



## Subgroup dairy products consumption on the risk of stroke and CHD: A systematic review and meta-analysis

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### Abstract

**Background:** There is no global consensus about the relationship between dairy consumption and cardiovascular diseases (CVD). This study aimed at integrating the results of several studies to predict the dairy effects on CVD, e.g. stroke and CHD.

**Methods:** In the present study, some major databases such as Scopus, Science Direct, and PubMed were searched up to September 2014. All prospective cohort studies dealing with dairy products consumption and CVD were surveyed regardless of their publication date or language. This reference population includes all individuals without any delimitation with regard to age, gender, or race. The quality of the study was evaluated using STROBE Checklist. Study selection and data extraction were done by 2 independent researchers separately. The indices in this study were RR and HR. The random model was used to combine the results.

**Results:** Out of 6234 articles, 11 were included in the meta-analysis. No relationship was found between stroke and consumption of milk, cream, and butter, and the results are as follow: RR = 0.91 (95%CI: 0.81-1.01) for milk, RR = 0.97 (95%CI: 0.88-1.06) for cream, and RR = 0.95 (95%CI: 0.85-1.07) for butter. However, cheese was found to decrease stroke risk: RR = 0.93 (95%CI: 0.88-0.99). The relationship of CHD with consumption of milk, cheese, cream, and butter are as follows, respectively: RR = 1.05 (95% CI: 0.96-1.15), RR = 0.90 (95%CI: 0.81-1.01), RR = 0.96 (95% CI: 0.87-1.06), and RR = 0.99 (95%CI: 0.89-1.11). In other words, no relationship existed between dairy products and CHD.

**Conclusion:** No relationship was found between consumption of various dairy products and CHD or stroke, except for cheese that decreased stroke risk by 7%. Considering the small number of studies, the result of the present study is not generalizable and more studies need to be conducted.

**Keywords:** Dairy Products, CHD, Stroke, Cardiovascular Disease, Meta-analysis

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### Introduction

Cardiovascular diseases (CVD) are one of the 10 most important causes of death worldwide. According to World Health Organization (WHO) statistics, 17.5 million people died of CVD around the world in 2012, making up 31% of the total mortality rate worldwide. Of these death cases, 7.4 million were due to CHD (coronary heart disease) and 6.7 million were caused by stroke. It is predicted that the mortality from CVD will increase to 23.6 million cases in 2030 (1).

Dairy products are rich in minerals (calcium, potassium,

and magnesium), proteins (casein and whey), and vitamins (riboflavin and Vitamin B12); thus, dairy products can have positive effects on CVD (2). On the other hand, intake of saturated fat increases low-density lipoprotein cholesterol (LDL-C), and in turn, raises the incidence of CVD, e.g. stroke and coronary heart diseases (3). Because full fat dairy products contain saturated fat, it is recommended that they be replaced by low-fat dairy; for example, margarine could be replaced by butter to decrease the intake of saturated fat (4, 5).

#### ↑What is "already known" in this topic:

To date, no relationship has been found between consumption of various dairy products and CHD or stroke; however, it was found that only cheese decreases stroke risk by 7%.

#### →What this article adds:

Considering the small number of studies conducted on this topic, the result of the present study is not generalizable, and more studies need to be done.

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Some evidence shows that low fat dairy products lower blood pressure (6, 7). It has been proven in some studies that Dietary Approaches to Stop Hypertension (DASH) dietary pattern, including high amount of vegetables, fruit, nuts, fish, and low fat dairy, decrease blood pressure; it can be partly put down to low fat dairy products, which play a role in cutting down on CVD (8). European handbooks also recommend DASH diet and low fat dairy products to prevent CVD; yet, it has not been fully documented with appropriate evidence (9).

Different studies have yielded different results as to the link between dairy products and stroke or CHD. Several prospective cohort studies indicated that milk, cheese, butter, and cream stand in an inverse relationship to stroke or CHD (10-12). However, some other prospective studies revealed a direct relationship between dairy products and stroke or CHD (13-15). A meta-analysis of 17 cohort studies in 2011 showed that milk consumption has an inverse relationship with overall CVD, whereas it bears no relationship to CHD and stroke (16).

As no meta-analysis was conducted to find the relationship between consumption of various dairy products and stroke and CHD and as each dairy product's mechanism acts differently in causing CVD, the need for performing a meta-analysis on this subject is highly felt to determine the effect of each dairy product one by one.

