REVIEW

Influence of Dairy Product and Milk Fat Consumption on Cardiovascular Disease Risk: A Review of the Evidence[1,2]

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ABSTRACT

Although evidence has linked the consumption of saturated fat (SF) to increased LDL levels and an increased risk of the development of cardiovascular disease (CVD), recent findings have indicated that the link between CVD and SF may be less straightforward than originally thought. This may be due to the fact that some food sources high in SF contain an array of saturated and unsaturated fatty acids, each of which may differentially affect lipoprotein metabolism, as well as contribute significant amounts of other nutrients, which may alter CVD risk. The purpose of this review is to examine the published research on the relationship between milk fat containing dairy foods and cardiovascular health. The findings indicate that the majority of observational studies have failed to find an association between the intake of dairy products and increased risk of CVD, coronary heart disease, and stroke, regardless of milk fat levels. Results from short-term intervention studies on CVD biomarkers have indicated that a diet higher in SF from whole milk and butter increases LDL cholesterol when substituted for carbohydrates or unsaturated fatty acids; however, they may also increase HDL and therefore might not affect or even lower the total cholesterol:HDL cholesterol ratio. The results from the review also indicate that cheese intake lowers LDL cholesterol compared with butter of equal milk fat content. In addition, the review highlights some significant gaps in the research surrounding the effects of full-fat dairy on CVD outcomes, pointing to the need for long-term intervention studies. *Adv. Nutr. 3: 266–285, 2012.*

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States, claiming 631,636 lives in 2006 and accounting for >1 in 4 (26%) of all deaths that year (1). In 2010, it was estimated that heart disease in the United States cost $316.4 billion in health care, medication, and lost productivity (2). A number of modifiable risk factors for CVD[5] have been identified including high blood cholesterol, hypertension, diabetes, obesity/overweight, and an atherogenic diet. A high intake of saturated fat (SF) and industrial sources of *trans* fatty acids (TFA) have been linked to an increased risk of CVD, and this effect is thought to be mediated predominantly by increased blood levels of LDL cholesterol (LDL-C). Decreasing the consumption of SF, particularly C12:0, C14:0, and C16:0, as well as industrial sources of TFA is the primary dietary recommendation for decreasing the risk of CVD. The WHO and the 2010 Dietary Guidelines for Americans recommended consuming <10% of total energy from SF, and the American Heart Association recommended consuming <7% energy to reduce CVD risk. However, despite the well-established evidence in humans that high intake of SF increases plasma levels of LDL-C (3), along with pharmacological evidence showing that interventions that reduce LDL-C result in decreased ischemic heart disease (IHD) events and stroke (4), a causal relationship between the intake of SF and CVD risk remains controversial (5–9).

Dairy products containing milk fat are major food sources of SF, accounting for ~21% of total SF intake in the U.S. diet (10). Consequently, only low-fat and fat-free milk and milk products are recommended as part of a healthy diet to reduce the risk of CVD through the maintenance of healthy plasma lipids and lipoprotein cholesterol levels (11,12). However, prospective cohort evidence has shown no consistent evidence that higher intakes of milk and dairy products, regardless of milk fat levels, are associated with an

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[5] Abbreviation used: ATBC, Alpha-Tocopherol, Beta-Carotene; CHD, coronary heart disease; CHO, carbohydrate; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; HDL-C, HDL cholesterol; IHD, ischemic heart disease; LDL-C, LDL cholesterol; RCT, randomized, clinical trial; SF, saturated fat; TC, total cholesterol; TFA, *trans* fatty acids; TG, trigycerides.

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increased risk of CVD, coronary heart disease (CHD), or stroke (13–16). Further, prospective cohort studies have suggested an inverse relationship between calcium and vitamin D status and dairy food intake and the development of the metabolic syndrome and type 2 diabetes mellitus (17). Conversely, it should be noted, that there is a lack of long-term intervention studies that definitively assess the effects that dairy foods and milk fat consumption have on CVD, CHD, and type 2 diabetes mellitus risk. Although SF constitute a large proportion of milk fat, bovine milk is a complex mixture of lipids, protein, and micronutrients, many of which, when consumed separately or as a component of intact dairy products, have shown favorable or neutral effects on outcome measures of CVD risk (14,17,18).

The purpose of this review is to summarize the current evidence on the relationship between the intake of milk fat and dairy products containing milk fat and CVD risk from prospective cohort studies and randomized clinical trials (RCT). In addition, areas identified where additional work is needed are discussed.

Milk and dairy products: impact on CVD risk

Results from observational studies

Prospective epidemiological studies provide the most reliable observational information to estimate the risk of CHD and stroke associated with dietary intakes. Large, well-designed prospective cohort studies can provide statistical power to adjust for covariates, thereby enabling evaluation of the effects of specific food groups, foods, or single nutrient intakes on disease risk. Nonetheless, prospective studies have limitations including 1) a reliance on food intake assessment methods whose validity and reliability may vary (19); 2) the assumption that diets remain similar over the long term (20,21); and 3) variable adjustment for covariates by different investigators. Additionally, large cohort studies assessing the effect of a single nutrient or food component (e.g., milk fat) on CHD risk may ignore the potential effects of other components in the food that may contribute significant favorable or unfavorable effects on risk.

Total milk and dairy

Over the past 20 y, several prospective cohort studies examined the relationship between milk and milk product intake and the risk of CVD and stroke. The results of most, but not all, studies (15,22–24) showed no relationship (15,22–34) or an inverse association (35–42) between the intake of dairy foods and the risk of CVD and stroke **Table 1**.

In a series of recent meta-analyses, using many of these studies, the relationship between dairy intake and heart disease and stroke was assessed (13,14,43).

Elwood et al. (43) conducted a meta-analysis of 10 prospective cohort studies to examine the associations between total milk and dairy intake and the risk of IHD (7 studies) (23,25,30,31,35,44,45) and stroke (4 studies) (35,39,41,42). The pooled estimate of the relative odds for IHD and stroke in subjects with the highest total milk and dairy intakes compared with those with the lowest intakes showed no association with IHD (RR: 0.87; 95% CI: 0.74–1.03) and a significant inverse association for stroke (RR: 0.83; 95% CI: 0.77–0.90) (43). These results, along with findings from a combined estimate of risk for both IHD and stroke across all 10 studies (RR: 0.84; 95% CI: 0.78–0.90) indicated that the consumption of milk and milk products may be associated with a modest reduction in CVD risk.

In a follow-up meta-analysis, Elwood et al. (13) examined 9 cohort studies of milk and dairy consumption and IHD and 11 cohorts for a relationship to stroke. The results indicated a small inverse association for overall risk of IHD in individuals with the highest milk and dairy intake relative to those with the lowest intakes (RR: 0.92; 95% CI: 0.80–0.99) with no heterogeneity between studies ($P = 0.570$). Additionally, a significant inverse association was observed for the risk of stroke (primarily ischemic stroke) (RR: 0.79; 95% CI: 0.68–0.91); however, substantial heterogeneity existed between the studies ($P < 0.0001$), which made interpretation of these results difficult. The relationship between dairy intake and hemorrhagic stroke specifically was also examined and showed an overall inverse association in relation to dairy intake [5 studies (24,33,37–39); RR: 0.79; 95% CI: 0.68–0.91], but these too exhibited significant heterogeneity among studies ($P < 0.014$). Overall, these results indicated a reduction in the incidence of heart disease and stroke in subjects consuming the highest compared with the least amount of milk and dairy products. It was not possible, however, to differentiate the effects of consuming whole milk from the effects of consuming reduced-fat, low-fat, and fat-free milk because most studies included in the meta-analysis only reported consumption of total milk and milk products.

However, it is important to note that for most of the studies included in this analysis, food intake data were collected before 1980 when whole milk was the predominant milk consumed. Whole milk constituted >83% of total fluid milk consumed from 1950 to 1970 in the United States, and by 1980, it represented 62.7% of total milk intake, with the balance of consumption coming from reduced fat, low-fat, and nonfat milk at 24.9%, 7.0%, and 5.3%, respectively (**Table 2**). By 1990, consumption of reduced fat, low-fat, and nonfat milk together (58.5%) exceeded that of whole milk (41.4%). In the United Kingdom, the progression of lower fat milk consumption lagged behind the United States, with data showing that whole milk constituted 88.2% of milk purchased in 1985 and by 1995 had decreased to 41.1%, with the balance predominantly semiskim and skim milk at 58.9% (46). Although this may suggest that the observed inverse association between dairy intake and risk of CHD and stroke is largely the result of whole-milk consumption, there is little specific food intake information to support this notion.

