European Journal of Clinical Nutrition (2011) 65, 1027–1031

0954-3007/11
www.nature.com/ejcn

ORIGINAL ARTICLE

Dairy consumption and risk of type 2 diabetes mellitus: a meta-analysis of cohort studies

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Background/Objectives: Milk intake is widely recommended for a healthy diet. Epidemiological studies have suggested that the consumption of dairy products may be associated with a reduction in type 2 diabetes mellitus (T2DM). A meta-analysis was conducted to elucidate the association between dairy products consumption and T2DM.
Subjects/Methods: A systematical literature search was done through the Medline database and seven related cohort studies were identified. The adjusted relative risks (RRs) with the highest and the lowest categories from each study were extracted to calculate the combined RR. A least-square trend estimation was applied to assess the dose-response relationships.
Results: A combined RR of 0.86 (95% confidence interval (CI), 0.79–0.92) was revealed on T2DM risk associated to dairy intake, with little evidence of heterogeneity. For subgroup analysis, a combined RR was 0.82 (95% CI, 0.74–0.90), 1.00 (95% CI, 0.89–1.10), 0.95 (95% CI, 0.86–1.05) and 0.83 (95% CI, 0.74–0.93) for the intake of low-fat dairy, high-fat dairy, whole milk and yogurt, respectively. Dose-response analysis showed that T2DM risk could be reduced 5% for total dairy products and 10% for low-fat dairy products.
Conclusion: An inverse association of daily intake of dairy products, especially low-fat dairy, with T2DM was revealed, indicating a beneficial effect of dairy consumption in the prevention of T2DM development.
European Journal of Clinical Nutrition (2011) **65,** 1027–1031; doi:10.1038/ejcn.2011.62; published online 11 May 2011

Keywords: dairy products; type 2 diabetes mellitus; meta-analysis

Introduction

The world prevalence of type 2 diabetes mellitus (T2DM) is increasing at an alarming rate. T2DM affects approximately 190 million people worldwide and it is very likely to increase to 366 million by 2030 (Wild *et al*., 2004). Epidemiological data suggest that the prevalence will continue to increase globally without effective prevention and control (Alberti *et al*., 2007). Human studies have shown that diet and lifestyle modifications may have an important role in preventing T2DM (Eriksson and Lindgarde, 1991; Lindstrom *et al*., 2003).

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Contributors: L-QQ designed this article and supported the research. XT collected the data and performed the statistical analysis. J-YD assisted the statistical analysis. Z-WW and WL assisted the collection of data. All authors read and approved this article.
Received 23 August 2010; revised 1 March 2011; accepted 9 March 2011; published online 11 May 2011

In recent years, the role of dairy products in the etiology of T2DM has created considerable attention in research fields. Some cohort studies aiming at examining the relationship between the intake of dairy products and T2DM observed a significantly inverse association, but others showed negative results. Some factors related to the dairy components have been assumed to modify the effect of dairy intake on T2DM, such as the type and fat level of the dairy products, as well as the amount of daily consumption. Although a recent review reported the prevention of dairy intake to T2DM (Pittas *et al*., 2007), these factors have not been included. To clarify the mechanism by which dairy consumption prevents human from T2DM, it is reasonable to examine the association between these factors and T2DM risk, using a meta-analysis of cohort studies.

Materials and methods

The literature search was conducted with the Medline database through April 2010, using the English terms in combination of milk/dairy products and T2DM, with

extended search on diet and T2DM. References listed in the searched papers were used for additional screening of relevant data.