## Methods

Our search was done using the strategy of combining the following keywords: ("milk" OR "cheese" OR "butter" OR "cream") AND ("cerebrovascular disease" OR "cardiovascular diseases" OR "stroke" OR "cerebral infarction" OR "coronary heart disease" OR "myocardial infarction" OR "MI" OR "ischemic heart disease" OR "IHD"). The search was limited to the following databases: PubMed, April 1945 to September 2014; Science Direct, April 1823 to September 2014; and Scopus, April 1973 to September 2014. Systematic browsing studies were used to search the journal articles. The search strategy for Medline was developed first and was then adapted for the remaining databases.

### Inclusion criteria

All cohort studies that examined the relationship between dairy products and stroke or CHD were included regardless

of their publication date and language. Our population of interest included all individuals irrespective of their age, gender, or race. Our main focus was all dairy products and the result was incidence or mortality (stroke or CHD). Based on WHO International Classification of Diseases, ICD-10 stroke includes the following: I60-I69 (ICD)-10, and CHD is defined as acute myocardial infarction, angina pectoris, and other ischemic heart diseases ([www.who.int/classifications/icd/en](http://www.who.int/classifications/icd/en)).

### Data collection and validity assessment

Two researchers (FG and MK) independently took the responsibility of article selection to ensure that articles were selected properly, relevant to research topic, and matched the inclusion criteria. Authors' names, journals' names, and the results were available for the 2 researchers. Any disagreement between the 2 researchers was settled via consultation with a third researcher (YA).

The 2 researchers extracted the data out of the selected studies. Variables for data analysis consisted of the corresponding author's name, study title, publication date, place of the study, baseline age, population size, number of cases, follow-up period, gender, total dairy, low fat dairy, high fat dairy, the result focused (incidence or mortality of CHD or Stroke), RR (95% CI) or HR (95% CI) for the ratio of the highest group to the lowest group, and the variables adjusted for the analysis. In case a study was repeated more than once, the study with higher number of desired results were selected.

STROBE checklist was used to assess quality of the studies (17). Two researchers (FG & MK) assessed the quality of the studies independently. The assessment items were as follow: (a) accurate study plan (here prospective), (b) clear and precise explanation of measurement method of dairy products, (c) precise description of measurement method of the incidence or mortality of CHD or Stroke, (d) stating the data gathering time span, (e) follow-up period, (f) referring to inclusion and exclusion criteria, and (g) explaining how loss to follow-up was addressed (Fig. 1).

### Measures of exposure effect and data analysis

The general index for the assessment of the strength of RR and HR was determined with 95% confidence interval. Relative risk or hazard ratio was defined as the risk rate of

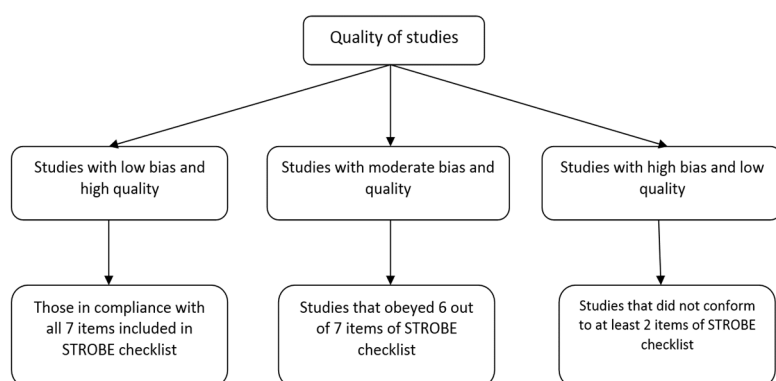


Fig. 1. Flowchart of quality of the studies

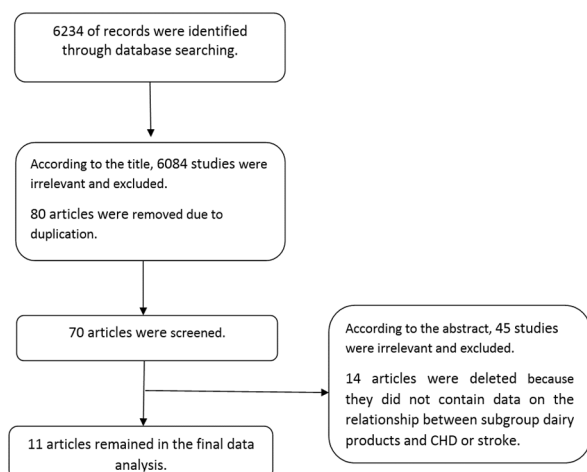


Fig. 2. Flowchart of the selection of studies for inclusion in the meta-analysis

stroke or CHD in individuals with the highest rate of consumption of dairy products in proportion to the risk rate of stroke or CHD in those with the lowest rate of consumption of dairy products. This index weight depends on the average weight of all studies based on inverse square root of studies variance. The results for males and females were reported separately. The Stata software Version 12 was used for data analysis. The data were reported via random model method. The p value less than 0.05 was considered significant.

