Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies[1–3]

Sabita S Soedamah-Muthu, Eric L Ding, Wael K Al-Delaimy, Frank B Hu, Marielle F Engberink, Walter C Willett, and Johanna M Geleijnse

ABSTRACT

Background: The consumption of dairy products may influence the risk of cardiovascular disease (CVD) and total mortality, but conflicting findings have been reported.

Objective: The objective was to examine the associations of milk, total dairy products, and high- and low-fat dairy intakes with the risk of CVD [including coronary heart disease (CHD) and stroke] and total mortality.

Design: PubMed, EMBASE, and SCOPUS were searched for articles published up to February 2010. Of >5000 titles evaluated, 17 met the inclusion criteria, all of which were original prospective cohort studies. Random-effects meta-analyses were performed with summarized dose-response data. Milk as the main dairy product was pooled in these analyses.

Results: In 17 prospective studies, there were 2283 CVD, 4391 CHD, 15,554 stroke, and 23,949 mortality cases. A modest inverse association was found between milk intake and risk of overall CVD [4 studies; relative risk (RR): 0.94 per 200 mL/d; 95% CI: 0.89, 0.99]. Milk intake was not associated with risk of CHD (6 studies; RR: 1.00; 95% CI: 0.96, 1.04), stroke (6 studies; RR: 0.87; 95% CI: 0.72, 1.05), or total mortality (8 studies; RR per 200 mL/d: 0.99; 95% CI: 0.95, 1.03). Limited studies of the association of total dairy products and of total high-fat and total low-fat dairy products (per 200 g/d) with CHD showed no significant associations.

Conclusion: This dose-response meta-analysis of prospective studies indicates that milk intake is not associated with total mortality but may be inversely associated with overall CVD risk; however, these findings are based on limited numbers. *Am J Clin Nutr* 2011;93:158–71.

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of death in the Western world, claiming 17 million lives per year (1). The burden from coronary heart disease (CHD) as its main component is projected to rise from ≈47 million disability-adjusted life-years in 1990 (DALY = healthy years of life lost) to 82 million DALYs in 2020 (1). It has been postulated that the consumption of dairy products influences the risk of CVD (including CHD and stroke) or all-cause mortality, but findings from epidemiologic studies have been conflicting. Several prospective cohort studies have suggested inverse associations of milk in particular with stroke (2–5), but also with CHD (3) and all-cause mortality (6). Whereas other cohort studies reported that milk was positively associated with CHD (7) or stroke (8). Many studies also reported no significant association between milk and CHD (9–13), stroke (14, 15), or all-cause mortality (16–19). Total dairy intake was rarely reported (compared with milk) and yielded conflicting evidence, with no relation to CHD (20, 21). Meanwhile, high-fat dairy product consumption has been shown to be positively related to CHD (22, 23), whereas low-fat dairy product consumption has been shown to be inversely associated with CHD (22) or stroke (15).

The mechanisms by which dairy products can exert certain effects on CVD are diverse, with divergent mechanisms suggesting both positive and negative influences. Dairy products are rich in minerals (calcium, potassium, and magnesium), protein (casein and whey), and vitamins (riboflavin and vitamin B-12) that can exert beneficial effects on CVD. On the other hand, saturated fat in dairy products can adversely influence CHD, although the effect of saturated fat on CHD risk depends on the source of calories (unsaturated fatty acids or carbohydrates) by which it is substituted to maintain energy balance (24). There is some suggestion that low-fat dairy products may beneficially influence blood pressure (25, 26). Studies have shown that the Dietary Approaches to Stop Hypertension (DASH) dietary pattern—which is high in fruit, vegetables, nuts, fish, and low-fat dairy products—lowers blood pressure effectively, which may in part be attributed to its relatively high content of low-fat dairy products (27). Whether these effects on blood pressure can be specifically addressed by low-fat dairy products is not clear from

[1] From the Division of Human Nutrition, Wageningen University, Wageningen, Netherlands (SSS-M, MFE, and JMG); the Department of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA (ELD, FBH, and WCW); the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (ELD, FBH, and WCW); and the Department of Family and Preventive Medicine, University of California, San Diego, San Diego, CA (WKA-D).

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[3] Address correspondence and requests for reprints to SS Soedamah-Muthu, Division of Human Nutrition, Wageningen University, PO Box 8129, 6700 EV Wageningen, Netherlands. E-mail: sabita.soedamah-muthu@wur.nl.

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DASH, but European guidelines on CVD prevention do recommend the DASH diet with low-fat dairy products, albeit such a recommendation is not yet fully evidence-based (28). Two meta-analyses (29, 30) and 2 narrative reviews (31, 32) combined with individual studies produced conflicting conclusions. Combining evidence from different study designs (ecologic, case-control, and prospective) and different study populations (age, sex, country, and various mean milk intakes) may explain the conflicting results. Pooling different exposures (calcium and milk) and the use of inappropriate statistical methods could also lead to conflicting conclusions.

Therefore, we conducted a new systematic evaluation of the association between intakes of milk, total dairy products, total high-fat dairy products, and total low-fat dairy products with risk of total CVD, CHD, stroke, and all-cause mortality via a dose-response meta-analysis of prospective cohort studies in healthy adult men and women.

SUBJECTS AND METHODS

Study selection for the meta-analysis

A systematic literature review was conducted by using the databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com), and SCOPUS (http://www.scopus.com) from 10 February 2009 until 1 June 2009, based on the query syntax shown in supplemental Table 1 (*see* "Supplemental data" in the online issue). An updated secondary search was conducted until 22 February 2010. First, titles of the articles were screened, on basis of which we excluded animal studies, children aged <18 y, and diseased populations (including diabetes and CVD). Second, abstracts of the articles were screened for the following inclusion criteria: prospective cohort studies, original articles, general population, dairy products as main exposure, and fatal or nonfatal CVD (CHD and stroke) or mortality outcomes. For articles that met the inclusion criteria, the full text was retrieved. An additional hand search for relevant articles was performed by using bibliographies of scientific articles (eg, review articles).

Dairy intake data as well as relative risks (RRs) for CVD, CHD, stroke, and all-cause mortality (with 95% CIs) were extracted from the selected articles. If insufficient data were reported in the article (eg, absence of RRs, CIs, dairy intakes, or number of cases), additional information was requested from the authors (7, 14, 20–22). All data were extracted into a predefined spreadsheet and checked several times. The selection and data extraction process was executed by 2 independent reviewers (SSS-M and JMG). If multiple articles were on the same study sample with the same exposure and outcome [Caerphilly cohort study (4, 10), Iowa Women's Health study (9, 23)], only the publication with the largest number of outcome cases was retained. In one study population (Oxford Vegetarian Study) (7, 11), because different outcomes were reported in different articles, both articles on the same study population were included.

