Dairy Products Consumption and Risk of Type 2 Diabetes: Systematic Review and Dose-Response Meta-Analysis

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Abstract

Background: The consumption of dairy products may influence the risk of type 2 diabetes mellitus (T2DM), but inconsistent findings have been reported. Moreover, large variation in the types of dairy intake has not yet been fully explored.

Methods and Results: We conducted a systematic review and meta-analysis to clarify the dose–response association of dairy products intake and T2DM risk. We searched PubMed, EMBASE and Scopus for studies of dairy products intake and T2DM risk published up to the end of October 2012. Random-effects models were used to estimate summary relative risk (RR) statistics. Dose-response relations were evaluated using data from different dairy products in each study. We included 14 articles of cohort studies that reported RR estimates and 95% confidence intervals (95% CIs) of T2DM with dairy products intake. We found an inverse linear association of consumption of total dairy products (13 studies), low-fat dairy products (8 studies), cheese (7 studies) and yogurt (7 studies) and risk of T2DM. The pooled RRs were 0.94 (95% CI 0.91–0.97) and 0.88 (0.84–0.93) for 200 g/day total and low-fat dairy consumption, respectively. The pooled RRs were 0.80 (0.69–0.93) and 0.91 (0.82–1.00) for 30 g/d cheese and 50 g/d yogurt consumption, respectively. We also found a nonlinear association of total and low-fat dairy intake and T2DM risk, and the inverse association appeared to be strongest within 200 g/d intake.

Conclusion: A modest increase in daily intake of dairy products such as low fat dairy, cheese and yogurt may contribute to the prevention of T2DM, which needs confirmation in randomized controlled trials.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is a growing public-health burden worldwide, particularly in developing countries. The prevalence of T2DM is estimated to reach 552 million worldwide by 2030 [1]. T2DM may cause substantial morbidity and mortality and is associated with enormous economic, health, and societal costs [2,3]. Moreover, as compared with unaffected people, those with T2DM are at increased risk of other chronic illnesses, including cardiovascular disease; T2DM more than doubles the risk of a heart attack or stroke [4,5]. Therefore, the identification of modifiable risk factors for primary prevention of T2DM is of considerable public health importance.

T2DM has genetic components but is also directly influenced by modifiable lifestyle factors, including dietary behaviors [6]. Dairy consumption might affect T2DM. Experimental studies indicated that dairy protein, such as whey protein, has insulinotropic and glucose-lowering properties [7]. The Multi-Ethnic Study Atherosclerosis [8] and Cardiovascular Health study [9] suggested that fatty acids in dairy might be responsible for lower risk of T2DM.
Methods

Data Sources and Search Strategy

We followed standard criteria for conducting and reporting meta-analyses of observational studies (MOOSE). Two authors (DG and NN) independently did a literature search MEDLINE via PubMed (published from 1966 to March 2013), EMBASE (published from 1980 to March 2013), and Scopus (www.scopus.com) with no restriction on language. To identify studies of milk or dairy product intake and T2DM risk, we used both the medical subject heading (MeSH) terms (“Diabetes Mellitus” AND [milk OR dairy]) and searched the text using the terms (“dairy”/exp OR “diabetes”) AND (“dairy”/exp OR dairy OR ‘milk’/exp OR milk). We also searched the reference lists of all studies retrieved and published systematic reviews and meta-analysis.

Study Selection

All abstracts retrieved were examined independently by 2 investigators (DG and NN) who then reviewed the full text of potential articles. Disagreements were resolved by consensus, and if necessary, with a third author (CW). We included prospective cohort studies and case-cohort studies assessing the association of consumption of total dairy products or specific types of dairy products and T2DM. To be included in the analyses, articles needed to contain estimates of the relative risk (RR) (such as odds ratios [ORs], hazard ratios [HRs] or risk ratios) with 95% confidence intervals (95% CIs). We excluded animal studies, clinical trials, cross-sectional studies, case-control studies, and studies that examined other associations. For the dose-response analysis, a quantitative measure of intake had to be provided. If the article lacked data, we attempted to contact the author.

Data Extraction and Quality Assessment

We extracted the following data from each study: country where the study was conducted, follow-up period, sample size, gender, age, number of cases, dietary assessment method (type, number of food items and whether the food intake had been validated), type of dairy product (e.g., total dairy, milk, cheese), quantity of intake, HRs, RR values, and ORs and 95% CIs for dairy product intake and, when available, the number of cases and participants or person-years for each category of dairy product consumption. Two authors (YL and ZM) independently performed the data extraction. Any disagreements were resolved by discussion.

Two independent reviewers (DG and NN) evaluated the quality of the selected studies by using a modified scoring system that was based on a recently used system (designed with reference to QUATSO [25], MOOSE [26], and STROBE [27]) that allowed for a total score of 0 to 6 points (6 indicating highest quality) [28]. The system allocates one point each for 1) any justification given for the cohort; 2) appropriate inclusion and exclusion criteria used; 3) outcome (diagnosis of T2DM not solely based on self-reporting); 4) intervention (participants’ usual dairy consumption assessed with a validated tool); 5) statistical analysis (adjustments made for age, sex, body mass index, and family history of T2DM, total energy intake and physical activity, these being proven risk factors for type 2 diabetes); and 6) any other adjustments performed (such as glycemic load and dietary factors).