#### Heterogeneity, publication bias, and sensitivity analysis

Heterogeneity was quantified via  $I^2$ , for which Higgins

classification was used, with 25% showing low heterogeneity, 50% mid heterogeneity, and 75% high heterogeneity (18). Funnel diagram was used for publication bias (19) and was statistically examined using Egger test (20). Sensitivity meta-analysis was used to exclude any study which would remarkably change the study results compared to when that study was not included (21).

#### Results

In the present research, 6234 studies were found in databases. After title-based assessment, 150 articles were selected and 70 were chosen after the deletion of repeated studies. After abstract examination, 25 articles with complete texts were found, and 14 studies were deleted, because they did not contain the relevant data on the relationship between dairy products and CHD and stroke. Finally, 11 studies were entered into the meta-analysis (Fig. 2).

We found 9 studies with 10 separate results in which milk was included in CHD meta-analysis of 212 767 individuals with 4866 CHD cases. Ten studies were included, with 11 separate results in which milk was included in stroke meta-analysis of 440 397 individuals, with 22 946 stroke cases. To estimate dairy products in 10 studies, FFQ questionnaire was used, and a 7- day household inventory method was used only in 1 study (22). The follow-up period of all studies was equal to or more than 10 years. Nine studies were adapted with respect to the main variables such as age, gender, cigarette smoking, alcohol, total energy intake, and body mass index (BMI); 2 studies were not adapted to the mentioned variables (22,23). Seven studies were of high quality, 2 of mid quality (13, 24), and 2 had low quality (11,25) (Table 1).

Table 1. Characteristics of the cohort studies by subgroup dairy products consumption and CHD or stroke

Author	Study, Country	Age (Years)	Participants	Sex	Quality	Follow-up (Years)	Outcome (Cases)
Praagman et al., 2014 (15)	The Rotterdam Study, Netherlands	≥ 55	4235	Both	High	17.3	Incidence Stroke (564) CHD (567)
Dalmeijer et al., 2013 (12)	EPIC-NL Study, Netherlands	49-70	33625	Both	High	13.1	Incidence Stroke (531) CHD (1648)
Larsson et al., 2012 (27)	The Swedish Mammography Cohort and the Cohort of Swedish Men	45-83	74961	Both	High	10.2	Incidence Stroke (4089)
Sonestedt et al., 2011 (10)	Malmo Diet and Cancer Cohort, Sweden	44-74	26445	Both	High	12	Incidence Stroke (1176) Coronary Event (1344) CVD (2520)
Goldbohm et al., 2011 (14)	Netherlands Cohort Study, Netherlands	55-69	58279	Male	High	10	Mortality Stroke (842) IHD (2689)
van der Pols et al., 2009 (22)	The Body Orr Cohort, England and Scotland	8	4374	Both	High	65	Mortality CHD (378) Stroke (121)
Larsson et al., 2009 (13)	The ATBC Study, Finland	50-69	26556	Male	Moderate	13.6	Incidence Stroke (3281)
Elwood et al., 2004 (24)	The Caerphilly Cohort Study, UK	45-59	2403	Male	Moderate	20-24	Incidence Stroke (185) IHD (493) CVD (628)
Sauvaget et al., 2003 (23)	Life Span Study(LSS), Japanese	56	37130	Both	High	16	Mortality Stroke (1462)
Ness et al., 2001 (11)	The Collaborative Study, Scotland	35-64	5765	Male	Low	25	Mortality Stroke (196) CHD (892) CVD (1212)
Kinjo et al., 1999 (25)	Japanese	40-69	223170	Both	Low	15	Mortality Stroke (11030)

