The effect of dairy consumption on the prevention of cardiovascular diseases: A meta-analysis of prospective studies

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Abstract

Introduction: There is no global consensus on the relationship of dairy products with cardiovascular diseases. This study was conducted to evaluate the effect of the consumption of dairy products on cardiovascular diseases, including stroke and coronary heart disease (CHD).

Methods: Important electronic databases such as the Scopus, Science Direct, and PubMed were evaluated up to September 2014. All prospective cohort studies that evaluated the relationship between dairy products consumption and cardiovascular diseases were included regardless of their publication date and language. The study participants were evaluated regardless of age, sex, and ethnicity. The STROBE checklist was used to assess quality of the study. Two investigators separately selected the studies and extracted the data. The designated effects were risk ratio (RR) and hazard ratio (HR). The random effect model was used to combine the results.

Results: Meta-analysis was performed on 27 studies. There were 8648 cases of cardiovascular diseases (CVD), 11806 cases of CHD, and 29300 cases of stroke. An inverse association was found between total dairy intake and CVD (RR=0.90, 95% CI: 0.81-0.99) and stroke (RR=0.88, 95% CI: 0.82-0.95) while no association was observed between total dairy intake and CHD. The total dairy intake was associated with decreased mortality of stroke (RR=0.80, 95% CI: 0.76-0.83) although it had no association with its incidence (RR=0.96, 95% CI: 0.88-1.04).

Conclusion: This is the first meta-analysis of the relationship of total dairy intake with CVD. This study showed an inverse relationship between total dairy intake and CVD while no relationship was found for CHD. Considering the limited number of studies in this regard, more studies are required to investigate the effect of different factors on the association of dairy intake and CVD.

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Introduction

Cardiovascular diseases (CVD) are one of the top 10 causes of mortality worldwide. According to the World Health Organization (WHO) statistics, an estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease (CHD) and 6.7 million were due to stroke.1 In 2008, the European Union estimated that the direct and indirect costs related to CVD were €192 billion.2 CVD includes CHD and the diseases related to cerebral vessels3 (3) and is almost responsible for half of deaths in developed and 25% of deaths in developing countries.4 Despite the decrease of mortality from CVD in developed countries since 1970, its mortality is on the rise in developing countries.5 Different factors have been suggested as the causes of CVD, including behavioral risk factors related to unhealthy diet and obesity, lack of physical activity, excess alcohol consumption, and smoking, among which inappropriate diet is the most important.6,7 Dairy products are a major source of energy, protein, and calcium. The pattern of the dairy consumption is different in different parts of the world depending on cultural patterns and income. The highest consumption of dairy products is...
reported in North American and European countries. The consumption of milk is markedly high in the northernmost and Central European and North American countries while the consumption of cheese is high in Mediterranean countries like France, Italy, and Spain.6-11 Previous studies have published different reports regarding the effect of dairy consumption on CVD like stroke and CHD. Some researchers believe that increased intake of dairy products increases the risk of CVD12-15 while some other researchers believe that dairy products have a protective effect.16-19 The results of some studies have shown no relationship between the consumption of dairy products and the mortality of cardiovascular diseases.20-22 There is no global consensus on the relationship of dairy consumption with CVD. Since no meta-analysis has evaluated the effect of total dairy intake on CVD and the available studies have either addressed dairy consumption and stroke, or the number of the studies or their exposures are limited.23-25 It seems that a meta-analysis is essential to summarize the previous studies. Therefore, this study was conducted to summarize the results of the previous studies in order to reach a single conclusion.

Materials and Methods

Searching
Our search strategy was to use a combination of the following keywords: “dairy” OR “milk” OR “cheese” OR “butter” OR “cream” OR “yogurt” OR “yoghurt” AND “cerebrovascular disease” OR “cardiovascular diseases” OR “stroke” OR “cerebral infarction” AND “coronary heart disease” OR “myocardial infarction” OR “MI” OR “ischemic heart disease” OR “IHD” AND “mortality” OR “incidence” OR “survival”. We searched three databases: PubMed (1945 to September 2014), Science Direct (1823 to September 2014), and Scopus (1973 to September 2014). We used the references of the studies, especially systematic review studies.

