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Plenary Lecture 2: Milk and dairy produce and CVD: new perspectives on dairy and cardiovascular health

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NEW PERSPECTIVES ON DAIRY AND CARDIOVASCULAR HEALTH

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Abbreviations: BP, blood pressure; CVD, cardiovascular disease; CHD, coronary heart disease; COMA, committee on medical aspects of food and nutrition policy; CI, confidence interval; DASH, dietary approach to stop hypertension; FAO, food and agriculture organisation; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; iTFA, industrial *trans* fatty acid; IHD, ischaemic heart disease; LDL-C, low-density lipoprotein cholesterol; MUFA, monounsaturated fatty acids; MESA, Multi Ethnic Study of Atherosclerosis; NDNS, National Diet and Nutrition Survey; PUFA, polyunsaturated fatty acids; RNI, recommended nutrient intake; rTFA, ruminant *trans* fatty acids; RR, relative risk; RCT, randomised control trial; SFA, saturated fatty acids; SNP, single nucleotide polymorphism; TAG, triacylglycerol; WHO, world health organisation.

Abstract

Cardiovascular diseases (CVD) are the leading cause of mortality and morbidity worldwide. One of the key dietary recommendations for CVD prevention is reduction of saturated fat intake. Yet despite milk and dairy foods contributing on average 27 % of saturated fat intake in the UK diet, evidence from prospective cohort studies does not support a detrimental effect of milk and dairy foods on risk of CVD. This paper provides a brief overview of the role of milk and dairy products in the diets of UK adults, and will summarise the evidence in relation to the effects of milk and dairy consumption on CVD risk factors and mortality. The majority of prospective studies and meta-analyses examining the relationship between milk and dairy product consumption and risk of CVD show that milk and dairy products, excluding butter, are not associated with detrimental effects on CVD mortality or risk biomarkers, that include serum LDL cholesterol. In addition, there is increasing evidence that milk and dairy products are associated with lower blood pressure and arterial stiffness. These apparent benefits of milk and dairy foods have been attributed to their unique nutritional composition, and suggest that the elimination of milk and dairy may not be the optimum strategy for CVD risk reduction.

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide. The World Health Organisation (WHO) estimated that 17.3 million people in the world died from CVD in 2008, including 7.3 million from coronary heart disease (CHD), and 6.2 million from strokes[1]. There are a number of modifiable risk factors for CVD, such as high levels of serum low-density lipoprotein cholesterol (LDL-C), hypertension, diabetes, overweight/obesity, smoking, low physical activity and diet. Indeed, diets that are rich in saturated fatty acids (SFA) and *trans* fatty acids (TFA) are associated with an increased risk of CVD, and it is largely agreed that this is due, in the most part, to increased serum LDL-C[2]. Furthermore, evidence from pharmacological studies show that lowering LDL-C by an average of 1.8 mmol/L (by use of statins) reduces risk of ischaemic heart disease (IHD) and stroke by 60 % and 17 %, respectively[3]. Despite this, the relationship between SFA and CVD risk remains controversial[4].

The UK dietary guidelines recommend <10 % of total energy intake from SFA, but according to the most recent National Diet and Nutrition Survey (NDNS) consumption of SFA is above these recommendations, at 11.9 % of total energy intake[5]. Milk and dairy products contribute around 27 % of SFA intake in the UK diet[5]. However, evidence from a number of prospective cohort studies show that consumption of particularly milk and other dairy products, except butter, are not consistently associated with an increased risk of CVD. Milk is a unique and complex food that is nutritionally complete for the sustenance of young mammals. Milk consumption in most mammals ceases soon after weaning, this coincides with down-regulation of the gene for lactase, leading to a severe compromise in the ability to digest lactose, the sugar contained within milk. However, humans are unique within the animal kingdom being the only mammal that continues to consume another animals' milk past infancy and throughout our lifespan. This is made possible in the majority of the population by possession of one of a number of single nucleotide polymorphism (SNP) in the lactase gene, which results in persistence of lactase throughout life. The majority of individuals of European origin possess a version of the gene that remains active, which results in about 90 % of Europeans being able to digest lactose[6]. Selection of these mutant SNPs in the lactase gene throughout human development suggests there may be some advantage to the ability to consume milk.

This paper will provide a brief overview of the consumption of milk and dairy products in the diets of UK adults, and will summarise the evidence on the effects of milk and dairy consumption on CVD mortality and biomarkers.

Trends in milk and dairy consumption

In the UK current milk consumption is around 1.5 litres of milk per person per week, with the majority of this consumed as semi-skimmed milk (70 %) followed by whole milk (20 %) and skimmed milk (10 %). Over the last few decades, trends in milk and dairy product consumption have shown considerable variation (Figure 1)[(7)]. For example, consumption of whole milk has shown a dramatic decline since the 1970s from around 2.7 litres per person per week in 1974 to 0.3 litres per person per week in 2012 (Figure 1A). In the early 1990s the decline in whole milk consumption was partially replaced by semi-skimmed milk, consumption of which has remained fairly constant at around 1 litre per person per week over the last decade, while the intake of whole milk continues to decline. Figure 1B shows the UK trends in consumption of other dairy products such as cheese, yogurt and fromage frais, cream and butter. The trend for cheese and cream consumption has remained fairly constant at around 100 g and 20 mL per person per week for cheese and cream, respectively since the 1970s. In contrast, the trend for yogurt and fromage frais consumption has increased significantly from the early 1970s with 33 mL per person per week to around 200 mL per person per week in 2012. The consumption of butter in the UK shows a similar downward trend as for whole milk, due, in part, to recommendations to reduce the amount of total and saturated fat in the diet, but also because of the increasing availability of other spreads.

