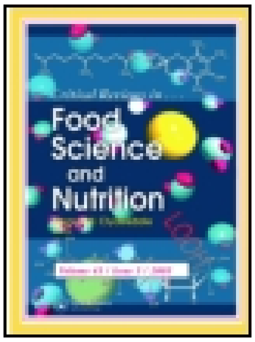

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REVIEW

Fermented dairy foods intake and risk of cardiovascular diseases: A meta-analysis of cohort studies

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ABSTRACT
Since the associations of fermented dairy foods intake with risk of cardiovascular diseases (CVD) remained inconsistent, we carried out this meta-analysis on all published cohort studies to estimate the overall effect. We searched the PubMed and CNKI (China National Knowledge Infrastructure) databases for all articles within a range of published years from 1980 to 2018 on the association between fermented dairy foods intake and CVD risk. Finally, 10 studies met the inclusion criteria for this study, with 385,122 participants, 1,392 Myocardial infarction, 4,490 coronary heart disease (CHD), 7,078 stroke, and 51,707 uncategorized CVD cases. Overall, statistical evidence of significantly decreased CVD risk was found to be associated with fermented dairy foods intake (OR = 0.83, 95% CI = 0.76–0.91). In subgroup analysis, cheese and yogurt consumptions were associated with decreased CVD risk (OR = 0.87, 95% CI = 0.80–0.94 for cheese and OR = 0.78, 95% CI = 0.67–0.89 for yogurt). Our meta-analysis indicated that fermented dairy foods intake was associated with decreased CVD risk.

KEYWORDS
Fermented dairy foods; probiotics; cardiovascular diseases; meta-analysis

Introduction

Cardiovascular diseases are the leading cause of death and morbidity worldwide (Benjamin et al. 2017), and diet plays a crucial role in the disease prevention and pathology (Badimon, Vilahur, and Padro 2010; Lordan et al. 2018). Fermented dairy foods are synonymous with fermentation process using microorganisms, which are microorganisms that are alive when they arrive to the gut and have the potential for therapeutic and preventative health benefits upon consumption by improving host intestinal microbiota (Zoumpopoulou et al. 2017). Diets including fermented dairy foods such as cheese and yogurt have a positive or neutral effect on CVD (Lordan et al. 2018; Tapsell 2015). It has recently been shown that the probiotics contained in fermented dairy foods may play an important role in risk of CVD through the formation of specific metabolites that may regulate in a direct or indirect way the formation of atherosclerotic plaques (Torres et al. 2015).

Besides the use of micro-organisms for fermentation, specific live bacteria, known as probiotics, have been used safely in foods and dairy products for over a hundred years (Aryana and Olson 2017). Recently, there has been increasing interest in their use to prevent, mitigate or treat specific diseases (Doron and Snydman 2015). A multitude of clinical trials have investigated the use of probiotics for diseases ranging from necrotizing colitis in premature infants to hypertension in adults (Bernardo et al. 2013; Khalesi et al. 2014). Because of their suggested, but debatable, role in health improvement, such as reduced risk of lowering of blood cholesterol levels (Praagman et al. 2015a). The associations of risk relating to CVD with fermented dairy foods intake have already been widely studied (Bonthuis et al. 2010; Goldbohm et al. 2011; Larsson, Virtamo, and Wolk 2012; Patterson et al. 2013; Praagman et al. 2015a, 2015b; Rogler and Rosano 2014; Soedamah-Muthu et al. 2013; Sonestedt et al. 2011). However, the results remained inconsistent.

In the present study, in order to detect the overall effects from a quantitative synthesis of the accumulated data from different studies to provide evidence on the association of fermented dairy foods intake with CVD risk. We carried out this meta-analysis on published cohort studies to estimate the overall CVD risk of fermented dairy foods intake and to quantify heterogeneity between the individual studies as well as to investigate the existence of potential publication bias.

Methods

Publication search and inclusion criteria

We searched the PubMed and CNKI (China National Knowledge Infrastructure) databases for all articles within a range of published years from 1980 to 2018 on the association between fermented dairy foods intake and cardiovascular diseases risk (last search was update 2 September, 2018). The following terms were used in this search: 'fermented food or cheese or fermented milk or cultured milk or yogurt or lactic acid bacteria' and 'coronary heart

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/bfsn.
*These authors contributed equally to this work.