In another meta-analysis, Soedamah-Muthu et al. (14) conducted a carefully designed dose-response analysis of prospective cohort studies by converting milk intakes from servings or other various units into a common unit (mL/d). This provided greater power of analysis across

Table 1. Prospective cohort studies on milk and milk product intake and cardiovascular disease, coronary heart disease, and stroke[1]

Authors (ref.)	Study, country	Age, mean or range, *y*	% Men/ women	Subjects, *n*/cases, *n*/follow-up, *y*	Outcome measure	Dairy predictor (range, or category or lowest and highest amount)	Results	Adjustments
Abbott et al. (42)	Honolulu Heart Program, Hawaii	60	100/0	3150/229/22	Thromboembolic stroke	Milk: 16 oz/d vs. nondrinkers	RR: 0.67 (95% CI: 0.45–1.00)	Age, dietary K, and Na, alcohol, smoking, activity, blood pressure, glucose, cholesterol, glucose, uric acid, hematocrit
Appleby et al. (29)	Oxford Vegetarian Study, UK	34	38/62	10,802/63/12	Fatal CHD	Milk: >0.5 pints/d vs. <0.5 pint/d	RR: 1.5 (95% CI: 0.81–2.78; *P*-trend NS)	Age, sex, smoking, socioeconomic status
						Cheese: <once/wk vs. > 5 times/wk	RR: 2.47 (95% CI: 0.97–6.26; *P*-trend <0.01)	
Al-Delaimy et al. (28)	Health Professionals Follow-up Study, USA	37	100/0	39,800/1458/12	Total IHD	Highest vs. lowest dairy Ca intake	Highest vs. lowest Ca intake: RR: 1.03 (95% CI: 0.85–1.26; *P* -trend NS)	Age, time period, energy intake, history of DM, history of hypercholesterolemia, family history of MI, smoking, aspirin, BMI, alcohol, physical activity, vitamin E, *trans* fat, PUFA:SF ratio, total protein, cereal fiber, folate, (n-3) fatty acids, and α-linolenic acid
						Total dairy product intake	Total dairy intake: RR: 1.01 (95% CI: 0.83–1.23; *P*-trend NS)	
Bernstein et al. (16)	Nurses' Health Study, USA	58	0/100	84,136/3162/26	Nonfatal and fatal CHD	High-fat dairy: 0.33 vs. 3.0 servings/d	RR: 1.09 (95% CI: 0.97–1.22; *P*-trend <0.01)	Age, BMI, energy intake, smoking, menopausal status, alcohol, parental history of MI, exercise, vitamin E, aspirin, multivitamin use, time period, cereal fiber, trans fat intake
						Low-fat dairy: 0.7 vs. 2.32 servings/d	RR: 0.90 (95% CI: 0.80–1.01; *P*-trend = 0.66)	
Bonthuis et al. (27)	Australian adults, Australia	25–78	43/57	1529/61/14.4	Fatal CVD	Highest vs. lowest tertile for:		Age, sex, energy, BMI, alcohol, education, exercise, smoking, dietary supplement, β-carotene, medication use, hypertension, DM, or cardiac disorder and β-adrenergic blocking agent use
						Total dairy	HR: 0.28 (95% CI: 0.06–1.34; *P*-trend = 0.20)	
						Low-fat dairy	HR: 1.45 (95% CI: 0.56–3.77; *P*-trend = 0.69)	

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Table 1. (*Continued*)

Authors (ref.)	Study, country	Age, mean or range, *y*	% Men/ women	Subjects, *n*/cases, *n*/follow-up, *y*	Outcome measure	Dairy predictor (range, or category or lowest and highest amount)	Results	Adjustments
						Full-fat dairy	HR: 0.31 (95% CI: 0.12–0.79; *P*-trend = 0.04)	
						Milk	HR: 0.60 (95% CI: 0.20–1.81; *P*-trend = 0.63)	
						Yogurt	HR: 0.65 (95% CI: 0.26–1.58 *P*-trend = 0.52)	
						Full-fat cheese	HR: 0.64 (95% CI: 0.27–1.49; *P*-trend = 0.54)	
Bostick et al. (31)	Iowa Women's Health Study, USA	61.5	0/100	34,486/387/8	Fatal CHD	Total dairy: highest vs. lowest quartile of intake.	RR: 0.94 (95% CI: 0.66–1.35; χ^2 for trend 0.22, *P*-trend = 0.64)	Age, BMI, WHR, energy intake, smoking, estrogen, alcohol use, marital status, physical activity, vitamin E, saturated fat intake, education, history of DM
						Fat containing dairy: Highest vs. lowest quartile of Intake.	RR: 1.14 (95% CI: 0.78–1.66; χ^2 for trend = 0.22, *P*-trend = 0.68)	
Elwood et al. (43)	Caerphilly cohort, South Wales, UK	52	100/0	2512/493 CHD, 185 stroke/22	Fatal and nonfatal CHD, stroke	Milk: >1.0 pints/d	HR: 0.71 (95% CI: 0.40–1.26; *P*-trend = 0.48)	Age, BMI, SBP, energy intake, smoking, alcohol use, fat, previous vascular disease
						vs. no milk	HR: 0.66 (95% CI: 0.24–1.81; *P*-trend = 0.23)	
Goldbohm et al. (15)	Netherlands Cohort Study, the Netherlands	62	48/52	120,852/4288/10	Fatal IHD	Total milk, per 100 g/d		Age, education, BMI, smoking, physical activity, multivitamin use, alcohol use, energy intake, MUFA and PUFA intake, vegetable and fruit intake
						Men	RR: 1.00 (95% CI: 0.97–1.04; *P*-trend = 0.806)	
						Women	RR: 1.07 (95% CI: 1.01–1.13; *P*-trend = 0.050)	
						Full-fat milk		
						Men	RR: 0.98 (95% CI: 0.93–1.03; *P*-trend = 0.931)	
						Women	RR: 1.02 (95% CI: 0.92–1.13; *P*-trend = 0.455)	
						Low-fat milk		
						Men	RR: 1.05 (95% CI: 1.00–1.10; *P*-trend = 0.117)	
						Women	RR: 1.04 (95% CI: 0.97–1.12; *P*-trend = 0.594)	

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Table 1. (*Continued*)

Authors (ref.)	Study, country	Age, mean or range, *y*	% Men/ women	Subjects, *n*/cases, *n*/follow-up, *y*	Outcome measure	Dairy predictor (range, or category or lowest and highest amount)	Results	Adjustments
						Total cheese, per 10 g/d		
						Men	RR: 1.01 (95% CI: 0.97–1.05; *P*-trend = 0.639)	
						Women	RR: 1.01 (95% CI: 0.95–1.07; *P*-trend = 0.832)	
						Butter		
						Men	RR: 0.95 (95% CI: 0.90–1.01; *P*-trend = NR)	
						Women	RR: 1.11 (95% CI: 1.01–1.21; *P*-trend = NR)	
						Fat from dairy		
						Men	RR: 0.94 (95% CI: 0.89–1.00; *P*-trend = 0.029)	
						Women	RR: 1.11 (95% CI: 1.01–1.22; *P*-trend = 0.106)	
					Fatal stroke	Total milk, per 100 g/d		
						Men	RR: 0.98 (95% CI: 0.93, 1.03; *P*-trend = 0.551)	
						Women	RR: 0.97 (95% CI: 0.91, 1.04; *P*-trend = 0.557)	
						Full-fat milk		
						Men	RR: 0.96 (95% CI: 0.89–1.03; *P*-trend = 0.667)	
						Women	RR: 1.10 (95% CI: 0.99–1.23; *P*-trend = 0.215)	
						Low-fat milk		
						Men	RR: 1.05 (95% CI: 0.98–1.13; *P*-trend = 0.199)	
						Women	RR: 0.96 (95% CI: 0.87–1.05; *P*-trend = 0.806)	
						Total cheese, per 10 g/d		
						Men	RR: 1.02 (95% CI: 0.96–1.08; *P*-trend = 0.403)	
						Women	RR: 0.94 (95% CI: 0.87–1.02; *P*-trend = 0.169)	
						Butter		
						Men	RR: 0.97 (95% CI: 0.89–1.05; *P*-trend = NR)	
						Women	RR: 1.05 (95% CI: 0.92–1.19; *P*-trend = NS)	

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Table 1. (*Continued*)

