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ORIGINAL CONTRIBUTION

Cheese consumption and risk of cardiovascular disease: a meta-analysis of prospective studies

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Abstract

Purpose Cheese contains a high content of saturated fatty acids but also lists of potentially beneficial nutrients. How long-term cheese consumption affects the development of cardiovascular disease (CVD) is unclear. A meta-analysis of prospective observational studies was conducted to evaluate the risks of total CVD, coronary heart disease (CHD), and stroke associated with cheese consumption.

Methods Potentially eligible studies were identified by searching PubMed and EMBASE databases and by carefully reviewing the bibliographies of retrieved publications and related reviews. The summary relative risks (RRs) with 95 % confidence intervals (CIs) were calculated using the random-effects model.

Results The final analyses included 15 prospective studies. Most of the studies excluded prevalent CVD at baseline (14/15) and had a duration >10 years (13/15). The summary RR for high vs. low cheese consumption was 0.90 (95 % CI 0.82–0.99) for total CVD (7 studies, 8076 events), 0.86 (95 % CI 0.77–0.96) for CHD (8 studies, 7631 events),

and 0.90 (95 % CI 0.84–0.97) for stroke (7 studies, 10,449 events), respectively. The restricted cubic model indicated evidence of nonlinear relationships between cheese consumption and risks of total CVD ($P_{nonlinearity} < 0.001$) and stroke ($P_{nonlinearity} = 0.015$), with the largest risk reductions observed at the consumption of approximately 40 g/d.

Conclusions This meta-analysis of prospective studies suggests a nonlinear inverse association between cheese consumption and risk of CVD.

Keywords Dairy · Cheese · Cardiovascular disease · Meta-analysis

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Introduction

Cheese is a widely consumed, easily digestible, and well-tolerated dairy product, with each person consuming 15.5 kg cheese per year (~42.5 g/d) in the USA and 17.9 kg in the Europe (~49.0 g/d) [1]. Cheese is a rich source of dietary calcium, with each 50 g of hard cheese containing approximately 360 mg of calcium [2]. For the purpose of maintaining bone health, cheese may be a good alternative of milk for individual who are lactose intolerant. On the other hand, cheese also contains a high content of saturated fatty acids (SFA) that could contribute to elevated low-density lipoprotein cholesterol (LDL-C), a well-defined risk factor for cardiovascular disease (CVD) [3]. Dietary guidelines recommend increasing intake of low-fat dairy and avoiding high-fat dairy products as parts of a balanced diet to prevent CVD [4, 5]. Despite large body of research conducted to evaluate the health effect of SFA, no definite conclusion of a deleterious effect has been drawn [6–10]. There has been evidence that SFA intake may affect health differentially by food sources [11–13], with reduced risks

of CVD and type 2 diabetes (T2D) by dairy SFA intake and increased risks by meat SFA intake [12, 13].

The potential cardiovascular effects of cheese have also received great attention over the past two decades, with considerable animal studies and human intervention trials investigating the effects of cheese on CVD risk factors [14–17], along with prospective observational studies that examined whether long-term cheese consumption affects the development of CVD [13, 18–31]. Currently, there are limited certainties achieved. Two recent meta-analyses [32, 33] reported inverse associations of cheese consumption with risks of coronary heart disease (CHD) and/or stroke. The summary relative risk (RR) was 0.84 (95 % confidence interval [CI] 0.71–1.00) for CHD in the analysis by Qin et al. [33] (seven cohorts), and the summary RR was 0.94 (95 % CI 0.89–1.00) for stroke in the one by Hu et al. [32] (six cohorts). However, since the amounts of cheese consumed varied substantially across different populations (e.g., individuals who were classified in the lowest category of cheese consumption in some studies [23, 26] may be classified as the highest category in others [19, 20, 28]), high vs. low analyses are less interpretable than dose–response analyses. A dose–response meta-analysis can provide a solution to the problem with distinct ranges of exposure in different studies and would better quantify the association. Furthermore, a number of other studies that evaluated the risk of CHD [20], stroke [22], or total CVD [13, 19, 30, 31] associated with cheese consumption were not included in the previous meta-analyses. In addition, potential nonlinear relationship between cheese consumption and risk of CVD remains to be determined. It is relevant to both scientific research and public to understand any threshold effects of cheese consumption on CVD development given the evidence that cheese consumption may be detrimental to certain diseases (e.g., prostate cancer and Parkinson's disease) [34, 35]. To fill these scientific gaps, a meta-analysis was carried out.

Materials and methods

Data search

This study was planned, conducted, and reported in adherence to the guidelines of the "Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group" [36]. A literature search was performed on PubMed (January 1, 1966–December 15, 2015) and EMBASE (January 1, 1980–December 30, 2015) databases using the search strategy as follows: (dairy OR cheese) and (cardiovascular OR heart disease OR myocardial infarction OR stroke) and (cohort OR prospective OR nested). Bibliographies in the retrieved full articles and previous meta-analyses [11, 32,

33, 37] as well as related reviews [17] were also carefully hand searched for additional studies. Attempts were also made to contact relevant authors for additional information [13, 30, 31].

