Lead Article

Effect of cheese consumption on blood lipids: a systematic review and meta-analysis of randomized controlled trials

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Context: *Cheese may affect lipids and lipoproteins differently than other high-fat dairy foods.*
Objective: *The present systematic review and meta-analysis was performed to evaluate randomized controlled trials that examined the effect of cheese consumption compared with another food product on blood lipids and lipoproteins.*
Data Sources: *A systematic literature search of the MEDLINE, Embase, Scopus, CAB Abstracts, the Cochrane Controlled Trials Register, and the clinicaltrials.gov website was performed.*
Study Selection: *A total of 12 randomized controlled trials (RCTs) were identified that examined the effect of cheese consumption on blood lipids and lipoproteins in healthy adults.*
Data Extraction**:** *A meta-analysis of 5 RCTs that compared the effects of hard cheese and butter, both of which had a similar ratio of polyunsaturated fatty acids to saturated fatty acids (P/S ratio), was performed.*
Data Synthesis: *Compared with butter intake, cheese intake (weighted mean difference: 145.0 g/d) reduced low-density lipoprotein cholesterol (LDL-C) by 6.5% (−0.22 mmol/l; 95%CI: −0.29 to −0.14) and high-density lipoprotein cholesterol (HDL-C) by 3.9% (−0.05 mmol/l; 95%CI: −0.09 to −0.02) but had no effect on triglycerides. Compared with intake of tofu or fat-modified cheese, cheese intake increased total cholesterol or LDL-C, as was expected on the basis of the P/S ratio of the diets. There was insufficient data to compare intake of cheese with intake of other foods.*
Conclusion: *Despite the similar P/S ratios of hard cheese and butter, consumption of hard cheese lowers LDL-C and HDL-C when compared with consumption of butter. Whether these findings can be attributed to calcium, specific types of saturated fatty acids, or the food matrix of cheese warrants further research.*

INTRODUCTION

Coronary heart disease (CHD) caused 1 of every 6 deaths in the United States in 2008.[1] Each year, an estimated 785 000 Americans will suffer from a first event of CHD, and approximately 470 000 will have recurrent CHD.[1] Dyslipidemia is a major risk factor for CHD.[2] A healthy diet is of utmost importance for the prevention of dyslipidemia and CHD.[3,4]

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In many Western countries, dairy consumption is recommended as part of a healthy diet.[5] For example, in the United States 3 daily servings of dairy, mainly low-fat or fat-free, is recommended.[6] Cheese, which is essentially concentrated or solid milk, is a nutrient-dense product that is rich in potentially cardioprotective nutrients such as blood-pressure-lowering minerals, including calcium.[7] In the United States cheese provides 9.2% of total calcium intake.[5] Cheese is also a source of vitamin K_2, which may protect against vascular calcification.[8,9] On the other hand, cheese may increase the risk of CHD because it contains sodium[10] and saturated fatty acids (SFAs).[11] Sodium has been related to hypertension and CHD,[10,12] and, compared with unsaturated fat, SFAs raise low-density lipoprotein cholesterol (LDL-C) levels, thereby increasing CHD risk.[2,13,14] Cheese is a leading contributor of saturated fat in the United States, contributing 7.7% of total solid fat intake.[5]

Dietary guidelines focus mainly on SFAs and their LDL-C-raising effects.[15] However, the link between food sources of SFAs and CHD may be less straightforward because some food sources high in SFAs contain an array of saturated and unsaturated fatty acids, each of which may differentially affect lipoprotein metabolism and contribute significant amounts of other nutrients, which may alter CHD risk.

Recent reappraisals of the impact of dairy foods and milk fat on cardiovascular disease risk concluded there is no clear evidence that cheese consumption is consistently associated with a higher or lower risk of cardiovascular disease.[16,17] In addition, some intervention studies that examined the effect of adding cheese to the diet suggested that hard cheese may have a different effect on lipids and lipoproteins than other high-fat dairy products.[18–21] As far as can be determined, to date, there have been no published meta-analyses or systematic reviews of randomized controlled trials (RCTs) on the relationship between cheese and blood lipids and lipoproteins. Therefore, the present systematic review and meta-analysis of RCTs was performed to examine the effect of cheese consumption compared with intake of another food product on blood lipids and lipoproteins in healthy populations.

METHODS

Search strategy

A systematic literature search was conducted for randomized trials that investigated the effects of various types of cheese on lipids and lipoproteins. The following databases were searched until February 2013: MEDLINE, Embase, Scopus, CabAbstracts, the Cochrane Controlled Trials Register, and the clinicaltrials.gov website. The complete search strategy is outlined in Appendix S1 and the completed PRISMA checklist is available in Appendix S2, both of which are available in the Supporting Information for this article online. Searches for new publications appearing between February 2013 and March 2014 were also performed. The bibliographies of published trials eligible for this review, as well as any appropriate review articles, were additionally searched for citations of further relevant published and unpublished research. No restrictions were imposed on language, publication date, or publication status.

Inclusion and exclusion criteria

The studies selected were RCTs of healthy adults that compared the effect of dietary supplementation with cheese versus another food product on total cholesterol, LDL-C, HDL-C, very-low density lipoprotein cholesterol (VLDL-C), triglycerides, apolipoprotein A1, and apolipoprotein B as a primary or secondary study outcome (Table 1). Studies in diabetic patients, sham feeding studies, studies without cheese as an independent exposure, studies testing the effects of conjugated linoleic acid in cheese, and studies with acute effects on blood lipids were excluded.

Data extraction

Data were collected on trial design (parallel or crossover), duration of intervention, type of intervention (fully controlled diet or dietary advice), type of cheese and dose, effects on blood lipids, and whether lipids were of primary or secondary interest. Data on sample size and characteristics of the study population, including mean age, sex, baseline lipids or lipoprotein values (fasting or nonfasting), methods of lipid assessment, and baseline cheese intake, were tabulated.

Quantitative data synthesis for cheese intake vs butter intake

If at least 3 trials that compared cheese with a comparable control treatment were available, which was the case for cheese and butter, a quantitative meta-analysis was performed. Two authors (J.G. and S.S.S.M.) obtained the differences in blood lipids and variance measures for each trial (all crossover trials) according to a standardized procedure using a data abstraction form. Means of within-person differences in lipid and lipoprotein levels and corresponding standard errors of the cheese intervention compared with the butter

Table 1 **Summary of the PICOS criteria used to identify studies for inclusion**

Parameter	Description
Population	Healthy adults
Intervention	Cheese consumption
Comparator	Consumption of another food product or modified cheese
Outcome	Effect on blood lipids
Study design	Randomized controlled trials

intervention were provided by 2 authors upon request.[19,21] For 1 trial, the standard error of the mean difference was calculated on the basis of the confidence interval provided in the publication.[18] For 2 trials, data from the authors were not available.[20,22] Mean differences in those studies were estimated by subtracting the follow-up means of intervention and control periods. Standard errors of mean differences in lipids were estimated[23] using a within-subject correlation coefficient of 0.5.[24] This was a conservative estimation, as the lowest observed correlation in the other studies was 0.64. From one publication, results of LDL-C and triglycerides could not be used because only medians and interquartile ranges were available.[20] The mean percentage change in lipids was calculated as the mean difference of the cheese intervention minus the mean difference of the control intervention divided by the mean difference of the control intervention for each study, multiplied by100, weighted for the number of participants in each study.

The meta-analysis was performed using STATA software (version 11.0; STATA Corp., College Station, Texas) using the METAN command. Each study was weighted by the inverse of its variance, including both the within- and between-study variances. Between-study heterogeneity was assessed via the I^2 statistic, which expresses the percentage of variation attributable to between-study heterogeneity.[25] Random-effects pooling was conducted according to DerSimonian and Laird.[26] Forest plots were used to visualize and summarize the associations of cheese with lipid and lipoproteins outcomes. Estimates were reported with 95% confidence intervals (CIs). Funnel plots were created in order to detect publication bias. Two-sided P values lower than 0.05 were considered statistically significant.