Authors (ref.)	Study, country	Age, mean or range, *y*	% Men/ women	Subjects, *n*/cases, *n*/follow-up, *y*	Outcome measure	Dairy predictor (range, or category or lowest and highest amount)	Results	Adjustments
						Fat from dairy		
						Men	RR: 0.96 (95% CI: 0.88–1.05; *P*-trend = 0.262)	
						Women	RR: 1.01 (95% CI: 0.89–1.15; *P*-trend = 0.286)	
He et al. (33)	Health Professionals Follow-up Study, USA	40–75	100/0	43,732/455 ischemic stroke, 125 hemorrhagic stroke/10	Ischemic stroke, hemorrhagic stroke	High-fat dairy, ≥ once/d vs. < once/wk	RR: 1.23 (95% CI: 0.74–2.03); *P*-trend = 0.38)	BMI, exercise, hypertension, smoking, aspirin, multivitamin use, alcohol use, potassium, fiber, vitamin E, fruit and vegetable intake, total energy intake, hypercholesterolemia
							RR: 1.22 (95% CI: 0.47–3.16); *P*-trend = 0.53)	
Hu et al. (22)	Nurses' Health Study, USA	46.5	0/100	41,254/939/14	Fatal CHD + nonfatal MI	High fat dairy: 1 serving/d	RR: 1.04 (95% CI: 0.96–1.12; *P*-trend = 0.33)	Age, BMI, energy intake, smoking, menopausal status, alcohol use, parental history of MI, DM, exercise, vitamin E, aspirin, hypertension history, multivitamin use, time period
						Low-fat dairy:	RR: 0.93 (95% CI: 0.85–1.02; *P*-trend = 0.11)	
						Whole milk: almost never vs.1 glass/d	RR: 1.67 (95% CI: 1.14–1.90; *P*-trend < 0.0001)	
						Skim milk:	RR: 0.78 (95% CI: 0.63–0.96; *P*-trend = 0.09)	
Iso et al. (41)	Nurses' Health Study, USA	46	0/100	85,764/347/14	Fatal and nonfatal stroke	Total dairy, highest vs. lowest quintile of intake	RR: 0.70 (95% CI: 0.51–0.97; P-trend = 0.08)	Age, BMI, smoking, menopausal status, alcohol use, hypercholesterolemia, physical activity, vitamin E, aspirin use, hypertension history, multivitamin use, time period, (n-3) intake
						Hard cheese: almost never vs. >1 times/d	RR: 0.63 (95% CI: 0.40–0.99; *P*-trend = 0.20)	
						Milk: almost never vs. >2 times/d+	RR: 0.74 (95% CI: 0.51–1.06; *P*-trend = 0.44)	
						Ice cream: almost never vs. >5 times/wk	RR: 0.70 (95% CI: 0.42–1.17; *P*-trend = 0.14)	

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Table 1. (*Continued*)

Authors (ref.)	Study, country	Age, mean or range, *y*	% Men/ women	Subjects, *n*/cases, *n*/follow-up, *y*	Outcome measure	Dairy predictor (range, or category or lowest and highest amount)	Results	Adjustments
						Cottage cheese: almost never vs. > 5 times/wk.	RR: 0.94 (95% CI: 0.60–1.47; *P*-trend = 0.71)	
Kinjo et al. (39)	Japanese Prefecture Study, Japan	55	56/44	223,170/11,030/15	Fatal stroke	Milk: <1 times/wk vs. >4 times/wk		Sex, attained age, alcohol use, smoking, prefecture (= unit of administration or county in China)
						All stroke	RR: 0.79 (95% CI: 0.75–0.83)	
						Cerebral hemorrhage	RR: 0.74 (95% CI: 0.68–0.80)	
						Cerebral embolism and thrombosis	RR: 0.85 (95% CI: 0.77–0.92)	
Larsson et al. (24)	Within the Alpha Tocopherol Beta-Carotene Cancer Prevention Study, Finland	57	100/0	26,556/2702/13.6	Fatal and nonfatal stroke: cerebral infarction, intracerebral hemorrhage,[2] subarachnoid hemorrhage[2]	Total dairy: (287 g/d vs. 1296 g/d)	RR: 1.14 (95% CI: 0.99–1.32; *P*-trend = 0.12)	Age, education, smoking, BMI, TC, HDL-C, history of DM and heart disease, exercise, total energy, alcohol use, caffeine, sugar, red meat, poultry, fish, fruit, juice, whole grain, refined grain, vegetables, potatoes, supplementation group
						Cerebral infarction:		
						Low-fat milk: (64 g/d vs. 783 g/d), Cerebral infarction:	RR: 1.04 (95% CI: 0.92, 1.18; *P*-trend = 0.60)	
						Whole milk: (0 g/d vs. 850 g/d), (CI):	RR: 1.08 (95% CI: 0.95, 1.23; *P*-trend = 0.04)	
						Yogurt: (0 g/d vs. 86 g/d), (CI):	RR: 1.08 (95% CI: 0.95, 1.24; *P*-trend = 0.033)	
						Cheese: (3 g/d vs. 60 g/d), (CI):	RR: 0.88 (95% CI: 0.77–1.01; *P*-trend = 0.02)	
						Cream: (2 g/d vs. 51 g/d), (CI):	RR: 0.81 (95% CI: 0.72–0.92; *P*-trend = 0.02)	
						Ice cream: (0 g/d vs. 11 g/d), (CI):	RR: 0.92 (95% CI: 0.81–1.03; *P*-trend = 0.14)	
						Butter: (3 g/d vs. 79 g/d), (CI):	RR: 1.00 (95% CI: 0.87–1.14; *P*-trend = 0.99)	
Mann et al. (23)	Vegetarian and nonvegetarian controls, UK	16–79	38/62	10,802/456/13.3	All-cause and IHD mortality	Milk: < 0.5 vs. > 0.5 pints/d		Age, sex, smoking, social class
						IHD	DRR: 150 (95% CI: 81–278; *P*-trend = NS)	
						all-cause	DRR: 87 (95% CI: 68–113; *P*-trend = NS)	

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Table 1. (*Continued*)

Authors (ref.)	Study, country	Age, mean or range, *y*	% Men/ women	Subjects, *n*/cases, *n*/follow-up, *y*	Outcome measure	Dairy predictor (range, or category or lowest and highest amount)	Results	Adjustments
						Cheese: < once/wk vs. ≥ 5 times/wk		
						IHD	DRR: 247 (95% CI: 97–626; *P*-trend < 0.01)	
						all-cause	DRR: 102 (95% CI: 76–137; *P*-trend = NS)	
Ness et al. (35)	Scottish men, UK	48	100/0	5765/2350/25	Fatal CVD Fatal CHD Fatal stroke	Milk: none vs. > than 1 pint/d		Age, smoking, blood pressure, BMI, cholesterol, forced expiratory volume, social class, angina, education, alcohol use, ECG ischemia, siblings, car user, bronchitis, exercise, deprivation
						CVD mortality	RR: 0.64 (95% CI: 0.40–1.00; *P*-trend = 0.05)	
						CHD mortality	RR: 0.68 (95% CI: 0.40–1.13; *P*-trend = 0.11)	
						Stroke mortality	RR: 0.84 (95% CI: 0.31–2.30; *P*-trend = 0.58)	
Panagiotakos et al. (26)	ATTICA Study, Greece	53	50/50	686/30/5	Fatal and nonfatal CVD	Low-fat dairy: per one serving increase/wk	HR: 0.97 (95% CI: 0.73–1.27; *P*-trend NS)	Age, sex, BMI, smoking, exercise, education, DM, hypercholesterolemia, hypertension
Sauvaget et al. (40)	Life Span Study, Japan	56	38/62	31,832/1462/16	Fatal stroke	Milk: Never vs. almost daily	HR: 0.94 (95% CI: 0.79–1.12; *P*-trend = 0.232)	Age, sex, BMI, smoking, education, radiation dose, history of hypertension or DM, city
						Dairy products	HR: 0.73 (95% CI: 0.57–0.94; *P*-trend = 0.024)	
Shaper et al. (30)	British Regional Heart Study, UK	50	100/0	7735/608/9.5	Fatal and nonfatal IHD	Milk: milk intake vs. none	RR: 0.88 (95% CI: 0.55–1.40)[3]	Age, social class, smoking, blood cholesterol, SBP, IHD, DM
						Butter: butter intake vs. none	RR: 0.87 (95% CI: 0.79–1.06)	
Sonestedt et al. (57)	Malmo Diet and Cancer cohort, Sweden	44–74	38/62	26,445/2520/12	Fatal and nonfatal CVD	Total dairy, portions/day, highest vs. lowest quintile of intake	HR: 0.89 (95% CI: 0.78–1.01; *P*-trend = 0.05)	Age, sex, season, method, energy intake, BMI, smoking, alcohol intake, exercise, education, intake of vegetables, fruit, berries, fish, shellfish, meat, coffee, whole grains