Statistical analysis

HRs and RRs were assumed to be approximately the same measure of relative risk. For articles reporting ORs, we estimated the RRs from the ORs using a previously published correction method [29]. To take into account heterogeneity between studies, we used a random-effects models to calculate summary RRs and 95% CIs for the highest versus lowest level of dairy product intake and for the dose–response analysis. The natural logarithm of the RR from each study was weighted by the inverse of its variance and pooled across studies. A two-tailed P<0.05 was considered statistically significant. Articles that reported findings for men and women separately were considered 2 studies when the observed items were combined.

For the dose–response analysis, we used GLST command in Stata software as the method proposed by Greenland and Longnecker [30] and Orsini et al. [31] to compute study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and 95% CIs across categories of dairy product intake.

For each study, the median or mean level of dairy product intake for each category was assigned to each corresponding RR. When the median or mean intake per category was not provided, we assigned the midpoint of upper and lower boundaries in each category as the average intake. If the highest or the lowest category was open-ended, we assumed that the open-ended interval length had the same length as the adjacent interval. If the intake was reported in densities (i.e., per 1000 kcal), we recalculated the reported intake as absolute intake using the mean or median energy intake reported in the article [14]. When studies reported the intake in servings and times per day or week, we converted the...
| Author, Year | Population | Country | Men (%) | Age, Year | Follow-up (y) | Subjects (cases) | Dietary Assessment | Dairy Quantity | Relative Risk | Assessment of T2DM | Adjustment |
|--------------|------------|---------|---------|-----------|--------------|-----------------|-----------------|---------------|--------------|-----------------|------------|
| Sluijs, 2012 | EPIC-InterAct | Europe | 50% | 52 | 16 | 24,475 | FFQ | Total dairy (628.9 g vs. 79.7 g) | 0.97 (0.82, 1.15) | Self-reporting, primary care register, level of smoking, physical activity, alcohol intake, fruit plus vegetables, red meat, processed meat, sugar use (drug register), hospital admissions, | Center, age, sex, BMI, educational level, physical activity, smoking, fruit plus vegetables, red meat, processed meat, sugar use (drug register), hospital admissions, |
| Grantham, 2012 | AusDiab | Australia | 45% | 52 | 5 | 5,582 | 121-item FFQ | Total dairy (408 g vs. 346 g) | 0.71 (0.48, 1.05) | 75 g OGTT | Age, sex, energy intake, family history of diabetes, education level, level of physical activity, smoking, TAG, HDL cholesterol, systolic blood pressure, waist circumference and hip circumference, | | |
| Louie, 2012 | BMES | Australia | 42% | 63.5 | 10 | 1,824 | 145-item FFQ | Total dairy (31.1 g vs. 0.5 g) | 1.50 (0.47, 4.77) | Self-reporting, taking medication | Age, sex, smoking, physical activity, diet and lifestyle, smoking status, alcohol intake, total energy intake, | | |
| Struijk, 2012 | Inter99 | Denmark | 47.5% | 30–60 | 5 | 5,232 | FFQ | Total dairy (578 g vs. 47 g) | 0.96 (0.58, 1.58) | 75 g OGTT | Age, gender and intervention group, diabetes family history, obesity, | | |
| Soedamah-Whitehall II, 2012 | England | 72% | 56 | 9.8 | 4,186 | 114-item FFQ | Total dairy (575 g vs. 246 g) | 1.30 (0.95, 1.77) | Self-reporting, and confirmed by review | Age, ethnicity and employment grade, smoking, alcohol intake, BMI, physical activity and family history of CHD/hypertension, fruit and vegetables, bread, meat, fish, coffee, tea, fruit, vegetable, energy intake, change in diet, waist circumference, | | |
| Muthu, 2011 | WHI-OS | USA | 0 | 50–79 | 8 | 82,076 | 122-item FFQ | Total dairy (3.4 g vs. 0.5 g) | 0.93 (0.83, 1.04) | Self-reporting | Age, race/ethnicity, total energy intake, income, education, smoking, alcohol intake, family history of diabetes, | | |
| Margolis, 2011 | | | | | | | | Total dairy (2.8 g vs. 0.5 g) | 0.65 (0.44, 0.96) | confirmed by review | intake, income, education, smoking, alcohol intake, family history of diabetes, | | |
Table 1. Cont.