A study was included as a candidate if it met the following criteria: (1) The paper presented original data from a cohort study. (2) Among multiple publications based on the same population study or the same results published in different journals, only the most recent one would be included for the analysis. (3) Whole milk, yogurt, low-fat dairy or high-fat dairy foods were not included in the analysis of 'dairy products' if they were presented individually. However, a combined relative risk (RR) would be calculated if they were observed as an independent item in more than three studies. To avoid confusion, 'dairy' and 'total dairy foods' used in the original studies were termed as 'dairy products' and 'milk' as 'whole milk' in this meta-analysis. (4) RR and its 95% confidence interval (95% CI) were provided, or raw data were available in the paper for calculating these parameters. (5) The RR and the corresponding 95% CI extracted from the literature were compared to obtain the highest and the lowest amount of dairy consumption. When more than one risk estimates presented, the one adjusted for the greatest number of potential confounders was used to meet with the optimal control of confounding factors.

Communication letters, abstracts and conference proceedings published in non-peer-reviewed journals, and participants with type 2 diabetes at baseline were excluded for analysis to avoid bias.

Data extracted from the selected papers included the name of the first author, publication year, gender, study design, location of the study, duration of follow-up, sample size, adjustments and risk estimates with 95% CI.

Combined RR was calculated using the 'META' command in the Stata statistical software package (version, 8.0, Stata Corporation, College Station, TX, USA). Statistical heterogeneity among studies was assessed using the Q statistic. P-value <0.10 was considered as heterogeneous and random effects models were selected for statistics. We also examined I^2 statistic, which measures the percentage of the total variation across studies that is due to heterogeneity, rather than chance (Higgins and Thompson, 2002). In addition, we conducted a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting one study in each turn. A dose-response analysis is performed on the basis of the data for categories of dairy products intake levels on median dose, number of cases and participants and adjusted logarithm of the RR with its SE using the 'GLST' command in Stata software package (Greenland and Longnecker, 1992). This analysis was restricted to the studies reporting three or more exposure levels. For different units used in individual studies, we chose serving, used by most studies, as the standard unit of measure to express the daily dairy products consumption. When the median intake value was not reported, we used the midpoint of each category. For an open-ended upper category of intake, the intake amount was estimated by assuming the same amplitude as the previous category.

Publication bias was assessed by two formal tests: the Begg-adjusted rank correlation test (Begg and Mazumdar, 1994) and the Egger's regression asymmetry test (Egger *et al*., 1997). If a potential bias was detected, we further conducted a sensitivity analysis to assess the robustness of combined effect estimates and the possible influence of the bias.

Results

A total of seven publications with cohort studies (Choi *et al*., 2005; Liu *et al*., 2006; Pittas *et al*., 2006; van Dam *et al*., 2006; Elwood *et al*., 2007; Kirii *et al*., 2009; Villegas *et al*., 2009) on dairy and milk consumption and T2DM were included according to the criteria (Table 1). In the study by Kirii *et al*. (2009), participants were divided to men and women for observation. Thus, it was considered two studies when the observed items were combined. Among these studies, dairy products appeared as items in six studies (Choi *et al*., 2005; Liu *et al*., 2006; Pittas *et al*., 2006; van Dam *et al*., 2006; Elwood *et al*., 2007; Kirii *et al*., 2009), low-fat and high-fat dairy foods appeared in three studies (Choi *et al*., 2005; Liu *et al*., 2006; van Dam *et al*., 2006), whole milk appeared in four studies (Choi *et al*., 2005; Liu *et al*., 2006; Kirii *et al*., 2009; Villegas *et al*., 2009) and yogurt appeared in three studies (Choi *et al*., 2005; Liu *et al*., 2006; Kirii *et al*., 2009).

When we compared the highest with the lowest dairy products intake, the combined RR was 0.86 (95% CI, 0.79–0.92), with little evidence of heterogeneity ($Q=8.53$, $P=0.20$; $I^2=29.7\%$) (Figure 1). The test for publication bias yielded a P-value of 0.26 by Begg test and a P-value of 0.20 by Egger test. The sensitivity analyses omitting one study at a time and calculating the combined RRs for the remaining studies yielded consistent results, with a narrow range from 0.85 (95% CI, 0.77–0.93) to 0.88 (95% CI, 0.82–0.96). Thus, any single study did not appear to substantially influence the combined risk estimate.