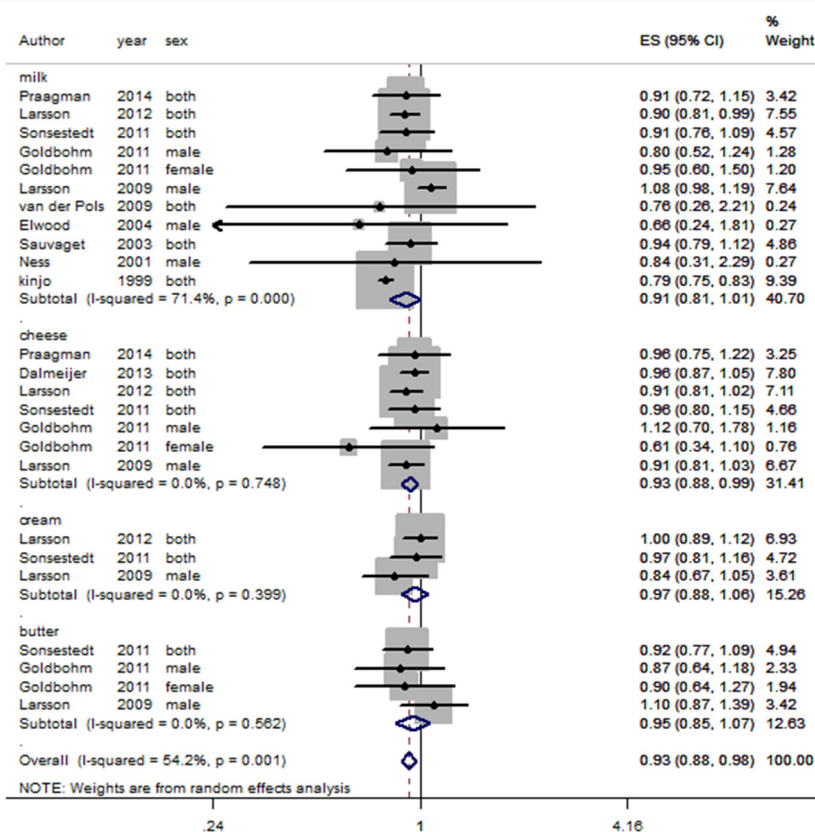


Fig. 3. Forest plot of relative risk by subgroup dairy products consumption and stroke (highest versus lowest intake)

#### The effect of milk, butter, cheese, and cream on stroke or CHD

Generally, there is no relationship between stroke and consumption of milk, cream, and butter: RR = 0.91 (95%

CI: 0.81-1.01) for milk, RR = 0.97 (95% CI: 0.88-1.06) for cream, and RR = 0.95 (95% CI: 0.85-1.07) for butter. However, it has been found that cheese decreases stroke risk: RR = 0.93 (95% CI: 0.88-0.99) (Fig. 3).

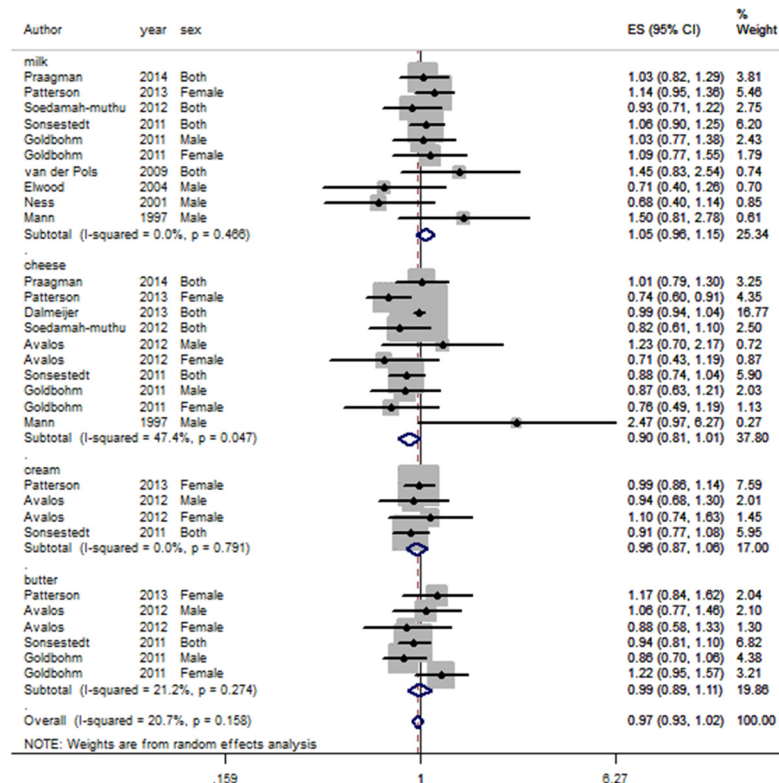


Fig. 4. Forest plot of relative risk by subgroup dairy products consumption and CHD (highest versus lowest intake)



