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# Conference on 'The future of animal products in the human diet: health and environmental concerns'
# Plenary Lecture 2: Milk and dairy produce and CVD

# New perspectives on dairy and cardiovascular health

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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. The present 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.

**Milk: Dairy products: CVD: Blood pressure: Serum lipids**

CVD remains the leading cause of morbidity and mortality worldwide. The WHO estimated that 17·3 million people in the world died from CVD in 2008, including 7·3 million from CHD, and 6·2 million from strokes[1]. There are a number of modifiable risk factors for CVD, such as high levels of serum LDL-cholesterol (LDL-C), hypertension, diabetes, overweight/obesity, smoking, low physical activity and diet. Indeed, diets that are rich in 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 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 consumption of SFA is above these recommendations, at 11·9 % of total energy intake[5]. Milk and dairy products contribute about 27 % of SFA intake in the UK diet[5]. However, evidence from a number of prospective cohort studies show that consumption of milk and other dairy products (excluding 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

**Abbreviations:** BP, blood pressure; HDL-C, HDL-cholesterol; HR, hazard ratio; iTFA, industrial *trans* fatty acid; LDL-C, LDL-cholesterol; rTFA, ruminant *trans* fatty acids; RR, relative risk; RCT, randomised control trial.

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for lactase, leading to a severe compromise in the ability to digest lactose, the sugar contained within milk. However, human subjects 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 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 SNP in the lactase gene throughout human development suggests that there may be some advantage to the ability to consume milk.

The present 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 about 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 past few decades, trends in milk and dairy product consumption have shown considerable variation (Fig. 1)[7]. For example, consumption of whole milk has shown a dramatic decline since the 1970s from about 2·7 litres per person per week in 1974 to 0·3 litres per person per week in 2012 (Fig. 1(a)). 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 about 1 litre per person per week over the last decade, while the intake of whole milk continues to decline. Fig. 1(b) shows the UK trends in consumption of other dairy products such as cheese, yoghurt and fromage frais, cream and butter. The trend for cheese and cream consumption has remained fairly constant at about 100 g and 20 ml per person per week for cheese and cream, respectively since the 1970s. In contrast, the trend for yoghurt and fromage frais consumption has increased significantly from the early 1970s with 33 ml per person per week to about 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, yoghurt, butter, cream and fromage frais to

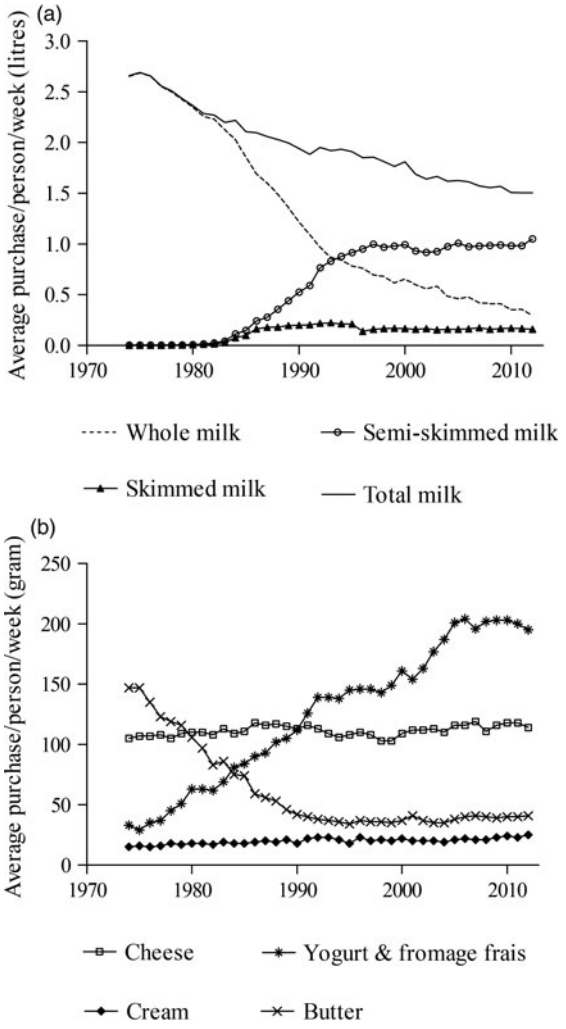


**Fig. 1.** Trends in milk, cheese, yoghurt and fromage frais, cream and butter purchase, 1974–2012. Source: AHDB Dairy.

energy and nutrient intakes in UK adults (age 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 for vitamin $B_{12}$ and provides about 50 % of the recommended nutrient intake for calcium and phosphorus. Milk and dairy products are also the main source of iodine in the UK diet, contributing about 40 % of the recommended nutrient intake. 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 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.