The contribution of milk and dairy foods to nutrient intakes

Milk and dairy products are complex foods containing a number of different components. Table 1 shows the contribution of the dairy food group, which includes milk, cheese, yogurt, butter, cream and fromage frais to energy and nutrient intakes in UK adults (19-64 years)[(5)]. It is clear that milk and other dairy products are important sources of a number of nutrients in the UK diet. Indeed, the dairy food group alone contributes more than the daily Reference Nutrient Intake (RNI) for vitamin B12 and provides around 50 % of the RNI for calcium and phosphorus. Milk and dairy products are also the main source of iodine in the UK diet, contributing about 40 % of the RNI. Adequate iodine levels are important for both men and women throughout life, but particularly in women of childbearing age as iodine levels below recommendations during pregnancy have been associated with reduced cognitive outcome of in their children[(8)]. Although dairy is an important contribution to iodine intake in the UK diet, there have been inconsistent reports of iodine concentrations in milk with a recent study showing a 30 % lower iodine concentration in organic compared with conventional milk[(9)].

Therefore, although milk and dairy products are not an essential dietary component, they make an important contribution to the provision of key nutrients.

Saturated fat from milk and CVD

Higher dietary SFA consumption is associated with increased risk of CVD, due primarily to the serum total cholesterol and LDL-C raising effects of SFA[(2)]. The association between SFA and increased serum LDL-C has led to dietary recommendations world-wide for the restriction of SFA intake. Dietary recommendations by the Food and Agriculture Organisation/World Health Organisation (FAO/WHO, 2010)[(10)], UK dietary recommendations (Department of Health, 1991)[(11)] and, dietary guidelines for Americans[(12)] recommend intake of dietary SFA to less than 10 % of total energy intake. Despite these recommendations current SFA intakes in the UK are around 11.9 % of total energy[(5)].

Milk and dairy products are the greatest contributor to dietary SFA in the UK diet, contributing around 27 % of SFA intake. As a result, guidance to reduce or eliminate dairy from the diet has been a common practice for CVD risk reduction. However, the evidence for the relationship between dairy consumption and CVD mortality does not support dairy restriction as an effective strategy for CVD reduction. It is important to recognise that we do not consume individual nutrients, but complex foods and diets that contain specific nutrients within various matrices. This can give rise to disparity between the biological effects of nutrients in different foods that may have contributed to the inconsistencies in the relationships of different SFA-rich foods and CVD mortality. Clear evidence for this comes from the Multi Ethnic Study of Atherosclerosis (MESA), in which different SFA-rich foods were shown to produce differential effects on CVD risk[(13)].in 5,209 subjects after a 10 year period (from 2000 to 2010). A lower hazard ratio (HR) for CVD was reported for every 5 g/d (HR 0.79; 95 % confidence interval (CI); 0.68-0.92) or 5 % of energy from dairy SFA (HR 0.62; 95 % CI 0.47- 0.82), whereas the equivalent intake of SFA from meat sources was associated with greater HR for CVD (HR for +5 g/d and a +5 % of energy from meat sources of SFA: 1.26; 95 % CI 1.02-1.54 and 1.48; 95 % CI 0.98-2.23, respectively)[(13)]. Furthermore, the substitution of 2 % of energy from meat sources of SFA with energy from dairy SFA was associated with a 25 % lower CVD risk (HR: 0.75; 95 % CI 0.63-0.91), suggesting that dairy foods containing SFA attenuated the detrimental association of SFA with CVD mortality. While this finding was attributed to the effects of other components within dairy foods, such as calcium, magnesium, bioactive peptides and proteins, it may also have been due to a difference in the relative proportions of different SFA between meat and dairy.

Further evidence for the beneficial association between dairy and CVD, comes from an investigation of the association between plasma phospholipid fatty acids and incidence of CHD[14]. In this study, the enrichment of plasma phospholipid with even chain SFA: palmitic acids (C16:0) and stearic (C18:0), but not myristic (C12:0), was associated with significantly higher risk of CHD, while the odd chain SFA indicative of dairy consumption: pentadecanoic C15:0 and hexadecanoic acid C17:0 were associated with lower risk. These finding were corroborated by associations between similar circulating biomarkers of dairy fat and the incidence of stroke in US men (Health Professionals Follow-up Study *n*=51,529) and women (Nurses' Health Study *n*=121,700)[15]. Odd chain fatty acids are found in milk and dairy products and result from bovine biohydrogenation[16]. Their appearance in human plasma or tissue samples is now recognised as a specific biomarker of dairy intake, as humans are unable to synthesise these fatty acids endogenously[17]. These data support the prospective cohort data that suggest that milk and dairy products are not associated with detrimental effects on CVD risk.