Inclusion criteria
All cohort studies that evaluated the relationship between dairy intake and CVD were included in the study regardless of their language and publication year. Our population was all healthy individuals regardless of age, gender, and ethnicity; therefore, studies whose baseline population had diseases like diabetes or CVD were excluded from our study. We defined exposure as all dairy products and the outcome of the study was the incidence or mortality of CVD (stroke or CHD). CVD included stroke and CHD (WHO International Classification of Diseases [ICD]-10 I60-69; http://www.who.int/classifications/icd/en). In addition, it included cardiac arrest (I46), heart failure (I50), and sudden death (R69). CHD was considered as acute myocardial infarction, angina pectoris, and other ischemic heart disease (as in ICD-10 I20-I25).

Data collection and validity assessment
To ensure correct selection of the studies according to the inclusion criteria, two researchers (FG and MK) were responsible for selecting the studies independently. These researchers were not blind to the name of the authors and the journal and their results. When there was an opinion disagreement, decision was made after consulting with the third researcher (NS). The two researchers extracted the data from the selected studies. The extracted variables for data analysis included the name of the first author, study title, publication year, study location, age of the participants in the beginning of the study, sample volume, number of cases, follow-up duration, sex, type of dairy product, study outcome (incidence or mortality of CVD), RR (95% CI) or HR (95% CI) for the highest vs. lowest categories of dairy foods and variables adjusted in the analysis. RR was considered with greatest degree of control for potential confounders. If data were duplicated in more than one study, we included the study with the largest number of cases.

The STROBE checklist was used to evaluate the risk of bias and the quality of the studies.26 Two researchers (FG and MK) evaluated the quality of the studies separately. The evaluated items included (a) mentioning the study design accurately (here prospective), (b) explaining how the exposure was measured accurately (here dairy products), (c) explaining how the outcome was measured accurately (here incidence or mortality of CVD), (d) explaining the duration of data collection and follow-up, (e) explaining the inclusion and exclusion criteria, and (f) explaining how loss to follow-up was addressed.

Measures of exposure effect and data analysis
Pooled measures were calculated as the inverse variance-weighted mean of the logarithm of RR and HR with 95% CI to assess the strength of association. As for the relationship of dairy products with CVD, if more than two products were evaluated in a study, they were first merged and one overall effect was reported for each study. The results were reported separately for men and women. Butter, cream, ice cream, high fat milk, cream cheese, and chocolate milk were considered high fat or whole dairy products. Stata version 12 was used for data analysis. The effect was reported using the random effect model. P value less than 0.05 was considered significant.

Heterogeneity, publication bias and sensitivity analysis
Heterogeneity was evaluated quantitatively using I² according to the Higgins classification in which I² values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively.27 We used a funnel plot28 and the Egger test29 to evaluate publication bias.
Sensitivity analysis was performed with one study removed at a time,30 and a study is excessively influential if the significance of its "omitted" meta-analytic estimate differed relative to the overall estimate. Meta-regression was used to evaluate heterogeneity between studies.31