Main outcomes

Outcomes in this study included incident major CVD (fatal and nonfatal CHD and stroke), CHD (fatal and nonfatal), stroke (fatal and nonfatal), and all-cause mortality, defined as such in the underlying studies. CVD was defined as CHD or stroke [WHO *International Classification of Diseases* (ICD)-10 I60-69; http://www.who.int/classifications/icd/en] and other CVD, including cardiac arrest (I46), heart failure (I50), and sudden death (R96). CHD was defined as acute myocardial infarction, angina pectoris, and other ischemic heart disease (as in ICD-10 I20-I25).

Statistical methods

Dairy intakes were converted from servings or other units into g/d by using standard conversions from the Food Standards Agency (pint = 585 g; milk, 1 glass = 200 mL; and total dairy = 200 g) (33, 34). Assumptions were made to convert all dairy exposure data into g/d or for milk into mL/d. For this 1 serving, dairy products or milk were estimated to be on average 200 g or 200 mL, respectively.

We examined the association between milk consumption and CVD, CHD, stroke, and all-cause mortality. Because there were insufficient numbers of studies for dairy products and outcomes other than CHD, we analyzed total dairy, total low-fat dairy, and total high-fat dairy products only for CHD risk. There were insufficient numbers of studies ($\leq$2) including certain exposures, such as cheese, yogurt, and high-fat or low-fat milk; therefore, these analyses could not be pursued.

Only studies with similar exposures and outcomes were pooled to avoid heterogeneity, according to a predefined data-analysis plan.

We used STATA version 11.0 (StataCorp, College Station, TX) for meta-analysis using the *METAN* command, whereas dose-response meta-analyses were conducted by using the *GLST* command with the generalized least-squares method for trend estimation of summarized dose-response data, based on the Greenland and Longnecker method (35). All statistical tests were 2-sided with $\alpha = 0.05$. Restricted cubic splines were used to assess for potential curvilinear relations.

Between-study heterogeneity was assessed via the I^2 statistic (36), which expresses the percentage of variation attributable to between-study heterogeneity. Random-effects pooling were conducted by using DerSimonian and Laird random-effects models (37). Forest plots were made for the relation between milk or dairy and CVD, CHD, stroke, and all-cause mortality. From each publication, we used the results from the main multivariable model that included most confounders. Subgroup analyses were performed by sex, age (young compared with old), continent, and degree of adjustment for confounding, providing sufficient numbers of studies. For year of publication and BMI, variation was insufficient across studies to conduct subgroup analyses. To assess whether studies of lesser quality could have influenced the results, meta-analyses were split by categorizing studies by whether or not they adjusted for the most essential confounders (age, sex, BMI, smoking, and total energy intake). Most of the associations were not adjusted for physical activity or other aspects of diet, including intakes of fruit and vegetables and specific fatty acids; therefore, these could not be included.

To explore heterogeneity with a statistical test, further meta-regression analyses were performed to relate the size of effect to one or more characteristics (age, sex, and confounder adjustments) of the studies involved. In addition, interaction terms were added, and statistical significance was evaluated. For the analysis on total mortality, which included most studies ($n = 8$), we used a funnel plot to assess the presence of publication bias. In addition, we

tested for publication bias with the Begg's test (38). A spaghetti plot, developed by Ding (ELD), was used to illustrate the direction of the association between milk and all-cause mortality.

RESULTS

Study populations

We identified a total of 87 articles from PubMed, 40 from EMBASE, and 22 from SCOPUS (**Figure 1**). In the full-text stage, we narrowed the number of studies from 27 to 17 after applying our search criteria. Nine studies were excluded because of insufficient data on dairy intakes or if RRs or 95% CIs could not be extracted (2, 12, 13, 19, 39–43). One study (23) was excluded because the same analyses were already included in an earlier larger study of the same population (9). A total of 17 studies were included, the study characteristics of which are presented in **Table 1** (3, 5–11, 14–18, 20–22, 44). The mean (± SD) age of the study populations included was 56 ± 13 y (range: 34–80 y) for a total of 611,430 participants across 17 studies, and the mean (± SD) duration of follow-up was 14.0 ± 6.0 y. Five studies were conducted in the United States, 2 in Japan, and 10 in Europe. The mean BMI (in kg/m^2) was 25, as reported in 11 (65%) studies. The studies were pooled to assess milk intake according to the outcomes: 8 studies on all-cause mortality, 6 studies on CHD, 6 studies on stroke, and 4 studies on CVD outcomes (*see* supplemental Table 2 under "Supplemental data" in the online issue). The intake range for milk across all studies was 0–850 mL/d, with a mean (± SD) intake of 266 ± 210 mL/d. For total dairy products and CHD, 4 studies were pooled; for total high-fat dairy products and CHD, 4 studies were pooled; and for total low-fat dairy products and CHD, 3 studies were pooled (*see* supplemental Table 3 under "Supplemental data" in the online issue). The mean (± SD) intake for total dairy products across the 4 studies was 419 ± 215 g/d (range: 114–828 g/d).

Total CVD

Data from a total of 13,518 participants and 2283 CVD (fatal and nonfatal) cases were analyzed in 4 prospective cohort studies, with milk as the main exposure. The mean (±SD) age was 55 ± 8 y. Two studies comprised only men, and 2 studies had a similar distribution of men and women; the mean (± SD) follow-up was 16 ± 9 y. The mean (±SD) milk intake across these 4 studies was 313 ± 214 mL/d. Pooled results indicated an inverse association between milk and total CVD risk (RR: 0.94; 95% CI: 0.89, 0.99) per glass (200 mL/d) (**Figure 2**), with no evidence of between-study heterogeneity (I^2 = 0%, P = 0.5). From a stratified analysis, effect-modification heterogeneity was suggestive for sex and degree of confounding, albeit not statistically significant (P for interaction $>$ 0.05). An inverse association between milk and CVD was shown in studies that included only men (RR: 0.93; 95% CI: 0.87, 0.99), and no association was shown in studies that included both men and women (RR: 1.10; 95% CI: 0.67, 1.80). By degree of confounding, studies that used full adjustment showed an inverse association between milk and CVD (RR: 0.94; 95% CI: 0.88, 1.01), whereas studies that did not use full adjustment showed no association (RR: 1.10; 95% CI: 0.66, 1.84).