Trans **fatty acids and CVD**

Other important fatty acids present in milk and dairy foods are *trans* fatty acids (TFA), which are synthesised via bacterial metabolism of unsaturated fatty acids in the rumen of cows[18]. The intake of TFA from industrially hydrogenated vegetable oils (iTFA) has a negative impact on cardiovascular health[19, 20]. However, the association between ruminant TFA (rTFA) and CVD remains inconclusive[21, 22], with some studies showing a cardio-protective association[19, 23]. In an attempt to resolve conflicting reports, a systematic review and meta-analysis was undertaken by Bendsen *et al.* (2011)[24] who reported that the relative risk (RR) for high vs. low quintiles of total TFA intake (2.8 to approximately 10 g/day) was 1.22 (95 % CI 1.08–1.38; P=0.002) for CHD events and 1.24 (95 % CI 1.07–1.43; P=0.003) for fatal CHD. In addition, rTFA intake (0.5–1.9 g/day) was not significantly associated with CHD risk (RR 0.92; 95 % CI 0.76–1.11; P=0.36), although there was a trend towards a positive association for iTFA (RR 1.21; 95 % CI 0.97–1.50; P=0.09). The authors concluded that while iTFA may be positively related to CHD, rTFA were not, but the limited number of studies available prevented a firm conclusion on the critical importance of the source of TFA. In contrast to previous findings, a recent prospective cohort study by Kleber *et al.* (2015)[25] showed that total TFA content in erythrocyte membranes of 3,259 participants of the Ludwigshafen Risk and Cardiovascular Health Study (LURIC) was inversely associated with adverse cardiac outcomes, while rTFA (*trans*-palmitoleic acid) was associated with reduced risk. In addition, erythrocyte membrane iTFA was associated with no increased risk of adverse cardiac outcomes[25]. However, it is important to highlight that total TFA concentration in erythrocyte membranes in this study population was relatively low compared with levels in other studies, and this may have been too low to observe an effect of TFA on CVD mortality. Furthermore, it has been suggested that the lack of an association between rTFA and CHD risk may be due to a lower intake from ruminant sources compared with iTFA[24]. Despite this controversy, there is little doubt that dietary iTFA are associated with increased CVD mortality[26]. In response there has been a substantial decrease in iTFA over the past 10–15 years, due to the voluntary action by the UK food industry[27]. This has led to an increase in the relative proportion of rTFA in the UK diet, although the absolute intake of ruminant fat is unchanged, with the current mean population intake of total TFA (0.7 % food energy in adults)[5] below the recommended population maximum of 2 % of food energy intake[11]. Although milk and milk products (including butter) contribute to 32 % of this intake[5], current rTFA intake is not considered to be a major cause for concern with respect to cardiovascular health at a population level[22, 28]. However, the impact of any increase in dietary TFA would need to be monitored.

Effects of milk and dairy foods on CVD risk: evidence from observational studies

The potential effects of milk and dairy consumption on CVD mortality would best be determined using adequately powered randomised control intervention studies, which have CVD events and CVD-related deaths as outcomes. However, for obvious financial and logistical reasons such studies have not been performed. The most informative data on the relationship between milk and dairy consumption and CVD is provided by long-term prospective cohort studies[29].

Several influential reviews have focused on the impact milk and dairy food consumption and CVD risk, some of which have conducted meta-analyses of available cohort data (Table 2)[29-32]. Elwood *et al.* (2004)[32] conducted a meta-analyses of 10 prospective cohort studies that examined the associations between milk and risk of IHD and stroke. Using a pooled estimate of the relative odds for IHD and stroke, the meta-analysis revealed no association with IHD (RR 0.87; 95 % CI 0.74-1.03) and a significant inverse association for stroke (RR 0.83; 95 % CI 0.77-0.90) in the subjects with the highest milk compared with those with the lowest intakes. These findings, together with a combined estimate of risk for both IHD and stroke (10 studies RR 0.84 95 % CI 0.78-0.90), suggested that consumption of milk was associated with a modest reduction in CVD risk. This work was extended by Elwood *et al.*[29]

to include 9 prospective cohort studies of milk and dairy products and IHD and 11 studies for stroke. The meta-analysis indicated a 15 % lower RR for all-cause mortality (RR: 0.85; 95 % CI 0.77-0.98) and an 8 % lower overall RR of IHD (RR: 0.92; 95 % 0.80-0.99) in the subjects with the highest dairy consumption compared with those with the lowest intakes. Furthermore, a significant inverse association was observed for the risk of stroke (RR: 0.79; 95 % CI 0.68-0.91) in the subjects with the highest dairy consumption compared with those with the lowest intakes. These findings supported previous meta-analyses by Elwood and colleagues[32], and support a reduction in IHD and stroke in subjects consuming the highest amount of milk and dairy products compared with the lowest intakes.

In another meta-analysis of 17 prospective cohort studies Soedamah-Muthu *et al.*[30] showed a modest inverse association between milk intake and risk of overall CVD (4 studies; RR: 0.94 per 200 mL/d; 95 % CI 0.89-0.99). However, milk intake was not associated with risk of CHD (6 studies; RR: 1.00 per 200 mL/d; 95 % CI 0.96-1.04), stroke (6 studies; RR: 0.87; 95 % CI 0.72-1.05) or total mortality (8 studies; RR per 200 mL/d: 0.99; 95 % CI 0.95-1.03). A recent meta-analysis by Qin *et al*. (2015)[31], which included a total of 22 prospective cohort studies, showed an inverse association between dairy consumption and overall risk of CVD (9 studies RR 0.88; 95 % CI 0.81-0.96) and stroke (12 studies RR 0.87; 95 % CI 0.77-0.99). However, no association was found between dairy consumption and CHD risk (12 studies RR 0.94; 95 % CI 0.82-1.07), which supports previous findings[30]. Qin *et al*.[31] also investigated the association between individual dairy foods on risk of CVD, including stroke and CHD. Interestingly, cheese consumption was associated with a significantly reduced risk of stroke (4 studies; RR: 0.91, 95% CI 0.84-0.98) and CHD (7 studies; RR: 0.84 95% CI 0.71-1.0). Recently Praagman *et al*. (2015)[33] also reported a significant association between cheese consumption and stroke mortality, although no impact on CHD mortality was found[33]. One possible explanation for the observed beneficial effects of cheese consumption on stroke and CHD risk may be the relatively high calcium content that increases saponification of SFA in the gut, rendering them resistant to digestion leading to increased faecal fat excretion[34]. This mechanism is supported by the results from a prospective cohort study in which the observed inverse association between cheese consumption and CHD was attenuated when calcium content was used as a confounder in the analysis[35]. Furthermore a meta-analysis of RCT investigating the impact of calcium from dairy and dietary supplements estimated that increasing dairy calcium intake by 1241 mg/d resulted in an increase in faecal fat of 5.2 (1.6-8.8) g/d[36].

