Original Article

Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies

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Background: Epidemiological studies to-date provided inconsistent findings on the effects of dairy consumption on the risk of cardiovascular disease (CVD). We aimed to examine the association of dairy consumption and its specific subtypes with CVD risk, including the risk of stroke and coronary heart disease (CHD) by a meta-analysis. **Methods**: PubMed, EMBASE, and Cochrane Library databases were searched for articles published up to February 2014 to identify prospective cohort studies. Random-effects model or fix-effects model was used to compute the summary risk estimates. **Results**: A total of 22 studies were eligible for analysis. An inverse association was found between dairy consumption and overall risk of CVD [9 studies; relative risk (RR)=0.88, 95% confidence interval (CI): 0.81, 0.96] and stroke (12 studies; RR=0.87, 95% CI: 0.77, 0.99). However, no association was established between dairy consumption and CHD risk (12 studies; RR=0.94, 95% CI: 0.82, 1.07). Stroke risk was significantly reduced by consumption of low-fat dairy (6 studies; RR=0.93, 95% CI: 0.88, 0.99) and cheese (4 studies; RR=0.91, 95% CI: 0.84, 0.98), and CHD risk was significantly lowered by cheese consumption (7 studies; RR=0.84, 95% CI: 0.71, 1.00). Restricting studies according to various inclusion criteria yielded similar results for CVD and CHD analyses, but showed attenuated results for stroke analysis. Heterogeneity across studies was found for stroke and CHD analyses, and publication bias was found for stroke analysis. **Conclusion**: This meta-analysis provided further evidence supporting the beneficial effect of dairy consumption on CVD. Low-fat dairy products and cheese may protect against stroke or CHD incidence.

Key Words: dairy, cardiovascular disease, stroke, coronary heart disease, meta-analysis

INTRODUCTION

Cardiovascular disease (CVD) remains the major cause of morbidity and mortality worldwide, thereby imposing a large burden on public health. The World Health Organization (WHO) reported that 17.3 million individuals (approximately 30% of global death) died from CVD in 2008, in which 7.3 million and 6.2 million deaths were due to coronary heart disease (CHD) and stroke, the two major subclasses of CVD, respectively.[1] Established behavioural risk factors for CVD include unhealthy diet, physical inactivity, harmful alcohol consumption, and tobacco use.[2] Dairy foods are a part of dietary guidelines in many developed and developing countries. The Chinese balanced dietary pagoda recommends the consumption of 300 g of milk and dairy products per day for adults.[3] However, epidemiological studies investigating the link between dairy products and CVD risk have reported inconclusive results. A previous meta-analysis reported a weak and marginally significant inverse association between milk consumption and total CVD, but not with either stroke or CHD. Limited evidence (4, 6, and 6 studies for CVD, stroke, and CHD, respectively) was available at that time, and specific dairy foods were difficult to examine.[4] The different types of dairy products should be considered because varying nutrient compositions in such products may have different effects on CVD risk. Since then, emerging prospective cohort studies have provided an excellent opportunity to update and extend previous analyses.[5-17] The aim of this study was to perform a meta-analysis of prospective cohort studies to assess the extent of the association between the consumption of dairy products, including specific dairy subtypes, and the risk of CVD and its major subclasses, such as stroke and CHD.

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METHODS

Literature search

This meta-analysis was reported in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines.[18] A systematic literature search was conducted in PubMed, Web of Science, and Cochrane Library databases up to February 2014. Search terms included dairy, milk, yoghurt, cheese and butter in combination with cardiovascular, stroke and CHD, with no restrictions. The reference lists of retrieved articles were also reviewed. Authors of the original studies were not contacted for additional information.

Study selection

Studies were included in this meta-analysis if the following criteria were satisfied: 1) the design was of a prospective cohort study; 2) the participants were adults (≥18 years old); 3) the participants were exposed to dairy products and other dairy item, e.g., low- and high-fat dairy products, yogurt, cheese, and butter; 4) the endpoint of interest was CVD (fatal and/or non-fatal), or individual stroke and CHD; and 5) relative risk (RR), and hazard ratio (HR), and their corresponding 95% confidence interval (CI) for the highest category vs the lowest categories were reported. A study that reported RR/HR as a continuous variable (for example, per SD increase) was excluded. We selected the report with the largest population size for multiple studies that used the same population. Communication letters, abstracts, and posters of conferences, which were generally published without peer-review, were excluded.

Data extraction and quality assessment

The following data were extracted from the selected papers by using a standardized data-collection form: the name of the first author; publication year; location of the study; gender; follow-up duration; population characteristics and size; case number; adjustments; and risk estimates with 95% CI. Each study had a different definition for milk and dairy products. Thus, we used dairy products as the main exposure to represent both milk and dairy products in the meta-analysis. Whole milk, yogurt, cheese, butter, low-fat or high-fat dairy products, and other single subtypes were not considered as dairy products termed in this analysis. However, the combined RR was calculated for subtypes that were independently observed in more than three studies. Because fat content in dairy products was a factor of interest, low/non-fat milk and whole milk were considered as low- and high-fat dairy products, respectively. Ischemic heart disease and myocardial infarction were classified as CHD, and cerebrovascular disease was considered as stroke. If disease subclasses (e.g., cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage for stroke) were reported, such subclasses would then be combined in advance.

We assessed the quality of individual studies by reporting the key components of the study designs instead of providing aggregate scores.[18] The characteristics of the study populations, assessments of exposure, and control for potential confounding factors were used as quality parameters. Two authors independently conducted literature search, study selection, and data extraction. Any disagreements were resolved by discussion.