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**Table 1.** Energy and major nutrients provided by milk and dairy products to adults (age 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 | 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 | 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 | 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 |

EAR, estimated average requirement; DRV, daily recommended value; RNI, reference nutrient intake.

## 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 worldwide for the restriction of SFA intake. Dietary recommendations by the FAO/WHO[10], UK dietary recommendations (Department of Health, 1991)[11] and, dietary guidelines for Americans[12] recommend intake of dietary SFA to <10 % of total energy intake. Despite these recommendations current SFA intakes in the UK are about 11·9 % of total energy[5].

Milk and dairy products are the greatest contributor to dietary SFA in the UK diet, contributing about 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, in which different SFA-rich foods were shown to produce differential effects on CVD risk[13]. In 5209 subjects after a 10-year period (from 2000 to

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2010). A lower hazard ratio (HR) for CVD was reported for every 5 g/d (HR 0·79; 95 % 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 the present 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 man is 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 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 cardioprotective association[19,23]. In an attempt to resolve conflicting reports, a systematic review and meta-analysis was undertaken by Bendsen *et al.*[24] who reported that the relative risk (RR) for high *v.* low quintiles of total TFA intake (2·8 to approximately 10 g/d) 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/d) 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.*[25] showed that total TFA content in erythrocyte membranes of 3259 participants of the Ludwigshafen Risk and Cardiovascular Health Study 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 the present 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.*[32] conducted a meta-analyses of ten prospective cohort studies that examined the associations between milk and risk of IHD and stroke. Using a pooled estimate of the relative odds for

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**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.*[32] | Milk | Meta-analysis: ten prospective cohorts | Inverse association (RR = 0·83; 95 % CI 0·77, 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.*[29] | Total dairy and/or milk | Meta-analysis: nineteen 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.*[30] | Milk | Meta-analysis: seventeen 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.*[31] | Total dairy | Meta-analysis: twenty-two 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) | |
| | Yoghurt | | | 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) | |

RR; relative risk.

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 (ten 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 nine prospective cohort studies of milk and dairy products and IHD and eleven 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 % CI 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 *et al.*[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 seventeen prospective cohort studies Soedamah-Muthu *et al.*[30] showed a modest inverse association between milk intake and risk of overall CVD (four studies; RR 0·94 per 200 ml/d; 95 % CI 0·89, 0·99). However, milk intake was not associated with risk of CHD (six studies; RR 1·00 per 200 ml/d; 95 % CI 0·96, 1·04), stroke (six studies; RR 0·87; 95 % CI 0·72, 1·05) or total mortality (eight studies; RR per 200 ml/d 0·99; 95 % CI 0·95, 1·03). A recent meta-analysis by Qin *et al.*[31], which included a total of twenty-two prospective cohort studies, showed an inverse association between dairy consumption and overall risk of CVD (nine studies; RR 0·88; 95 % CI 0·81, 0·96) and stroke (twelve studies; RR 0·87; 95 % CI 0·77, 0·99). However, no association was found between dairy consumption and CHD risk (twelve 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 (four studies; RR 0·91; 95 % CI 0·84, 0·98) and CHD (seven studies; RR 0·84; 95 % CI 0·71, 1·0). Recently, Praagman *et al.*[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

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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 randomised control trials (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 4235 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/d; 95 % CI 0·79, 0·99), but not incident stroke (HR 0·96 per 100 g/d; 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.*[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 were reanalysed, 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 dataset require further investigation. Furthermore, since the study by Michaelsson *et al.*[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 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: HDL-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 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 dairy 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 twenty RCT 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