Since publication of the meta-analyses above (Table 2), additional prospective cohort studies have been published. For example, the Rotterdam Study consisting of 4,235 men and women aged 55 years and above showed that total dairy, milk, low-fat dairy, and fermented dairy were not significantly related to incident stroke or fatal stroke after a 17.3 year follow up period[37]. In addition, the authors reported a significant inverse relationship between high-fat dairy consumption and fatal stroke (HR 0.88 per 100 g/day; 95 % CI 0.79-0.99), but not incident stroke (HR 0.96 per 100 g/day; 95 % CI 0.90-1.02). Total dairy or individual dairy foods were not associated with incident CHD or fatal CHD.

Contrary to these data, and since these meta-analyses a study conducted by Michaelsson *et al.* (2014)[38], reported that the milk intake was significantly associated with markedly higher total and CVD mortality and fracture risk in 61,433 Swedish women from the mammography cohort. This relationship was also observed in a cohort of 45,339 Swedish men, although the relationship was considerably weaker[38]. However, the authors concluded that the study should be 'interpreted with caution, due to the inherent possibility of residual confounding and reverse causation phenomena, which is often associated with observational study designs'. In addition, when this data was re-analysed, an inverse association was observed for the number of CVD deaths against milk consumption[39]. These inconsistent findings between milk intake and CVD mortality observed with the same data set requires further investigation. Furthermore, since the study by Michaelsson *et al.* (2014)[38], two further large prospective cohort studies have been published on the relationship between milk and myocardial infarction and IHD mortality in Japanese (*n*=94,980; 19 years follow-up)[40] and Danish (*n*=98,529; 5.4 years follow-up)[41] populations, both of which reported no association with myocardial infarction or IHD.

The balance of current evidence, including meta-analyses of prospective cohort studies, indicates that milk and dairy products are associated with no detrimental effect on risk of CVD, with some evidence of a moderately protective effect of milk consumption. However, a further meta-analysis that includes all of the current prospective cohort data is required to confirm this and more studies are required to determine the effects of individual dairy products on CVD risk.

Effects of dairy on blood lipids and lipoproteins

In the absence of randomised control dairy intervention studies with clinical endpoints, the bulk of evidence for cause and effect relationships between dairy foods and CVD has relied heavily upon validated CVD biomarkers as outcome measures in randomised control trials

(RCT). There is consistent evidence that consumption of dietary SFA increases total and LDL-C concentrations, a robust biomarker of CHD risk[2]. Replacement of SFA with unsaturated fatty acids has a beneficial reduction on serum LDL-C and the clinically relevant total cholesterol: high-density lipoprotein cholesterol (total-C:HDL-C) ratio[2, 42, 43]. However, not all classes of SFA have the same effects on blood lipids. High dietary intakes of lauric (C12:0), myristic (C14:0) and palmitic (C16:0) acids have been shown to elevate serum total and LDL-C, whereas stearic acid (C18:0) has minimal impact, due, in part, to its more limited absorption[44]. These SFA are also associated with a concomitant increases in high density lipoprotein cholesterol (HDL-C) concentrations, a lipoprotein that is generally considered to be anti-atherogenic[45]. This differential effect of dietary fats on different lipoprotein fractions highlights the importance of expressing dietary effects on the clinically relevant total-C:HDL-C ratio[46]. Given that a high proportion of the C12:0, C14:0 and C16:0 in the human diet is derived from milk fat, it would be predicted that the consumption of milk and dairy foods would be associated with adverse effects on serum LDL-C and total-C:HDL-C. However, evidence indicates that diary food consumption, with the exception of butter[47], is associated with limited or no significant detriment to serum lipids. In support of this, a cross-sectional analysis of 2,512 Welsh men from the Caerphilly cohort study showed no significant difference in serum total cholesterol or LDL-C concentrations, and a significant negative association between the highest compared with the lowest quartile of dairy consumers[48]. Negative associations between dairy consumption, confirmed by dietary assessment and biomarkers of dairy intake: plasma phospholipid levels of C15:0 and C17:0, and the proportion of the pro-atherogenic small dense LDLIII particles, was reported in another cross-sectional study in 291 healthy men[49]. Stronger evidence from a meta-analysis of 20 randomised controlled trials with a total of 1,677 subjects showed that there was no significant change in LDL-C with either low and full-fat dairy consumption[50]. In contrast, studies that used butter, invariably produced the predicted increases in LDL-C[47]. This again suggests that the other components of dairy foods, such as proteins, bioactive peptides and calcium may be involved with the amelioration of the detrimental effects of dairy SFA.

