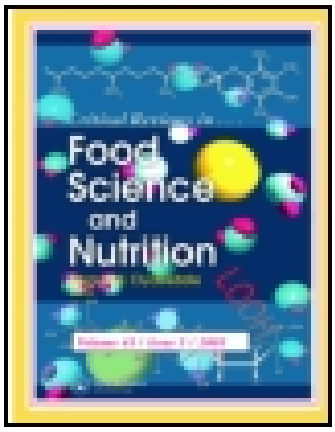

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Cheese and Cardiovascular Disease Risk: A Review of the Evidence and Discussion of Possible Mechanisms

Julie Hjerpsted[a] & Tine Tholstrup[a]
[a] Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, 1958 Frederiksberg, Denmark
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Cheese and cardiovascular disease risk: A review of the evidence and discussion of possible mechanisms

JULIE HJERPSTED, TINE THOLSTRUP

Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, 1958 Frederiksberg, Denmark.

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Corresponding author: Julie Hjerpsted, Department of Nutrition, Exercise and Sports, Faculty of Science, Copenhagen University, Denmark juliehj@life.ku.dk

ABBREVIATIONS

AMI: Acute myocardial infarction

CHD: Coronary heart disease

CI: Confidence interval

CVD: Cardiovascular disease

E%: Energy percentage

FFQ: Food frequency questionnaire

HDL: High density lipoprotein

IHD: Ischaemic heart disease

LDL: Low density lipoprotein

OR: Odds ratio

RR: Relative risk

SCFA: Short chain fatty acid

WHO: World Health Organisation

ABSTRACT

Currently, the effect of dairy products on cardiovascular risk is a topic with much debate and conflicting results. The purpose of this review is to give an overview of the existing literature regarding the effect of cheese intake and risk of cardiovascular disease (CVD).

Studies included reporting the intake of cheese and risk of CVD or risk factors of CVD represent four human intervention studies, nine prospective studies, one prospective case-cohort study, one prospective nested case-control study, five case-control studies, five cross-sectional studies and three correlation studies. The possible mechanisms that may be of importance include calcium, protein, fermentation and the fatty acid composition of cheese.

Results from four prospective studies reported no association between cheese intake and CVD risk, whereas one reported an increased risk, two reported a decreased risk and one reported no association in men but a decreased risk in women. In addition, results from four intervention studies indicated no harmful effect on cholesterol concentrations when comparing fat intake from cheese with fat from butter. The underlying mechanisms for these findings still need to be elucidated.

KEYWORDS

Dairy, cholesterol, fat, protein, calcium, fermentation

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death worldwide (WHO 2012). Saturated fat intake increases low-density lipoprotein (LDL) cholesterol and thereby the risk of CVD. Thus, dietary guidelines from both the American Heart Association and dietary guidelines from European countries suggest lowering the intake of saturated fat (Lichtenstein *et al*. 2006;Perk *et al*. 2012). Dairy fat is characterized by a high content of saturated fatty acids and has therefore been suggested to increase coronary heart disease (CHD) mortality (Artaud-Wild *et al*. 1993;Tholstrup 2006). Therefore, only low-fat dairy products are recommended as part of a healthy diet (Lichtenstein *et al*. 2006). Surprisingly, Bonthuis and colleagues suggested a possible beneficial association between intake of full-fat dairy and cardiovascular mortality (Bonthuis *et al*. 2010). Others have found that the intake of dairy fat was related to ischeamic heart disease (IHD), when cheese was excluded from the analyses (Renaud and de Lorgeril 1989). As cheese usually is categorized as being a full-fat dairy product it is interesting that several correlation studies find no correlation or cheese to be inversely related to CVD (Artaud-Wild *et al*. 1993;Moss and Freed 2003;Seely 1988). The original purpose of cheese making was to process milk into a stable and storable product. Today the consumption of cheese is mainly based on pleasure and it contribute with important nutrients (Walther *et al*. 2008). Therefore, it is important to stress if it is safe to eat in regard to cardiovascular health. This review summarizes the current evidence regarding the effect of cheese intake on CVD risk. In addition, possible mechanisms by how cheese could affect CVD risk are discussed.

LITERATURE STRATEGY

This review is mainly based on original research papers available in PubMed in September 2012. Key search words used were 'cheese' in combination with 'cardiovascular', 'coronary', 'cholesterol' or 'blood lipids'. The search was limited to humans and English language. No restriction in publication date was made. The titles and abstracts of the publications were screened to assess the eligibility of the studies. In addition, reference lists of publications were thoroughly investigated to include any other relevant publications. To layout all evidence, all types of human studies were included (correlation studies, cross-sectional studies, prospective cohort studies, case-control studies and intervention studies). Studies reporting only overall dairy intake or cheese in combination with other dairy products and not cheese intake alone were not included. In addition studies reporting food patterns where cheese was incorporated as part of the food pattern were not included. A total of 40 studies were assessed in full text and read carefully. To make results from the studies more comparable and focus on cheese that is commercially available, five intervention studies comparing cheese enriched with specific test fat e.g. sterols and CLA or cheese that in any way had been modified were excluded. In addition seven intervention studies comparing cheese with dietary products containing less saturated fatty acids were excluded. The 28 human studies included reporting the impact of cheese intake on cardiovascular disease risk or cardiovascular disease risk factors are presented in Table 1. Although, the association between cheese intake and CVD risk may not have been the main purpose of the study, they have still been included to lay out all existing evidence.

The review has been divided into the studies investigating the effect of cheese intake on CVD risk and the effect of cheese intake on CVD risk factors. The latter has again been divided into two sections: human observational studies and human intervention studies. Finally, a section of possible mechanisms of how cheese may affect CVD risk or CVD risk factors has been included.

EFFECT OF CHEESE INTAKE ON CARDIOVASCULAR DISEASE

Human observational studies

In three correlation studies the link between cheese intake and CVD has been investigated with conflicting results (Artaud-Wild *et al*. 1993;Moss and Freed 2003;Seely 1988). Seely reported no correlation between male mortality rates from ischaemic heart disease (IHD) and the consumption of cheese ($r = 0.05$) in eight countries. Also, Artaud-Wild *et al*. found no significant correlation between cheese intake and CHD mortality rates in men aged 55 to 64 years in 40 countries (Artaud-Wild *et al*. 1993). France, with a relatively low coronary mortality, and Finland, with the highest coronary mortality, was then excluded from the analyses. This resulted in a positive relation between cheese and CHD mortality ($r = 0.35$, $p = 0.03$). However, sub analyses of countries with the highest intake of cholesterol and saturated fat resulted in a negative correlation between cheese and CHD mortality ($r = -0.69$, $p = 0.002$). These findings were supported in a correlation study by Moss and Freed (Moss and Freed 2003) who found a negative correlation between cheese intake and CHD death rates for males ($r = -0.14$) and in 1993 ($r = -0.25$). However, these correlations were not significantly different.

