JNS
JOURNAL OF NUTRITIONAL SCIENCE

REVIEW

Dairy intake and risk of hip fracture in prospective cohort studies: non-linear algorithmic dose-response analysis in 486 950 adults

Suruchi Mishra[1], Kavitha Baruah[2], Vasanti S. Malik[3,4] and Eric L. Ding[3,5,6]*†

[1]*University of Maryland, College Park, MD, USA*
[2]*Ascenian Consulting, Rochester, NY, USA*
[3]*Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA*
[4]*Department of Nutritional Sciences, University of Toronto, Toronto, ON, Canada*
[5]*New England Complex Systems Institute, Cambridge, MA, USA*
[6]*Microclinic International, San Francisco, CA, USA*

(Received 19 January 2023 – Final revision received 5 June 2023 – Accepted 16 June 2023)

Journal of Nutritional Science (2023), vol. 12, e96, page 1 of 13 doi:10.1017/jns.2023.63

Abstract

Previous studies on the relationship between dairy consumption and hip fracture risk have reported inconsistent findings. Therefore, we aimed to conduct an algorithmically driven non-linear dose-response meta-analysis of studies assessing dairy intake and risk of developing incident hip fracture. Meta-analysis from PubMed and Google Scholar searches for articles of prospective studies of dairy intake and risk of hip fracture, supplemented by additional detailed data provided by authors. Meta-regression derived dose-response relative risks, with comprehensive algorithm-driven dose assessment across the entire dairy consumption spectrum for non-linear associations. Review of studies published in English from 1946 through December 2021. A search yielded 13 studies, with 486 950 adults and 15 320 fractures. Non-linear dose models were found to be empirically superior to a linear explanation for the effects of milk. Milk consumption was associated with incrementally higher risk of hip fractures up to an intake of 400 g/d, with a 7 % higher risk of hip fracture per 200 g/d of milk (RR 1·07, 95 % CI 1·05, 1·10; $P < 0·0001$), peaking with 15 % higher risk (RR 1·15, 95 % CI 1·09, 1·21, $P < 0·0001$) at 400 g/d versus 0 g/d. Although there is a dose-risk attenuation above 400 g/d, milk consumption nevertheless continued to exhibit elevated risk of hip fracture, compared to zero intake, up to 750 g/d. Meanwhile, the analysis of five cohort studies of yoghurt intake per 250 g/d found a linear inverse association with fracture risk (RR 0·85, 95 % CI 0·82, 0·89), as did the five studies of cheese intake per 43 g/d (~1 serving/day) (RR 0·81, 95 % CI 0·72, 0·92); these studies did not control for socioeconomic status. However, no apparent association between total dairy intake and hip fracture (RR per 250 g/d of total dairy = 0·97, 95 % CI 0·93, 1·004; $P = 0·079$). There were both non-linear effects and overall elevated risk of hip fracture associated with greater milk intake, while lower risks of hip fracture were reported for higher yoghurt and cheese intakes.

Key words: Cheese: Dairy: Fracture: Hip fracture: Milk: Yoghurt

Introduction

Hip fractures are common among elderly individuals and often have devastating sequelae. Dairy consumption has been promoted for fracture prevention because dairy products contain calcium, along with protein and phosphorus, and are sometimes fortified with vitamin D. However, prior systematic reviews have offered a conflicting and incomplete information for the beneficial effect of total dairy intake for hip fracture

* **Corresponding author:** Eric L. Ding, email eding@post.harvard.edu

†Former affiliated with Harvard TH Chan SPH Department of Nutrition.

risk possibly due to the omission of certain studies and the failure to conduct careful dose-response analyses[1–5].

Dairy consumption may carry potential adverse health consequences. Dairy products are the leading source of saturated fat in the US diet[6], and dairy consumption has been associated with risk of cancer of the prostate and other organs[7–11], raising questions about the overall health effects of recommending this product group for fracture prevention.

We therefore undertook an evidence-based review and non-linear dose-response algorithmic meta-analysis of prospective studies to examine associations between dairy intake and hip fracture risk. Notably, we implemented a unique 1000+ model data-driven non-linear analysis algorithm to sequentially compare thousands of knots to determine the optimum non-linear dose-effect association for various dairy products, including milk, yoghurt, cheese and total dairy.

Methods

Search strategy

We searched the published scientific literature for prospective cohort studies of human participants reporting dairy or milk intake and the end point of incident hip fracture. Literature review was conducted in two phases, prior to July 2016, and after July 2016 until the end of 2021. In the first phase, two investigators identified articles published in English from 1946 to July 2016 through a search of MEDLINE (PubMed) and Google Scholar. We also identified additional articles from the reference lists of the extracted articles and reviews, and articles that cited extracted articles. The following terms were used for the MEDLINE search: *(dairy[All Fields] OR milk [All Fields] OR human milk[All Fields] OR milk [MeSH Terms] OR yoghurt[All Fields] OR cheese[All Fields]) AND humans [MeSH Terms] AND (bone [All Fields] OR bones [All Fields] OR bone and bones [All Fields] OR bone [All Fields] OR fractures, bone [MeSH Terms] OR fractures [All Fields] OR bone fractures [All Fields] OR fracture [All Fields] OR accidental falls [MeSH Terms] OR dxa[All Fields] OR dexa[All Fields] OR (osteoporosis, postmenopausal[MeSH Terms] OR osteoporosis [All Fields]) OR bone diseases, metabolic[MeSH Terms] OR (bone[All Fields] OR osteopenia[All Fields]) OR (osteomalacia[MeSH Terms] OR osteomalacia[All Fields]) OR (bone density[MeSH Terms] OR bone[All Fields] OR bone density[All Fields] OR (bone[All Fields] AND mineral[All Fields] AND density[All Fields]) OR bone mineral density[All Fields]))*. Similar search terms were used for Google Scholar. No language restriction was applied.