CHD

Data from a total of 259,162 participants and 4391 CHD (fatal and nonfatal) cases were analyzed in 6 prospective cohort studies, with milk as the main exposure. The mean (±SD) age was 50 ± 11 y. Three studies included only men, 2 studies included 40% men and 60% women, and 1 study included only women; the mean (±SD) follow-up was 16 ± 6 y. The mean milk intake was 263 mL/d (range: 0–659 mL/d) for these 6 studies. The pooled results from these 6 studies (**Figure 3**) with CHD outcomes suggested no association between milk

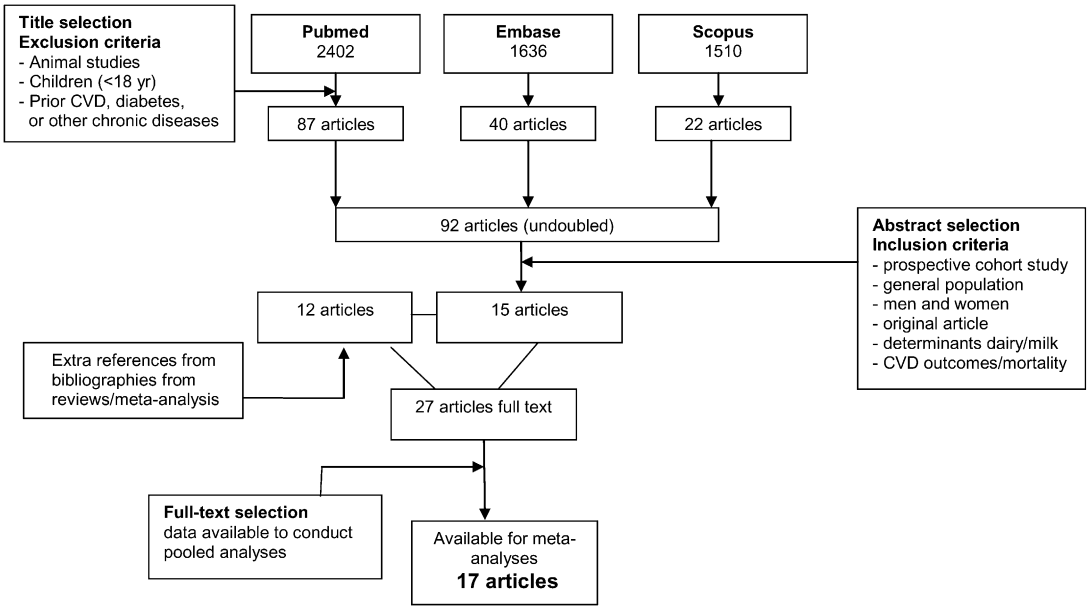

FIGURE 1. Flow chart of the meta-analysis of dairy product consumption and incident cardiovascular disease (CVD) and all-cause mortality. The numbers of studies retrieved from 3 electronic databases [PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com), and SCOPUS (http://www.scopus.com)] are shown. Each box contains the number of studies found. The steps from title to abstract to full-text screening are indicated, as are the inclusion and exclusion criteria. Hand searches are indicated separately from the electronic search.

TABLE 1
Characteristics of 17 prospective cohort studies on dairy products and milk consumption and cardiovascular disease (CVD) and all-cause mortality events[1]

Reference	Study, country	Percentage of men/ women	Mean age	Follow-up time	No. of subjects	No. of cases	Results available[2]	Exposure[3]	Year dietary data collected	Outcome	Main confounders
		%	*y*	*y*							
Appleby et al, 1999 (7)	Oxford Vegetarian Study, UK	38/62	34	12	10,800	63 deaths from CHD	Milk and cheese and fatal CHD; RR (95% CI)	Simple FFQ (not validated); milk: 3 categories (pints/d); cheese: 3 categories (frequency/ wk)	1984	Fatal CHD collected from national registry death certificates, ICD coded	Age, sex, smoking, socioeconomic status
Bostick et al, 1999 (9)	Postmenopausal women, Iowa, USA	0/100	61.5	8	34,486	387	Total dairy and high-fat dairy and fatal CHD; RR (95% CI)	FFQ (validated); dairy products: 4 categories (units/d); fat-containing dairy products: 4 categories (servings/wk); defined as milk products, excluding butter	1986	Fatal CHD collected from registry and follow-up questionnaires, ICD coded, not validated	Age, total energy intake, BMI, WHR, history of DM, smoking, estrogen, alcohol, education, marital status, physical activity, vitamin E, saturated fat intake
Elwood et al, 2004 (10)	Caerphilly cohort, men, South Wales, UK	100/0	52	22	2512	493 CHD, 185 stroke, 811 deaths	Milk and several outcomes (fatal and nonfatal CHD, nonfatal stroke, fatal and nonfatal CVD, death); RR (95% CI)	FFQ (validated); milk: 4 categories (pints/d)	1983	Fatal and nonfatal CHD and CVD, stroke, and all-cause mortality; examination by ECG, GP + hospital records were used, ICD coded	Age, total energy, smoking, social class, BMI, systolic BP, alcohol and fat, prior vascular disease

(Continued)

TABLE 1 (*Continued*)

Reference	Study, country	Percentage of men/ women	Mean age	Follow-up time	No. of subjects	No. of cases	Results available[2]	Exposure[3]	Year dietary data collected	Outcome	Main confounders
		%	*y*	*y*							
Fortes et al, 2000 (6)	Elderly residents from public home, Rome, Italy	32/68	80	5	162	53 deaths	Milk and yogurt and all-cause mortality; RR (95% CI)	FFQ (validated); milk and yogurt (frequency/wk)	1993	All-cause mortality, collected from registry, no cause of death	Age, sex, education, BMI, smoking, cognitive function, chronic diseases
Hu et al, 1999 (22)	Nurses' Health study, female registered nurses in 11 states, USA	0/100	46.5	14	41,254	939	Total, high-, and low-fat dairy and milk and fatal and nonfatal CHD; RR (95% CI)	FFQ (validated); total, high-, and low-fat dairy products and milk: 5 categories (servings/d)	1980	Nonfatal MI + fatal CHD by medical records reviewed by physicians blind to risk factors; deaths from registry, hospital records, autopsy reports	Age, time period, BMI, smoking, menopausal status (including hormone replacement therapy), parental history of MI, vitamin E supplement, alcohol, history of hypertension, aspirin, physical activity, total energy intake
Iso et al, 1999 (14)	Nurses' Health study, female registered nurses in 11 states, USA	0/100	46	14	85,764	347	Milk, low-fat and high-fat milk, yogurt, cheese, and risk of fatal and nonfatal stroke; RR (95% CI)	FFQ (validated), 2 categories for yogurt (5 times/wk), cheese (1 time/d), milk (2 times/d)	1980	Fatal and nonfatal stroke by questionnaire, medical records (reviewed blind), and death certificates	Age, smoking, time period, BMI, alcohol, menopausal status (including hormone replacement therapy), physical activity, multivitamin use, vitamin E supplementation, history of hypertension, DM, and hypercholesterolemia