Statistical analyses

RR was used as the common measure of association across studies, and HR was directly considered as RR. Homogeneity of effect size across studies was tested by Q statistic at $p<0.10$ level of significance. We also calculated the I^2 statistic, a quantitative measure of inconsistency across studies.[19] In case of significant heterogeneity, the random-effects model was used to calculate the pooled effect size; otherwise, fixed-effects model was applied.[20]

Pre-specified subgroup analyses were planned, but not performed because of the following reasons: 1) a limited number of studies reported the association of gender with the results of exposure and outcome; 2) most studies were conducted in Western countries (particularly in Europe); and 3) the length of follow-up was variably expressed across the studies as the mean or the entire length. However, we conducted a sensitivity analysis according to various inclusion criteria to examine the robustness of the combined risk estimates. We also investigated the impact of a single study on the overall risk estimate by omitting one study in turn.

Potential publication bias was assessed by Begg's funnel plots and Egger's regression test.[21] All of the analyses were performed using STATA version 11.0 (StataCorp, College Station, TX, USA). $p<0.05$ was considered statistically significant, except when otherwise specified.

RESULTS

Literature search

We initially identified 861 potential studies; the majority were excluded because they were not prospective studies or because the exposure or endpoint was not relevant to our analysis. After assessing the full text of the 33 remaining articles, we yielded 22 eligible studies.[5-17,22-30] The main reasons for exclusion were as follows: participants were less than 18 years old; the exposure of interest was calcium, fat, or protein from dairy; and dairy consumption was expressed as a continuous variable, but not as a category of intake. The study of Dalmeijer et al was excluded because of the reporting of continuous variables, except for the association between dairy and CHD.[6] He et al[31] and Hu et al[32] reported the incidence of stroke in the Nurses' Health Study (NHS). However, their studies were excluded because they duplicated the results of Bernstein et al (2012).[12] The study by Bernstein et al (2010) was retained because the incidence of CHD was used as the outcome.[17] The flow of the literature search is presented in Figure 1.

Study characteristics

The characteristics of the selected prospective cohort studies are presented in Table 1. The studies were published between 1997 and 2013. Among the included studies, 10 were conducted in Europe, 5 in the USA, 4 in Japan, 2 in Australia, and 1 in Taiwan. The length of follow-up ranged from 8 years to 26 years, and cohort size ranged from 1,529 to 127,160 subjects. Fifteen studies enrolled men and women. Four studies separated the results by gender,[5,7,13,15] whereas 3 studies included men only,[23,25,27] and 4 studies included women only.[10,17,24,28]

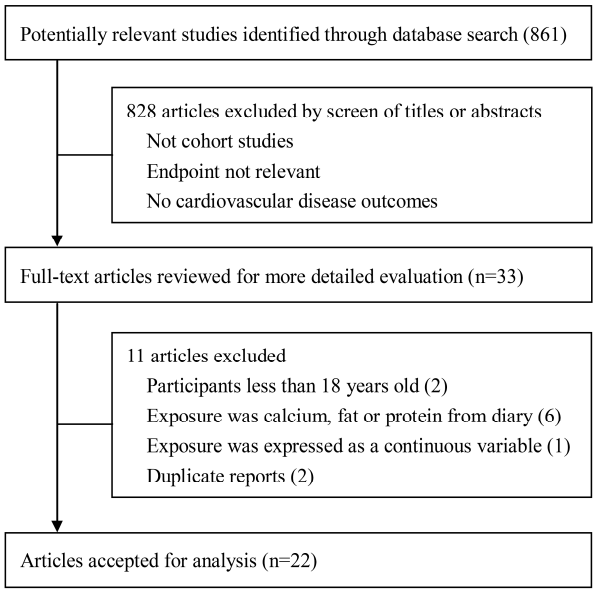

Figure 1. Flow chart of study selection

The studies that reported the results by gender were dispersed across different exposures. All studies claimed a population- or community-based design, but some of these studies limited the population to a certain characteristic or occupation. Among 22 studies, 20 measured the dietary intake by using a validated food-frequency questionnaire (FFQ). The intake amount was differently classified among studies. Tertile classification was used in nine studies and quintle classification was used in seven studies. The intake amount was expressed in gram, duration, portion, or serving. In Larson's study (2009), which was conducted in Sweden, the highest quintle for dairy intake was as high as 1,296 g/d, whereas in Kondo study conducted in Japan, the highest tertile was only 132.6 g/d for men and 168.3 g/d for women. A small number of studies observed a dose-response relationship. For example, a significantly inverse association was found between dairy intake and CVD in Kondo study for women and in Ness study (Supplementary Table 1). All of the included studies presented cases that were diagnosed according to the WHO International Classification of Diseases (ICD) at that time, except the studies conducted in the USA.[12,17,24,28] Nearly all studies were adjusted for confounding factors, such as age, gender (if necessary), body mass index, smoking, alcohol consumption, physical activity, energy and certain food intakes, and diseases related to CVD. Sixteen out of 22 studies were adjusted for all of the aforementioned confounders.[6-12,14-17,22-25,28] Finally, the association of dairy products with total CVD, stroke, and CHD was observed in 9, 12, and 12 studies, respectively. High- and low-fat dairy, yogurt, cheese, and butter were used to analyze the association between consumption of such products and the risks of stroke (n=4,6,3,4,3, respectively) and CHD (n=7,8,5,7,5, respectively), but the association of the intake of such foods with CVD was not analyzed because of the insufficient numbers of studies (n=3,3,2,1,1, respectively).

Effects of dairy consumption on the risk of total CVD, stroke and CHD

A total of 91,057 participants with 7,641 cases were included in the CVD meta-analysis. The multivariable-adjusted RRs of the highest categories versus the lowest categories in each study, and the combined RR from the fixed-effects meta-analysis, are presented in Figure 2. All studies except one showed an inverse association, with two studies reaching statistical significance. No evidence of heterogeneity was found across the studies (p=0.18, I^2=29.6%). Overall, dairy consumption was associated with a significantly decreased CVD risk (RR=0.88, 95% CI: 0.81, 0.96).

A total of 504,803 participants with 21,801 cases were included in the stroke meta-analysis. Similar to the results from the CVD analysis, an inverse association was observed in all studies except one; three studies reached statistical significance. An evidence of heterogeneity was found across the studies (p<0.001, I^2=69.8%). Dairy consumption was also associated with a significantly decreased risk of stroke (RR=0.87, 95% CI: 0.77, 0.99) (Figure 3).

