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Saturated fats, dairy foods and health: A curious paradox?

D. I. Givens

Institute of Food, Nutrition and Health, University of Reading, Reading, UK

Abstract

Cardiovascular diseases (CVD) remain a major cause of death and morbidity worldwide. Dietary guidelines aim to restrict the intake of saturated fatty acids (SFA) as they are regarded as an important risk factor for CVD due to their association with increased blood cholesterol. As dairy foods are major contributors of dietary SFA, there have been guidelines to reduce consumption of these foods. However, it is now generally accepted that the effects of reducing intake of SFA are dependent on what replaces them in the diet. Reduced CVD risk has been associated with replacement of SFA with *cis*-polyunsaturated fatty acids (*cis*-PUFA) and/or *cis*-monounsaturated fatty acids (*cis*-MUFA), with replacement by carbohydrate leading to no reduction or even increased CVD risk. Most studies on the effect of diet/food on CVD risk have used total cholesterol (TC) and/or low-density lipoprotein cholesterol (LDL-C) in blood as the marker(s) of risk. However, because of potentially attenuating effects of dairy foods (*e.g.* effect of protein on blood lipids and blood pressure; food matrix effects on fat bioavailability), a wider range of markers is needed to more fully evaluate disease risk. Nevertheless, whilst prospective evidence shows no increase in CVD risk from high dairy consumption, it is still unclear whether replacing a proportion of SFA in dairy fat with *cis*-MUFA will lead to reduced CVD risk. The relatively few randomised controlled trials that have examined this using TC/LDL-C as risk markers give some indications of reduced CVD risk from consumption of milk and dairy products with modified fatty acid composition, compared with those of normal milk fat composition. The results of ongoing studies will add valuable new evidence on this issue.

Keywords: cardiovascular disease, dairy products, fatty acids, milk

Introduction

Despite improved prevention and treatment programmes, cardiovascular disease (CVD) remains a major cause of death and morbidity in the European Union (EU) (Wilkins *et al.* 2017) and worldwide (Forouzanfar *et al.* 2015). Although CVD mortality is now decreasing in most European countries, there are some 49 million people living with CVD in the EU with an estimated cost of €210 billion/year (Wilkins *et al.* 2017). Moreover, the increase in prevalence of overweight/obesity and type 2 diabetes seen in the EU in recent times casts doubt on whether the current reduction in CVD mortality is sustainable. It is therefore imperative that modifiable risk factors for CVD, such as diet, are used to their full advantage.

Correspondence: Professor Ian Givens, Director, Institute of Food, Nutrition and Health, University of Reading, Whiteknights, PO Box 266, Reading RG6 6AR, UK.
E-mail: d.i.givens@reading.ac.uk

Table 1 Mean daily intake of saturated fatty acids (SFA) and as a percentage of food energy (FE) and total energy (TE) by gender and age, together with the contribution of dairy foods to SFA intake in the UK (from Bates *et al.* 2014)

	Males (years of age)				Females (years of age)			
	4–10	11–18	19–64	65+	4–10	11–18	19–64	65+
SFA (g/day)	23.0	27.8	28.4	28.7	22.3	21.7	22.1	23.0
SFA % FE	13.1	12.7	12.6	13.9	13.3	12.4	12.6	13.8
SFA % TE	13.1	12.6	11.9	13.2	13.3	12.3	12.1	13.5
Contribution of dairy foods to total SFA intake (%)	34	26	25	34	41	25	28	36

A high intake of saturated fatty acids (SFA) has for many years been regarded as an important risk factor for CVD, leading to public health targets recommending a dietary SFA intake that should not be exceeded. In the UK, this recommendation, currently being reviewed, is that SFA intake should not exceed 11% of food energy intake but, as shown in Table 1, intake for all age groups in the *National Diet and Nutrition Survey* (Bates *et al.* 2014) exceeds this target. Table 1 also shows that milk and dairy products (including butter) are major sources of dietary SFA and this has led to some proposals to reduce dairy product consumption in order to reduce SFA intake. Recent evidence suggests that this approach is likely to be too simplistic (Thorning *et al.* 2017).

Effects of saturated fat consumption

Recent meta-analyses of prospective studies (Siri-Tarino *et al.* 2010; Chowdhury *et al.* 2014; de Souza *et al.* 2015) have raised doubts about whether a high intake of SFA is a risk factor for CVD. The specific effect of SFA on CVD risk is well established and is mainly mediated via increases in blood lipids, particularly low-density lipoprotein cholesterol (LDL-C) (Griffin 2017). There is strong evidence implicating LDL-C as a risk factor in CVD events (Ridker 2014) and randomised controlled trials (RCT) with LDL-C lowering interventions have confirmed a causal relationship between blood LDL-C and CVD, particularly coronary heart disease (CHD; Marz *et al.* 2016). However, as highlighted by Mensink *et al.* (2003), SFA can also increase high-density lipoprotein cholesterol (HDL-C), generally regarded as being associated with reduced CVD risk. It should also be noted that blood LDL-C contains the cholesterol present in all LDL particles, with the small, dense LDL particles (sdLDL), whilst containing less cholesterol per particle than other LDL particles, are more strongly associated with increased CHD risk than the larger less dense LDL particles (Hoogeveen *et al.* 2014). One cross-sectional study in healthy Swedish men indicated that dietary fatty acids typically found in dairy foods gave rise to significantly less sdLDL particles (Sjogren *et al.* 2004). In particular, SFA 4:0 to 10:0 and 14:0 ($P < 0.05$) in the diet and 15:0 and 17:0 (markers of dairy fat intake) in serum phospholipids ($P < 0.05$) were associated with fewer sdLDL particles. This study suggests that LDL particle size distribution may be favourably modified by dairy products in the diet but this needs further investigation.