In the second search phase, spanning July 2016 through December 2021, we conducted three parallel searches in effort to be more comprehensive, using two sets of Google Scholar searches, which limits results to <1000 results per search, and using MEDLINE to find additional prospective studies on dairy and risk of hip fractures. The following terms were used for the first Google Scholar search: *(Dairy OR milk OR yoghurt OR cheese) AND (Bone OR fracture OR hip fractures OR dxa OR dexa OR osteoporosis OR bone diseases OR osteopenia OR osteomalacia OR bone mineral density)*. For the second wider Google Scholar search, we used the broader terms: *(Dairy OR milk OR yoghurt OR cheese) AND (hip fracture OR fracture)*. We also conducted a search of MEDLINE between July 2016 through December 2021 using the following search terms: *(dairy[All Fields] OR milk [All Fields] OR human milk[All Fields] OR milk [MeSH Terms] OR yoghurt[All Fields] OR cheese[All Fields]) AND humans [MeSH Terms] AND (bone [All Fields] OR bones [All Fields] OR bone and bones [All Fields] OR bone [All Fields] OR fractures, bone [MeSH Terms] OR fractures [All Fields] OR bone fractures [All Fields] OR fracture [All Fields] OR accidental falls [MeSH Terms] OR dxa[All Fields] OR dexa[All Fields] OR (osteoporosis, postmenopausal[MeSH Terms] OR osteoporosis [All Fields]) OR bone diseases, metabolic[MeSH Terms] OR (bone[All Fields] OR osteopenia[All Fields]) OR (osteomalacia[MeSH Terms] OR osteomalacia[All Fields]) OR (bone density[MeSH Terms] OR bone[All Fields] OR bone density[All Fields] OR (bone[All Fields] AND mineral[All Fields] AND density[All Fields]) OR bone mineral density[All Fields]))*. All search results were downloaded, cross-matched for de-duplication processing before assessment for eligibility within the phase of the search.

Study selection

We first conducted an initial screening of all titles. Abstracts were reviewed if the titles appeared to meet the inclusion criteria. Then, we assessed all potentially relevant studies based on text reviews. We included prospective studies of dairy intake and risk of hip fracture in humans and excluded literature reviews, clinical trials and studies with an ecological, case–control or cross-sectional design. We excluded papers using the criteria listed below. Papers were excluded based on the first applicable exclusion category: animal studies, no dairy consumption, no fracture, review, not prospective, correction, duplicate population or identified in prior search (if second search phase). And for those nearly qualified studies that report any/total fracture but not hip fracture, we emailed authors for additional information, but conditionally excluded such studies unless additional data is provided. We also excluded studies of individuals with pre-existing bone diseases and studies that did not report relative risks (RRs) or hazard ratios (HRs), dairy dose data and the corresponding 95 % confidence intervals (CIs).

Data extraction

Two authors (S.M. and K.B.) independently selected studies and performed the data extraction. To resolve any discrepancies, a third investigator (E.L.D.) was consulted, and any disagreements were settled by consensus of all three authors. The primary exposure variables were milk, yoghurt, cheese, cream, soured milk and yoghurt, total dairy without cream and total dairy with cream consumption. Total dairy with cream included milk, yoghurt, frozen yoghurt and cheese. The outcome of interest was risk of hip fracture. Data extraction was conducted using a standardised data collection form. The following characteristics of the identified articles were recorded: first author, year of publication, cohort name, study population, study design, country, mean/median age, adjustment for body mass index (BMI), adjustment for energy intake (kilocalories), industry funding, percentage of women, follow-up duration, calcium and vitamin D supplement use, and baseline dietary calcium and vitamin D levels, where available, as well as the quality measures noted below.

When data were incomplete or missing, we contacted the authors to obtain additional data. We also attempted to contact authors who we believed were likely to have data on dairy intake and fracture risk based on their prior publications, and obtained additional updated data from the Nurses' Health Study, Health Professionals Follow-up Study, Swedish Mammography Cohort and the Framingham Offspring Study through personal communication with study authors or research staff. Other authors of cohort studies with potentially relevant data were contacted, but none provided dairy and hip fracture risk data that could allow for their inclusion.

Quality measures

Study reports were qualitatively examined for means of dietary assessment, diagnosis and fracture assessment, sample size and statistical measures.

Statistical analysis

To determine whether results indicated non-linear or linear relationships between dairy product consumption and fracture risk, the linearity of associations was first examined using spline analyses and dose-response meta-regressions. For non-linear analysis, we comprehensively assessed the dose across the entire dairy consumption spectrum for non-linear associations, for both single-knot and dual-knot splines for comparative model analysis, at individual 25 g intervals, and used data-driven algorithms to select for the optimal single spline. If a single-knot spline was found superior to linear coefficient model, then upon identification of the optimal single spline, double-spline dose models were tested straddling around the single spline to further assess for potential model superiority. Splined variables were created with the use of MKSPLINE in STATA version 13.1 (College Station, TX). Goodness-of-fit tests and chi-square statistics were used to determine the most appropriate knot points and maximal goodness of fit to assess the fit of potential non-linear relationships and to determine the best dose-response inflection point of any potential non-linear association across a range of intakes. The Greenland and Longnecker dose-response generalised least-square meta-regression analysis using GLST command in STATA was used to derive the dose-response RRs, P-values and 95 % CIs[12]. For non-linear associations, the shapes of the associations within individual studies were assessed via repeated modelling of different knot points in order to determine potential splines for best model fit, indicating the optimal non-linear spline model. The pooled non-linear dose curves were visualised using Spaghetti Plots, as previously applied[13]. Where non-linearity was not indicated, forest plots were produced to portray linear dose-response relationships and corresponding 95 % CIs via random-effects models. Begg's funnel plots and Begg's test are used to assess potential publication bias. To assess 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[14]. Potential publication bias was assessed with Egger's test. Two-sided P-values $<0{\cdot}05$ were considered to be statistically significant.

Results

The Phase 1 PubMed and the Google Scholar searches prior to July 2016 yielded 8781 citation titles for review that yielded 11 relevant studies, two of which were identified from the search of references of the retrieved publications and subsequent author contact. The Nurses' Health Study, Health Professionals Follow-up Study, Swedish Mammography Cohort and Framingham Offspring Study were among the studies that also provided their updated data through personal communication to the senior author. The Phase 2 set of searches of PubMed and Google Scholar from July 2016 to December 2021 yielded 2218 citation titles for review, of which 2 were new relevant and eligible articles, not previously included or captured in personal communications. Altogether, across the two phases of searches, thirteen articles were included in this analysis. The flow of these articles is described in Fig. 1.