Differential impact of high and low-fat dairy foods

There is no established nutritional benefit of whole-fat dairy consumption, except in children under 2 years, compared with lower fat alternatives. With respect to the latter, skimming milk fat to produce low-fat milk and dairy products is a common and an effective way of lowering SFA intake. However, there is currently no consensus on whether fat-reduced dairy foods are associated with a reduced risk of CVD[50] and studies in this area give inconsistent data, with few RCT that directly compare whole with low fat alternatives. Minimal benefit has been reported in a prospective study of 33,636 women, which suggested no significant differences between consumption of high vs low fat dairy products on risk of myocardial infarction[51]. Furthermore, findings from a 12-month RCT concluded that in overweight adults inclusion of reduced-fat dairy foods had no impact on blood lipids, blood pressure (BP) and arterial compliance[52]. Furthermore, a meta-analysis conducted by Soedamah-Muthu *et al*. (2011)[30], showed that there was no significant difference between consumption of high-fat (RR: 1.04; 95 % CI 0.89-1.21) or low-fat dairy (RR: 0.93; 95 % CI 0.74-1.17) on CHD risk.

In contrast, data from the *Nurses' Health Study* cohort illustrated that the associated RR of CHD varied according to the fat content of dairy foods with an estimated 20% lower RR with low-fat dairy consumption (RR 0.80; 95 % CI 0.73–0.87) compared with a 12% higher RR with high-fat dairy consumption (RR 1.12; 95 % CI 1.05–1.20)[53]. Furthermore, observational studies investigating the relationship between consumption of different types of dairy on cardio-metabolic risk factors have indicated that low-fat dairy consumption is an effective strategy to promote lower BP levels[54-56], circulating markers of inflammation[57], the ratio of total-C:HDL-C [2] and LDL-C concentration[58], as well as aid in weight maintenance or reduction[59]. Further evidence from well-controlled dietary intervention studies is required before a definitive conclusion can be drawn on the benefits of low and high fat dairy.

There have also been a number of studies suggesting that specific milk proteins have differential effects on lipids. Whey (60 g/day for 12 weeks) has been shown to produce significant reductions in serum triacylglycerol (TAG) and total and LDL- cholesterol in comparison to a casein control group[60]. Furthermore, a significant decrease in the postprandial appearance of TAG after consuming a whey meal of 21 % compared to control and 27 % compared to the casein meals were reported[61]. In addition to specific dairy proteins, different dairy foods have been shown to have a range of lipid effects[62]. It has been reported that cheese may have a differential effect on blood lipids compared with other dairy foods[34, 63, 64], with prolonged ripening of cheddar cheese resulting in more pronounced lipid-lowering effects in a pig model[65]. A meta-analysis that included five of these randomised control studies showed that when compared with butter intake, cheese consumption reduced LDL-C by 6.5 % (-0.22 mmol/L; 95 % -0.2 to -0.14) and HDL-C by 3.9 % (-0.05 mmol/L 95 % CI -0.09 to -0.02) but had no effect on TAG[66]. In addition, a recent RCT reported that consumption of 80 g/day of a high fat cheese (27 % fat) compared with no cheese or 50 g/day of fat and salt-free cheese for 8 weeks resulted in no changes in total or LDL-C. Those in the high fat cheese group with metabolic syndrome at baseline had significant reductions in total cholesterol (-0.70 mmol/l) compared with control and a significantly higher reduction in TAG[67]. These data show that dairy products do not exert the negative effects on blood lipids which would be predicted solely from their SFA content, and highlights a need for additional studies before firmer conclusions can be made on the differential effects of dairy products on serum lipid and lipoprotein concentrations.

Overall, the current evidence presented in this section suggests that the fatty acid profile of milk may not be as detrimental for lipid risk factors as previously thought, and supports differential effects of dairy foods, particularly cheese.

Manipulating the fatty acid profile of milk

Modification of the fatty acid profile of bovine milk offers an alternate strategy for lowering the population's intake of SFA, by removing SFA from the food chain, while preserving the beneficial contributions that dairy products make to the protein and micronutrient content of the human diet[68]. Partial replacement of milk SFA with *cis*-monounsaturated fatty acids (*cis*-MUFA) or *cis*-polyunsaturated fatty acids (*cis*-PUFA) through supplementation of the cows' diet with plant oils or oilseeds reduces synthesis of short- and medium-chain SFA by the bovine mammary gland, and increases the long-chain (>C18) unsaturated fatty acid concentration in the milk[69, 70]. Inclusion of 49 g/kg of dry matter of rapeseed oil in the ruminant diet for a 28-day period increased *cis*-MUFA from 20 to 33 g/100 g fatty acids, while reducing SFA from 70 to 55 to 60 g/day fatty acids[71]. This feeding regimen inadvertently leads to increased concentrations of naturally produced rTFA, predominantly *trans*-linoleic acid (*trans*-18:1) and *trans*-MUFA, in the milk. However, despite this increase in rTFA, the consumption of the modified dairy products is not thought to have a major impact on CVD risk[25]. In addition, cell culture studies have shown that rTFA has minimal impact on endothelial function and gene expression[72], though whether rTFA intake, through manipulation of the fatty acid profile of milk and dairy products to decrease SFA content, impacts on cardiovascular health, has yet to be determined.