Substitution of dietary saturated fatty acids with unsaturated fatty acids

As noted above, data from prospective studies (Siri-Tarino *et al.* 2010; de Souza *et al.* 2015) have cast doubts on the traditional view of SFA as a risk factor for CVD. Recently, an expert group met to review this conflict (Nettleton *et al.* 2017). Their key recommendation was that it is vitally important to understand the effect of replacing SFA in the diet. Nettleton *et al.* (2017) concluded that the greatest reduction in CHD risk was seen when dietary SFA are replaced with *cis*-polyunsaturated fatty acids (*cis*-PUFA) although there was little effect on risk of stroke. They cited RCTs which showed that replacement of 10% and 5% of energy from SFA by *cis*-PUFA reduced CVD events by 27% and 10%, respectively. It is also noteworthy that replacement of SFA with refined carbohydrate is associated with no improvement or even an increase in CVD risk (Micha & Mozaffarian 2010).

Nettleton *et al.* (2017) also reported that there are insufficient data to draw conclusions on the effect of replacing SFA with *cis*-MUFA, although there are a number of important studies. A cross-sectional population study by Miura *et al.* (2013) reported a linear inverse association between *cis*-MUFA (especially oleic acid) intake and diastolic blood pressure, and in the recruited population study of Hassan *et al.* (2015), dietary oleic acid intake was negatively associated with systolic and diastolic blood pressure. Recently, the RCT of Liu *et al.* (2016) compared diets high in *cis*-PUFA with those high in *cis*-MUFA and showed that the latter reduced abdominal obesity with accompanying reductions in blood pressure and blood

triacylglycerols (TAG). The *Reading, Imperial, Surrey, Cambridge, and Kings* (*RISCK*) study (Jebb *et al.* 2010) showed that replacing SFA with *cis*-MUFA, compared to replacement with carbohydrate, reduced the total cholesterol (TC):HDL-C ratio and, more recently, the *Dietary Intervention and VAScular function* (*DIVAS*) study (Vafeiadou *et al.* 2015) showed that replacement of about 9.6% of energy from SFA by MUFA lowered serum TC by 8.4%, LDL-C by 11.3% and TC:HDL-C by 5.6% ($P < 0.001$). Thus, overall, there is mounting evidence that replacing dietary SFA with *cis*-MUFA may be beneficial for reducing the risk of CVD and associated factors in the metabolic syndrome.

Dairy consumption and cardiometabolic disease

Evidence from prospective cohort studies

Numerous studies have investigated the association between milk and dairy product consumption and cardiometabolic diseases (CMD; CVD + type 2 diabetes). Whilst prospective study data are regarded as providing weaker evidence than RCT data on the diet/food–disease relationship, they have the advantage of looking at long-term effects and use real disease events as the outcome measures. Very long-term RCTs using disease data would be impractical and very expensive, and this means that most RCTs use markers of disease risk (*e.g.* LDL-C) as primary outcome measures. Meta-analysis of prospective studies is a valuable tool for looking at the overall association between dairy foods and CMD risk, although there remains a concern that in many studies the dairy foods involved are poorly defined which limits assessment of the relative effects of different dairy foods. This is particularly the case when comparing high-fat vs. low-fat dairy products. Early meta-analyses of prospective cohort studies reported that, overall, high milk consumption does not increase the relative risk (RR) of CHD (Elwood *et al.* 2008, 2010). A further meta-analysis, which combined prospective cohort and clinical studies, also indicated no significant increase in the RR of CHD in high vs. low milk consumers (RR 0.94; 95% CI, 0.75–1.13) (Mente *et al.* 2009).

A number of dose–response meta-analyses have been published recently examining the association between dairy food consumption and type 2 diabetes (Gijsbers *et al.* 2016), stroke (de Goede *et al.* 2016), and CVD and all-cause mortality (Guo *et al.* 2017). These are the most up-to-date dose–response meta-analyses available and the results are summarised in Table 2. Overall, these studies show no increase in risk of CVD per unit increase in milk and cheese consumptions and a significant reduction in risk of stroke per unit consumption of cheese and milk. Interestingly, yoghurt consumption was associated with a reduced risk of type 2 diabetes (Gijsbers *et al.* 2016). There are few studies examining the effects of butter on CMD but the recent dose–response meta-analysis of Pimpin *et al.* (2016) indicates no significant association between butter consumption and all-cause mortality, CVD, CHD or stroke, although there was a significant negative association with type 2 diabetes (Table 2). The meta-analysis of Pimpin *et al.* (2016) involved relatively few cohorts for CVD ($n = 4$), CHD ($n = 3$), stroke ($n = 3$) although 11 cohorts were suitable for inclusion for type 2 diabetes.