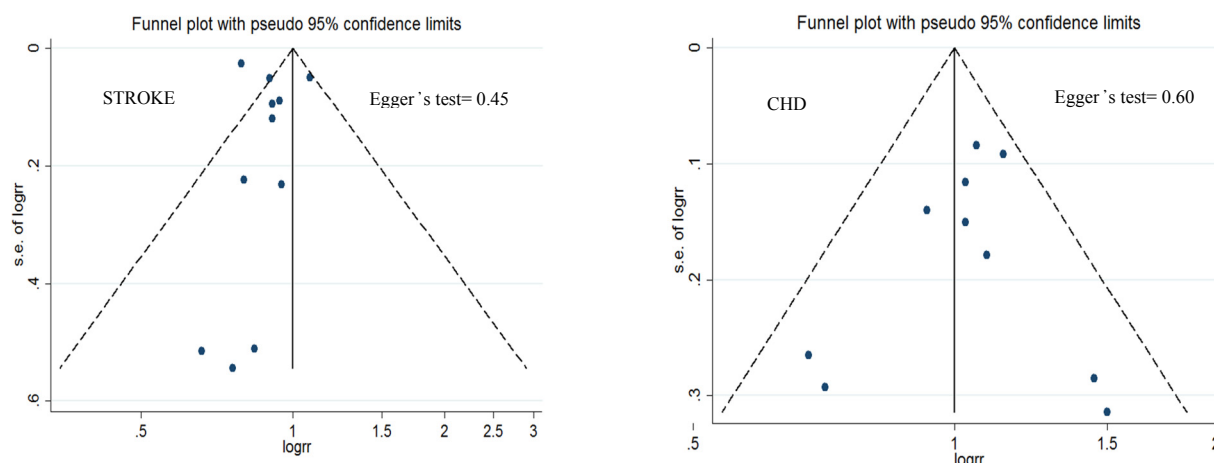


Fig. 5. Funnel plots for the analysis of milk consumption and stroke or, CHD

This meta-analysis showed different results concerning the relationship between dairy products consumption and CHD; some reported a positive effect and some negative, none of which was significant. The relationship between CHD and consumption of milk, cheese, cream, and butter is as follows, respectively:  $RR = 1.05$  (95% CI: 0.96-1.15),  $RR = 0.90$  (95% CI: 0.81-1.01),  $RR = 0.96$  (95% CI: 0.87-1.06),  $RR = 0.99$  (95% CI: 0.89-1.11). In other words, there is no relationship between consumption of dairy products and CHD (Fig. 4).

#### Heterogeneity, meta-regression, publication bias, and sensitivity analysis

Heterogeneity was  $I^2=0\%$  ( $P=0.46$ ) for milk,  $I^2=21.2\%$  ( $P=0.27$ ) for butter, and  $I^2=0\%$  ( $p=0.79$ ) for cream, showing no heterogeneity for milk, butter, and cream in relation to CHD. However, heterogeneity did exist for cheese in relation to CHD, ie,  $I^2=47.4\%$  ( $p=0.04$ ). With regards to the heterogeneity of stroke and dairy, heterogeneity only existed for milk,  $I^2=71.4\%$  ( $p<0.001$ ) and not for other products ( $I^2=0\%$ ).

It was not possible to execute a meta-regression to detect heterogeneity sources, because there were not enough studies in each subgroup.

However, considering the results of Egger test, there were not any publication bias about the relationship of subgroup dairy products and CHD. Egger test results for milk was  $p = 0.60$ , it was  $p = 0.38$  for cheese,  $p = 0.44$  for cream, and  $p = 0.45$  for butter, but the funnel plot was asymmetric only in the relationship between milk and CHD because of small study effects in 4 studies, which were deleted (11, 22, 24, 26). The study index of  $RR = 1.06$  (95% CI: 0.97-1.16) was obtained, which did not differ remarkably from the main index for CHD (Fig. 5).

For stroke, Egger test-based publication bias results was  $p = 0.45$  for milk,  $p = 0.65$  for cheese,  $p = 0.30$  for cream, and  $p = 0.87$  for butter, so all of them were meaningless. However, the funnel plot was asymmetric only in the relationship between milk and stroke due to small study effects in 3 studies (11, 22, 24), which were deleted, and a general estimation of the study index of  $RR = 0.91$  (95% CI: 0.81-1.02) was obtained, which did not differ remarkably from

the main index (Fig. 5).