| Author, Country and Year | Study Population | Age, y (years) | Subjects (cases) | Dietary Assessment | Dairy Quantity (high vs. low intake) | Relative Risk | Assessment of T2DM | Adjustment |
|--------------------------|------------------|----------------|------------------|--------------------|-------------------------------------|--------------|-------------------|------------|
| Malik, 2011, USA | NHS II cohort | 0 | 34–53 | 8 | Total dairy (2.14 vs. 0.62) (550) | 0.75 (0.55, 1.02) | self-reporting | Age, BMI, total energy intake, family history of diabetes, smoking, alcohol use, hormone replacement therapy. |
| | | | | | Low-fat dairy (1.44 vs. 0.18) | 0.74 (0.54, 1.01) | confirmed by medical records | Polyunsaturated, saturated fat, glycemic load, dietary total fat, dietary total fiber, magnesium. |
| | | | | | Full-fat dairy (1.14 vs. 0.19) | 0.72 (0.53, 0.99) | review of medical records | Polyunsaturated, saturated fat, glycemic load, fiber, trans fat, processed meat, carbonated soft drinks, fruit drinks. |
| | | | | | | | | |
| Kirili, 2009, Japan | JPHC cohort | 57% | 40–69 | 5 | Total dairy (300 g vs. 50 g) (1,114) | 1.18 (0.90, 1.56) | self-reporting | Age, area, BMI, family history of diabetes mellitus, smoking, alcohol intake. |
| | | | | | Milk (200 g vs. 50 g) | 1.02 (0.85, 1.24) | medical record data | Hypertension, exercise, coffee, magnesium, total energy. |
| | | | | | Cheese (5 g vs. 0 g) | 1.12 (0.80, 1.57) | and plasma glucose | |
| | | | | | Yogurt (60 g vs. 0 g) | 1.01 (0.75, 1.36) | random samples. | |
| Villegas, Spain, 2009 | SWHS cohort | 0 | 51 | 6.9 | Milk (250 vs. 0) (2,270) | 0.60 (0.41, 0.88) | self-reporting | Age, energy intake, BMI, waist-hip ratio, smoking status, alcohol consumption, physical activity, income level, education level, occupation, and hypertension. |
| | | | | | FFQ | 1.19 (0.90, 1.60) | fasting glucose and OGTT | |
| Elwood, UK, 2007 | Caerphilly, prospective study | 100 | 45–59 | 20 | Milk (500 vs. 0) (41) | 0.57 (0.20, 1.63) | Self-reporting | Age, smoking, BMI and social class. |

Dairy Products and Diabetes
| Author, Year, Population | Country | Men (%) | Age, y (Mean) | Follow-up, y (cases) | Dietary Assessment | Dairy Quantity (high vs. low intake) | Relative Risk (95% CI) | Assessment of T2DM | Adjustment |
|--------------------------|---------|---------|---------------|----------------------|-------------------|-------------------------------------|-----------------------|-------------------|------------|
| Liu, 2006 WHS cohort USA | 0       | 55      | 10            | 37,183               | 131-item FFQ      | Total dairy (>2.9 vs. <0.85)        | 0.68 (0.52,0.89)     | Diagnostic criteria | Age, total energy intake, BMI, cancer, smoking, hypertension, physical activity, family history of diabetes, smoking, alcohol, fiber, total fat intake, dietary glycemic load, calcium, vitamin D, and magnesium. |
| Van Dam, Black Women's Health Study USA | 0 | 21–69 | 8 | 41,186 | FFQ | Total dairy (2.53 vs. 0.07) | 0.93 (0.75,1.15) | Self-reporting | Age, total energy intake, BMI, cancer, smoking, hypertension, physical activity, family history of diabetes, smoking, alcohol, fiber, total fat intake, dietary glycemic load, calcium, vitamin D, and magnesium. |
| Pittas, 2006 NHS cohort US | 0 | 30–55 | 20 | 83,779 | FFQ | Total dairy (3.9 vs. 0.9) | 0.79 (0.70,0.90) | Criteria by National Diabetes Data Group and ADA self-reporting | Age, BMI, hypertension, family history, smoking, physical activity, caffeine, alcohol, and state of residence, fat (saturated, polyunsaturated, or trans), cereal fiber, glycemic load, magnesium, and calcium or magnesium intake. |
| Choi, 2005 HPFS cohort USA | 100 | 43–75 | 12 | 41,254 | FFQ | Total dairy (>2.9 vs. <0.9) | 0.75 (0.61,0.93) | Criteria by National Diabetes Data Group and ADA self-reporting | Age, total energy intake, family history, smoking, physical activity, caffeine, alcohol, and state of residence, fat (saturated, polyunsaturated, or trans), cereal fiber, glycemic load, magnesium, and calcium or magnesium intake. |
| Montonen, Finnish Mobile Clinic Health Finland | 50 | 40–69 | 23 | 4304 | dietary history | Regular dairy (>305 vs. <390) | 0.81 (0.62,1.08) | from the Social Insurance Number study | Adjusted for age, sex, body mass index, energy intake, smoking, family history. |
| Author, examination | Country | Men | Age, y | Follow-up, y | Subjects (cases) | Dietary Assessment (high vs. low intake) | Relative risk | Assessment of T2DM | Adjustment |
|-------------------|---------|-----|--------|-------------|-----------------|----------------------------------|-------------|----------------|------------|
| Examination       | Whole milk (>878 vs. <326) | 1.06(0.75,1.50) | Institution’s nationwide register area | history of diabetes, and geographic area of persons receiving drug reimbursement |
| Ericson, Malmo, Diet and Sweden | 57 | 8 | 23 531 | 148-FFQ | Total dairy women (6.0 vs. 1.8) | 0.88 (0.70, 1.09) | Self report, and sex, smoking status, alcohol verified with an inquiry to the treating physician, hypertension, history of high blood lipid local cancer levels at baseline, education, vitamin registries supplementation, non-consumption of the respective food group, total energy intake (kJ/day) |
| 2013 Cancer cohort | Total dairy men (6.3 vs. 1.8) | 1.20 (0.98, 1.47) |