In the subgroup analysis stratified by sex, the combined RR for the highest versus lowest quartiles of dairy intake was 0.86 (95% CI, 0.79–0.93) in women, whereas in men, the combined RR was 0.89 (95% CI 0.56, 1.21).

Considering fat level of dairy products, analysis on low-fat and high-fat dairy foods consumption yielded a combined RR of 0.82 (95% CI, 0.74–0.90) and 1.00 (95% CI, 0.89–1.10), respectively. For the type of products, the combined RR was 0.95 (95% CI, 0.86–1.05) in the studies reported, RR estimates for whole milk consumption and risk of T2DM and 0.83 (95% CI, 0.74–0.93) in the studies observing yogurt consumption (Table 2).

Three cohort studies (Choi *et al*., 2005; Liu *et al*., 2006; van Dam *et al*., 2006) were included in the dose-response analysis of the association between dairy products, low-fat and high-fat dairy foods intake and risk of T2DM. The combined RR for an increment of one serving per day was 0.94 (95% CI,

Table 1 Characteristics of the cohort studies of dairy products intake and T2DM

First author, year	*Location of study*	*Sex*	*Age, mean or range (year)*	*BMI (kg/m^2)*	*No. of cases/total (year of follow-up)*	*Items*	*Predictor, lowest and highest category*	*RR (95%CI)*	*Adjustments*
Choi *et al.*, 2005	USA	Men	53	25.4	1243/41 254 (12 year)	Dairy products	⩾2.9 vs <0.9 s/day	0.77 (0.62–0.95)	Age, energy, biennial follow-up time, family history of diabetes, smoking, BMI, hypercholesterolemia, hypertension, physical activity, alcohol, dietary factors.
						Low-fat dairy foods	>1.58 vs <0.14 s/day	0.73 (0.59–0.89)	
						High-fat dairy foods	>1.72 vs <0.38 s/day	0.97 (0.78–1.21)	
						Whole milk	⩾2/week vs <1/month	1.19 (1.00–1.43)	
						Yogurt	⩾2/week vs <2/month	0.83 (0.66–1.06)	
Liu *et al.*, 2006	USA	Women	55	25.8	1603/37 183 (10 year)	Dairy products	>2.9 vs <0.85 s/day	0.79 (0.67–0.94)	Age, energy, randomized-treatment assignment, family history of diabetes, smoking, BMI, hypercholesterolemia, hypertension, physical activity, hormones, alcohol consumption.
						Low-fat dairy foods	>2.00 vs⩽0.27 s/day	0.79 (0.67–0.93)	
						High-fat dairy foods	>1.329 vs <0.20 s/day	1.05 (0.88–1.24)	
						Whole milk	⩾2/week vs <1/month	1.04 (0.84–1.30)	
						Yogurt	⩾2/week vs <2/month	0.82 (0.70–0.97)	
van Dam *et al.*, 2006	USA	Women	39	27.6	1964/41 186 (8 year)	Dairy products	⩾2s/day vs <1 s/week	0.93 (0.75–1.15)	Age, energy, BMI, smoking, physical activity, alcohol consumption, parental history of diabetes, education, coffee, diet.
						Low-fat dairy foods	⩾1 vs <1 s/week	0.87 (0.76–1.00)	
						High-fat dairy foods	⩾1/day vs <2 s/week	1.03 (0.88–1.20)	
Pittas *et al.*, 2006	UAS	Women	46	24.2	4843/83 779 (20 year)	Dairy products	⩾3 vs <1 s/day	0.89 (0.81–0.99)	Age, BMI, exercise, diabetes family history, smoking, alcohol, coffee, diet, hypertension.
Elwood *et al.*, 2007	UK	Men			41/640 (25 year)	Dairy products	Highest vs lowest quintile	0.57 (0.20–1.63)	Age, smoking, BMI, social class.
Kirii *et al.*, 2009	Japan	Men	57	23.6	634/25 877 (5 year)	Dairy products	⩾300 vs <50 g/day	1.18 (0.90–1.56)	Age, area, BMI, family history of diabetes mellitus, smoking, alcohol, history of hypertension, exercise frequency, coffee, energy-adjusted magnesium and total energy.
						Whole milk	⩾200 vs <50 g/day	1.02 (0.85–1.24)	
						Yogurt	⩾60 vs 0 g/day	1.01 (0.75–1.36)	
		Women	57	23.5	480/33 919 (5 year)	Dairy products	⩾300 vs <50 g/day	0.71 (0.51–0.98)	
						Whole milk	⩾200 vs <50 g/day	0.87 (0.70–1.09)	
						Yogurt	⩾60 vs 0 g/day	0.77 (0.58–1.01)	
Villegas *et al.*, 2009	China	Women	51	23.8	2270/64 191 (6.9 year)	Whole milk	>200 g/day vs None	0.60 (0.41–0.88)	Age, BMI, smoking, alcohol, waist-hip ratio, activity, income, education, occupation, hypertension, energy.