Study selection

Studies that met the following criteria were considered: (1) The study design was prospective; (2) the exposure of interest was cheese consumption; (3) the outcome of interest was fatal/nonfatal CVD, CHD, or stroke; (4) RRs with corresponding 95 % CIs were reported or could be estimated. When multiple publications from the same study were available, the one with the most comprehensive data (e.g., reporting disease subtypes or providing data for dose–response analysis) was selected. We only considered prospective studies because they collected exposure information before the diagnosis of disease and were less prone to biases (e.g., recall and selection biases) than retrospective case-control studies.

Data extraction and quality assessment

Using a standardized data-collection form, the following data were extracted from each included study: the first author's last name, publication year, country of origin, study name, study duration, age and sex of participants, number of events and participants, categories of cheese consumption, the maximally adjusted RRs with 95 % CIs for each category of cheese consumption or for per unit increase in cheese consumption, prevalent diseases excluded at baseline, and variables accounted for in the statistical model. The study quality was evaluated using the 9-star Newcastle-Ottawa Scale (NOS) [38]. Literature selection, data extraction, and quality assessment were conducted independently by two authors (G-CC and L-QQ), with any disagreement resolved by consensus.

Statistical analysis

A DerSimonian and Laird random-effects model [39], which considers both within- and between-study variation, was assigned to calculate the summary risk estimates. Separate meta-analyses were conducted for the outcomes of overall CVD, CHD, and stroke across this study. Results reported by sex, CVD subgroup (CHD and stroke), or stroke subtype without an overall risk estimate were pooled with a fixed-effects model, and the combined estimates were included in the main analyses. First, we pooled estimates for the highest compared with lowest categories of cheese consumption. There were three studies [13, 30, 31] that reported results as per unit

increase in cheese consumption. Attempts were made to contact relevant authors for the risk estimates comparing extreme categories of cheese consumption, but no eligible responses were received. Thus, RRs reported in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort [31] (for cheese per 30 g/d) and the Multi-Ethnic Study of Atherosclerosis [13] (for cheese per 1 serving/d) were directly used in the high versus low analysis because the levels of consumption in the two studies were each comparable with the means of the upper cheese categories in another EPIC cohort [27] (per 30.2 g/d) or in other two US cohorts [20, 22] (1 serving/d). For the Dutch cohort of the Hoorn Study [30] that reported results as per 23 g/d of cheese consumption, we calculated new RRs with 95 % CIs for a 43-g/d increment, which approximates the means of the highest categories of two studies [21, 27] from the Netherlands. A number of subgroup analyses were conducted according to area, disease outcome (fatal, or fatal and nonfatal combined), sex, duration of follow-up, fat content of cheese, quality score, age, prevalent diseases excluded at baseline.

Subsequently, we conducted a dose–response analysis by use of the method proposed by Greenland and Longnecker [40] and Orsini et al. [41]. Accordingly, the number of cases and person-years and the risk estimates with their variance for at least three quantitative exposure categories were extracted. Most studies reported cheese in weight (g), and we converted the intake into g by using 43 g as a serving size for the studies that reported the consumption in frequency without providing a serving size [34, 42]. Afterward, we pooled study-specific risk estimates with the random-effects model. To be consistent with previous meta-analyses [34, 42] on cheese consumption, the results of linear dose–response in the forest plot were presented for a 50-g/d increment. We further examined a potential nonlinear relationship between cheese consumption and CVD risk by modeling exposure levels using restricted cubic splines with three knots at percentiles 10, 50, and 95 % of the distribution [43, 44]. A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero.

Heterogeneity test was performed using Q and I^2 statistics [45]. For the Q statistic, $P < 0.1$ was considered as statistically significant; and for the I^2 statistic, the following cutoff points were used: <30 % (little or no heterogeneity), 30–75 % (moderate heterogeneity), and >75 % (high heterogeneity). Potential publication bias was investigated using Begg's rank correlation test, Egger's linear regression test, and Begg's funnel plots [46, 47]. We also used the "trim-and-fill" method [48] to correct such a bias. All statistical analyses were performed using STATA software, version 11.0 (STATACorp, College Station, TX, USA).