The main results from these correlation studies shows no or even a negative correlation between cheese intake and CVD. However, most results were not statistically significant. In addition, correlation studies are not the best evidence, but can merely give an indication of a possible correlation between cheese intake and CVD.

Several case-control studies also report the intake of cheese and risk of CVD. In 1990 Gramenzi and colleagues reported no association between cheese intake and risk of acute myocardial infarction in 287 cases and 649 controls (Gramenzi *et al*. 1990). Later, in 2002 Tavani *et al*. reported a negative association between cheese intake and risk of nonfatal acute myocardial infarction, although the result was not statistical significant (P for trend = 0.153) (Tavani *et al*. 2002). A much more profound result was reported on year later, when a study including 485 cases of nonfatal acute myocardial infarction and 508 controls from Costa Rica found that consumption of 1.4 servings of cheese per day (1 serving corresponding to 28 g of cheese) compared to those who did not consume cheese was associated with a three-fold increase in risk of nonfatal acute myocardial infarction (P for trend = 0.0001) (Kabagambe *et al*. 2003). In contrast to these findings, Kontogianni and colleagues reported that yellow (e.g. Edam, Gouda) and white cheese (e.g. Greek Feta) was associated with 23% and 53% lower odds of nonfatal acute coronary syndrome compared to no intake (OR = 0.77, P < 0.001 and OR = 0.47, P < 0.001, respectively) (Kontogianni *et al*. 2006). The study included 848 cases and 1078 control subjects. In a smaller case-control study including 111 cases with myocardial infarction and 107 controls cheese was also included in the analyses (Biong *et al*. 2008). Increasing cheese intake was associated with a decreased risk of myocardial infarction when adjusted for age and sex (P

for trend = 0.005). This remained significant after adjustment for waist-to-hip ratio (P for trend = 0.02), but after adjustment for smoking the results were no longer significant (P for trend = 0.37).

Only one case-control study reported an increased risk of CVD, whereas four reported a decreased risk or no association with cheese intake. It should be mentioned that the case-control studies included subjects who were diagnosed as survivors of acute myocardial infarction. This may blur the picture somewhat as subjects not surviving acute myocardial infarction may consume different diets than the survivors which could affect their chances of survival. Furthermore, selection bias may exist and bias related to the recall of past diet is strong weaknesses of these types of studies and results should be interpreted with caution. Prospective studies give better evidence to stress if a connection between cheese intake and CVD exists.

Warensjö *et al*. conducted a prospective case-control study nested within the Northern Sweden Health and Disease Study with the main purpose of investigating the association between biomarkers of milk fat (15:0 and 17:0) and risk of myocardial infarction, but also investigated the association between cheese intake and risk of myocardial infarction (Warensjö *et al*. 2010). The study included 444 cases of myocardial infarction and 565 controls. In both men and women increasing intake of cheese was inversely associated with myocardial infarction (P for trend = 0.025 and P for trend = 0.005, respectively). However, after multivariate adjustments, the results were no longer significant (P for trend=0.31 and P for trend = 0.36, respectively). A much larger prospective case-cohort study has been conducted in the Netherlands (Goldbohm *et al*. 2011) including 120,852 subjects followed for 10 years. The subcohort consisted of 4,646 subjects and

3,234 cases of IHD and 1,054 cases of stroke were ascertained. No association between cheese intake and risk of IHD (RR = 1.01, 95% CI: 0.97 - 1.05 for men; RR = 1.01, 95% CI: 0.95 - 1.07 for women) or stroke (RR = 1.02, 95% CI: 0.96 - 1.08 for men; RR = 0.94, 95% CI: 0.87 - 1.02 for women) was observed.

In 1984 results from a prospective study of 25,153 California Seventh-Day Adventists followed for 21 years indicated no association between cheese intake and fatal IHD (Snowdon *et al*. 1984). However, the main purpose of the study was to investigate the relation between meat consumption and IHD. Later, Mann *et al*. conducted a prospective study of 10,802 vegetarians, semi-vegetarians and non-vegetarians followed for an average of 13.3 years (Mann *et al*. 1997). An increasing trend was observed for IHD with increasing intake of cheese (excluding cottage cheese) with subjects consuming cheese five times or more per week compared to those consuming cheese less than once per week (RR = 2.47; 95% CI:0.97 - 6.26; P for trend < 0.01). These results were reported again in 1999 in an overview of the study (Appleby *et al*. 1999).
In contrast to these findings, Gartside and colleagues in 1998 published a prospective study where cheese intake was found inversely associated with CHD (OR = 0.88, P = 0.002) (Gartside *et al*. 1998). The study included 5,811 subjects. During 16 years of follow-up 1,958 suffered from CHD. As mentioned by the authors, the results were puzzling as increased cheese intake suggests increased saturated fat and cholesterol intake which is expected to increase CHD events. However, the findings were supported in a study based on data from the Nurses' Health study (Iso *et al*. 1999). The main aim of the study was calcium, potassium and magnesium intake on

the risk of stroke in 85,764 women followed for 14 years. As part of the result was reported that an inverse trend was observed with intake of hard cheese and risk of stroke when comparing women who ate cheese once or more per day with women who almost never ate cheese (RR = 0.63; 95% CI: 0.40 - 0.99; P for trend = 0.20). No association was observed for cottage cheese when comparing women who ate cottage cheese five or more times per week with women who almost never ate it (RR = 0.94; 95% CI: 0.60 - 1.47; P for trend = 0.71).