FFQ, food-frequency questionnaire; OGGT, oral glucose tolerance test; BMI, body mass index; TAG, triglyceride; HDL, High density lipoproteins; ADA, American Diabetes Association; CHD, coronary heart disease; EPIC-InterAct European Prospective Investigation into Cancer and Nutrition cohort; AusDiab, Australian Diabetes Obesity and Lifestyle Study; BMES, Blue Mountains Eye Study; WHI-OS, Women’s Health Initiative observational study; NHS, The Nurses’ Health Study; JPHC, Japan Public Health Center-based Prospective Study; SWHS, Shanghai Women’s Health Study; WHS, Women’s Health Study; HPFS, Health Professionals Follow-up Study. doi:10.1371/journal.pone.0076613.t001
intake to grams of intake per day using standard units of 244 g (or 244 ml) for milk, 43 g for cheese (2 slices) and 177 g for total dairy products from the serving sizes reported in the US Department of Agriculture Food and Nutrient Database for Dietary Studies [32]. Pooled estimates were expressed in rounded numbers that approximated a normal portion size and fitted within the range of dairy intake of all studies (i.e., 200 g for milk and total, low-fat, and full-fat dairy; 50 g for yogurt; and 30 g for cheese).

To examine a potential nonlinear association between dairy products intake and T2DM risk, we performed a 2-stage, random-effects, dose-response meta-analysis, as recently summarized [33]. In the first stage, we constructed study-specific restricted cubic spline models, with 4 knots at fixed percentiles (3%, 35%, 65%, 95%) of the exposure distribution by using generalized least-squares regression. In the second stage, we combined the 2 regression coefficients and the variance/covariance matrix that had been estimated within each study, using the restricted maximum likelihood method in a multivariate random-effects meta-analysis. The pooled relative risks for specific exposure values were then estimated. A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero.

Heterogeneity among studies was assessed by $I^2$, the amount of total variation explained by the between-study variation, and the Q test. We conducted subgroup and random effects univariate and multivariate meta-regression to investigate potential sources of heterogeneity we performed for the primary outcomes. Publication bias was assessed with funnel plots, Begg’s test and Egger's test. On univariate meta-regression analysis, geographic location, adjustment for family T2DM history, and glycemic load were significant predictors of the heterogeneity ($p = 0.05, p = 0.04$ and $p = 0.04$, respectively). But on multivariate meta-regression, we failed to identify the source of heterogeneity. We found no evidence of publication bias by Egger’s test ($p = 0.37$, Begg's test ($p = 0.58$) or funnel plot(see Appendix Figure 1). We also found a nonlinear association of total dairy product intake and T2DM risk, $P_{\text{for nonlinearity}} < 0.001$, with most of the risk reduction occurring with intake up to about 200 g/d; higher intake were associated with a further but more modest decrease in risk (Figure 4A).

**Results**

**Study characteristics**

We included 15 prospective cohort studies and 1 case–cohort study in our analysis (Figure 1), 6 of the studies [12,13,14,15,16,18] were performed in the United States, 6 in Europe [11,19,21,23,34,35], 2 in Asia [17,22] and 2 in Australia [10,20]. The articles were published between 2005 and 2013 and included 526,998 subjects (29,789 T2DM cases) were analyzed. In all, 13 studies [10,11,12,13,14,15,16,18,19,20,23,34] including 457,893 subjects (27,095 cases) were analyzed.

**Total Dairy Products Intake and T2DM Risk**

In all, 13 studies [10,11,12,13,14,15,16,17,18,19,20,23,34] including 457,893 subjects (27,095 cases) were analyzed.