Characteristics of included studies

We based our analyses on 13 studies from 16 unique study populations involving 486 950 participants and 15 320 fractures. Additional data from the Swedish Mammography cohort[15] (Michaelsson, personal communication, November 2017) added information on 1568 additional hip fractures beyond the original published study data set[16], for an updated total of 5827 hip fractures from that cohort.

Although all studies assessed dietary intake by food frequency questionnaires, repeat measurements of dietary intake were available only in the Nurses' Health Study, Health Professionals Follow-up Study and Swedish Mammography Cohorts. All other cohorts collected dietary data only at baseline. Diagnosis of fracture was based on self-report confirmed by medical records, death certificates, radiographic and operative report or events validated through linkage with national patient registries.

Five studies provided data that were not separated by gender[17–22]. Two cohorts included only men[16,23]. Four cohorts included only women[15,23–25], and two provided data for men and women separately[26,27]. One study provided data pooled by gender and also separately for women[28]. Seven studies were conducted in the USA[19–25], two in Sweden[15,16], two in Norway[26,27], one in Denmark[22] and one each in Japan[26], France[18] and Europe[17]. Of the thirteen studies included in this meta-analysis, three reported receiving industry funding[18,19,21], and one study with partial industry funding for a doctoral student[22]. Table 1 shows the baseline characteristics for all included studies.

Total dairy consumption and hip fracture

Among the eight cohorts that investigated associations between total dairy intake and hip fracture risk, six found no

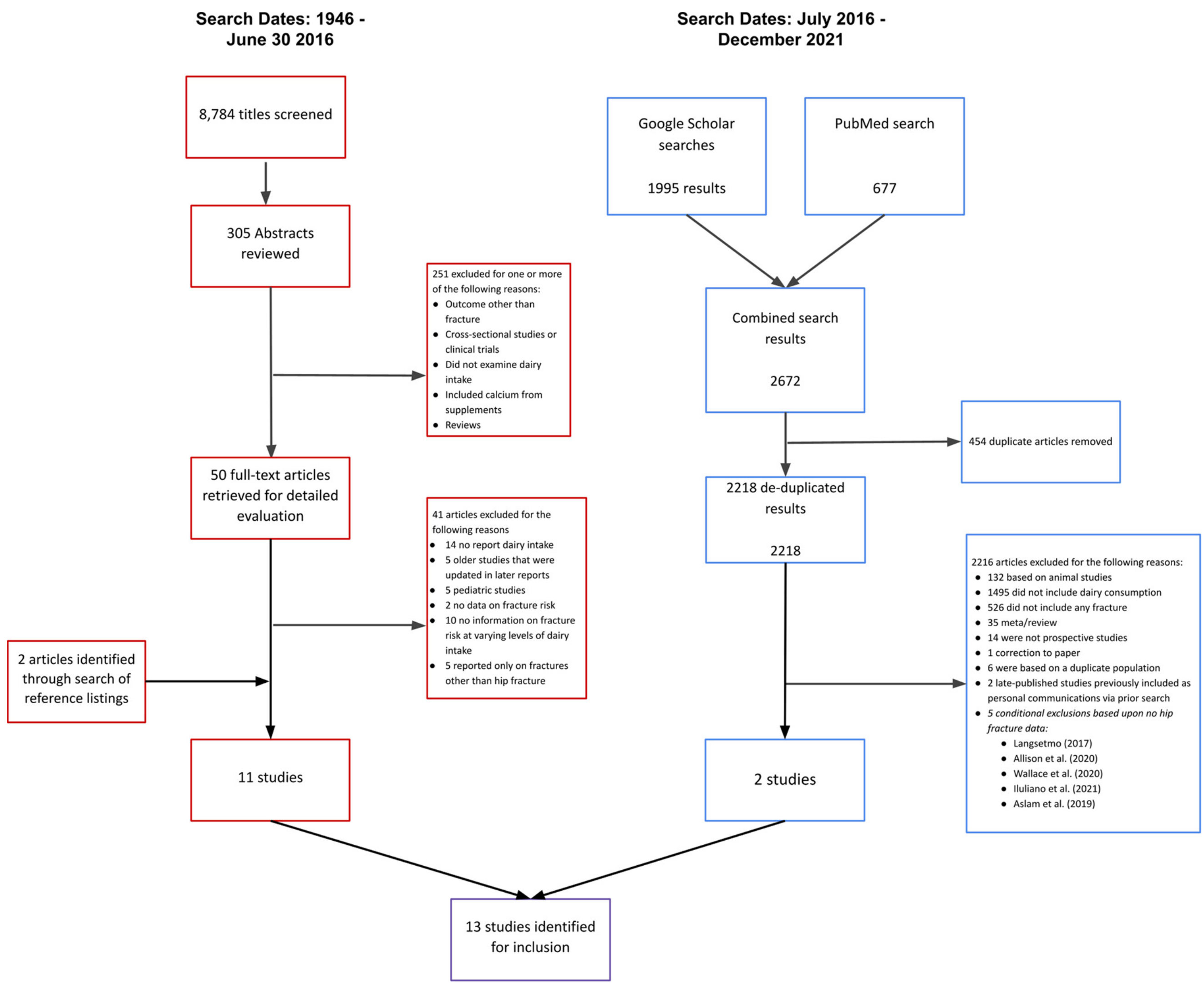

Fig. 1. Flowchart diagram showing the number and disposition of articles assessed for eligibility and included in the review from searches of PubMed and Google Scholar.

association (Health Professionals Follow-up Study[23], Adventist Health Study-2[20], Three-City Study[18], Framingham Offspring Study[19], EPIC Elderly Network on Aging and Health[17], NHANES-1 Epidemiologic Follow-up study[24]). Two reported decreased risk of hip fracture with increased dairy intake (Feskanich, personal communication, October 2016 and Michaelsson, personal communication, November 2017), albeit only with moderate dairy intake in one of these (Michaelsson, personal communication, November 2017).