(Continued)

TABLE 1 (*Continued*)

Reference	Study, country	Percentage of men/ women	Mean age	Follow-up time	No. of subjects	No. of cases	Results available[2]	Exposure[3]	Year dietary data collected	Outcome	Main confounders
		%	*y*	*y*							
Kahn et al, 1984 (17)	California Seventh-day Adventist group compared with non-Adventists, USA	40/60	—	21	27,530	6000	Cheese and milk and all-cause mortality; RR (95% CI)	Questionnaire (not validated); milk: 3 categories (glasses/d); cheese: 4 categories (days/wk)	1960	All-cause mortality, 85% of deaths were matched by computer tapes of local registry, no cause of death, no good validation	Age, sex, smoking, history of chronic diseases
Kinjo et al, 1999 (5)	Japanese prefecture study, Japan	56/44	55	15	223,170	11,030	Milk and fatal stroke; RR (95% CI)	One-page questionnaire (not well assessed milk data); milk: 3 categories (frequency/ wk)	1965	Fatal stroke, deaths ascertained by vital statistics, coded cause of death	Sex, attained age, follow-up, prefecture (= unit of administration or county in China), alcohol, smoking, occupation
Knoops et al, 2006 (16)	HALE study (combination of SENECA and FINE studies), Europe	66/34	75	10	3117	1382	Milk and milk products and all-cause mortality; RR (95% CI)	Dietary history, food during 1 mo in SENECA Study, 2–4 wk in FINE Study; validated methods; continuous variable (in g/d)	1988	All-cause mortality ascertained by vital statistics, ICD-coded cause of death, death certificates, or medical doctor	Age, sex, alcohol, physical activity, smoking, number of years of education, BMI, chronic diseases at baseline, center
Larsson et al, 2008 (8)	Within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finland	100/0	57	13.6	26,556	2702	Total dairy products, low-fat milk, whole milk, yogurt, cheese, and fatal and nonfatal stroke; RR (95% CI)	FFQ (validated); intake (g/d) in quintiles	1988	Fatal and nonfatal stroke data collected by record linkage with hospital discharge register and register for causes of death; agreement was checked	Age, supplementation group, education, smoking, BMI, total cholesterol, serum HDL, history of DM and heart disease, physical activity, total energy, alcohol, caffeine, sugar, red meat, poultry, fish, fruit, juice, vegetables, potatoes, whole grain, refined grain

(*Continued*)

TABLE 1 (*Continued*)

Reference	Study, country	Percentage of men/ women	Mean age	Follow-up time	No. of subjects	No. of cases	Results available[2]	Exposure[3]	Year dietary data collected	Outcome	Main confounders
		%	*y*	*y*							
Mann et al, 1997 (11)	Vegetarian participants and nonvegetarian controls, UK	38/62	34	13.3	10,802	392	Milk and cheese and mortality; RR (95% CI)	FFQ (not validated); milk (pints/d); cheese (frequency/ wk) in tertiles	1981	All-cause mortality, collected with Office for National Statistics and coded blinded	Age, sex, smoking, social class
Ness et al, 2001 (3)	Scottish working men, UK	100/0	48	25	5765	2350 deaths, 892 deaths from CHD	Milk and mortality (all-cause, CVD and CHD, stroke death separated); RR (95% CI)	Questionnaire (checked by interview); milk (pints/d = 0.586 L) in tertiles	1973	All-cause mortality, fatal CHD, fatal CVD, and fatal stroke collected with Office for National Statistics	Age, smoking, BP, cholesterol, BMI, forced expiratory volume, social class, education, deprivation, siblings, car user, angina, ECG ischemia, bronchitis, alcohol
Paganini-Hill et al, 2007 (18)	Leisure World Cohort Study, California, USA	37/63	74	23	13,624	11,386	Milk and mortality; RR (95% CI)	Questionnaire (not validated); milk (glasses/d) in quartiles	1981	All-cause mortality, vital status by death certificates, hospital discharge data	Age, sex, smoking, exercise, BMI, alcohol, hypertension, angina, MI, stroke, diabetes, rheumatoid arthritis, cancer
Sauvaget et al, 2003 (15)	Life Span Study, Japan	38/62	56	16	31,832	1094	Milk and dairy products and fatal stroke; RR (95% CI)	FFQ (validated); milk and dairy products (butter and cheese) (frequency/wk) in quartiles	1979	Fatal stroke, linkage to registration, death certificates, trained coders, ICD	Age, sex, city, radiation dose, BMI, smoking, alcohol, education, history of diabetes, or hypertension
Panagiotakos et al, 2009 (20)	ATTICA Study, Greece	50/50	53	5	686	30	Dairy products, milk, cheese, yogurt, and milk and fatal and nonfatal CVD; RR (95% CI)	FFQ (validated); dairy, milk, cheese, yogurt in tertiles (servings/d)	2002	Fatal and nonfatal CVD, medical records	Age, sex, BMI, hypertension, diabetes, hypercholesterolemia, current smoking, physical activity

(Continued)

TABLE 1 (*Continued*)

Reference	Study, country	Percentage of men/ women	Mean age	Follow-up time	No. of subjects	No. of cases	Results available[2]	Exposure[3]	Year dietary data collected	Outcome	Main confounders
		%	*y*	*y*							
Al Delaimy et al, 2003 (21)	Health Professionals Follow-Up Study, USA	100/0	53	12	194,276	14468	Total, high-fat, and low-fat dairy products and milk and fatal and nonfatal CHD; RR (95% CI)	FFQ (validated), dairy products (milk, yogurt, ice-cream, and cheese) in quintiles (servings/d)	1986	Fatal and nonfatal CHD, medical records reviewed, autopsy reports, death certificates	Age, time period, energy intake, history of diabetes, history of hypercholesterolemia, family history of MI, smoking, aspirin, BMI, alcohol intake, physical activity, vitamin E, *trans* fatty acids, PUFA:SFA ratio, total protein intake, fiber, folate, omega-3 (n−3) fatty acids, and α-linolenic acid
Engberink et al, 2009, abstract (44)	Rotterdam ERGO Study, Netherlands	27/63	67	11	4664	558	Total high and low-fat dairy products, milk, and cheese and fatal and nonfatal CHD, fatal CVD, all-cause mortality; RR (95% CI)	FFQ (validated); total, high-, and low-fat dairy products (milk and cheese in g/d)	1993	Fatal and nonfatal CHD, fatal CVD, and all-cause mortality data collected by GP medical records, discharge reports from specialists, and vital status from municipal registry	Age, sex, BMI, smoking, educational level, and intakes of alcohol, total energy, PUFAs, vegetables, fruit, meat, fish, bread, coffee, and tea