A total of 253,260 participants with 8,792 cases were included in the CHD meta-analysis. Results from individual studies differed, and both positive and negative associations were reported. An evidence of heterogeneity was observed across the studies (p=0.005, I^2=58.5%). All combined, dairy consumption failed to show association with CHD risk (RR=0.94, 95% CI: 0.82, 1.07) (Figure 4).

Sensitivity analyses

Table 2 shows the results of sensitivity analysis according to various inclusion criteria. The combined RR failed to show any change in the sensitivity analysis of the association of CVD and CHD with dairy products. However, some RRs were attenuated, as observed in the association between dairy products and stroke. Further analysis examining the effect of a single study on the combined RR suggested similar results (data not shown). However, when we excluded the study of Larsson et al (the only study showing a positive association), the inverse association of dairy consumption with stroke risk was stronger (RR=0.81, 95% CI: 0.77, 0.84) with no evidence of heterogeneity across the studies (p=0.69, I^2=0%), suggesting that this study was the main source of heterogeneity.[23]

Other subtypes of dairy products and stroke/CHD

We separately analyzed the associations between the consumption of high-fat dairy, low-fat dairy, yogurt, cheese, and butter and the risks of stroke and CHD (Table 3). The number of studies related to these subtypes was greater in the CHD analysis than in the stroke analysis. For stroke risk, all subtypes showed an inverse association with significant difference in the consumption of low-fat dairy (RR=0.93, 95% CI: 0.88, 0.99) and cheese (RR=0.91, 95% CI: 0.84, 0.98). For CHD risk, a significantly decreased risk was observed in cheese consumption (RR=0.84, 95% CI: 0.71, 1.00), but not in low-fat dairy consumption (RR=1.02, 95% CI: 0.92, 1.14). Notably, high-fat dairy consumption resulted in a borderline increase in the CHD risk (RR=1.08, 95% CI: 0.99, 1.17).

Table 1. The characteristics of the prospective cohort studies

Study	Location (Project and recruited period)	Length of follow-up	Size of cohort	Men (%)	Age at recruitment	Exposure assessment	Exposure	Outcomes (Case number)
Avalos 2013	USA (Rancho Bernardo 1984-1987)	16.2	1759	42.7	≥49 (70.4)	Validated FFQ	Low-fat milk, whole milk, yoghurt, cheese, butter	CHD (454)
Dalmeijer 2013	Netherlands (EPIC-NL 1993-1997)	13.1	33625	25.5	21-64 (49.0±11.9)	Validated FFQ	Total dairy	Non-fatal and fatal CHD (1648)
Kondo 2013	Japan (NIPPON DATA80 1980)	24.0	9243	43.8	≥30 (50.5±13.1)	3 day diet records	Milk and dairy products	Fatal CVD (893), stroke (417), CHD (174)
Lin 2013	Taiwan (CVDFACTS 1989-2002)	12.0	2061	42.9	45.5±14.2	Validated FFQ	Dairy products	Non-fatal and fatal stroke (123)
Louie 2013	Australia (BMES 1992-1994)	15.0	2662	44.2	≥49 (65.4±9.3)	Validated FFQ	Total dairy, low/reduced fat dairy, whole fat dairy	Fatal CVD (548), stroke (176), CHD (432)
Patterson 2013	Sweden (Swedish Mammography Cohort 1997)	11.6	33636	0	48-83 (61.2)	Validated FFQ	Total dairy, milk, low-fat milk, full-fat milk, cultured milk, cheese, butter	Non-fatal and fatal MI (1392)
Soedamah-Muthu 2013	UK (Whitehall II study 1997-1999)	10.8	4255	72.0	35-55	Validated FFQ	Total dairy, total milk, High-fat dairy, low-fat dairy, fermented dairy, yogurt, cheese	Non-fatal and fatal CHD (323)
Bernstein 2012	USA (NHS1980, HEPS 1986)	26, 22	127160	33.9	30-55 40-75	Validated FFQ	Whole-fat dairy, low-fat dairy	Non-fatal and fatal stroke (4030)
Eguchi 2012	Japan (JACC 1988-1990)	16.5	43010	43.6	40-79 (55.9)	Validated FFQ	Milk products	Fatal CVD (1907)
Larsson 2012	Sweden (Swedish Mammography Cohort, Cohort of Swedish Men 1997)	10.2	74961	53.8	45-83 (60.3)	Validated FFQ	Total dairy, milk, low-fat dairy, full-fat dairy, sour milk and yogurt, cheese	Non-fatal and fatal stroke (4089)
Goldbohm 2011	Netherlands (NLCS 1986)	10	120852	45.9	55-69 (61.6)	Validated FFQ	Milk products, low-fat dairy, cheese, butter	Fatal stroke (842), IHD (2689)
Sonestedt 2011	Sweden (MDC 1991-1996)	12	26445	38.1	44-74 (57.3)	Validated FFQ	Total dairy, milk, low-fat milk, high-fat milk, fermented milk, cheese, butter	Non-fatal and fatal CVD (2520)
Bernstein 2010	USA (NHS 1980)	26	84136	0	30-55	Validated FFQ	Low-fat dairy, full-fat dairy	Non-fatal and fatal CHD (3162)

Table 1. The characteristics of the prospective cohort studies (Count.)