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Table 1. (*Continued*)

Authors (ref.)	Study, country	Age, mean or range, *y*	% Men/ women	Subjects, *n*/cases, *n*/follow-up, *y*	Outcome measure	Dairy predictor (range, or category or lowest and highest amount)	Results	Adjustments
						Milk, g/day	HR: 1.00 (95% CI: 0.88–1.13; *P*-trend = 0.89)	
						Low-fat milk, g/day	HR: 0.93 (95% CI: 0.82–1.05; *P*-trend = 0.13)	
						High-fat milk, g/day	HR: 1.03 (95% CI: 0.91–1.17; *P*-trend = 0.60)	
						Cheese, g/day	HR: 0.94 (95% CI: 0.83–1.06; *P*-trend = 0.30)	
						Butter, g/day	HR: 0.94 (95% CI: 0.83–1.07; *P*-trend = 0.16)	
						Cream, g/day	HR: 0.93 (95% CI: 0.83–1.06; *P*-trend = 0.10)	
Trichopoulou et al. (32)	Greek population, Greece		42/58	1013/46/4.5	Fatal CVD	Total dairy: 150 g increase in dairy products	HR: 0.95 (95% CI: 0.68–1.31)	Age, sex, BMI, smoking, education, hypertension, DM, weight, height, hip circumference, insulin, food groups
Umesawa et al. (37)	Japan Collaborative Cohort, Japan	40–79	39/61	21,068 men, 32,319 women/800/9.6		Dairy calcium: highest vs. lowest quintile of intake		Age, sex, BMI, smoking, alcohol use, sodium, potassium, fatty acids, area, menopause, hypercholesterolemia, DM
					Total stroke	Men	RR: 0.53 (95% CI: 0.34–0.81; *P*-trend < 0.01)	
						Women	RR: 0.57 (95% CI: 0.38–0.86; *P*-trend = 0.04)	
					CHD Total	Men	RR: 0.80 (95% CI: 0.45–1.44; *P*-trend = 0.63)	
						Women	RR: 1.06 (95% CI: 0.50–2.25); *P*-trend = 0.40)	
					CVD	Men	RR: 0.73 (95% CI: 0.55–0.95); *P*-trend = 0.06)	
						Women	RR: 0.77 (95% CI: 0.58–1.03); *P*-trend = 0.01)	
Umesawa et al. (38)	Japan Public Health Center cohort, Japan	40–59	48/52	41,526/1643/12.9		Dairy calcium: highest vs. lowest quintile of intake		Age, sex, BMI, DM, hypercholesterolemia, menopause, smoking, alcohol use, sodium, potassium, (n-3), public health center

(Continued)

Table 1. (*Continued*)

Authors (ref.)	Study, country	Age, mean or range, *y*	% Men/ women	Subjects, *n*/cases, *n*/follow-up, *y*	Outcome measure	Dairy predictor (range, or category or lowest and highest amount)	Results	Adjustments
					Total stroke		HR: 0.70 (95% CI: 0.57–0.86); *P*-trend = 0.01)	
					CHD		HR: 1.09 (0.74–1.61); *P*-trend = 0.40)	
Van der Pols et al. (34)	Carnegie ("Boyd Orr") cohort, UK	73	49/51	4374/378/66–68	Fatal CHD	Dairy products: highest vs. lowest quartiles of intake	HR: 0.74 (95% CI: 0.45–1.22); *P*-trend = 0.64)	Age, sex, area, energy, fruit, vegetables, eggs, protein, fat, energy
						Milk:	HR: 0.80 (95% CI:.49–1.31); *P*-trend = 0.83)	
					Fatal stroke	Dairy products: highest vs. lowest quartiles of intake	HR: 0.61 (95% CI: 0.27–1.38); *P*-trend = 0.16)	
						Milk:	HR: 0.60 (95% CI: 0.28–1.33); *P*-trend = 0.26)	

[1] CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; ECG, electrocardiography; DRR, death rate ratio; HR, hazard ratio; HDL-C, HDL cholesterol; IHD, ischemic heart disease; K, potassium; MI, myocardial infarction; Na, sodium; NR, not reported; SBP, systolic blood pressure; TC, total cholesterol; WHR, waist-to-hip ratio.

[2] Results not reported here; see Larsson et al. (24).

[3] Reported from Elwood (13).

various studies, with different dairy food categories and different ranges of intake. Results showed a weak inverse association between milk intake and overall CVD risk, i.e., CHD and stroke [4 studies (25,26,35,47); RR: 0.94 per 200 mL/d; 95% CI: 0.89–0.99] with no heterogeneity between studies ($P < 0.5$). Milk intake was found not to be associated with the risk of CHD [6 studies (22,25,28,29,35,47); RR: 1.00 per 200 mL/d; 95% CI: 0.96–1.04], total mortality [8 studies (23,25,35,47–51); RR: 0.99 per 200 mL/d; 95% CI: 0.95–1.03], or stroke [6 studies (24,25,35,39–41); RR: 0.87; 95% CI: 0.72–1.07]. These results are not consistent with the significant inverse relationships observed between dairy product intake and IHD and stroke in other meta-analyses (13). Some suggested explanations for these dissimilarities may include differences in methodological rigor for assessing dairy exposure (e.g., dose-response methodology vs. highest compared with lowest exposure), evaluating study heterogeneity, and study inclusion and exclusion criteria (14).

Last, some recent results were not reviewed in these meta-analysis studies. A very large Netherlands Cohort Study consisting of 120,852 men and women with 10 y of follow-up showed no association between total milk product consumption and stroke mortality in both men and women (15). Similarly, no association was found between total milk intake and IHD mortality in men, whereas in women, there was a weak but significant positive association (RR: 1.07; 95% CI: 1.01–1.13; *P*-trend = 0.05). These results, in general, appear to be consistent with the meta-analysis findings of Soedamah-Muthu et al. (14).

High-fat vs. low-fat dairy

There is limited information on the specific influence of high-fat and lower fat dairy consumption and heart disease risk because the majority of prospective cohort studies only reported total dairy or total milk intake. However, 5 publications were reviewed that did examine the potential differential effects of high- versus low-fat dairy.

Hu et al. (22) examined the association between the intake of specific food sources including full-fat and low-fat dairy products and the risk of CHD (nonfatal myocardial infarction and fatal CHD) in a prospective cohort of 80,082 female nurses ages 34–59 y. The study included 14 y of follow-up, and food intake was measured with a food-frequency questionnaire (FFQ) in 1980. After adjustments for age, diet, pharmaceutical, and lifestyle variables, no significant association was observed between CHD risk and the intake of full-fat dairy products (whole milk, hard and cream cheese, ice cream, and butter; RR: 1.04; 95% CI: 0.96–1.12; *P*-trend = 0.33) or for low-fat dairy products (skim and low-fat milk, yogurt, and cottage cheese; RR: 0.93; 95% CI: 0.85–1.02; *P*-trend = 0.11). Despite the nonsignificant findings for full-fat and low-fat dairy products, the intake of whole milk was found to be significantly and positively associated with CHD risk (RR: 1.67; 95% CI: 1.14–1.90; *P*-trend <0.0001), whereas skim milk intake was associated with a nonsignificant, but trending lower risk (RR: 0.78; 95% CI: 0.63–0.96; *P*-trend = 0.09). In a later

Table 2. U.S. per capita availability of fluid milk[1]

Year	Whole (3.2%)	Reduced fat (2%)	Low fat (1%)	Nonfat (<0.5%)
		Pounds, (%)		
1950	291.1 (99)	0.0	0.0	2.8 (0.9)
1960	263.9 (95.6)	2.2 (0.7)	0.0	10.2 (3.1)
1970	213.5 (83.8)	28.0 (11.0)	1.8 (0.7)	11.6 (4.5)
1980	137.5 (62.7)	54.7 (24.9)	15.3 (7.0)	11.6 (5.3)
1985	119.5 (55.4)	68.1 (31.5)	27.6 (12.8)[2]	
1990	85.5 (41.4)	78.4 (37.9)	19.8 (9.6)	22.8 (11.0)
2000	65.4 (36.5)	61.3 (34.2)	22.5 (12.5)	29.9 (16.2)
2009	48.9 (30.2)	63.2 (39.1)	22.7 (14.0)	26.8 (16.6)

[1] Adapted from (111). 1 lb = 0.454 kg.
[2] Combined low-fat and non-fat milk consumption, http://www.ers.usda.gov/data/foodconsumption/FoodAvailSpreadsheets.htm#dyfluid.

analysis of this same female nurses cohort ($N = 84,136$) 30–55 y of age with a longer follow-up period (26 y), results also showed that full-fat dairy product intake (whole milk, ice cream, hard cheese, full-fat cheese, cream, sour cream, cream cheese, butter) was significantly associated with increased risk of CHD, whereas low-fat dairy (skim/low-fat milk, 1% and 2% milk, yogurt, cottage and ricotta cheeses, low-fat cheese, sherbet) was not (16). After continued updating of diet throughout the follow-up period, however, these workers no longer observed a significant association between full-fat dairy intake and CHD risk.