[1] PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; BP, blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; MI, myocardial infarction; WHR, waist-to-hip ratio; FFQ, food-frequency questionnaire; CHD, coronary heart disease; RR, relative risk; ICD, International Classification of Diseases; ERGO, Erasmus University Rotterdam Health Research; ATTICA, a health and nutritional survey carried out in the Attica region of Greece; HALE, the Healthy Ageing Longitudinal Study in Europe; GP, general practitioner; FINE, the Finland, Italy, Netherlands, Elderly studies; SENECA, Survey in Europe on Nutrition and the Elderly, a Concerted Action.

[2] "Results available" indicates main exposures and outcomes and the way the association was expressed RR (95% CI).

[3] "Exposure" refers to dairy product consumption and how the data were collected.

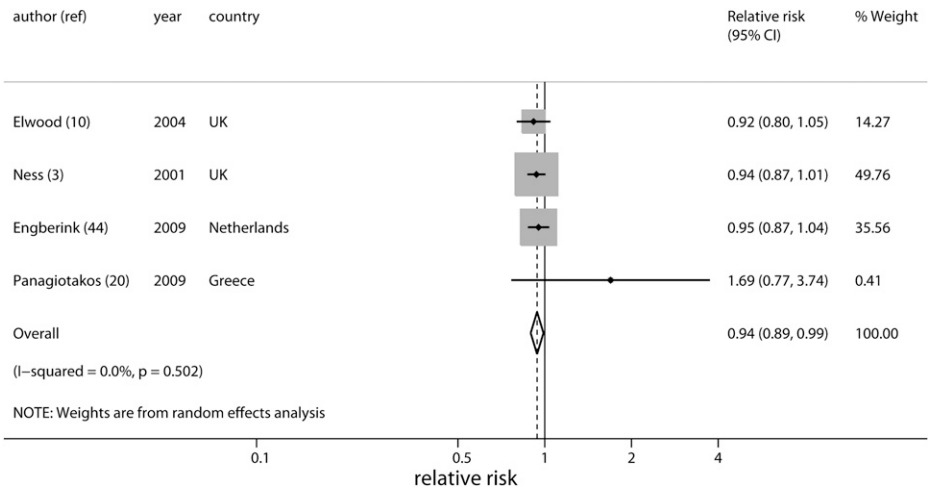

FIGURE 2. Relation between milk (per 200 mL/d) and cardiovascular disease: dose-response meta-analyses of 4 prospective cohort studies (n = 13,518, no. of cases = 2283). Shown are author names, reference number, year of publication, country of study, and the size of the association per study expressed in squares (size of square indicates weight of the study to the overall meta-analysis); the horizontal lines indicate 95% CIs. The last 2 columns contain the actual estimated relative risks (RRs) and 95% CIs pooled across the categories of milk exposure with the generalized least-squares method and the actual weights. On the x axis, the RR is plotted with a line through the RR (= 1) that indicates no significant association between exposure and outcome. The diamond at the bottom indicates the pooled result, with the RR in the middle and the 95% CI. A test for heterogeneity, the Higgins and Thompson I-squared value, shows how much heterogeneity is due to between-study variation with a P value (if $P < 0.05$).

(per 200 mL/d) and CHD (RR: 1.00; 95% CI: 0.96, 1.04). There was no evidence of between-study heterogeneity in these analyses (I^2 = 27%, P = 0.2). From stratified analyses by continent, differences were found between the studies in the United States (n = 2) and those in Europe (n = 4), with RRs of 1.03 (95% CI: 0.99, 1.08) and 0.96 (95% CI: 0.92, 1.02), respectively, which were not significant (P = 0.3). No significant effect modification for age (P for interaction = 0.8), sex (P for interaction = 0.4), or degree of confounding (fully compared with not fully adjusted; P for interaction = 0.6) was seen.

Pooled results from a limited number of studies on the association between total dairy (n = 4), total high-fat (n = 4), and total low-fat (n = 3) dairy consumption and CHD risk showed no significant association between total dairy product intake and CHD (RR: 1.02; 95% CI: 0.93; 1.11, I^2 = 26%, P = 0.3), total high-fat dairy and CHD (RR: 1.04; 95% CI: 0.89, 1.21; I^2 = 0%, P = 0.9), and total low-fat dairy and CHD (RR: 0.93; 95% CI: 0.74, 1.17; I^2 = 56%, P = 0.1) (*see* supplemental Figures 1–3 under "Supplemental data" in the online issue). We assessed for nonlinear relations via restricted cubic spline functions, but found none to be significant.

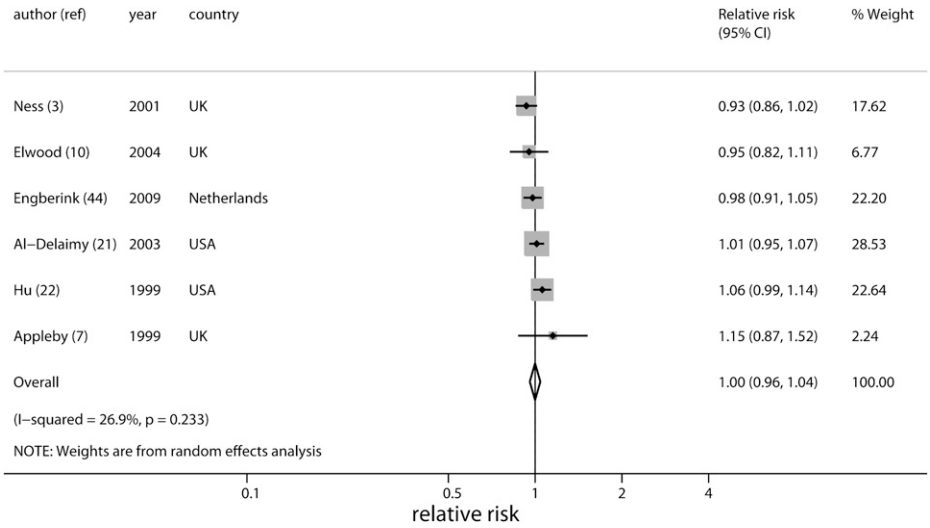

FIGURE 3. Relation between milk (per 200 mL/d) and coronary heart disease: dose-response meta-analyses of 6 prospective cohort studies (n = 259,162, no. of cases = 4391). Shown are author names, reference number, year of publication, country of study, and the size of the association per study expressed in squares (size of square indicates weight of the study to the overall meta-analysis); the horizontal lines indicate 95% CIs. The last 2 columns contain the actual estimated relative risks (RRs) and 95% CIs pooled across the categories of milk exposure with the generalized least-squares method and the actual weights. On the x axis, the RR is plotted with a line through the RR (= 1) that indicates no significant association between exposure and outcome. The diamond at the bottom indicates the pooled result, with the RR in the middle and the 95% CI. A test for heterogeneity, the Higgins and Thompson I-squared value, shows how much heterogeneity is due to between-study variation with a P value (if $P < 0.05$).

