramsden and colleagues subsequently repeated their meta-analysis including data recovered from the Sydney Diet Heart Study, in which very high PUFA intakes (15%E, largely *n*-6 PUFA) led to a 17% increased risk of cardiovascular mortality and a 16% increased risk of coronary heart disease mortality in 458 men aged 30-59 years with a recent coronary event. Pooled analysis of four datasets from three trials (i.e. including the findings from the Sydney Diet Heart Study) resulted in a hazard ratio of death from coronary heart disease with increased *n*-6 PUFA of 1.33, which approached statistical significance (95%CI 0.99, 1.79; p=0.06) (Ramsden *et al.* 2013). In contrast, analysis of studies that increased both n-6 and n-3 PUFA resulted in a significant reduction in risk of non-fatal MI (RR 0.73; 95%CI 0.54, 0.99; p=0.04), and a non-significant reduction in risk of CHD death (RR0.81; 95%CI 0.64, 1.03; p=0.08) and all-cause mortality (RR 0.92; 95%CI 0.80, 1.06; p=0.25) (Ramsden *et al.* 2010, 2013). Based on their findings, the authors of the systematic review concluded that advice to increase

n-6 PUFA should be reconsidered, because there is no indication of benefit, and there is a possibility of harm (Ramsden *et al.* 2010, 2013).

Although the findings and conclusions by Ramsden *et al.* have been applauded by some (Calder 2010), others have argued that Ramsden's findings in fact support those of many other studies, i.e. that consumption of vegetable oils rich in *n*-6 PUFA lowers the risk of CHD (Harris *et al.* 2011). The four studies in the 'mixed *n*-3/*n*-6' analysis used soybean oil, which only contains small amounts of *n*-3 PUFA and has a relatively high *n*-6/*n*-3 ratio, but still resulted in a 22% risk reduction of CHD events. Harris and colleagues note that in these trials *n*-6 PUFA consumption was often raised to very high levels, in fact exceeding the recommended upper intake levels for PUFA and producing high *n*-6:*n*-3 ratios, yet they still demonstrated a CHD benefit, not detriments, therefore contradicting the hypothesis that high *n*-6 PUFA intakes increase the risk of CHD (Harris *et al.* 2011).

The hypothesis by Ramsden is also not supported by findings of a meta-analysis of RCTs that randomised adults to increased total or *n*-6 PUFA consumption (but not mainly *n*-3 PUFA), which resulted in a significant 19% reduction of occurrence of CHD events (RR 0.81; 95%CI 0.70, 0.95), corresponding to a risk reduction for each 5%E greater PUFA consumption of 10% (RR 0.90; 95%CI 0.83, 0.97) (Mozaffarian *et al.* 2010; see more details in the SFA section). Although it cannot be completely excluded that the beneficial effect on cardiovascular health may be partly due to a simultaneous increase in *n*-3 PUFA, these findings suggest that increasing *n*-6 PUFA is certainly not detrimental to health. More evidence to support this comes from two recently published papers. In a U.S. cohort study in 2792 participants age 65+ years and free of CVD at baseline researchers used plasma levels of LA as an objective measure for LA intake. The researchers found that those who had the highest plasma levels of LA had a significantly lower risk of all-cause mortality compared to those with the lowest levels (HR 0.87, p for trend=). The lower risk of death was largely attributable to lower cardiovascular mortality, in particular nonarrhythmic CHD (Wu et al. 2014). A recent systematic review and meta-analysis of prospective cohort studies, investigated the association between LA consumption and coronary heart disease (CHD) in subjects free of CHD at baseline. The researchers found that LA consumption was inversely associated with risk of CHD events and CHD deaths. Those with the highest LA consumption had a 15% lower risk of CHD events and a 21% lower risk of CHD death compared to those with the lowest intakes. An increase of LA intake by 5% of total energy replacing SFA was associated with a 9% lower risk of CHD events and a 13% lower risk of CHD death, while replacing carbohydrates was associated with a 13% lower risk of both CHD events and deaths (Farvid et al. 2014).

Questions about the safety of increasing *n*-6 PUFA have also been raised based on several suggested mechanisms for a potential detrimental effect of *n*-6 PUFA on cardiovascular health, including: 1) increased sensitivity to oxidation of LDL cholesterol with increased LA content, leading to increased atherosclerotic plaque growth; 2) increased tissue/plasma levels of AA, which is produced by the metabolism of linoleic acid, also increasing atherosclerotic plaque growth and rupture (Calder 2010). However, recent systematic reviews of clinical trials have not found evidence to support the concept that modifying current intakes of dietary LA has an effect on changing levels of AA in plasma/serum or erythrocytes in adults consuming Western-type diets (Rett & Whelan 2011), or that addition of LA to the diet increases the concentration of inflammatory markers (Johnson & Fritsche 2012). Wu et al. (2014) found no association between plasma AA levels and total or CVD mortality. Overall, there does not seem to be a need to reconsider current recommendations. Firstly, the intakes of n-PUFA (mainly LA) in intervention studies included by Ramsden *et al.* (2010, 2013) are very high. The FAO Expert Consultation acknowledges that high intakes of PUFA (>11% of energy) may be detrimental to health due to risk of lipid peroxidation, particularly when tocopherol intake is low. Therefore, an upper intake limit of 11%E total PUFA and an upper intake limit of 9%E of *n*-6 PUFA is recommended (FAO 2010). Intakes of LA in most countries are between 3 and 7% (Elmadfa & Kornsteiner 2009), and an intake

above 9%E may not be achieved by most people, although they may be above recommended upper limits in some people.