Results

Study selection and characteristics

A flow chart of study selection is reported in Fig. 1. Briefly, a total of 377 independent citations were identified after duplicates exclusion, of which 27 were retrieved for more detailed reviews. Fourteen publications were excluded after carefully reading the full texts. Most of these reports were excluded because they studied total dairy without data on cheese consumption ($N = 6$), or cheese were included in specific diet patterns ($N = 6$). Further excluded were one publication [49] that was an overlapping report of another [27] with more comprehensive data for the dose–response analyses and one publication [50] where risk estimate cannot be extracted or calculated. Finally, 15 independent prospective studies that investigated the relationship between cheese consumption and risk of total and/or individual CVD were included in this meta-analysis.
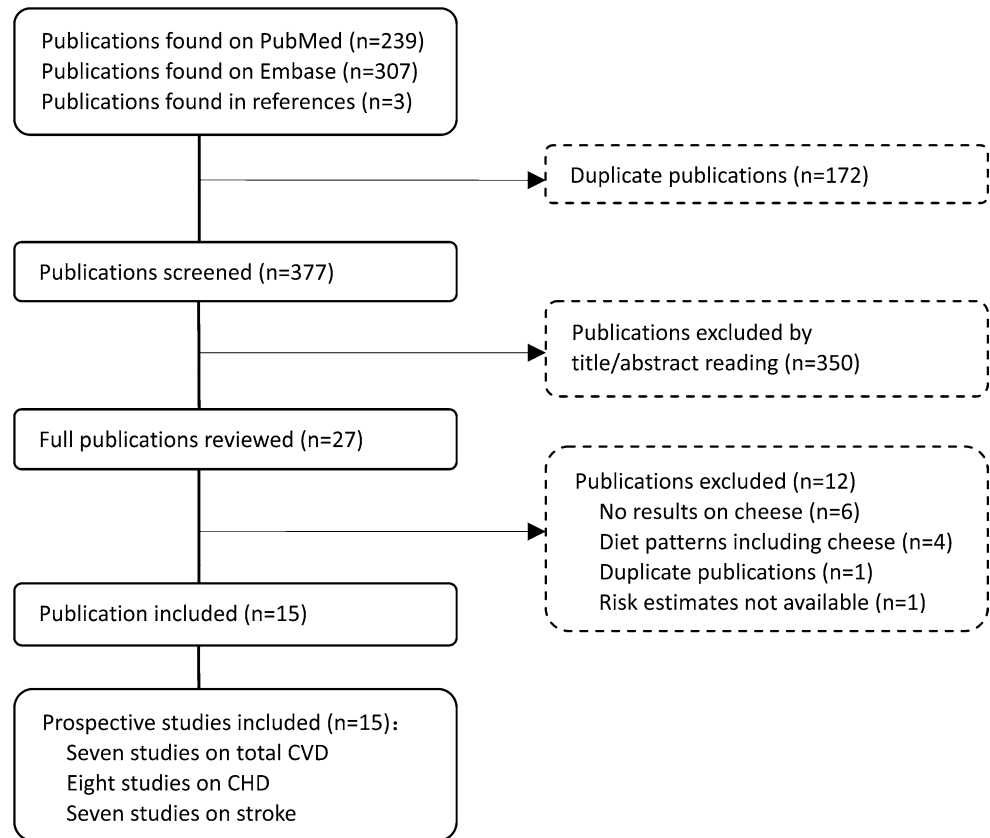
The characteristics of the included studies are summarized in Supplementary Table 1. The 15 studies were published between 1997 and 2015. The studies were largely from Europe ($N = 10$) or the USA ($N = 4$), with the exception of one [19] that was conducted in Australia. Most of the studies included both sexes, but two [22, 26] consisted of merely women and one [23] included entirely of male smokers. All but two studies [13, 31] had a follow-up duration of at least 10 years, and all except one study [19] excluded prevalent CVD at baseline, both of which contributed to the high scores of included studies. The details of quality assessment according to the 9-star NOC are presented in Supplementary Table 2. Eight of these studies were given scores of ≥8. Overall, there were seven studies [13, 19, 21, 27, 29–31] on overall CVD (8076 events), eight studies [18, 20, 21, 25–29] on CHD (7631 events), and seven studies (six publications [21–24, 27, 29] including one [24] that contained two independent cohorts) on stroke (10,449 events).

Main analysis

A meta-analysis of the included studies showed that the summary RR for the highest compared with lowest categories of cheese consumption was, respectively, 0.90 (95 % CI 0.82–0.99) for total CVD, 0.86 (95 % CI 0.77–0.96) for CHD, and 0.90 (95 % CI 0.84–0.97) for stroke, with little evidence of heterogeneity ($P_{heterogeneity}$ = 0.58, 0.31, and 0.42, respectively; and I^2 = 0, 14.9, and 0 %, respectively) (Fig. 2).

Subgroup and sensitivity analyses

Results of stratified analysis by various pre-specified study and population characteristics are shown in Table 1. Cheese consumption was inversely associated with CVD, CHD,

Fig. 1 Flow chart for study selection

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┌─────────────────────────────────────────┐
│ Publications found on PubMed (n=239)      │
│ Publications found on Embase (n=307)      │
│ Publications found in references (n=3)    │
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              │──────────────────►  ┌ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┐
              │                       Duplicate publications (n=172)
              │                     └ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘
┌─────────────────────────────────────────┐
│ Publications screened (n=377)             │
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              │                       Publications excluded by
              │                       title/abstract reading (n=350)
              │                     └ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘
┌─────────────────────────────────────────┐
│ Full publications reviewed (n=27)         │
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              │
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              │                       Publications excluded (n=12)
              │                         No results on cheese (n=6)
              │                         Diet patterns including cheese (n=4)
              │                         Duplicate publications (n=1)
              │                         Risk estimates not available (n=1)
              │                     └ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘
┌─────────────────────────────────────────┐
│ Publication included (n=15)               │
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              │
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│ Prospective studies included (n=15):      │
│    Seven studies on total CVD             │
│    Eight studies on CHD                   │
│    Seven studies on stroke                │
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and stroke in most of the subgroups. There was a suggestion that the observed cardiovascular benefits of cheese consumption may be sex-specific, with a significant inverse association in women but not in men. However, the differences between sexes were not statistically significant. Few studies reported findings by the fat content of cheese, and there was no indication of an adverse effect of high-fat cheese consumption on overall CVD risk (RR = 0.74, 95 % CI 0.44–1.24).