Although there were eight study populations for which data on total dairy intake were available (Nurses' Health Study[23], Health Professionals Follow-up Study[23], Swedish Mammography Cohort[15], Adventist Health Study-2[20], The Three-City Study[18], Framingham Offspring Cohort[19], EPIC Elderly Network on Aging and Health[17], NHANES-1 Epidemiologic Follow-up study[24]) (Feskanich, personal communication, October 2016 and Michaelsson, personal communication, November 2017), we first conducted an assessment of potential non-linearity of the association among the eight studies with multiple dose-response data points per study (19 total data points). These included the (Nurses' Health Study[23], Health Professionals Follow-up Study[23], Swedish Mammography Cohort[15], Adventist Health Study-2[20], Framingham Offspring Cohort[19], EPIC Elderly Network on Aging and Health[17]) (Feskanich, personal communication, October 2016 and Michaelsson, personal communication, November 2017).

Across the range of doses, no spline knot point yielded significant evidence of a non-linear association, with 100 g/d of total dairy being the closest potential spline point, which was not significant for non-linearity ($P = 0{\cdot}19$). Thus, we analysed all available studies of total dairy and hip fracture in linear dose response fashion. Pooling of the studies in a linear dose increment, expressed per 250 g/d, yielded no significant association between total dairy consumption and hip fracture risk (RR 0·97, 95 % CI 0·93, 1·00). There was no significant heterogeneity, with $I^2 = 34{\cdot}5$ % and overlapping null (95 % CI 0, 71 % and $P = 0{\cdot}15$). The forest plot is shown in Fig. 2. No publication bias trend was observed (Egger's Test $P = 0{\cdot}66$).

Table 1. Characteristics of studies selected for inclusion in the review

No.	Author and study population	Country	Race	Sex	Mean age at baseline (years)	No. of participants	Follow-up period (years) and person-time	End points (no. of cases)	Outcome assessment	Adjusted covariates
1	Huang *et al.*[25], NHANES-1 Epidemiologic Follow-up	USA	White	F	67·7	2513	13·4; n/a	Hip fracture (130)	Self-reported hip fractures. Hip fractures were ascertained by health care records or death certificates	Height, weight, total energy intake, serum albumin, age, previous fracture history, menopausal status, parity, physical activity and frequency of alcohol use.
2	Cumming *et al.*[26], Study of Osteoporotic fractures	USA	White	F	71·4	9704	6·6; n/a	Hip fracture (306)	Women were asked whether they had had a fracture and radiologic reports were reviewed, and only radiologically confirmed fractures were included	Age, clinic, weight, history of osteoporosis, history of fractures since age 50, fall in past 12 months, protein intake, caffeine intake, recreational physical activity, impaired low-frequency contrast sensitivity, estrogen replacement therapy, thiazide use, and use of calcium supplements, vitamin D supplements and Tums antacid tablets
3	Fujiwara *et al.*[29], Adult Health Study	Japan	Asian (Japanese)	F and M	58·5	4573	14; n/a	Hip fracture (55)	Hip fracture diagnosis was made by physician based on the history of hip fracture taken at the biennial exam. Diagnosis on death certificates, medical charts and radiographs were reviewed for validation	Age, gender, BMI, milk intake, alcohol intake, age at menarche, number of children, history of vertebral fracture, self-rated health, marital status, food preference, intake of tofu, fish, coffee, tea, smoking and exposure to atomic radiation, cerebrovascular disease, paralysis, epilepsy, Parkinson's syndrome, cataract, hypo and hypertension, anaemia, hypo and hyperthyroidism
4	Meyer *et al.*[28], Norwegians Middle-aged adults	Norway	No information	F	47·1	19 752 women and 20 035 men	11·4; 225 285 women and 224 792 men	Hip fracture (210)	All fractures were confirmed by review of the individual medical records or discharge letters including a description of the operation	Age, height, BMI, physical activity at work and during leisure time, diabetes mellitus, disability pension, marital status, smoking and total energy intake
5	Benetou *et al.*[18], EPIC Elderly Network on Ageing and Health	Europe	No information	M and F	64·8	29 122	8; 243 330	Hip fracture (275)	Information on hip fracture was collected through self-report, record linkage, and through hip fracture registries	Age, sex, BMI, height, education level, smoking status, physical activity at leisure, dietary supplement use, history of diabetes at enrolment and total energy intake
6	Sahni *et al.*[20], Framingham Offspring Study	USA	White	M and F	55	3224	12; n/a	Hip fracture (43)	Hip fractures were reported by hospitalisation review, death review, interview at each 4-year examination	Age, sex, total energy intake, weight, height, smoking, physical activity, menopause, estrogen, alcohol, caffeine, calcium supplement use and vitamin D supplement use