**High versus low intake.** The summary RR for all studies was 0.89 (95% CI 0.81–0.96), with moderate heterogeneity, $I^2 = 65.4\%$ and $P_{\text{heterogeneity}} = 0.000$ (Figure 3A). We conducted subgroup analysis (Table 2), we found an inverse association of total dairy intake and T2DM risk in all strata except European studies and studies not adjusting for family history of T2DM, although in some analyses the associations were not statistically significant. None of the results differed significantly by sex ($P = 0.21$ for all comparisons). On univariate meta-regression analysis, geographic location, adjustment for family T2DM history, and glycemic load were significant predictors of the heterogeneity ($p = 0.05, p = 0.04$ and $p = 0.04$, respectively). But on multivariate meta-regression, we failed to identify the source of heterogeneity. We found no evidence of publication bias by Egger’s test ($p = 0.37$), Begg's test ($p = 0.58$) or funnel plot(see Appendix Figure 1). We also found a nonlinear association of total dairy product intake and T2DM risk, $P_{\text{for nonlinearity}} < 0.001$, with most of the risk reduction occurring with intake up to about 200 g/d; higher intake were associated with a further but more modest decrease in risk (Figure 4A).

**Low- and Full-fat Dairy Intake and T2DM Risk**

8 studies [10,11,12,13,14,15,16,23] including 260,700 subjects (9,398 cases) were analyzed.

**High versus low intake.** Low-fat dairy consumption was inversely associated with T2DM risk, with a pooled RR of 0.81 (0.74–0.89) (Figure 5A). Full-fat dairy consumption was not associated with T2DM risk, with a summary RR of 0.95 (0.85–1.07) (Figure 6A). We found no significant heterogeneity for the associations of low-fat ($I^2 = 1.8\%$; $P_{\text{heterogeneity}} = 0.42$) or full-fat dairy consumption ($I^2 = 38.1\%$; $P_{\text{heterogeneity}} = 0.13$).

**Dose–response analysis.** The summary RR for an increase of 200 g/day in low-fat dairy intake was 0.95 (0.91–0.97), with moderate heterogeneity, $I^2 = 51.6\%$, $P_{\text{heterogeneity}} = 0.02$ (Figure 3B). On subgroup analysis (Table 2), we found an inverse association of total dairy intake and T2DM risk in all strata except European studies and studies not adjusting for family history of T2DM, although in some analyses the associations were not statistically significant. None of the results differed significantly by sex ($P = 0.21$ for all comparisons). On univariate meta-regression analysis, geographic location, adjustment for family T2DM history, and glycemic load were significant predictors of the heterogeneity ($p = 0.05, p = 0.04$ and $p = 0.04$, respectively). But on multivariate meta-regression, we failed to identify the source of heterogeneity. We found no evidence of publication bias by Egger’s test ($p = 0.37$), Begg's test ($p = 0.58$) or funnel plot(see Appendix Figure 1). We also found a nonlinear association of total dairy product intake and T2DM risk, $P_{\text{for nonlinearity}} < 0.001$, with most of the risk reduction occurring with intake up to about 200 g/d; higher intake were associated with a further but more modest decrease in risk (Figure 4A).

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**Figure 2. Methodological quality across included studies.**

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Figure 3. Forest plot of relative risk (RR) for total dairy products intake and T2DM. A, highest versus lowest intake. B, dose–response analysis (200 g/d). Weights are from random effects analysis. doi:10.1371/journal.pone.0073965.g003
Table 2. Subgroup analyses of total and low-fat dairy products intake and T2DM, dose–response analysis.