Study	Location (Project and recruited period	Length of follow-up	Size of cohort	Men (%)	Age at recruitment	Exposure assessment	Exposure	Outcomes (Case number)
Bonthuis 2010	Australia (Skin cancer prevention trial 1992)	14.4	1529	43.2	25-78 (49.8±13.1)	Validated FFQ	Total dairy	Fatal CVD (61)
Larsson 2009	Finland (ATBC 1985-1988)	13.6	26556	100	50-69 (57.7)	Validated FFQ	Total dairy, low-fat milk, whole milk, sour milk, yogurt, cheese, butter	Non-fatal and fatal stroke (3281)
Kelemen 2005	USA (Iowa Women's Health Study 1986)	15	29017	0	55-69 (60.8)	Validated FFQ	Dairy	Fatal CHD (739)
Elwood 2004	UK (Caerphilly cohort 1979-1983)	20-24	2403	100	45-59 (52.0)	Validated FFQ	Milk	Non-fatal and fatal stroke (185), CVD, IHD (439)
Sauvaget 2003	Japan (LSS cohort 1979)	16	37130	38.3	34-103 (56)	Validated FFQ	Dairy products, milk	Fatal stroke (1462)
Ness 2001	UK (Collaborative Study 1970-1973)	25	5765	100	35-64 (48.3)	Validated FF	Milk	Fatal CVD (1088), stroke (196), CHD (892)
Bostick 1999	USA (Iowa Women's Health Study 1986)	8	34486	0	55-69	Validated FFQ	Fat-containing dairy	Fatal IHD (387)
Kinjo 1999	Japan (1966)	15	223170	A/N	40-69	FFQ	Dairy milk	Fatal cerebrovascular disease (11030)
Mann 1997	UK (1984)	13.3	10802	38.0	18-79 (33.5)	Validated FFQ	Milk, cheese	IHD (64)

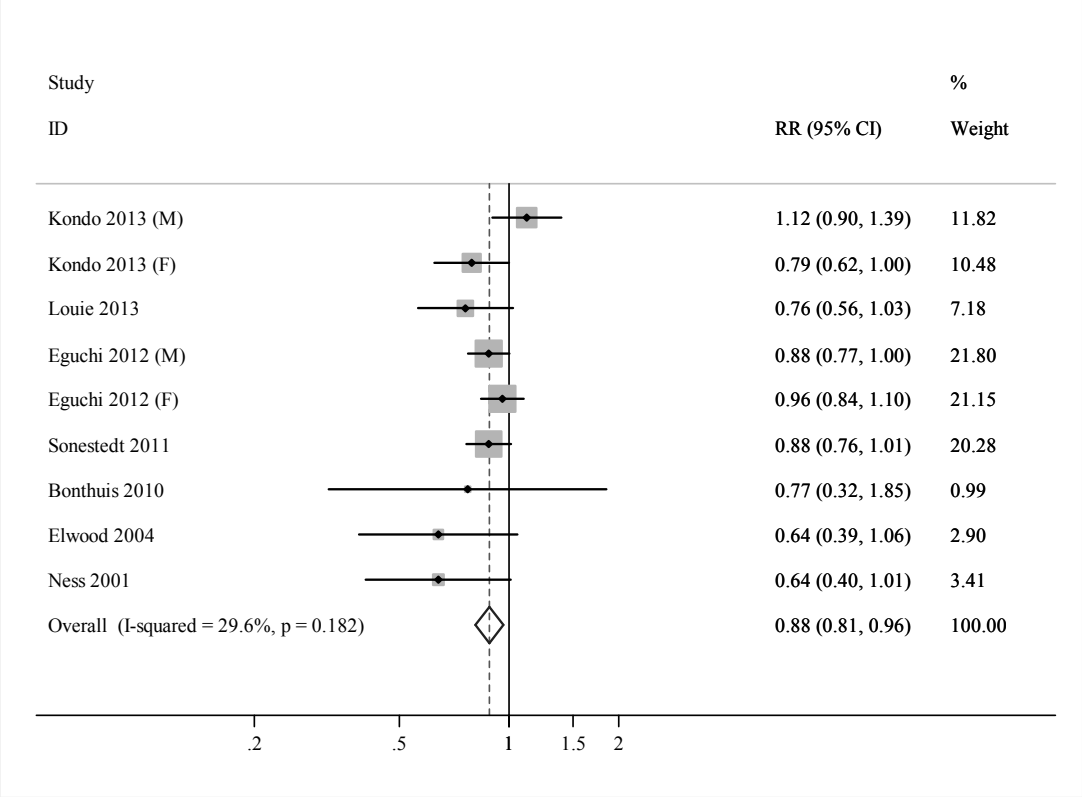

Figure 2. The effect of dairy consumption on total CVD. The size of the gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% CIs.