Evidence from randomised controlled trials

Given the evidence linking SFA intake with blood levels of LDL-C, and blood levels of LDL-C with CVD risk, and the fact that dairy foods are major contributors to SFA, the consistent neutral or beneficial associations between dairy foods and CVD from analysis of prospective data remain something of a paradox to many. There is, however, increasing evidence

Table 2 Recent dose–response meta-analyses examining the relative risk (RR) of cardiometabolic disease in relation to consumption of dairy foods

Dairy food	Outcome	RR (95% CI)	Reference
Milk (per 244 g/day)	All-cause mortality	1.00 (0.93–1.07)	Guo *et al.* (2017)
Milk (per 244 g/day)	CVD	1.01 (0.93–1.10)	Guo *et al.* (2017)
Cheese (per 10 g/day)	CVD	0.98 (0.95–1.00)	Guo *et al.* (2017)
Yoghurt (per 50 g/day)	CVD	1.03 (0.97–1.09	Guo *et al.* (2017)
Milk (per 200 g/day)	Stroke	0.93 (0.88–0.98)	de Goede *et al.* (2016)
Cheese (per 40 g/day)	Stroke	0.97 (0.94–1.01)	de Goede *et al.* (2016)
Yoghurt (per 80 g/day)	Type 2 diabetes	0.86 (0.83–0.90)	Gijsbers *et al.* (2016)
Butter (per 14 g/day)	All-cause mortality	1.01 (1.00–1.03)	Pimpin *et al.* (2016)
Butter (per 14 g/day)	CVD	1.00 (0.98–1.02)	Pimpin *et al.* (2016)
Butter (per 14 g/day)	CHD	0.99 (0.96–1.03)	Pimpin *et al.* (2016)
Butter (per 14 g/day)	Stroke	1.01 (0.93–0.99)	Pimpin *et al.* (2016)
Butter (per 14 g/day)	Type 2 diabetes	0.96 (0.93–0.99)	Pimpin *et al.* (2016)

CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.

that goes some way to explain why meta-analyses of prospective studies show no increased risk of CVD in high dairy consumers.

In the UK, up to 30% of adults are hypertensive (Townsend *et al.* 2015) and hypertension is one of the major risk factors for CVD development and stroke, in particular. Gene polymorphisms, nutrition, the environment and interactions between these factors contribute to the development of hypertension. Milk and milk-derived products provide essential micronutrients (*e.g.* calcium, magnesium, iodine and vitamin D) and proteins (whey, casein and specific bioactive peptides) some of which have been associated with beneficial hypotensive effects, either independently or in combination within dairy foods (Kris-Etherton *et al.* 2009). A recent 8-week RCT (Fekete *et al.* 2016) showed that whey protein isolate (two doses of 28 g, mixed with water, per day) had a greater hypotensive effect than casein and the effects were seen on both central and peripheral blood pressures. A number of mechanisms by which milk and its components could lower blood pressure (BP) have been proposed (Fekete *et al.* 2013). Peptides released during digestion of casein and whey proteins have been shown to have hypotensive effects by inhibiting the action of angiotensin-I-converting enzyme, resulting in vasodilation (FitzGerald & Meisel 2000) by modulating the release of endothelin-1 by endothelial cells (Maes *et al.* 2004) and acting as opioid receptor ligands increasing nitric oxide production, which mediates arterial tone (Kris-Etherton *et al.* 2009). There is little firm evidence for differential effects of low- vs. high-fat dairy foods on hypertension. For example, whilst Engberink *et al.* (2009) reported an inverse association between low-fat dairy intake and risk of hypertension in older adults, others have shown that both low- and high-fat milk products have hypotensive effects (Ralston *et al.* 2012). In addition, results from the *Caerphilly Prospective Study* showed that when compared with non-milk consumers, men who consumed >586 ml/day of milk had on average a 10.4 mmHg lower systolic BP after a 22.8-year follow-up (Livingstone *et al.* 2013). Some of the inconsistencies between studies may well relate to the lack of a consistent definition of what constitutes low- and high-fat dairy foods.

There is now good evidence that arterial stiffness, especially of the large vessels, is an important predictor of CVD events (Cockcroft & Wilkinson 2000) and this can be affected by dietary patterns (Kesse-Guyot *et al.* 2010). The measurement of carotid-femoral pulse wave velocity (PWV) is regarded as the gold standard for assessing arterial stiffness and can independently predict CVD events (Sutton-Tyrrell *et al.* 2005; Van Bortel *et al.* 2012). Livingstone *et al.* (2013), using data from the *Caerphilly Prospective Study*, showed for the first time in a longitudinal study that dairy product consumption (not including butter) does not increase PWV (*i.e.* no indication of increased arterial stiffness). Moreover, the measurement of augmentation index, another indicator of arterial stiffness, was 1.9% units lower ($P = 0.021$) in men with the highest dairy consumption (Livingstone *et al.* 2013). A cross-sectional study also reported that consumption of dairy foods was negatively associated with PWV (Crichton *et al.* 2012).

Food matrix effects of dairy products on blood lipids

Traditional nutritional evaluation of foods and diets and their relationship with the health of the consumer has generally been based on separate assessments of individual food components such as protein, fat, carbohydrates and micronutrients. This approach of associating one nutrient to one health effect (*e.g.* SFA intake to CVD risk) may explain some of the discrepancies between a food's predicted health effect, based on its nutrient content, and its actual health effect when consumed as a whole food. There is increasing evidence that for an accurate evaluation of the health effects of some dairy foods, the so-called food matrix does indeed need to be taken into account. This topic has recently been extensively reviewed by a Working Party set up by the Universities of Copenhagen and Reading, and the conclusions are reported by Thorning *et al.* (2017). The Working Party concluded that 'Evidence to date indicates the dairy matrix has specific beneficial effects on health, as the metabolic impact of whole dairy on bodyweight, cardiometabolic disease risk, and bone health differ to that of single dairy constituents. Also, different types of dairy products seem to be distinctly linked to various health effects and disease risk markers. In addition, different processing methods and dairy structures can enhance interactions in the dairy matrix, thereby modifying the metabolic effects of dairy consumption. The nutritional value of dairy products should therefore be considered as the biofunctionality of the sum of nutrients within the dairy matrix structures'.

