Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies\textsuperscript{1,2}

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ABSTRACT

Background: A growing number of cohort studies suggest a potential role of dairy consumption in type 2 diabetes (T2D) prevention. The strength of this association and the amount of dairy needed is not clear.

Objective: We performed a meta-analysis to quantify the associations of incident T2D with dairy foods at different levels of intake.

Design: A systematic literature search of the PubMed, Scopus, and Embase databases (from inception to 14 April 2015) was supplemented by hand searches of reference lists and correspondence with authors of prior studies. Included were prospective cohort studies that examined the association between dairy and incident T2D in healthy adults. Data were extracted with the use of a predefined protocol, with double data-entry and study quality assessments. Random-effects meta-analyses with summarized dose-response data were performed for total, low-fat, and high-fat dairy, (types of) milk, (types of) fermented dairy, cream, ice cream, and sherbet. Nonlinear associations were investigated, with data modeled with the use of spline knots and visualized via spaghetti plots.

Results: The analysis included 22 cohort studies comprised of 579,832 individuals and 43,118 T2D cases. Total dairy was inversely associated with T2D risk (RR: 0.97 per 200-g/d increment; 95% CI: 0.95, 1.00; \( P = 0.04; \ F^2 = 66\% \)), with a suggestive but similar linear inverse association noted for low-fat dairy (RR: 0.96 per 200 g/d; 95% CI: 0.92, 1.00; \( P = 0.072; \ F^2 = 68\% \)). Nonlinear inverse associations were found for yogurt intake (at 80 g/d, RR: 0.86 compared with 0 g/d; 95% CI: 0.83, 0.90; \( P < 0.001; \ F^2 = 73\% \)) and ice cream intake (at \( \sim 10 \) g/d, RR: 0.81; 95% CI: 0.78, 0.85; \( P < 0.001; \ F^2 = 86\% \)), but no added incremental benefits were found at a higher intake. Other dairy types were not associated with T2D risk.

Conclusion: This dose-response meta-analysis of observational studies suggests a possible role for dairy foods, particularly yogurt, in the prevention of T2D. Results should be considered in the context of the observed heterogeneity.

Keywords: dairy, milk, yogurt, cheese, type 2 diabetes, meta-analysis, prospective/observational studies, dose-response associations

INTRODUCTION

The prevalence of type 2 diabetes (T2D) is increasing worldwide, from 8.3% in 2014 to an expected 10.1% (~592 million adults) in 2035 (1). T2D is considered to be a diet- and lifestyle-related disease. Large-scale intervention studies have demonstrated that a healthy diet and increased physical activity reduce the risk of progression to T2D by ~40% (2). An increasing number of prospective cohort studies suggest a potential role of modest dairy consumption in T2D prevention. Although meta-analyses are typically meant to be conclusive, the widely conflicting conclusions from prior meta-analyses of dairy and T2D (3–9) show that a more comprehensive systematic review is necessary, especially taking into account the potential dose-dependent effects of dairy. Prior meta-analyses of observational studies showed (nonlinear) inverse associations of total dairy with T2D, which was mainly confined to the intake of low-fat dairy (~10% lower risk for a 200-g daily intake) (3, 7, 9). These older meta-analyses also showed inverse associations with intake of yogurt (3, 7, 9) and cheese (3, 7), but not all studies have agreed. On the other hand, a more recent meta-analysis of 14 prospective studies, which included 3 large US cohorts with 18–30 y of follow-up, conflictingly showed no association for total dairy and T2D risk (per daily serving, RR: 0.98; 95% CI: 0.96, 1.01) (4) and also no associations for low-fat or high-fat dairy in a separate analysis of the 3 US cohorts (4). The meta-analysis did show, however, a significant 18% lower risk per daily serving of yogurt (4). Recently, several new population-based cohorts on dairy consumption and T2D have been published (10–12). Therefore, to resolve conflicts and use all the available data (a total of 22 prospective cohort studies)

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\textsuperscript{1}This meta-analysis project on dairy products and incident diabetes was funded by Wageningen University.

\textsuperscript{2}Supplemental Methods, Supplemental Figures 1–28, and Supplemental Tables 1–5 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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(4, 10–28), we systematically examined a wide range of dairy foods in relation to risk of T2D in healthy adults by means of a comprehensive dose-response meta-analysis. This project used approaches similar to those gained from our previously published dairy meta-analyses with cardiovascular disease (29) and hypertension (30) as the outcome.