In a separate group from the Alpha-Tocopherol, Beta-Carotene (ATBC) cohort, Larsson et al. (24) examined the association between the intake of various dairy foods including whole and low-fat milk and risk of stroke subtypes including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. The average follow-up of this cohort was 13.6 y; the cohort consisted of 26,556 Finnish male smokers aged 50–69 y who had no history of stroke and completed an FFQ in 1988. No significant associations were observed between total dairy intake (whole milk, low-fat milk, sour milk, yogurt, cheese, cream, ice cream, and butter) or low-fat milk intake and the risk of any subtype of stroke. Likewise, no association was found between whole-milk intake and cerebral infarction or subarachnoid hemorrhage, whereas a positive association was observed for whole-milk intake and risk of cerebral hemorrhage (RR: 1.41 for the highest vs. lowest quintile; 95% CI: 1.02–1.96; P-trend = 0.05). The authors noted that the results did not change after adjustment for dairy-related nutrients including myristic acid (a marker of dairy fat), calcium, potassium, magnesium, and phosphorus, suggesting that other factors may account for the whole-milk observations. As indicated previously, some prospective studies reported strong or weak protective associations (25,41,42) or no association (35) between milk or dairy intake and the risk of stroke; however, these studies only assessed total milk or dairy and did not differentiate between full-fat and low-fat products.

Furthermore, in a study described previously, Goldbohm et al. (15) investigated the association between full-fat and low-fat milk consumption and the risk of IHD and stroke mortality in a Netherlands cohort that included 10 y of follow-up from 1986 to 1996, with the completion of an FFQ in 1985. In multivariate analyses, no association was found between the intake of full-fat (whole milk, cream, condensed whole milk, whole-milk cocoa, pudding, and ice cream) or low-fat milk products (low-fat and skim milk, condensed low-fat milk, low-fat and skim-milk cocoa) and the risk of IHD or stroke in men or women. These results are consistent with other studies in women that found no association between total full-fat and low-fat dairy product intake and CHD risk (16,22,31), although in the study by Hu et al. (22), whole-milk intake specifically was found to increase CHD risk and low-fat milk to decrease CHD risk. The finding of no association between full-fat milk and overall risk of stroke reflects an assessment of mortality from all types of stroke.

In their dose-response meta-analysis, Soedamah-Mutha et al. (14) also assessed the relationship between total high-fat and low-fat dairy intake and risk of CHD. The results indicated no association between total high-fat dairy and CHD (RR: 1.04; 95% CI: 0.89–1.21; $P = 0.9$), and no association for total low-fat dairy intake and CHD (RR: 0.93; 95% CI: 0.74–1.17; $P = 0.1$).

In general, of the limited number of the studies that examined the association between the intake of total high-fat or total low-fat dairy products and the risk of CHD or stroke, most reported no associations (15,16,22,24,28,31). However, additional information is needed on the relationship between the intake of whole milk and stroke subtypes because 1 study reported a moderate positive association between whole-milk intake and intracerebral hemorrhage (24). Likewise, the association between whole-milk intake and CHD risk should be further studied because a positive association was shown in women in 1 study (22), whereas no association was observed in both men and women in another study (15). Consequently, until there is consensus, these results suggest that caution should be considered in recommending whole-milk consumption for those at the greatest risk of CHD and stroke.

Butter and milk fat

A number of case-control (52–54) and cohort studies (15,24,30,55–57) examined the relationship between the intake of butter or milk fat from dairy products and vascular disease risk. Early reports by Gartside et al. (55) and Gillman et al. (56) are not discussed because there is a lack of adequate data on the reported associations.

In an earlier study from the British Regional Heart Study cohort, Shaper et al. (30) followed 7,735 men aged 40–59 y for 9.5 y and found no significant association between the use butter as a fat spread and fatal and nonfatal IHD events compared with nonusers of fat spreads (RR: 0.87; 95% CI: 0.79–1.06).

Larsson et al. (24) in an analysis of butter intake and the incidence of stroke subtypes in the ATBC cohort found no strong associations between butter consumption and any stroke subtype in men. Although there were no associations between butter intake and the risk of cerebral infarction or subarachnoid hemorrhage, the risk of intracerebral

hemorrhage was slightly increased for men in the highest quintile of butter intake (79 g/d, equivalent to 5.6 tbsp/d) compared with those in the lowest quintile (RR: 1.44; 95% CI: 1.01–2.07). However, the effects were not linear throughout the range of butter intake (*P*-trend = 0.19).

Goldbohm et al. (15) assessed the relationship between the intake of butter and total milk fat from dairy products and the risk of mortality due to IHD and stroke in men and women followed for 10 y. For men, no association was found between butter or milk fat intake and IHD or stroke. For women, no association was observed between butter and milk fat intake and stroke; however, a slight increase in the risk of IHD mortality with the intake of butter or milk fat was observed (RR: 1.11; 95% CI: 1.01–1.21; P-trend = NR, and RR: 1.11; 95% CI: 1.01–1.22; P-trend = 0.106, respectively). These latter results showing a slight positive association between dairy fat intake and IHD mortality in women, but not in men, are not readily explainable because there is little evidence for sex-specific associations between saturated fat intake and CHD (58). Additionally, other studies in women found no association between high-fat dairy product intake and incident CHD (16,22).

In a recent cohort study, Sonestedt et al. (57) examined the association between butter and cream intake and the incidence of CVD (fatal and nonfatal) in middle-aged Swedish men and women followed for 12 y. Comparing the highest with the lowest levels of intake, no association was found between the intake of butter or cream and incident CVD (HR: 0.94; 95% CI: 0.83–1.07; *P*-trend = 0.16 and HR: 0.93; 95% CI: 0.83–1.06; *P*-trend = 0.10, respectively). These associations remained insignificant after adjustment for physical, dietary, and lifestyle covariates.

Last, in a meta-analysis of 3 prospective studies that examined butter intake as a possible predictor of vascular disease, results showed that the overall relationship between butter consumption and vascular events was not statistically significant (RR: 0.93; 95% CI: 0.84–1.02) with no heterogeneity between studies ($P = 0.333$) (13). These results are consistent with several studies discussed earlier. Furthermore, findings from an early study from the Framingham Study cohort, in which 832 men age 45–64 y and free of CHD were followed for 21 y, indicated that butter intake did not predict CHD incidence (56). In contrast, some case-control studies that examined the association between butter intake and vascular disease showed positive associations in women with acute myocardial infarction (53) and in diabetic patients with peripheral arterial disease (54) compared with matched controls (OR: 2.3 and 2.06, 95% CI: 1.15–3.68, respectively).

Cheese

A number of prospective cohort studies evaluated the association between cheese intake and the risk of CVD and stroke (15,23,24,27,41,44,55,57,59) (**Table 1**).

Earlier studies involving a large cohort of California Seventh-Day Adventists followed for 20 y (44,59) and another that used the NHANES I Epidemiologic 16-Year Follow-up Study (55) all showed either no significant association (44,59) or an inverse association (55) between cheese intake and CHD. However, the absence of detailed data including the lack of CI and trend analysis data makes the strength of these results less certain.

In a cohort of 10,802 vegetarians and nonvegetarians from the United Kingdom followed for 13.3 y, a positive trend of increasing IHD mortality across tertiles was observed with increasing intake of SF, total animal fat, and cholesterol (*P*-trend = <0.01) (23). When individual dairy food intakes were assessed, a positive trend was found with cheese intake in those consuming cheese ≥5 times/wk compared with < 1 time/wk with IHD (RR: 2.47; 95% CI: 0.97–6.26; *P*-trend <0.01).