Secondly, the general recommendation is not to replace SFA with exclusively *n*-6 PUFA, but with total PUFA, which includes both *n*-3 and *n*-6 PUFA, which Ramsden *et al.* (2013) acknowledge reduces cardiovascular risk. Most (but not all) sources of *n*-6 PUFA are also sources of *n*-3 PUFA. However, possibly there may be a need to give more specific recommendations regarding the replacement of SFA with PUFA as to not risk an intake of total PUFA above 11%E and of *n*-6 PUFA above 9%E.

n-3 PUFA

Intake of *n*-3 PUFA, and more specifically the *n*-3 LCPUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been associated with cardioprotective properties and are some of the best studied types of fat.

Meta-analysis of observational data by Skeaff and Miller (2009) resulted in a significantly reduced risk of fatal CHD by 18% (RR 0.82; 95% CI, 0.71–0.94) when comparing highest with lowest *n*-3 LCPUFA or fish consumption levels. Fish and *n*-3 LCPUFA consumption was not significantly associated with risk of total CHD events (RR 0.87; 95% CI, 0.71–1.06), non-fatal CHD (RR 0.81; 95% CI, 0.59–1.10) or total MI (RR 0.79; 95% CI, 0.53–1.17) (Skeaff & Miller 2009). A meta-analysis of prospective cohort studies that compared intakes of <250mg and ≥250mg *n*-3 LCPUFA per day with regard to risk of CHD resulted in a significant 35% reduction in the risk of sudden cardiac death when consumption was above as compared to below 250mg/day (RR 0.65; 95%CI 0.54, 0.79; p<0.0001). Consuming at least 250mg *n*-3 LCPUFA per day was also associated with a non-significant lower risk of fatal coronary events (RR 0.83; 95%CI 0.68, 1.03; p=0.085) but was not associated with risk of non-fatal MI (RR 0.93; 95%CI 0.82, 1.06; p=0.290) (Musa-Veloso *et al.* 2011). Two meta-analyses of prospective cohort studies found highest vs. lowest intake of fish was associated with a significantly reduced incidence of heart failure (Djoussé *et al.* 2012; Li *et al.* 2013).one of which also analysed *n*-3 LCPUFA intakes and found a borderline significant reduction in risk of heart failure (RR 0.86; 95%CI 0.74, 1.00; p=0.05) (Djoussé *et al.* 2012).

Clinical trials investigating the effect of *n*-3 LCPUFA supplementation are largely carried out in people who have an underlying cardiovascular condition or have suffered a cardiovascular event. A meta-analysis of data from RCTs by Skeaff and Miller (2009) resulted in no significant reduction in risk of CHD death associated with *n*-3 LCPUFA treatment (RR 0.88; 95% CI, 0.76–1.01, p = 0.061). The risk of fatal MI (RR 0.92; 95% CI, 0.65–1.29, p = 0.626) and sudden cardiac death (RR 1.02; 95% CI, 0.78–1.33, p = 0.889) were also not significantly decreased by treatment with *n*-3 LCPUFA, and neither were nonfatal CHD outcomes including revascularisation events (RR 0.94; 95% CI, 0.86–1.04, p = 0.211), non-fatal MI (RR 1.03; 95% CI, 0.77–1.37, p = 0.864) and angina (RR 0.89; 95% CI, 0.75–1.04, p = 1.49). Skeaff and Miller found exclusion of one study with methodological concerns (DART II) considerably altered the summary estimates, such that *n*-3 LCPUFA treatment significantly reduced the risk of fatal CHD by 19% (RR 0.81; 95% CI, 0.71–0.92, p = 0.001) and fatal MI by 26% (RR 0.74; 95% CI, 0.57–0.96, p = 0.025). But risk of sudden cardiac death was still not significantly reduced after exclusion of the DART II trial (RR 0.89; 95% CI, 0.77–1.09, p = 0.251) (Skeaff & Miller 2009). These outcomes are supported by another meta-analysis which resulted in a significantly reduced risk of cardiovascular death (OR 0.87; 95%CI 0.79, 0.95), a significantly risk of sudden cardiac death (OR 0.87; 95%CI 0.76, 0.99) and a significantly reduced risk of all-cause mortality (OR 0.92; 95%CI 0.85, 0.99) with supplementation of EPA and DHA (Marik & Varon 2009).

Two subsequent meta-analyses, including studies published since 2009, found no protective effect of *n*-3 LCPUFA supplementation on risk of cardiovascular events, cardiovascular death or all-cause mortality (Rizos *et al.* 2012; Kwak *et al.* 2012), whereas another meta-analysis published in the same year but using different inclusion and exclusion criteria found a significantly reduced risk of cardiovascular events (OR 0.90; 95%CI 0.85, 0.96), cardiac death (OR 0.91; 95%CI 0.83, 0.99) and

coronary events (OR 0.82; 95%CI 0.75, 0.90) (Delgado-Lista *et al.* 2012). The most recently published meta-analysis of RCTs found supplementation with *n*-3 LCPUFA was associated with a significantly reduced risk of cardiac death (RR 0.68; 95%CI 0.56, 0.83), sudden death (RR 0.67, 95%CI 0.52, 0.87) and MI (RR 0.75; 95%CI 0.63, 0.88), but no significant effect on all-cause mortality (RR 0.89; 95%CI 0.78, 1.02) (Casula *et al.* 2013).