Abbreviation: BMI, body mass index.

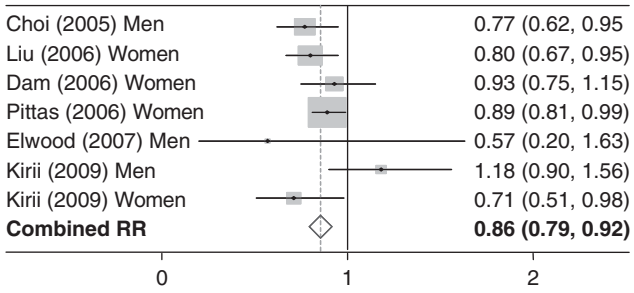

Figure 1 Estimated RRs (highest versus lowest category) of T2DM associated with dairy products consumption. Tests for heterogeneity between all studies, $Q = 8.53$, $P = 0.20$, $I^2 = 29.7\%$.

Table 2 Summary of the relative risk for milk and/or dairy food consumption and T2DM

Item	*Number of cohort studies*	*Combined RR*[a]	*95% CI*
Dairy products	6	0.86	0.79–0.92
Low-fat dairy foods	3	0.82	0.74–0.90
High-fat dairy foods	3	1.00	0.89–1.10
Whole milk	5	0.95	0.86–1.05
Yogurt	4	0.83	0.74–0.93

[a]RR and CI extracted from these studies compared the highest with the lowest quantile of consumption and reflected the greatest degree of control for confounders.

0.92–0.97) for total dairy consumption, 0.90 (95% CI, 0.85–0.95) for low-fat dairy foods and 0.98 (95% CI, 0.92–1.05) for high-fat dairy foods.

Statistical test gave rise to no evidence of publication bias with regard to consumption of dairy and milk and T2DM risk.

Discussion

The result of the present analysis revealed a 14% reduction in T2DM risk in population with highest consumption of dairy products compared with the lowest intake. In the recent meta-analysis focusing on the consumption of milk and dairy foods and incidence of vascular disease, the reduction in the consumption of milk and dairy foods in diabetes was referred and not further analysis and discussion (Elwood *et al*., 2010). Our analysis included two more updated cohort studies and analyzed the different kinds of dairy and dose-response relationship.

In the subgroup analysis, consumption of low-fat dairy foods was found to be associated with a significantly lower risk of 18% in T2DM development. However, intake of high-fat dairy foods and whole milk was not associated with the risk of T2DM. The dose-response analysis also showed that the T2DM risk significantly lowered by 10% with one serving per day increment for low-fat dairy foods. However, dose-response relationship was insignificant for high-fat dairy foods. The weak association between high-fat dairy foods intake and T2DM in our study can be, at least partly, explained by the high-fat dairy foods contributing considerable fat to dietary intake. Some epidemiological studies have shown that consumption of diets high in saturated fat is associated with obesity and increased prevalence of diabetes (van Dam *et al*., 2002; Thanopoulou *et al*., 2003). Thus, the protective effect may largely due to other nutrients in milk and its products.