A good example of the differential effects on blood lipids of SFA intake from cheese and butter is shown in the RCT of Hjerpsted *et al.* (2011), which consisted of two 6-week crossover periods with 49 men and women replacing part of their habitual dietary fat with 13% of energy from cheese or butter (80 g/day

and 36 g/day of total fat and SFA, respectively). The cheese and butter diets provided 1192 g and 417 g of calcium/day, respectively. Relative to baseline, cheese did not increase TC or LDL-C whereas butter increased both (P <0.001 and <0.05, respectively), and additionally cheese intake led to a 5.7% and 6.9% lower TC and LDL-C concentrations, respectively (P <0.0001), compared with butter. Various mechanisms have been suggested as being responsible for the health benefits of this so-called matrix effect, and the study of Lorenzen and Astrup (2011) identified mechanisms which could contribute to the differential effects of cheese and butter on blood cholesterol. They randomised study participants to one of four isoenergetic diets comprising low-fat (25% energy intake) and high-fat diets (40% energy intake), each of which contained either low (700 mg/day) or high (2800 mg/day) calcium. The key results are summarised in Table 3. Increasing calcium intake increased faecal fat and bile acid excretion in both low- and high-fat diets, although the high-fat diets also increased faecal fat loss. Lorenzen and Astrup (2011) proposed that the key effect of calcium on faecal fat and bile acid excretion is likely to be the result of formation of insoluble calcium-fatty acid soaps and/or of hydrophobic aggregations with phosphorus and bile acids. Increased faecal fat excretion is indicative of reduced fat absorption and hence a moderated blood cholesterol response, whilst increased bile acid excretion would reduce the amount that was recycled via the enterohepatic circulation. Reduced bile acid recycling would lead to increased metabolism of cholesterol for bile acid synthesis, thus reducing that in the circulation.

These studies indicate that the impact of dairy foods on CVD risk factors may be dependent on the food matrix, even for dairy foods that supply the same amount of dairy fat and SFA. However, as concluded by Thorning *et al.* (2017), further work is needed to fully understand food matrix effects on health and how these relate to specific dairy foods and methods of processing.

Table 3 The effect of diets high or low in fat and calcium (Ca) on faecal losses of fat, calcium and bile acids (from Lorenzen & Astrup 2011)

	High fat		Low fat		*P* for	
Faecal losses	Low Ca	High Ca	Low Ca	High Ca	Ca	Fat
Fat (g/day)	6.6	11.3	5.5	8.0	***	**
Ca (mg/day)	549	2477	576	2478	***	NS
Bile acid (μmol/day)	274	393	178	346	**	NS

***P <0.001; **P <0.01; NS: non-significant P >0.05.

Effects of milk proteins on blood lipids

Whilst most studies have reported on the effect of dairy fat/fatty acids on blood lipids, there is now evidence that milk proteins can also influence blood lipids. The study of Tong *et al.* (2014), using a high-fat diet with rats, found that whey protein significantly increased HDL-C, although studies with humans have not always shown the same effect (Chiu *et al.* 2014). Some studies have shown that whey protein tends to reduce plasma TAG (Pal *et al.* 2010) and TC (Petyaev *et al.* 2012). The study of Mariotti *et al.* (2015) showed that compared with whey protein, casein markedly reduced postprandial TAG (22 ± 10% reduction in the 6-hour area under the curve, P <0.05). Similar effects were seen for plasma chylomicrons (apoB-48; P <0.05). The recent study of Fekete *et al.* (2016) reported that whilst whey protein and calcium caseinate both significantly reduced TC (−20.26 mmol/l, P = 0.013 and −20.20 mmol/l, P = 0.042, respectively), only whey protein reduced TAG (−20.23 mmol/l, P = 0.025) compared with the control.

Overall, these studies indicate that milk proteins can have important lowering effects on blood lipids, which may moderate any opposite effects of dairy fats and be a contributing factor to the neutral or health benefits of dairy foods observed in prospective studies. Nevertheless, it is clear that more work in this area is needed and supports the proposal of Lovegrove and Givens (2016) for a meta-analysis of effects of milk proteins on blood lipids.

Replacing saturated fatty acids in milk fat by modifying the diet of the dairy cow

Milk fat per 100 g typically contains 70–75 g SFA, 20–25 g *cis*-MUFA and small (2–5 g) amounts of *cis*-PUFA (Kliem *et al.* 2013a). Fatty acids in milk fat originate from two sources, either by direct incorporation from the peripheral circulation or from *de novo* synthesis in the mammary gland using short-chain (2:0 and 4:0) precursors. Mammary *de novo* synthesis accounts for all 4:0 to 12:0 fatty acids, most of the 14:0 and typically about half of 16:0 secreted in milk, while all 18:0 and longer-chain fatty acids are derived entirely from circulating plasma lipids (Hawke & Taylor 1995). Modification of the fatty acid profile of milk offers a strategy for lowering the population's