Dose–response analysis

Two studies [18, 22] were not eligible for this analysis because risk estimates for only two cheese categories were available. The dose-risk meta-analysis of the remaining studies showed that the summary RR for cheese consumption of 50 g/d was 0.92 (95 % CI 0.83–1.02) for total CVD, 0.90 (95 % CI 0.84–0.95) for CHD, and 0.94 (95 % CI 0.85–1.04) for stroke, respectively (Fig. 3). There was a somewhat U-shaped association between cheese consumption and risk of total CVD ($P_{\text{nonlinearity}} < 0.001$) (Fig. 4), with the largest reductions in risk observed at cheese consumption of approximately 40 g/d. Stratifying by disease subtypes, the nonlinearity was found for the association with stroke ($P_{\text{nonlinearity}} = 0.015$) but not with CHD ($P_{\text{nonlinearity}} = 0.427$) (Fig. 4).

Publication bias

Neither Begg's test nor Egger's test suggested publication bias with regard to CVD or stroke risk associated with cheese consumption (all P values > 0.10). In terms of CHD risk, Egger's test ($P = 0.04$) but not Begg's test ($P = 0.17$) suggested evidence of a publication bias. The asymmetry in the Begg's funnel plot (Fig. 5) indicates that smaller studies with null effects, which would be expected to locate at the lower right corner of the plot, may have been unpublished. Using "trim-and-fill" method to correct the bias, only the summary RR of CHD was slightly changed with three missing studies imputed (RR = 0.83, 95 % CI 0.73–0.94).

Discussion

In this large meta-analysis of 15 generally well-designed prospective studies, we found that high compared with low cheese consumption was significantly associated with 10–14 % lower risks of CVD and its subgroups. Furthermore, there was a somewhat U-shaped association between cheese consumption and overall CVD risk, with the largest risk reduction observed at cheese consumption of approximately 40 g/d. The lack of significance in the linear dose–response analyses of CVD or stroke in relation to cheese
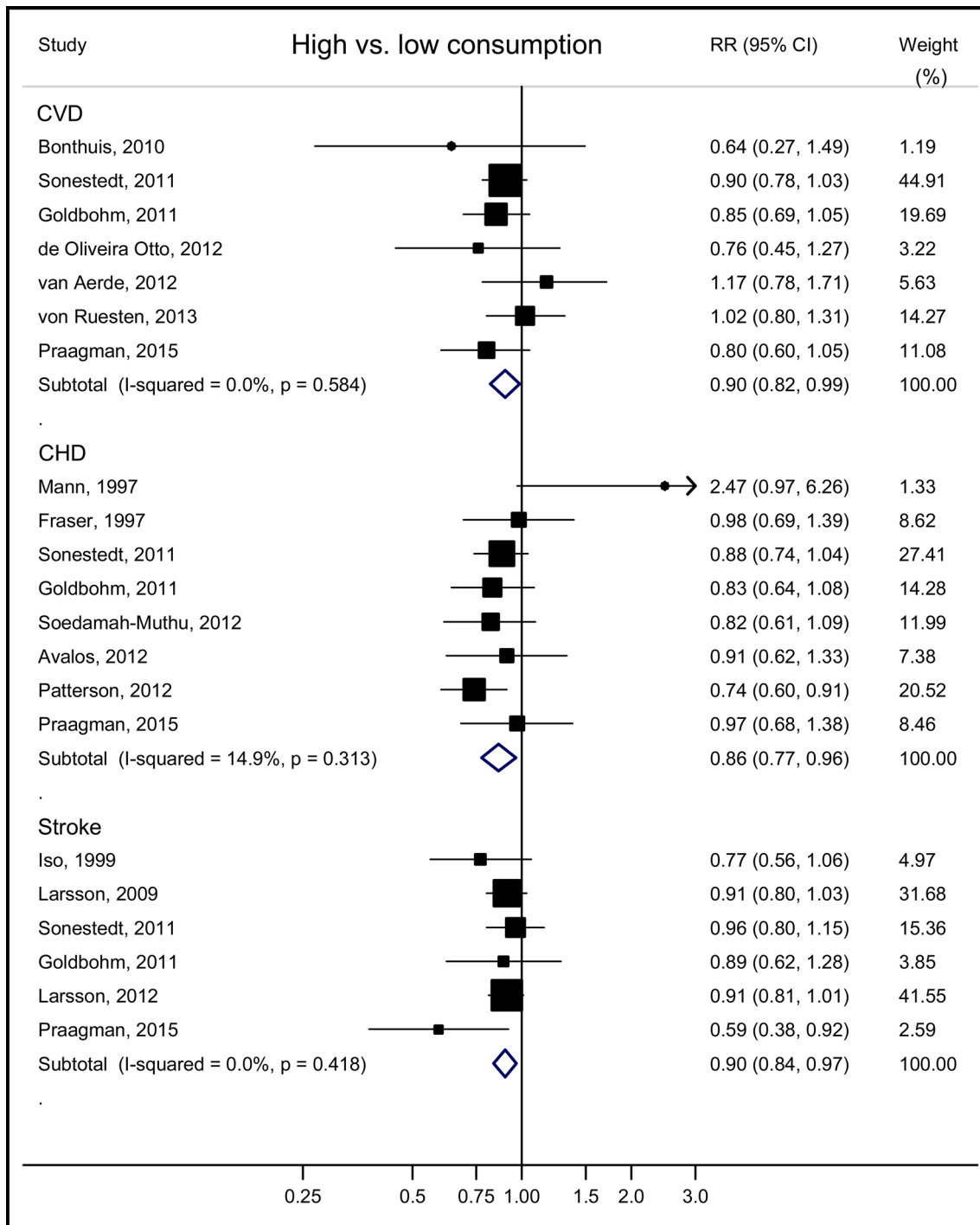
Fig. 2 Meta-analysis of highest compared with lowest cheese consumption and risk of cardiovascular disease (CVD), coronary heart disease (CHD), and stroke