METHODS

Data sources and searches

This review was conducted and reported in accordance with the Meta-analysis Of Observational Studies in Epidemiology guidelines (31). Two analysts (LG and SSS-M) performed a systematic literature search based on the query syntax shown in the Supplemental Methods in the databases PubMed, Scopus, and Embase (from inception through 14 April 2015).

Study selection

Titles, abstracts, and full texts of retrieved articles were screened for the following predefined inclusion criteria: dairy intake as main exposure, T2D as outcome, prospective cohort as design, healthy adults (baseline age of ≥20 y), original article, and English language. Excluded were studies in animals, children, and ill populations. In addition, we hand-searched reference lists of identified relevant studies and of previous reviews and meta-analyses. Of 76 fully reviewed articles, 33 articles (4, 10–28, 32–44) met the inclusion criteria (see Figure 1). Subsequently, 13 articles were excluded for the following reasons: duplicate analysis of the same study population (32–35, 38–40, 42, 43), not able to separate T2D from impaired fasting glucose (37), data not suitable for nonlinear associations (44), and insufficient data (36, 41). Eventually, 20 articles based on 22 different cohorts (4, 10–28), of which 2 (12, 22) were case-cohort studies, were available for the meta-analysis. Kirii et al. (16) presented data for men and women separately, which were entered as 2 study populations in the meta-analysis.

Data extraction and quality assessment

Data were extracted from published articles with the use of a predefined protocol, and double data-entry was performed. Apart from descriptive characteristics, we extracted the following data for each category of dairy intake: range of intake, median, number of subjects and T2D cases, person-years at risk, and RR with the corresponding 95% CI. For studies that presented several multivariable-adjusted RRs, the model with the largest number of covariates was taken. For studies not reporting the median of each category, we took the mean of the lower and the upper limit. When dairy intake was presented in servings or times per day, week, or month, we converted the intake to grams per day with the use of standard units of 177 g for total, low-fat, and high-fat dairy; 244 g for total, low-fat, and high-fat milk (585 g for 1 pint of milk); 244 g for yogurt; 43 g for cheese; and 25 g for cream (45, 46). When studies reported conversion factors, these factors were applied (14, 18, 19, 28). For several studies (13, 15, 19–22, 24) additional data were provided by the authors or coworkers.

FIGURE 1 Flowchart of literature search for meta-analysis on dairy intake and incident T2D. T2D, type 2 diabetes.
There were overlapping data for 2 studies, namely, the European Prospective Investigation into Cancer and Nutrition (EPIC)–InterAct (22) and EPIC-Norfolk (12). When both studies reported on the same dairy food item, data from the EPIC-InterAct study (22) were extracted. For dairy items not analyzed in the EPIC-InterAct study (22), the EPIC-Norfolk (12) data were extracted.

Two reviewers (LG and SSS-M) independently evaluated the quality of the included studies with the use of the Newcastle-Ottawa quality scale (47). The rating system scores studies from 0 (highest degree of bias) to 9 (lowest degree of bias), taking into account selection, comparability, and outcome assessment.

Data synthesis and analysis

Meta-analysis was performed when ≥3 cohort studies/dairy type were available, which was the case for total dairy, low-fat dairy, high-fat dairy, total milk, low-fat milk, high-fat milk, cheese, yogurt, fermented dairy, cream, ice cream, and sherbet. Linearity of associations between dairy foods and risk of T2D were analyzed with the use of spline analysis and dose-response (generalized least-square trend) meta-regression. Splined variables were created with the use of MKSPLINE in Stata version 11.0. Goodness-of-fit tests and chi-square statistics were used to determine the most appropriate knot points and maximal goodness of fit, to determine the best dose-response inflection point of the nonlinear association. Linear and non-linear associations were further analyzed with the use of dose-response generalized least-square trend meta-regression analysis. Random-effects meta-regression trend estimation of summarized dose-response data, described by Greenland and Longnecker (48), was used to derive the incremental dose-response RRs. For linear associations, the incremental dose-response RRs were expressed per serving size and fitted within the range of dairy intake of all studies. For non-linear associations, the knot points defined these numbers. The shapes of the associations within individual studies were visualized by means of spaghetti plots, as described previously (49). Forest plots were made to visually assess the linear dose-response slopes and corresponding 95% CIs across studies (Supplemental Figures 1–12). We performed sensitivity analysis (based on linear dose-response slopes) by excluding one study at a time from the analyses.