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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- *v.* 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]. Moreover, a meta-analysis conducted by Soedamah-Muthu *et al.*[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 the specific milk proteins have differential effects on lipids. Whey (60 g/d for 12 weeks) has been shown to produce significant reductions in serum TAG and total and LDL-C in comparison with 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 with the casein meals were reported[61]. In addition to the 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 RCT showed that when compared with butter intake, cheese consumption reduced LDL-C by 6·5 % (−0·22 mM/l; 95 % CI −0·2, −0·14) and HDL-C by 3·9 % (−0·05 mM/l 95 % CI −0·09, −0·02) but had no effect on TAG[66]. In addition, a recent RCT reported that consumption of 80 g/d of a high-fat cheese (27 % fat) compared with no cheese or 50 g/d 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 mM/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*-MUFA or *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 ($>C_{18}$) 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-d period increased *cis*-MUFA from 20 to 33 g/100 g fatty acids, while reducing SFA from 70 to 55 to 60 g/d 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], although 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 with conventional dairy products[73]. Poppitt *et al.* demonstrated that consumption of 20 % energy daily 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/d of high-oleic sunflower oil.

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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, BP, 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 $\geqslant$ 140 mm Hg and/or diastolic BP of $\geqslant$ 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 modifiable by environmental and lifestyle factors, with diet as one of the most important mediators[76]. The Dietary Approaches to Stop Hypertension trial demonstrated that a diet consisting of reduced total and SFA fats, high intakes of low-fat dairy products, and fruits 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[48,55,56,78–83]. These findings were confirmed in a meta-analysis by Soedamah-Muthu *et al.*[83], 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/d) and intake of total dairy[83]. A few RCT have examined the effects of dairy products on BP[56,84,85]. For example, a randomised cross-over trial by Van Meijl and Mensink[56] in thirty-five 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 *et al.*[85] observed no significant effects of consuming low-fat dairy products, compared with low-fat non-dairy products, on BP in sixty-two men and women with prehypertension or stage 1 hypertension[85].

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[86], heart failure[87] and total mortality[88], as well as stroke[89] and renal disease[90]. Arterial stiffness is measured by pulse wave velocity and augmentation index, both of which are predictive of heart attacks and stroke [91] and all-cause mortality[92]. Pulse wave velocity measures the speed of propagation along the artery, whereas augmentation index is calculated from the BP 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[93] and longitudinal[48] cohort studies. Livingstone *et al.*[48] used data from the Caerphilly Prospective Study, based on 2512 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/d), excluding butter, had 2 % ($P = 0{\cdot}02$) lower augmentation index compared with subjects with the lowest dairy intake (mean 154 g/d), whereas across increasing quartiles of butter intake there was no impact on augmentation index, but a significant increase in insulin, serum TAG 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[94,95]. 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.*[96] showed that consumption of 5 g whey-derived peptide daily for a 2-week period significantly improved brachial artery flow-mediated dilation response[96]. A further study reported that although whey and casein exerted similar hypotensive effects, whey protein supplementation (60 g/d for 12 weeks) significantly reduced augmentation index compared with casein (60 g/d for 12 weeks)[97], 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 BP[98]. Milk also contains a variety of other biologically active components such as calcium, potassium and magnesium that may exert impact on BP and arterial stiffness[99].

## 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 BP 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-C-raising property of SFA. Our present dietary guideline to reduce intake of dietary

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SFA to 10 % of the 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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## Authorship