consumption may be because the linear model does not fit well with the data covering a nonlinear trend.

Potential mechanisms whereby cheese may reduce CVD have been well discussed by Hjerpsted and Tholstrup [17]. Cheese is a good source of dietary vitamins, minerals, and protein, all of which may be of cardiovascular

protective properties. Interestingly, two recent meta-analyses of prospective studies reported a U-shaped association between dietary calcium and risk of CVD mortality [51] or risk of stroke [52], which are agreement with our results of a nonlinear relationship between cheese consumption and risk of CVD or stroke. Cheese is also rich in

Table 1 Summary relative risk of cardiovascular disease associated with cheese consumption (high vs. low)

		CVD (N = 8)					CHD (N = 8)					Stroke (N = 7)				
		N	RR (95 % CI)	P^a	I^2 (%)	P^b	N	RR (95 % CI)	P^a	I^2 (%)	P^b	N	RR (95 % CI)	P^a	I^2 (%)	P^b
Area	Europe	1	0.76 (0.45–1.28)	–	–	0.55	2	0.95 (0.73–1.23)	0.78	0	0.50	1	0.77 (0.56–1.06)	–	–	0.39
	USA	5	0.91 (0.83–1.00)	0.46	0		6	0.85 (0.74–0.98)	0.19	33.4		6	0.91 (0.84–0.98)	0.40	0.7	
Outcome	Fatal/nonfatal	4	0.87 (0.74–1.01)	0.38	2.5	0.59	4	0.83 (0.74–0.93)	0.60	0	0.33	5	0.91 (0.85–0.98)	0.71	0	0.27
	Fatal	3	0.92 (0.82–1.03)	0.53	0		4	0.97 (0.76–1.25)	0.17	40.9		2	0.74 (0.50–1.10)	0.16	49.7	
Sex	Men	1	0.95 (0.72–1.23)	–	–	Ref.	3	0.99 (0.76–1.28)	0.45	0	0.16	2	0.92 (0.82–1.04)	0.40	0	0.27
	Women	1	0.70 (0.49–1.00)	–	–	0.21	4	0.76 (0.65–0.90)	0.85	0		2	0.73 (0.55–0.97)	0.49	0	
Years of follow-up	≥10 years	5	0.89 (0.80–0.98)	0.53	0	0.52	8	0.86 (0.77–0.96)	0.31	14.9	–	7	0.90 (0.84–0.97)	0.42	0	–
	<10 years	2	0.97 (0.77–1.21)	0.32	0.8		0	–	–	–		0	–	–	–	
Fat content	High fat	3	0.74 (0.44–1.24)	0.05	67.6	0.58	1	0.83 (0.68–1.01)	–	–	0.66	0	–	–	–	–
	Low fat	1	1.00 (0.77–1.29)	–	–		2	1.13 (0.63–2.05)	0.001	90.5		0	–	–	–	
Quality score	≥8	5	0.89 (0.81–0.98)	0.68	0	0.41	5	0.83 (0.75–0.93)	0.67	0	0.21	5	0.90 (0.79–1.01)	0.26	25.4	0.85
	<8	2	0.98 (0.57–1.68)	0.21	36.8		2	1.08 (0.74–1.58)	0.15	48.0		2	0.89 (0.79–1.00)	0.34	0	
Mean/median baseline age	≥60 years	3	0.90 (0.73–1.11)	0.30	16.8	0.94	4	0.82 (0.71–0.94)	0.53	0	0.43	3	0.91 (0.82–1.01)	0.91	0	0.83
	<60 years	4	0.90 (0.81–1.01)	0.52	0		4	0.93 (0.75–1.14)	0.16	41.6		4	0.87 (0.75–1.00)	0.18	38.8	
Baseline diseases excluded																
CVD	Yes	6	0.90 (0.82–0.99)	0.54	0	0.45	8	0.86 (0.77–0.96)	0.31	14.9	–	7	0.90 (0.84–0.97)	0.42	0	–
	No	1	0.64 (0.27–1.50)	–	–		0	–	–	–		0	–	–	–	
Diabetes	Yes	3	0.92 (0.82–1.03)	0.53	0	0.59	3	0.89 (0.66–1.21)	0.03	70.8	0.66	1	0.96 (0.80–1.15)	–	–	0.50
	No	4	0.87 (0.74–1.01)	0.38	2.5		5	0.88 (0.77–1.02)	0.89	0		6	0.88 (0.81–0.96)	0.36	8.8	
Cancer	Yes	2	0.91 (0.72–1.16)	0.20	38.7	0.82	4	0.95 (0.71–1.29)	0.05	62.0	0.96	4	0.80 (0.64–1.01)	0.13	51.9	0.52
	No	5	0.89 (0.80–0.99)	0.56	0		4	0.86 (0.76–0.97)	0.96	0		3	0.92 (0.84–1.02)	0.88	0	