intake of SFA, by reducing SFA in the food chain, whilst preserving the beneficial contributions that dairy products make to the protein and micronutrient content of the human diet (Kliem & Givens 2011). Over 100 studies have explored the potential of partially replacing milk SFA with *cis*-MUFA or *cis*-PUFA through supplementation of the dairy cow diet with plant oils or oilseeds (Glasser *et al.* 2008). Broadly, the target is to increase the supply of long-chain fatty acids (of chain length 18 carbons and above) to the mammary gland, which inhibit the synthesis of short- and medium-chain SFA (Givens & Shingfield 2006). The inclusion of oilseeds in cows' diets typically produces reductions in the SFA content of 100 g of milk fat from 70 g to between 55 and 60 g (Givens & Shingfield 2006). One study in the EU-funded *LIPGENE* project (involving BNF and the University of Reading) examined the effect of form of rapeseed lipid in the diet of the dairy cow on the reduction in milk SFA and increase in *cis*-MUFA that could be achieved (Givens *et al.* 2009). The cows' diet treatments were no rapeseed lipid (control) or rapeseed lipid in the form of rapeseed oil, whole, unprocessed rapeseeds or milled rapeseeds. The inclusion of 49 g of rapeseed oil per kg of dry matter in the diet for a 28-day period increased *cis*-MUFA from 23 to 29 g per 100 g of milk fat, while reducing SFA from 70 to 56 g per 100 g of milk fat. It is clear that using whole, unprocessed rapeseed is not a viable option but the other two rapeseed lipid forms reduced SFA (notably 16:0) and increased *cis*-MUFA (notably *cis*-18:1). As part of the Biotechnology and Biological Sciences Research Council Diet and Health Research Industry Club (BBSRC DRINC) funded series of studies, Kliem *et al.* (2013b) showed that increasing amounts of an experimental calcium salt of *cis*-MUFA in the cows' diet produced a linear reduction in SFA and a linear increase in *cis*-MUFA in the milk fat. A summary of these results is shown in Table 4. The recent study of Markey *et al.* (2015a) showed similar changes in the composition of milk fat as a result of using high oleic sunflower oil in the diet of the cow.

As seen in Table 4, the inclusion of unsaturated fatty acids in the dairy cow diet can lead to increased concentrations of naturally produced ruminant *trans*-fatty acids (rTFA), predominantly *trans*-MUFA, in the milk. The intake of *trans*-fatty acids (TFA) from industrially hydrogenated vegetable oils is known to substantially increase the risk of CVD (de Souza *et al.* 2015) and, as a result, there has been a substantial reduction in the amount of industrial TFA (iTFA) in the UK food chain (SACN 2007). The association between rTFA and CVD risk has lacked good experimental evidence although negative associations between plasma *trans*-palmitoleic acid (*trans*-16:1n-7) concentration (assumed to be mainly of dairy origin) and type 2 diabetes have been reported (Mozaffarian *et al.* 2010, 2013). The recent meta-analysis by de Souza *et al.* (2015) reported that intake of iTFA, but not rTFA, was positively associated with CHD mortality and risk of CHD, and intake of rTFA inversely associated with risk of type 2 diabetes. Clearly, there is a need for more RCT-based evidence on the impact of rTFA in particular.

Does replacing saturated fatty acids in dairy products provide health benefits?

Based on the long-standing association between SFA intake and plasma cholesterol, it would seem that changing the fatty acid composition of dairy foods to replace some SFA with *cis*-PUFA and/or *cis*-MUFA could provide a useful way to reduce SFA intake whilst retaining the nutritional and cardiometabolic

Table 4 Effect of calcium salts of *cis*-monounsaturated fatty acids (MUFA) supplementation on key milk fatty acid families (g/100 g total fatty acids; from Kliem *et al.* 2013b)

	Treatments*					$P^{\dagger}$ for		
Fatty acids	Control	CS2	CS4	CS6	SEM	Diet	Linear	Quadratic
Σ SFA	71.0	63.1	57.1	51.6	1.66	<0.001	<0.001	0.008
Σ *cis*-MUFA	19.9	24.4	26.7	30.8	0.91	<0.001	<0.001	0.073
Σ *trans* total	6.1	9.6	12.9	15.6	0.74	<0.001	<0.001	<0.001
Σ *trans*-MUFA	4.3	6.2	8.7	10.5	0.22	<0.001	<0.001	0.691
Σ *n*-6 PUFA	3.1	3.0	3.1	3.2	0.20	0.048	0.033	0.050
Σ *n*-3 PUFA	0.40	0.41	0.42	0.38	0.013	0.001	0.054	<0.001

*Where CS2, CS4 and CS6 are diets containing 20, 40 and 60 g/kg diet dry matter calcium salt, respectively; SEM, standard error of the mean.
†Significance of overall effect of diet and/or linear/quadratic responses.

benefits of milk. Indeed, using published models of cholesterol responses to SFA intake, it was predicted that, in the EU, reductions of some 10 500 and 3900 deaths from CHD and stroke per annum, respectively, could result from such a strategy (Givens 2008), although it is now clear that such a simple model is not likely to apply to all dairy foods for some of the reasons discussed above.