To explore the presence of statistical heterogeneity, Cochran’s Q test was conducted and the I^2 statistic was calculated, representing the percentage of total variation attributable to between-study heterogeneity (50). Subgroup analyses were performed (based on linear dose-response slopes) by sex, age (<50, 51–60, and >60 y), continent, follow-up duration (≤5, 6–10, and >10 y), and degree of adjustment. Subgroups for degree of adjustment were based on whether or not studies adjusted for the major confounders of age, sex, smoking, total energy intake, and BMI. We performed subgroup analyses by the Newcastle-Ottawa quality score (<7 or ≥7), but the subgroups were identical to the subgroups based on degree of adjustment; therefore, we only presented the results for the latter. Potential publication bias was assessed by the Egger’s test (51) and by symmetry of individual study linear dose-response slopes of the funnel plot, if ≥8 cohort studies were available. Values reported in text and tables are RRs and 95% CIs. Two-sided P values < 0.05 were considered to be statistically significant.

RESULTS

Study characteristics

An overview of 22 prospective cohort studies based on 23 study populations (mean age >36 y), with a total of 579,832 individuals and 43,118 T2D cases, is provided in Table 1. The sample size of the cohorts ranged from 640 to 85,884, and the duration of follow-up ranged from 2.6 to 30 y. Nine studies were conducted in the United States (4, 14, 17, 19, 21, 25, 26), 8 in Europe (10–13, 20, 22–24), 3 in Asia (16, 27, 28), and 2 in Australia (15, 18). The dairy foods studied and definitions of dairy categories differed across studies, as described in Supplemental Table 1. Total dairy consumption (based on median intake amounts in populations) ranged from 111 to 400 g/d for all studies combined, and from 121 to 347 g/d in the United States, from 121 to 400 g/d in Europe, from 111 to 171 g/d in Asia and from 266 to 347 g/d in Australia. In studies reporting total dairy, milk made the largest contribution to total dairy intake (range: 62–331 g of milk/d), and more low-fat dairy (range: 65–294 g/d) than high-fat dairy (range: 17–135 g/d) was consumed. Study characteristics by dairy type are shown in Supplemental Table 2. The study-specific quality assessment ratings and scores are shown in Supplemental Table 3. Total scores ranged from 3 to 9, with 14 studies scoring ≥7.

Total, low-fat, and high-fat dairy and T2D

Total dairy intake (16 studies) (4, 10, 11, 13, 15–19, 22–25, 28) was linearly associated with a 3% lower T2D risk per 200 g/d (equal to 1.1 serving/d or 7.1 ounces/d) (RR: 0.97; 95% CI: 0.95, 1.00; P = 0.044) (Figure 2). Significant heterogeneity was present (I^2 = 66%, P < 0.001). Subgroup analyses (Supplemental Table 4) suggested a stronger inverse association in Asian populations (RR: 0.85 per 200 g/d; 95% CI: 0.65, 1.12), but no association in European populations. Also, in studies not adjusting for the major confounders, the association tended to be stronger (RR: 0.88 per 200 g/d; 95% CI: 0.76, 1.03). There was no evidence of publication bias, as indicated by the funnel plot (Supplemental Figure 13) and the Egger’s test (P = 0.11).

For low-fat dairy (13 studies) (4, 10–12, 17–19, 21, 23–25), a borderline significant linear inverse association with T2D risk was observed, with a 4% lower risk per 200 g/d (RR: 0.96; 95% CI: 0.92, 1.00; P = 0.072) (Figure 3). Significant heterogeneity was present (I^2 = 68%, P < 0.001). Subgroup analyses (Supplemental Table 4) indicated stronger inverse associations in populations aged >60 y (RR: 0.84 per 200 g/d; 95% CI: 0.77, 0.93) and in studies with a follow-up of 6–10 y (RR: 0.88 per 200 g/d; 95% CI: 0.82, 0.94). There was no evidence of publication bias (Supplemental Figure 14; Egger’s test: P = 0.096).