[a] P value for heterogeneity among studies

[b] P value for heterogeneity between subgroups by meta-regression analysis
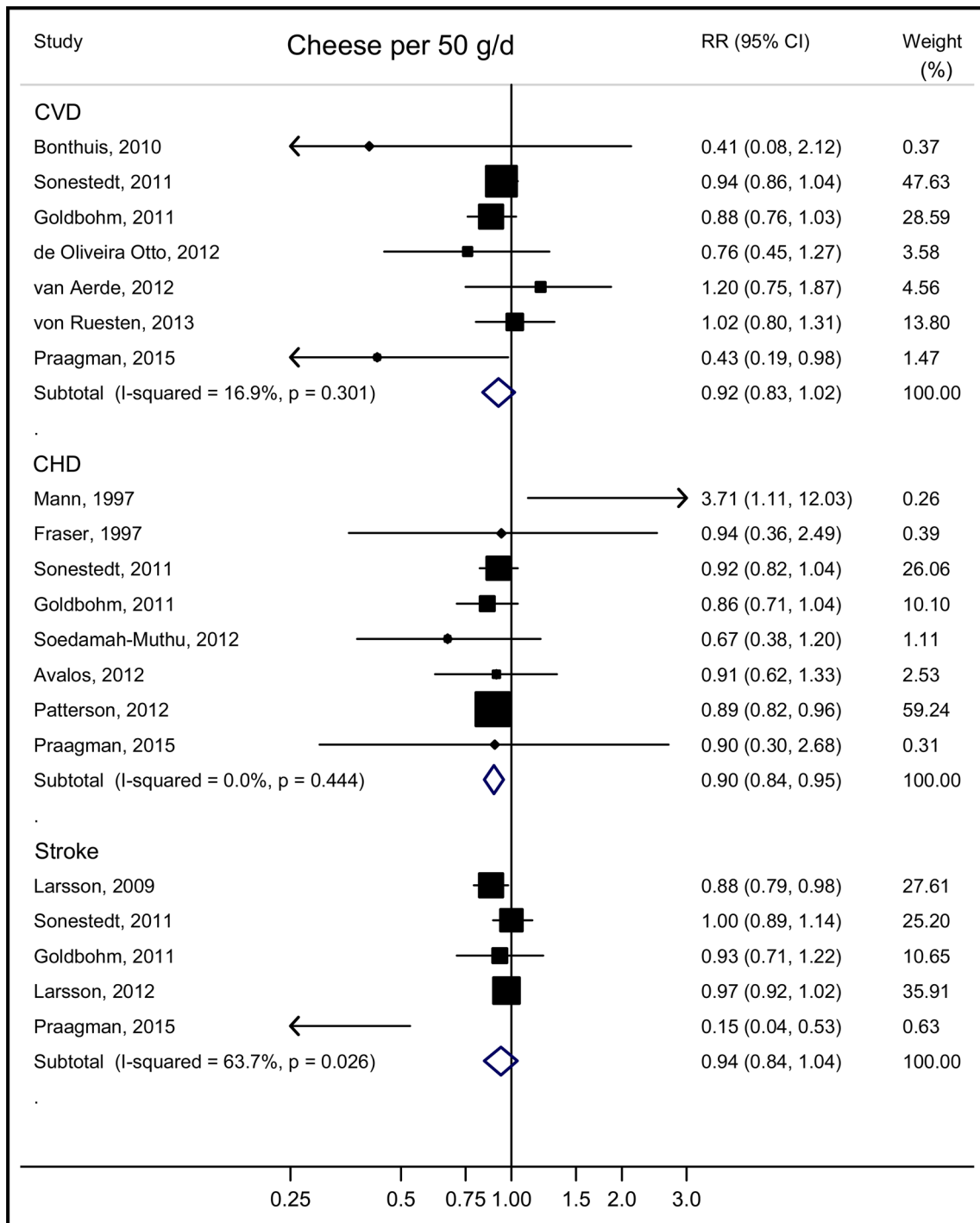
Fig. 3 Meta-analysis of cheese consumption of per 50 g/d and risk of cardiovascular disease (CVD), coronary heart disease (CHD), and stroke