Livingstone *et al.* (2012) reviewed the RCT-based evidence on the effect on CVD risk markers of consuming dairy products modified by changing the nutrition of the dairy cow. Of the nine RCT studies identified, most used modified butter as the main test food and change in blood cholesterol was used as the primary risk marker. Of the six comparable studies that measured blood cholesterol, five and four reported significant reductions in TC and LDL-C, respectively, one showed a rise in TC and two showed no effect on LDL-C following chronic consumption of modified milk and dairy products. One study (Seidel *et al.* 2005) was of particular interest as it was the only study to compare the effects of modified dairy products in normocholesterolaemic (NC) and hypercholesterolaemic (HC) subjects. Dairy cows were fed a diet containing *cis*-MUFA-rich rapeseed cake to achieve the changes in milk fatty acid concentrations and the milk was used to produce butter and yogurt. In a 13-week, three-phase, randomised, crossover, controlled study, subjects were fed modified milk, butter and yogurt, as well as non-modified milk, margarine and yogurt. The results showed that, overall, LDL-C was reduced (−0.38 mmol/l; $P < 0{\cdot}05$) and HDL-C was increased (+0·33 mmol/l; $P < 0{\cdot}05$) when the modified products were consumed, resulting in a reduced LDL:HDL ratio (−0.43 mmol/l; $P < 0.05$). These changes were seen in both the HC and NC subjects, interestingly, with greater change in the NC subjects. Seidel *et al.* (2005) proposed that this may be due to lipid metabolism in HC subjects being more complex and/or dietary intervention being less effective.

As discussed earlier, it is now clear that the use of a single marker (*e.g.* blood cholesterol) for predicting the cardiometabolic risk/benefit associated with consumption of fatty acid-modified dairy foods may not be adequate and that a wider range and more holistic markers are needed. A study of this type is presently underway at the University of Reading in the *REplacement of SaturatEd fat in dairy on Total cholesterol* (*RESET*) study (ClinicalTrials.gov NCT02089035) – a 3.5-year project funded by the UK Medical Research Council. It is investigating the impact of reducing SFA in milk and dairy products on vascular function and a wide range of CMD risk biomarkers, after both acute and chronic consumption. Some early findings on the fatty acid composition of the dairy foods used were presented by Markey *et al.* (2015a) and on consumer acceptance of the SFA reduced milk, cheese and butter by Markey *et al.* (2015b). The blinded consumer test indicated that most consumers preferred the conventional products. This suggests that further development of modified dairy foods is needed to ensure they are acceptable to consumers. This would need to be accompanied by clear health-related information to allow consumers to make informed decisions on purchase and consumption.

Conclusions

It is now clear that the effects of reducing dietary SFA are best interpreted by an understanding of which macronutrients replace them, with reduced CVD risk being associated with the replacement of SFA with *cis*-PUFA and *cis*-MUFA. Most judgements have, however, been made using TC/LDL-C as the primary markers of CVD risk, and because of potentially counterbalancing effects in dairy food (*e.g.* effect of protein on blood lipids and blood pressure; matrix effects on fat bioavailability), a wider range of markers are needed. Nevertheless, whilst prospective evidence shows no increase in CVD risk from high dairy consumption, it is still unclear whether replacing a proportion of SFA in dairy fat with *cis*-MUFA will lead to reduced CVD risk. The relatively few RCTs that have examined this, using TC/LDL-C as the risk marker, provide some indication of reduced CVD risk from consumption of milk and dairy products with modified fatty acid composition, compared with those of normal milk fat composition. The results of ongoing studies will add valuable new evidence on this issue.

Conflict of interest

The author has no conflict of interest to disclose.

References

Bates B, Lennox A, Prentice A *et al.* (2014). *National Diet and Nutrition Survey, Results from Years 1-4 (combined) of the Rolling Programme (2008/2009-2011/12)*. A survey carried out on behalf of Public Health England and the Food Standards Agency.

Chiu S, Williams PT, Dawson T *et al.* (2014) Diets high in protein or saturated fat do not affect insulin sensitivity or plasma

concentrations of lipids and lipoproteins in overweight and obese adults. *Journal of Nutrition* **144**: 1753–9.

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. *Annals of Internal Medicine* **160**: 398–406.

Cockcroft JR & Wilkinson IB (2000) Large arterial stiffness: an important therapeutic target. *Journal of Human Hypertension* **14**: 533–5.

Crichton GE, Elias MF, Dore GA *et al.* (2012) Relations between dairy food intake and arterial stiffness: pulse wave velocity and pulse pressure. *Hypertension* **59**: 1044–51.

Elwood PC, Givens DI, Beswick AD *et al.* (2008) The survival advantage of milk and dairy consumption: an overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *Journal of the American College of Nutrition* **27**: 723S–34S.

Elwood PC, Pickering JE, Givens DI *et al.* (2010) The consumption of milk and dairy foods and the incidence of vascular disease and diabetes: an overview of the evidence. *Lipids* **45**: 925–39.

Engberink MF, Geleijnse JM, de Jong N *et al.* (2009) Dairy intake, blood pressure, and incident hypertension in a general Dutch population. *Journal of Nutrition* **139**: 582–7.

Fekete ÁA, Givens DI & Lovegrove JA (2013) The impact of milk proteins and peptides on blood pressure and vascular function: a review of evidence from human intervention studies. *Nutrition Research Reviews* **26**: 177–90.

Fekete ÁA, Giromini C, Chatzidiakou Y *et al.* (2016) Whey protein lowers blood pressure and improves endothelial function and lipid biomarkers in adults with prehypertension and mild hypertension: results from the chronic Whey2Go randomized controlled trial. *American Journal of Clinical Nutrition* **104**: 1534–1154.

FitzGerald RJ & Meisel H (2000) Milk protein-derived peptide inhibitors of angiotensin-I-converting enzyme. *British Journal of Nutrition* **84**: S33–7.