High-fat dairy intake (13 studies) (4, 10–12, 17, 18, 20, 21, 23–25) showed no association with T2D risk (RR: 0.98 per 200 g/d; 95% CI: 0.93, 1.04; P = 0.52) (Supplemental Figure 15). There was significant heterogeneity (I^2 = 52%, P = 0.016). In sensitivity analyses (Supplemental Table 5), excluding the study by Ericson et al. (11) reduced I^2 to 26% (P = 0.42), with results remaining similar (RR: 1.01 per 200 g/d; 95% CI: 0.97,
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<tr>
<th>Author, year</th>
<th>Cohort (follow-up duration) and baseline examination</th>
<th>Location</th>
<th>Men, %</th>
<th>Mean age, y</th>
<th>Mean BMI, kg/m²</th>
<th>Cases/total, n</th>
<th>Dairy type included in meta-analysis</th>
<th>Dietary assessment</th>
<th>Diabetes ascertainment</th>
<th>Adjustments</th>
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<tr>
<td>Chen et al., 2014 (4)</td>
<td>Health Professionals Follow-Up Study (24 y) 1986</td>
<td>United States</td>
<td>100</td>
<td>53</td>
<td>24.9</td>
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<td>Updated validated FFQ</td>
<td>Self-report plus supplementary questionnaire about symptoms, diagnostic tests, and hypoglycemic therapy, validated by medical records</td>
<td>Age, BMI, total energy intake, race, smoking, physical activity, alcohol consumption, diabetes family history, hypertension, hypercholesterolemia, trans fat intake, glycemic load, red and processed meat intake, nut intake, sugar-sweetened beverage intake, and coffee intake</td>
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<td>Chen et al., 2014 (4)</td>
<td>Nurses' Health Study (30 y) 1980</td>
<td>United States</td>
<td>0</td>
<td>46</td>
<td>24.2</td>
<td>7841/67,138</td>
<td>Total dairy</td>
<td>Updated validated FFQ</td>
<td>Self-report plus supplementary questionnaire about symptoms, diagnostic tests, and hypoglycemic therapy, validated by medical records</td>
<td>Age, BMI, total energy intake, race, smoking, physical activity, alcohol consumption, menopausal status and menopausal hormone use, diabetes family history, hypertension, hypercholesterolemia, trans fat intake, glycemic load, red and processed meat intake, nut intake, sugar-sweetened beverage intake, and coffee intake</td>
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<tr>
<td>Chen et al., 2014 (4)</td>
<td>Nurses' Health Study II (18 y) 1991</td>
<td>United States</td>
<td>0</td>
<td>36</td>
<td>24.5</td>
<td>3951/85,884</td>
<td>Total dairy</td>
<td>Updated validated FFQ</td>
<td>Self-report plus supplementary questionnaire about symptoms, diagnostic tests, and hypoglycemic therapy, validated by medical records</td>
<td>Age, BMI, total energy intake, race, smoking, physical activity, alcohol consumption, menopausal status and menopausal hormone use, oral contraceptive use, diabetes family history, hypertension, hypercholesterolemia, trans fat intake, glycemic load, red and processed meat intake, nut intake, sugar-sweetened beverage intake, and coffee intake</td>
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<th>Diabetes ascertainment</th>
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<td>Díaz-López et al., 2015 (10)</td>
<td>PREDIMED Study (4.1 y) 2003–2009</td>
<td>Spain</td>
<td>38 67 30.0</td>
<td>270/3454</td>
<td>Total dairy Low-fat dairy High-fat dairy Total milk Low-fat milk High-fat milk Fermented dairy Cheese Yogurt</td>
<td>Validated 137-item FFQ</td>
<td>Fasting plasma glucose ≥7 mmol/L or 2-h plasma glucose ≥11.1 mmol/L after a 75-g oral glucose load</td>
<td>Age, sex, BMI, dietary intervention group, leisure-time physical activity, education level, smoking, hypertension or antihypertensive use, fasting glucose, HDL cholesterol, triglycerides, and intake of vegetables, legumes, fruits, cereals, meat, fish, olive oil, nuts, alcohol and alcohol-squared in g/d</td>
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<td>Elwood et al., 2007 (13)</td>
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<td>100 52 26</td>
<td>41/640</td>
<td>Total dairy Total milk</td>
<td>7-d weighed dietary intake records</td>
<td>Self-report</td>
<td>For total dairy: age, smoking, social class, prevalent heart disease, total cholesterol, HDL cholesterol, alcohol, and total fat. Milk intake: Age, smoking, BMI, and social class</td>
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<td>Ericson et al., 2015 (11)</td>
<td>Malmö Diet and Cancer Cohort (14 y) 1991–1996</td>
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<td>39 58 25.8</td>
<td>2860/26,930</td>
<td>Total dairy Low-fat dairy High-fat dairy Total milk Low-fat milk High-fat milk Low-fat and high-fat fermented dairy Cheese Yogurt Cream Ice cream</td>
<td>Validated 7-d menu book, 168-item FFQ, and interview</td>
<td>Registries with a physician diagnosis of fasting plasma glucose ≥7.0 mmol/L or fasting whole-blood concentration ≥6.1 mmol/L, measured at 2 different occasions, or ≥2 glycated hemoglobin values &gt;6.0%</td>
<td>Age, sex, method version, season, total energy intake, leisure-time physical activity, smoking, alcohol intake, education, and BMI</td>
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<td>Puerto Rico Heart Health Program (2.6 y) 1965–1968</td>
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<td>Grantham et al., 2013 (15)</td>
<td>Australian Diabetes Obesity and Lifestyle Study (5 y) 1999–2000</td>
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<td>Total dairy</td>
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<td>121-item FFQ</td>
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<td>Age, sex, energy intake, family history of diabetes, education level, level of physical activity, smoking status, triglycerides, HDL cholesterol, systolic blood pressure, waist circumference, and hip circumference</td>