conjugated linoleic acid, which has been suggested to prevent the progression of atherosclerosis in animal models [53] and decrease inflammatory response in human [54]. Clinical trials showed that cheese intervention increased high-density lipoprotein cholesterol (HDL-C) and/or reduced LDL-C [14, 16], and one of the contributors to

the improved lipid profile may be the probiotics (added or emerging during the fermentation process) in cheese [55, 56]. Evidence from prospective studies showed significant inverse associations between cheese consumption and risks of metabolic syndrome (MetS) [57] and T2D [42], and the association with T2D also appeared nonlinear,
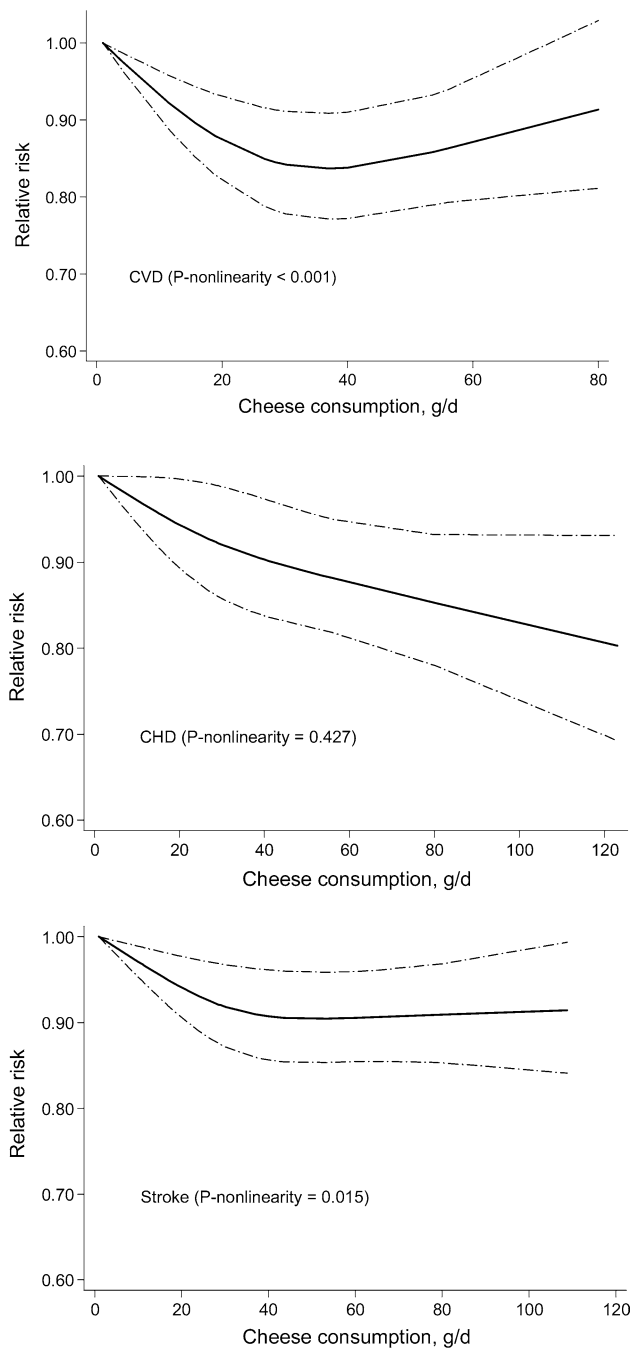
Fig. 4 Relative risk with 95 % confidence interval for the relationship between cheese consumption and risks of cardiovascular disease (CVD), coronary heart disease (CHD), and stroke in a restricted cubic spline random-effects meta-analysis
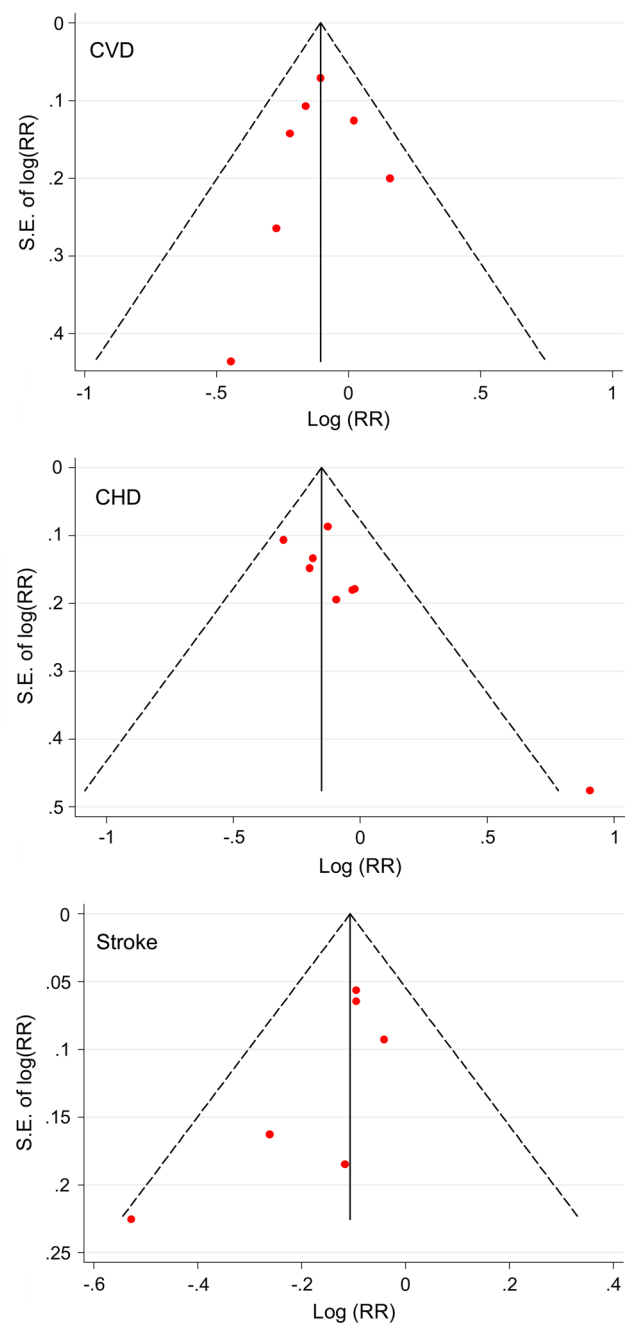
Fig. 5 Begg's funnel plot with pseudo 95 % confidence limits for the relative risks of cardiovascular disease (CVD), coronary heart disease (CHD), and stroke (highest compared with lowest cheese consumption)