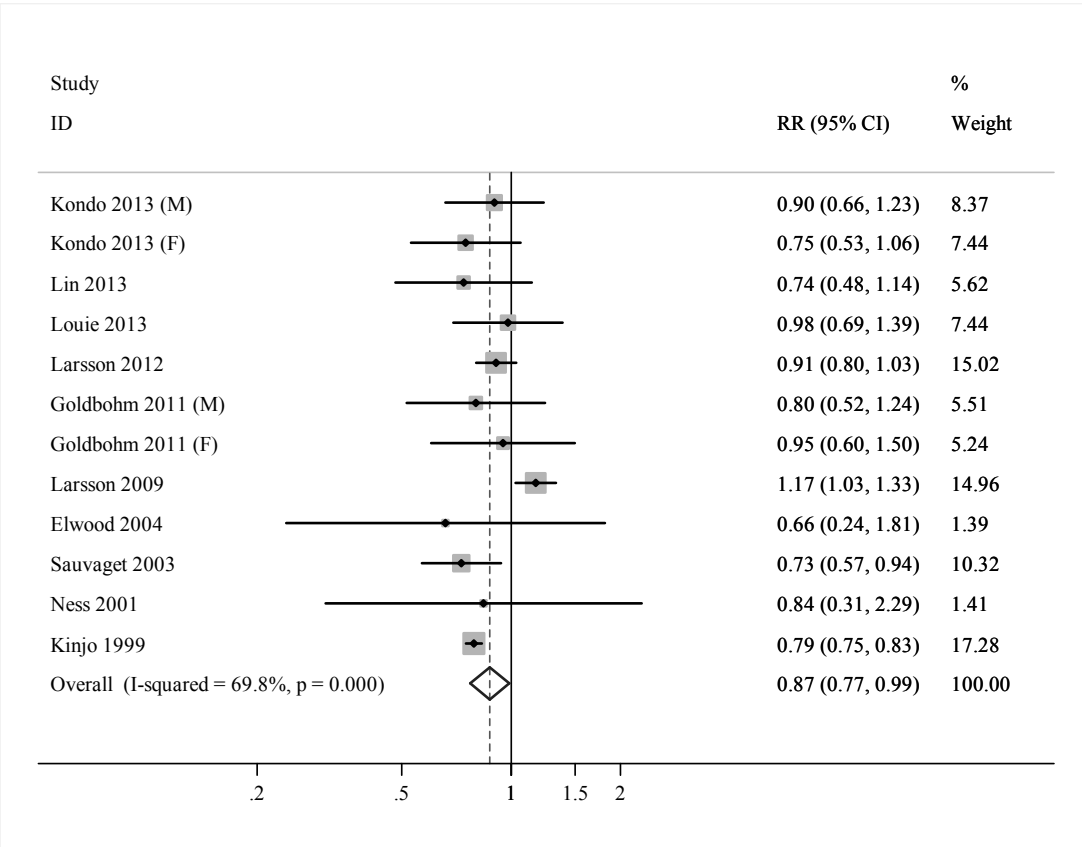

Figure 3. The effects of dairy consumption on stroke. The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% CIs.

Except the association between stroke and high-fat dairy, others have no heterogeneity across studies.

Publication bias

Begg's funnel plot failed to show any substantial asymmetry. Egger's regression test also indicated little evidence of publication bias in the association between dairy consumption and CVD (p=0.99) and CHD (p=0.17) risks. However, Begg's funnel plot and Egger's test (p=0.01) suggested a publication bias in the association of dairy products with stroke risk. No publication bias was found in the combination of other subtypes of dairy products and the risk of stroke or CHD.

DISCUSSION

Our meta-analysis showed that dairy consumption can significantly reduce the risk of total CVD and stroke by 12% and 13%, respectively, but dairy consumption cannot reduce the risk of CHD. Low-fat dairy also elicited beneficial effects on stroke, while cheese exhibited beneficial effects on stroke and CHD. In contrast, high-fat dairy consumption had a non-significant tendency to be

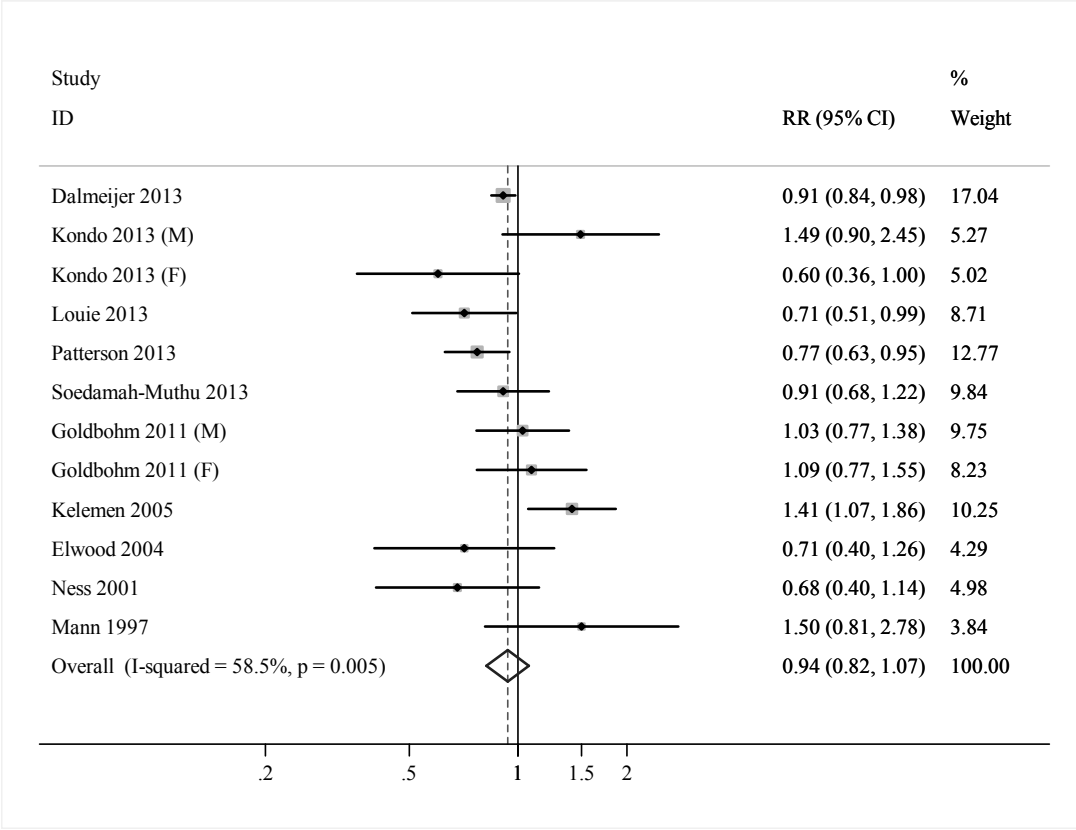

Figure 4. The effects of dairy consumption on CHD. The size of the gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% CIs.

Table 2. Results of sensitivity analysis according to various inclusion criteria

Inclusion criteria	Total CVD		Stroke		CHD	
	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Total	9	0.88 (0.81-0.96)	12	0.87 (0.77-0.99)	12	0.94 (0.82-1.07)
Free of CVD at baseline	6	0.91 (0.85-0.99)	8	0.88 (0.75-1.00)	10	0.99 (0.86-1.10)
Conducting in Western countries	5	0.83 (0.73-0.93)	7	0.92 (0.78-1.07)	10	0.96 (0.85-1.09)
Validated FFQ as exposure assessment	7	0.88 (0.82-0.95)	9	0.88 (0.75-1.05)	10	0.96 (0.85-1.09)
Adjusting for important confounders	6	0.87 (0.75-1.00)	9	0.90 (0.79-1.00)	10	0.96 (0.84-1.10)