The varying outcomes of RCTs (and meta-analyses) may be due to variations in study design (and inclusion criteria), and also due to variations in statin use in the included RCTs, with studies including fewer statin users generally showing a significant effect of EPA and DHA supplementation, and some studies with a high proportion of statin users (in particular more recent RCTs) finding no effect (see Weichselbaum *et al.* 2013). A large number of studies fail to characterise fully the quality and concentration of the LCPUFA used in the studies. For instance many fish oils are oxidised and historically have contained contaminants such as heavy metals and dioxins. Modern omega-3 oils are much better today with gloabal quality standards being used and monitored. For example, researchers from one large trial found supplementation with *n*-3 LCPUFA reduced incidence of major cardiovascular events by 54% (although this did not reach statistical significance [p=0.051], possibly due to a relatively small number of subjects in this group), whereas no treatment effect in statin users was found (Eussen *et al.* 2012). However, more studies are needed to shed light on the reasons for varying outcomes of RCTs, in particular because it has been suggested that, in certain circumstances and depending on the pathophysiological status of the patient (e.g. ventricular tachycardia), *n*-3 LCPUFA supplements may have a pro-arrhythmic effect (Burr 2007; Jenkins *et al.* 2008), which may suggest n-3 LCPUFA supplementation is counter-indicative for some individuals.

Several meta-analyses have found a significant inverse association between fish consumption and risk of stroke, with those with the highest consumption of fish having a 12-13% lower risk of stroke compared to those with the lowest intakes (Larsson & Orsini 2011; Xun *et al.* 2012; Chowdhury *et al.* 2012). Two meta-analyses found a reduced risk of ischaemic but not haemorrhagic stroke (Larsson & Orsini 2011; Xun *et al.* 2012), whereas one meta-analysis found a significantly reduced risk for haemorrhagic stroke but not for ischaemic stroke (Chowdhury *et al.* 2012). Chowdhury and colleagues (2012) also carried out a separate analysis for *n*-3 LCPUFA and found no association with cerebrovascular disease based on observational data, which was supported by a separate analysis of data from RCTs which resulted in no effect of *n*-3 LCPUFA supplementation on cerebrovascular disease and either stroke subtype (Chowdhury *et al.* 2012).

There is some evidence to suggest that higher fish intake, dietary DHA intake and DHA levels in the blood may be positively associated with a lower risk of dementia and Alzheimer's disease, and a slower rate of cognitive decline, but not all studies have found an association. Data from RCTs do not suggest that *n*-3 LCPUFA are effective in preventing cognitive decline (Weichselbaum *et al.* 2013)

Overall, there is convincing evidence from observational studies that fish and *n*-3 LCPUFA consumption is associated with a lower risk of heart disease. This is generally supported by data from RCTs, although more recent RCTs have found no beneficial effects which may be at least partly due to a higher use of statins and other modern treatments of CHD. The uncertainty about the effect of *n*-3 LCPUFA supplementation on CHD risk while observational data generally support a beneficial effect of fish and/or *n*-3 LCPUFA may also indicate that other factors in fish may contribute to a protective effect. Fish intake is also associated with a lower risk of stroke, but more studies are needed to investigate whether this is due to *n*-3 LCPUFA.

TRANS-FATTY ACIDS (TFA)

Naturally occurring *trans*-fats are rare and are only found in dairy products and meats from ruminant animals. However, the introduction of catalytic hydrogenation for conversion of liquid unsaturated oils to solid fats led to a stark increase in TFA in the diet. This is because partial hydrogenation converts many unsaturated double bonds from a *cis*- to a *trans*-configuration, which can result in 30-60% of all fatty acids being TFA in the partially hydrogenated oil (Nishida & Uauy 2009). The WHO recommendations state as a goal that TFA should provide no more than 1% of total energy due to their adverse effects on blood lipoprotein profiles and CHD risk (WHO 2003).

A more recent review of the evidence to support a scientific update on TFA by the WHO summarised evidence from observational and experimental studies (Mozaffarian *et al.* 2009). Both controlled trials and observational studies consistently show that TFA consumption has adverse effects on lipids, including increased LDL cholesterol, reduced HDL cholesterol and an increased total/HDL cholesterol ratio, and has pro-inflammatory effects and adverse effects on endothelial function. Controlled and observational studies also suggest that TFA worsens insulin resistance, particularly among predisposed individuals, but further study is needed to confirm apparent effects on weight gain and diabetes incidence in humans. Together, the findings suggest TFA consumption produces a unique cardiometabolic effect, stimulating multiple related pathways linked to the insulin resistance/metabolic syndrome (Mozaffarian *et al.* 2009).

Data from retrospective case-control and prospective cohort studies have demonstrated significant positive associations between TFA consumption and CHD events. Differential effects of specific TFA are less well established, and it is difficult to draw firm conclusions. Evidence from observational studies does not support an adverse effect of ruminant TFA (in contrast to industrial TFA) on risk of CHD. Also, because ruminant fat contains low levels of TFA (usually <6% of fatty acids), the quantities of ruminant TFA consumed were generally low in most of the populations studied. Even when total ruminant fat intake is relatively high, the potential amount of TFA from this source is still quite modest (Mozaffarian *et al.* 2009).