Consumption of SFA-reduced milk and milk products, by feed modification has been shown to be beneficial to CVD risk, in healthy and hypercholesterolaemic populations when compared to conventional dairy products[73]. Poppitt *et al.* (2002) demonstrated that consumption of 20 % energy per day as conventional or feed-modified SFA-reduced butter for a 3 week period resulted in significant reduction in both total cholesterol and LDL-C during the modified butter feeding[74]. However, the evidence is relatively limited and the majority of studies have used butter only and relied on serum lipid levels as biomarkers of CVD risk. This knowledge gap is being addressed at the University of Reading with the *RESET* (REplacement *of SaturatEd fat in dairy on Total cholesterol) Study* investigating the impact of reducing SFA intake by using modified milk and dairy products on vascular function and CVD risk biomarkers, without limiting dairy product consumption. Milk that has a substantial proportion of SFA replaced with *cis*- MUFA will be collected from cows fed a diet supplemented with 1 kg/day of high-oleic sunflower oil. Cheddar cheese and butter will be produced from this milk and these dairy foods will be supplied to volunteers with increased CVD risk for a 12-week period in a randomised, crossover, double-blind, controlled study. The impact of these modified dairy products on fasted and postprandial vascular function, blood pressure, lipids, insulin sensitivity and inflammatory biomarkers will be determined relative to typical commercially available products. The project, which started in late 2013, will provide unique evidence of the physiological effects of modified SFA-reduced dairy products, which could contribute to food-based dietary recommendations for CVD risk reduction.

Effects of milk and dairy products on blood pressure and arterial stiffness

Hypertension, defined as systolic BP ≥140 mm Hg and/or diastolic BP of ≥90 mm Hg, is one of the leading risk factors in the development of stroke, CHD, heart failure and end stage renal disease[75]. BP is a modifiable by environmental and lifestyle factors, with diet as one of the most important mediators[76]. The Dietary Approaches to Stop Hypertension (DASH) trial demonstrated that a diet consisting of reduced total and SFA fats, high intakes of low-fat dairy products, and fruit and vegetables significantly lowered BP in normotensive and hypertensive individuals[77]. Moreover, the magnitude of BP reduction was of greater magnitude after the diet rich in low-fat dairy products compared with the fruit and vegetable rich diet, which omitted dairy products altogether[77]. The findings from cross-sectional and prospective studies have shown an inverse association between consumption of dairy products, particularly low-fat varieties and risk of hypertension[48, 56, 78-84]. These findings were confirmed in a meta-analysis by Soedamah-Muthu *et al.* (2012)[84], in which nine prospective cohort studies and a total of 57,256 participants, showed a reduced RR for hypertension (pooled RR: 0.97; 95 % CI, 0.95-0.99 per 200 g/day) and intake of total dairy[84]. A few RCTs have examined the effects of dairy products on BP[56, 85, 86]. For example, a randomised cross-over trial by Van Meijl and Mensink (2011)[56] in 35 healthy overweight and obese men and women indicated that daily consumption of low-fat dairy products compared with carbohydrate-rich products for 8 weeks, significantly reduced systolic BP by 2.9 mm Hg. However, a recent study by Maki and colleagues (2013)[86] observed no significant effects of consuming low-fat dairy products, compared with low-fat non-dairy products, on BP in 62 men and women with prehypertension or stage 1 hypertension[86].

The impact of dairy foods on BP and other more novel markers of vascular health are becoming increasingly relevant. Increased central arterial stiffening is a hallmark of the ageing process and the consequence of many diseases such as diabetes, atherosclerosis and chronic renal failure. Arterial stiffness is also a marker for increased CVD risk, including myocardial infarction[87], heart failure[88] and total mortality[89], as well as stroke[90] and renal disease[91]. Arterial stiffness is measured by pulse wave velocity and augmentation index, both of which are predictive of heart attacks and stroke [92] and all-cause mortality[93]. Pulse wave velocity measures the speed of propagation along the artery, whereas augmentation index is calculated from the blood pressure wave form and is based on the degree of wave reflection. Significant relationships between dairy product intake and arterial pulse wave velocity have been shown in a cross-sectional[94] and longitudinal[48] cohort studies. Livingstone *et al.* (2013)[48] used data from the Caerphilly Prospective Study, based on 2,512 men followed for a mean of 15 years and showed a significant inverse relationship between dairy product intake and augmentation index. The subjects in the highest quartile of dairy product intake (mean 480 g/day), excluding butter, had 2 % (P=0.02) lower augmentation index compared with subjects with the lowest dairy intake (mean 154 g/day), whereas across increasing quartiles of butter intake there was no impact on augmentation index, but a significant increase in insulin, serum triacylglycerol and total cholesterol concentrations, and diastolic BP[48].

The mechanisms by which milk and dairy products may reduce BP and arterial stiffness are unclear. It has been hypothesised that bioactive peptides released during milk protein digestion, dairy fermentation or industrially by enzyme or chemical treatments, may be involved in the relationship between dairy consumption and BP[95, 96]. It has been proposed that these bioactive peptides may inhibit the action of angiotensin I converting enzyme, thereby reducing blood levels of angiotensin, preventing blood vessel constriction, and modulating endothelial integrity. Ballard *et al.* (2009)[97] showed that consumption of 5 g of whey-derived peptide daily for a 2 week period significantly improved brachial artery flow-mediated dilation response[97]. A further study reported that although whey and casein exerted similar hypotensive effects, whey protein supplementation (60 g/day for 12 weeks) significantly reduced augmentation index compared with casein (60 g/day for 12 weeks)[98], an effect that requires confirmation. There is also evidence to suggest that certain peptides from milk proteins may modulate the release of vasoconstrictor endothelin-1 by endothelial cells, thus preventing an increase in blood pressure[99]. Milk also contains a variety of other biologically active components such as calcium, potassium and magnesium that may exert impact on blood pressure and arterial stiffness[100].

