

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

Article

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NEW PERSPECTIVES ON DAIRY AND CARDIOVASCULAR HEALTH

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Running title: New perspectives on dairy and CVD health

Key words: Milk; dairy products; cardiovascular disease; blood pressure; serum lipids

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.

1 **Abstract**

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

17 **Introduction**

18 Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality
19 worldwide. The World Health Organisation (WHO) estimated that 17.3 million people in the
20 world died from CVD in 2008, including 7.3 million from coronary heart disease (CHD), and
21 6.2 million from strokes⁽¹⁾. There are a number of modifiable risk factors for CVD, such as
22 high levels of serum low-density lipoprotein cholesterol (LDL-C), hypertension, diabetes,
23 overweight/obesity, smoking, low physical activity and diet. Indeed, diets that are rich in
24 saturated fatty acids (SFA) and *trans* fatty acids (TFA) are associated with an increased risk
25 of CVD, and it is largely agreed that this is due, in the most part, to increased serum LDL-
26 C⁽²⁾. Furthermore, evidence from pharmacological studies show that lowering LDL-C by an
27 average of 1.8 mmol/L (by use of statins) reduces risk of ischaemic heart disease (IHD) and
28 stroke by 60 % and 17 %, respectively⁽³⁾. Despite this, the relationship between SFA and
29 CVD risk remains controversial⁽⁴⁾.

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

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

51 **Trends in milk and dairy consumption**

52 In the UK current milk consumption is around 1.5 litres of milk per person per week, with the
53 majority of this consumed as semi-skimmed milk (70 %) followed by whole milk (20 %) and
54 skimmed milk (10 %). Over the last few decades, trends in milk and dairy product
55 consumption have shown considerable variation (Figure 1)⁽⁷⁾. For example, consumption of
56 whole milk has shown a dramatic decline since the 1970s from around 2.7 litres per person
57 per week in 1974 to 0.3 litres per person per week in 2012 (Figure 1A). In the early 1990s the
58 decline in whole milk consumption was partially replaced by semi-skimmed milk,
59 consumption of which has remained fairly constant at around 1 litre per person per week over
60 the last decade, while the intake of whole milk continues to decline. Figure 1B shows the UK
61 trends in consumption of other dairy products such as cheese, yogurt and fromage frais,
62 cream and butter. The trend for cheese and cream consumption has remained fairly constant
63 at around 100 g and 20 mL per person per week for cheese and cream, respectively since the
64 1970s. In contrast, the trend for yogurt and fromage frais consumption has increased
65 significantly from the early 1970s with 33 mL per person per week to around 200 mL per
66 person per week in 2012. The consumption of butter in the UK shows a similar downward
67 trend as for whole milk, due, in part, to recommendations to reduce the amount of total and
68 saturated fat in the diet, but also because of the increasing availability of other spreads.

69

70 **The contribution of milk and dairy foods to nutrient intakes**

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

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

86

87 **Saturated fat from milk and CVD**

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

96 Milk and dairy products are the greatest contributor to dietary SFA in the UK diet,
97 contributing around 27 % of SFA intake. As a result, guidance to reduce or eliminate dairy
98 from the diet has been a common practice for CVD risk reduction. However, the evidence for
99 the relationship between dairy consumption and CVD mortality does not support dairy
100 restriction as an effective strategy for CVD reduction. It is important to recognise that we do
101 not consume individual nutrients, but complex foods and diets that contain specific nutrients
102 within various matrices. This can give rise to disparity between the biological effects of
103 nutrients in different foods that may have contributed to the inconsistencies in the
104 relationships of different SFA-rich foods and CVD mortality. Clear evidence for this comes
105 from the Multi Ethnic Study of Atherosclerosis (MESA), in which different SFA-rich foods
106 were shown to produce differential effects on CVD risk⁽¹³⁾.in 5,209 subjects after a 10 year
107 period (from 2000 to 2010). A lower hazard ratio (HR) for CVD was reported for every 5 g/d
108 (HR 0.79; 95 % confidence interval (CI); 0.68-0.92) or 5 % of energy from dairy SFA (HR
109 0.62; 95 % CI 0.47- 0.82), whereas the equivalent intake of SFA from meat sources was
110 associated with greater HR for CVD (HR for +5 g/d and a +5 % of energy from meat sources
111 of SFA: 1.26; 95 % CI 1.02-1.54 and 1.48; 95 % CI 0.98-2.23, respectively)⁽¹³⁾. Furthermore,
112 the substitution of 2 % of energy from meat sources of SFA with energy from dairy SFA was
113 associated with a 25 % lower CVD risk (HR: 0.75; 95 % CI 0.63-0.91), suggesting that dairy
114 foods containing SFA attenuated the detrimental association of SFA with CVD mortality.
115 While this finding was attributed to the effects of other components within dairy foods, such
116 as calcium, magnesium, bioactive peptides and proteins, it may also have been due to a
117 difference in the relative proportions of different SFA between meat and dairy.