In New Zealand and many other countries TFA has largely been removed from many products, including table spreads. In December 2014 FSANZ (Food Standards Australia New Zealand) completed its evaluation of a labelling review recommendation on TFAs. The survey results were consistent with previous survey results, showing exposure to TFAs is well below WHO limits of more than 1 percent of dietary intake. (FSANZ 2015)

SELECTED OILS AND SOURCES OF FAT

PALM OIL

Consumption of TFA from partially hydrogenated fats is associated with an increased risk of CVD (see TFA section above), resulting in increasing efforts to reduce TFA in foods. Hydrogenated fats are used for their mouth-feel, stability and low-cost, and an acceptable alternative for the industry needs to provide similar advantages. Palm oil is commonly used by industry as an alternative due to its unique properties. However, due to its relatively high content of SFA (around 50%), there is evidence Palm oil affects blood lipids (in particular LDL cholesterol) less favourably compared to unhydrogenated vegetable oils rich in unsaturated fatty acids including; sunflower oil, olive oil, soybean oil or rapeseed oil. However it should be noted not all studies have come to this conclusion (Clifton 2011; Mensink *et al.* 2003; Fattore *et al.* 2014). A recently published meta-analysis found diets rich in palm oil compared to diets rich in stearic acid (a SFA), MUFA and PUFA showed significantly higher total cholesterol, LDL cholesterol, but also higher HDL cholesterol, whereas the same biomarkers were significantly lower when compared to the two fatty acids myristic and lauric acid. Compared to TFA, a diet rich in palm

oil significantly increased HDL, which significantly lowered total:HDL cholesterol ratio (Fattore *et al.* 2014). However, the authors noted that they did not assess the quality of the included studies, most of which used a cross-over design and more than half of these did not have (or report) a wash-out period between interventions.

Overall, although palm oil is less favourable compared to other vegetable oils in terms of the effect on total:HDL cholesterol, palm oil is still better than the partially hydrogenated vegetable oils high in TFA (Mensink *et al.* 2003).

COCONUT FAT/OIL

Coconut oil is high in SFA, yet is often heralded to be a healthy fat in popular media. It has been suggested that the high proportion of medium chain fatty acids, in particular the SFA lauric acid, may be partly responsible for their purported beneficial effects. In a recent position statement the New Zealand Heart Foundation concluded research often quoted to support use of coconut oil is largely based on animal data or extrapolated from research on medium chain triglycerides (MCTs) which contain almost no lauric acid. The Heart Foundation suggests it is erroneous to extrapolate research on MCTs to coconut oil as the main fatty acid in coconut oil is lauric acid, which is different to those in commercially produced MCT oils and that lauric acid does not behave like a medium-chain fatty acid in the body. In addition, the triglycerides in coconut oil are much larger than those in MCT oils so their effect is different (Heart Foundation 214). Mensink *et al.* (2003) found in their systematic review and meta-analysis that lauric acid markedly increases cholesterol, more so than other SFAs, but that much of this is due to HDL cholesterol. As a result, lauric acid had a more favourable effect on total:HDL cholesterol than any other fatty acid, either saturated or unsaturated. The authors predicted that coconut fat would lead to a reduced total:HDL cholesterol ratio compared to the average US dietary fat, butter or carbohydrates, but would do so to a lesser degree than fats high in unsaturated fatty acids including olive oil, soybean oil and rapeseed oil (Mensink et al. 2003). This is in line with findings from two intervention studies carried out in New Zealand, which suggest that coconut oil has a more beneficial effect on blood lipids than butter, but a less favourable effect than safflower oil, which is high in PUFA (Cox *et al.* 1995; Cox *et al.* 1998). A study carried out in Sri Lanka, where coconut fat is a major source of fat, showed that reduction of SFA (and total fat) in the diet and partial replacement with unsaturated fat is associated with beneficial effects on blood lipid parameters (Mendis *et al.* 2001). The effects of coconut oil on triglyceride levels versus unsaturated oils are generally not significant (Heart Foundation 2014). Overall, evidence seems to suggest that despite its high SFA content coconut oil has a more favourable effect on blood lipids compared to carbohydrates and other fats high in SFA, such as butter, but has a less favourable effect compared to dietary fats high in PUFA (Heart Foundation 2014).

OLIVE OIL

Olive oil has traditionally been viewed as the heart healthiest of oils, mainly due to the fact that is an important staple of the traditional Mediterranean diet, which has been associated with lower risk of CVD. To investigate whether olive oil is associated with CVD, heart disease or stroke, researchers from Spain systematically reviewed the evidence from case-control, prospective cohort and intervention studies. Based on findings from nine studies, all of which were carried out in the Mediterranean region, the authors found that a 25g increment of olive oil consumed per day is associated with an 18% lower risk of CVD (RR 0.82; 95%CI 0.70, 0.96). When looking at stroke and heart disease separately, the researchers found a 26% lower risk of stroke for every 25g olive oil (RR 0.74; 95%CI 0.60, 0.92), but no significant association with risk of heart disease (Martínez-González *et al.* 2014). These findings are in line with results from the PREDIMED study, a large randomised trial where supplementary virgin olive oil had a significant protective effect on stroke, but not myocardial infarction (Estruch *et al.* 2013). As all of the included studies were carried out in the Mediterranean region, it is difficult to draw conclusions on how adding olive oil to a different dietary pattern, such as

the Western diet, may affect cardiovascular risk. It also has to be noted that simply adding olive oil to the diet without reducing overall calorie intake may lead to body weight gain, which is an independent risk factor for CVD.

The lack of association between consumption of olive oil, a rich source of MUFA, and CHD is in line with a lack of association between MUFA and CHD (see MUFA section for details). It is likely that the health protective effect of the Mediterranean diet is due to the overall healthy profile of this dietary pattern, which is high in fruits, vegetables, legumes and unrefined grains, rather than one single component.