Results

Literature search and study characteristics
A total of 11890 studies were found in the databases of
which 275 were selected after evaluating their titles. Then, 143 studies were selected after removing duplication studies. After evaluating their abstracts, 62 articles with full texts were found. Five studies32,37 were excluded due to reporting the results of the populations of other studies33,35,36,37 and 30 studies were excluded because they did not report the data required for evaluating the relationship between dairy intake and CVD. Finally, 27 studies entered the meta-analysis. Ten studies with 12 separate results were entered into the CVD meta-analysis, covering a total of 140851 individuals and 8648 CVD cases. Seventeen studies with 21 separate results were entered into the CHD meta-analysis, including 47190 individuals and 11806 CHD cases. Sixteen studies with 19 separate results were entered into the stroke meta-analysis, including 765026 individuals and 29300 stroke cases. The FFQ questionnaire was used to estimate the consumption of dairy products in the 25 studies. One study used the 7-day household inventory method38 and another used to 3-day diet records39 to estimate the consumption of dairy products. The duration of follow-up was at least 10 years except for 3 studies.39-41 The results were presented according to sex in 5 studies.18,34,40,42,43 Twenty out of 27 studies were adjusted for important variables like age, sex, cigarette smoking, alcohol consumption, total energy intake, and BMI while adjustment for the above-mentioned variables was not performed in 7 studies.12,13,17,43-46 Twenty-one, four, and two studies were of high, moderate, and low quality, respectively (Table 1).

Quantitative data synthesis
The main results are summarized in Tables 2 and 3.

Effects of total dairy on the risk of CHD, stroke and CVD
In general, total dairy intake reduced the risk of CVD by 10% (RR=0.90, 95% CI: 0.81-0.99) (Figure 1) while no association was observed for CHD (RR=0.99, 95% CI: 0.92-1.06) (Figure 2). Dairy intake had a protective role against stroke (RR=0.88, 95% CI: 0.82-0.95) (Figure 3).

Heterogeneity, publication bias and sensitivity analysis
Heterogeneity was I²=55.8% for CVD (Figure 1). Considering the limited number of studies, it was not possible to perform meta-regression. There was publication bias according to the Egger test (P=0.04). Asymmetry was observed in the funnel plot (Figure 4A) due to small-study effects47 in a study by Bonthuis et al48; no change was observed in overall estimate (RR) of the study after it was excluded. The results of sensitivity analysis for CVD showed that excluding each study did not change the overall estimate of the study significantly; the relationship was 0.90, ranging from 0.90 to 1.08.

Heterogeneity was I²=63.1% for stroke (P<0.001) (Figure 3). Heterogeneity changed to I²=34.6% after excluding the ATBC study49 that included male smokers, indicating that this study played an important role in heterogeneity. Meta-regression was used to detect heterogeneity. An inverse association was found between the total dairy intake and the mortality of stroke (RR=0.80 [95% CI: 0.76-0.83]) while there was no association with its incidence (RR=0.96 [95% CI: 0.88-1.04]) (P<0.001). Total dairy intake may lower the risk of stroke in Asian studies (RR=0.79 [95% CI: 0.75-0.82]) compared to European studies (RR=0.96 [95% CI: 0.89-1.04]) (P<0.001). The estimated effect had no relationship with the following: moderate quality (RR=1.01 [95% CI: 0.84-1.04]) compared to high quality (RR=0.89 [95% CI: 0.85-0.94]) (P=0.05) and low quality (RR=0.79 [95% CI: 0.75-0.83]) compared to high quality (P=0.26), adjustment for 4 or more of the following covariates (smoking, alcohol, total energy intake, BMI, physical activity and ≥ 3 other dietary variables) yes: RR=0.96 (95% CI: 0.89-1.04); no: RR=0.79 (95% CI: 0.75-0.83) (P=0.1), sex/female: RR=0.78 (95% CI: 0.66-0.91), male: RR=0.92 (95% CI: 0.79-1.07) (P=0.90), and also fat content of dairy products (high-fat: RR=0.95 [95% CI: 0.85-0.91]; low-fat: RR=1.11 [95% CI: 0.94-1.09]) (P=0.74; Table 2).

Duration of follow-up (year) (P=0.71), mean age (P=0.91), and number of cases (P=0.52) were not among the sources of heterogeneity. There was no publication bias according to the Egger test (P=0.84). Its funnel plot is shown in Figure 4B. The results of sensitivity analysis showed that excluding each study did not change the overall estimate of the study significantly; the relationship was 0.90, ranging from 0.90 to 1.08.