J. A. L. and D. A. H. are sole authors of this manuscript.

## References


1. World Health Organisation (2015) WHO Media centre. Cardiovascular diseases. Fact sheet no 317, Geneva: World Health Organisation; available at: http://www.who.int/mediacentre/factsheets/fs317/en/ (accessed September 2015).
2. 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. *Am J Clin Nutr* **77**, 1146–1155.
3. Law MR, Wald NJ & Rudnicka AR (2003) Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* **326**, 1423.
4. 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 Intern Med* **160**, 398–406.
5. Bates B, Lennox A, Prentice A *et al.* (2014) National Diet and Nutrition Survey: headline results from years 1 and 4 combined of the rolling programme 2008/2009–2011/12). Department of Health; available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310995/NDNS_Y1_to_4_UK_report.pdf (accessed September 2015).
6. Sahi T (1994) Hypolactasia and lactase persistence. Historical review and the terminology. *Scand J Gastroenterol Suppl* **202**, 1–6.
7. Agriculture and Horticulture Development Board (AHDB) Dairy (2013) Datum: Purchases of milk and dairy products based on data from the DEFRA Family Food Survey from 1973–2013; available at: http://dairy.ahdb.org.uk/market-information/dairy-sales-consumption/uk-dairy-consumption/#.VgKqoH39yzl (accessed September 2015).
8. Bath SC, Steer CD, Golding J *et al.* (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet* **382**, 331–337.
9. Payling LM, Juniper DT, Drake C *et al.* (2015) Effect of milk type and processing on iodine concentration of organic and conventional winter milk at retail: implications for nutrition. *Food Chem* **178**, 327–330.
10. Food and Agriculture Organization (FAO) of the United Nations (2008) Fats and fatty acids in human nutrition: report of an expert consultation; available at: http://www.fao.org/3/a-i1953e.pdf (accessed September 2015).
11. Department of Health (1991) *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom*. vol. **41**: Report on Health and Social Subjects. London: Her Majesty's Stationery Office.
12. U.S. Department of Agriculture, U.S. Department of Health and Human Services: Dietary Guidelines for Americans, 2010.
13. de Oliveira Otto MC, Mozaffarian D, Kromhout D *et al.* (2012) Dietary intake of saturated fat by food source and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. *Am J Clin Nutr* **96**, 397–404.
14. Khaw KT, Friesen MD, Riboli E *et al.* (2012) Plasma phospholipid fatty acid concentration and incident coronary heart disease in men and women: the EPIC-Norfolk prospective study. *PLoS Med* **9**, e1001255.
15. Yakoob MY, Shi P, Hu FB *et al.* (2014) Circulating biomarkers of dairy fat and risk of incident stroke in U.S. men and women in 2 large prospective cohorts. *Am J Clin Nutr* **100**, 1437–1447.
16. Vlaeminck B, Fievez V, Cabrita ARJ *et al.* Factors affecting odd- and branched-chain fatty acids in milk: a review. *Anim Feed Sci Technol* **131**, 389–417.
17. Smedman AE, Gustafsson IB, Berglund LG *et al.* (1999) Pentadecanoic acid in serum as a marker for intake of milk fat: relations between intake of milk fat and metabolic risk factors. *Am J Clin Nutr* **69**, 22–29.
18. Lock AL & Bauman DE (2004) Modifying milk fat composition of dairy cows to enhance fatty acids beneficial to human health. *Lipids* **39**, 1197–1206.
19. Mozaffarian D, Katan MB, Ascherio A *et al.* (2006) Trans fatty acids and cardiovascular disease. *N Engl J Med* **354**, 1601–1613.
20. Brouwer IA, Wanders AJ & Katan MB (2010) Effect of animal and industrial trans fatty acids on HDL and LDL cholesterol levels in humans – a quantitative review. *PLoS ONE* **5**, e9434.
21. Gebauer SK, Chardigny JM, Jakobsen MU *et al.* (2011) Effects of ruminant trans fatty acids on cardiovascular disease and cancer: a comprehensive review of epidemiological, clinical, and mechanistic studies. *Adv Nutr* **2**, 332–354.
22. Brouwer IA, Wanders AJ & Katan MB (2013) Trans fatty acids and cardiovascular health: research completed? *Eur J Clin Nutr* **67**, 541–547.
23. Jakobsen MU, Overvad K, Dyerberg J *et al.* (2008) Intake of ruminant trans fatty acids and risk of coronary heart disease. *Int J Epidemiol* **37**, 173–182.
24. Bendsen NT, Christensen R, Bartels EM *et al.* (2011) Consumption of industrial and ruminant trans fatty acids and risk of coronary heart disease: a systematic review and meta-analysis of cohort studies. *Eur J Clin Nutr* **65**, 773–783.


https://doi.org/10.1017/S002966511600001X Published online by Cambridge University Press