Continued

Table 1. Continued

No.	Author and study population	Country	Race	Sex	Mean age at baseline (years)	No. of participants	Follow-up period (years) and person-time	End points (no. of cases)	Outcome assessment	Adjusted covariates
7	Feart *et al.*[19], Three-City Study	France	No information	M and F	76·7	1482	8; n/a	Hip fracture (57)	Information on hip fracture was collected through self-report at each visit	Mediterranean diet score, age, gender, physical activity, total energy intake, education level, marital status, BMI, self-reported osteoporosis, osteoporosis treatment, calcium and/or vitamin D treatment
8	Lousuebsakul-Matthews *et al.*[21], Adventist Health Study-2	USA	White	M and F	76·8	33 208	5·1; n/a	Hip fracture (305)	Hip fracture question was asked and ascertained by linking database with the National Death Index database	Fruits and vegetable intake, age, height, weight, gender, energy intake, physical activity, smoking, health status and total calcium intake
9.1	Michaelsson *et al.*[17], Cohort of Swedish Men and Swedish Mammography Study (replaced by updated data via personal communication)	Sweden	No information	M and F	60·7	45 339	11·2; 534 094	Hip fracture (1166)	Fractures events were collated using the individual personal registration number, which was used to match and identify all incident hip fracture events in the national patient registries	Age, BMI, height, total energy intake, total alcohol intake, healthy dietary pattern, calcium and vitamin D supplementation, ever use of cortisone, educational level, living alone, physical activity level, smoking, and Charlson's comorbidity index, intake of calcium, vitamin D, phosphorus, total fat, saturated fat, total protein, retinol and previous fracture history
9.2	Michaelsson *et al.*[16], Additional data provided by the authors, Swedish Mammography Cohort	Sweden	No information	F	53·5	61 240	22 1 375 900	Hip fracture (5827)	Fractures events were collated using the individual personal registration number, which was used to match and identify all incident hip fracture events in the national patient registries	Age, BMI, height, education, smoking (never, former, current), physical activity level (METs), living alone, total energy intake, alcohol consumption, intake of fruit and vegetables and of red and processed meat, use of antioxidant containing supplements, soured milk and yoghurt, and cheese, calcium containing supplements, ever estrogen replacement therapy, ever cortisone use
10	Sahni *et al.*[23], Framingham Original Cohort	USA	White	M and F	77	764	11·6; n/a	Hip fracture (97)	Hip fractures were reported by interview at each examination and reported hip fractures were confirmed by review of medical records, radiographic and operative reports	Age, sex, height, weight, total energy intake, current smoking, physical activity, current estrogen use in women, calcium supplement, vitamin D supplement and multivitamin supplement use

11.1	D Feskanich *et al.*[24], Health Professionals Follow-up Study, additional data provided by the authors	USA	White	M	57·7	43 306	17·5; 383 784	Hip fracture (694)	Self-reported fracture incidents. No validation study among men	Age, follow-up cycle, total energy intake, intakes of calcium, vitamin D and retinol from supplements, frequencies of meat, fish, egg and soda consumption, intakes of vitamin K, caffeine and alcohol, milk consumption during teenage years, BMI, height, physical activity, smoking, use of thiazide diuretics, furosemide-type diuretics and oral steroids, and diagnoses cancer, diabetes and cardiovascular disease; milk, yoghurt and cheese were also adjusted for one another
11.2	D Feskanich *et al.*[24], Nurses' Health Study, additional data provided by the authors	USA	White	F	53·6	80 600	20·8; 837 285	Hip fracture (2138)	Self-reported fracture incidents. Validation study was conducted previously for self-reported fractures among nurses	Age, follow-up cycle, total energy intake, intakes of calcium, vitamin D and retinol from supplements, frequencies of meat, fish, egg and soda consumption, intakes of vitamin K, caffeine and alcohol, milk consumption during teenage years, BMI, height, physical activity, smoking, use of postmenopausal hormones, use of thiazide diuretics, furosemide-type diuretics and oral steroids, and diagnoses cancer, diabetes and cardiovascular disease; milk, yoghurt and cheese were also adjusted for one another
12	Bergholdt *et al.*[22]	Denmark	White	M and F	57	73 715	5·5; n/a	Hip fracture (686)	Occurrence of hip fracture was obtained from the National Danish Patient Registry and the National Danish Causes of Death Registry	Sex, age, physical activity at work, physical activity in leisure time, alcohol intake, smoking status, educational level and BMI
13.1	Holvik *et al.*[30]	Norwegian Counties Study	No information	M and F	50	35 114	25; 613 017	Hip fracture (1865)	Hip fractures were identified by linkage to the NOREPOS hip fracture database (NORHip)	Sex, county, BMI, smoking, height, number of self-reported chronic diseases, use of vitamin supplement, use of cod liver oil supplement, physical inactivity, marital status, energy intake and education
13.2	Holvik *et al.*[30]	Five Counties Study, Norway	No information	M and F	66	23 298	25; 252 991	Hip fracture (1466)	Hip fractures were identified by linkage to the NOREPOS hip fracture database (NORHip)	Sex, county, BMI, smoking, height, number of self-reported diseases, use of any vitamin or mineral supplement, use of cod liver oil supplement, use of acid suppressing drugs, marital status, self-rated health, physical inactivity and education