Discussion
The findings of our meta-analysis showed that total dairy

J Cardiovasc Thorac Res, 2017, 9(1), 1-11 | 3
| Author               | Study, country             | Age (y) | Subjects | Sex       | Quality | Follow-up (y) | Outcome (cases)                                      | Exposure                                                                                  |
|----------------------|----------------------------|---------|----------|-----------|---------|--------------|------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Praagman et al<sup>11</sup> | The Rotterdam Study, Netherlands | ≥55     | 4235     | Both      | High    | 17.3        | Incidence Stroke (564) CHD (567)                      | Total dairy, Low-fat dairy, High-fat dairy, Total milk, Fermented dairy, Cheese, Yogurt. |
| Patterson et al<sup>19</sup> | The Swedish Mammography Cohort, Swedish | 48-83   | 33636    | Female    | High    | 11.6        | Incidence MI (1392)                                  | Total dairy, Milk, Cultured milk/Yogurt, Cheese, Cream, Butter.                           |
| Dalmeijer et al<sup>20</sup> | EPIC-NL Study, Netherlands | 49-70   | 33625    | Both      | High    | 13.1        | Incidence Stroke (531) CHD (1648)                    | Total dairy intake, Milk and milk products, Fermented dairy, Cheese, High-fat dairy, Low-fat dairy. |
| Kondo et al<sup>27</sup> | NIPPON-DATA80, Japanese   | ≥30     | 4045     | Male/Female | High    | 24        | Mortality Stroke (417) CHD (174) CVD (893)            | Milk and dairy products.                                                                   |
| Maruyama et al<sup>27</sup> | JACC Study, Japanese      | 40-79   | 26598    | Male      | High    | 12.6        | Mortality Stroke (1077) CHD (479) CVD (2311)         | Dairy products.                                                                            |
| Louie et al<sup>18</sup> | BMES, Australia           | 49-97   | 2900     | Both      | Moderate | 15        | Mortality Stroke (176) CHD (482) CVD (548)           | Total dairy, Low/reduced, fat dairy, Whole fat dairy.                                     |
| Lin et al<sup>23</sup> | CVDFACTS, China           | 32-60   | 2061     | Both      | High    | 12        | Incidence Stroke (123)                               | Dairy.                                                                                    |
| Ruesten et al<sup>39</sup> | EPIC-Potsdam Study, Germany | 35-65   | 23531    | Both      | High    | 8         | Incidence CVD (363)                                  | Low-fat dairy, High-fat dairy, Low-fat cheese, High-fat cheese, butter.                   |
| Larsson et al<sup>77</sup> | The Swedish Mammography Cohort and the Cohort of Swedish Men | 45-83   | 74961    | Both      | High    | 10.2       | Incidence Stroke (4089)                              | Total dairy, Low-fat dairy, Full-fat dairy, Milk, Sour milk and yogurt, Cheese, Cream and cream fraiche. |
| Bernstein et al<sup>15</sup> | HFP, USA                   | 40-75   | 43150    | Male      | High    | 26        | Incidence Stroke M: 2633 F: 1397                     | Whole-fat dairy, Low-fat dairy.                                                          |
| Soodamah-mothu et al<sup>40</sup> | The Whitehall 2 Cohort, UK | 35-55   | 4255     | Both      | High    | 10        | Incidence CHD (323)                                  | Total dairy, High-fat dairy, Low-fat dairy, Milk, Fermented dairy, Yogurt, Cheese.       |
| Avalos et al<sup>42</sup> | Rancho Bernardo, USA      | 50-93   | 751      | Male      | High    | 16.2       | Incidence CHD M: 222 F: 229                          | Non-fat milk, Yogurt, Ice-cream, Low-fat cheese, Cheese, Cottage cheese, Cream, Cream cheese, Whole milk, Butter, Milk chocolate. |
| van Aerde et al<sup>51</sup> | The Hoorn Study, Netherlands | 50-75   | 1956     | Both      | High    | 12.4       | Mortality CVD (116)                                  | Total dairy, High-fat dairy, Low-fat dairy, Milk and milk products, Milk, cheese, Fermented dairy. |
**Table 1. Continued**