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<td>Kiri et al., 2009 (16)</td>
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<td>23.6 634/25,877</td>
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<td>United States</td>
<td>0 55</td>
<td>25.9 1603/37,183</td>
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<td>Blue Mountains Eye Study (10 y) 1992–1994</td>
<td>Australia</td>
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<td>26.2 145/1824</td>
<td>Total dairy</td>
<td>Low-fat dairy</td>
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<td>145-item FFQ</td>
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<td>Margolis et al., 2011 (19)</td>
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<td>Finnish Mobile Clinic Health Examination Survey (23 y) 1967–1972</td>
<td>Finland</td>
<td>53</td>
<td>52</td>
<td>26.5</td>
<td>383/4304</td>
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<td>Dietary history interview with the use of a 100-item questionnaire</td>
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<td>Nettleton et al., 2008 (21)</td>
<td>Multi-Ethnic Study of Atherosclerosis (5 y) 2000–2002</td>
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<td>47</td>
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<td>O’Connor et al., 2014 (12)</td>
<td>EPIC-Norfolk Study (11 y) 1993–1997</td>
<td>United Kingdom</td>
<td>44</td>
<td>59</td>
<td>26.3</td>
<td>753/4127</td>
<td>Low-fat dairy</td>
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<td>7-d food diary</td>
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<p>| Author, year              | Cohort (follow-up duration) and baseline examination | Location   | Men, %  | Age, y | BMI, kg/m² | Cases/total, n/n | Dairy type included in meta-analysis² | Dietary assessment                  | Diabetes ascertainment               | Adjustments                                                                 |
|-------------------------|-----------------------------------------------------|------------|---------|--------|------------|-----------------|--------------------------------------|-------------------------------------|-------------------------------------|
| Sluijs et al., 2012 (22)| EPIC-InterAct Study (12 y) 1992–1998               | 8 countries in Europe | 38      | 52     | 26.1       | 10,694/24,475  | Total dairy                          | Validated quantitative dietary questionnaire or validated FFQ | Self-report, linkage to primary-care registers, secondary-care registers, medication use, hospital admissions, and mortality data, verified by review of medical records; in Denmark and Sweden, identified by diabetes and pharmaceutical registers | Center, age, sex, BMI, education level, smoking status, physical activity level, alcohol intake, energy intake, energy-adjusted intake of fruit plus vegetables, red meat, processed meat, sugar-sweetened drinks, coffee, cereals, cereal products, and dietary intake of calcium, magnesium, and vitamin D |
| Soedamah-Muthu et al., 2013 (23) | Whitehall II study (10 y) 1985–1988                      | United Kingdom | 72      | 56     | 25.9       | 273/4186       | Total dairy                          | Validated 114-item FFQ                   | Self-report of doctor’s diagnosis, initiation of antidiabetic medication, and a 2-h 75-g oral-glucose-tolerance test | Age, sex, ethnicity, employment grade, smoking, alcohol intake, BMI, physical activity, family history of coronary heart disease/hypertension, fruit and vegetables, bread, meat, fish, coffee, tea, and total energy intake |
| Struijk et al., 2013 (24) | Inter99 Study (5 y) 1999–2001                           | Denmark     | 48      | 46     | 26.1       | 214/5232       | Total dairy                          | Validated 198-item FFQ                  | Fasting plasma glucose ≥7.0 mmol/L and/or 2-h plasma glucose ≥11.1 mmol/L based on 1 oral-glucose-tolerance test | Age, sex, intervention group, diabetes family history, education level, physical activity, smoking status, intake of alcohol, whole-grain cereal, meat, fish, coffee, tea, fruit, vegetables, and energy, change in diet form baseline to 5-y follow-up, and waist circumference |</p>
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<tr>
<th>Author, year</th>
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<td>van Dam et al., 2006 (25)</td>
<td>Black Women's Health Study (8 y) 1995</td>
<td>United States</td>
<td>0/39 27.6</td>
<td>Total dairy Low-fat dairy High-fat dairy</td>
<td>Validated 68-item FFQ</td>
<td>Self-report, validated by questionnaires filled out by physicians</td>
<td>Age, total energy intake, BMI, smoking, strenuous physical activity, alcohol consumption, parental history of diabetes, education level, coffee consumption, sugar-sweetened soft drink intake, processed meat and other red meat, and whole grain</td>
</tr>
<tr>
<td>Vang et al., 2008 (26)</td>
<td>Adventist Mortality Study and Adventist Health Study (17 y) Adventist Mortality Study: 1960 Adventist Health Study: 1976</td>
<td>United States</td>
<td>62/65 24.5</td>
<td>Total milk Cheese</td>
<td>FFQ</td>
<td>Self-report</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Villegas et al., 2009 (27)</td>
<td>Shanghai Women's Health Study (6.9 y) 1996–2000</td>
<td>China</td>
<td>0/50 23.8</td>
<td>High-fat milk</td>
<td>In-person interviews using a validated 77-item FFQ</td>
<td>Self-report and fasting glucose concentration (\geq 7) mmol/L on (\geq 2) separate occasions, or an oral-glucose-tolerance test (\geq 11.1) mmol/L, and/or use of hypoglycemic medication</td>
<td>Age, energy intake, BMI, waist:hip ratio, smoking status, alcohol consumption, physical activity, income level, education level, occupation, and hypertension</td>
</tr>
</tbody>
</table>