RESULTS

Results of the search

Two researchers each independently identified the same set of 12 RCTs of cheese supplementation in human participants with blood lipids as a primary or secondary study outcome, which fulfilled the inclusion criteria (Figure 1). Results that were published in 1 conference proceeding[27] could not be retrieved. For 1 trial, the results for plasma lipids were published in 2 publications.[28,29] According to the trial register, 1 other RCT on cheese intake is currently under way (clinicaltrials.gov ID NCT01739153) for which results could not yet be retrieved. A sufficient number of RCTs to conduct a meta-analysis was only available for hard cheese compared with butter.

Description of trials

Tables 2 and 3 show the characteristics of all 12 RCTs included in this systematic review.[18–22,28–35] The trials differed in terms of study population, cheese intervention, and control groups. The trials were published between 1978 and 2014, and most had a crossover design. Trials included only men,[18,22,30] only women,[31,32] or men and women combined,[19–21,28,33–35] with mean ages ranging between 22 and 56 years. Participants were healthy,[18,19,21,22,28,31] had moderately increased cholesterol levels,[20,32–34] or were lacto-ovo vegetarians.[30,35] The number of participants ranged from 5 to 49, and interventions lasted 2–8 weeks. Three crossover trials did not include a washout period.[30,33,35] All trials were focused primarily on the effects of interventions on blood lipids, and the interventions did not result in weight change. LDL-C was measured directly[20,21,31] or calculated[18,19,22,28,30,32–34] using the Friedewald equation.[36] One study did not report LDL-C.[35] RCTs were grouped by control treatment, i.e., butter, milk, tofu, or fat-modified cheese. Two studies comparing cheese with mackerel[35] and egg white[32] are discussed separately because they could not be grouped otherwise. Some of the RCTs were partly[18–20,22,33,34] or fully[21] funded by the dairy industry. Two RCTs provided no information on funding.[30,32]

Trials comparing cheese with butter

Five crossover trials were located that compared the effects of cheese and butter on blood lipids.[18–22] Tholstrup et al.[18] compared the effects of hard cheese (Samso, 205 g/d) with the effects of butter (64 g/d) in 14 men in Denmark who received a fully controlled diet for 3 weeks, separated by 1 month on their habitual diet. The cheese and butter diets were similar in energy, macronutrients, and fatty acid composition. The trial also contained a milk intervention to investigate the impact of differences in the physical form of the dietary milk fat. The cheese and butter arms were enriched with casein and lactose and used dosages similar to those of milk. The cheese diet resulted in borderline significantly lower total cholesterol ($P = 0.054$) and

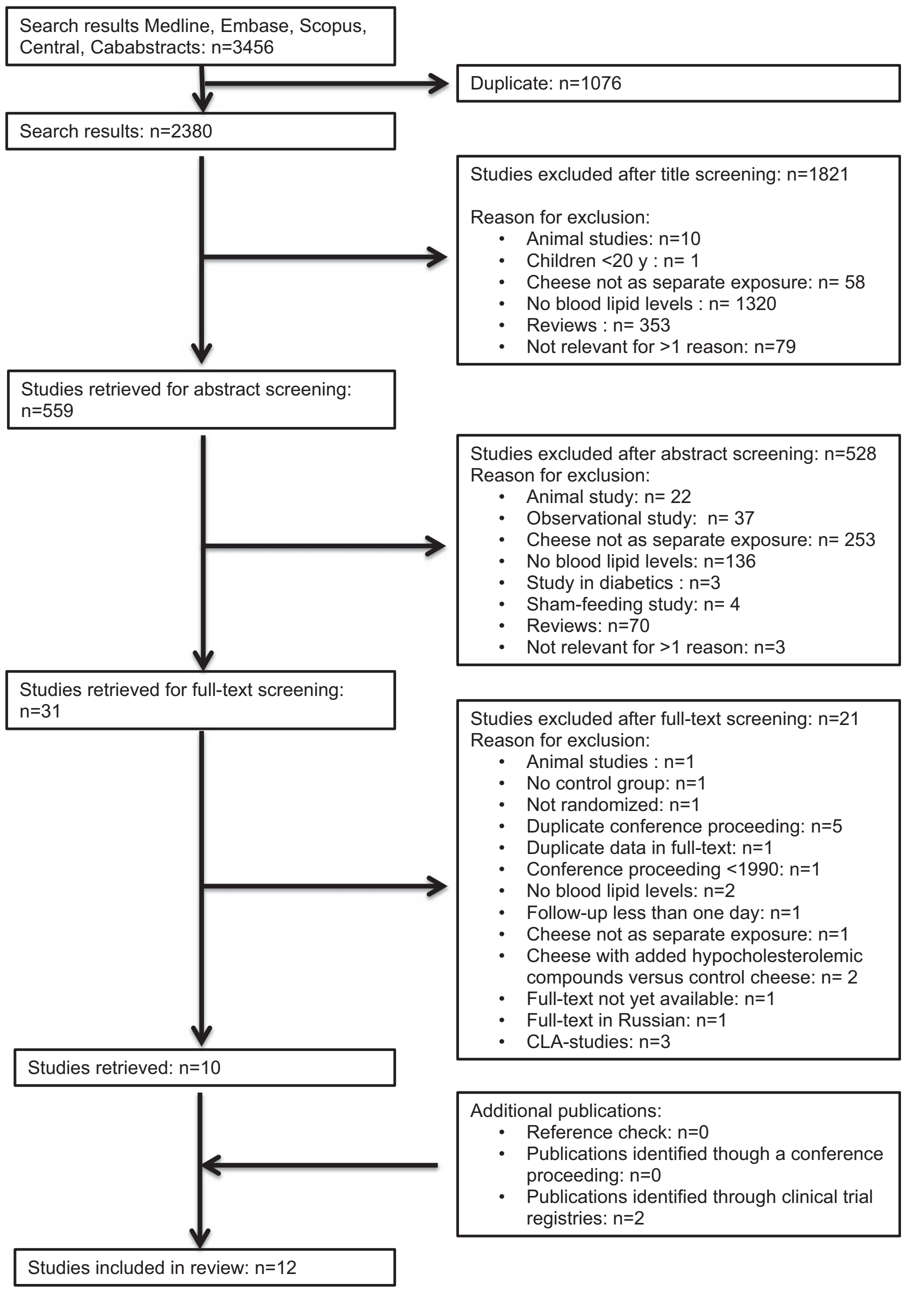

Figure 1 **Flow diagram of the selection process for randomized controlled trials (RCTs) investigating cheese consumption and plasma lipid levels**

significantly lower LDL-C ($P = 0.037$) compared with the butter diet (4.05 ± 0.15 vs 4.26 ± 0.18 mmol/L for total cholesterol, and 2.67 ± 0.15 vs 2.87 ± 0.17 mmol/L for LDL-C). No statistically significant differences were observed for plasma HDL-C, VLDL-C, apolipoprotein A-1, and apolipoprotein B concentrations.

Biong et al.[19] compared the effects of hard cheese (Jarlsberg, 150 g/day) with butter (butter [52 g/day] + calcium − caseinate [BC diet] or butter [52 g/day] + egg white [BE diet]) on serum lipids in 22 individuals in Norway. The treatments were similar for energy, macronutrients, and ratio of polyunsaturated fatty acids to saturated fatty acids (P/S ratio). The participants received, consecutively, 3 fully controlled diets for 3 weeks, separated by habitual diets for 1-week washout periods. The cheese diet resulted in significantly lower serum total cholesterol (5.40 ± 1.34 vs 5.66 ± 1.16 mmol/L; $P = 0.03$) and a borderline significantly lower serum LDL-C (3.57 ± 1.15 vs 3.78 ± 1.04 mmol/L; $P = 0.06$) than the butter (BC) diet. Levels of HDL-C, triglycerides, apolipoprotein A1, apolipoprotein B, and lipoprotein(a) did not differ between the groups.