| Study                  | Cohort/Study Details       | Age (years) | Participants | Gender | Dietary Group | Incidence/ Mortality | Findings                                                                 |
|------------------------|----------------------------|-------------|--------------|--------|---------------|----------------------|--------------------------------------------------------------------------|
| Sonestedt et al.       | Malmo Diet and Cancer Cohort, Sweden | 44-74       | 26445        | Both   | High          | Incidence 12         | Total dairy, Milk, Non-fermented milk, Fermented milk, Low-fat milk, High-fat milk, Cheese, Butter. |
| Goldbohm et al.        | Netherlands Cohort Study, Netherlands | 55-69       | 58279 Male, 62573 Female | Male | High          | 10 Mortality Stroke (842), IHD (2689) | Milk products, Non-fermented, full-fat milk, Non-fermented low-fat milk, Milk Fermented, full-fat milk, Fermented low-fat, Cheese, Butter, Low-fat dairy. |
| Bernstein et al.       | NHS, USA                    | 30-55       | 84136 Female | Female | High          | 26 Incidence CHD (3162) | High-fat dairy, Low-fat dairy.                                             |
| Bonthuis et al.        | Skin Cancer Prevention Trial, Australia | 25-78       | 1529 Both | Both | High          | 14.4 Mortality CVD (61) | Total dairy, Low-fat dairy, Full-fat dairy, Full-fat cheese, Milk, Yogurt. |
| Panagiotakos et al.    | ATTICA Study, Greece        | ≥18         | 3042 Both | Both | High          | 5 Incidence CVD (32) | Dairy products (low fat).                                                 |
| van der Pols et al.    | The Body Orr Cohort, England and Scotland | 8           | 4374 Both | Both | High          | 65 Mortality CHD (378), Stroke (121) | Total dairy, Milk.                                                        |
| Larsson et al.         | The ATBC Study, Finland     | 50-69       | 26556 Male | Male | Moderate      | 13.6 Incidence Stroke (3281) | Total dairy, Low-fat dairy, Whole milk, Sour milk, Yogurt, Cheese, Cream, Ice-cream, Butter. |
| Kelemen et al.         | Iowa Women's Health Study  | 55-69       | 29017 Female | Female | High          | 15 Mortality CHD (739) | Dairy                                                                     |
| Elwood et al.          | The Caerphilly Cohort Study, UK | 45-59       | 2403 Male | Male | Moderate      | 20-24 Incidence Stroke (185), IHD (493), CVD (628) | Milk                                                                     |
| Sauvaget et al.        | Life Span Study(LSS), Japanese | 56          | 37130 Both | Both | High          | 16 Mortality Stroke (1462), Mortality Stroke (196), IHD (892), CVD (1212) | Milk, Dairy products.                                                  |
| Ness et al.            | The Collaborative Study, Scotland | 35-64       | 5765 Male | Male | Low           | 25 Mortality Stroke (387) | Milk                                                                     |
| Bostic et al.          | The Iowa Women's Health Study, USA | 55-69       | 34486 Female | Female | High          | 8 Mortality Stroke (11030) | Total dairy                                                               |
| Kinjo et al.           | Japanese                    | 40-69       | 223170 Both | Both | Low           | 15 Mortality Stroke (11030) | Dairy milk.                                                              |
| Mann et al.            | The Vegetarian Society of the United Kingdom, UK | 18-79       | 10802 Both | Both | Moderate      | 13.3 IHD(64) | Milk, Cheese.                                                           |
Table 2. Summary risk estimates of the association between dairy foods and risk of CHD

| N  | No. of cases | Risk estimate (95% CI) | Heterogeneity test | References |
|----|--------------|------------------------|--------------------|------------|
|    |              | REM | I² (%) | P    | P    |
|---|---------------|-----|--------|------|------|
| Total dairy | 21 | 11806 | 0.99 (0.92-1.06) | 51.6 | 0.003 |
| Outcome | | | | | 0.44 |
| Incidence | 9 | 7787 | 1.03 (0.88-1.21) | 44.9 | 0.06 |
| Mortality | 12 | 4019 | 0.97 (0.97-1.04) | 51.6 | 0.003 |

