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META-ANALYSIS

Dairy foods and risk of stroke: A meta-analysis of prospective cohort studies

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Abstract *Background and aims:* Epidemiological studies evaluating the association of dairy foods with risk of stroke have produced inconsistent results. We conducted a meta-analysis to summarize the evidence from prospective cohort studies regarding the association between dairy foods and risk of stroke.
Methods and results: Pertinent studies were identified by searching Embase (1950–November, 2013), Web of Knowledge (1950–November, 2013) and Pubmed (1945–November, 2013). Random-effect model was used to combine the results. Dose–response relationship was assessed by restricted cubic spline. Eighteen separate results from fifteen prospective cohort studies, with 28 138 stroke events among 764 635 participants, were included. Total dairy [relative risk (95% CI): 0.88 (0.82–0.94)], low-fat dairy [0.91 (0.85–0.97)], fermented milk [0.80 (0.71–0.89)] and cheese [0.94 (0.89–0.995)] were significantly associated with reduced risk of stroke, but whole/high-fat dairy, nonfermented milk, butter and cream were not significantly associated with risk of stroke. Stronger association was found for stroke mortality than incidence, and for studies conducted in Asia than Europe, while the association did not differ significantly by sex. Limited data did not find any significant association with either ischemic or hemorrhagic stroke. A non-linear dose–response relationship ($P = 2.80^{*}10^{-13}$) between milk and risk of stroke was found, and the relative risk of stroke was 0.88 (0.86–0.91), 0.82 (0.79–0.86), 0.83 (0.79–0.86), 0.85 (0.81–0.89), 0.86 (0.82–0.91), 0.91 (0.84–0.98) and 0.94 (0.86–1.02) for 100, 200, 300, 400, 500, 600 and 700 ml/day of milk, respectively.
Conclusions: Dairy foods might be inversely associated with the risk of stroke.

Introduction

Stroke is the fourth leading cause of global disease burden [1]. Over the past four decades, stroke incidence declined by 42% in high-income countries but increased by 100% in low to middle income countries [2]. About 87% of stroke deaths occurred in low to middle income countries, and the number of stroke deaths is projected to rise to 6.5 million in 2015 and to 7.8 million in 2030 globally without intervention [3]. According to American Heart Association, health behaviors including smoking, physical inactivity, nutrition, and overweight and obesity should be taken into account to reduce the risk of stroke [4]. Dairy foods are rich in saturated fatty acids, which can enhance cardiovascular disease by increasing cholesterol levels; however, dairy foods contribute many more compounds of health importance [5]. Dairy foods are shown to have a potential benefit on risk of developing metabolic syndrome [5,6],

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and a recent meta-analysis of prospective cohort studies suggested that total dairy, low-fat dairy and milk are significantly inversely associated with hypertension incidence [7]. In recent years, prospective cohort studies focusing on the relationship between dairy foods and risk of stroke have reported both positive [8,9] and negative [10–12] associations. However, findings from recent prospective cohort studies on dairy foods and risk of stroke have not been summarized systematically with a meta-analysis. Given studies with relatively small number of participants might be underpowered to detect the effect, and even small health effects of dairy foods on risk of stroke could have considerable public health consequences considering the popularity of dairy foods, thus we conducted a meta-analysis to (1) first assess the risk of stroke for the highest vs. lowest categories of dairy foods consumption; (2) then evaluate the possible dose–response relationship of dairy foods with risk of stroke when possible; (3) and assess the heterogeneity among studies and publication bias.

Methods

Literature search and selection

We performed a literature search using the databases of Embase (1950–November, 2013), Web of Knowledge (1950–November, 2013) and Pubmed (1945–November, 2013), using the search term (((((((dairy) OR milk) OR cheese) OR butter) OR cream) OR yogurt) OR yoghurt)) AND ((((cerebrovascular disease) OR cardiovascular disease) OR stroke) OR cerebral infarction) without restrictions. Moreover, we reviewed reference lists from retrieved articles to search for further relevant studies. Two investigators (DH and JQH) independently reviewed all identified studies, and studies were included if they met the following criteria: (1) a prospective cohort design; (2) the exposure of interest was dairy foods; (3) the outcome of interest was stroke; (4) relative risk (RR) with 95% confidence interval (CI) was provided. If data were duplicated in more than one study, we included the study with the largest number of cases.

Data extraction

The following data were extracted from each study by two investigators (DH and JQH): the first author's last name, publication year, follow-up duration, location where the study was performed, sample size and number of cases, type of dairy foods, RR (95% CI) for the highest vs. lowest categories of dairy foods, variables adjusted for in the analysis. For dose–response analysis, the number of cases and participants (person-years), and RR (95% CI) for each category of dairy foods were also extracted. The median or mean level of dairy foods for each category was assigned to the corresponding RR for every study. If upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category. We extracted RRs that reflected the greatest degree of control for potential confounders.

Statistical analysis

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI to assess the strength of association. Random-effects model was used to combine study-specific RR (95%CI), which considers both within-study and between-study variation. Heterogeneity was assessed quantitatively with I^2, and I^2 values of 25, 50 and 75% represent low, moderate and high heterogeneity [13], respectively. Sensitivity analysis was performed with one study removed at a time, [14] and a study is excessively influential if the significance of its "omitted" meta-analytic estimate differed relative to the overall estimate. Publication bias was evaluated using Egger regression asymmetry test [15]. Meta-regression was performed to assess the potential sources of between-study heterogeneity [16]. Study quality was assessed using the 9-star Newcastle–Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, accessed 10/14/2013).

For the association of total dairy foods with risk of stroke, we first combined the results within each study if two or more types of dairy foods were reported. The result for male and female was included as two separate results. Butter, cream, ice cream and whole/high-fat milk were included in the whole/high-fat dairy foods group.

A two-stage random-effects dose–response meta-analysis [17] was performed to compute the trend from the correlated log RR estimates across levels of dairy foods, taking into account the between-study heterogeneity. In the first stage, a restricted cubic spline model with three knots at 25th, 50th and 75th percentiles of the levels of dairy foods was estimated using generalized least-square regression. Then the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis. A *P*-value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0. Dose–response analysis was conducted when more than 3 separate results were available. All statistical analyses were performed with STATA version 12.0, with $P < 0.05$ considered statistically significant.

Results

Literature search and study characteristics

Procedure of literature search was shown in Supplementary Fig. 1. Two case–control studies and one study did not provide the RR (95%CI) were also excluded. Three studies [18–20] were further excluded because of duplicate reports from the same study population [21,22]. Finally, eighteen separate results from fifteen prospective cohort studies were included [2 separate results (male and female) were available in 3 studies [8,11,23]] (Table 1).

Eight [8,11,12,23–27] of the fifteen prospective cohort studies focused on dairy foods and stroke mortality, and the other seven [9,10,21,22,28–30] focused on dairy foods and stroke incidence. Most of the studies adjusted results