(Continued)
Milk and T2D

Total milk intake (11 studies) (10, 11, 13–16, 22–24, 26, 28) was not associated with T2D risk (RR: 0.97 per 200 g/d; 95% CI: 0.93, 1.02; \( P = 0.25 \)) (Supplemental Figure 17). Significant heterogeneity was present (\( I^2 = 57\% \), \( P = 0.007 \)). Subgroup analyses (Supplemental Table 4) suggested a direct association (RR: 1.03 per 200 g/d; 95% CI: 1.00, 1.06) in European populations, and an inverse association (RR: 0.87 per 200 g/d; 95% CI: 0.72, 1.05) in Asian populations. Also, a direct association was suggested for studies adjusting for the major confounders (RR: 1.03 per 200 g/d; 95% CI: 1.00, 1.06), and an inverse association for studies not adjusting for these major confounders (RR: 0.94 per 200 g/d; 95% CI: 0.88, 1.01). There was no evidence of publication bias (Supplemental Figure 18; Egger’s test, \( P = 0.071 \)).

Low-fat milk (7 studies) (4, 10, 11, 15, 17) showed no association with T2D risk (RR: 1.01; 95% CI: 0.97, 1.05; \( P = 0.55 \)) (Supplemental Figure 19). There was significant heterogeneity (\( I^2 = 72\% \), \( P = 0.002 \)). Subgroup analyses indicated a direct association for studies with a long-term (>10 y) follow-up duration (RR: 1.03 per 200 g/d; 95% CI: 1.01, 1.06) and for studies adjusted for major confounders (RR: 1.03 per 200 g/d; 95% CI: 1.00, 1.06). An inverse association was seen for studies not adjusting for these major confounders (RR: 0.81 per 200 g/d; 95% CI: 0.71, 0.93), although this subgroup was only based on 2 studies, and these had a short-term (<5 y) follow-up duration.