In a prospective study conducted in Finland no strong associations were found between intakes of cheese and risk of stroke subtypes (cerebral infarction, intracerebral haemorrhage, subarachnoid haemorrhage and unspecified stroke) (Larsson *et al*. 2009). The study was originally designed to test whether alpha-tocopherol, beta-carotene or both could reduce cancer incidence in male smokers. Therefore, all 26,556 males included were smokers. Also, no association between full-fat cheese intake and CVD mortality was found in a cohort of 1,529 adult Australians followed for an average of 14.4 years (P for trend = 0.63) (Bonthuis *et al*. 2010). Most recently, Larsson *et al*. published a prospective study conducted in Sweden with the aim to investigate the intake of dairy foods and the risk of stroke (Larsson *et al*. 2012). The study included 74,961 men and women with a mean follow-up of 10.2 years. They found that low-fat dairy was inversely associated with risk of stroke (RR = 0.88; 95% CI: 0.80 - 0.97; P for trend = 0.03). Additionally, cheese was found to be inversely associated with the risk of stroke (RR = 0.86; 95% CI: 0.78 - 0.94; P for trend = 0.02) but after adjusting for multiple factors, these results were no longer statistically significant (RR = 0.91; 95% CI: 0.81 - 1.01; P for trend = 0.11).

The role of cheese intake on CVD risk may also differ between genders as Sonestedt *et al*. found different results for men and women from the Swedish Malmö Diet and Cancer cohort (Sonestedt *et al*. 2011). Among 26,445 subjects, 2,520 cases of CVD were identified during a mean follow-up of 12 years. Cheese intake was associated with a decreased CVD risk in women (P for trend = 0.03) but not in men (P for trend = 0.98). The authors argued that these differences could be due to a lower relative validity of cheese intake among men compared to women but also that gender differences or unmeasured confounding factors could explain the differences in results between genders.

In general, results from the observational studies investigating cheese intake and CDV risk provide contradictory results. However, in only one prospective study an increasing risk of CVD with increasing intake of cheese was reported whereas four reported no association. Additionally, two prospective studies reported cheese to be inversely associated with CVD risk and one reported cheese to be inversely associated with CVD in women but found no association in men. Although, prospective studies have several strengths, some limitations exist. Among others, dietary assessment methods may not be reproducible and subjects may change dietary patterns over time. Furthermore, most prospective studies do not differ between the types of cheese e.g. low-fat and full-fat cheese. However, it provides significant long term evidence investigating dietary intake and risk of CVD.

EFFECT OF CHEESE INTAKE ON CARDIOVASCULAR RISK FACTORS

The relationship between low density lipoprotein (LDL) cholesterol and saturated fat intake has been well-established and a strong causal relationship between LDL cholesterol and CVD risk exist (Sacks *et al*. 1996;Shepherd *et al*. 1995). While decreasing LDL cholesterol concentrations is known to decrease the risk of CVD, much evidence suggests that increasing high density lipoprotein (HDL) cholesterol concentrations lowers the risk (Sacks and Willett 1991). This section will focus on the studies were the association between cheese intake and cholesterol concentrations has been investigated.

Human observational studies

D'Avanzo and colleagues investigated the relationship between intake of different foods and serum cholesterol concentrations in 792 subjects included as the control group in a case-control study (D'Avanzo *et al*. 1995). Although, close to zero, the correlation coefficient between serum total cholesterol and cheese intake was slightly positive ($r = 0.08$, $P < 0.08$). The authors stated that no relationship emerged between serum cholesterol concentrations and frequency of consumption of any of the food items included.

A cross-sectional study included 93 15-year-old boys and girls (Samuelson *et al*. 2001). Cholesterol concentrations were measured from fasting blood samples. Cheese intake was negatively associated with serum cholesterol concentrations in the boys ($r = -0.35$; $p < 0.05$). The number of participants was relatively small and they did not differ between LDL and HDL cholesterol concentrations. Results from a study including cross-sectional data from 1,896

subjects, participating in the Hoorn Study, showed no associations between cheese intake and LDL and HDL cholesterol concentrations (Snijder *et al*. 2007). Another, larger cross-sectional study included 10,872 men and women, although only 4,272 were included in the LDL cholesterol analyses (Houston *et al*. 2008). LDL cholesterol concentrations were calculated from measures of total cholesterol, HDL cholesterol and triacylglyceride concentrations (Friedewald *et al*. 1972). No difference in total cholesterol concentrations was observed. HDL cholesterol concentrations increased with increasing cheese intake in both men (P for trend = 0.03) and women (P for trend = 0.04). Remarkably, the LDL cholesterol results differed between men and women. Men had higher LDL cholesterol concentrations with increasing cheese intake (P for trend = 0.05) and women had lower LDL cholesterol concentrations with increasing cheese intake (P for trend = 0.03). The possible reason for the difference between genders was argued to be due to women eating more low-fat cheese than men. Høstmark *et al.* did a similar study including 17,717 men and women (Høstmark *et al*. 2009). They found that cheese intake was positively associated with HDL cholesterol (P for trend < 0.05).

In addition of examining the effect of cheese intake and CVD risk in the prospective study, Sonestedt *et al*. also investigated the association of cheese intake and serum lipid concentrations from 4,535 subjects (Sonestedt *et al*. 2011). They found that high intakes of cheese was associated with higher HDL-cholesterol concentrations (P for trend = 0.002). No association between cheese intake and LDL-cholesterol concentrations were observed (P for trend = 0.23).

Carotid artery media thickness has been suggested to be a risk factor of myocardial infarction and stroke (O'Leary *et al*. 1999). Ivey and colleagues conducted a prospective study examining

the association between yoghurt, milk and cheese consumption and common carotid artery intima-media thickness in 1,080 elderly women (Ivey *et al*. 2011). At baseline food intake was assessed along with blood samples. Three years later carotid artery intima-mediate thickness was measured. Cheese intake was not associated with common carotid artery intima-media thickness (P = 0.057). In addition, no association was observed between cheese intake and HDL cholesterol (P = 0.607), LDL cholesterol (P = 0.760), systolic blood pressure (P = 0.243) and diastolic blood pressure (P = 0.112).

Most observational studies reported no association between cheese intake and total or LDL cholesterol concentrations although one reported increased LDL cholesterol concentrations with cheese intake in men and lower LDL cholesterol concentrations in women. In addition, three studies reported higher HDL cholesterol concentrations with cheese intake.

Human intervention studies

Human intervention studies provide strong evidence regarding dietary intake and CVD risk factors as the specific exposure is known and the effect after a given time of exposure is measured. Although these studies usually are of shorter duration than the prospective studies and therefore the long-term effect is often not known.