In contrast, no association was found between cheese intake and IHD mortality in the Netherlands Cohort Study (15). Also, no significant association between full-fat cheese intake and CVD mortality was observed in a community-based sample of Australian adults followed for 14.4 y (27). Finally, in a recent study involving 26,445 adults from the Swedish Malmo Diet and Cancer cohort with 12 y of follow-up, cheese intake was not significantly associated with CVD risk in those with the highest intake of cheese compared with the lowest intake (57). However, it was noted that there were sex differences such that cheese intake was significantly associated with decreased CVD risk in women (RR over quintiles: 1.00, 0.80, 0.77, 0.79, 0.82; *P*-trend <0.03) but not in men. After adjusting for food group covariates (whole grain, fruits, vegetables, fish, meat), the association in women was attenuated (*P*-trend = 0.11).

In a study based on the Nurses' Health Study cohort of 85,764 middle-aged women followed for 14 y, a modest inverse association was observed between hard cheese intake and risk of ischemic stroke in women who ate cheese ≥1 times/d compared with those who almost never ate it (RR: 0.63; 95% CI: 0.40–0.99). However, the effects were not linear throughout the range of cheese intake (*P*-trend = 0.20), and no information was provided on what adjustments were made for known lifestyle and dietary CVD risk factors (41).

In a prospective study that evaluated the relationship between intake of specific dairy foods and the risk of stroke in the ATBC cohort, no significant association was observed between the highest intake of cheese and any of the stroke subtypes evaluated (cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage) (24). In the Netherlands Cohort Study of older adults (15), in addition to showing no significant association between cheese intake and IHD mortality, they also observed that the intake of total cheese and full-fat cheese was not associated with stroke mortality in men or women (15).

Although 1 meta-analysis reported no association between the highest intakes of cheese and risk of vascular disease including stroke (RR: 0.90; 95% CI: 0.79–1.03) (13), the analysis consisted of only 2 studies whose reported numbers of vascular disease events were highly divergent (2702 and 64) such that there was significant heterogeneity between studies ($P = 0.032$), indicating that the strength of the

findings is limited. In light of additional studies published since then on cheese intake and stroke, a follow-up meta-analysis may provide a stronger estimate of the potential relationship.

Results from intervention studies

RCT provide important causality about the ability of dietary interventions to affect biomarkers of future disease. They afford the ability to carefully control the diet and directly adjust for covariables that may dramatically alter research findings. However, clinical trials have limitations including 1) the time between change in the level of a dietary component (e.g., SF) and any expected change in the incidence of disease (e.g., CHD events) is typically uncertain, so trials must be of long duration; 2) compliance with the intervention diet is likely to decrease during an extended trial; 3) the control group may well adopt the dietary behavior of the intervention group if the intervention diet is thought to be beneficial.

Effects of milk fat/SF, and dairy foods on CHD risk

In a limited number of RCT in which the effects of reducing SF intake on fatal and nonfatal CHD endpoints were assessed by replacing animal fat–based foods (including full-fat dairy) with PUFA-containing vegetable oils, most (60–64), but not all (65–67), resulted in a reduced risk of CVD. In 2 studies, SF intake was reduced mainly by replacing whole milk with an emulsion of soybean oil in skim milk ("filled milk") and by replacing butter and ordinary margarine with a "soft margarine" with a high content of PUFA (62,63). As a result, dairy fats were almost totally replaced by vegetable oils, mainly soybean oil, resulting in a diet high in PUFA (13% energy) and low in SF (9% energy). Results showed that, compared with the control diet, there was a considerable reduction in plasma cholesterol and CHD events in men on the high PUFA:SF ratio diet, whereas in women, events were fewer on the high PUFA:SF diet, but failed to reach statistical significance. Recent meta-analyses summarized the evidence from all of these intervention studies (7,8). In an analysis of 8 studies that tested the effect of altered PUFA:SF ratios on CHD incidence, results showed that the risk of fatal CHD was not reduced by high PUFA:SF diets (RR: 0.84; 95% CI: 0.62–1.12: $P = 0.867$), whereas total CHD events were significantly reduced (RR: 0.83; 95% CI: 0.69–1.00; $P = 0.050$) (7). When the meta-analysis was restricted to intervention trials of PUFA/SF diets in which serum cholesterol levels were significantly lower in the high PUFA/SF treatment group, results showed that the risk of both fatal and total CHD events were significantly reduced by the high PUFA:SF diets (RR: 0.52; 95% CI: 0.30–0.87: $P = 0.014$ and RR: 0.68; 95% CI: 0.49–0.94L $P = 0.020$, respectively).

In another meta-analysis of the same 8 RCT in which the mean PUFA intake level was 5.0% energy (control) and 14.9% energy (intervention), with a median study duration of 4.25 y, results showed that increasing PUFA consumption as a replacement for SF reduced the occurrence of CHD events by 19% (8). Furthermore, each 5% energy increase in PUFA consumption reduced CHD risk by 10% (8). These results are consistent with epidemiological evidence that indicate a 13% reduction in CHD risk for each 5% energy exchange of PUFA for SF (68). Although these results cannot distinguish between the potential benefits of increasing PUFA versus decreasing SF intake, due to the simultaneous alterations in both PUFA and SF in the intervention studies, other lines of evidence suggest that lower risk may be more strongly related to increased PUFA rather than decreased SF consumption. For example, based on either the predicted effects on CHD risk by altering the total cholesterol (TC):HDL cholesterol (HDL-C) ratio (3), or the results from the Women's Health Initiative, the largest controlled dietary intervention trial to date (69), or from the meta-analysis of 11 prospective epidemiological studies (68), replacing SF with carbohydrate (CHO) does not appear to lower CHD risk (8). CHO intake, especially refined CHO, may in fact exacerbate CHD risk (68). In addition, the evidence for replacing SF with MUFA is mixed and unclear (8). Epidemiological results found that reduction in Eastern Europe CHD mortality was most strongly related to increased intake of vegetable oil containing PUFA rather than reduced intake of high SF containing animal fats or increases in overall vegetable consumption (70).

More conclusive evidence of the direct effect of full-fat dairy products on CHD risk may require RCT that substitute dairy SF with other macronutrients rather than PUFA. Although such studies are feasible, their undertaking would be challenging due to expense, study duration (years), numbers of subjects required, and compliance necessary to achieve adequate power. Despite these hurdles, health agencies in the United States and elsewhere have identified the need for a better understanding of the role that dairy products play in cardiovascular health as a research priority (10).

Effects of milk fat and dairy foods on plasma lipid biomarkers

Dietary guidelines have long recommended limiting the intake of full-fat dairy products, stemming from their contribution to the dietary intake of SF and the well-established relationship between SF intake and increased plasma LDL-C. LDL-C is the primary target of lipid-lowering therapy through diet and drugs because multiple lines of evidence indicate a strong causal relationship between elevated LDL-C and CHD risk (71). However, meta-analyses of RCT have demonstrated that SF also differentially affect other lipid biomarkers including HDL-C and triglycerides (TG), depending on the macronutrient comparison (3,72,73). Substituting CHO with SF increases TC and LDL-C, but also lowers TG and increases HDL-C. The net effect is that SF does not alter the TC:HDL-C ratio, arguably the best overall predictor of CHD risk (73).

Butter

As with numerous studies that assessed the effects of SF on plasma lipids and lipoproteins (3), there is consistent evidence from well-controlled RCT that diets high in SF derived predominantly or appreciably from butter fat increases plasma TC and LDL-C when substituted for CHO or unsaturated fatty acid food sources (74–77). Butter fat–enriched diets also result in higher or similar levels of plasma HDL-C, apo A-1, and the TC:HDL-C ratio compared with high MUFA and PUFA diets (74–77).

In a crossover study in which participants consumed a diet lower in CHO (45% energy), higher in SF (21% energy), and containing appreciable butter fat for 5 wk, results showed significantly higher HDL-C and apo A-1 and lower TG compared with an average U.S. diet containing higher CHO (54% energy) and lower SF (12% energy) (75). These results are consistent with those of a meta-analysis of RCT that predict a lower TC:HDL-C ratio for butter compared with CHO when each replaces 10% energy of total fat in an average U.S. diet (3).

Cheese

Cheese consumption is the leading contributor of SF in the U.S. diet (10) and therefore would be predicted to increase LDL-C and consequently increase the risk of CVD. However, as discussed in an earlier section, most (15,24,27,41,57) but not all (29) prospective cohort studies found no or an inverse relationship between cheese intake and the risk of CHD and stroke.

A number of intervention studies assessed the effects of cheese consumption on blood lipids compared with baseline diets (78), lower SF-containing products (79–82), and other dairy products including whole milk and butter (83–86). In a crossover study that examined the effects of ewe cheese naturally rich in conjugated linoleic acid compared with bovine cheese on blood lipids, 10 older male and female subjects consumed 200 g/wk of each cheese type for 10 wk with a 10-wk washout period between the treatments. Total cholesterol, LDL-C, HDL-C, and TG showed no significant changes from baseline for either of the cheeses and no significant differences in lipid responses between cheese treatments (78).