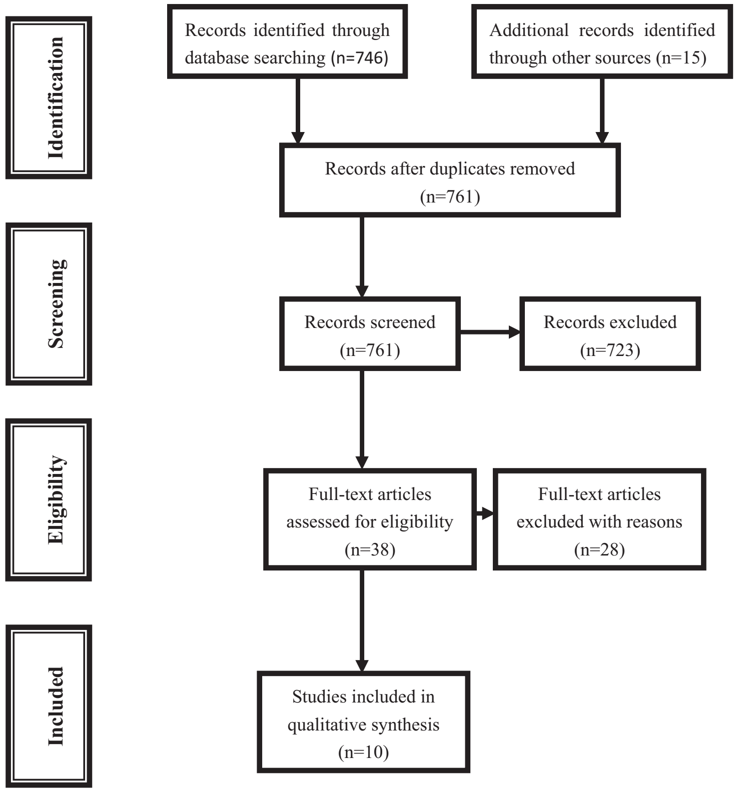

Figure 1. Flowchart for identification of studies.

disease (CHD) or cardiovascular disease (CVD) or angina or myocardial infarction or stroke or cerebral ischemia'. In order to identify the relevant publications, the references cited in the research papers were also scanned. Combining searches resulted in 746 abstracts (Figure 1). An additional 15 studies were identified through review articles and meta-analysis, for a total of 761 studies.

We evaluated the eligible studies if all the following conditions were met: (1) evaluation of the association of yogurt or cheese consumption and cardiovascular disease risk; (2) diet was generally assessed by food frequency questionnaire; (3) inclusion of sufficient data or the data can be acquired from the manuscript or supplementary materials to calculate ORs and 95% CIs; (4) the publication was a cohort study; and (5) the study was published in English.

Data extraction

Two authors (Kui Zhang and Xiao-gang Chen) independently reviewed and extracted the data needed. Disagreements were resolved through discussion among the authors to achieve a consensus. Publications were read by Kui Zhang in order to check original data extraction. The following information was recorded for each study: first author, year of publication, region, follow-up period, disease type, dairy type, sex, dietary assessment, number of cases, number of controls (all of the data are shown in Table 1).

Statistical analysis

The odds ratio (OR) corresponding to the 95% confidence interval (95% CI) was used to assess the association between fermented dairy foods intake and cardiovascular diseases risk. In addition to the comparison among all subjects, we also performed stratified analyses to assess the association between cheese and yogurt intake and cardiovascular diseases risk.

The statistical heterogeneity among studies was assessed with the Q-test and I^2 statistics (Higgins and Thompson 2002). If no obvious heterogeneity, the fixed-effects model (the Mantel-Haenszel method) was used to estimate the summary OR (Mantel and Haenszel 1959); otherwise, the random-effects model (the DerSimonian and Laird method) was used (DerSimonian and Laird 1986). Finally, random effects models were used to calculate the overall OR estimates and 95% CIs comparing the consumption versus never intake of fermented dairy foods. To explore sources of heterogeneity across studies, we did logistic meta-regression analyses. We examined the following study characteristics: publication year, region, follow-up period, disease type, and dairy type, number of cases, number of controls, morbidity of cases, and morbidity of controls. Publication bias was evaluated with funnel plot and Begg's rank correlation method (Begg and Mazumdar 1994). The statistical analyses were performed by STATA 12.0 software (Stata Corp., College Station, TX).