Table 2 **Characteristics of 12 randomized controlled trials on the effects of cheese consumption on blood lipids**

Reference	Country	Health status of participants	No. of participants	Mean age (y)	Male (%)	Mean dietary intake at baseline or run-in	Intervention	Control	Design	Duration	Controlled factors
Cheese vs butter											
Tholstrup et al. (2004)[18]	Denmark	Healthy	14	23	100	NR	Samso (hard) cheese (45% fat of dry weight) 205 g cheese/10 MJ 26% fat and 1989 mg Ca/10 MJ Milk fat contributed 20% of total energy	64 g butter/10 MJ (54 g fat and 10 mg Ca/10 MJ)	Crossover: 3-group comparison[a] Fully controlled diets were provided	3 wk Washout: $\geq$1 mo Run-in: no	Treatments were equalized for energy, en% protein, en% fat, and en% carbohydrates Cheese and butter adjusted for lactose and casein content of milk
Biong et al. (2004)[19]	Norway	Healthy	22	31.5	41	NR	150 g/d Jarlsberg (hard) cheese; equivalent to 20% of total fat Total diet: 8 MJ	52 g/d butter (with casein) equivalent to 20 en% fat Total diet: 8 MJ	Crossover: 3-group comparison Fully controlled diets were provided	3 wk Washout: 1 wk Run-in: no	Treatments were equalized for energy, en% protein, en% fat, and en% carbohydrate
Nestel et al. (2005)[20]	Australia	Moderately increased LDL-C (3.6 mmol/L<LDL-C<6.0 mmol/L)	19	56.3	74	Run-in: P/S ratio: 0.37 (cheese diet: 0.29; butter diet: 0.24)	120 g/d cheddar (hard) cheese (33% fat); equivalent to 40 g fat/d	40 g fat/d as butter (amount NR)	Crossover: 2-group comparison Background diet was self-selected within constructed set of foods within prespecified groups of foods	4 wk Washout: 2 wk Run-in: 2 wk	Treatments were equalized for fat
Hjerpsted et al. (2011)[21]	Denmark	Healthy	49	55.5	57.1	Run-in: P/S ratio: 0.45 (during both interventions: 0.29) Ca: 906 mg/d Protein: 16.8 en%	143 g Samso (hard) cheese/d (27 g fat/100 g) at median energy level Cheese fat contributed 13% of total energy	47 g salted butter at median energy level Butter fat contributed 13% of total energy	Crossover: 2-group comparison Remaining diet was self-selected	6 wk Washout: $\geq$2 wk Run-in: 2 wk	Treatments were equalized for en% fat
Soerensen et al. (2014)[22]	Denmark	Healthy	15	27.7	100	Habitual Ca: 1120 mg/d; no other baseline dietary information provided	120 g Klovborg (semi-hard) cheese/d (per 10 MJ); 45% fat of dry weight 810 mg Ca from cheese 362 mg Ca from non-dairy sources	Butter (amount NR, no other dairy) 362 mg Ca from non-dairy sources	Crossover: 3-group comparison Fully controlled diets were provided	2 wk Washout: $\geq$2 wk Run-in: no	Treatments were equalized for total energy, en% total fat, en% SFA, en% protein, en% carbohydrates, and Ca from nondairy sources

(continued)

Table 2 **Continued**

Reference	Country	Health status of participants	No. of participants	Mean age (y)	Male (%)	Mean dietary intake at baseline or run-in	Intervention	Control	Design	Duration	Controlled factors
Cheese vs milk											
Tholstrup et al. (2004)[18]	Denmark	Healthy	14	23	100	NR	Samso (hard) cheese (45% fat of dry weight); 205 g cheese/10 MJ 26% fat and 1989 mg Ca/10 MJ Milk fat contributed 20% of total energy	1.5 L whole-fat milk/ 10 MJ (54 g fat and 1779 mg Ca/ 10 MJ)	Crossover: 3-group comparison[a] Fully controlled diets were provided	3 wk Washout: ≥1 mo Run-in: no	Treatments were equalized for energy, en% protein, en% fat, en% carbohydrates Cheese adjusted for lactose and casein content of milk
Soerensen et al. (2014)[22]	Denmark	Healthy	15	27.7	100	Habitual Ca: 1120 mg/d; no other baseline dietary information provided	120 g Klovborg (semi-hard) cheese/d (per 10 MJ); 45% fat/ of dry weight 810 mg Ca from cheese 362 mg Ca from non-dairy sources	670 mL semi-skimmed milk/d (per 10 MJ) 781 mg Ca from milk 362 mg Ca from non-dairy sources	Crossover: 3-group comparison Fully controlled diets were provided	2 wk Washout: ≥2 wk Run-in: no	Treatments were equalized for total energy, en% total fat, en% SFA, en% protein, en% carbohydrates, and Ca from nondairy sources Cheese and milk diets were equalized for total Ca content
Cheese vs tofu											
Dunn & Liebman (1986)[30]	USA	Lacto-ovo vegetarian, regularly consuming cheese	12	31.8	100	53 g/d cheese 53 g/d tofu	Monterey Jack (semi-hard) cheese, 63 g/d	Tofu, 336 g/d	Crossover: 2-group comparison Rest of diet was self-selected	3 wk Run-in: no Washout: no	Cheese and tofu provided similar amounts of energy
Meredith et al. (1989)[31], experiment 1	USA	Healthy normolipidemic adult women not taking oral contraceptives	10	27.3	0	Run-in and washout diet: 40 g/d cheese and 140 g/d tofu	80 g/d cheddar	Tofu, 280 g/d	Crossover: 2-group comparison Diets fully provided	3 wk Run-in:1 wk Washout: 1 wk	–
Meredith et al. (1989)[31], experiment 2	USA	Healthy normolipidemic adult women not taking oral contraceptive	5	29.8	0	Run-in and washout diet: 40 g/d cheese and 140 g/d tofu	80 g/d cheddar	Tofu, 280 g/d	Crossover: 2-group comparison Diets fully provided	3 wk Run-in:1 wk Washout: 1 wk	Diet equalized for total fat and P/S ratio
Asato et al. (1996)[32]	Taiwan	Moderately hypercholesterolemic female students	24	22	0	NR	Cheese (type unknown) (n = 6): 100 g/d, 30% of total protein and 5% of total energy	Tofu (n = 9): 338 g/d 30% of total protein and 5% of total energy	Parallel: 3 groups Diets prepared by a dietician See also "Other comparisons with cheese"	4 wk Run-in: no	Treatments were equalized for en% fat and protein
Fat-modified cheese											
Davis et al. (1993)[33]	USA	Mild cholesterolemia (TC > 5.69 mmol/L and < 7.24 mmol/L)	26	37.6	65	NR	Fatty acid-modified mozzarella; animal fats replaced with	Partial skim-milk mozzarella, 96 g/d	Double-blind crossover: 2-group comparison	8 wk, Run-in: no Wash-out: no	Energy content of the cheeses

(continued)