| Subgroup                          | Total dairy | Low-fat dairy |
|-----------------------------------|-------------|---------------|
|                                  | n RR (95% CI) I² (%) Pa Pb Pc | n RR (95% CI) I² (%) Pa Pb Pc |
| All studies                       | 12 0.94 (0.91,0.97) 51.6 0.02 | 8 0.88 (0.84,0.93) 16.3 0.30 |
| Duration                          |             |               |
| <10                               | 6 0.95 (0.92,0.98) 4.3 0.39 | 4 0.88 (0.82,0.95) 32.5 0.21 |
| ≥10                               | 6 0.94 (0.89,0.99) 68.6 0.01 0.65 | 4 0.89 (0.82,0.96) 23.5 0.27 0.93 |
| Sex                               |             |               |
| Female                            | 6 0.93 (0.90,0.96) 26.9 0.23 | 4 0.86 (0.80,0.92) 29.6 0.23 |
| Male                              | 2 0.97 (0.80,1.18) 78.2 0.03 | 1 0.85 (0.76,0.96) |
| Both                              | 5 0.92 (0.92,1.05) 24.5 0.26 0.21 | 3 0.94 (0.71,1.23) 0 0.94 0.16 |
| Geographic location               |             |               |
| United States                     | 6 0.92 (0.90,0.95) 42.7 0.12 | 5 0.86 (0.82,0.91) 8 0.36 |
| Europe                            | 3 1.01 (0.94,1.08) 18.6 0.29 | 2 0.97 (0.87,1.06) 0 0.94 0.10 0.57 |
| Asia                              | 1 0.96 (0.72,1.28) 75.5 0.04 | 1 0.94 (0.71,1.24) |
| Australia                         | 2 0.90 (0.81,1.01) 0 0.62 0.04 0.08 |               |
| No. of cases                      |             |               |
| <500                              | 4 0.98 (0.88,1.10) 41.5 0.16 | 3 0.97 (0.88,1.06) 0 0.94 |
| 500–1500                          | 4 0.91 (0.86,0.95) 38.5 0.17 | 3 0.88 (0.82,0.93) 0.9 0.37 |
| ≥1500                             | 4 0.95 (0.92,0.98) 32.7 0.22 0.43 | 3 0.83 (0.74,0.94) 40 0.20 0.10 |
| Study type                        |             |               |
| Prospective                       | 11 0.93 (0.90,0.96) 44.7 0.05 | 8 0.88 (0.84,0.93) 16.3 0.30 |
| Case cohort                       | 1 0.99 (0.94,1.05) | 0.22 |
| Adjustment method                 |             |               |
| Logistic                          | 4 0.94 (0.86,1.04) 28.4 0.26 0.92 | 0.95 (0.82,1.10) 0 0.95 0.39 |
| Adjustment factors                |             |               |
| BMI                               | Yes 9 0.94 (0.91,0.97) 53 0.02 | 6 0.87 (0.83,0.92) 8 0.37 |
| No 3 0.98 (0.84,1.16) 60.9 0.02 0.57 | 2 0.97 (0.86,1.10) 2 0.79 0.14 0.45 |
| Diabetes history                  | Yes 1 0.93 (0.90,0.95) 30.2 0.16 | 1 0.87 (0.83,0.92) 0 0.45 |
| No 2 1.04 (0.91,1.19) 58.2 0.12 0.048 0.24 | 0 0.98 (0.86,1.12) 0.16 |
| Glycemic load                     | Yes 6 0.92 (0.89,0.95) 33.7 0.18 | 5 0.86 (0.81,0.92) 13.3 0.33 |
| No 6 0.98 (0.92,1.03) 37.7 0.14 0.067 0.41 | 3 0.93 (0.86,1.00) 0 0.47 0.20 |
| Fat                               | Yes 5 0.92 (0.89,0.95) 46.4 0.11 | 4 0.85 (0.80,0.92) 28.9 0.24 |
| No 7 0.98 (0.93,1.03) 27.7 0.21 0.067 0.56 | 4 0.93 (0.86,1.00) 0 0.68 0.17 |
| Fiber intake                      | Yes 5 0.92 (0.89,0.95) 46.4 0.11 | 4 0.85 (0.80,0.92) 28.9 0.24 |
| No 7 0.94 (0.91,0.97) 27.7 0.21 0.067 | 4 0.93 (0.86,1.00) 0 0.68 0.17 |
| Coffee                            | Yes 6 0.98 (0.93,1.03) 38 0.14 | 4 0.83 (0.77,0.89) 0 0.64 |
| No 6 0.92 (0.89,0.95) 38 0.17 0.069 0.47 | 4 0.92 (0.87,0.98) 0 0.68 0.06 0.41 |
| Fruit, vegetables                 | Yes 9 0.93 (0.90,0.96) 37.1 0.11 | 2 0.94 (0.87,1.01) 0 0.55 |
| No 3 0.99 (0.90,1.08) 63.1 0.07 0.17 | 6 0.85 (0.81,0.91) 0 0.44 0.1 |
| Meat                              | Yes 7 0.92 (0.89,0.95) 44.5 0.08 | 4 0.83 (0.77,0.89) 0 0.64 |
| No 5 0.97 (0.93,1.02) 28.4 0.23 0.098 0.58 | 4 0.92 (0.87,0.98) 0 0.68 0.06 0.34 |
| Calcium, magnesium                | Yes 7 0.95 (0.91,0.98) 44.5 0.08 | 4 0.84 (0.78,0.90) 0 0.50 |
| No 5 0.93 (0.88,0.99) 48.4 0.10 0.50 | 4 0.92 (0.86,0.97) 0 0.43 0.12 |
| Energy intake                     | Yes 9 0.93 (0.90,0.96) 43.3 0.08 | 7 0.88 (0.83,0.94) 28.2 0.21 |
| No 3 0.98 (0.92,1.04) 33.6 0.21 0.13 | 1 0.88 (0.78,0.99) 0.95 |

BMI, body mass index; n, the number of studies; Pa for heterogeneity within each subgroup; Pb for heterogeneity between subgroups with univariate meta-regression analysis; Pc for heterogeneity with multivariate meta-regression analysis.

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studies with than without adjustment for coffee and meat intake (P = 0.06 for both). But on multivariate meta-regression, we failed to identify the source of heterogeneity. On We found a nonlinear association of low-fat dairy intake and T2DM risk, P for nonlinearity = 0.02, with most of the risk reduction occurring with intake up to about 300 g/day; higher intake (>400 g/day) was not associated with a further decrease in risk (Figure 4B).