MILK AND DAIRY PRODUCTS

Dairy products (dairy) are a significant source of SFA in Western dietary patterns and as such would be expected to be associated with an increased risk of CVD. However, evidence from observational studies does not support the hypothesis that dairy, including high-fat dairy foods, is linked to an increased cardiovascular risk (Gibson *et al.* 2009; Soedamah-Muthu *et al.* 2011; Kratz *et al.* 2013). In a dose-response meta-analysis of data from 17 prospective cohort studies there was a moderate but statistically significant inverse association between milk and total CVD risk, with a 6% risk reduction per glass (200mL) milk per day (RR 0.94; 95%CI 0.89, 0.99). Pooled results from 6 studies suggested no association between milk consumption and CHD. Pooled results from a limited number of studies on the association between total dairy (n=4), total high-fat dairy (n=4), and total low-fat dairy (n=3) consumption and CHD risk showed no significant association between total dairy product intake and CHD (RR 1.02; 95%CI 0.93, 1.11), total high-fat dairy and CHD (RR 1.04; 95%CI 0.89, 1.21) and total low-fat dairy and CHD (RR 0.93; 95%CI 0.74, 1.17). Analysis of data from 6 prospective studies suggests milk intake is associated with a non-significant inverse association between milk and risk of stroke (RR 0.87; 95%CI 0.72, 1.07) Pooled analysis from 8 observational studies suggests no association between milk consumption and all-cause mortality (Soedamah-Muthu *et al.* 2011). Overall, these data do not suggest dairy is associated with an increased risk of CVD, despite dairy being a main contributor to SFA intakes. Dairy is a nutrient-dense food rich in minerals and vitamins, which can exert beneficial effects on CVD (Soedamah-Muthu *et al.* 2011). It has been suggested bioactive fatty acids present in dairy, including butyric acid, phytanic acid, cis- and trans palmitoleic acid and conjugated LA, may also play a role in counteracting negative effects of SFA, although more evidence is needed to support this (Kratz *et al.* 2013). Although the data is limited, based on the above meta-analysis there is also no evidence for a clear benefit of low- compared to high-fat dairy. The effect of SFA on CHD depends on the source of energy by which it is substituted to maintain energy balance (see SFA section), and low-fat dairy products may not provide a cardiovascular benefit if the proportion of carbohydrate is simultaneously increased.

DIETARY INTAKES OF FAT AND FATTY ACIDS IN NEW ZEALAND

Mean total fat intake in New Zealand adults is just above the recommended upper level of 33%E. The median intake is 33% in men and 34% in women. By definition, 50% of the population lie above (i.e. have higher intakes) and 50% lie below (i.e. have lower intakes) the median intake level. This means that around half of the New Zealand adult population have fat intakes above the recommended upper level. Both mean and median SFA intake was 13%E, which means more than half of NZ adults have intakes above the recommended level, whereas more than half of the NZ adult population has PUFA intakes below the minimum recommended level. The intakes of MUFA were generally within the guideline levels (University of Otago & Ministry of Health 2011).

In order to reduce their risk of CVD, it would be beneficial to replace some SFA in the NZ diet with PUFA.

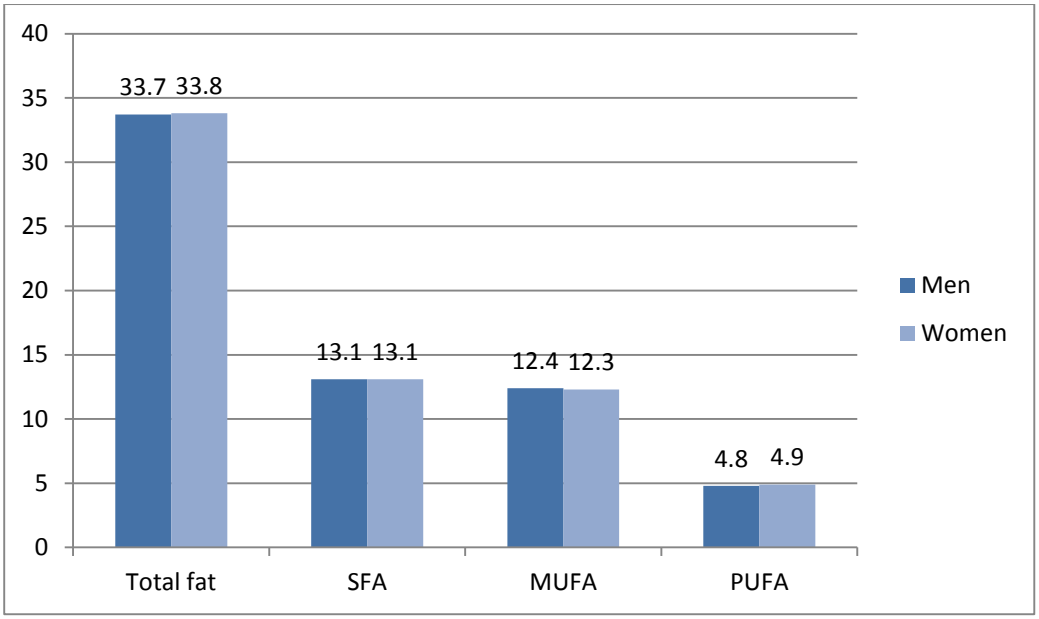

Figure 3: Intake of total fat, saturated fatty acids (SFA), mono-unsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) in New Zealand adults, given as % of total energy intake (%E).
Source: University of Otago & Ministry of Health 2011