Table 3. The associations between the consumption of specific dairy subtypes and stroke or CHD

Item	Stroke				CHD			
	No	RR (95% CI)	p^*	I^2 (%)	No	RR (95% CI)	p^*	I^2 (%)
High-fat dairy	4	0.95 (0.83-1.08)	0.013	72.1	7	1.08 (0.99-1.17)	0.993	0
Low-fat dairy	6	0.93 (0.88-0.99)	0.282	20.0	8	1.02 (0.92-1.14)	0.160	33.5
Yogurt	3	0.98 (0.92-1.06)	0.589	0	5	1.06 (0.90-1.34)	0.135	42.9
Cheese	4	0.91 (0.84-0.98)	0.466	0	7	0.84 (0.71-1.00)	0.185	31.8
Butter	3	0.94 (0.84-1.06)	0.317	12.9	5	1.02 (0.88-1.20)	0.217	30.7

$^*p$ for heterogeneity.

associated with an increased risk of CHD, based on analyzing data from seven studies.

Our current work is comparable with a previous meta-analysis, which reported a strong inverse association between dairy consumption and stroke.[33] However, in that study, the exposure was not strictly limited to dairy products, and a solid conclusion was lacking because sensitivity analyses and publication bias were not formally evaluated. A recent meta-analysis further showed the protective effect of dairy foods on the risk of stroke with a slightly different study selection from our analysis. They also found that low-fat dairy and cheese were significantly associated with reduced risk of stroke.[34] In another recent meta-analysis, RR between milk and overall risk of CVD was 0.94 (95% CI 0.89, 0.99) per 200 mL consumed daily, but milk intake was not associated with stroke or CHD risk.[4] Although a dose-response analysis was conducted, dairy consumption was expressed in various units across the studies, and unit conversion (e.g., from serving to g/d) was inconsistent. Besides RR (95% CI), successful dose-response analysis requires median dose, and number of cases and participants in every exposure level. However, such information was not fully provided in recently published cohort studies. Thus, data accumulation is required to update dose-response analysis in further research.

Complex mechanisms, which are beyond our scope, may be involved in the potentially protective effects of dairy products against CVD. Dairy products are rich in minerals (calcium, potassium, and magnesium), protein (casein and whey), and vitamins (riboflavin and vitamin B_{12}). Such components showed beneficial effects on CVD incidence. For example, intake of calcium, potassium, or magnesium was inversely associated with the risk of ischemic stroke as described in an NHS study.[35] The protective effect of dairy calcium intake on stroke mortality was also demonstrated in a Japanese population.[36] The present meta-analysis showed that the reduced CVD risk was mainly due to the effects of dairy consumption on stroke risk, and the association of dairy consumption with stroke was stronger than that with CHD.[7,9,15,25] However, the underlying mechanisms of the different effects of dairy products on stroke and CHD remain unknown.

With the accumulated evidence, we were able to analyze the association between the other subtypes of dairy products and the risks of stroke and CHD. We found a beneficial effect of low-fat dairy on stroke and a possible adverse effect of high-fat dairy on CHD (although this was not significant). The reduced risk of stroke by low-fat dairy may be mediated by a decrease in blood pressure, which is a major risk for most CVD. A previous meta-analysis reported a significant inverse association between increased blood pressure and low-fat dairy foods, but not between increased blood pressure and high-fat dairy foods.[37] On the other hand, fat intake commonly regulates the lipid profile, thereby indicating the effect of fat on CVD risk. Findings from a randomized controlled trial (RCT) indicated that low-density/high-density lipoprotein cholesterol and total/high-density lipoprotein cholesterol ratios decreased when saturated fats derived from full-fat dairy foods are replaced with low-fat dairy.[38] The NHS study also found that the ratio of high- to low-fat dairy food consumption was positively associated with an increased CHD risk.[32] A most recent meta-analysis further confirmed the beneficial effects of the Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in low-fat dairy products, on CVD, stroke, and CHD.[39]

Cheese, a relatively high fat content food, was found to decrease the risk of stroke and CHD in our meta-analysis. Several studies have reported that cheese exhibits a more favourable effect on blood lipid and cholesterol than butter, although they contain the same amount of fat.[40,41] A possible explanations is that the high calcium content of cheese may increase fecal fat excretion. In one cohort study, the observed inverse association between cheese consumption and CHD risk was attenuated after adjustment for calcium intake, suggesting that calcium content was a factor in this association.[9] Other possible explanations may include the high protein content of cheese or the presence of fermentation by-products, including microbial cultures, prebiotic substrates, a bioactive form of vitamin K, and bioactive peptides.[40,42]

This meta-analysis was primarily limited by considerable heterogeneity across studies, which complicated the interpretation of our findings. This was not surprising given the variation in study designs and characteristics of participants. Our sensitivity analyses suggested that the Larsson study[23] was the main source of heterogeneity. Certain characteristics have distinguished this study from others. For instance, older male smokers (a population at high risk of stroke) were selected as the participants. Moreover, approximately 22% of the participants stopped smoking during the follow up. Smoking is an established risk factor,[2] but the above mentioned study provided no smoking data during the entire follow-up period. On the other hand, a very narrow range of dairy foods and a high mean daily intake of dairy food (789 g) were used in that study. The association between dairy foods and stroke may differ in populations with relatively low dairy intake.

In addition, other limitations of the present meta-analysis should be mentioned and explained. First, observational studies failed to establish a causal relationship and the residual confounding factors remain a major concern. However, RCT design for dairy consumption with adequate power is not feasible.[7] In our meta-analysis, only prospective design studies were selected. Furthermore, the sensitivity analysis omitting the studies including patients with a history of CVD provided similar results. Although each study used a different set of possible confounders for adjustments, most studies adjusted for almost all the important confounders. An additional sensitivity analysis combining these studies showed that there was little change of results. Second, dairy products were used as the main exposure in our meta-analysis, which may have weakened the association with the study outcomes because dairy is a heterogeneous group. In fact, this issue was raised in the meta-analysis of Soedamah-Muthu.[4] Most studies, which observed dairy consumption, were conducted during the 1980's when whole-fat dairy products were mainly consumed. Our meta-analysis included some studies that collected dietary information after the 1980's. However, the content of dairy products used in our meta-analysis was still different across studies.