Conclusions

The weight of existing evidence indicates that milk and dairy products (excluding butter) are not associated with detrimental effects on CVD risk factors and mortality, and may even exert favourable effects on CVD risk, by lowering blood pressure and arterial stiffness. While the specific mechanisms that underpin these effects are not clear, the unique nutritional composition of milk and dairy foods has been implicated in improving vascular function and in attenuating the LDL cholesterol-raising property of SFA. Our current dietary guideline to reduce intake of dietary SFA to 10 % of total energy to lower CVD risk is still valid, but the elimination of milk and dairy from our diet is clearly not an evidence-based strategy for achieving this aim.

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Tables

Table 1 Energy and major nutrients provided by milk and dairy products to adults (19-64 years) diets in the UK

		1% Fat Milk	**Butter**	**Cheese**	**Ice cream**	**Other milk and cream**	**Semi-skimmed milk**	**Skimmed milk**	**Whole milk**	**Yoghurt, fromage frais and dairy desserts**	**Total dairy contribution**
Energy	Intake (MJ/d)	0.0	0.1	0.2	0.0	0.1	0.2	0.0	0.1	0.1	0.8
	% of EAR[1]	0.0	1.0	2.2	0.4	0.6	1.7	0.3	0.6	0.9	7.8
Total fat	Intake (g/d)	0.0	2.8	4.8	0.6	1.2	1.6	0.0	1.0	0.7	12.7
	% of DRV[2]	0.0	3.2	6.4	0.9	0.9	2.5	0.0	1.4	1.0	16.3
Saturated fat	Intake (g/d)	0.0	1.7	3.0	0.4	0.7	1.0	0.0	0.6	0.4	7.9
	% of DRV	0.0	4.8	10.6	1.5	1.6	4.4	0.0	2.2	1.6	26.6
Protein	Intake (g/d)	0.1	0.0	3.7	0.2	0.4	3.4	0.7	0.8	1.2	10.5
	% of RNI[3]	0.1	0.0	6.8	0.3	0.7	6.3	1.2	1.5	2.2	19.1
Potassium	Intake (mg/d)	2.6	0.9	14.5	9.1	18.3	154.0	31.9	37.7	59.2	328.2
	% of RNI	0.1	0.0	0.4	0.3	0.5	4.4	0.9	1.1	1.7	9.4
Calcium	Intake (mg/d)	2.0	0.6	102.4	5.2	11.7	118.3	24.2	28.8	39.3	332.4
	% of RNI	0.3	0.1	14.6	0.7	1.7	16.9	3.5	4.1	5.6	47.5
Phosphorus	Intake (mg/d)	1.6	0.8	74.7	4.8	11.2	94.6	19.1	23.1	36.0	265.8
	% of RNI	0.3	0.1	13.6	0.9	2.0	17.2	3.5	4.2	6.5	48.3
Magnesium	Intake (mg/d)	0.2	0.1	4.2	0.8	1.7	10.0	2.3	2.5	4.2	25.9
	% of RNI	0.1	0.0	1.4	0.3	0.6	3.3	0.8	0.8	1.4	8.6
Zinc	Intake (mg/d)	0.0	0.0	0.5	0.0	0.1	0.4	0.1	0.1	0.1	1.4
	% of RNI	0.1	0.0	5.7	0.2	0.5	4.2	1.0	1.0	1.5	14.3
Iodine	Intake (µg/d)	0.6	1.3	4.6	1.5	2.9	25.5	5.7	6.9	8.5	57.6
	% of RNI	0.4	0.9	3.3	1.1	2.1	18.2	4.1	4.9	6.1	41.1
Riboflavin	Intake (mg/d)	0.0	0.0	0.1	0.0	0.0	0.2	0.0	0.1	0.1	0.5
	% of RNI	0.3	0.1	4.6	1.1	1.6	17.5	3.3	4.3	4.4	37.3
Vitamin B_{12}	Intake (µg/d)	0.0	0.0	0.3	0.0	0.0	0.8	0.2	0.2	0.1	1.6
	% of RNI	1.0	0.5	22.0	1.9	2.8	50.9	10.6	12.2	5.4	107.3
Vitamin B_5	Intake (mg/d)	0.0	0.0	0.1	0.0	0.0	0.7	0.1	0.1	0.1	1.2
	% of RNI	0.3	0.1	1.5	0.9	0.7	13.7	1.8	2.7	2.7	24.3

[1] EAR, estimated average requirement.
[2] DRV, daily recommended value.
[3] RNI, reference nutrient intake.

Figure 1. Trends in milk, cheese, yogurt and fromage frais, cream and butter purchase, 1974-2012. Source: AHDB Dairy.