Results

Characteristics of studies

Out of a total of 761 abstracts were screened, 38 were retrieved for more detailed evaluation. Of the 28 excluded studies, 11 papers were reviews, 2 papers had nothing on

Table 1. Characteristics of literatures included in the meta-analysis.

Reference	Region	Outcome	Follow up time (year)	Disease	Dairy type	Sex	No. of cases	No. of subjects
Patterson et al. (2013)	Sweden	Incidence	11.6	Myocardial infarction	Yogurt/Cheese	Women	1,392	33,636
Soedamah-Muthu et al. (2013)	UK	Mortality	10.8	CHD	Yogurt/Cheese	Both	323	4,255
Goldbohm et al. (2011)	Netherlands	Mortality	10	Cardiovascular disease	Cheese	Both	48,399	129,763
Bonthuis et al. (2010)	Australia	Mortality	14.4	Cardiovascular disease	Yogurt	Both	61	1,529
Larsson, Virtamo, and Wolk (2012)	Sweden	Incidence	10.2	Stroke	Yogurt/Cheese	Both	4,089	74,961
Sonestedt et al. (2011)	Sweden	Incidence	12	Cardiovascular disease	Yogurt/Cheese	Both	2,520	26,445
Praagman et al. (2015b)	Netherlands	Incidence	17.3	Stroke	Yogurt/Cheese	Both	564	4,235
Praagman et al. (2015b)	Netherlands	Incidence	17.3	CHD	Yogurt/Cheese	Both	567	4,235
Avalos et al. (2013)	USA	Incidence	16.2	CHD	Yogurt/Cheese	Both	451	1,759
Buendia et al. (2018)	USA	Incidence	38/32	CHD	Yogurt	Both	2,896	74,130
Buendia et al. (2018)	USA	Incidence	38/32	Stroke	Yogurt	Both	2,266	74,130
Praagman et al. (2015a)	Netherlands	Mortality	15	Cardiovascular disease	Yogurt/Cheese	Both	727	34,409

CHD, coronary heart disease.

Table 2. Associations between fermented dairy foods and risk of cardiovascular diseases.

	All				Cheese				Yogurt			
	N[a]	Case/control	OR (95%CI)	P^b	N[a]	Case/control	OR (95%CI)	P^b	N[a]	Case/control	OR (95%CI)	P^b
Overall	19	61,989/385,122	**0.83 (0.76–0.91)**	<0.001	8	58,305/279,289	**0.87 (0.80–0.94)**	<0.001	10	15,129/299,315	**0.78 (0.67–0.89)**	<0.001
Incidence	14	14,745/215,166	**0.80 (0.72–0.89)**	<0.001								
Mortality	5	49,410/169,956	0.94 (0.80–1.11)	0.010								
Myocardial infarction	2	1,392/33,636	**0.82 (0.76–0.89)**	0.409								
Stroke	6	4,490/118,788	0.87 (0.75–1.01)	<0.001								
CHD	8	7,078/187,735	0.85 (0.67–1.08)	<0.001								
Uncategorized cardiovascular disease	5	51,707/192,146	**0.79 (0.66–0.96)**	<0.001								

[a]Number of comparisons.
[b]P value of Q-test for heterogeneity test.
Boldfaced values indicate a significant difference at the 5% level.

fermented dairy foods, 4 papers lacked control populations, and 1 paper is case-control study (shown in Figure 1). Finally, 10 cohort studies met the inclusion criteria for this study (Avalos et al. 2013; Bonthuis et al. 2010; Buendia et al. 2018; Goldbohm et al. 2011; Larsson, Virtamo, and Wolk 2012; Patterson et al. 2013; Praagman et al. 2015a, 2015b; Soedamah-Muthu et al. 2013; Sonestedt et al. 2011), with 385,122 participants, 1,392 Myocardial infarction, 4,490 coronary heart disease, 7,078 stroke, and 51,707 uncategorized cardiovascular disease cases. The details of including first author, year of publication, region, follow-up period, disease type, dairy type, sex, dietary assessment, number of cases, number of controls in the selected studies were listed in table 1.