Location where the study was conducted

|   | No. of cases | Risk estimate (95% CI) | Heterogeneity test | References |
|---|--------------|------------------------|--------------------|------------|
|   |              | REM | I² (%) | P    | P    |
|   |              |     |        |      |      |
| Europe | 12 | 6136 | 0.98 (0.89-1.08) | 56.8 | 0.008 |
| Asia | 4 | 1494 | 0.98 (0.68-1.42) | 58.6 | 0.06 |
| Others | 9 | 4176 | 1.01 (0.9-1.14) | 42.5 | 0.13 |
| Sex | | | | | 0.95 |
| Male | 6 | 2485 | 1.01 (0.89-1.15) | 35.6 | 0.17 |
| Female | 8 | 6930 | 0.99 (0.85-1.16) | 64.9 | 0.006 |
| Quality | | | | | |
| High | 17 | 11185 | 1 (0.94-1.07) | 45.4 | 0.02 |
| Moderate | 3 | 425 | 0.95 (0.53-1.68) | 77.7 | 0.01 |
| Low | 1 | 196 | 0.68 (0.40-1.14) | 0 | 0.00 |

Adjusting for 4 or more covariates (smoking, alcohol, total energy intake, BMI, Physical activity and ≥3 other dietary variables) (0.15)*

|   | No. of cases | Risk estimate (95% CI) | Heterogeneity test | References |
|---|--------------|------------------------|--------------------|------------|
|   |              | REM | I² (%) | P    | P    |
|   |              |     |        |      |      |
| Yes | 16 | 10974 | 0.96 (0.88-1.04) | 47.2 | 0.01 |
| No | 5 | 832 | 1.11 (0.94-1.30) | 46.3 | 0.11 |
| Fat content of dairy | | | | | 0.74 |
| Low fat | 11 | 8620 | 1.01 (0.94-1.09) | 62.6 | 0.00 |
| High fat | 11 | 8620 | 0.98 (0.94-1.01) | 2.4 | 0.41 |

BMI: body mass index, REM: random effect model.

* P value for meta-regression, and location where the study was conducted (Europe as the reference) and Quality (high as the reference) and sex (male as the reference).

b Number of results; 2 separate results (male and female) were available in 4 studies. 17,37,41,42

Figure 1. The association of total dairy foods with total CVD events, CVD incidence and CVD mortality. The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% confidence intervals.
Effect of dairy consumption on the prevention of cardiovascular diseases

Table 3. Summary risk estimates of the association between dairy foods and risk of stroke

| N  | No. of cases | Risk estimate (95% CI) | Heterogeneity test | References |
|----|-------------|------------------------|--------------------|------------|
|    |             | REM                    | I² [%] | p     |                      |
| Total dairy | 19 | 29300 | 0.88 (0.82-0.95) | 63.1 | 0.00 | [13, 15, 20, 21, 36, 43, 47, 49] |
| Incidence | 8 | 13979 | 0.96 (0.88-1.04) | 49.7 | 0.05 | [11, 16-18, 37, 41, 44, 45] |
| Mortality | 11 | 15321 | 0.80 (0.76-0.83) | 0.00 | 0.66 | [11, 16-18, 37, 41, 44, 45] |