Forouzanfar MH, Alexander L, Anderson HR *et al.* (2015) Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* **386**: p2287–323.

Gijsbers L, Ding EL, Malik VS *et al.* (2016) Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies. *American Journal of Clinical Nutrition* **103**: 1111–24.

Givens DI (2008) Impact on CVD risk of modifying milk fat to decrease intake of saturated fatty acids and increase intake of *cis*-monounsaturates. *Proceedings of the Nutrition Society* **67**: 419–27.

Givens DI & Shingfield KJ (2006) Optimising dairy milk fatty acid composition. In: *Improving the Fat Content of Foods*, (CM Williams & J Buttriss eds), pp. 252–80. Woodhead Publishing Ltd.: Cambridge UK.

Givens DI, Kliem KE, Humphries DJ *et al.* (2009) Effect of replacing calcium salts of palm oil distillate with rapeseed oil, milled or whole rapeseeds on milk fatty-acid composition in cows fed maize silage-based diets. *Animal* **3**: 1067–74.

Glasser F, Ferlay A & Chilliard Y (2008) Oilseed lipid supplements and fatty acid composition of cow milk: a meta-analysis. *Journal of Dairy Science* **91**: 4687–703.

de Goede J, Soedamah-Muthu SS, Pan A *et al.* (2016) Dairy consumption and risk of stroke: a systematic review and updated dose-response meta-analysis of prospective cohort studies. *Journal of American Heart Association* **5**: e002787.

Griffin BA (2017) Serum low-density lipoprotein as a dietary responsive biomarker of cardiovascular disease risk: consensus and confusion. *Nutrition Bulletin* **42**: 266–73.

Guo J, Astrup A, Lovegrove JA *et al.* (2017) Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *European Journal of Epidemiology* **32**: 269–87.

Hassan NE, El Shebini SM, Ahmed NH *et al.* (2015) Association between macronutrients intake, visceral obesity and blood pressure in a sample of obese Egyptian women. *Macedonian Journal of Medical Sciences* **3**: 184–8.

Hawke TW & Taylor JC (1995) Influence of nutritional factors on the yield, composition and physical properties of milk fat. In: *Advanced Dairy Chemistry Volume 2: Lipids*, (PF Fox ed), pp. 37–88. Chapman and Hall: London (UK).

Hjerpsted J, Leedo E & Tholstrup T (2011) Cheese intake in large amounts lowers LDL-cholesterol concentrations compared with butter intake of equal fat content. *American Journal of Clinical Nutrition* **94**: 1479–84.

Hoogeveen RC, Gaubatz JW, Sun W *et al.* (2014) Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Arteriosclerosis Thrombosis and Vascular Biology* **34**: 1069–77.

Jebb SA, Lovegrove JA, Griffin BA *et al.* (2010) Effect of changing the amount and type of fat and carbohydrate on insulin sensitivity and cardiovascular risk: the RISCK trial. *American Journal of Clinical Nutrition* **92**: 748–58.

Kesse-Guyot E, Vergnaud A-C, Fezeu L *et al.* (2010) Associations between dietary patterns and arterial stiffness, carotid artery intima-media thickness and atherosclerosis. *European Journal of Cardiovascular Prevention and Rehabilitation* **17**: 718–24.

Kliem KE & Givens DI (2011) Dairy products in the food chain: their impact on health. *Annual Review of Food Science and Technology* **2**: 21–36.

Kliem KE, Shingfield KJ, Livingstone KM *et al.* (2013a) Seasonal variation in the fatty acid composition of milk available at retail in the United Kingdom and implications for dietary intake. *Food Chemistry* **141**: 274–81.

Kliem KE, Reynolds CK, Humphries DJ *et al.* (2013b) Incremental effect of a calcium salt of cis-monounsaturated fatty acids supplement on milk fatty acid composition in cows fed maize silage-based diets. *Journal of Dairy Science* **96**: 3211–21.

Kris-Etherton PM, Grieger JA, Hilpert KF *et al.* (2009) Milk products, dietary patterns and blood pressure management. *Journal of the American College of Nutrition* **28**: 103S–19S.

Liu X, Kris-Etherton PM, West SG *et al.* (2016) Effects of Canola and high-oleic-acid Canola oils on abdominal fat mass in individuals with central obesity. *Obesity* **24**: 2261–8.

Livingstone KM, Lovegrove JA & Givens DI (2012) The impact of substituting SFA in dairy products with MUFA or PUFA on CVD risk: evidence from human intervention studies. *Nutrition Research Reviews* **25**: 193–206.

Livingstone KM, Lovegrove JA, Cockcroft JR *et al.* (2013) Does dairy food intake predict arterial stiffness and blood pressure in

men? Evidence from the caerphilly prospective study. *Hypertension* **61**: 42–7.

Lorenzen JK & Astrup A (2011) Dairy calcium intake modifies responsiveness of fat metabolism and blood lipids to a high-fat diet. *British Journal of Nutrition* **105**: 1823–31.

Lovegrove JA & Givens DI (2016) Dairy food products: good or bad for cardiometabolic disease? *Nutrition Research Reviews* **29**: 249–67.

Maes W, Van Camp J, Vermeirssen V *et al.* (2004) Influence of the lactokinin Ala-Leu-Pro-Met-His-Ile-Arg (ALPMHIR) on the release of endothelin-1 by endothelial cells. *Regulatory Peptides* **118**: 105–9.