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

132

133 ***Trans* fatty acids and CVD**

134 Other important fatty acids present in milk and dairy foods are *trans* fatty acids (TFA), which
135 are synthesised via bacterial metabolism of unsaturated fatty acids in the rumen of cows⁽¹⁸⁾.
136 The intake of TFA from industrially hydrogenated vegetable oils (iTFA) has a negative
137 impact on cardiovascular health^(19, 20). However, the association between ruminant TFA
138 (rTFA) and CVD remains inconclusive^(21, 22), with some studies showing a cardio-protective
139 association^(19, 23). In an attempt to resolve conflicting reports, a systematic review and meta-
140 analysis was undertaken by Bendtsen *et al.* (2011)⁽²⁴⁾ who reported that the relative risk (RR)
141 for high vs. low quintiles of total TFA intake (2.8 to approximately 10 g/day) was 1.22 (95 %
142 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
143 CHD. In addition, rTFA intake (0.5–1.9 g/day) was not significantly associated with CHD
144 risk (RR 0.92; 95 % CI 0.76–1.11; $P=0.36$), although there was a trend towards a positive
145 association for iTFA (RR 1.21; 95 % CI 0.97–1.50; $P=0.09$). The authors concluded that
146 while iTFA may be positively related to CHD, rTFA were not, but the limited number of
147 studies available prevented a firm conclusion on the critical importance of the source of TFA.
148 In contrast to previous findings, a recent prospective cohort study by Kleber *et al.* (2015)⁽²⁵⁾
149 showed that total TFA content in erythrocyte membranes of 3,259 participants of the
150 Ludwigshafen Risk and Cardiovascular Health Study (LURIC) was inversely associated with
151 adverse cardiac outcomes, while rTFA (*trans*-palmitoleic acid) was associated with reduced

152 risk. In addition, erythrocyte membrane iTFA was associated with no increased risk of
153 adverse cardiac outcomes⁽²⁵⁾. However, it is important to highlight that total TFA
154 concentration in erythrocyte membranes in this study population was relatively low compared
155 with levels in other studies, and this may have been too low to observe an effect of TFA on
156 CVD mortality. Furthermore, it has been suggested that the lack of an association between
157 rTFA and CHD risk may be due to a lower intake from ruminant sources compared with
158 iTFA⁽²⁴⁾. Despite this controversy, there is little doubt that dietary iTFA are associated with
159 increased CVD mortality⁽²⁶⁾. In response there has been a substantial decrease in iTFA over
160 the past 10–15 years, due to the voluntary action by the UK food industry⁽²⁷⁾. This has led to
161 an increase in the relative proportion of rTFA in the UK diet, although the absolute intake of
162 ruminant fat is unchanged, with the current mean population intake of total TFA (0.7 % food
163 energy in adults)⁽⁵⁾ below the recommended population maximum of 2 % of food energy
164 intake⁽¹¹⁾. Although milk and milk products (including butter) contribute to 32 % of this
165 intake⁽⁵⁾, current rTFA intake is not considered to be a major cause for concern with respect
166 to cardiovascular health at a population level^(22, 28). However, the impact of any increase in
167 dietary TFA would need to be monitored.