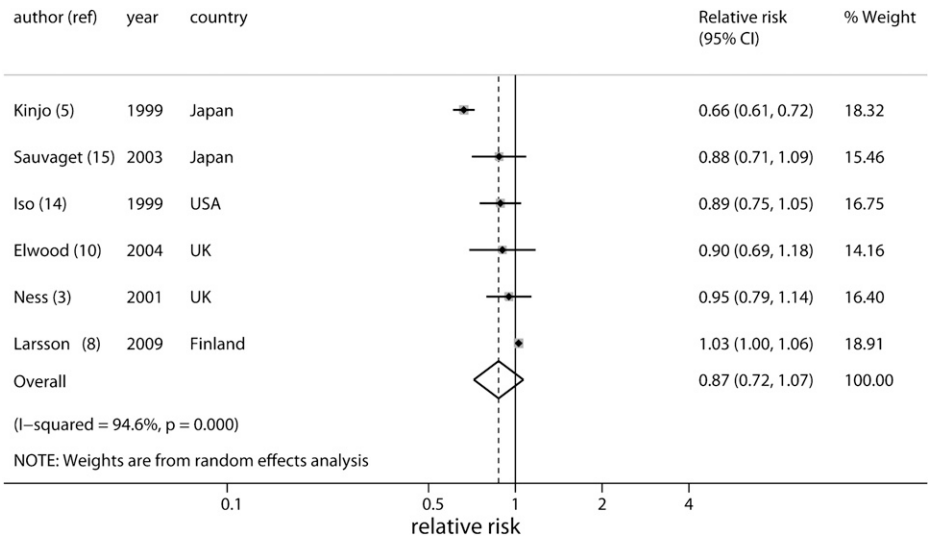

FIGURE 4. Relation between milk (per 200 mL/d) and stroke; dose-response meta-analyses of 6 prospective cohort studies (n = 375,381, no. of cases = 15,554). This figure includes the data from the Larsson study on high-fat milk. The pooled relative risk (RR) including Larsson's low-fat milk instead of high-fat milk is similar (RR: 0.87; 95% CI: 0.72, 1.05). Shown are author names, reference number, year of publication, country of study, and the size of the association per study expressed in squares (size of square indicates weight of the study to the overall meta-analysis); the horizontal lines indicate 95% CIs. The last 2 columns contain the actual estimated RRs and 95% CIs pooled across the categories of milk exposure with the generalized least-squares method and the actual weights. On the x axis, the RR is plotted with a line through the RR (= 1) that indicates no significant association between exposure and outcome. The diamond at the bottom indicates the pooled result, with the RR in the middle and the 95% CI. A test for heterogeneity, the Higgins and Thompson I-squared value, shows how much heterogeneity is due to between-study variation with a P value (if $P < 0.05$).

Stroke

Data from a total of 375,381 participants and 15,554 fatal and nonfatal stroke cases were analyzed in 6 prospective cohort studies, with milk as the main exposure. The mean (±SD) age was 52 ± 5 y. Most of the studies consisted of men, and the mean (± SD) follow-up was 18 ± 5 y. The mean milk intake over these 6 studies was 219 mL/d (range: 0–850 mL/d). The most recent study, by Larsson et al (8), presented the results of high-fat and low-fat milk separately and did not have data on total milk. Two separate meta-analyses were carried out, including either the low-fat or high-fat milk results of Larsson et al (8). The pooled estimate of all studies (**Figure 4**) with Larsson et al's high-fat milk data suggested an inverse association, but it was not statistically significant (RR: 0.87; 95% CI: 0.72, 1.07). The pooled estimate for the studies including Larsson et al's low-fat milk data showed similar results (RR: 0.87; 95% CI:

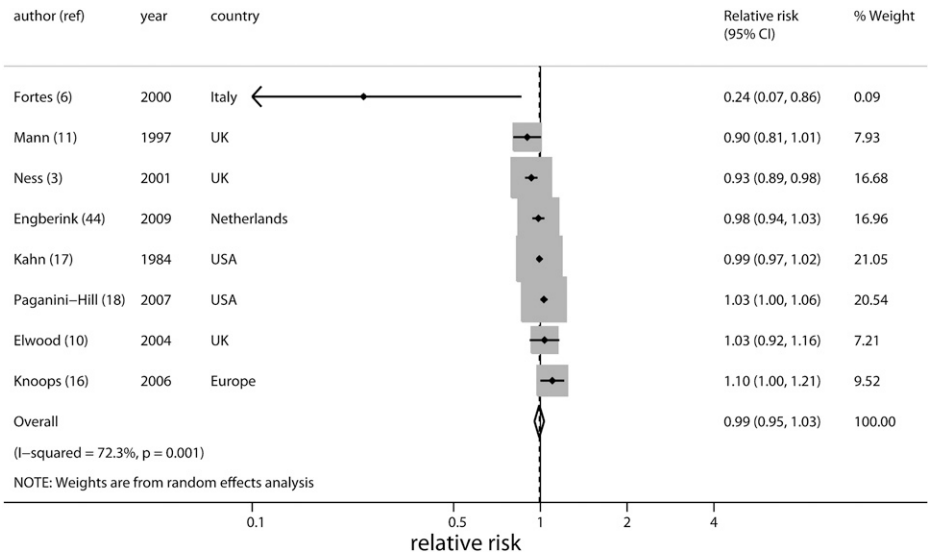

FIGURE 5. Relation between milk (per 200 mL/d) and all-cause mortality: dose-response meta-analyses of 8 prospective cohort studies (n = 62,779, no. of cases = 23,949). Shown are author names, reference number, year of publication, country of study, and the size of the association per study expressed in squares (size of square indicates weight of the study to the overall meta-analysis); the horizontal lines indicate 95% CIs. The last 2 columns contain the actual estimated relative risks (RRs) and 95% CIs pooled across the categories of milk exposure with the generalized least-squares method and the actual weights. On the x axis, the RR is plotted with a line through the RR (= 1) that indicates no significant association between exposure and outcome. The diamond at the bottom indicates the pooled result, with the RR in the middle and the 95% CI. A test for heterogeneity, the Higgins and Thompson I-squared value, shows how much heterogeneity is due to between-study variation with a P value (if $P < 0.05$).