Table 2 **Continued**

Reference	Country	Health status of participants	No. of participants	Mean age (y)	Male (%)	Mean dietary intake at baseline or run-in	Intervention	Control	Design	Duration	Controlled factors
							vegetable oil, 112 g/d Fat composition of cheese (percentage of total fatty acids): PUFA (linolenic acid and alpha-linolenic acid): 49.1%; MUFA (oleic acid): 16.1% SFA (C12, C14, C16, and C18): 31.9%	Fat composition of cheese (percentage of total fatty acids): PUFA (linoleic acid, alpha-linolenic acid): 3.4%; MUFA (oleic acid): 29.1 %; SFA (C12, C14, C16, and C18): 64.3%	Diets were self-selected, but nutritionists monitored dietary intake with 3-d food records		
Karvonen et al. (2002)[34]	Finland	Mild hypercholesterolemia ($TC \geq 5$ and ≤ 8 mmol/L and TG <3 mmol/L)	31	52.9	55	NR	65 g/d rapeseed-oil-based hard cheese (with 17% rapeseed oil and no other fat) providing 11 g fat, of which 1 g was SFA (type of cheese NR)	65 g/d ordinary medium-fat hard cheese providing 15 g fat, of which 10 g was SFA (type of cheese NR)	Single-blind crossover: 2-group comparison Rest of the diet was self-selected	4 wk Run-in: 2 wk Washout: 2 wk	Amount of cheese
Intorre et al. (2011)[28]	Italy	Healthy	30	29.3	37	NR	21.4 g/d hard (raw milk) cheese produced from cows fed a grass and maize silage-based diet +5% linseed (type of cheese NR)	21.4 g/d hard (raw milk) cheese produced from cows fed a grass and maize silage-based diet (type of cheese NR)	Double-blind crossover: 2-group comparison Rest of diet was self-selected	4 wk Run-in: 1 wk Washout: 1 wk	Amount of cheese
Other comparisons with cheese											
Von Lossonczy et al. (1978)[35]	Netherlands/ Belgium	Lacto-ovo vegetarian nuns and monks	42	45.7	45	NR	Gouda cheese, 150 g/d	Mackerel fish, 200 g/d	Crossover: 2-group comparison Rest of diet was self-selected	3 wk Run-in: 2 wk Washout: no	
Asato et al. (1996)[32]	Taiwan	Moderately hypercholesterolemic female students	24	22	0	NR	Cheese (type unknown) ($n = 6$): 100 g/d, 30% of total protein and 5% of total energy	Egg white ($n = 9$): 221 g/d, 30% of total protein and 5% of total energy See also cheese vs tofu	Parallel: 3 groups Diets prepared by a dietician	4 wk Run-in: no	Treatments equalized for en% fat, protein

Abbreviations: Ca, calcium; en%, energy percentage; LDL-C, low-density lipoprotein cholesterol; MUFA, monounsaturated fatty acids; MJ, megajoule; NR, not reported; P/S, polyunsaturated fatty acids to saturated fatty acids ratio; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TC, total cholesterol; TG, triglycerides
[a]See also cheese vs milk

Table 3 **Results and conclusions of 12 randomized controlled trials on the effects of cheese consumption on blood lipids**

Reference	Baseline lipids (mmol/L)	Mean differences in blood lipids (cheese vs control diet) mmol/L (95%CI)	Differences (cheese vs control diet)	Conclusion
Cheese vs butter				
Tholstrup et al. (2004)[18]	TC: 4.11 LDL-C: 2.64 HDL-C: 1.23 TG: 0.89	TC: −0.20 (−0.41 to 0.00) LDL-C: −0.21 (−0.40 to −0.01) HDL-C: −0.03 (−0.12 to 0.06) TG: 0.03 (−0.06 to 0.13)	P/S ratio: 0[a] Ca: 1979 mg/d Protein:7.8 g/d[a] Based on total energy intake of 10 MJ	Cheese consumption resulted in a moderately lower LDL-C compared with butter
Biong et al. (2004)[19]	TC: 5.55 LDL-C: 3.61 HDL-C: 1.47 TG: 1.07	TC: −0.27 (−0.47 to −0.07)[b] LDL-C: −0.22 (−0.39 to −0.04)[b] HDL-C: −0.05 (−0.10 to −0.004)[b] TG: 0 (−0.13 to 0.13)[c]	P/S ratio: 0.02[a] Ca: 965[a] Protein: 19 g/d[a] Based on total energy intake of 8.5 MJ	Cheese may be less cholesterol-increasing than butter with identical fat content
Nestel et al. (2005)[20]	After run-in: TC: 5.6 LDL-C: 3.4 HDL-C: 1.5 TG: 1.1	TC: −0.30 (−0.63 to 0.03)[d] LDL: not available[e] HDL-C: −0.10 (−0.28 to 0.08)[d] TG: not available[e] LDL-C: median and IQR 3.7 (3.3 to 3.9) after cheese 3.9 (3.5 to 4.1) after butter TG: median and IQR 1.5 (0.8 to 1.6) after cheese 1.1 (0.9 to 1.4) after butter	P/S ratio: 0.05[f] Ca: NR Protein: 6 g/d[f] Energy: 292 kJ (NS)[f] Based on total energy intake of 7.4 MJ of cheese diet and 7.1 MJ of butter diet	Compared with a moderately reduced fat diet (run-in), the LDL-C-raising effect of cheese was, on average, 6% less than that of butter at comparable intakes of total fat and saturated fat
Hjerpsted et al. (2011)[21]	After run-in: TC: 5.24 LDL-C: 3.17 HDL-C: 1.48 TG: 1.06	TC: −0.29 (−0.41 to −0.17)[b] LDL-C: −0.21 (−0.31 to −0.11)[b] HDL-C: −0.06 (−0.12 to −0.00)[b] TG: −0.02 (−0.12 to 0.08)[b]	P/S ratio: 0[f] Ca: 775 mg/d[f] Protein: 28 g/d[f] Energy: −265 kJ[f]	Cheese intake resulted a 6.9% lower LDL-C compared with butter with the same fat content. Cheese did not increase LDL-C compared with run-in, despite a lower P/S ratio
Soerensen et al. (2014)[22]	NR	TC: −0.48 (−0.99 to 0.03)[d] LDL-C: −0.38 (−0.80 to 0.04)[d] HDL-C: −0.09 (−0.21 to 0.03)[d] TG: −0.06 (−0.20 to 0.08)[d]	P/S ratio: −0.01[f] Ca: 810 mg/d[f] Protein: 0.2 en% = ∼1.2 g/d[f] Energy: 0[f,g]	Both diets increased TC and LDL-C, but cheese significantly attenuated the increase compared with the control diet. HDL-C and TG did not differ between diets
Cheese vs milk				
Tholstrup et al. (2004)[18]	TC: 4.11 LDL-C: 2.64 HDL-C: 1.23 TG: 0.89	TC: −0.13 (−0.33 to 0.08) LDL-C: −0.14 (−0.34 to 0.05) HDL-C: 0.01 (−0.08 to 0.10) TG: 0.01 (−0.08 to 0.10)	P/S ratio: 0.04[a] Ca: 210 mg/d[a] Protein: 0 g/d[a] Based on total energy intake of 10 MJ	No statistically significant different effect between milk and cheese for TC, LDL-C, HDL-C, or TG
Soerensen et al. (2014)[22]	NR	TC: −0.16 ($P > 0.05$) LDL-C: −0.06 ($P > 0.05$) HDL-C: −0.03 ($P > 0.05$) TG: −0.17 ($P > 0.05$)	P/S ratio: −0.015[f] Ca: 29 mg/d[f] Protein: 0.1 en% = ∼0.6 g/d[f] Energy: 0[f,g]	No statistically significant different effect between milk and cheese for TC, LDL-C, HDL-C, or TG

(continued)