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

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

175 Several influential reviews have focused on the impact milk and dairy food consumption
176 and CVD risk, some of which have conducted meta-analyses of available cohort data (Table
177 2)⁽²⁹⁻³²⁾. Elwood *et al.* (2004)⁽³²⁾ conducted a meta-analyses of 10 prospective cohort studies
178 that examined the associations between milk and risk of IHD and stroke. Using a pooled
179 estimate of the relative odds for IHD and stroke, the meta-analysis revealed no association
180 with IHD (RR 0.87; 95 % CI 0.74-1.03) and a significant inverse association for stroke (RR
181 0.83; 95 % CI 0.77-0.90) in the subjects with the highest milk compared with those with the
182 lowest intakes. These findings, together with a combined estimate of risk for both IHD and
183 stroke (10 studies RR 0.84 95 % CI 0.78-0.90), suggested that consumption of milk was
184 associated with a modest reduction in CVD risk. This work was extended by Elwood *et al.*⁽²⁹⁾

185 to include 9 prospective cohort studies of milk and dairy products and IHD and 11 studies for
186 stroke. The meta-analysis indicated a 15 % lower RR for all-cause mortality (RR: 0.85; 95 %
187 CI 0.77-0.98) and an 8 % lower overall RR of IHD (RR: 0.92; 95 % 0.80-0.99) in the subjects
188 with the highest dairy consumption compared with those with the lowest intakes.
189 Furthermore, a significant inverse association was observed for the risk of stroke (RR: 0.79;
190 95 % CI 0.68-0.91) in the subjects with the highest dairy consumption compared with those
191 with the lowest intakes. These findings supported previous meta-analyses by Elwood and
192 colleagues⁽³²⁾, and support a reduction in IHD and stroke in subjects consuming the highest
193 amount of milk and dairy products compared with the lowest intakes.

194 In another meta-analysis of 17 prospective cohort studies Soedamah-Muthu *et al.*⁽³⁰⁾
195 showed a modest inverse association between milk intake and risk of overall CVD (4 studies;
196 RR: 0.94 per 200 mL/d; 95 % CI 0.89-0.99). However, milk intake was not associated with
197 risk of CHD (6 studies; RR: 1.00 per 200 mL/d; 95 % CI 0.96-1.04), stroke (6 studies; RR:
198 0.87; 95 % CI 0.72-1.05) or total mortality (8 studies; RR per 200 mL/d: 0.99; 95 % CI 0.95-
199 1.03). A recent meta-analysis by Qin *et al.* (2015)⁽³¹⁾, which included a total of 22 prospective
200 cohort studies, showed an inverse association between dairy consumption and overall risk of
201 CVD (9 studies RR 0.88; 95 % CI 0.81-0.96) and stroke (12 studies RR 0.87; 95 % CI 0.77-
202 0.99). However, no association was found between dairy consumption and CHD risk (12
203 studies RR 0.94; 95 % CI 0.82-1.07), which supports previous findings⁽³⁰⁾. Qin *et al.*⁽³¹⁾ also
204 investigated the association between individual dairy foods on risk of CVD, including stroke
205 and CHD. Interestingly, cheese consumption was associated with a significantly reduced risk
206 of stroke (4 studies; RR: 0.91, 95% CI 0.84-0.98) and CHD (7 studies; RR: 0.84 95% CI
207 0.71-1.0). Recently Praagman *et al.* (2015)⁽³³⁾ also reported a significant association between
208 cheese consumption and stroke mortality, although no impact on CHD mortality was
209 found⁽³³⁾. One possible explanation for the observed beneficial effects of cheese consumption
210 on stroke and CHD risk may be the relatively high calcium content that increases
211 saponification of SFA in the gut, rendering them resistant to digestion leading to increased
212 faecal fat excretion⁽³⁴⁾. This mechanism is supported by the results from a prospective cohort
213 study in which the observed inverse association between cheese consumption and CHD was
214 attenuated when calcium content was used as a confounder in the analysis⁽³⁵⁾. Furthermore a
215 meta-analysis of RCT investigating the impact of calcium from dairy and dietary supplements
216 estimated that increasing dairy calcium intake by 1241 mg/d resulted in an increase in faecal
217 fat of 5.2 (1.6-8.8) g/d⁽³⁶⁾.