Biong et al. (83) assessed the effects cheese compared with those of butter (in combination with casein or egg white protein) on serum lipids and lipoproteins in 22 male and female subjects who were provided diets containing equal amounts of fat (28% energy), protein (26% energy), and CHO (46% energy) for 3 wk in a crossover design. Total cholesterol was significantly lower for cheese compared with butter-casein ($P = 0.03$) and LDL-C tended to be lower ($P = 0.06$). There were no significant differences in HDL-C, the LDL-C:HDL-C ratio, TG, apolipoprotein A-1, apolipoprotein B, or lipoprotein(a) between cheese, butter-casein, or butter–egg white diets.

In another 3 wk crossover study, Tholstrup et al. (84) compared the effects of whole milk, cheese, and butter intake (adjusted to the same content of lactose and casein) on plasma lipids and lipoproteins in 14 young, healthy men who were provided isocaloric diets containing 35% energy fat, 17% energy protein, and 48% energy CHO designed to provide 20% energy from milk fat, as either whole milk, butter, or hard cheese. Compared with the butter diet, plasma LDL-C levels were significantly reduced after the hard cheese diet (−0.21 mmol/L; $P = 0.037$). No significant differences were observed between diets for any other plasma lipids, lipoproteins or apolipoproteins.

Nestel et al. (85) conducted a randomized, crossover trial designed to investigate the effects of milk fat in cheese versus milk fat in butter on serum lipids in 14 hypercholesterolemic older men and postmenopausal women. After a 2-wk run-in with a moderately higher CHO (45% energy), lower fat (31% energy), and SF (12.5% energy) diet, subjects were randomly assigned to a lower CHO (mean 41% energy), higher fat (mean 36.8% energy), and SF (mean 17% energy) diet that included 40 g/d dairy fat as butter or 40 g/d dairy fat as matured cheddar cheese (equivalent to 120 g/d) for 4 wk. Compared with the run-in period, TC and LDL-C were significantly ($P < 0.05$) higher with butter (9% and 15%, respectively), whereas these parameters did not differ significantly between the cheese and run-in periods. In those hypercholesterolemic subjects with an initial LDL-C >4 mmol/L, LDL-C after the cheese period was significantly lower than after the butter period (3.9 vs. 4.4 mmol/L, $P = 0.014$).

In the largest and longest crossover study to date, Hjerpsted et al. (86) compared the effects of hard cheese and butter on serum blood lipids in 49 adult male and female subjects. After consuming their habitual diet during a 2-wk run-in period, subjects replaced 13% energy of their habitual dietary fat intake with 143 g/d of hard cheese or 47 g/d of butter for 6 wk separated by a 2-wk washout period on their habitual diet. The amounts of SF, PUFA, and MUFA did not differ between the butter and cheese periods, but total fat and SF were higher than the usual diet ($P < 0.05$). Compared with butter, the cheese intervention resulted in significantly lower TC (5.7%), LDL-C (6.9%), and HDL-C (4.4%) ($P < 0.005$). Compared with the run-in period, which was lower in total fat and SF, TC, LDL-C, and HDL-C did not differ for cheese, whereas TC and LDL-C were significantly higher during the butter intervention. Taken together, the evidence is quite consistent that cheese intake results in lower LDL-C compared with butter of equal fat and SF content and may not increase LDL compared with an habitual lower SF diet.

Milk

Results from early studies suggested that supplementing whole milk into the diet lowered or did not alter TC or LDL-C (87–90). However, these studies lacked adequate control groups, control of dietary composition, and compliance measures. In a later crossover study that evaluated the effects of whole-milk intake on plasma TC in 12 young, healthy men who were provided 1 L/d (∼4 cups) of whole milk for 3 wk, TC levels were significantly higher after the whole-milk period compared with the habitual control

diet (91). No results were provided on other plasma lipids and lipoproteins.

In another crossover study, Steinmetz et al. (92) assessed the blood lipid effects of consuming ~2–3 cups/d (236 mL/1000 kcal) of whole milk or skim milk in diets with controlled nutrient compositions that differed only by the addition of whole milk (fat: 33% energy, SF: 11.5% energy) or skim milk (fat: 27.8% energy, SF: 7.75 energy) for 6 wk in 8 adult male subjects. Compared with whole milk, skim milk significantly reduced TC and LDL-C ($P < 0.001$), whereas no significant changes were observed in any of the other lipids, lipoproteins, or apolipoproteins.

Taken as a whole, the results are fairly consistent in showing that whole milk increases TC and LDL-C more than milks containing low levels of milk fat such as skim milk. However, the effects of whole milk on HDL-C and the TC:HDL ratio are less clear. Furthermore, given the emerging dataset indicating that diets lower in CHO can favorably alter blood lipid and lipoprotein responses to high-SF diets containing milk fat (93), there is a need to better understand the blood lipid effects of whole milk in lower CHO diets.

Yogurt

Since the 1970s, a number of human studies assessed the effects of fermented milk and yogurt products on plasma lipids and lipoproteins (88–90,94–105). Although a review of the early human studies suggested a moderate cholesterol-lowering action of fermented milk and yogurt products, many of these studies lacked appropriate control groups and/or had experimental design confounders such as not controlling for fat and SF levels in the diet, making conclusions about independent effects difficult (106).

In a recent study, Ejtahed et al. (105) assessed the blood lipid effects of a supplementing the habitual diet of 60 overweight adults with type 2 diabetes with 300 g/d of either a conventional yogurt containing *Lactobacillus bulgaricus* and *Streptococcus thermophilus* or a probiotic yogurt. This yogurt, in addition to containing the conventional yogurt cultures, was also enriched with *Bifidobacterium lactis* Bb12 and *Lactobacillus acidophilus* La51. The study was performed for 6 wk in a parallel design ($n = 30$/group). There were no differences in energy, total fat, SF, MUFA, PUFA, or dietary fiber among the diets during the intervention period. Compared with the control yogurt, consumption of the probiotic yogurt resulted in a 4.5% reduction in TC, a 7.4% reduction in LDL-C ($P < 0.01$ for both), and a 5.4% reduction in the TC:HDL-C ratio ($P = 0.02$). However, no changes in HDL-C or TG were observed. Compared with baseline values from a 1-wk run-in diet that contained no yogurt, TC and LDL-C concentrations were significantly decreased in the probiotic group, but not in the control yogurt group. HDL-C and TG remained unchanged in the probiotic group compared with baseline, whereas in the control yogurt group, TG were also unchanged, but HDL-C levels were significantly reduced.

Conversely, in another study that compared the same bacterial strains in a conventional yogurt and probiotic yogurt using a similar 6-wk experimental design, no differences in LDL-C or TG levels were observed for either the probiotic or conventional yogurt compared with a control diet without any yogurt. However, TC levels and the TC:HDL-C ratio was significantly reduced in both groups compared with the control diet, and HDL-C was significantly increased in the probiotic group but was not altered in the conventional yogurt group (104). Although drawing conclusions about the favorable blood lipid effects of the probiotic yogurt is unclear, the results with conventional yogurts suggest little, if any, effect.

These results are partially consistent with those of Thompson et al. (90) in which blood lipid effects were assessed in groups of young adult subjects who supplemented their habitual diet with 1 of 3 types of fluid milk (whole, 2%, or skim) or yogurt (1.8% fat) containing *L. bulgaricus and S. thermophilus* and buttermilk (1.9% fat) with *Streptococcus cremoris* and *Streptococcus lactis*. After 3 wk of supplementation, no significant changes in TC, LDL-C, or HDL-C were observed for any of the milk types, yogurt, or buttermilk regardless of milk fat content, whereas TG levels were modestly increased after yogurt and buttermilk consumption ($P < 0.05$). Similarly, McNamara et al. (94) found that plasma TC, LDL-C, and HDL-C were unaffected by the consumption of low-fat yogurt or low-fat milk concentrate in normolipidemic adult men.

De Roos et al. (98) conducted a double-blind, placebo-controlled parallel study that assessed the blood lipid effects of supplementing the habitual diet of 78 normo- and hypercholesterolemic adults ($n = 39$/treatment group) with 500 mL/d of a conventional yogurt containing *S. thermophilus* or a probiotic yogurt with *L. acidophilus* L-1 for 6 wk after a 2-wk run-in period on the conventional yogurt. Energy and macronutrient intakes were constant and identical throughout the run-in and experimental periods. Results showed that TC, LDL-C, HDL-C, and TG were unaffected by either the control or probiotic yogurt over the test period, and no significant differences were observed between the control and test yogurts.