Cheese has in some intervention studies been used to test the effect of conjugated linoleic acid or plant sterols on cholesterol concentrations (Huang *et al*. 1994;Jauhiainen *et al*. 2006;Korpela *et al*. 2006;Sofi *et al*. 2010;Tricon *et al*. 2006). In addition, several intervention studies have assessed the effect of cheese consumption with diets containing less saturated fat or with cheese

modified to contain less saturated fat (Asato *et al*. 1996;Davis *et al*. 1993;Intorre *et al*. 2011;Karvonen *et al*. 2002;Meredith *et al*. 1989;von Lossonczy *et al*. 1978). However, these intervention studies do not give evidence regarding the commercial available cheese consumed by the average person and are therefore not discussed further.

As cheese and butter are two dairy products with similar fatty acid composition, the effect on the blood lipids would be expected to be similar. Some intervention studies have been performed with the purpose of investigating the different effect of fat intake from butter and from cheese on the blood lipids (Biong *et al*. 2004;Hjerpsted *et al*. 2011;Nestel *et al*. 2005;Tholstrup *et al*. 2004). An intervention conducted in Norway included 22 subjects who were provided with diets with the same nutrient composition (28% energy from fat, 26% energy from protein and 46% energy from carbohydrate) in a crossover design for three weeks (Biong *et al*. 2004). Of the fat intake, 29% energy came from the dairy products. The cheese diet was compared with two butter diets; one containing casein powder and another containing egg-white. Total cholesterol was lower after the cheese diet compared to the butter and casein diet ($P = 0.03$). LDL cholesterol concentrations tended to be lower with the cheese diet compared to the butter and casein diet but the result was not significant ($P = 0.06$). Another crossover intervention published the same year included 14 men (Tholstrup *et al*. 2004). Three isocaloric diets were provided for three weeks containing 20% of total energy from dairy fat, as whole milk, butter or cheese. The dairy products were adjusted to contain the same amount of protein and lactose. LDL cholesterol concentrations were lower during the cheese diet compared to the butter diet ($P = 0.037$). Total cholesterol concentrations also tended to be lower but the result was not significant ($P = 0.054$).

Nestel *et al*. conducted a crossover intervention testing the daily consumption of 40 g fat as butter or as cheddar cheese (Nestel *et al*. 2005). The study included 14 men and five women. The duration of each intervention period was 4 weeks. Both total and LDL cholesterol concentrations tended to be higher with the butter period compared to the cheese period but the results were not significantly different ($P = 0.054$ for total cholesterol and $P = 0.07$ for LDL cholesterol). In another intervention study by Hjerpsted *et al*. 49 subjects consumed either cheese or butter for 6 weeks, replacing approximately 13% energy of their daily fat intake with fat from the dairy products (Hjerpsted *et al*. 2011). To our knowledge, this intervention is the longest and largest to date comparing cheese and butter. The cheese period resulted in lower total, LDL and HDL concentrations compared to the butter diet ($P < 0.0001$ for both total and LDL cholesterol and $P < 0.005$ for HDL cholesterol).

As mentioned, most observational studies report no association between cheese intake and CVD risk and some even found an inverse association. Likewise, the observational studies investigating the association between cheese and risk markers of CVD seem to find no association or even a beneficial increase of HDL concentrations with increasing cheese intake. However, intervention studies are much more precise in this manner as they control the dietary intake of the subjects during a specific period and measure the risk factors during this period. When comparing cheese and butter with similar fat composition a lowering effect of both total and LDL cholesterol concentrations is observed with fat from cheese compared with fat from butter. Some of the possible mechanisms for these findings are discussed in the following.

MECHANISMS

The effect of calcium

Cheese has a high content of calcium and therefore could be a component influencing the risk of CVD. Intake of calcium has shown to affect both the lipid profile (Denke *et al*. 1993;Ditscheid *et al*. 2005;Jacqmain *et al*. 2003;Lorenzen and Astrup 2011;Reid *et al*. 2002), blood pressure (van Mierlo *et al*. 2006), and overall CVD risk (Li *et al*. 2012).

Results from a cross-sectional study conducted by Jacqmain *et al.* including 235 men and 235 women showed that a daily calcium intake was negatively correlated with total cholesterol, LDL cholesterol and the ratio total:HDL cholesterol ($P < 0.05$) (Jacqmain *et al*. 2003). These findings has been supported in an intervention study by Lorenzen and Astrup (Lorenzen and Astrup 2011). This study included nine men randomized to consume a diet with low calcium and low fat content and a diet with high calcium and low fat content; or a diet with low calcium and high fat content and a diet with high calcium and high fat content. Total, LDL and HDL cholesterol concentrations increased with increasing dairy fat intake, however, independent of dairy fat intake, total and LDL cholesterol concentrations were lower with high calcium intake compared with low calcium intake ($P = 0.0051$ and $P < 0.0001$, respectively). It should be mentioned that this intervention study was very small and of short duration as each intervention period was of only 10 days.

The effect of calcium intake on the lipid profile may differ depending on the source. The source of calcium in the study by Jacqmain *et al*. was calculated from the diet and they found that most of the dietary calcium was derived from dairy products. Also, in the study by Lorenzen and

Astrup the calcium source was mainly from dairy products. In addition, calcium taken as supplement has shown no effect on the lipid profile in two long term intervention studies (Rajpathak *et al*. 2010;Reid *et al*. 2010) while others have found reductions in total and LDL cholesterol concentrations when providing calcium as supplement or by fortification (Denke *et al*. 1993;Ditscheid *et al*. 2005;Reid *et al*. 2002).

Calcium may affect the lipid profile by increasing the excretion of fat in faeces through inhibition of fat absorption. Several animal and human studies have resulted in increased amounts of fat in faeces with calcium intake (Denke *et al*. 1993;Jacobsen *et al*. 2005;Lorenzen and Astrup 2011;Yuangklang *et al*. 2005). Christensen and colleagues estimated that an increase in dairy calcium intake by 1,241 mg/day resulted in an increase in faecal fat of 5.2 g/day (Christensen *et al*. 2008). Calcium and free fatty acids may form insoluble calcium soaps resulting in increased faecal fat excretion (Denke *et al*. 1993). In addition, calcium may bind to bile acids and inhibit the reabsorption of these into the enterohepatic circulation followed by an increased conversion of cholesterol to bile acids in the liver which would result in a decrease in cholesterol concentrations (Denke *et al*. 1993;Van der Meer *et al*. 1990).