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

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

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

247

248 *Effects of dairy on blood lipids and lipoproteins*

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

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

280

281 **Differential impact of high and low-fat dairy foods**

282 There is no established nutritional benefit of whole-fat dairy consumption, except in children
283 under 2 years, compared with lower fat alternatives. With respect to the latter, skimming milk
284 fat to produce low-fat milk and dairy products is a common and an effective way of lowering
285 SFA intake. However, there is currently no consensus on whether fat-reduced dairy foods are

286 associated with a reduced risk of CVD⁽⁵⁰⁾ and studies in this area give inconsistent data, with
287 few RCT that directly compare whole with low fat alternatives. Minimal benefit has been
288 reported in a prospective study of 33,636 women, which suggested no significant differences
289 between consumption of high vs low fat dairy products on risk of myocardial infarction⁽⁵¹⁾.
290 Furthermore, findings from a 12-month RCT concluded that in overweight adults inclusion of
291 reduced-fat dairy foods had no impact on blood lipids, blood pressure (BP) and arterial
292 compliance⁽⁵²⁾. Furthermore, a meta-analysis conducted by Soedamah-Muthu *et al.* (2011)⁽³⁰⁾,
293 showed that there was no significant difference between consumption of high-fat (RR: 1.04;
294 95 % CI 0.89-1.21) or low-fat dairy (RR: 0.93; 95 % CI 0.74-1.17) on CHD risk.

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

306 There have also been a number of studies suggesting that specific milk proteins have
307 differential effects on lipids. Whey (60 g/day for 12 weeks) has been shown to produce
308 significant reductions in serum triacylglycerol (TAG) and total and LDL- cholesterol in
309 comparison to a casein control group⁽⁶⁰⁾. Furthermore, a significant decrease in the
310 postprandial appearance of TAG after consuming a whey meal of 21 % compared to control
311 and 27 % compared to the casein meals were reported⁽⁶¹⁾. In addition to specific dairy
312 proteins, different dairy foods have been shown to have a range of lipid effects⁽⁶²⁾. It has been
313 reported that cheese may have a differential effect on blood lipids compared with other dairy
314 foods^(34, 63, 64), with prolonged ripening of cheddar cheese resulting in more pronounced lipid-
315 lowering effects in a pig model⁽⁶⁵⁾. A meta-analysis that included five of these randomised
316 control studies showed that when compared with butter intake, cheese consumption reduced
317 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
318 % CI -0.09 to -0.02) but had no effect on TAG⁽⁶⁶⁾. In addition, a recent RCT reported that
319 consumption of 80 g/day of a high fat cheese (27 % fat) compared with no cheese or 50 g/day

320 of fat and salt-free cheese for 8 weeks resulted in no changes in total or LDL-C. Those in the
321 high fat cheese group with metabolic syndrome at baseline had significant reductions in total
322 cholesterol (-0.70 mmol/l) compared with control and a significantly higher reduction in
323 TAG⁽⁶⁷⁾. These data show that dairy products do not exert the negative effects on blood lipids
324 which would be predicted solely from their SFA content, and highlights a need for additional
325 studies before firmer conclusions can be made on the differential effects of dairy products on
326 serum lipid and lipoprotein concentrations.

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

330

331 **Manipulating the fatty acid profile of milk**

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

349 Consumption of SFA-reduced milk and milk products, by feed modification has been
350 shown to be beneficial to CVD risk, in healthy and hypercholesterolaemic populations when
351 compared to conventional dairy products⁽⁷³⁾. Poppitt *et al.* (2002) demonstrated that
352 consumption of 20 % energy per day as conventional or feed-modified SFA-reduced butter
353 for a 3 week period resulted in significant reduction in both total cholesterol and LDL-C

354 during the modified butter feeding⁽⁷⁴⁾. However, the evidence is relatively limited and the
355 majority of studies have used butter only and relied on serum lipid levels as biomarkers of
356 CVD risk. This knowledge gap is being addressed at the University of Reading with the
357 *RESET* (REplacement of SaturatEd fat in dairy on Total cholesterol) Study investigating the
358 impact of reducing SFA intake by using modified milk and dairy products on vascular
359 function and CVD risk biomarkers, without limiting dairy product consumption. Milk that
360 has a substantial proportion of SFA replaced with *cis*- MUFA will be collected from cows fed
361 a diet supplemented with 1 kg/day of high-oleic sunflower oil. Cheddar cheese and butter will
362 be produced from this milk and these dairy foods will be supplied to volunteers with
363 increased CVD risk for a 12-week period in a randomised, crossover, double-blind,
364 controlled study. The impact of these modified dairy products on fasted and postprandial
365 vascular function, blood pressure, lipids, insulin sensitivity and inflammatory biomarkers will
366 be determined relative to typical commercially available products. The project, which started
367 in late 2013, will provide unique evidence of the physiological effects of modified SFA-
368 reduced dairy products, which could contribute to food-based dietary recommendations for
369 CVD risk reduction.