**Milk Intake and T2DM Risk**

**High versus low analysis.** 9 studies [11,13,15,17,18,19,20,22,23] including 327,039 subjects (21,755...
The hypothesis that dairy products intake protects against T2DM has received much interest among medical professionals and the general population. In intervention studies, the Dietary Approaches to Stop Hypertension (DASH) diet (a dietary pattern focusing on low-fat milk and other dairy products) increased high-density lipoprotein levels, reduced triglycerides levels, reduced blood pressure (both systolic and diastolic), contributed to weight loss, and reduced fasting blood glucose in both men and women as compared with the control diet [36]. In epidemiological studies, the association of dairy products intake and T2DM has been explored with inconsistent results [37].

Our findings for high versus low dairy intake are consistent with results from previous meta-analyses [24], which only included 7 studies. High versus low analyses are limited because true differences in the level and range of intake between studies are not considered and may contribute to heterogeneity in the results. With the accumulated evidence, we were able to enhance the precision of the risk estimates, perform dose–response analyses of different dairy products and explore the shape of the dose–response curve and sources of heterogeneity, thereby increasing the clinical relevance of our findings [38].

In addition, the presence of both linear and nonlinear dose–response relationships of specific dairy products strengthened the findings of an association of dairy products intake and risk of T2DM. In the linear dose-response analysis, we found a 6% lower risk of T2DM per 200 g/day increase of total and low-fat dairy products, respectively. Furthermore, we discovered a nonlinear association of both total and low-fat dairy intake and incidence of T2DM.

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Dairy is a major source of dietary calcium and magnesium, 2 minerals that have a role in the development of T2DM, for potential in improving pancreatic B-cell function and insulin sensitivity [39].

Experimental [39], prospective cohort studies [40,41] and a recent meta-analysis [42] have provided convincing evidence to support the direct effects of calcium and magnesium intake on insulin resistance and T2DM. In this study, we found that the association of dairy intake and T2DM risk remained unchanged after adjusting for diet calcium and/or magnesium (7 studies), so other major components in dairy products could account for the association. Recently, the beneficial physiological effects of dairy protein, such as...
Whey protein, on the control of food intake and glucose metabolism have been reported. Studies have shown the insulinotropic and glucose-lowering properties of whey protein in healthy and T2DM subjects [43]. Furthermore, in addition to milk proteins, trans-palmitoleate, obtained primarily from dairy intake, is associated with reduced incidence of diabetes [9].

Our analysis of high- and low-fat dairy products revealed an inverse association of only low-fat dairy food intake and T2DM risk. This support the present recommendations by health authorities and governments to eat low-fat rather than full-fat dairy products [44]. We think the most prominent relationship was from residual confounding by factors related to a more unhealthy diet or lifestyle. On the other hand, we can not rule out the association between the intake of saturated fatty acid (SFA). Dairy products contributed to 15% of the total dietary SFA intake [45]. Although prospective cohorts demonstrate no significant association between SFA intake and risk of T2DM, some findings from experimental and observational studies have showed that SFA intake was inversely associated with insulin sensitivity [45,46,47]. Finally, the likelihood of publication bias effects may cause
### A

| Study                | Total milk, high vs. low | RR (95% CI) |
|----------------------|-------------------------|-------------|
| Pittas (2006)        |                         | 0.79 (0.70, 0.90) |
| Elwood (2006)        |                         | 0.57 (0.20, 1.63) |
| Kirri-men (2009)     |                         | 1.02 (0.85, 1.24) |
| Kirri-women (2009)   |                         | 0.87 (0.70, 1.09) |
| Villegas (2009)      |                         | 0.60 (0.41, 0.88) |
| Sluijs (2012)        |                         | 1.08 (0.90, 1.31) |
| Struijk (2012)       |                         | 0.95 (0.58, 1.57) |
| Soedamah (2012)      |                         | 0.93 (0.71, 1.23) |
| Overall (I-squared = 51.8%, p = 0.043) | | 0.89 (0.78, 1.01) |

### B

| Study             | Low-fat milk, high vs. low | (95% CI) |
|-------------------|----------------------------|----------|
| Choi (2005)       |                           | 0.78 (0.63, 0.97) |
| Liu (2006)        |                           | 0.92 (0.78, 1.09) |
| Grantham (2012)   |                           | 0.65 (0.44, 0.94) |
| Overall (I-squared = 40.1%, p = 0.188) | | 0.82 (0.69, 0.97) |

### C

| Study                | Full-fat milk, high vs. low | RR (95% CI) |
|----------------------|-----------------------------|-------------|
| Choi (2005)          |                             | 1.19 (1.00, 1.42) |
| Montonen (2005)      |                             | 1.06 (0.75, 1.50) |
| Liu (2006)           |                             | 1.04 (0.84, 1.29) |
| Grantham (2012)      |                             | 1.18 (0.78, 1.79) |
| Overall (I-squared = 0.0%, p = 0.792) | | 1.12 (0.99, 1.27) |
uncertain results. For analysis of the milk products, only 3 of 14 studies separately evaluated whole vs. low-fat milk, and thus it seems that publication bias could account for the observed difference between low vs. whole fat milk. Furthermore, because cheese, even low-fat cheese, has higher fat and saturated fat than whole milk yet was still associated with lower risk, it appears less likely that the observed difference between whole and low fat milk would be due to higher fat or saturated fat content in whole milk. Further confirmatory results of appropriately powered studies are still needed.