On the other hand, the intake amount largely differed between studies conducted in the Western countries and studies conducted in Eastern countries. Third, we failed to consider the effect of dietary changes during the follow-up period because diet was measured in the beginning of most studies. The participants may have changed their dairy intake during the follow-up period because many new dairy products (especially low-fat and fermented dairy products) have become available for the past decades. To resolve these two issues, our analysis narrowing to specific dairy subtypes became necessary for the support of the overall conclusion.

In conclusion, the findings of the present meta-analysis have suggested that dairy consumption is significantly and inversely associated with the risks of CVD and stroke. Low-fat dairy consumption shows a significant beneficial association reduce the incidence of stroke, and cheese shows a significant beneficial association to reduce the incidence of stroke and CHD. However, the association of dairy consumption with stroke should be interpreted with caution because of the evidence of heterogeneity across studies along with possible publication bias.

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AUTHOR DISCLOSURES

The authors report no conflicts of interest.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013;127:143-52. doi: 10.1161/CIR.0b013e318282ab8f.
2. World Health Organization. WHO Media centre. Cardiovascular diseases (CVDs). Fact sheet N°317, updated March 2013. Geneva: World Health Organization. 2013/15/3 [cited 2013/09]; Available from: http://www.who.int/mediacentre/ factsheets/fs317/en/index.html.
3. Chinese Nutrition Society. Chinese balance dietary pagoda (2007). Lhasa: The Tibet People's Publishing House; 2008.
4. Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, Hu FB, Engberink MF, Willett WC, Geleijnse JM. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. Am J Clin Nutr. 2011;93:158-71. doi: 10.3945/ajcn.2010.29866.
5. Avalos EE, Barrett-Connor E, Kritz-Silverstein D, Wingard DL, Bergstrom JN, Al-Delaimy WK. Is dairy product consumption associated with the incidence of CHD? Public Health Nutr. 2013;16:2055-63. doi: 10.1017/S1368980012004168.
6. Dalmeijer GW, Struijk EA, van der Schouw YT, Soedamah-Muthu SS, Verschuren WM, Boer JM, Geleijnse JM, Beulens JW. Dairy intake and coronary heart disease or stroke-A population-based cohort study. Int J Cardiol. 2013;167:925-9. doi: 10.1016/j.ijcard.2012.03.094.
7. Kondo I, Ojima T, Nakamura M, Hayasaka S, Hozawa A, Saitoh S et al. Consumption of dairy products and death from cardiovascular disease in the Japanese general population: the NIPPON DATA80. J Epidemiol. 2013;23:47-54. doi: 10.2188/jea.JE20120054.
8. Lin PH, Yeh WT, Svetkey LP, Chuang SY, Chang YC, Wang C, Pan WH. Dietary intakes consistent with the DASH dietary pattern reduce blood pressure increase with age and risk for stroke in a Chinese population. Asia Pac J Clin Nutr. 2013;22:482-91. doi: 10.6133/apjcn.2013.22.3.05.
9. Louie JC, Flood VM, Burlutsky G, Rangan AM, Gill TP, Mitchell P. Dairy consumption and the risk of 15-year cardiovascular disease mortality in a cohort of older Australians. Nutrients. 2013;5:441-54. doi: 10.3390/nu5020441.
10. Patterson E, Larsson SC, Wolk A, Åkesson A. Association between dairy food consumption and risk of myocardial infarction in women differs by type of dairy food. J Nutr. 2013;143:74-9. doi: 10.3945/jn.112.166330.
11. Soedamah-Muthu SS, Masset G, Verberne L, Geleijnse JM, Brunner EJ. Consumption of dairy products and associations with incident diabetes, CHD and mortality in the Whitehall II study. Br J Nutr. 2013;109:718-26. doi: 10.1017/S0007114512001845.
12. Bernstein AM, Pan A, Rexrode KM, Stampfer M, Hu FB, Mozaffarian D, Willett WC. Dietary protein sources and the risk of stroke in men and women. Stroke. 2012;43:637-44. doi: 10.1161/STROKEAHA.111.633404.
13. Eguchi E, Iso H, Tanabe N, Wada Y, Yatsuya H, Kikuchi S et al. Healthy lifestyle behaviours and cardiovascular mortality among Japanese men and women: the Japan collaborative cohort study. Eur Heart J. 2012;33:467-77. doi: 10.1093/eurheartj/ehr429.
14. Larsson SC, Virtamo J, Wolk A. Dairy consumption and risk of stroke in Swedish women and men. Stroke. 2012;43:1775-80. doi: 10.1161/STROKEAHA.111.641944.
15. Goldbohm RA, Chorus AM, Galindo Garre F, Schouten LJ, van den Brandt PA. Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands. Am J Clin Nutr. 2011;93:615-27. doi: 10.3945/ajcn.110.000430.
16. Sonestedt E, Wirfält E, Wallström P, Gullberg B, Orho-Melander M, Hedblad B. Dairy products and its association with incidence of cardiovascular disease: the Malmö diet and cancer cohort. Eur J Epidemiol. 2011;26:609-18. doi: 10.1007/s10654-011-9589-y.
17. Bernstein AM, Sun Q, Hu FB, Stampfer MJ, Manson JE, Willett WC. Major dietary protein sources and risk of coronary heart disease in women. Circulation. 2010;122:876-83. doi: 10.1161/CIRCULATIONAHA.109.915165.
18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008-12. doi: 10.1001/jama.283.15.2008.
19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88. doi: 10.1016/01972456(86)90046-2.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34. doi: 10.1136/bmj.315.7109.629.
22. Bonthuis M, Hughes MC, Ibiebele TI, Green AC, van der Pols JC. Dairy consumption and patterns of mortality of Australian adults. Eur J Clin Nutr. 2010;64:569-77. doi: 10.1038/ejcn.2010.45.
23. Larsson SC, Männistö S, Virtanen MJ, Kontto J, Albanes D,