370

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

372 Hypertension, defined as systolic BP ≥ 140 mm Hg and/or diastolic BP of ≥ 90 mm Hg, is one
373 of the leading risk factors in the development of stroke, CHD, heart failure and end stage
374 renal disease⁽⁷⁵⁾. BP is modifiable by environmental and lifestyle factors, with diet as one of
375 the most important mediators⁽⁷⁶⁾. The Dietary Approaches to Stop Hypertension (DASH) trial
376 demonstrated that a diet consisting of reduced total and SFA fats, high intakes of low-fat
377 dairy products, and fruit and vegetables significantly lowered BP in normotensive and
378 hypertensive individuals⁽⁷⁷⁾. Moreover, the magnitude of BP reduction was of greater
379 magnitude after the diet rich in low-fat dairy products compared with the fruit and vegetable
380 rich diet, which omitted dairy products altogether⁽⁷⁷⁾. The findings from cross-sectional and
381 prospective studies have shown an inverse association between consumption of dairy
382 products, particularly low-fat varieties and risk of hypertension^(48, 56, 78-84). These findings
383 were confirmed in a meta-analysis by Soedamah-Muthu *et al.* (2012)⁽⁸⁴⁾, in which nine
384 prospective cohort studies and a total of 57,256 participants, showed a reduced RR for
385 hypertension (pooled RR: 0.97; 95 % CI, 0.95-0.99 per 200 g/day) and intake of total
386 dairy⁽⁸⁴⁾. A few RCTs have examined the effects of dairy products on BP^(56, 85, 86). For
387 example, a randomised cross-over trial by Van Meijl and Mensink (2011)⁽⁵⁶⁾ in 35 healthy

388 overweight and obese men and women indicated that daily consumption of low-fat dairy
389 products compared with carbohydrate-rich products for 8 weeks, significantly reduced
390 systolic BP by 2.9 mm Hg. However, a recent study by Maki and colleagues (2013)⁽⁸⁶⁾
391 observed no significant effects of consuming low-fat dairy products, compared with low-fat
392 non-dairy products, on BP in 62 men and women with prehypertension or stage 1
393 hypertension⁽⁸⁶⁾.

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

413 The mechanisms by which milk and dairy products may reduce BP and arterial stiffness
414 are unclear. It has been hypothesised that bioactive peptides released during milk protein
415 digestion, dairy fermentation or industrially by enzyme or chemical treatments, may be
416 involved in the relationship between dairy consumption and BP^(95, 96). It has been proposed
417 that these bioactive peptides may inhibit the action of angiotensin I converting enzyme,
418 thereby reducing blood levels of angiotensin, preventing blood vessel constriction, and
419 modulating endothelial integrity. Ballard *et al.* (2009)⁽⁹⁷⁾ showed that consumption of 5 g of
420 whey-derived peptide daily for a 2 week period significantly improved brachial artery flow-
421 mediated dilation response⁽⁹⁷⁾. A further study reported that although whey and casein exerted

422 similar hypotensive effects, whey protein supplementation (60 g/day for 12 weeks)
423 significantly reduced augmentation index compared with casein (60 g/day for 12 weeks)⁽⁹⁸⁾,
424 an effect that requires confirmation. There is also evidence to suggest that certain peptides
425 from milk proteins may modulate the release of vasoconstrictor endothelin-1 by endothelial
426 cells, thus preventing an increase in blood pressure⁽⁹⁹⁾. Milk also contains a variety of other
427 biologically active components such as calcium, potassium and magnesium that may exert
428 impact on blood pressure and arterial stiffness⁽¹⁰⁰⁾.

429

430 **Conclusions**

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

440

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447 **Conflict of interest**

448 None

449

450 **Authorship**

451 JAL and DAH are sole authors of this manuscript.

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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 B₁₂	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 B₅	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.