Table 3 **Continued**

Reference	Baseline lipids (mmol/L)	Mean differences in blood lipids (cheese vs control diet) mmol/L (95%CI)	Differences (cheese vs control diet)	Conclusion
Cheese vs tofu				
Dunn et al. (1986)[30]	TC: 4.0 LDL-C: 2.6 HDL-C: 0.98 TG: 0.81	TC: 0.32 (sig. NR) LDL-C: 0.33 (sig. NR) HDL-C: −0.01 (sig. NR) TG: −0.07 (sig. NR)	P/S ratio: −0.9[f] Ca: NR Protein: −11 g/d[f] Energy: −335 kJ[f]	Tofu improved lipid levels compared with cheese
Meredith et al. (1989),[31] experiment 1	TC: 3.90 LDL: 2.40 HDL: 1.22 TG: 0.79	TC: 0.31 ($P < 0.01$) LDL-C: 0.34 ($P < 0.001$) HDL-C: 0.03 TG: 0.03	P/S ratio: −1.5[a] Ca: NR Protein: −2 g/d[a] Energy: 393 kJ[a]	See also results of exp 2 The relatively low fat and high P/S ratio of tofu, rather than protein type, appear to be responsible for the observed alterations in plasma lipids
Meredith et al. (1989) [31], experiment 2	TC: 4.97 LDL: 2.66 HDL: 1.58 TG: 1.11	TC: −0.31 (NS) LDL-C: −0.26 (NS) HDL-C: −0.03 (NS) TG: −0.05 (NS)	P/S ratio: 0.21[a] Ca: NR Protein: −2 g/d[a] Energy: −21 kJ[a]	See also results of exp 1 The relatively low fat and high P/S ratio of tofu, rather than protein type, appear to be responsible for the observed alterations in plasma lipids
Asato et al. (1996)[32]	NR	Cheese vs baseline: TC: +5%* LDL-C: +7% HDL-C: −2% TG: −9% Tofu vs baseline: TC: −8% LDL-C: −10% HDL-C: −5% TG: −30%	P/S ratio: NR Ca: NR Protein: NR Energy: −887 kJ[f] (based on 1st day only)	Cheese increased TC compared with tofu. LDL-C, HDL-C, and TG did not differ
Fat-modified cheese				
Davis et al. (1993)[33]	Baseline lipids: TC: 6.31 LDL: 4.15 HDL: 1.40 TG: 1.66	Linoleate-enriched mozzarella cheese vs skim-milk mozzarella TC: −0.42 (−0.19 to −0.84) LDL-C: −0.38 (−0.20 to −0.70) HDL-C: −0.05 (−0.14 to 0.01) TG: 0.002 (−0.34 to 0.19)	P/S ratio:1.5 (based on cheeses only) Ca: NR Protein: NR Energy: NR	TC and LDL-C were decreased by linoleate-enriched cheese compared with normal cheese
Karvonen et al. (2002)[34]	TC: 6.13 [h] LDL: 4.17 [h] HDL: 1.34 [h] TG: 1.36 [h]	Rapeseed vs control cheese TC: −0.32 (−0.48 to −0.16) LDL-C: −0.28 (−0.43 to −0.13) HDL-C: −0.04 (−0.09 to 0.01) TG: 0 (−0.18 to 0.19)	Rapeseed vs control diet P/S ratio: 0.3[f] Ca: 73 mg/d[f] Protein: 11 g/d[f] Energy: 430 kJ[f]	Fat-modified cheese significantly affected serum lipids compared with the control cheese
Intorre et al. (2011)[28]	TC: 0.21 LDL-C: 2.45 HDL-C: 1.25 TG: 0.80	Linseed vs control cheese TC: 0.14 (sig NR) LDL-C: 0.06 (sig NR) HDL-C: 0.02 (sig NR) TG: 0.14 (sig NR)	Linseed vs control cheese P/S ratio: 0.03[f] Ca: −30 mg/d[f] Protein: 0.6 g/d[f] Energy: −29.3 kJ[f]	Neither cheese affected lipid levels

(continued)

Table 3 **Continued**

Reference	Baseline lipids (mmol/L)	Mean differences in blood lipids (cheese vs control diet) mmol/L (95%CI)	Differences (cheese vs control diet)	Conclusion
Other comparisons with cheese				
Von Lossonczy et al. (1978)[35]	TC: 5.51 LDL: NR HDL: 1.43 TG: 0.91	TC: 0.42 ($P < 0.01$) LDL-C: NR HDL-C: −0.09 ($P < 0.01$) TG: 0.29 ($P < 0.01$)	NR	Cheese diet, compared with mackerel, resulted in significantly higher TC and TG and significantly lower HDL-C
Asato et al. (1996)[32]	NR	Cheese vs baseline: TC: +5%** LDL-C: +7%** HDL-C: −2%** TG: −9% Egg white vs baseline: TC: −12% LDL-C: −21% HDL-C: +17% TG: −18%	P/S ratio: NR Ca: NR Protein: NR Energy: −561 kJ[f] (based on the first day only)	Cheese increased TC and LDL-C and decreased HDL-C compared with egg-white. TG did not differ

Abbreviations: Ca, calcium; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; kJ, kilojoule; LDL-C, low-density lipoprotein cholesterol; MJ, megajoule; NR, not reported; NS, not statistically significant; sig, significance; sig diff, significantly different; TC, total cholesterol; TG, triglycerides
[a]Values based on chemical analysis of duplicate portions
[b]Values provided by the authors
[c]Confidence interval of TG was estimated on basis of the confidence interval of the other lipids
[d]Confidence intervals conservatively estimated by using a correlation of 0.5 between intervention and control periods. Estimations for LDL-C and TG were not possible
[e]Estimations for LDL-C and TG were not possible
[f]Values based on dietary assessment and food consumption databases
[g]Chemical measurements of total energy and total fat in the diet differed from estimated values. Per 10 MJ/day, the milk and cheese diet provided approx. 1.5 MJ/d more energy than the control diet. For all diets, the total fat content was approx. 3 en% lower
[h]Moment of measurement (before or after run-in) not clear
*Significant difference from tofu ($P < 0.05$)
**Significant difference from egg white ($P < 0.05$)

Nestel et al.[20] compared the effects of 120 g/d cheddar cheese with 40 g/d fat as butter on total cholesterol, LDL-C, and HDL-C cholesterol, and triglycerides in 19 individuals in Australia with moderately increased total cholesterol levels. The background diet was self-selected from a constructed set of foods within prespecified food groups. The participants received two 4-week treatments after a run-in of 2 weeks and a washout period of 2 weeks between the treatments. Both treatments contained approximately 4.5 energy percent (en%) more SFAs than the run-in diet. The butter treatment increased total cholesterol by 9% ($P < 0.05$) and LDL-C by 15% ($P < 0.05$) compared with the run-in diet. Blood lipids, however, were not affected by the cheese diet compared with the run-in diet. Total cholesterol ($P = 0.054$) and LDL-C ($P = 0.07$) were borderline significantly lower, and triglycerides were borderline significantly (50%; $P = 0.052$) higher after the cheese diet compared with the butter diet.

The largest study with the longest duration to date is that of Hjerpsted et al.,[21] which included 49 healthy men and women in Denmark. The participants received 2 treatments, of 6 weeks each, of either hard cheese (Samso, 143 g/d) or butter (47 g/d), with a run-in period of 2 weeks and a washout period of at least 2 weeks in between. The remaining diet was self-selected. Cheese and butter contained similar proportions of various fatty acids. The amounts of SFAs, monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) did not significantly differ between the total diets, and therefore the P/S ratios were similar (0.29 for both treatments). The cheese diet contained less total fat (33.4 vs 35.7 en%) and carbohydrates (44.9 vs 48.1 en%) and more protein (19.2 vs 13.4 en%) (all $P < 0.05$) than the butter diet. The cheese intervention resulted in a 5.7% lower serum total cholesterol ($P < 0.0001$), a 6.9% lower LDL-C ($P < 0.0001$), and a 4.2% lower HDL-C ($P < 0.005$) compared with the butter intervention. The increase in SFA intake was similar for the cheese and butter diets compared with the run-in diet. However, compared with the run-in diet, the cheese diet did not affect total cholesterol and LDL-C, whereas the butter diet increased total cholesterol and LDL-C (all $P < 0.05$). The ratio of total cholesterol to HDL-C did not differ between treatments or between each treatment and the run-in diet.