DISCUSSION

The topic of dietary fats is highly debated among nutrition and health experts. In particular, there is an ongoing debate around the role of SFA and its association with cardiovascular risk. Although some recent meta-analyses suggest there is no association between SFA and risk of CVD (Siri-Tarino *et al.* 2010a; Chowdhury *et al.* 2014), many experts argue that not taking into account what SFA is replaced with (as was done in these two reviews) is a major limitation, as evidence suggests that replacing SFA with PUFA is beneficial for cardiovascular health, whereas replacing SFA with carbohydrates (particularly readily digestible carbohydrates) is not. Another issue in many of the studies included by Siri-Tarino and Chowdhury is the use of 1-day records to assess nutrient intake, which provide poor estimation of the *usual* dietary intake of an individual and cannot reliably rank individuals by their long-term intake. This leads to so called regression dilution bias, which can consequently lead to a lack of significant associations (Skeaff & Miller 2009). It seems diverging opinions on the relationship between SFA and the replacement of SFA with other macronutrients and cardiovascular health outcomes seem to stem from the type of evidence included or excluded from systematic reviews. Overall, evidence suggests replacing SFA with PUFA is associated with cardiovascular benefits, whereas replacing SFA with carbohydrates is not, and may possibly be detrimental for cardiovascular health.

The recommendation to increase PUFA intake while reducing SFA intake, both *n*-6 and *n*-3 PUFA, has also been challenged as it was argued that replacing SFA with *n*-6 PUFA may be detrimental to health. However, evidence does not suggest increasing *n*-6 PUFA alongside *n*-3 PUFA is detrimental for health, which is in line with the general recommendation to replace SFA with PUFA (both *n*-3 and *n*-6). The studies used to back the argument that increasing n-6 PUFA without also increasing n-3 PUFA is detrimental for health are intervention studies with very high n-6 PUFA intakes. This is not in contrast to current recommendations, which suggest limiting PUFA intake to no more than 11%E as it is well established that very high intakes may be detrimental to health due to risk of lipid peroxidation. Current intakes of PUFA in New Zealand are below 5%E, and it is unlikely that the 11%E upper level would be surpassed on a population level if some SFA was replaced with PUFA.

Although most New Zealanders are recommended to lower their SFA intakes, which are generally above the recommended upper level of 12%E, there may be a need to be more specific in dietary recommendations as to what SFA should be replaced with, as replacing SFA with carbohydrates will not lead to a cardiovascular benefit, and may potentially be detrimental to health. Simply telling consumers to lower their intake of SFA will give the impression that SFA *per se* is bad for health and that it does not matter what they replace SFA with, as long as they lower their intakes overall. It is important to remember consumer attitudes, as well as efforts by governmental and non-governmental organisations, also drive product development and product reformulations by the food industry. In an attempt to satisfy consumer demands for 'healthier' products, many food producers have reformulated their products so as to reduce the levels of fat and saturated fat. This has often led to the content of carbohydrates (including sugar) being increased for sensory and/or texture purposes. Such reformulations may have (unwittingly) contributed to increased intakes of carbohydrates in place of SFA, which evidence suggests is not beneficial for health.

It may be necessary to be more precise in dietary recommendations about replacing SFA with PUFA rather than carbohydrates, and to ensure that this is considered in efforts of product reformulation.

The vehicle a certain nutrient is delivered in, e.g. whether PUFAs come from biscuits made with margarine or from nuts, or whether SFA comes from a pot of full-fat yoghurt or a sausage, may also play a role in the potential benefit or detriment of a nutrient, and possibly this needs to be considered when making recommendations.

The challenging positions by several health experts, in particular regarding SFA and its role in cardiovascular health, may be an opportunity to rethink whether scientific evidence is translated into recommendations, and also government and industry efforts around reformulation, that truly benefit the consumer.

RECOMMENDATIONS AND KEY MESSAGES

- There is convincing evidence that replacing SFA with PUFA (both *n*-6 and *n*-3 PUFA) is associated with improved blood lipid parameters and a lower risk of CHD, whereas replacing SFA with largely refined carbohydrates does not seem to provide a benefit or may even increase risk.

- Although MUFA have a beneficial effect on blood lipid parameters, evidence from cohort studies and some experimental animal data does not suggest that MUFA are associated with a lower risk of CHD. This may be at least partly explained by the origin of MUFA in the respective studies, as many of the main sources of MUFA in Western dietary patterns are also major sources of SFA.

- There is convincing evidence from observational studies that fish and *n*-3 LCPUFA consumption is associated with a lower risk of heart disease. This is generally supported by data from RCTs, although more recent RCTs have found no beneficial effects which may be at least partly due to a higher use of statins and other modern treatments of CHD.

- There is convincing evidence TFA consumption is associated with adverse effects on blood lipids and an increased risk of CHD. Evidence from observational studies does not support an adverse effect of ruminant TFA (in contrast to industrial TFA) on risk of CHD. In New Zealand TFA has largely been removed from many products.

- There is some evidence the total matrix of a food may be more important than just its fatty acid content when predicting the effect of a food on CHD risk. For example, dairy is a main contributor to SFA intake in the New Zealand diet, but data from observational studies does not suggest that dairy is associated with an increased risk of CVD.

- In light of the challenges posed to the paradigm that SFA is associated with an increased risk of CVD, there may be the need to rethink current recommendations, in particular in respect to what SFA should be replaced with in the diet, making it clear replacing SFA with PUFA is beneficial for cardiovascular health, whereas replacing SFA with carbohydrates is not.

REFERENCES

Astrup A, Dyerberg J, Elwood P *et al.* (2011) The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010? *Am J Clin Nutr* **93**:684-688.

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.

Burr (2007) Secondary prevention of CHD in UK men: the Diet and Reinfarction Trial and its sequel. *Proc Nutr Soc* **66**:9-15.