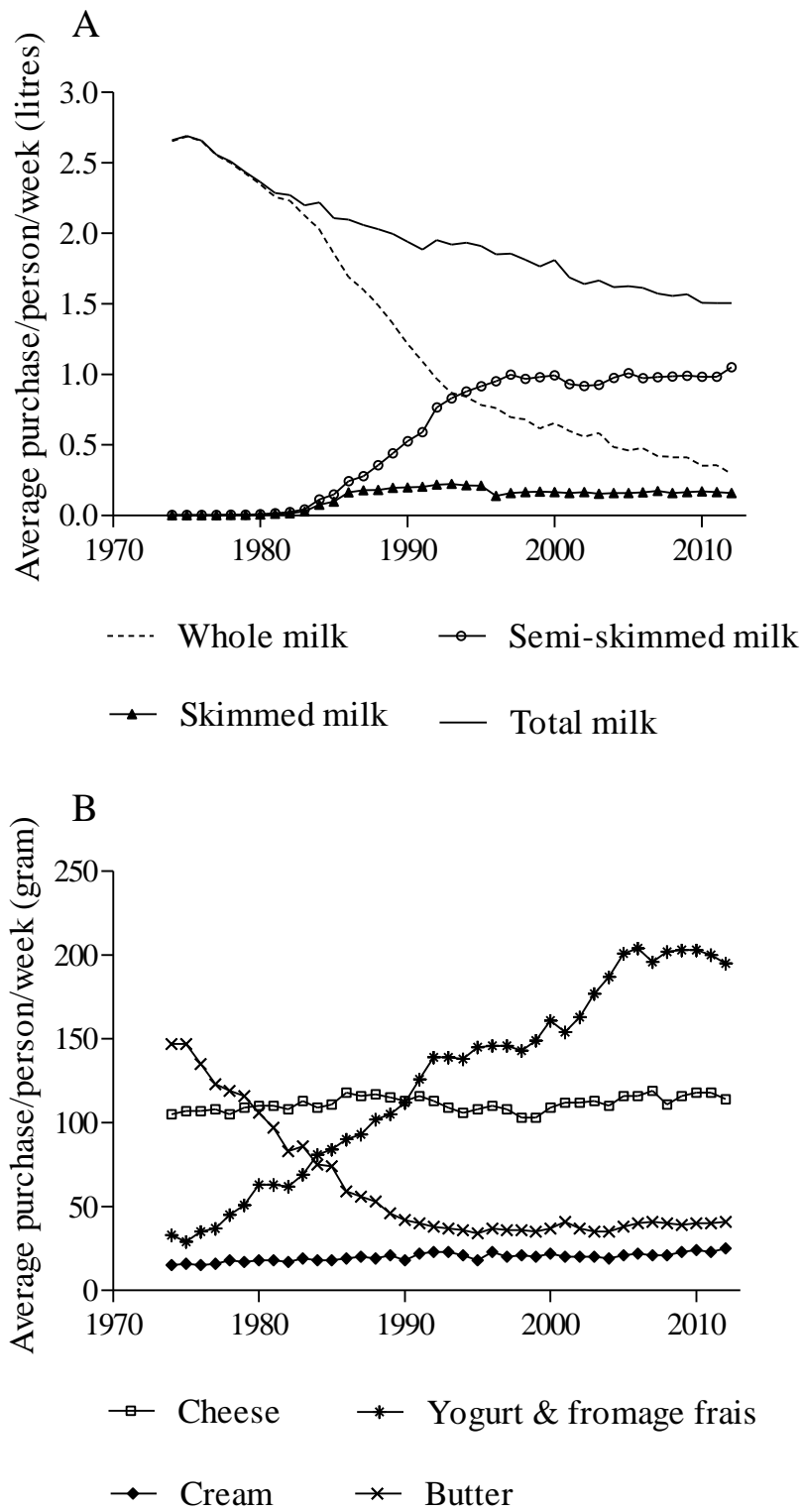


Table 2. Summary of recent reviews and meta-analyses on milk or total dairy intake and risk of CVD

Reference	Dairy food	Methodology	Overall CVD	Stroke	CHD	IHD
Elwood <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (2015) ⁽³¹⁾	Total dairy			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	Meta-analysis: 22 prospective cohorts	Inverse association (RR=0.88, 95% CI 0.81-0.96)	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