Quantitative synthesis

The evaluation of fermented dairy foods intake and CVD risk was shown in Table 2 and Figure 2. Overall, there was statistical evidence of significantly decreased CVD risk was found to be associated with fermented dairy foods intake (OR = 0.83, 95% CI = 0.76–0.91), especially with the incidence of CVD (OR = 0.80, 95% CI = 0.72–0.89). In subgroup analysis, cheese and yogurt consumptions were significantly associated with decreased CVD risk (OR = 0.87, 95% CI = 0.80–0.94 for cheese and OR = 0.78, 95% CI = 0.67–0.89 for yogurt). As shown in Table 2, in terms of subgroup analyses by disease type, fermented dairy foods intake was significantly with decreased myocardial infarction, and uncategorized CVD risk (OR = 0.82, 95% CI = 0.76–0.89 for myocardial infarction, and OR = 0.79, 95% CI = 0.66–0.96 for uncategorized CVD) .

Evaluation of heterogeneity

There was heterogeneity among studies in overall comparisons ($P_{heterogeneity} < 0.001$, $I^2 = 94.0\%$, $Tau^2 = 0.0345$). To explore sources of heterogeneity across studies, we assessed publication year, region, follow-up period, disease type, and dairy type, number of cases, number of controls, morbidity of cases, and morbidity of controls. Finally, logistic meta-regression analyses revealed that morbidity of cases and morbidity of controls could substantially influence the initial heterogeneity.

Sensitivity analysis

The influence of a single study on the overall meta-analysis estimate was investigated by omitting one study at a time, and the omission of any study made no significant difference, indicating that our results were statistically reliable.

Publication bias

The Begg's test was performed to evaluate the publication bias of selected literatures. Figure 3 displays a funnel plot that examined the fermented dairy foods and cardiovascular diseases risk included in the meta-analysis. No evidence of publication bias in our study was observed ($P = 0.484$).