Calder P (2010) The American Heart Association advisory on *n*-6 fatty acids: evidence based or biased evidence? *Brit J Nutr* **104**:1575-1576.

Casula M, Soranna D, Catapano AL, Corrao G (2013) Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: A meta-analysis of randomized, double blind, placebo controlled trials. *Atherosler Suppl* **14**:243-251.

Chowdhury R, Stevens S, Gorman D *et al.* (2012) Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. *BMJ* **345**:e6698.

Chowdhury R, Warnakula S, Kunutsor S et al. (2014) Association of dietary, circulating, and supplement fatty acids with coronary risk. A systematic review and meta-analysis. *Ann Int Med* 160:398-406.

Chua ME, Sio MCD, Sorongon MC, Dy JS (2012) Relationship of dietary intake of omega-3 and omega-6 fatty acids with risk of prostate cancer development: a meta-analysis of prospective studies and review of literature. *Prostate Cancer* **2012**:Article ID 826254.

Clifton PM (2011) Palm oil and LDL cholesterol. *Am J Clin Nutr* **94**:1392-1393.

Cox C, Mann J, Sutherland W *et al.* (1995) Effects of coconut oil, butter, and safflower oil on lipids and lipoproteins in persons with moderately elevated cholesterol levels. *J Lipid Res* **36**:1787-1795.

Cox C, Sutherland W, Mann J *et al.* (1998) Effects of dietary coconut oil, butter and safflower oil on plasma lipids, lipoproteins and lathosterol levels. *Eur J Clin Nutr* **52**:650-654.

Dawczynski C, Kleber M, März W *et al.* (2014) Comment on Chowdhury *et al.* (2014), posted on 15 April 2014. Available at: http://annals.org/article.aspx?articleid=1846638 (accessed 3 July 2014).

Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J *et al.* (2012) Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. *Brit J Nutr* **107**:S201-S213.

DiNicolantonio JJ (2014) The cardiometabolic consequences of replacing saturated fats with carbohydrates or Ω-6 polyunsaturated fats: Do the dietary guidelines have it wrong? *Open Heart* **1**:e000032.

Djoussé L, Akinkuolie AO, Wu JHY *et al.* (2012) Fish consumption, omega-3 fatty acids and risk of heart failure: a meta-analysis. *Clin Nutr* **31**:846-853.

Elmadfa I, Kornsteiner M (2009) Dietary fat intake – a global perspective. *Ann Nutr Metab* **54**(Suppl1):8-14.

Estruch R, Ros E, Salas-Salvado J *et al*. (2013) Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* **368**:1279-1290.

Eussen S, Geleijnse J, Giltay E *et al.* (2012) Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. *Eur Heart J* **33**:1582-1588.

FAO (2010) Fats and fatty acids in human nutrition. Report of an Expert Consultation, 10-14 November 2008 in Geneva. Food and Agriculture Organization of the United Nations, Rome.

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.

Fattore E, Bosetti C, Brighenti F *et al.* (2014) Palm oil and blood lipid-related markers of cardiovascular disease: a systematic review and meta-analysis of dietary intervention trials. *Am J Clin Nutr* **99**:1331-50.

Food Standards Australia New Zealand (December 2014) Review of Food Labelling Law and Policy (accessed February 2015)

Gibson RA, Makrides M, Smithers LG *et al.* (2009) The effect of dairy foods on CHD: a systematic review of prospective cohort studies. *Brit J Nutr* **102**:1267-1275.

Gleijnse JM, Brouwer IA, Kromhout D (2014) Comment on Chowdhury *et al.* (2014), posted on March 27 2014. Available at: http://annals.org/article.aspx?articleid=1846638 (accessed 3 July 2014).

Harris WS, Brouwer I, Mozaffarian D (2011) *n*-6 Fatty acids and risk for CHD: consider all the evidence. *Brit J Nutr* **106**:951-952.

Heart Foundation (2014) Coconut and the heart. Online: http://www.heartfoundation.org.nz/uploads/Coconut_position_statement_2014.pdf (accessed 20 February 2015).

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.

Jenkins D, Josse A, Dorian P *et al.* (2008) Heterogeneity in randomized controlled trials of long chain (fish) omega-3 fatty acids in restenosis, secondary prevention and ventricular arrhythmias. *J Am Coll Nutr* **27**:367-378.

Johnson G, Fritsche K (2012) Effect of dietary linoleic acid on markers of inflammation in healthy persons: a systematic review of randomized controlled trials. *J Acad Nutr Diet* **112**:1029-1041.

Katan MB, Brouwer IA, Clarke R *et al.* (2010) Comment on Siri-Tarino *et al.* (2010a), *Am J Clin Nutr* **92**:459-460.

Keys (1980) Coronary heart disease in seven countries. *Circulation* **41**:1-211.

Keys A, Menotti A, Karvonen MJ *et al.* (1986) The diet and 15-year death rate in the Seven Countries Study. *Am J Epidemiol* **124**:903-915.

Kratz M, Baars T, Guyenet S (2013) The relationship between high-fat dairy consumption and obesity, cardiovascular, and metabolic disease. *Eur J Nutr* **52**:1-24.

Kwak S, Myung SK, Lee Y *et al.* (2012) Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease. A meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch Int Med* **172**:686-694.

Larsson S, Orsini N (2011) Fish consumption and the risk of stroke: a dose-response meta-analysis. *Stroke* **42**:3621-3623.

Lartey A, Koletzko BV, Diekman C *et al.* (2014) Comment on Chowdhury *et al.* (2014), posted on April 7 2014. Available at: http://annals.org/article.aspx?articleid=1846638 (accessed 3 July 2014).