In a crossover intervention 10 subjects consumed four isocaloric diets with various calcium content (400, 1200 and 2500 mg from dairy and 1200 mg from calcium carbonate) for 7 days (Boon *et al*. 2007). The 2500 mg calcium diet resulted in 56% higher faecal fat excretion compared to the 400 mg calcium diet, although this difference was not statistically significant (P = 0.159). These results are in accordance with the intervention by Hjerpsted *et al*. where cheese

intake compared to butter intake resulted in slightly higher faecal fat excretion, although this difference was not statistically significant (P = 0.1035) (Hjerpsted *et al*. 2011). As the content of calcium in butter is very low compared to cheese, it seems that calcium alone may not be able to explain the entire effect on cholesterol concentrations. In this intervention blood pressure was also measured and no difference was observed during cheese intake compared to butter intake. Still, both calcium and dairy have shown to have an inverse relationship with blood pressure (Engberink *et al*. 2009;Jorde and Bonaa 2000;van Mierlo *et al*. 2006) and therefore could support the findings of no association between cheese intake and overall CVD risk. However, a recent meta-analysis of prospective studies, examining the effect of dairy consumption and incidence of hypertension, found no association between cheese intake and hypertension (Soedamah-Muthu *et al*. 2012).

Results from some prospective studies report no effect on overall CVD risk with dietary calcium intake (Al-Delaimy *et al*. 2003;Li *et al*. 2012) and results from an intervention study suggest calcium intake to be associated with CVD risk (Bolland *et al*. 2008). Although the latter study investigated calcium supplementation and not calcium intake from dairy products other possible mechanisms by which cheese intake may affect CVD risk and CVD risk markers may be relevant.

The high protein content

The high amounts of protein in cheese could also affect CVD risk and risk factors. Bernstein *et al*. conducted a prospective study examining the association between different dietary protein

sources and risk of stroke in 84,010 women and 43,150 men (Bernstein *et al*. 2012). They found no association between protein from dairy intake and risk of stroke. This result is in line with the results from the prospective studies of cheese and stroke also showing no association.

In an intervention study the effect of dietary calcium on energy expenditure, fat oxidation and faecal fat excretion was examined in 10 subjects who consumed three different diets (Jacobsen *et al*. 2005). The diets were provided for one week and contained low calcium and normal protein, high calcium and normal protein or high calcium and high protein. The high calcium and normal protein diet resulted in increased faecal fat compared to the low calcium and normal protein and high calcium and high protein diet (14.2 vs. 6.0 and 5.9 g/day; $P < 0.05$). This suggests that the intake of high amounts of protein together with high amounts of calcium may decrease the faecal fat excretion. This does not support the theory that the high calcium content in cheese lowers cholesterol concentrations by increasing the excretion of fat as cheese also contains high amount of protein. Maki *et al*. conducted an intervention study comparing the effect of soy protein and milk protein intake on the lipid profile and on fecal bile acid excretions in 58 responders to colesevelam (a bile acid sequestrant). They found a cholesterol lowering effect of both protein types (Maki *et al*. 2010). However, the milk protein diet also contained much more calcium than the soy protein group (700 mg/day vs. < 5mg/day). However, as no differences were observed in the fecal bile acid excretion between the groups this does not support the theory that the high calcium content in cheese lowers cholesterol concentrations by increasing the excretion of bile acids. As mentioned by the authors, fecal fat excretion was not measured and therefore calcium could still explain the cholesterol lowering effect observed with the milk protein intake.

In the intervention study by Tholstrup *et al.*, where the effect of cheese and butter intake on cholesterol concentrations were compared, 52 g of milk protein were added to the butter diet to make the cheese and butter diets similar in protein content (Tholstrup *et al*. 2004). Still, they found lower LDL cholesterol concentrations with the cheese diet. This indicates that the high protein content of cheese cannot explain the effect of cheese intake on cholesterol concentrations. Although, it is possible that the structure of cheese affects the cholesterol concentrations as the fat globules in cheese are trapped within the casein matrix formed from aggregated micelles (Everett and Auty 2008).

Fermentation

Several studies have shown a cholesterol lowering effect of fermented dairy products (Agerholm-Larsen *et al*. 2000b). Agerbæk *et al.* conducted an intervention study exploring the effects of a milk product fermented with a strain of *Enterococcus faecium* and two strains of *Streptococcus termophilus* on the blood lipids in 58 men (Agerbaek *et al*. 1995). For comparison a placebo product was made with organic acid instead of live bacterial culture. After 6 weeks lower total cholesterol concentrations were observed in the group consuming the fermented milk product while no changes were observed in the group consuming the placebo product. As no differences were observed in HDL cholesterol concentrations, the lowering effect of total cholesterol concentrations with the fermented milk product was ascribed to be due to lowering of LDL cholesterol concentrations. Different species and strains of bacteria used in the fermentation process may exert different effects on cholesterol concentrations, as observed in another

intervention study including 70 subjects (Agerholm-Larsen *et al*. 2000a). In this study three groups received yoghurt fermented with *Enterococcus faecium* and *Streptococcus termophilus*, *Lactobacillus acidophilus* and *Streptococcus termophilus* or *Lactobacillus rhamnosus* and *Streptococcus termophilus.* In addition, two groups consumed a placebo product made with organic acid or placebo tablets. After 8 weeks of intervention a decrease in LDL cholesterol concentrations in the group receiving the yoghurt fermented with *Enterococcus faecium* and *Streptococcus termophilus* was observed. No differences in LDL cholesterol concentrations were observed in the other groups. It was suggested that the cholesterol-lowering effect was due to *Enterococcus faecium*. In addition, in a rat study a mixture of bacteria strains had greater effects on cholesterol concentrations than a single bacteria type (Fukushima and Nakano 1996). The results from these studies suggest that fermented dairy may affect CVD risk markers; however, to conclude if cheese affects CVD risk markers, more research focusing on the bacteria strains most commonly used in cheese production is needed. This is a difficult task as different cheeses are fermented using different bacteria strains. Not only may the different bacteria strains exert different effects on cholesterol concentrations, it could be speculated if the duration of the ripening of cheese may also affect CVD risk. A study has been performed where genetic obese, type 2 diabetic mice were fed lyophilized cheese differing in the duration of ripening (0, 15 or 35 days) (Geurts *et al*. 2012). After 4 weeks, the diets with both 15 days and 35 days of ripening decreased hepatic lipid content. However, no change in plasma lipids was observed. To our knowledge, no other studies have focused on the effect of ripening duration on plasma lipids and therefore this could be of interest to further investigate.