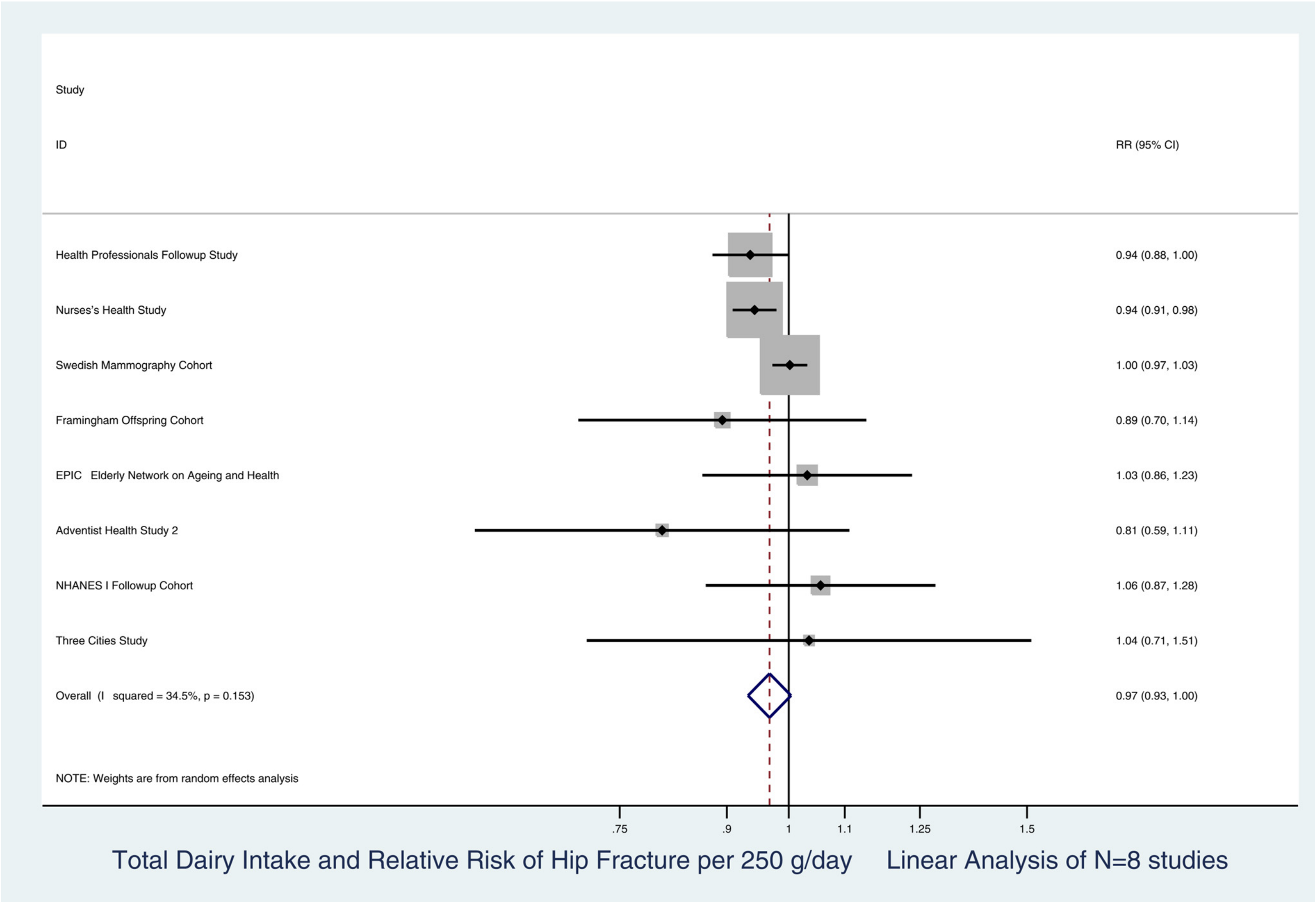

Fig. 2. Forest plot for the association of total dairy intake with risk of hip fracture.

Milk intake and hip fracture

For milk intake, one study (Michaelsson, personal communication, November 2018)[15] showed elevated risk of hip fracture with increased milk intake, seven showed no association[16,18,19,21,22,25,28], and three studies (Nurses' Health Study[23], Health Professionals Follow-up Study[23] and middle-aged Norwegian cohort[26]) (Feskanich, personal communication, October 2016) showed lower risk with increased milk intake.

We conducted an assessment of potential non-linearity of the association among the studies with multiple dose-response data points per study (fifty-nine data points total). Across the ranges of different doses algorithmically tested, a strong spline knot point yielded significant strongest evidence of a non-linear association, with 400 g/d being the most robust dose-risk inflection point (P for non-linearity $< 0{\cdot}0001$); double-knot spline models straddling 400 g/d were not superior to a single knot at 400 g/d. Thus, we analysed the fourteen populations with milk and hip fracture data in a non-linear dose response fashion. Up to a daily dose of 400 g/d, the results showed that milk intake was associated with increased fracture risk, with a dose effect of 7 % increased risk per 200 g/d of milk (RR 1·07, 95 % CI 1·05, 1·10; $P < 0{\cdot}0001$). At 400 g/d of milk intake, compared to 0 g/d, there was a 15 % higher risk of hip fracture (RR 1·15, 95 % CI 1·09, 1·21, $P < 0{\cdot}0001$). However, above 400 g/d of milk, although there is a slight attenuation in the higher risk with a dose trend effect of a −4·5 % per 200 g/d of milk (RR 0·955, 95 % CI 0·92, 0·99, $P = 0{\cdot}007$) compared to the risk peak of 400 g/d – milk consumption nevertheless continued to exhibit elevated risk of hip fracture with intakes up to 750 g/d. In no range of observed milk intake did the analysis show any significantly lower risk of hip fracture compared to 0 g/d. The test of heterogeneity yielded a between-study variance of 0 in all models, indicating no significant heterogeneity. Results are shown in the Spaghetti Plot of Fig. 3.

Yoghurt, fermented milk, cheese and hip fracture

A smaller number of studies examined yoghurt, fermented milk or cheese intake in relation to hip fractures, and none of these studies controlled for socioeconomic status (SES). Because of the limited number of studies, we did not perform a non-linear analysis, which requires more datapoints for reliable computation; and none were apparent via tested knots. Thus, pooling the five studies[15,16,18,19,21] (Michaelsson personal communication, November 2017) of yoghurt and fermented milk intake with hip fracture, the linear analysis per 250 g/d yielded an inverse association of 15 % lower hip fracture risk (RR 0·85, 95 % CI 0·82, 0·89). The model did not reveal significant heterogeneity, with between-study variance

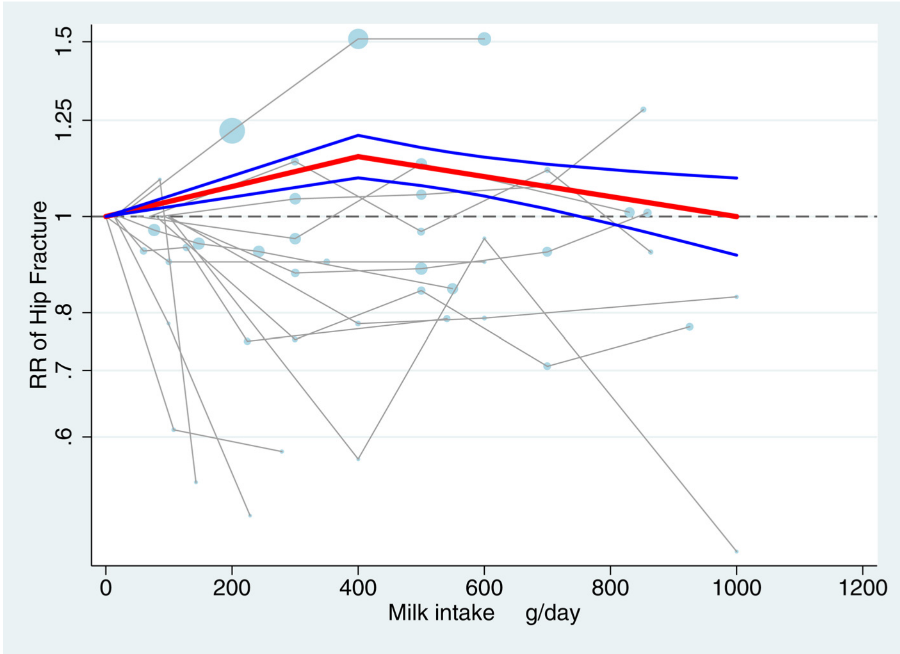

Fig. 3. Spaghetti plot for the association of milk intake with risk of hip fracture. Each thin gray-colored 'noodle' of the spaghetti plot represents an individual study. The pooled non-linear association is represented by the red curve, with 95 % confidence intervals in blue.