Virtamo J. Dairy foods and risk of stroke. Epidemiology. 2009;20:355-60. doi: 10.1097/EDE.0b013e3181935dd5.
24. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. Am J Epidemiol. 2005;161:239-49. doi: 10.1093/aje/kwi038.
25. Elwood PC, Pickering JE, Fehily AM, Hughes J, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. Eur J Clin Nutr. 2004;58:711-7. doi: 10.1038/sj.ejcn.1601868.
26. Sauvaget C, Nagano J, Allen N, Grant EJ, Beral V. Intake of animal products and stroke mortality in the Hiroshima/ Nagasaki Life Span Study. Int J Epidemiol. 2003;32:536-43. doi: 10.1093/ije/dyg151.
27. Ness AR, Smith GD, Hart C. Milk, coronary heart disease and mortality. J Epidemiol Community Health. 2001;55: 379-82. doi: 10.1136/jech.55.6.379.
28. Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol. 1999;149:151-61. doi: 10.1093/oxfordjournals.aje.a009781.
29. Kinjo Y, Beral V, Akiba S, Key T, Mizuno S, Appleby P, Yamaguchi N, Watanabe S, Doll R. Possible protective effect of milk, meat and fish for cerebrovascular disease mortality in Japan. J Epidemiol. 1999;9:268-74. doi: 10.2188/jea.9.268.
30. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. Heart. 1997;78:450-5. doi: 10.1136/hrt.78.5.450.
31. He K, Merchant A, Rimm EB, Rosner BA, Stampfer MJ, Willett WC, Ascherio A. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. BMJ. 2003;327:777-82. doi: 10.1136/bmj.327.7418.777.
32. Hu FB, Stampfer MJ, Manson JE, Ascherio A, Colditz GA, Speizer FE, Hennekens CH, Willett WC. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. Am J Clin Nutr. 1999;70:1001-8.
33. Elwood PC, Pickering JE, Givens DI, Gallacher JE. The consumption of milk and dairy foods and the incidence of vascular disease and diabetes: an overview of the evidence. Lipids. 2010;45:925-39. doi: 10.1007/s11745-010-3412-5.
34. Hu D, Huang J, Wang Y, Zhang D, Qu Y. Dairy foods and risk of stroke: a meta-analysis of prospective cohort studies. Nutr Metab Cardiovasc Dis. 2014;24:460-9. doi: 10.1016/j.numecd.2013.12.006.
35. Iso H, Stampfer MJ, Manson JE, Rexrode K, Hennekens CH, Colditz GA, Speizer FE, Willett WC. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke. 1999;30:1772-9. doi: 10.1161/01.STR.30.9.1772.
36. Umesawa M, Iso H, Date C, Yamamoto A, Toyoshima H, Watanabe Y et al. Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study. Stroke. 2006;37:20-6. doi: 10.1161/01.STR.0000195155.21143.38.
37. Ralston RA, Lee JH, Truby H, Palermo CE, Walker KZ. A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. J Hum Hypertens. 2012;26:3-13. doi: 10.1038/jhh.2011.3.
38. Ohlsson L. Dairy products and plasma cholesterol levels. Food Nutr Res. 2010;54. doi: 10.3402/fnr.v54i0.5124.
39. Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L. Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases--incidence: a systematic review and meta-analysis on observational prospective studies. Nutrition. 2013;29: 611-8. doi: 10.1016/j.nut.2012.12.018.
40. Hjerpsted J, Leedo E, Tholstrup T. Cheese intake in large amounts lowers LDL-cholesterol concentrations compared with butter intake of equal fat content. Am J Clin Nutr. 2011; 94:1479-84. doi: 10.3945/ajcn.111.022426.
41. Nestel PJ, Chronopulos A, Cehun M. Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. Eur J Clin Nutr. 2005;59: 1059-63. doi: 10.1038/sj.ejcn.1602211.
42. Nagpal R, Behare P, Rana R, Kumar A, Kumar M, Arora S, Morotta F, Jain S, Yadav H. Bioactive peptides derived from milk proteins and their health beneficial potentials: an update. Food Funct. 2011;2:18-27. doi: 10.1039/c0fo00016g.

Original Article

Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies

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奶制品消费和冠心病发病风险：前瞻性队列研究的 meta 分析

背景：目前有关奶制品消费和心血管疾病(CVD)发病风险的流行病学研究结论并不一致，本研究采用 meta 分析的方法探讨了奶制品与总的 CVD、中风以及冠心病发病风险的关系。**方法**：我们搜索了 PubMed、EMBASE 和 Cochrane 图书馆等数据库（截止 2014 年 2 月）中相关的前瞻性队列研究，采用固定效应模型或随机效应模型计算总效应值。 **结果**：最终 22 个研究纳入 meta 分析，奶制品消费和总的 CVD [9 个研究; 相对危险度（RR）=0.88，95%可信区间（CI）：0.81，0.96]以及中风（12 个研究; RR=0.87, 95% CI：0.77， 0.99）呈负相关，但是没有发现奶制品消费和冠心病之间存在相关性（12 个研究; RR=0.94，95% CI：0.82，1.07）。低脂奶制品（6 个研究；RR=0.93，95% CI：0.88，0.99）和奶酪（4 个研究；RR=0.91，95% CI：0.84，0.98）消费显著降低中风的发病风险，奶酪（7 个研究；RR=0.84，95% CI：0.71，1.00）还显著降低冠心病的发病风险。根据不同的入选标准限定研究后没有明显改变 CVD 和冠心病的结果，但削弱了奶制品消费和中风的关系。中风和冠心病的研究存在异质性，中风的研究还显示存在发表偏倚。 **结论**：我们的 meta 分析进一步证实奶制品消费有利于预防 CVD，低脂奶制品和奶酪降低了中风和冠心病的发病风险。

关键词： 奶制品、心血管疾病、中风、冠心病、meta 分析