In another study, a conventional whole-milk yogurt (3.5% fat) containing *S. thermophilus* and *L. lactis* was tested against a probiotic yogurt that, in addition to containing the control cultures, was also enriched with *L. acidophilus* 145 and *Bifidobacterium longum* 913 and 1% of oligofructose. In this study, 29 normo- and hypercholesterolemic women were treated in a crossover design for 7 wk (102). There were no significant differences between the control and probiotic yogurts for serum LDL-C and TG level. However, consumption of the probiotic yogurt resulted in a higher HDL-C and a lower LDL-C:HDL-C ratio compared with the control ($P = 0.002$ and $P < 0.001$, respectively).

In a series of randomized, parallel, and cross-over studies with durations ranging from 4 to 24 wk, the potential hypocholesterolemic effects of a probiotic yogurt fermented with *Enterococcus faecium* and 2 strains of *S. thermophilus* were compared with those of a placebo yogurt fermented with an organic acid in normo- and hypercholesterolemic adult

men and women (96,97,99–101). In a meta-analysis of the 4-wk blood lipid results from these studies, the intake of the probiotic yogurt produced a reduction in plasma TC and LDL-C of 4% and 5% ($P < 0.001$), respectively, whereas there was no effect on HDL-C or TG in any of the studies. However, in a longer term parallel study lasting 6 mo, consumption of the probiotic yogurt resulted in significant reductions in LDL-C at 1 and 3 mo but was not different from the control at 6 mo (97).

Finally, Ataie-Jafari et al. (103) conducted a randomized, crossover study that assessed the blood lipid effects of adding to the habitual diet of 14 hypercholesterolemic adults 300 g/d of a conventional yogurt containing *S. thermophilus* and *L. bulgaricus* or 300 g/d of a probiotic yogurt that contained, in addition to the conventional yogurt bacteria, the probiotic bacteria *L. acidophilus* and *B. lactis* for 6 wk. Consumption of the probiotic yogurt significantly reduced TC compared with the baseline 2-wk run-in diet containing no yogurt and the conventional yogurt group, but had no significant effects on other plasma lipid or lipoproteins. Additionally, consumption of the conventional yogurt resulted in no significant changes in any blood lipid and lipoprotein levels compared with the baseline run-in diet.

Taken as a whole, although a number of clinical studies examined the effects of consuming probiotic and conventional yogurts on plasma lipids and lipoproteins, it is difficult to draw firm conclusions because of experimental design issues as well as the apparent potential for different "probiotic" bacterial strains to have unique blood lipid effects. Nonetheless, based on results from the better designed intervention studies, there is little evidence indicating that commercial yogurts fermented with conventional starter cultures (e.g., *L. bulgaricus*, *S. thermophilus*) significantly lower plasma LDL-C and TG or increase HDL-C. The blood lipid effects of yogurts fermented with other so-called probiotic bacteria are less clear, with results indicating that some, but not all, may favorably affect LDL-C, HDL-C, and/or TG. It is clear, however, that to achieve consistent and reliable results in assessing blood lipid effects of novel probiotic bacterial strains requires attention to study design issues that include, among others, controlling energy and macronutrient intake, appropriate bacterial concentrations, subject cholesterolemic status, study duration, and prebiotic confounding.

Summary

This review highlights our limited knowledge on how milk fat–containing dairy products affect the risk of the development of CVD. In a review of several prospective cohort studies and meta-analyses examining the relationship between milk and milk product intake and risk of CVD and stroke, most, but not all, showed either no relationship or an inverse association (Table 1). In a limited number of studies examining the association between the intake of total high-fat or total low-fat dairy products and the risk of CHD or stroke, most reported no association. Additional research is needed on the relationship between whole milk and stroke and stroke subtypes because 1 study reported a moderate positive association between whole milk intake and intracerebral hemorrhage, but no association for cerebral infarction or subarachnoid hemorrhage. Furthermore, more research is needed on whole milk and CHD because at least 1 study indicated a potential for an increased risk of CHD with whole-milk consumption.

There is clearly a discordance between the observational evidence that indicates the lack of a positive association or, in some cases, inverse associations between the intake of dairy products and the risk of CVD and stroke and the short-term clinical evidence that has consistently demonstrated that butter and whole milk increase plasma TC, LDL-C, and apolipoprotein B levels. The absence of direct evidence on the effect of full-fat dairy products and CVD outcomes indicates that perhaps not all milk fat–containing dairy products have the predicted effect on plasma lipids and lipoproteins. For example, fermented dairy products may be considerably different from their butter fat or whole milk counterparts. In 4 of 4 short-term clinical studies, the intake of natural cheese resulted in a significant or nearly significant ($P = 0.06$) lowering of LDL-C compared with butter intake of equal total fat and SF content. The mechanism of action for the relative neutral effect of cheese on blood lipids is unknown. One suggested explanation includes the relatively high content of calcium in cheese. This line of evidence is based on animal and human studies that demonstrated increased fecal fat with higher intakes of dietary calcium as a result of the intestinal formation of insoluble fatty acid calcium soaps. Indeed, the largest study to date on the effects of cheese consumption and blood lipids reported a trend for higher fecal fat excretion after the cheese intervention compared with butter, although the increase failed to reach statistical significance. Changes during fermentation due to bacterial bioactivity have also been strongly considered as a mechanism allowing cheese to differentially affect blood lipids. However, these effects may be highly bacterial strain dependent because our review of the evidence on fermented yogurt products suggest that results showing favorable effects of yogurt on plasma lipids and lipoproteins were strain specific. For instance, there is little evidence indicating that conventional yogurts fermented with conventional starter cultures (e.g., *L. bulgaricus, S. thermophilus*) significantly lower plasma LDL-C and TG or increase HDL-C, whereas studies with yogurts fermented with other so-called probiotic bacteria showed that some, but not all, may favorably affect blood lipids and lipoproteins. These effects may be due to the ability of certain bacterial strains to ferment indigestible CHO in the large intestine, which can increase short-chain fatty acids and decrease circulating cholesterol levels by inhibiting hepatic cholesterol synthesis or by redistributing cholesterol from plasma to the liver. Additionally, the intestinal bacteria can bind bile acids to cholesterol, resulting in the excretion of bile acid–cholesterol complexes in the feces. Further work should be conducted regarding the mechanism behind the blood lipid neutrality of cheese.

Even though our review focuses on lipid markers of CVD, a growing body of evidence indicates that markers of inflammation are strong predictors of atherosclerotic CVD (107–109). There is limited research on the effects that dairy products have on inflammatory mediators. However, in a small number of short-term clinical trials that assessed the effect of diets high in butter fat or cheese on selected inflammatory and prothrombotic measures, there was no effect of these diets compared with the basal diets or diets high in unsaturated fat (76). In addition, a few studies examining the effect of diets enriched in low-fat dairy products on markers of inflammation, oxidative stress, and vascular adhesion molecules reported either no effect or an inverse relationship (110). Future studies should continue to track the effects that dairy products have on inflammation due to their strong association with CVD.

Conclusions

Based on results from numerous prospective observational studies and meta-analyses, most, but not all, have shown no association and in some cases an inverse relationship between the intake of milk fat containing dairy products and the risk of CVD, CHD, and stroke.

A limited number of prospective cohort studies found no significant association between the intake of total full-fat dairy products and the risk of CHD or stroke.

Diets higher in SF from whole milk and butter increase LDL-C when substituted for CHO or unsaturated fatty acids, but may also increase HDL-C, which may lower or not alter the TC:HDL-C ratio.

Most clinical studies showed that full-fat natural cheese, a highly fermented product, significantly lowers LDL-C compared with butter intake of equal total fat and saturated fat content.

Results showing favorable effects of fermented yogurt products on plasma lipids and lipoproteins appear to be strain specific. In studies with yogurts fermented with various probiotic bacterial strains some, but not all, showed favorable effects on blood lipids and lipoproteins.

Reliance on the level of a single lipid nutrient (SF) in a food and a single plasma biomarker (LDL-C) may not adequately characterize the cardiovascular impact of complex foods that contain, in addition to SF, multiple nutrients and other bioactive components that reduce CVD risk. The lack of a positive association or, in some cases, inverse associations between dairy product intake and CVD risk may be related to the net balance between positive and negative cardiovascular effects of nutrients and other bioactive components contained in dairy foods.

There is a lack of research examining the effect of full-fat dairy foods on CVD outcomes, indicating the need for longer term intervention studies. The results of these studies are important to the future of dietary guidance and our understanding of the role of foods in chronic disease.

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