0.72, 1.05). However, significant between-study heterogeneity was observed in these analyses (I^2 = 95%, $P < 0.0001$). From a stratified analysis, effect modification was suggested for sex and degree of confounding, with an inverse association between milk and stroke in studies that included mostly women (RR: 0.88; 95% CI: 0.78, 1.01; I^2 = 0%, P = 0.9) and no association in studies that included men (RR: 1.02; 95% CI: 0.99, 1.051; I^2 = 0%, P = 0.3), albeit not statistically significant (P for interaction = 0.24). By degree of confounding, studies that used full adjustment showed no association between milk and stroke (RR: 1.03; 95% CI: 0.99, 1.05; I^2 = 0%, P = 0.3) and studies that did not use full adjustment showed an inverse association (RR: 0.83; 95% CI: 0.68, 1.013; I^2 = 85%, $P < 0.0001$), which, again, was not statistically significant (P for interaction = 0.9).

All-cause mortality

Data from a total of 62,779 participants and 23,949 all-cause mortality cases were analyzed in 8 observational prospective cohort studies, with milk as the main exposure. The mean (± SD) age was 61 ± 17 y. Two studies consisted of only men, and the other studies combined both men and women; the mean duration of follow-up was 16 ± 7 y. The mean milk intake over these 8 studies was 278 mL/d (range: 0–659 mL/d). The pooled estimate of these 8 studies (**Figure 5**) indicated no significant association between milk intake per 200 mL/d and all-cause mortality (RR: 0.99; 95% CI: 0.95, 1.03). There was significant between-study heterogeneity in these analyses (I^2 = 72%, P = 0.001). From a stratified analysis, no effect modification was seen by sex or degree of confounding. When studies were stratified by mean age, studies with a lower mean age (≤55 y) suggested a borderline inverse association (RR: 0.94; 95% CI: 0.89, 1.01), with the I^2 value decreasing from 72% to 38% (P = 0.2). In studies with an older mean age (>55 y), no association was found for milk (RR: 1.02; 95% CI: 0.96, 1.09; I^2 = 70%, P = 0.02), albeit the overall P value for effect modification by mean age was 0.8. Ding's spaghetti plot illustrates for each study (8 studies with categories of milk intake) the direction of the association between milk and all-cause mortality (*see* supplemental Figure 4 under "Supplemental data" in the online issue). Most studies show a flat (horizontal) line, which indicates no association with all-cause mortality.

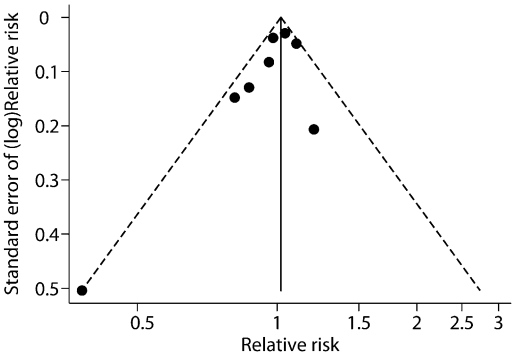

FIGURE 6. Funnel plot for studies of the association between milk intake and all-cause mortality to illustrate the presence of publication bias (n = 62,779; no. of cases = 23,949). Each dot indicates one study with its size and its relative risk (RR). The y axis contains the SEs of the log (RR). The smaller the SE, the larger the study. The RRs are plotted on the x axis. The lines are drawn around the dots to visualize how symmetrically the studies are divided around the true estimate; symmetry indicates no evidence of publication bias.

Assessment of publication bias

The funnel plot, as shown in **Figure 6**, shows reasonable symmetry and a nonsignificant Begg's test for publication bias (P = 0.11), which suggested no evidence of publication bias in studies of milk and all-cause mortality.

DISCUSSION

This meta-analysis indicates the challenges of summarizing data on food intake from published studies. Although 17 studies with data on dairy foods were identified, only 4 studies (representing only ≈5% of the total number of subjects) provided data on milk intake and risk of CVD in a manner that could be summarized statistically. A weak and marginally significant inverse association was seen between milk intake and total CVD, but no significant association was seen with risk of stroke or CHD. In 8 studies, risk of total mortality could be examined, and no association was observed with milk intake. Data on total dairy product and total high-fat and low-fat dairy product intakes did not indicate any association with incident CHD, but these results were based on very limited numbers of studies.

Strengths and limitations of the meta-analysis

Several issues warrant further discussion. We aimed at avoiding heterogeneity by including prospective cohort studies and stratifying by type of dairy product and disease outcomes. However, limited studies were available; therefore, splitting results into high- and low-fat dairy products was only possible for CHD. Heterogeneity was present for the all-cause mortality and stroke analyses, which were only partly explained in subgroup analyses. A significant association with a narrow CI between milk and CVD and not for stroke was found, even with a larger sample size in the stroke meta-analyses. This difference could be explained by the larger statistical heterogeneity in the underlying 6 studies with stroke outcomes than for the 4 studies with CVD outcomes, as evident by the result of the Higgins and Thompson test for heterogeneity, which was significant for stroke but not for CVD.

However, a notable strength of our methodology was the use of an advanced statistical approach for trend estimation of summarized dose-response data, which not only offers uniform analysis of different studies by different exposure categories and analysis of studies across different ranges of intake, but it also offers greater power using the full spectrum of continuous exposure data (35). A limitation of this meta-analysis regarding the exposure data are that each study expressed dairy consumption in different units (pints, frequency/wk, times/d, and servings/wk), and assumptions about what a serving is had to be made to convert values into g/d (or mL/d).

The results were consistent across studies with different degrees of adjustment for confounding; however, this did not rule out residual confounding (other aspects of diet) within each study, which still remained possible.

Although no publication bias was found for all-cause mortality, the power to detect publication bias was low given the limited number of studies. Finally, although we excluded some

studies on the basis of insufficient data (2, 12, 13, 19, 39–43) for reasons such as no range of intake for the exposures (dairy products and milk), the availability of only calcium data, no reported RR, or no CIs, all of these studies had indicated either no association or were similarly suggestive of an inverse association for CVD. Therefore, we would have expected similar findings and conclusions if we had included these studies.