Li YH, Zhou CH, Pei HJ *et al.* (2013) Fish consumption and incidence of heart failure: a meta-analysis of prospective cohort studies. *Chin Med J* **126**:942-948.

Malhotra A (2013) Saturated fat is not the major issue. Let's bust the myth of its role in heart disease. *BMJ* 347:f6340.

Marik P, Varon J (2009) Omega-3 dietary supplements and the risk of cardiovascular event: a systematic review. *Clin Cardiol* **32**:365-372.

Martínez-González MA, Dominguez LJ, Delgado-Rodríguez M (2014) Olive oil consumption and risk of CHD and/or stroke: a meta-analysis of case-control, cohort and intervention studies. *Brit J Nutr* **112**:248-259.

Mendis S, Samarajeewa U, Thattil RO (2001) Coconut fat and serum lipoproteins: effects of partial replacement with unsaturated fats. *Brit J Nutr* **85**:583-589.

Mensink RP, Zock PL, Kester ADM, Katan MB (2003) Effects of dietary fatty acids and carbohydrates on the ration of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* **77**:1146-1155.

Ministry of Health (2003) Food and Nutrition Guidelines for Healthy Adults: A background paper. Ministry of Health, Wellington.

Mozaffarian D, Aro A, Willett WC (2009) Health effects of trans-fatty acids: experimental and observational evidence. *Eur J Clin Nutr* **63**:S5-S21.

Mozaffarian D, Micha R, Wallace S (2010) Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* **7**(3):e1000252.

Musa-Veloso K, Binns MA, Kocenas A *et al.* (2011) Impact of low v. moderate intakes of long-chain n-3 fatty acids on risk of coronary heart disease. *Brit J Nutr* **106**:1129-41.

Nishida C, Uauy R (2009) WHO Scientific Update on health consequences of *trans* fatty acids: introduction. *Eur J Clin Nutr* **63**:S1-S4.

Ramsden CE, Hibbeln JR, Majchrzak SF, Davis JM (2010) n-6 Fatty acid-specific and mixed polyunsaturate dietary interventions have different effects on CHDrisk: a meta-analysis of randomised controlled trials. *Brit J Nutr* **104**:1586-1600.

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.

Ravnskov U, DiNicolantonio JJ, Harcombe Z *et al.* (2014) The questionable benefits of exchanging saturated fat with polyunsaturated fat. *Mayo Clin Proc* **89**:451–453.

Rett & Whelan (2011) Increasing dietary linoleic acid does not increase tissue arachidonic acid content in adults consuming Western-type diets: a systematic review. *Nutr Metab* **8**:36.

Rizos C, Ntzani E, Bika E *et al*. (2012) Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *J Am Med Assoc* **308**:1024-1033.

Sanders T (2010) The role of fat in the diet – quantity, quality and sustainability. *Nutrition Bulletin* **35**:138-146.

Scarborough P, Rayner M, van Dis I, Norum K (2010) Comment on Siri-Tarino *et al.* (2010a), *Am J Clin Nutr* **92**:458.

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

Schwingshackl L, Hoffmann G (2013) Comparison of effects of long-term low-fat vs. high-fat diets on blood lipid levels in overweight or obese patients: A systematic review and meta-analysis. *J Acad Nutr Diet* **113**:1640-1661.

Siri-Tarino PW, Sun Q, Hu FB, Krauss RM (2010a) Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* **91**:535-546.

Siri-Tarino PW, Sun Q, Hu FB, Krauss RM (2010b) Reply to Scarborough *et al.* (2010), *Am J Clin Nutr* **92**:459.

Sivakumaran S, Martell S, Huffman L (2012) The Concise New Zealand Food Composition Tables, 9th Edition. The New Zealand Institute for Plant & Food Research Limited and Ministry of Health, New Zealand.

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.

Soedamah-Muthu SS, Ding LE, Al-Delaimy WK *et al.* (2011) Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Am J Clin Nutr* **93**(1):158-171.

Stamler J (2010) Diet-heart: a problematic revisit. *Am J Clin Nutr* **91**:497-499.

University of Otago, Ministry of Health (2011) A Focus on Nutrition: Key findings of the 2008/09 New Zealand Adult Nutrition Survey. Ministry of Health, Wellington.

WCRF & AICR (World Cancer Research Fund & American Institute for Cancer Research) (2007) *Food, Nutrition, Physical Activityand the Prevention of Cancer: A Global Perspective*. WCRF & AICR: Washington, DC.

Weichselbaum E, Coe S, Buttriss J, Stanner S (2013) Fish in the diet: a review. *Nutrition Bulletin* **38**:128-177.

WHO (2003) Diet, nutrition and the prevention of chronic diseases. Report of a Joint WHO/FAO Expert Consultation. World Health Organization, Geneva.

Wu JHY, Lemaitre RN, King IB *et al.* (2014) Circulating omega-6 polyunsaturated fatty acids and total and cause-specific mortality. The cardiovascular health study. *Circulation* **130**:1245-1253.

Xun P, Qin B, Song Y *et al.* (2012) Fish consumption and risk of stroke and its subtypes: accumulative evidence from a meta-analysis of prospective cohort studies. *Eur J Clin Nutr* **66**:1199-1207.

Yang B, Ren XL, Fu YQ *et al.* (2014) Ratio of n-3/n-6 PUFAs and risk of breast cancer: a meta-analysis of 274135 adult females from 11 independent prospective studies. *BMC Cancer* **14**:105.