Location where the study was conducted

| Europe | 10 | 10985 | 0.96 (0.89-1.04) | 29.8 | 0.17 | 1 | [11, 13, 20, 21, 36, 41, 45, 47, 49] |
| Asia   | 7 | 14109 | 0.79 (0.75-0.82) | 0.00 | 0.73 | 0.00 | [16, 17, 37, 43, 44] |
| Others | 2 | 4206 | 0.91 (0.85-0.98) | 0.00 | 0.68 | 0.57 | [15, 18] |

Sex

| Male | 7 | 9007 | 0.92 (0.79-1.07) | 68.5 | 0.00 |
| Female | 4 | 1021 | 0.78 (0.66-0.91) | 0.00 | 0.67 | [17, 37, 41] |

Quality

| High | 13 | 10343 | 0.89 (0.85-0.94) | 0.00 | 0.44 | 1 | [11, 15, 17, 18, 20, 37, 41, 45, 44, 49] |
| Moderate | 4 | 7731 | 1.01 (0.84-1.21) | 63.9 | 0.04 | 0.05 | [13, 18, 36, 47] |
| Low  | 2 | 11226 | 0.79 (0.75-0.83) | 0.00 | 0.90 | 0.26 | [16, 45] |

Adjusting for 4 or more covariates (smoking, alcohol, total energy intake, BMI, physical activity and ≥3 other dietary variables) (0.10)\(^a\)

| Yes | 14 | 16368 | 0.91 (0.85-0.98) | 49.1 | 0.02 | [11, 15, 17, 18, 20, 36, 41, 47, 49] |
| No  | 5 | 12932 | 0.79 (0.75-0.83) | 0.00 | 0.98 |

Fat content of dairy

| Low fat | 9 | 14689 | 0.94 (0.90-0.98) | 0.00 | 0.61 | [13, 15, 18, 20, 41, 47, 49] |
| High fat | 9 | 14689 | 0.95 (0.91-1) | 0.00 | 0.61 | [13, 15, 18, 20, 41, 47, 49] |

BMI: body mass index, REM: random effect model.

\(^a\) P value for meta-regression, and location where the study was conducted (Europe as the reference) and Quality (high as the reference) and sex (male as the reference).

\(^b\) N: number of results; 2 separate results (male and female) were available in 3 studies.\(^{17,37,41}\)

Figure 2. The association of total dairy foods with total CHD events, CHD incidence and CHD mortality. The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% confidence intervals.
intake can lower the risk of CVD by 10% while it has no relationship with CHD. Total dairy intake has an inverse association with stroke and lowers its risk by up to 12%; this protective relationship can be attributed to low-fat dairy products while high-fat dairy products play no role in this regard. It should be noted that according to the results of our study, the consumption of dairy products only postpone stroke and lower its risk by 20% while it has no effect on its incidence.

A meta-analysis by Elwood et al in 2010 investigated the relationship between dairy intake and the risk of stroke and IHD (RR=0.79, 95% CI: 0.68-0.91 and RR=0.92, 95% CI: 0.80-0.99, respectively) and concluded that the dairy intake lowered the risk of IHD and stroke; the results of this study regarding stroke are in line with our findings while the results of IHD are slightly different due to the smaller number of IHD cases and exposure to other item like calcium intake in addition to dairy products in the study by Elwood et al.

Another meta-analysis study by Hu et al showed that the relationship between total dairy intake and stroke was protective (RR=0.88, 95% CI: 0.82-0.94). This relationship was attributed to low-fat dairy products. The results of this study are in line with our findings. Moreover, in 2012, Larsson et al conducted a cohort study on a population of 74961 participants and reported that the consumption of low-fat dairy products decreased the relative risk of stroke (RR=0.88, 95% CI: 0.87-0.97). As for the mechanisms of this protective relationship, it can be stated that the intake of dairy products can lower the blood pressure which is an important risk factor of cardiovascular diseases. A study in 2009 confirmed this finding and reported that the HR of the participants who consumed low-fat dairy products was in the highest quantile (HR=0.69, 95% CI: 0.56-0.86). The results of a randomized controlled trial study showed that the systolic blood pressure of the individuals who used milk protein supplements was 2.3 mm Hg lower than the systolic blood pressure of those who used carbohydrates. It seems that this phenomenon is due to calcium in dairy products because calcium can decrease platelet aggregation and total cholesterol through creating insoluble complexes with fatty acids and decreasing their absorbance. Similarly, Hiroyasu reported that the risk of stroke was 31% less in women in the highest quintile of calcium intake versus those in the lowest quintile. However, it should also be noted that people who consume dairy products often pay more attention to other aspects of health which can affect their health status. For example, in 2008, a preventive medicine specialist reported that people who consumed low-fat dairy products were less likely to smoke or drink alcohol and had more physical activity and more vitamin use; moreover, they consumed more fruits, vegetables, and cereal and less red meat.