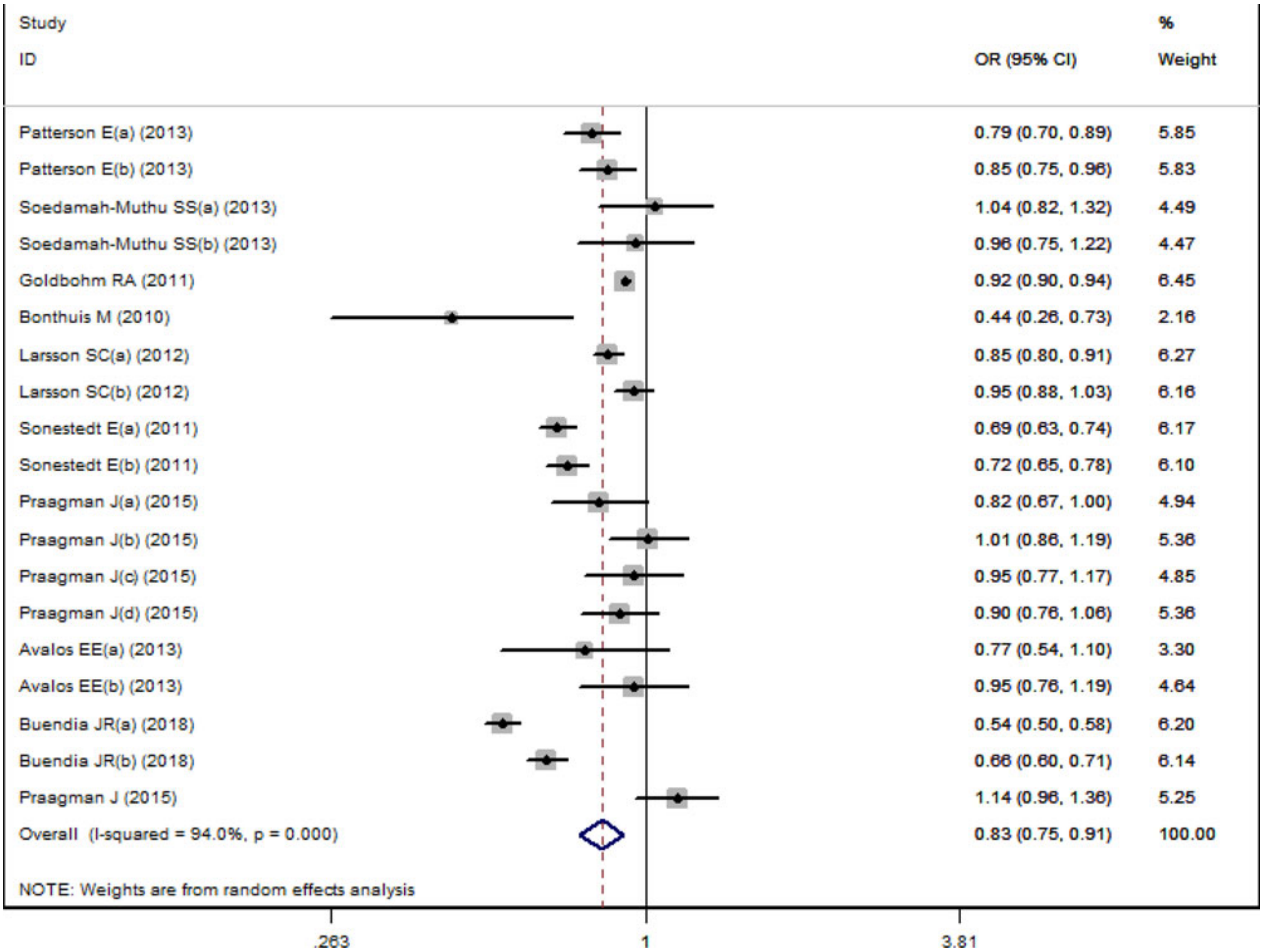

Figure 2. Forest plot of cardiovascular diseases risk associated with fermented dairy foods.

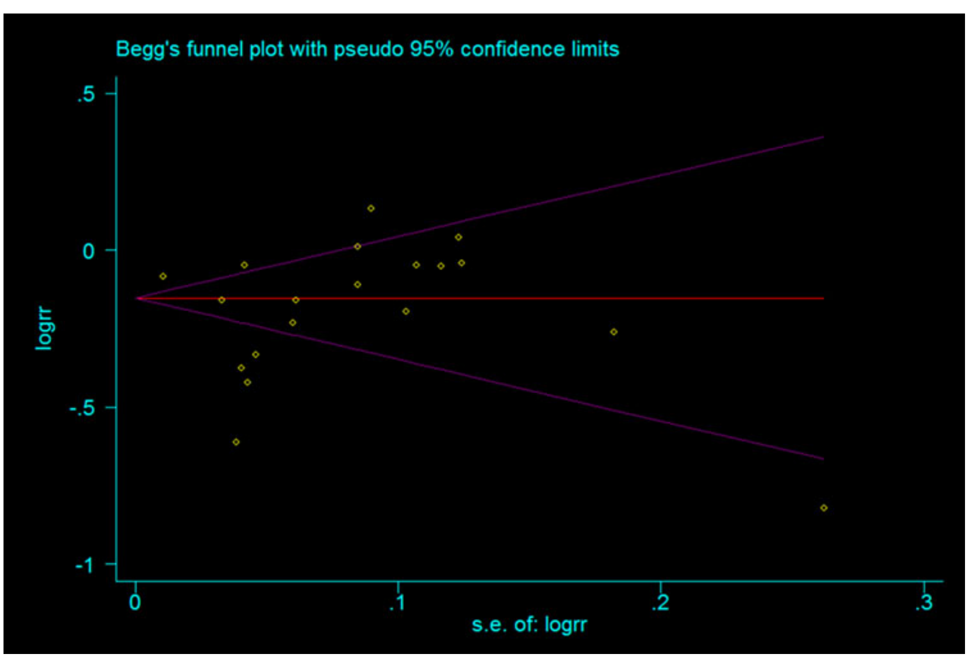

Figure 3. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. s.e., standardized effect.