25. Kleber ME, Delgado GE, Lorkowski S *et al.* (2015) Trans fatty acids and mortality in patients referred for coronary angiography: the Ludwigshafen risk and cardiovascular health study. *Eur Heart J* (Epublication ahead of print version).
26. 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. *BMJ* **351**, h3978.
27. SACN (2007) Update on Trans fatty acids and health; available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/339359/SACN_Update_on_Trans_Fatty_Acids_2007.pdf (accessed September 2015).
28. Tardy AL, Morio B, Chardigny JM *et al.* (2011) Ruminant and industrial sources of trans-fat and cardiovascular and diabetic diseases. *Nutr Res Rev* **24**, 111–117.
29. 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**, 925–939.
30. Soedamah-Muthu SS, Ding EL, 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**, 158–171.
31. Qin LQ, Xu JY, Han SF *et al.* (2015) Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies. *Asia Pac J Clin Nutr* **24**, 90–100.
32. Elwood PC, Pickering JE, Hughes J *et al.* (2004) Milk drinking, ischaemic heart disease and ischaemic stroke II. Evidence from cohort studies. *Eur J Clin Nutr* **58**, 718–724.
33. Praagman J, Dalmeijer GW, van der Schouw YT *et al.* (2015) The relationship between fermented food intake and mortality risk in the European prospective investigation into cancer and nutrition-Netherlands cohort. *Br J Nutr* **113**, 498–506.
34. Nestel PJ, Chronopulos A & Cehun M (2005) Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr* **59**, 1059–1063.
35. Louie JC, Flood VM, Burlutsky G *et al.* (2013) Dairy consumption and the risk of 15-year cardiovascular disease mortality in a cohort of older Australians. *Nutrients* **5**, 441–454.
36. Christensen R, Lorenzen JK, Svith CR *et al.* (2009) Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. *Obes Rev* **10**, 475–486.
37. Praagman J, Franco OH, Ikram MA *et al.* (2014) Dairy products and the risk of stroke and coronary heart disease: the Rotterdam Study. *Eur J Nutr* **54**, 981–990.
38. Michaelsson K, Wolk A, Langenskiold S *et al.* (2014) Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ* **349**, g6015.
39. Hellstrand S (2015) Comment for 'milk intake and risk of mortality and fractures in women and men: cohort studies' by Michaëlsson, K *et al* in BMJ 2014;349: p. 6015 available at: http://www.bmj.com/content/349/bmj.g6015/rr-4 (accessed August 2015). *BMJ*
40. Wang C, Yatsuya H, Tamakoshi K *et al.* (2015) Milk drinking and mortality: findings from the Japan collaborative cohort study. *J Epidemiol* **25**, 66–73.
41. Bergholdt HK, Nordestgaard BG, Varbo A *et al.* (2015) Milk intake is not associated with ischaemic heart disease in observational or Mendelian randomization analyses in 98,529 Danish adults. *Int J Epidemiol* **44**, 587–603.
42. 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 (Reading, Imperial, Surrey, Cambridge, and Kings) trial. *Am J Clin Nutr* **92**, 748–758.
43. 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. *Am J Clin Nutr* **102**, 40–48.
44. Kris-Etherton PM, Griel AE, Psota TL *et al.* (2005) Dietary stearic acid and risk of cardiovascular disease: intake, sources, digestion, and absorption. *Lipids* **40**, 1193–1200.
45. Mensink R (2005) Effects of stearic acid on plasma lipid and lipoproteins in humans. *Lipids* **40**, 1201–1205.
46. Lemieux I, Lamarche B, Couillard C *et al.* (2001) Total cholesterol/hdl cholesterol ratio vs ldl cholesterol/hdl cholesterol ratio as indices of ischemic heart disease risk in men: the quebec cardiovascular study. *Arch Internal Med* **161**, 2685–2692.
47. Engel S & Tholstrup T (2015) Butter increased total and LDL cholesterol compared with olive oil but resulted in higher HDL cholesterol compared with a habitual diet. *Am J Clin Nutr* **102**, 309–315.
48. 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**, 42–47.
49. 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. *J Nutr* **134**, 1729–1735.
50. Benatar JR, Sidhu K & Stewart RA (2013) Effects of high and low fat dairy food on cardio-metabolic risk factors: a meta-analysis of randomized studies. *PLoS ONE* **8**, e76480.
51. Patterson E, Larsson SC, Wolk A *et al.* (2013) Association between dairy food consumption and risk of myocardial infarction in women differs by type of dairy food. *J Nutr* **143**, 74–79.
52. Crichton GE, Howe PR, Buckley JD *et al.* (2012) Dairy consumption and cardiometabolic health: outcomes of a 12-month crossover trial. *Nutr Metab (Lond)* **9**, 19.
53. Hu FB, Stampfer MJ, Manson JE *et al.* (1999) Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. *Am J Clin Nutr* **70**, 1001–1008.
54. Engberink MF, Hendriksen MA, Schouten EG *et al.* (2009) Inverse association between dairy intake and hypertension: the Rotterdam Study. *Am J Clin Nutr* **89**, 1877–1883.
55. Toledo E, Delgado-Rodriguez M, Estruch R *et al.* (2009) Low-fat dairy products and blood pressure: follow-up of 2290 older persons at high cardiovascular risk participating in the PREDIMED study. *Br J Nutr* **101**, 59–67.
56. van Meijl LE & Mensink RP (2011) Low-fat dairy consumption reduces systolic blood pressure, but does not improve other metabolic risk parameters in overweight and obese subjects. *Nutr Metab Cardiovasc Dis* **21**, 355–361.
57. Esmaillzadeh A & Azadbakht L (2010) Dairy consumption and circulating levels of inflammatory markers among Iranian women. *Public Health Nutr* **13**, 1395–1402.