Studies included in the meta-analysis

In the underlying studies, diet was measured with a validated food-frequency questionnaire, which was based on self reported intake. This might have caused misclassification of dairy intake, which could have weakened the associations. The advantage of food-frequency questionnaires is that food consumption of a past longer-term period is measured, which is relevant for chronic diseases (45). Diet was measured at the start of the studies. The participants might have changed their dairy product intake during the follow-up period, especially because many new dairy products (especially fermented dairy products) became available over the past decades. This would be interesting to address in future prospective cohort studies by using multiple exposure assessments over time.

Conclusions from this meta-analysis only apply to the small proportion of analyzable study populations included in this work, within milk intakes of ≈200–600 mL/d (*see* supplemental Table 2 under "Supplemental data" in the online issue). Moreover, the internal validity of the different studies included in the meta-analysis (eg, methodology and confounding factors) also determines the quality of the present meta-analysis. Therefore, we recommend to investigators of future prospective observational studies to carefully report on all information needed for a meta-analysis, such as the number of cases, exposure ranges, RR (95% CI), units in g/d, categories of different types of dairy products, and details on study population and confounders. Many of these shortcomings could be overcome by pooling the primary data from all available cohort studies (24). Ideally, a randomized clinical trial would demonstrate more clearly whether an association between milk and CVD or all-cause mortality exists. Several small trials showed no benefits of milk or dairy products on the metabolic syndrome (46) or blood pressure change (47, 48). In our opinion, evidence of a recommendation to increase milk consumption or to alter guidelines is rather weak because no CVD outcomes were studied, and no clear effects on CVD risk factors were found. Larger trials are needed with well-documented cardiovascular endpoints, although these may be impossible to conduct (concerning resources, long-term compliance, and separating effects of milk from diet).

Comparison of the presents results with those in the literature

A very recent publication by the Nurses' Health Study investigators (49) showed an inverse association between low-fat dairy product intake and CHD with 26 y of follow-up, but no association with high-fat dairy product intake. After updating our meta-analyses, our conclusions did not change. In more detail, we showed with these new data no significant associations between high-fat (RR: 1.05 per 200 g/d; 95% CI: 0.93, 1.19) and low-fat (RR: 1.01 per 200 g/d; 95% CI: 0.95, 1.08) dairy product intake and CHD.

The previously reported stronger inverse associations between milk and dairy product intake and CHD (RR: 0.92; 95% CI: 0.80, 0.99) and stroke (RR: 0.79; 95% CI: 0.68, 0.91) and all-cause mortality (RR: 0.87; 95% CI: 0.77, 0.98) in meta-analyses were not confirmed by our data (29, 30). In these meta-analyses, highest compared with lowest dairy exposure results were pooled, which is a more crude (less precise) method for meta-analyses than is our dose-response methodology. Lack of formal assessment of heterogeneity (assessed via statistical methods but also predefined by which studies should be included or excluded) and pooling together different exposures (calcium and milk) and combining outcomes may have led to the difference in results. Furthermore, 2 recent narrative reviews (31, 32) on the association between dairy product intake and CHD included 12 prospective cohort studies. Eight of the 12 studies were conducted during or before 1970, when almost only whole milk high in saturated fat was available, and they concluded that there was no clear evidence that dairy food consumption is related to a higher risk of CVD. In our meta-analyses, most of the studies measured diet during the 1980s (Table 1). It could be that whole-fat milk was mainly consumed in these studies because semi-skim products were introduced in the late 1980s, but specific information on this is lacking.

Possible underlying mechanisms

Several mechanisms may explain an inverse association between milk and CVD; the most plausible ones will be discussed. The weak and marginally significant inverse association that we found for dairy intake in relation to CVD may have been due to beneficial effects on blood pressure (25, 26). With the DASH diet, reductions in systolic blood pressure of $\geq$5 mm Hg were found compared with the control diet, ≈50% of which could possibly be ascribed to intake of low-fat dairy products (27). However, this effect on blood pressure is not supported by randomized trials that used consumption of low-fat dairy products as the intervention (47, 48). Guidelines do recommend healthy nutrition with consumption of low-fat dairy products to prevent CVD based on the DASH trial, but whether this effect on CVD is due to dairy product intake is not yet proven in our opinion (28).

Milk minerals, especially calcium and potassium, might be responsible for an antihypertensive effect (50, 51). A recent study also described dairy phosphorus as a major blood pressure–lowering mineral (52).

On the other hand, dairy products contain saturated fat that could affect the blood lipid profile and promote atherosclerosis and CVD. A recent meta-analysis of 21 prospective cohort studies showed that the harmful effects of saturated fat on CHD have become controversial (53); however, in our opinion, this is not true. It depends on what substitutions for saturated fat have taken place, because they have different effects on risk of CHD (54).

Associations between dairy products and other health outcomes

In 2007 the World Cancer Research Fund team conducted several systematic reviews on the relation between dairy products and cancer (34). They concluded that there was no association between milk and dairy products and cancers of, for example, the

lung, stomach, and breast. Higher consumption of milk and dairy products was suggested to increase the risk of prostate cancer (34, 55). On the contrary, there was also suggestive evidence of an inverse association between milk intake and colon cancer (56) and possibly bladder cancer. For other health outcomes such as Parkinson disease, dairy products may increase its risk (57). Furthermore, the risk of hip or bone fractures does not seem to be associated with higher consumption of dairy products (58, 59). In summary, evidence from the literature on other health outcomes does not really support strong recommendations of increasing intakes of milk and dairy products.

Overall, this study showed no association between milk and total mortality, but modest inverse associations with CVD. Milk and dairy products cannot be recommended to benefit CVD health outcomes on the basis of this dose-response meta-analysis. Intake of milk and dairy products does not seem to be harmful, but whether the association is truly inverse cannot be firmly concluded. Further studies are warranted to investigate the relation between consumption of dairy products and risk of CVD and to investigate different dairy components separately with sufficient follow-up to assess multiple health outcomes.

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The authors' responsibilities were as follows—SSS-M: statistical design, analysis of the data, and writing of the manuscript; ELD: statistical design, review of the data analysis, and writing of the manuscript; WKA-D, FBH, and WCW: contribution of data, interpretation of data, and writing of the manuscript; MFE: writing of the manuscript; and JMG: principal investigator of the meta-analysis dairy projects, funding, and writing of manuscript. All authors directly participated in the planning, execution, or analysis of the study and reviewed the manuscript. SSS-M and JMG obtained an unrestricted grant from the Dutch Dairy Association to carry out this study. None of the other authors had a conflict of interest. The sponsors were not involved in the conduct and writing of the manuscript.

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