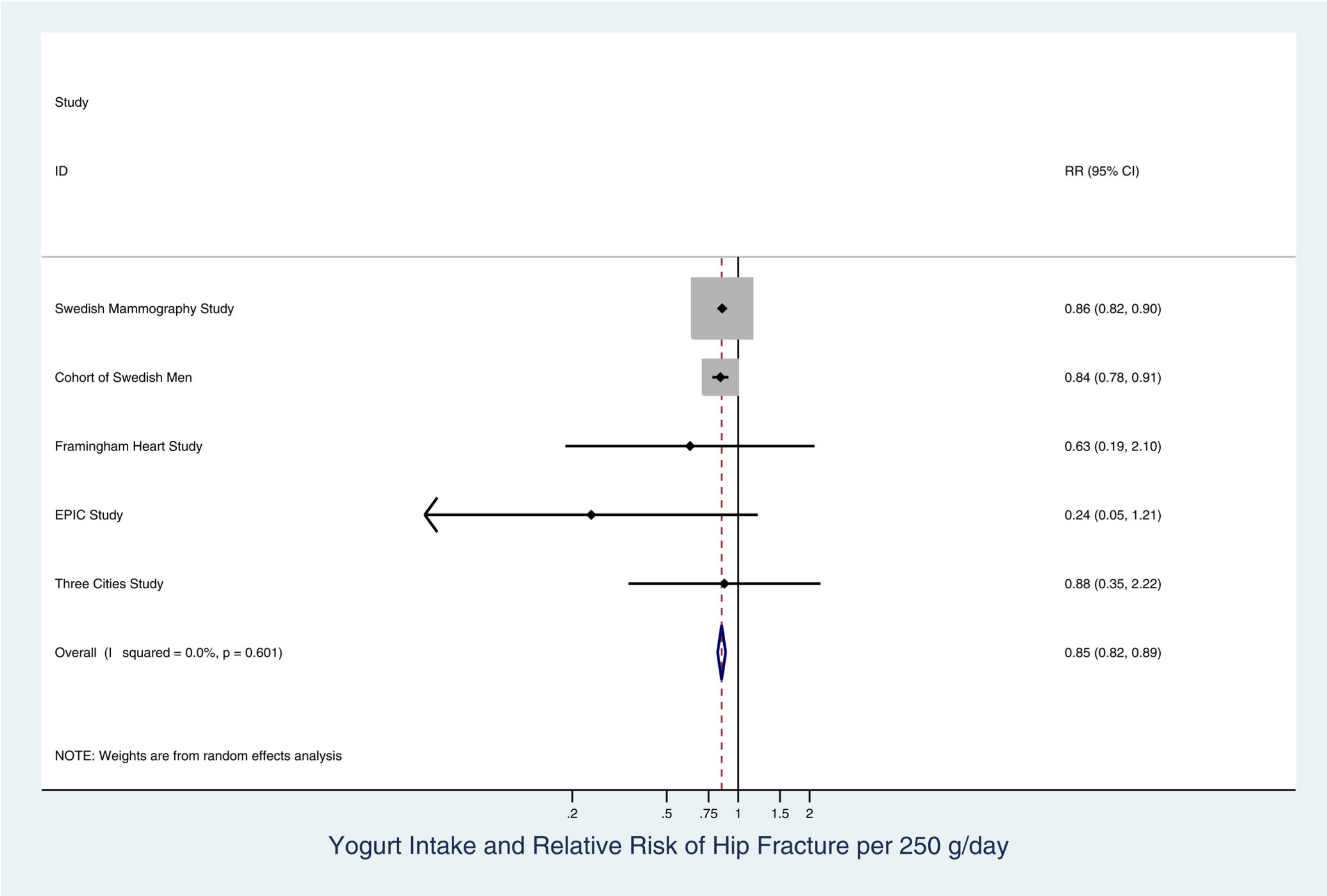

Fig. 4. Forest plot for the association of yoghurt intake with risk of hip fracture.