https://doi.org/10.1017/S002966511600001X Published online by Cambridge University Press

58. Kai SH, Bongard V, Simon C *et al.* (2013) Low-fat and high-fat dairy products are differently related to blood lipids and cardiovascular risk score. *Eur J Prev Cardiol* **21**, 1557–1567.
59. Abargouei AS, Janghorbani M, Salehi-Marzijarani M *et al.* (2012) Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. *Int J Obes* (*Lond*) **36**, 1485–1493.
60. Pal S, Ellis V & Dhaliwal S (2010) Effects of whey protein isolate on body composition, lipids, insulin and glucose in overweight and obese individuals. *Br J Nutr* **104**, 716–723.
61. Pal S, Ellis V & Ho S (2010) Acute effects of whey protein isolate on cardiovascular risk factors in overweight, postmenopausal women. *Atherosclerosis* **212**, 339–344.
62. Astrup A (2014) Yogurt and dairy product consumption to prevent cardiometabolic diseases: epidemiologic and experimental studies. *Am J Clin Nutr* **99**, 1235S–1242S.
63. Tholstrup T, Hoy CE, Andersen LN *et al.* (2004) Does fat in milk, butter and cheese affect blood lipids and cholesterol differently? *J Am Coll Nutr* **23**, 169–176.
64. Hjerpsted J, Leedo E & Tholstrup T (2011) Cheese intake in large amounts lowers LDL-cholesterol concentrations compared with butter intake of equal fat content. *Am J Clin Nutr* **94**, 1479–1484.
65. Thorning TK, Bendsen NT, Jensen SK *et al.* (2015) Cheddar cheese ripening affects plasma nonesterified fatty acid and serum insulin concentrations in growing pigs. *J Nutr* **145**, 1453–1458.
66. de Goede J, Geleijnse JM, Ding EL *et al.* (2015) Effect of cheese consumption on blood lipids: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev* **73**, 259–275.
67. Nilsen R, Hostmark AT, Haug A *et al.* (2015) Effect of a high intake of cheese on cholesterol and metabolic syndrome: results of a randomized trial. *Food Nutr Res* **59**, 27651.
68. Shingfield KJ, Bonnet M & Scollan ND (2013) Recent developments in altering the fatty acid composition of ruminant-derived foods. *Animal* **7**, Suppl. 1, 132–162.
69. Givens DI & Shingfield KJ (2006). Improving the fat content of foods. In *Optimising Dairy Milk Fatty Acid Composition*, pp. 252–280 [C Williams and J Buttriss, editors]. Cambridge: Woodhead Publishing Ltd.
70. Glasser F, Ferlay A & Chilliard Y (2008) Oilseed lipid supplements and fatty acid composition of cow milk: a meta-analysis. *J Dairy Sci* **91**, 4687–4703.
71. 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**, 1067–1074.
72. Livingstone KM, Givens DI, Jackson KG *et al.* (2014) Comparative effect of dairy fatty acids on cell adhesion molecules, nitric oxide and relative gene expression in healthy and diabetic human aortic endothelial cells. *Atherosclerosis* **234**, 65–72.
73. 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. *Nutr Res Rev* **25**, 193–206.
74. Poppitt SD, Keogh GF, Mulvey TB *et al.* (2002) Lipid-lowering effects of a modified butter-fat: a controlled intervention trial in healthy men. *Eur J Clin Nutr* **56**, 64–71.
75. Lawes CM, Vander Hoorn S & Rodgers A (2008) Global burden of blood-pressure-related disease, 2001. *Lancet* **371**, 1513–1518.
76. Appel LJ, Brands MW, Daniels SR *et al.* (2006) Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension* **47**, 296–308.
77. Appel LJ, Moore TJ, Obarzanek E *et al.* (1997) A clinical trial of the effects of dietary patterns on blood pressure. DASH collaborative research group. *N Engl J Med* **336**, 1117–1124.