Also in Denmark, Soerensen et al.[22] recently compared the effects of 120 g/d of semi-hard cow cheese (Klovborg) with the effects of butter (amount not reported) on serum lipids in 15 healthy men. Both fully controlled diets lasted 2 weeks and were separated by at least 2 weeks of washout time. Total energy, macronutrient content, and the P/S ratio were similar for both diets. Per 10 MJ, the cheese diet resulted in an 810 mg/d higher intake of dairy calcium. The amount of nondairy calcium was the same (362 mg/d) in both diets. Both diets increased total cholesterol and LDL-C. However, compared with the control diet, the cheese diet resulted in a smaller increase in total cholesterol and LDL-C than the control diet ($P < 0.01$). The effects on HDL-C and triglycerides did not differ between the diets.

Meta-analysis of trials comparing cheese with butter

Based on the above-mentioned randomized crossover trials from Denmark,[18,21,22] Norway,[19] and Australia,[20] a meta-analysis was performed to quantify the effect of cheese intake compared with butter intake on plasma levels of total cholesterol,[18–22] LDL-C,[18,19,21,22] HDL-C,[18–22] and triglycerides.[18,19,21,22] Data were insufficient for pooling results of VLDL-C, apolipoprotein A1, and apolipoprotein B. All 5 trials had a washout period of at least 1 week. Intake of cheese (weighted mean difference: 145.0 g/d) reduced total cholesterol significantly by 5.2% (−0.28 mmol/L; 95%CI: −0.36 to −0.19, $P < 0.001$), LDL-C by 6.5% (−0.22 mmol/L; 95%CI: −0.29 to −0.14, $P < 0.001$), and HDL-C by 3.9% (−0.05 mmol/L; 95%CI: −0.09 to −0.02, $P = 0.001$) compared with intake of butter (Figure 2A–D). The pooled effect on triglycerides was −0.008 (95%CI: −0.064 to 0.049, $P = 0.79$). No heterogeneity was observed (all $I^2 = 0\%$; Figure 2A–D). It was not possible to formally test for publication bias due to the limited number of trials. Funnel plots showed reasonable symmetry of RCTs with positive or negative effects, which suggested no evidence of publication bias (see Figures S1, S2, S3, and S4 in the Supporting Information online).

Trials comparing cheese with milk

In 2 crossover RCTs, intakes of cheese and milk were compared. Tholstrup et al.[19] compared the effects of hard cheese (Samso, 205 g/d) with the effects of whole-fat milk (1.5 L/d), in addition to comparing the effects of cheese vs butter, on blood lipids and lipoproteins in 14 men in Denmark. The men received each of the fully controlled diets for 3 weeks, with interventions separated by 1 month on a habitual diet. Per 10 MJ, the cheese diet contained 210 mg more calcium than the milk diet. Cheese resulted in lower values of total cholesterol and LDL-C compared with milk, but the differences were not statistically significant. HDL-C and triglycerides also did not differ. Cheese lowered the ratio of LDL-C/HDL-C by 0.22 compared with milk, which was borderline for statistical significance ($P = 0.069$).

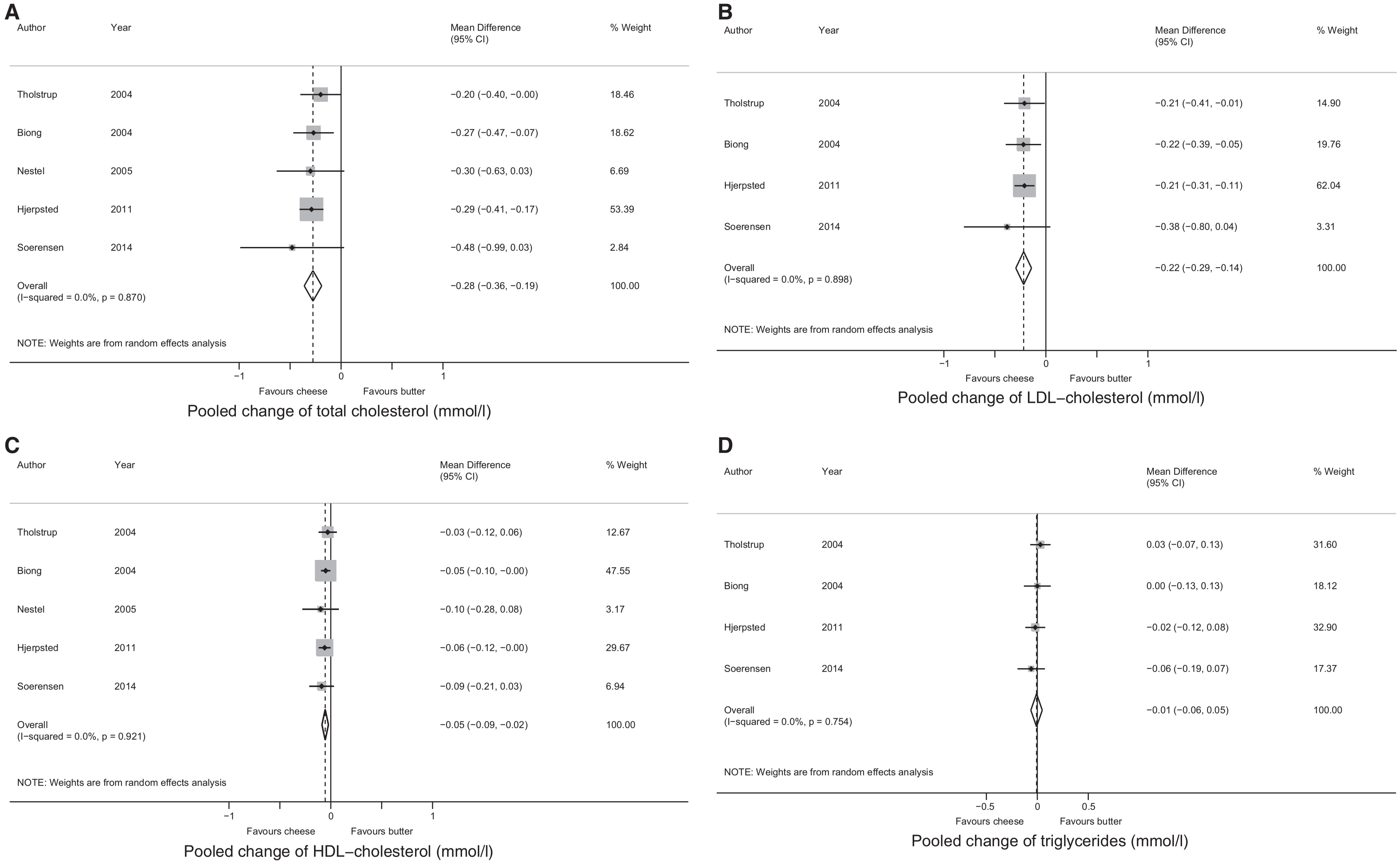

Figure 2 **Forest plots for the effect of cheese consumption (weighted mean difference: 145.0 g/d) vs butter consumption on (A) plasma levels of total cholesterol, (B) LDL-cholesterol, (C) HDL-cholesterol, and (D) triglycerides.** Data shown include the author names, year of publication, relative risks (RRs), 95% confidence intervals (95%CIs), and weight to the overall meta-analysis. Study-specific RRs and 95%CIs are represented as shaded squares. The area of the squares is within the overall meta-analysis. The diamond represents the pooled RR and the 95%CI. I^2 indicates the percentage of heterogeneity due to between-study variation.