High-fat milk intake (9 studies) (4, 10, 11, 15, 17, 20, 27) was not associated with T2D risk (RR: 0.98 per 200 g/d; 95% CI: 0.94, 1.11; \( P = 0.85 \)) (Supplemental Figure 20). There was significant heterogeneity (\( I^2 = 84\% \), \( P < 0.001 \)). In sensitivity analyses (Supplemental Table 5), excluding the Asian study by Villegas et al. (27) reduced \( I^2 \) to 44% (\( P = 0.08 \)), with results remaining similar (RR: 1.04 per 200 g/d; 95% CI: 0.97, 1.10). Subgroup analyses indicated a direct association for studies in American populations (RR: 1.11 per 200 g/d; 95% CI: 1.03, 1.20), and based on 2 studies in younger (<50 y) populations (RR: 1.10 per 200 g/d; 95% CI: 1.00, 1.22). There was no evidence of publication bias (Supplemental Figure 21; Egger’s test, \( P = 0.78 \)).

**Fermented dairy and T2D**

Ericson et al. (11) reported no risk estimates for total fermented dairy, but for low-fat and high-fat fermented dairy separately. A meta-analysis (5 studies) (10, 11, 22–24), including the low-fat estimate by Ericson et al. (11), showed no association with T2D (Supplemental Figure 22A), but when the high-fat estimate was included, a significant 12% lower risk for an intake of 40 g/d was observed, with no further decreases at a higher intake (Supplemental Figure 22B). Cheese (12 studies) (4, 10, 11, 15–17, 22–24, 26) was not associated with T2D risk (RR: 1.00 per 10 g/d; Supplemental Figure 23). Significant heterogeneity was present (\( I^2 = 62\% \), \( P = 0.002 \)). In men (Supplemental Table 4), based on 2 studies, cheese intake was associated with a 5% higher T2D risk per 10 g/d (RR: 1.05; 95% CI: 1.02, 1.09).
Yogurt (11 studies) (4, 10, 11, 15–17, 19, 22, 23) was non-linearly inversely related to T2D, showing a 14% lower risk for an intake of 80 g/d (RR: 0.86 compared with 0 g/d; 95% CI: 0.83, 0.90; \( P \), 0.001). The risk did not further decrease at higher intake amounts of yogurt (Figure 4). There was significant heterogeneity (\( I^2 = 73\% \), \( P \), 0.001). Subgroup analyses (Supplemental Table 4) indicated a stronger inverse association for studies in women (RR: 0.89 per 50 g/d; 95% CI: 0.83, 0.95), and based on 2 studies in older (>60 y) populations (RR: 0.74 per 50 g/d; 95% CI: 0.60, 0.90). There was no evidence of publication bias in the meta-analyses of cheese and yogurt (Supplemental Figures 24 and 25; Egger’s test: both \( P \). 0.15).

Other dairy foods and T2D

Cream (5 studies) (4, 11, 17) was not associated with T2D risk (RR: 0.99 per 5 g/d) and there was no significant heterogeneity (Supplemental Figure 26). Ice cream (5 studies) (4, 11, 17) was significantly associated with a 19% lower T2D risk at an intake of 10 g/d (RR: 0.81 compared with 0 g/d, 95% CI: 0.78, 0.85; \( P < 0.001 \)), with no further decrease at a higher intake (Supplemental Figure 27). Significant heterogeneity (\( I^2 = 86\% \), \( P < 0.001 \)) was present but could not be explored because of the limited number of studies. Sherbet intake (4 studies) (4, 17) was not associated with T2D risk (RR: 1.00 per 5 g/d; Supplemental Figure 28), and there was no heterogeneity.

DISCUSSION

This dose-response meta-analysis combining data from 22 prospective cohort studies showed nonlinear inverse associations for yogurt and ice cream intake and suggestive linear inverse associations for total and low-fat dairy with incident T2D. Given the considerable heterogeneity, results should be interpreted cautiously. For high-fat dairy, milk (total, low-fat and high-fat), cheese, cream, and sherbet intake, no significant associations were observed.