Mariotti F, Valette M, Lopez C *et al.* (2015) Casein compared with whey proteins affects the organization of dietary fat during digestion and attenuates the postprandial triglyceride response to a mixed high-fat meal in healthy, overweight men. *Journal of Nutrition* **145**: 2657–64.

Markey O, Kliem KE, Humphries DJ *et al.* (2015a) Effect of feeding high-oleic sunflower oil to dairy cows on the milk fatty acid profile – RESET study. *Proceedings of the Nutrition Society* **74** (OCE1): E52. https://doi.org/10.1017/S0029665115000671.

Markey O, Hargreaves A, Fagan CC *et al.* (2015b) Consumer acceptance of saturated fat-reduced dairy products: a novel approach for reducing intake of saturated fat at a population level. *Proceedings of the Nutrition Society* **74**(OCE5): E311. https://doi.org/10.1017/S0029665115003584.

Marz W, Scharnagl H, Gouni-Berthold I *et al.* (2016) LDL-cholesterol: standards of treatment: a German perspective. *American Journal of Cardiovascular Drugs* **16**: 323–36.

Mensink RP, Zock PL, Kester AD *et al.* (2003) Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *American Journal of Clinical Nutrition* **77**: 1146–55.

Mente A, de Koning L, Shannon HS *et al.* (2009) A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Archives of Internal Medicine* **169**: 659–69.

Micha R & Mozaffarian D (2010) Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. *Lipids* **45**: 893–905.

Miura K, Stamler J, Brown IJ *et al.* (2013) Relationship of dietary monounsaturated fatty acids to blood pressure: the International Study of Macro/Micronutrients and Blood Pressure. *Journal of Hypertension* **31**: 1144–50.

Mozaffarian D, Cao H, King IB *et al.* (2010) *trans*-palmitoleic acid, metabolic risk factors, and new-onset diabetes in U.S. adults. *Annals of Internal Medicine* **153**: 790–9.

Mozaffarian D, de Oliveira Otto MC, Lemaitre RN *et al.* (2013) *trans*-palmitoleic acid, other dairy fat biomarkers, and incident diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA). *American Journal of Clinical Nutrition* **97**: 854–61.

Nettleton JA, Brouwer IA, Geleijnse JA *et al.* (2017) Saturated fat consumption and risk of coronary heart disease and ischemic stroke: a science update. *Annals of Nutrition and Metabolism* **70**: 26–33.

Pal S, Ellis V & Dhaliwal S (2010) Effects of whey protein isolate on body composition, lipids, insulin and glucose in overweight and obese individuals. *British Journal of Nutrition* **104**: 716–23.

Petyaev IM, Dovgalevsky PY, Klochkov VA *et al.* (2012) Whey protein lycosome formulation improves vascular functions and plasma lipids with reduction of markers of inflammation and oxidative stress in prehypertension. *The Scientific World Journal*. https://doi.org/10.1100/2012/269476.

Pimpin L, Wu JHY, Haskelberg H *et al.* (2016) Is butter back? A systematic review and meta-analysis of butter consumption and risk of cardiovascular disease, diabetes, and total mortality. *PLoS ONE* **11**: e0158118.

Ralston RA, Lee JH, Truby H *et al.* (2012) A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. *Journal of Human Hypertension* **26**: 3–13.

Ridker PM (2014) LDL cholesterol: controversies and future therapeutic directions. *The Lancet* **384**: 607–17.

SACN (2007) *Update on trans* Fatty Acids and Health. Position Statement by the Scientific Advisory Committee on Nutrition. TSO Norwich, UK.

Seidel C, Deufel T & Jahreis G (2005) Effects of fat-modified dairy products on blood lipids in humans in comparison with other fats. *Annals of Nutrition and Metabolism* **49**: 42–8.

Siri-Tarino PW, Sun Q, Hu FB *et al.* (2010) Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *American Journal of Clinical Nutrition* **91**: 535–46.

Sjogren P, Rosell M, Skoglund-Andersson C *et al.* (2004) Milk-derived fatty acids are associated with a more favorable LDL particle size distribution in healthy men. *Journal of Nutrition* **134**: 1729–35.

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

Sutton-Tyrrell K, Najjar SS, Boudreau RM *et al.* (2005) Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation* **111**: 3384–90.

Thorning TK, Bertram HC, Bonjour J-P *et al.* (2017) Whole dairy matrix or single nutrients in assessment of health effects: current evidence and knowledge gaps. *American Journal of Clinical Nutrition* **105**: 1033–45.

Tong X, Li W, Xu JY *et al.* (2014) Effects of whey protein and leucine supplementation on insulin resistance in non-obese insulin resistant rats. *Nutrition* **30**: 1076–80.

Townsend N, Bhatnagar P, Wilkins E *et al.* (2015) *Cardiovascular Disease Statistics, 2015*. British Heart Foundation: London.

Vafeiadou K, Weech M, Altowaijri H *et al.* (2015) Replacement of saturated with unsaturated fats had no impact on vascular function but beneficial effects on lipid biomarkers, E-selectin, and blood pressure: results from the randomized, controlled Dietary Intervention and VAScular function (DIVAS) study. *American Journal of Clinical Nutrition* **102**: 40–8.

Van Bortel LM, Laurent S, Boutouyrie P *et al.* (2012) Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *Journal of Hypertension* **30**: 445–8.

Wilkins E, Wilson L, Wickramasinghe K *et al.* (2017) *European Cardiovascular Disease Statistics 2017*. European Heart Network: Brussels.