Soerensen et al.[22] compared the effects of 120 g/d of semi-hard cow cheese (Klovborg) vs 670 mL/day of semi-skimmed milk on serum lipids in 15 healthy men in Denmark. Both diets were fully controlled and lasted 2 weeks with at least 2 weeks of washout time in between. The cheese diet had a 29 mg/10 MJ higher calcium content than the milk diet. Milk increased total and LDL-C slightly more than cheese, but the effects did not differ statistically. The milk diet, but not the cheese diet, increased triglycerides, although the difference was not statistically significant. HDL-C did not change during the diets.

Trials comparing cheese with tofu

In 4 small RCTs, the effects of animal and vegetable proteins were compared.[30–32] Dunn et al.[30] assessed lipid changes for consumption of tofu (336 g/d) or an isocaloric amount of semi-hard cheese (Monterey Jack; 63 g/day) in 12 male lacto-ovo vegetarians in a 3-week crossover trial. Compared with the tofu intervention, the cheese intervention resulted in statistically significant higher intakes of animal protein and SFA, as well as lower intakes of vegetable protein, total fat, and PUFAs, in the total diet (all $P < 0.05$). No changes in plasma lipids occurred after cheese consumption, whereas tofu consumption resulted in a decrease in total cholesterol (0.43 mmol/L; $P < 0.01$) and LDL-C (0.38 mmol/L; $P < 0.01$), with no significant changes in HDL-C, VLDL-C, or triglycerides. The mean differences between the interventions were not reported. The authors explained a large part of the tofu-induced changes in lipid levels by the differences in the P/S ratio, based on the Keys equation.[37]

Meredith et al.[31] investigated the effects of diets containing either tofu (280 g/d) or cheddar cheese (80 g/day) on plasma lipids in healthy normolipidemic adult women in two 3-week crossover trials with 1-week run-in and washout diets. The diets were fully controlled. In the first trial (n = 10), the tofu diet was lower in energy, total fat, MUFAs, and SFAs and higher in PUFAs and the P/S ratio. The cheese diet resulted in higher total cholesterol (0.31 mmol/L; $P < 0.01$) and LDL-C (0.34 mmol/L; $P < 0.001$) compared with the tofu diet. In the second trial (n = 5), the diets of the first trial were modified by replacing margarine with soybean oil (cheese diet) or butter (tofu diet) in order to differ in protein source, but to be similar in energy, en% of macronutrients, and fatty acid content. In this small study with limited power (n = 5), the cheese diet resulted in nonsignificantly lower values of total cholesterol (−0.31 mmol/L), LDL-C (−0.26 mmol/L), HDL-C (−0.03 mmol/L), and triglycerides (−0.05 mmol/L) compared with the tofu diet. The data of the 2 experiments suggested that alterations in plasma lipids induced by the replacement of tofu with cheese were largely attributable to differences in the P/S ratio.

In a parallel RCT in Taiwan, cheese (type not specified) was compared with tofu in 15 female students with moderately increased cholesterol levels.[32] Cheese and tofu each contributed 30% of the protein of the total diet. The test diets were fully provided. After 1 month, total cholesterol (expressed as percentage compared with baseline) was significantly higher in the cheese group (105%) compared with the tofu group (92%; $P < 0.05$). LDL-C was also higher in the cheese group, but this was not significant. HDL-C and triglyceride responses did not differ significantly after the cheese intervention compared with the tofu intervention. The authors concluded that the effect on total cholesterol caused by the cheese diet was partially due to differences in the P/S ratio and cholesterol content of the diets. However, details on total nutrient intake were not provided.

Trials comparing regular cheese with fat-modified cheese

Based on the evidence of the LDL-C-raising effect of SFAs and the LDL-C-lowering effect of PUFAs,[14] 3 crossover trials that included cheese with a lower SFA content were performed.[28,33,34]

In the United States, Davis et al.[33] performed a double-blind trial of 2 × 8 weeks to compare the effects of consumption of 100 g/d fat-modified mozzarella and partial skim-milk mozzarella (control) on blood lipid levels in 26 participants with moderately increased total cholesterol levels. The animal fat of the modified cheese was removed (mainly C14:0 and C16:0) and replaced with vegetable oil, resulting in a linoleic acid and alpha-linolenic acid content of 45% and 4.3%, respectively, compared with 2.4% and 1.0% in the control cheese. Compared with baseline measures, there was no change in total intakes of calories, protein, carbohydrates, or fat in the participants, whereas PUFA intake (en%) increased by 13% during consumption of modified cheese. Total cholesterol (−0.42 mmol/L; 95%CI: −0.19 to −0.84), and LDL-C (−0.38 mmol/L; 95%CI: −0.20 to −0.70) decreased significantly after consumption of the modified cheese compared with consumption of the control cheese. HDL-C, triglycerides, apolipoprotein A1, and B did not change during the trial.

Karvonen et al.[34] performed a single-blind trial of 2 × 4 weeks to compare the effects of rapeseed-oil-based hard cheese (65 g/d) with ordinary milk-fat-based hard cheese (control) on blood lipids in 31 mildly hypercholesterolemic adults in Finland. Apart from the differences in the types of fatty acids, the total fat content was slightly lower in the rapeseed-oil-based cheese, and the protein content was higher. The modified cheese diet resulted in 5.0% lower total cholesterol (95%CI: −7.5 to −2.5%) and 6.4% lower LDL-C (95 CI: −10.0 to −2.8%) compared with the regular cheese diet. HDL-C and triglycerides did not differ. The findings were in accordance with the predicted effects of the P/S ratio on blood lipids.[37,38]

In a double-blind trial in 30 healthy young adults, Intorre et al.[28,29] compared the consumption of 2 varieties of (hard) cow's cheese (150 g/week) that differed in fat composition. The experimental cheese was produced by adding 5% linseed to the cow's feed. As a result, the experimental cheese contained less total fat (32.3% vs 35.2%), less SFA (63.4% vs 76.5% of total fat), more MUFA (21.3% vs 15.7% of total fat), and more alpha-linolenic acid (2.4% vs 0.6% of total fat). The protein and linoleic acid contents of the cheeses were similar. However, levels of fatty acids of the total diet were not statistically significantly different. In line with this, plasma levels of total cholesterol, triglycerides, HDL-C, and LDL-C remained unchanged after both cheese interventions. The differences between the interventions were not statistically tested.

Trials comparing cheese with other protein-rich foods

In a 6-week crossover study, the effect on lipids of 150 g/d full-fat Gouda cheese versus 200 g/d mackerel was investigated in 23 lacto-ovo vegetarian nuns and monks to study the potential lipid-lowering effects of n-3 PUFAs.[35] Cheese compared with mackerel increased total cholesterol by 0.42 mmol/L, decreased HDL-C by 0.09 mmol/L in males, and increased triglycerides by 0.29 mmol/L (all $P = 0.01$). The study did not have a washout period, and the diet was neither controlled for nor reported. Changes in LDL-C were not reported.

A parallel RCT compared cheese (100 g/d, type unknown) with egg white (221 g/d) in 15 female students in Taiwan with moderately increased cholesterol levels.[32] The cheese and egg white each contributed 30% of the protein of the total diet. The test diets were fully provided. After 1 month, total cholesterol and LDL-C (expressed as a percentage compared with baseline) were significantly higher and HDL-C was significantly lower in the cheese group compared with the egg white group (105% vs 88% for total cholesterol, 107% vs 79% for LDL-C, and 98% vs 117% for HDL-C; all $P < 0.05$). Triglyceride responses did not differ between groups. The authors concluded that the effects on lipids caused by the cheese diet were partially due to the differences in cholesterol concentration and the P/S ratio of the diets. However, details on the total nutrient intake were not provided.