The role of dairy foods in the prevention of diabetes received considerable attention in meta-analyses of observational (3–9) and intervention studies (52, 53). In our meta-analysis, a 3%
lower T2D risk was observed per 200 g total dairy/d, which likely was attributable to low-fat dairy (4% lower risk per 200 g/d). Chen et al. (4) showed in their meta-analysis of 14 prospective cohort studies no significant association for total dairy (RR: 0.98 · serving⁻¹ · d⁻¹; 95% CI: 0.96, 1.01), and, in a separate analysis of 3 large US cohorts, no association for low-fat dairy (RR: 1.00 · serving⁻¹ · d⁻¹; 95% CI: 0.98, 1.02). Earlier meta-analyses showed strong inverse associations for total and low-fat dairy (3, 7). Aune et al. (3) reported a significant 19% lower T2D risk at a total dairy intake of 400 g/d, based on 12 studies, with no additional benefit at a higher intake. For low-fat dairy, based on 9 studies, a 9% lower risk per 200 g/d was found. The lack of association in the study by Chen et al. (4) may be explained at least partly, as acknowledged by the authors, by the longer follow-up of the 3 large US cohorts (4). In our subgroup analysis of studies of longer duration (>10 y) we also found no associations with total or low-fat dairy intake.

Consistent with previous meta-analyses (3, 4, 7), yogurt intake was strongly inversely associated with incident T2D. The association appeared to be nonlinear, with an intake of 80–125 g/d related to a 14% lower T2D risk, which is in line with the results from Aune et al. (3). Yogurt may have contributed to our findings for total dairy and low-fat dairy intake. In our meta-analysis we had no data on the contribution of yogurt to total or low-fat dairy, which may vary considerably across countries. In the United States, the contribution of yogurt to total dairy based on the NHANES study was only 3%, of which 76% was low-fat or skimmed yogurt (54), whereas in the Spanish Prevención con Dieta Mediterránea study, it was 24% (70% skimmed) (10). The Prevención con Dieta Mediterránea study showed inverse associations for both low-fat and high-fat yogurt with T2D (10). Yogurt may exert beneficial metabolic effects because of probiotic bacteria, which have been reported to lower blood cholesterol (55). Yogurt also contains vitamin K-2 (menaquinone), which was inversely associated with the risk of T2D in a large prospective cohort (56). Cheese, however, is also rich in vitamin K-2 but was not related to the risk of T2D in our meta-analysis. We could not distinguish between plain and sugar-sweetened yogurt, for which intake may vary considerably across countries. The latter could adversely affect the cardiometabolic risk profile, and our findings may not be generalizable to all types of yogurt.

Ice cream intake was inversely associated with T2D risk, a finding comparable with other studies (3, 4, 7). In the US cohorts analyzed by Chen et al. (4), however, the strong inverse association for ice cream was attenuated when dietary information was no longer updated after hypertension or hypercholesterolemia had been diagnosed, implying that reverse causation may have influenced these findings. We could not examine this source of bias in our meta-analysis. Also, the narrow variations in ice cream intake (0–30 g/d) and the possibility of misreporting of ice cream intake are reasons to interpret these results with caution.

We observed no association with milk and T2DM. Findings of previous meta-analyses (3, 7) also showed no significant association between milk intake and the risk of T2D. In line with our results, a very recent publication not included in our meta-analysis that reported on a Mendelian randomization study indicated no evidence of an association between milk and T2D (57).

Dairy is a heterogeneous food group with products differing in water content, amount of fermentation, and nutrients such as fat and sodium. A major strength of this meta-analysis is that we examined a wide range of well-specified dairy foods in relation to T2D risk, making use of data from 22 prospective studies. We were able to examine dose-response relations and nonlinearity of the associations, which could be important for setting dietary guidelines. A limitation of this meta-analysis is that, for fermented dairy, ice cream, and several other dairy products, the variation in intake and the number of studies was small. These results, as well as the findings from subgroup analyses, therefore should be interpreted with caution. When evaluating data from stratified analysis, it should be noted that factors other than the stratifying variable may be responsible for differences across subgroups. To illustrate, the larger risk reductions observed in Asian populations may also be due to different amounts or types of dairy consumed, or the confounders adjusted for in the analysis. For our study, we extracted risk estimates from the papers that were adjusted for the largest number of covariates. However, a limitation of observational studies, including the present meta-analysis, is that residual confounding (for example by social economic status), selection bias, and information bias cannot be ruled out.

In conclusion, this dose-response meta-analysis of prospective cohort studies suggested an inverse association of dairy foods, in particular yogurt, with T2D. Associations for yogurt were supported with potential biological mechanisms, and were in line with previously published meta-analyses. However, the results should be considered in the context of the observed heterogeneity. The results from our updated meta-analysis imply a possible role of dairy foods in the prevention of T2D, but this needs confirmation by randomized controlled trials.

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