In Pittas *et al*.'s (2006) study, the inverse association between dairy products consumption and risk of T2DM appeared to be insignificant after adjusting for calcium and vitamin D, suggesting an effect of calcium and vitamin D on the prevention of diabetes. There are several potential mechanisms for the effects of calcium and vitamin D on T2DM. Calcium provided by dairy products could decrease accumulation of body fat and accelerate weight and fat loss during energy restriction (Zemel *et al*., 2000; Zemel, 2004). Additionally, calcium intake may increase fat oxidation, suppress adipose tissue oxidative and inflammatory stress, whereas adequate vitamin D may enhance the thermic effect of a meal and fat oxidation (Teegarden *et al*., 2008; Zemel and Sun, 2008).

On the other hand, Liu *et al*.'s (2006) study found that the association remained unchanged after adjusting for calcium and vitamin D. Thus, aside from calcium and vitamin D, there could be other major components in dairy products having a potential role in lowering the risk of T2DM. Recently, milk proteins, such as whey proteins, attracted increasing attention. It may enhance satiety and reduce the risk of overweight, high blood pressure and obesity, which are major risk factors for T2DM (Luhovyy *et al*., 2007). In animal study, whey protein was observed to enhance the insulin sensitivity (Belobrajdic *et al*., 2004). As insulin resistance is a pathologic basis in T2DM, the insulinotropic effects of whey proteins are prone to have an important role in preventing T2DM. Furthermore, in addition to milk proteins, trans-palmitoleate, which is obtained primarily from dairy intake, was associated with a lower incidence of diabetes. This finding supported a role of trans-palmitoleate in previously observed metabolic benefits of dairy consumption. So trans-palmitoleate may also have a beneficial effect on T2DM (Mozaffarian *et al*., 2010).

In addition, other factors, including sex, body mass index and age, are worth considering. Our analysis found an inverse association between dairy intake and the risk of T2DM in women, but not in men. Because evidence is limited, to explain this sex-related difference is challenging. In Kirii *et al*.'s (2009) study, women consumed greater amounts of dairy products than men, which may be one possible explanation. Among the included studies, two (Choi *et al*., 2005; Liu *et al*., 2006) have assessed the influence of body mass index on the association between dairy consumption and risk of T2DM, but no effect modification by body mass index was found. As for age, all included cohort studies have adjusted for this important confounder.

However, none of them examined the effect modification by age on the dairy and T2DM association. Therefore, whether age has potential impacts on the association remains unclear.

Several potential limitations are worth considering in this study. First, the publication bias cannot be completely excluded. However, no evidence of publication bias was observed by statistical tests. Second, the definition of dairy products was ambiguous in some studies and components in dairy products may be different according to countries. Thus, we analyzed whole milk and dairy foods classified by fat content, which should be less heterogeneous than dairy foods as total. In this subgroup analysis, we found that fat in dairy foods masked the protective effect of milk and its products on T2DM. Third, the efficiency of analysis was limited, because some items were combined from only three or four studies. Fourth, as only seven studies were included in this meta-analysis, the combined risk estimate may be affected by individual studies, especially the one weighted the highest (Pittas *et al*., 2006). Yet, the consistent results from the sensitivity analyses indicated a somewhat high degree of robustness of our findings. Finally, although a wide range of potential confounding factors was controlled in original studies, we still could not exclude the possibility that uncontrolled confounding factors could affect the association. Further studies with adequate control for potential confounders are needed to confirm the findings.

In conclusion, our findings indicated an inverse association of daily intake of dairy products with T2DM, suggesting a beneficial effect of dairy consumption in the prevention of T2DM.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This research was supported in part by a grant from National Natural Science Foundation of China (No. 30771808) to Dr Li-Qiang Qin.

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