St-Onge *et al.* suggested some possible mechanisms by how fermented dairy products may affect the cholesterol metabolism (St-Onge *et al*. 2000). The bacteria may bind to the bile acids in the intestine and inhibit the reabsorption of the bile acids into the enterohepatic circulation. In addition, bacteria in the intestine produce short-chain fatty acids (SCFAs) from unabsorbed carbohydrates which may alter cholesterol synthesis. However, the type of SCFAs produced may affect cholesterol concentrations differently. Wolever *et al.* investigated the interaction between the two SCFAs acetate and propionate and their effect on cholesterol concentrations in six subjects (Wolever *et al*. 1991). They found that rectal infusions of sodium acetate or sodium propionate increased the concentrations of the two SCFAs in serum. Furthermore, they found that the acetate increased cholesterol concentrations. However, if propionate was given together with acetate it inhibited the acetate-induced rise in cholesterol. Wolver *et al*. then speculated if the ratio acetate:propionate was related to serum cholesterol. This was investigated in 62 men and 69 women by measuring the acetate, propionate and cholesterol concentrations from fasting blood samples (Wolever *et al*. 1996). The ratio acetate:propionate was positively related to serum cholesterol in males but not in females. This suggests that higher acetate concentrations and lower propionate concentrations may increase serum cholesterol. However, both high serum acetate and propionate concentrations were associated with low serum cholesterol.

Thus, increasing or altering the bacteria in the intestine by the food ingested may result in increased SCFAs. Depending on which SCFAs that are produced, cholesterol concentrations may be affected differently.

If the bacteria used for fermentation of cheese exert any effect in the intestine, the bacteria must to be able to survive through the gastrointestinal tracts. Firmesse *et al.* conducted a study investigating if Camembert cheese microorganisms could be detected in human feces after consumption (Firmesse *et al*. 2008). Twelve subjects consumed Camembert cheese for four weeks after a two week exclusion period where no fermented products were allowed and followed by a two week washout period. *Lactococcus lactis* and *Leuconostoc mesenteroides*, found in the Camembert cheese, were both detected in fecal samples during consumption. In addition, they found increased fecal concentrations of *Geotrichum candidum* during Camembert cheese intake, which is an important component of the microflora of soft cheeses (Boutrou and Gueguen 2005). Although this study suggest that some microbiota of Camembert cheese can be detected after digestive transit in fecal samples, the question remains, whether the microbiota exerts any effect on CVD risk factors and thereby CVD risk.

Fatty acid composition

Cheese is a major source of the saturated lauric, myristic and palmitic acid which are considered to increase cholesterol concentrations (Kabagambe *et al*. 2003;Kris-Etherton and Yu 1997). However, a metaanalyses of prospective studies found that, saturated fat does not increase risk of CVD (Siri-Tarino *et al*. 2010) and a prospective study by Hu *et al*. reported that high-fat dairy products were weakly associated with coronary heart disease (Hu *et al*. 1999). This has recently been supported by results from a prospective study of 5,209 subjects followed for 10 years showing a higher intake of dairy saturated fat to be associated with lower CVD risk (de Oliveira Otto *et al*. 2012). One of the explanations for this may be that saturated fat increases the LDL

particle size and thereby have lower permeability into the arterial wall (Campos *et al*. 1992;Nordestgaard and Tybjaerg-Hansen 1992). St-Pierre and colleagues conducted a study using 13 year follow-up data from the Québec Cardiovascular Study and found that small dense LDL particles increased the risk of ischaemic heart disease whereas large LDL particles did not (St-Pierre *et al*. 2005). These findings were supported in a prospective study of 4,594 men and women followed for 12.2 years were small LDL particles were found related to CVD whereas large LDL particles were not (Musunuru *et al*. 2009). In addition, Sjogren *et al*. found that fatty acids from dairy were associated with fewer small dense LDL particles (Sjogren *et al*. 2004).

Cheese is a rich dietary source of conjugated linoleic acid, which has been suggested to lower blood pressure in rats (Inoue *et al*. 2004) and affect progression of atherosclerosis in rabbits (Kritchevsky *et al*. 2000). However, studies in humans have been inconsistent (Terpstra 2004). The conjugated linoleic acid content in cheese may vary, depending on several factors. These include the feeding of the cows, the seasonal variations in the milk, the bacteria strains used as starter cultures as well as different manufacturing conditions such as the duration of ripening (Sieber *et al*. 2004).

SUMMERY

The present paper reviewed the current evidence from studies investigating the intake of cheese and CVD risk or CVD risk factors in the form of cholesterol concentrations. Eight publications of prospective studies examining the association of cheese intake and CVD risk were included. Four found no association of cheese intake and risk of CVD, whereas one reported an increased

risk, two reported a decreased risk and one reported no association in men but a decreased risk in women. The findings of a decreased risk of CVD are in accordance with results from a prospective study and a correlation study reporting cheese to be negatively associated with the metabolic syndrome which is affiliated with the risk of CVD (Fumeron *et al*. 2011;Høstmark and Tomten 2011). Furthermore, interventions studies find that fat from cheese does not increase LDL cholesterol concentrations compared to the same amount of fat from butter. Cheese is rich in saturated fat and therefore would be expected to increase cholesterol concentrations. In addition to the effect on cholesterol concentrations, feta cheese was also negatively correlated with the inflammatory marker C-reactive protein in a cross-sectional study (Panagiotakos *et al*. 2010) and no association between cheese intake and blood pressure was recently reported in a meta-analysis (Ralston *et al*. 2012). This supports the findings of no association between cheese intake and CVD risk. However, the differences in study designs make results difficult to compare. The type of study, the number of participants, selection of participants, years of follow-up, type of CVD (e.g. stroke or CHD), number of cases, the serving sizes, the dietary questionnaire, adjustments, geographical area etc. may all affect the outcome. Moreover, a weakness of many of the included studies is that the examination of cheese and CVD risk was not the main purpose of the study. Still, they have been included in the review to lay out all existing evidence regarding cheese and CVD risk. Besides the different study designs which may influence the results, the type of cheese consumed may also affect the results as it is a food item that is very complex. Already in the beginning of the production the milk used may vary depending on e.g. the animal, season and feeding of the animals. Moreover, the differences in production, the fat content and the bacteria strains used, the duration of ripening differs

depending on the cheese. This also complicates the findings of possible mechanisms by how cheese may affect CVD risk and CVD risk factors.