A meta-analysis performed by Qin et al on the relationship of dairy foods with CVD, stroke, and CHD showed that dairy products lowered the risk of CVD by 12% which is in line with our results. However, few studies were included in this study, and combining of all dairy products was not done to investigate the relationship and limited exposures were considered. Nonetheless, this study showed the protective role of dairy intake against stroke.
which is similar to our findings. No relationship was found between dairy intake and CHD in this study, which is again in line with our results.\textsuperscript{25}

A prospective study on 4000 adults in London did not show any relationship between CHD and dairy products\textsuperscript{31} while in the study by Elwood et al, the risk of IHD was RR=0.79 (95% CI: 0.68–0.91) in individuals who had the highest consumption of dairy products.\textsuperscript{29} It seems that the contradictory results are due to different designs, different characteristics of the participants, adjustment for different confounders, different sample sizes, and the residual confounding effects of unknown variables.

The relationship between total dairy intake and stroke was significant in Asia and not in Europe, may be due to different patterns of dairy consumption in different parts of the world. The mean dairy intake was more than 200 g/d in the United States in 2000-2005 but less than 27 g in a country like China.\textsuperscript{3} Another reason could be different classifications in different continents; the highest quintile was 132.6 g/d for men and 168.3 g/d for women in a study by Kondo et al in Japan in 2013\textsuperscript{30} while the highest quintile was 1296 g/d in the study by Larsson et al in Sweden in 2009.\textsuperscript{14}

This study had some potential limitations and biases. It should be noted that although cohort studies are valuable ones, they are weaker than RCT studies for detecting causality; therefore, causal interpretations should be made with caution. Moreover, the limited number of studies and non-availability of the full text of some articles despite a great deal of efforts were other limitations of the study, which might have led to selection bias. On the other hand, it was not possible to calculate the crude effect because the required data were not available and analysis was performed on adjusted effects. Therefore, there is the possibility of residual confounding. However, considering the relatively good data of the studies, analysis was performed in different subgroups separately. Since few studies have evaluated the relationship between dairy consumption and different types of stroke and CHD, more studies are required in this regard. Despite the heterogeneity and lack of publication bias in our meta-analysis due to the limited number of included studies, caution should be exercised when interpreting the results. The results of sensitivity analysis in stroke showed that the study by Larsson et al in 2009 was a source of heterogeneity because male smokers were investigated in this study and smoking is a risk factor of stroke.\textsuperscript{14} Therefore, more studies are required to shed light on the relationship of dairy intake in male smokers and stroke. Considering these limitations, more studies should be performed in this regard. However, our study showed the protective role of dairy consumption on stroke and CVD which is of clinical significance.

Conclusion
This is the first meta-analysis addressing the relationship between total dairy intake and CVD. The results showed a possible inverse association between total dairy intake and CVD and stroke while no association was observed between total dairy intake and CHD. Due to the limited number of studies in this regard, more studies investigating all factors associated with cardiovascular diseases are required to make a definite conclusion.

Ethical Approval
The local ethical committee reviewed and approved the study.

Competing interests
None.

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Effect of dairy consumption on the prevention of cardiovascular diseases

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