DISCUSSION

The effect of cheese intake on blood lipids depends on the product with which that cheese is compared (control treatment). When compared with tofu or fat-modified cheese, which have a more favorable P/S ratio, cheese generally increased total cholesterol and LDL-C. When compared with butter of a similar P/S ratio, however, hard cheese consistently lowered total cholesterol by approximately 5%, LDL-C by approximately 6.5%, and HDL-C by approximately 4% without affecting triglycerides. Differences between the effects of cheese intake and milk intake on blood lipids were less pronounced than differences between the effects of cheese intake and butter intake. However, this is based on only 2 studies that found no statistically significant differences between cheese and milk. At present, evidence of the effects of cheese versus other dairy or protein-rich foods is insufficient to draw conclusions.

Twelve RCTs of cheese consumption were identified. However, the heterogeneity in study hypotheses, control treatments, populations, and interventions was a limitation of this review. The primary interest was the effect of cheese, as a source of SFAs, on blood lipids. Therefore, the studies that focused on fatty acid compositions, such as the comparisons of cheese with butter, milk, or modified cheese, had the most value. A test diet that was completely provided, which is the best way to control the fatty acid composition of the entire diet, was used in 3 of the 5 RCTs that compared cheese with butter.[18,19,22] However, based on the information provided on dietary intake, the P/S ratios of the interventions, including the background diet, were similar in all 5 RCTs.

Five RCTs could be pooled in a meta-analysis of the effect of hard cheese versus butter. The daily amount of cheese in these trials was rather large, i.e., approximately 3 to 5 servings. The results consistently showed that that the effects of cheese on lipids and lipoproteins were different than expected from the fat content.

The P/S ratios for the cheese and butter diets were similar in these trials, so the relative amounts of SFAs and PUFAs cannot explain the differential effects on lipid levels. It has, however, been hypothesized that the cholesterol-lowering effect of cheese consumption compared with butter consumption could be explained by a difference in calcium content.[21] Calcium, especially dairy calcium, has been shown to bind with fatty acids in the intestine to form insoluble soaps, which leads to reduced absorption of fat.[39] A meta-analysis of 3 RCTs showed that increasing dairy calcium intake by 1241 mg/d, compared with <700 mg/d, increased the excretion of fecal fat by 5.2 g/d.[39] The additional amount of calcium provided by cheese compared with butter in the 5 trials in the present meta-analysis ranged from 775 to 1979 mg/d.[18–22] A Danish blinded crossover trial with 9 participants showed that dairy calcium (difference, approximately 1500 mg/d) attenuated the increase in total cholesterol and LDL-C caused by increased dairy fat without affecting the increase in HDL-C.[40] In the RCT of Soerensen et al.,[22] a difference in dairy calcium of 810 mg/d resulted in a significantly lower fecal fat excretion (5.7 g/d in the cheese diet vs 3.9 g/d in the butter diet). There was no difference between the cheese diet and the milk diet, which both contained similar amounts of dairy calcium. Fecal fat excretion in this study also correlated with the change in LDL-C.[22] However, in the trial of Hjerpsted et al,[21] designed to investigate the effects of calcium on lipid levels, a difference of 775 mg of calcium between the cheese diet and the butter diet, however, did not result in a statistically significant different fecal fat excretion (fat content of feces in 23 participants: 22.6% after cheese diet vs 19.9% after butter diet).[21] The role of calcium, therefore, needs further investigation.

Dairy products contain an array of SFAs that differ in carbon chain lengths.[41] In the US diet, hard cheese is the main contributor of the short- to medium-chain SFAs C4:0–C10:0 and C14:0, but cheese is also rich in C12:0 and C16:0. Compared with carbohydrates, LDL-C is most strongly increased by C12:0, followed by C14:0 and C16:0, whereas C18 is probably neutral.[14] Therefore, the effects of SFA consumption on CHD could vary, depending on the dietary source of the SFAs.[42] According to the US Department of Agriculture nutrient database, cheese contains, relative to total SFAs, slightly less C12:0 and slightly more C16:0 and C18:0 compared with butter. This could, in theory, explain part of the difference in LDL-C response. However, in the trials of Tholstrup et al.[18] and Biong et al,[19] in which the fatty acid content of the total diet was reported, no clear differences in amounts of different SFAs were present between the cheese and butter interventions. Cheese, in contrast to butter, also contains proteins, such as casein and whey. However, neither the amount nor the type of protein is expected to have an important effect on plasma LDL-C and HDL-C levels in humans.[18,43,44] In addition, Tholstrup et al.[18] adjusted their interventions for casein.

Cheese is a source of vitamin K_2 (menaquinone).[45,46] In prospective cohort studies, the intake of vitamin K_2 was associated with a lower risk of aortic calcification and CHD.[8,9] In 1 of these cohort studies, vitamin K_2 intake was also associated with lower levels of serum total cholesterol and higher levels of serum HDL-C, although effects were small and could not explain the inverse relationship between vitamin K_2 and CHD.[8] In an RCT with 60 healthy middle-aged participants, 180 μg and 360 μg of vitamin K_2 supplementation during 12 weeks did not affect the plasma lipid profile.[47] However, it has been argued that the bioavailability of vitamin K_2 depends on the food matrix,[45] and that more studies of dietary vitamin K_2 are needed to draw conclusions. Vitamin K_2 is present in fermented dairy products, such as cheese, because of the bacterial starter fermentation.[45] Fermented dairy has been shown to increase the bacterial content of the human gut.[48] These bacteria, once resident in the large intestine, are believed to ferment food-derived indigestible carbohydrates. Such fermentation would increase the production of short-chain fatty acids, which could lead to lower circulating cholesterol concentrations.[48]

There is some evidence in humans that phospholipids, present in milk fat globule membranes, affect blood lipids and inhibit cholesterol intestinal uptake.[49,50] The hypothesis that the milk fat globule membranes, present in all dairy except butter, can affect blood lipids, is currently under investigation in an ongoing RCT in Sweden (ClinicalTrials.gov identifier: NCT01767077). Another recently postulated concept suggests that the physical structure of fat in a meal can affect blood lipids.[51] In a crossover RCT, emulsified fat resulted in earlier and sharper chylomicron and fatty acid peaks in plasma than spread fat.[51] However, this postprandial effect on lipid metabolism needs to be replicated and further studied in relation to cardiovascular risk markers in the longer term.

CONCLUSION

The consumption of hard cheese results in lower LDL-C and HDL-C levels than the consumption of butter, despite a similar P/S ratio. Further research is warranted to determine whether calcium, specific types of SFAs in cheese, or effects of the food matrix could explain this finding.

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Author contributions. The authors' responsibilities were as follows: J.G., J.M.G., E.D. and S.S.S-M. designed the research; J.G. performed the systematic review and meta-analysis; S.S.S-M. carefully checked the data extraction of the meta-analysis; J.G. wrote the paper

and had primary responsibility for the nal content of the manuscript; and all authors reviewed, and approved the nal manuscript.

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Declaration of interest. The authors have no relevant interests to declare.

SUPPORTING INFORMATION

The following Supporting Information is available through the online version of the article at the publisher s website.
Appendix S1. Literature search strategy.
Appendix S2. Completed PRISMA checklist.
Figure S1. Funnel plot to visualize publication bias in RCTs for the effects of hard cheese compared with butter on total cholesterol levels.
Figure S2. Funnel plot to visualize publication bias in RCTs for the effects of hard cheese compared with butter on LDL cholesterol levels.
Figure S3. Funnel plot to visualize publication bias in RCTs for the effects of hard cheese compared with butter on HDL cholesterol levels
Figure S4. Funnel plot to visualize publication bias in RCTs for the effects of hard cheese compared with butter on triglycerides.

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