Discussion

In the present study, we carried out this meta-analysis on 10 published cohort studies with 385,122 participants to estimate the overall CVD risk of fermented dairy foods. Overall, statistical evidence of significantly decreased CVD risk was found to be significantly associated with fermented dairy foods intake (OR = 0.83, 95% CI = 0.76–0.91), especially with the incidence of CVD (OR = 0.80, 95% CI = 0.72–0.89). In subgroup analysis, cheese and yogurt consumptions were also significantly associated with decreased CVD risk (OR = 0.87, 95% CI = 0.80–0.94 for cheese and OR = 0. 78, 95% CI = 0.67–0.89 for yogurt). As shown in Table 2, in terms of subgroup analyses by disease type, fermented dairy foods intake was significantly associated with decreased myocardial infarction, and uncategorized CVD risk (OR = 0.82, 95% CI = 0.76–0.89 for myocardial infarction, and OR = 0.79, 95% CI = 0.66–0.96 for uncategorized CVD). Previous meta-analysis suggested neutral associations of total, high and low-fat dairy, milk and yogurt with risk of CHD and CVD. In addition, a possible role of fermented dairy was found in CVD prevention, but the result was driven by a single study (Guo et al. 2017). Another meta-analysis assessed the association of non-fermented and fermented milk consumption with mortality of CVD, and they observed no consistent association between milk consumption and the cause or cause-specific mortality (Larsson et al. 2015).

Fermented dairy foods is known to be a nutrient-rich food and a source of probiotic bacteria (Buendia et al. 2018). Firstly, fermented dairy products are an important source of calcium in a westernized diet. Calcium is suggested to decreased cell proliferation induced either by cell differentiation or by binding of toxic bile acids and free fatty acids (Kampman et al. 1994). Furthermore, the protein content and composition of yogurt has been suggested to contribute to appetite control by inducing gastrointestinal hormone secretion, resulting in increased satiety, suppressed short-term food intake, and diet induced thermogenesis (Akhavan et al. 2010; Akhavan et al. 2014). Moreover, whey protein in yogurt is quickly digested, leading to a rapid rise in plasma amino acid concentrations (Boirie et al. 1997), and have a physiologic effect on satiety or blood glucose regulation (Mortensen et al. 2012). Fermented dairy foods are content with probiotics, which are alive when they arrive to the gut (Zoumpopoulou et al. 2017). Probiotics are amongst the most common microbes in the gastro-intestinal tract of humans and other animals. Prominent among probiotics are *Lactobacillus* and *Bifidobacterium*. They offer wide-ranging health promoting benefits to the host which include reduction in pathological alterations, stimulation of mucosal immunity and interaction with mediators of inflammation among others (Vinusha et al. 2018). The results from two trials have shown that conventional fermented foods intake may enhance the immune system (Elmadfa, Klein, and Meyer 2010; Olivares et al. 2006). The intestinal microbiota has a profound influence on mucosa barrier functions and on the nutritional and metabolic status of its 'host'. Certain bacterial families such as *Firmicutes* contribute to a higher uptake of short-chain fatty acids. In addition, a impaired intestinal epithelial barrier function allows bacterial products such as lipopolysaccharide, bacterial DNA (CpG motifs), or peptidoglycans to enter the circulation. Furthermore, the microbiota can directly influence the cytokine production of epithelial cells and innate immune cells. Those mediators also enter the circulation and recognized by specific receptors on or in endothelial cells, macrophages, or SMCs of the arterial wall to induce endothelial damage, foam cell formation, and SMC proliferations, which are features of CVD (Rogler and Rosano 2014).

A few limitations of our study should be considered. Although we did not observe significant publication bias, publication bias is possible in any meta-analysis. Moreover, original data were required to calculate ORs and 95% CIs, which may omit some valuable studies and ignore potential adjusted risk factors. Finally, due to the lack of unified cut-off value for the fermented dairy foods consumption in the enrolled studies, we only compared the consumption status versus never intake of fermented dairy foods.

In conclusion, our meta-analysis indicated that fermented dairy foods intake were associated with decreased CVD risk. Moreover, further studies estimating the functional effect and side effects may eventually provide a better, comprehensive understanding.

Conflicts of interest statement

No conflicts of interests to declare.

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