with the largest risk reduction around cheese consumption of 50–60 g/d [42].

Low-fat dairy are considered more favorable than high-fat dairy in dietary guidelines [4, 5], mainly because of their lower content of SFA. However, the health effects of SFA intake remain uncertain. Recent meta-analyses of

long-term prospective studies showed neutral effects of SFA intake on risk of CVD or T2D [6, 7]. Conversely, more recent prospective findings reported increased risk of all-cause and/or case-specific mortality associated with SFA intake in a population at high risk for CVD [8], in nurses and health professionals [9], as well as in elderly women [10]. The source of SFA matters [11–13]. Prospective

evidence suggests decreased risk of CVD and T2D by dairy SFA intake and increased risks by meat SFA intake [12, 13]. In a recent randomized controlled trial [15] of 153 participants, high-fat cheese intervention of 8 weeks did not increase total cholesterol or LDL-C, but reduced triglycerides among subjects with MetS at baseline. We observed a nonsignificant inverse association of high-fat cheese consumption with overall CVD risk (RR = 0.74, 95 % CI 0.44–1.24). Taken together, there has been limited evidence of an adverse effect of high-fat dairy consumption on major health outcomes.

Our subgroup analysis indicated that the cardiovascular benefits of cheese consumption may be sex-specific, although the difference between sexes was not statistically significant, possibly due to the limited power by including a small number of studies. In a large-scale, cross-sectional survey of 10,872 US population (NHANES III) [58], higher HDL-C and lower LDL-C were observed in women with high cheese consumption (P_{trend} < 0.05) whereas men consuming higher cheese had higher adiposity measures, HDL-C and LDL-C, and diastolic blood pressure (P_{trend} < 0.05). In the Malmo Diet and Cancer study [29], a cohort of 26,445 Swedish men and women, high versus low cheese consumption was associated with reduced risk of CVD in women (RR = 0.82, P_{trend} = 0.03), but not in men (RR = 0.99, P_{trend} = 0.98). Houston et al. [58] discussed that the difference may be due to the fact that women consumed more low-fat cheese than men, whereas Sonestedt et al. [29] tended to ascribe the difference to the less accurate measurement of cheese consumption in men than in women. We considered additional explanations including: (1) Some residual or unmeasured confounders differentially associated with cheese consumption and/or CVD risk in men and women; and (2) hormonal, genetic, and metabolic factors may affect the biology of how cheese consumption affects CVD risk.

This meta-analysis presents several strengths. Apart from the prospective design of original studies and the large number of events involved in the analyses, most of the individual studies had a long duration and excluded various chronic diseases (e.g., diabetes and CVD) at baseline. However, several limitations of this study should also be acknowledged. First, as this meta-analysis was based on observational studies, the potential impacts of residual/unknown confounders on our results cannot be completely excluded despite that most included studies have considered a wide range of confounders. Second, some misclassification of exposure in original studies appeared inevitable due to the use of self-reported food frequency questionnaires and the single collection of diet information at baseline. Such misclassification would most likely to be nondifferential and attenuate the true association. Third, whether the effects of cheese consumption on CVD vary according to fat content was not well addressed due to the limited data available. Fourth, the included studies were mostly from Europe and the USA, which limits the generalizability of our findings to other populations. Finally, our findings may have been affected by publication bias that results from a tendency to publish larger studies or studies with positive results.

In summary, this meta-analysis of prospective studies suggests a nonlinear inverse association between cheese consumption and risk of CVD. Future large prospective studies, in particular those investigating sex- and cheese subtype-specific differences, are warranted.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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