78. Pereira MA, Jacobs DRVan Horn L Jr *et al.* (2002) Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. *JAMA* **287**, 2081–2089.
79. Alonso A, Beunza JJ, Delgado-Rodriguez M *et al.* (2005) Low-fat dairy consumption and reduced risk of hypertension: the Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr* **82**, 972–979.
80. Snijder MB, van der Heijden AA, van Dam RM *et al.* (2007) Is higher dairy consumption associated with lower body weight and fewer metabolic disturbances? The hoorn study. *Am J Clin Nutr* **85**, 989–995.
81. Ruidavets JB, Bongard V, Simon C *et al.* (2006) Independent contribution of dairy products and calcium intake to blood pressure variations at a population level. *J Hypertens* **24**, 671–681.
82. Ralston RA, Lee JH, Truby H *et al.* (2012) A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. *J Hum Hypertens* **26**, 3–13.
83. Soedamah-Muthu SS, Verberne LD, Ding EL *et al.* (2012) Dairy consumption and incidence of hypertension: a dose-response meta-analysis of prospective cohort studies. *Hypertension* **60**, 1131–1137.
84. Stancliffe RA, Thorpe T & Zemel MB (2011) Dairy attentuates oxidative and inflammatory stress in metabolic syndrome. *Am J Clin Nutr* **94**, 422–430.
85. Maki KC, Rains TM, Schild AL *et al.* (2013) Effects of low-fat dairy intake on blood pressure, endothelial function, and lipoprotein lipids in subjects with prehypertension or stage 1 hypertension. *Vasc Health Risk Manag* **9**, 369–379.
86. Mitchell GF, Moye LA, Braunwald E *et al.* (1997) Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and ventricular enlargement. *Circulation* **96**, 4254–4260.
87. Chae CU, Pfeffer MA, Glynn RJ *et al.* (1999) Increased pulse pressure and risk of heart failure in the elderly. *JAMA* **281**, 634–639.
88. Benetos A, Safar M, Rudnichi A *et al.* (1997) Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension* **30**, 1410–1415.
89. Vaccarino V, Berger AK, Abramson J *et al.* (2001) Pulse pressure and risk of cardiovascular events in the systolic hypertension in the elderly program. *Am J Cardiol* **88**, 980–986.
90. Blacher J, Guerin AP, Pannier B *et al.* (1999) Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* **99**, 2434–2439.
91. Boutouyrie P, Tropeano AI, Asmar R *et al.* (2002) Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension* **39**, 10–15.
92. Janner JH, Godtfredsen NS, Ladelund S *et al.* (2013) High aortic augmentation index predicts mortality and cardiovascular events in men from a general population, but not in women. *Eur J Prev Cardiol* **20**, 1005–1012.


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93. 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.
94. FitzGerald RJ, Murray BA & Walsh DJ (2004) Hypotensive peptides from milk proteins. *J Nutr* **134**, 980S–988S.
95. Boelsma E & Kloek J (2009) Lactotripeptides and antihypertensive effects: a critical review. *Br J Nutr* **101**, 776–786.
96. Ballard K, Bruno R, Seip R *et al*. (2009) Acute ingestion of a novel whey-derived peptide improves vascular endothelial responses in healthy individuals: a randomized, placebo controlled trial. *Nutr J* **8**, 34.
97. Pal S & Ellis V (2010) The chronic effects of whey proteins on blood pressure, vascular function, and inflammatory markers in overweight individuals. *Obesity* (*Silver Spring*) **18**, 1354–1359.
98. 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. *Regul Pept* **118**, 105–109.
99. Fekete AA, 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. *Nutr Res Rev* **26**, 177–190.



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