The results of milk sensitivity analysis revealed that the general conclusion of the study did not differ significantly with the deletion of each study, and its index was 1.05 (95% CI: 0.93 -1.17). Moreover, the results for stroke revealed that the parameter was 0.91 (95% CI: 0.79-1.03). After excluding the ATBC study (13), the study index changed remarkably  $RR = 0.85$  (95% CI: 0.78-0.91), and the heterogeneity decreased from 71.4% to 12.3%. The results of sensitivity analysis on the relationship between consumption of cheese, butter, and milk with CHD and stroke indicated that deletion of each study did not considerably change the main index.

#### Discussion

As there is a great adverse effect of CVD on public health, implementing strategies to identify changeable factors that are capable of minimizing the likelihood of these diseases is highly important. Therefore, attempting to assess the possible associations between the rate of dairy intake and CHD and stroke, we used all accessible data reported by prospective cohort studies. Despite using the data of observational studies, our results indicated no significant effect of dairy intake on rate of CVD.

In this meta-analysis, no relationship was found between stroke or CHD event and consumption of milk, cheese, cream and butter. Nevertheless, in 2014, the meta-analysis of 15 cohort studies showed a non-linear relationship between milk and stroke. It was found that consumption of fermented milk (200 mL/day) decreases the incidence of stroke by 18%. This study expressed the relative risk of cheese consumption on stroke: [0.94(0.89-0.995)]. However, no relationship was found between the risk of stroke and consumption of non-fermented milk, cream and butter (28). Similarly, the meta-analysis done in year 2004 revealed that drinking milk has a slight effect on stroke or heart disease (29). However, in dose-response meta-analysis of prospective cohort studies, no relationship was found between milk intake and CHD or stroke (16).

Many cohort studies have conducted researches on the relationship between dairy subgroups and stroke and CVD,

among which a population-based study (2013) merits special remark; it showed that none of the dairy subgroups have any connection with CHD or stroke (12). In the Malmö Diet and Cancer Cohort, an interaction was observed between cheese and gender; and it was found that cheese consumption significantly decreases the risk of CVDs in females, but not in males (10). In addition, in Elwood prospective study on males, it was found that those with mid or high milk intake experienced stroke = 0.52 (0.27-0.99) and ischemic heart disease = 0.88 (0.56-1.40) (30). In contrast with these findings, in the Cohort Study of Male Stroke that included males aged 50 to 69 years, it was found that drinking milk increases intracerebral hemorrhage. (Disease incidence was 41% higher in the highest quintuple compared to the lowest one: RR=1.41 95% CI=1.02-1.96.) Meanwhile, no relationship was found between consumption of cheese, butter, and dairy subtypes and stroke (13). However, it should be taken into account that the population of the mentioned study was male smokers, a group who are more exposed to the risk of CVDs; thus, the findings of that study is not generalizable.

Considering the findings, if modified or processed milk products replace milk, it will be possible to lower the incidence of CHD. This is because processed milk products decrease hypercholesterolemia. Moreover, on the ground that cholesterol and triglyceride levels are 2 main factors causing CHD, so reducing their level will decrease CHD incidence. Additionally, an expert panel concluded that whole milk may not affect blood lipids as predicted from its fat content and fat composition (31). In Rossouw's study it was found that intake of skim milk and yoghurt lowers cholesterol level, but consuming milk has no effect on plasma cholesterol (32), and that fermented-milk consumers are 15% less prone to CVDs (10). In addition, a double blind crossover study indicated that daily intake of 90 gr immune milk decreases total cholesterol by 5.2% (95%CI=2.5- 7/9) and LDL by 7.4% (95%CI=4.1-10.7); this study claimed that immune milk can be efficient in nutritional management of those with hypercholesterolemia (33).

Limitations of this study were as follow: (1) Although the relative risk obtained in this study was adjusted for many important variables, some unadjusted variables may still be present and residual confounding may also exist; (2) While cohort studies are firm in causality, nutritional habits may change in the course of time, and therefore, the observed connection cannot be authentically approved.

### Conclusions

No relationship was found between various dairy products and CHD or stroke; only cheese decreased stroke risk by 7%. Moreover, considering the fewness of the studies, the results are not generalizable, and more studies need to be conducted.

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