Cheese, which has far more fat than whole-fat milk, more than half of which is saturated. Evidence suggests that saturated fat intake has an adverse effect on insulin sensitivity and increases the risk of T2DM. In our analysis, we found inverse associations between both cheese and yogurt intake and incidence of T2DM. The exact mechanisms responsible for the significant inverse association between cheese and yogurt and T2DM are unknown. It could be partly explained by the fact that both dairy subgroups are a good source for vitamin K2. Vitamin K2 is exclusively synthesized by bacteria and is therefore only present in fermented dairy products such as cheese and yogurt due to the bacterial starter fermentation [48]. Vitamin K2 has recently been linked to a reduced risk of T2DM [49]. Additionally, these dairy subcategories are particularly high in the fat-soluble vitamin D, which has been found to be inversely associated with T2DM [50,51].

We did not find a consistent pattern of difference or heterogeneity in results by sex or any other study characteristics examined, except for geographic location, which significantly modified the association between total dairy products intake and T2DM risk. We found a significant inverse association among US studies, with no evidence of a protective effect of total dairy food intake in European or Asia studies. This may be a chance finding, because only 3 European studies and 1 Asian study were included in this subgroup analysis or could be due to other factors. As well, differences in the ranges of intake or intake in the referent category could explain these results. Because of the nonlinear association between total dairy food intake and T2DM risk with the strongest reduction at low levels of intake, some studies may have missed an effect because the intake in the referent category may have been already sufficient to reduce risk. For example, in some European studies, intake of total dairy food in the referent category was >200 g/d but was <200 g/d for all US studies. As well, types of dairy food intake may vary between populations. In addition, differences in study size and follow-up time may contribute to the variations. Further cohort studies of specific dairy products and T2DM risk in different populations are needed.

Our meta-analysis contains some limitations. Publication bias is a major concern for analyses that depend on only a few studies. For example, in our analysis, only 4 of the 13 studies separately evaluated full or low-fat milk. So the efficiency of analysis on different milk production was limited. The inverse association we found between dairy products intake and T2DM risk could be due to unmeasured or residual confounding. Higher intake of dairy products, especially low-fat dairy products, is often associated with other lifestyle factors, including increased physical activity, low prevalence of smoking, and overweight/obesity, although different types of dairy products may be differentially associated with some of these confounders. In addition, the results were generally similar in the subgroup analyses when we stratified results by adjustment for confounding factors or other study characteristics, with no heterogeneity between subgroups for total and low-fat dairy product consumption. Only the analysis of total dairy products revealed some indication of heterogeneity, with studies that adjusted for family history of T2DM showing an inverse association with T2DM; studies that did not adjust for family history of T2DM showed a nonsignificant positive association, which suggests potential confounding.

Measurement errors in the assessment of dietary intake are known to bias effect estimates. Our results are based on data from cohort studies, in which dairy intake was mostly assessed by food-frequency questionnaires. In several studies, validation of the food-frequency questionnaires showed good correlations, of about 0.6–0.7 for milk or if not assessed) for protein and calcium, which are good indicators for milk intake. However, we cannot exclude that measurement errors might have resulted in attenuated associations. Dietary changes after baseline can also attenuate associations of dietary intake and T2DM risk; however, only 7 of the included studies [12,13,14,17,18,22,23] used repeated assessments of diet, and the results were similar when using only the baseline questionnaire for the analyses (data not shown). Furthermore, dietary intake data were collected between 1984 and 2003. In earlier studies, full-fat dairy was a major contributor to total dairy intake, whereas in later studies intake was more often low-fat dairy and publication year may have explained the study heterogeneity (p = 0.02). Finally, because all the studies were conducted primarily among middle-aged and older people, these results might not be generalizable to dairy intake in earlier life periods, which might have similar or different effects.

In conclusion, our results suggest a inverse association of intake of dairy products, such as low-fat dairy, cheese and yogurt and T2DM risk. Further cohort studies are warranted to investigate the specific types of dairy products in the association, the impact of measurement errors on estimates, any gender-specific recommendations, and biomarkers of dairy intake.

Supporting Information

Figure S1 Funnel plot of assessing evidence of publication bias. A. For total dairy; B. For low-fat dairy; C. For full-fat dairy.

(TIF)

Figure S2 Forest plot of RR for highest versus lowest yogurt and cheese intake and T2DM. A, yogurt. B, cheese. Weights are from random-effects analysis.

(TIF)

Checklist S1 PRISMA 2009 Checklist

(DOC)

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Author Contributions

Conceived and designed the experiments: DFG YHW CXW. Performed the experiments: DFG NN. Analyzed the data: YL ZM. Contributed reagents/materials/analysis tools: DFG QL QL. Wrote the paper: DFG NN.
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