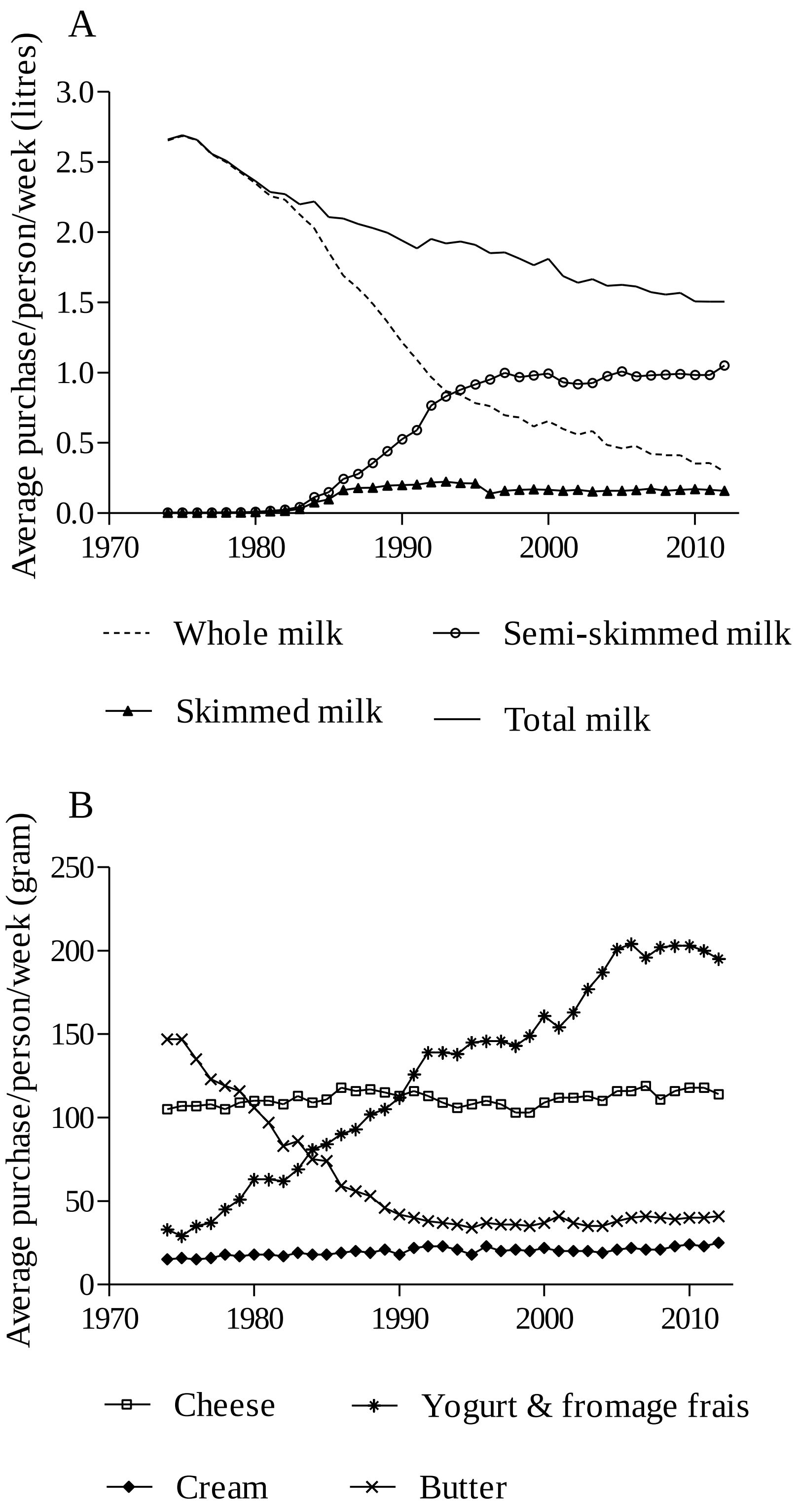

Table 2. Summary of recent reviews and meta-analyses on milk or total dairy intake and risk of CVD

Reference	Dairy food	Methodology	Overall CVD	Stroke	CHD	IHD
Elwood *et al* (2004)[32]	Milk	Meta-analysis. 10 prospective cohorts	Inverse association (RR=0.84; 95% CI 0.78-0.90)	Inverse association (RR=0.83; 95% CI 0.77-0.90)		No association (RR=0.87; 95% CI 0.74-1.03)
Elwood *et al* (2010)[29]	Total dairy and/or milk	Meta-analysis. 19 prospective cohorts		Inverse association (RR=0.79; 95% CI 0.68-0.91)		Inverse association (RR=0.92; 95% CI 0.80-0.99)
Soedamah-Muthu *et al* (2011)[30]	Milk	Meta-analysis. 17 prospective cohorts	Inverse association (RR=0.94, 95% CI 0.89-0.99)	No association (RR=0.87, 95% CI 0.72-1.05)	No association (RR=1.0, 95% CI 0.96-1.04)	
Qin *et al* (2015)[31]	Total dairy	Meta-analysis: 22 prospective cohorts	Inverse association (RR=0.88, 95% CI 0.81-0.96)	Inverse association (RR=0.87, 95% CI 0.77-0.99)	No association (RR=0.94, 95% CI 0.82-1.07)	
	High-fat dairy			No association (RR=0.95, 95% CI 0.83-1.08)	No association (RR=1.08, 95% CI 0.99-1.17)	
	Low-fat dairy			Inverse association (RR=0.93, 95% CI 0.88-0.99)	No association (RR=1.02, 95% CI 0.92-1.14)	
	Yogurt			No association (RR=0.98, 95% CI 0.92-1.06)	No association (RR=1.06, 95% CI 0.90-1.34)	
	Cheese			Inverse association (RR=0.91, 95% CI 0.84-0.98)	Inverse association (RR=0.84, 95% CI 0.71-1.00)	
	Butter			No association (RR=0.94, 95% CI 0.84-1.06)	No association (RR=1.02, 95% CI 0.88-1.20)	

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; IHD, ischaemic heart disease, RR; relative risk