In 2010 Elwood *et al.* reviewed the evidence of milk and dairy foods and the risk of vascular disease and diabetes and concluded that there was no evidence that dairy foods as a total group are associated with harm to health either in terms of death, diabetes, heart disease and stroke but are probably beneficial in relation to these diseases (Elwood PC *et al*. 2010). We can make a similar conclusion more specifically to the intake of cheese. It may not increase the risk of cardiovascular diseases. However, more research in this field is needed and the underlying mechanisms still need to be elucidated.

STATEMENT OF AUTHORS' CONTRIBUTION TO MANUSCRIPT

Julie Hjerpsted, wrote paper.

Tine Tholstrup, collaborated in writing the paper.

Julie Hjerpsted is PhD student at Department of Nutrition, Exercise and Sports, University of Copenhagen, Tine Tholstrup is Associate Professor at the same department.

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Table 1. Results regarding cheese and cardiovascular disease and risk factors listed by type of study and year of publication starting with the study types considered the best value of evidence and most recent published[1]

References	Study type	Study description (*n*, gender, age, country, data assessment)	Point in time/duration	Conclusions
Hjerpsted *et al*. (2011) (Hjerpsted *et al*. 2011)	Crossover intervention	49, both genders, 22 -69 years, Denmark, blood samples. Diet: 13E% from dairy fat as cheese or butter	2x6 weeks. 2 week washout	Cheese intake resulted in lower total, LDL and HDL cholesterol compared to butter intake (P < 0.0001, P < 0.0001 and P < 0.005, respectively).
Nestel *et al.* (2005) (Nestel *et al*. 2005)	Crossover intervention	19, both genders (healthy), mean age 56 years, Australia, blood samples. Diet: 40g fat/day from butter or matured cheddar cheese	2 × 4 weeks. 2 week washout	Butter, and not cheese, raised total and LDL cholesterol compared with a diet low in saturated fatty acids (P < 0.002 and 0.007, respectively)
Biong *et al.* (2004) (Biong *et al*. 2004)	Crossover intervention	22, both genders (healthy), 23 - 54 years, Norway, blood samples. Diet: 20E% from dairy fat as cheese, butter + casein or butter + egg-white	3 × 3 weeks. 1 week washout	Total cholesterol lower after cheese than after butter + casein (P = 0.03) and LDL cholesterol was slightly lower (P = 0.06)
Tholstrup *et al.* (2004) (Tholstrup *et al*. 2004)	Crossover intervention	14, men (healthy), 20 - 31 years, Denmark, blood samples. Diet: 20E% from dairy fat as whole milk, butter + casein + lactose or cheese + lactose	3 × 3 weeks. 3 week washout	Fasting LDL cholesterol was higher after butter + casein + lactose than after cheese (P = 0.04)
Larsson *et al*. (2012) (Larsson *et al*. 2012)	Prospective	74,961, both genders, 45 - 83 years, Sweden, FFQ	10.2 year follow-up (baseline: 1997)	4,089 cases of stroke. Cheese was not associated with risk of stroke (RR = 0.91; 95% CI: 0.81 - 1.01; P for trend = 0.11)
Ivey *et al*. (2011) (Ivey *et al*. 2011)	Prospective	1080, women, > 70 years, Australia, FFQ, B-mode carotid ultrasound and blood samples	3 year follow-up (baseline: 1998)	Cheese intake was not associated with common carotid artery intima-media thickness (P = 0.057), HDL cholesterol (P = 0.607), LDL cholesterol (P = 0.760), systolic blood pressure (P = 0.243) or diastolic blood pressure (P = 0.112)
Sonestedt *et al*. (2011) (Sonestedt *et al*. 2011)	Prospective	26,445, both genders, 44 - 74 years, the Swedish Malmö Diet and Cancer cohort, Sweden, FFQ and blood samples	12 year follow-up (baseline: 1991)	2,520 cases of CVD during follow-up. Cheese intake was associated with decreased CVD risk in women (P for trend = 0.03) but not in men (P for trend = 0.98). Cheese was associated with higher HDL cholesterol concentrations (P for trend = 0.002)

Bonthuis *et al.* (2010) (Bonthuis *et al.* 2010)	Prospective	1,529, both genders, 25 - 78 years, Australia, FFQ	14.4 year follow-up (baseline: 1992)	61 died due to CVD during follow-up. Cheese was not associated with cardiovascular mortality (P for trend = 0.63)
Larsson *et al.* (2009) (Larsson *et al.* 2009)	Prospective	26,556, men, 50 - 69 years, southwestern Finland, FFQ	13.6 year follow-up (baseline: 1985)	3,365 cases of stroke. Cheese was not associated with stroke risk (cerebral infarction: RR = 0.88; 95% CI: 0.77 - 1.01; P = 0.02; Intracerebral hemorrhage: RR = 1.01; 95% CI: 0.72 - 1.41; P = 0.90; subarachnoid hemorrhage: RR = 1.07; 95% CI: 0.66 - 1.72; P = 0.98)
Iso *et al.* (1999) (Iso *et al.* 1999)	Prospective	85,764, women, 34 - 59 years, Nurses' Health Study, USA, FFQ	14 years follow-up (baseline: 1980)	690 cases of stroke. An inverse trend between hard cheese intake and risk of stroke was observed (RR = 0.63; 95% CI: 0.40 - 0.99, P for trend = 0.2)
Gartside *et al.* (1998) (Gartside *et al.* 1998)	Prospective	5,811, both genders, 40 - 74 years, USA, FFQ	16 year follow-up (baseline: 1971)	1,958 subjects had CHD hospitalization or death during follow-up. Cheese was inversely associated with CHD (OR = 0.88, P = 0.002)
Mann *et al.* (1997) (Mann *et al.* 1997)	Prospective	10,802, both genders, 16 - 79 years, UK, semiquantitative FFQ	13.3 years follow-up (baseline: 1981)	64 cases of IHD. Cheese was positively associated with IHD (RR = 2.47; 95% CI: 0.97 - 6.26; P for trend < 0.01)
Snowdon *et al.* (1984) (Snowdon *et al.* 1984)	Prospective	25,153, both genders, 30 - 84 years, questionnaire	21 years follow-up (baseline: 1969)	Number of cases of IHD not stated. No association between cheese intake and IHD (RR = 0.91, NS)
Goldbohm *et al.* (2011) (Goldbohm *et al.* 2011)	Prospective case-cohort	120,852, 4646 in subcohort, 3,234 cases of IHD and 1,054 cases of stroke., both genders, 55 - 69 years, Netherlands, FFQ	10 year follow-up (baseline: 1986)	No association between cheese intake and risk of IHD or stroke was observed (IHD: RR = 1.01; 95% CI: 0.97 - 1.05 for men; RR = 1.01; 95% CI: 0.95 - 1.07 for women) (Stroke: RR = 1.02; 95% CI: 0.96 - 1.08 for men; RR = 0.94, 95% CI: 0.87 - 1.02 for women)
Warensjö *et al.* (2010) (Warensjö *et al.* 2010)	Prospective, nested case-control	444 cases of myocardial infarction, 556 controls, both genders, 49 - 64 years, Sweden, semiquantitative FFQ and blood samples (analyzed for fatty acids 15:0 and 17:0 as a reflection of dairy intake)	1987 - 1999	Cheese intake was inversely associated with myocardial infarction in both men (P for trend = 0.025) and women (P for trend = 0.005)

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Biong *et al*. (2008) (Biong *et al*. 2008)	Case-control	111 cases of myocardial infarction, 107 controls, both genders, 45 - 75 years, Norway, FFQ	1995 - 1997	An inverse trend regarding intake of cheese and risk of myocardial infarction was observed (P for trend = 0.005). This was no longer significant after adjustment for smoking (P for trend = 0.37)
Kontogianni *et al*. (2006) (Kontogianni *et al*. 2006)	Case-control	848 cases of nonfatal acute coronary syndrome, 1078 controls, both genders, age only stated according to groups of dairy intake, Greece, semi-quantitative FFQ	2000 - 2001	Compared to no intake yellow and white cheese intake was associated with lower odds of nonfatal acute coronary syndrome (OR = 0.77, P < 0.001 and OR = 0.47 , P < 0.001, respectively)
Kabagambe *et al*. (2003) (Kabagambe *et al*. 2003)	Case-control	485 cases of first nonfatal AMI (57 ± 10 years), 508 controls (58 ± 11 years), both genders, Costa Rica, FFQ	1995 - 1998	1.4 servings (one serving = 28g) of cheese per day compared to no servings per day was associated with an increased risk of nonfatal AMI (OR = 3.07; P for trend < 0.0001)
Tavani *et al.* (2002) (Tavani *et al*. 2002)	Case-control	507 cases of first nonfatal AMI. 478 controls (acute conditions unrelated to AMI), both genders, 25 - 79 years, Italy, FFQ	1995–1999	Cheese consumption was negatively correlated with non-fatal AMI, however result was not significant (P for trend = 0.153)
Gramenzi *et al*. (1990) (Gramenzi *et al*. 1990)	Case-control	287 cases of acute myocardial infarction, 649 controls, women, 21-69 years, Italy, FFQ	1985 – 1989	No correlation between myocardial infarction and cheese intake (OR = 0.7 for middle intake, OR = 1.0 for highest intake)
Høstmark *et al*. (2009) (Høstmark *et al*. 2009)	Cross-sectional	17,717, both genders, four age groups: young (30 y), middle-aged (40 - 45 y), seniors (59 - 60 y) and old (75 - 75 y), Oslo Health study, questionnaire, blood samples	2000 - 2001	Cheese intake was negatively associated with triacylglycerol and positively with HDL cholesterol (P for trend < 0.05)
Houston *et al*. (2008) (Houston *et al*. 2008)	Cross-sectional	10,872, both genders, 25 - 75 years, USA, FFQ, blood samples, LDL calculated from Friedewald *et al*. (Friedewald *et al*. 1972)	1988 - 1994	In women more frequent cheese consumption was associated with higher HDL and lower LDL cholesterol (P for trend < 0.05). In men frequent cheese consumption was associated with higher HDL and LDL cholesterol (P for trend < 0.05)
Snijder *et al*. (2007) (Snijder *et al*. 2007)	Cross-sectional	1896, both genders, 50 - 75 years, Netherlands, semiquantitative FFQ, blood samples	1989	No association between cheese intake and any metabolic variables (including LDL and HDL cholesterol) except from increased body mass index (β = 0.15 ± 0.8, P = 0.04)
Samuelson *et al.* (2001) (Samuelson *et al*. 2001)	Cross-sectional	93, both genders, 15 years, Sweden, 7-day weighed food record, fasting blood samples	Not stated	Negative correlation between intake of cheese and serum cholesterol (P < 0.05) and triacylglycerol (P < 0.05) in boys

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D'Avanzo *et al*. (1995) (D'Avanzo *et al*. 1995)	Cross-sectional	792, both genders, 23 - 74 years, interviews	1988 - 1989	A small correlation between intake of cheese and serum cholesterol was observed (r = 0.08, P < 0.05)
Moss and Freed (2003) (Moss and Freed 2003)	Correlation study	National data, men, 65 - 74 years, CHD death rates from WHO, national food consumption statistics	Food intake: 1971, 1989 CHD death rates: 1988, 1993	Cheese had a slight non-significantly negative correlation with CHD (r = -0.025 and r = -0.14, depending on the year)
Artaud-Wild *et al*. (1993) (Artaud-Wild *et al*. 1993)	Correlation study	National data, men, 55 - 64 years, CHD mortality from WHO statistics, food data from the Food and Agriculture Organization	Food intake: 1977 CHD mortality: 1977	Cheese was positively related with CHD (r = 0.35, P = 0.03) when France and Finland were excluded from the analyses. Subgroup results: negative correlation between cheese and CHD mortality in countries with high intake of saturated fatty acids and cholesterol (r = -0.69, P = 0.002)
Seely. (1988) (Seely 1988)	Correlation study	National data, mortality rates from ischaemic heart disease from WHO statistics, food consumption from Organization of Economic Cooperation and Development	Food intake: 1973 IHD mortality: 1983	No correlation between cheese and coronary mortality (r = 0.05)

[1]**AMI**: Acute myocardial infarction, **CHD**: Coronary heart disease, **CI**: Confidence interval, **CVD**: Cardiovascular disease, **E%**: Energy percentage, **FFQ**: Food frequency questionnaire, **HDL**: High density lipoprotein, **IHD**: Ischaemic heart disease, **LDL**: low density lipoprotein, **OR**: Odds ratio, **RR**: Relative risk, **WHO**: World Health Organization