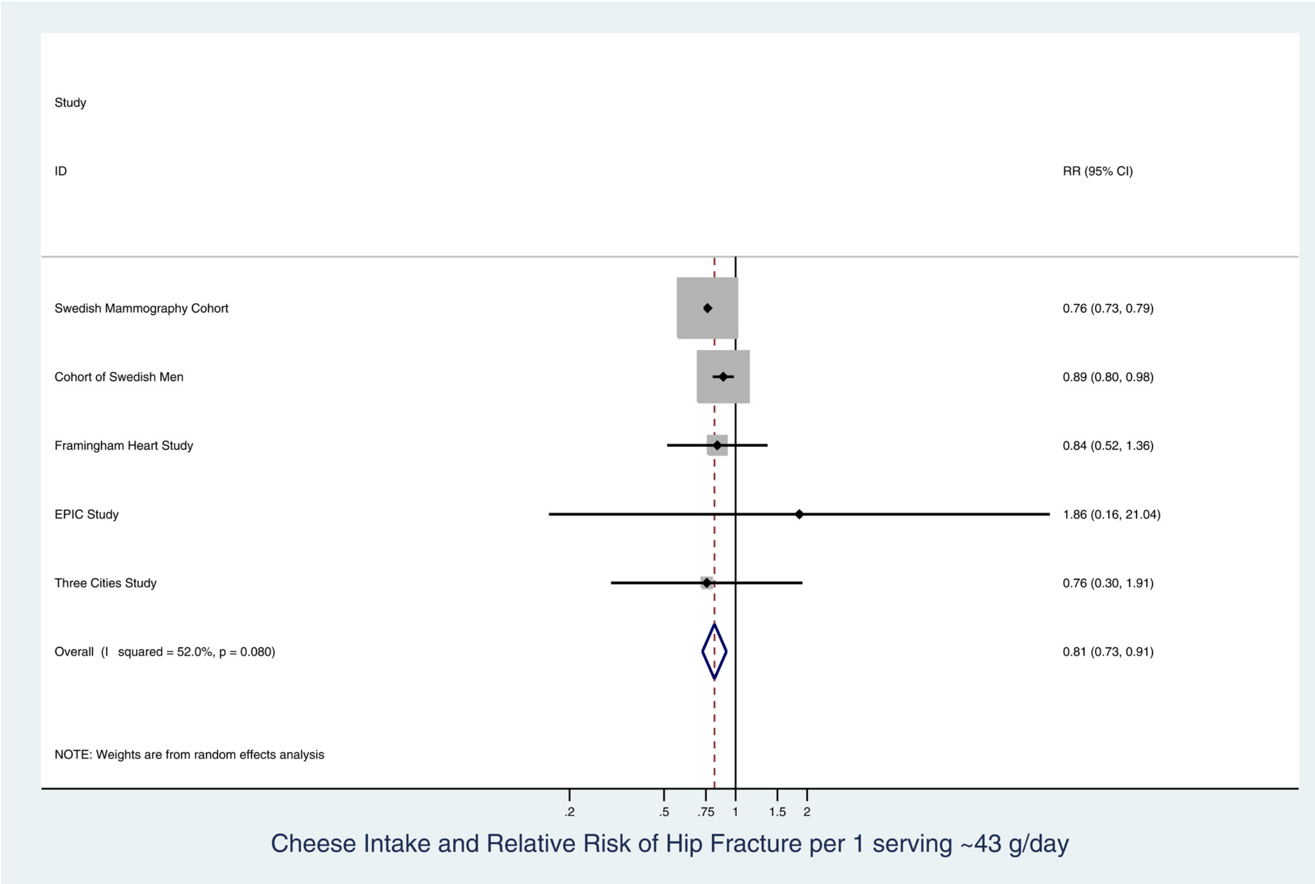

Fig. 5. Forest plot for the association of cheese intake with risk of hip fracture.

of 0, $P = 0{\cdot}60$ (Fig. 4). No publication bias trend was observed (Egger's Test $P = 0{\cdot}16$). Similarly, pooling the five studies of cheese intake and hip fracture in linear dose analysis found that cheese intake per 43 g/d (~1 serving/day) was associated with an inverse association of 19 % lower hip fracture risk (RR 0·81, 95 % CI 0·72, 0·92), while one study without precise cheese dose (any versus no cheese) found no association for cheese and hip fracture[22]. Heterogeneity was not significant, with $I^2 = 52$ (95 % CI 0–82, $P = 0{\cdot}08$) (Fig. 5). No publication bias trend was observed (Egger's Test $P = 0{\cdot}37$).

Discussion

In the present analysis, there was no significant relationship between overall dairy intake and hip fracture risk. These findings, derived from the most complete data set and most comprehensive and algorithmically driven meta-analysis of prospective cohorts to date, contradict the findings of earlier meta-analyses for milk[1,2,4–6].

Among dairy subfractions, the largest body of data was for milk intake, which was directly and significantly associated with risk of hip fracture. This risk was moderated at intakes above 400 g/d, but at no level of milk intake was there a suggestion of a significant protective association between milk and fracture risk.

There were noteworthy differences in findings between cohorts in the US and Swedish Mammography Cohort. However, even with sensitivity exclusion of the large Swedish Mammography cohort, milk still did not exhibit any inverse association with fractures. Moreover, the cohort of Swedish men and two cohorts in Norway also were in agreement with the overall findings on milk and fracture. Nevertheless, it is important to consider potential factors that could explain the observed variability. Although all studies included in this review used similar designs and diagnostic criteria, there were differences in age, body weight and vitamin D exposure, which may have influenced their findings.

Age

The three cohorts that reported protective effects of milk intake on hip fracture risk (middle-aged Norwegian cohorts, Nurses' Health Study and Health Professionals Follow-up Study) had participants with mean baseline ages ranging between 47 and 58 years, whereas mean baseline age of participants in all other cohorts ranged between 53·5 and 77 years.

Body weight

In the Nurses' Health Study and Health Professionals Follow-up Study, the inverse associations between dairy consumption and hip fracture risk were mainly limited to those with larger BMI[23]. Obesity is much more common in the US than in other countries[31], affecting approximately 40 %

among US adults >20 years old, compared with approximately 19 % of adults in Sweden[31,32].

Vitamin D

Vitamin D enhances calcium absorption[33,34]. It is noteworthy that the US-based Nurses' Health Study, which reported baseline intakes of 9·7 μg vitamin D and 1060 mg calcium per day, found a protective effect of milk intake, while the Swedish Mammography Cohort, which reported baseline intakes of 4·6 μg vitamin D and 916·5 mg calcium per day, found increased hip fracture risk with increased milk intake.

In the US, all milk is fortified with vitamin D and is the single biggest contributor to vitamin D intakes (58 % in men, 39 % in women)[35]. In Sweden, only low-fat milk are fortified[36] (although they remain significant contributors to vitamin D intake)[37]. In Norway, milk is not routinely fortified with vitamin D[38]. Milk's role in vitamin D status is not entirely straightforward, however. Despite vitamin D fortification, dairy calcium can suppress vitamin D activation, depressing circulating levels of 1,25-dihydroxyvitamin D[8].

These observations suggest that discordant findings among studies may be in part attributable to differences in age, participant weight and vitamin D fortification. Although differences in fat content of milk may seem to be an additional possible explanatory factor for between-study differences, analyses of fracture risk by fat content did not yield different effects (Michaelsson, personal communication, November 2017)[15,16].

The mechanisms behind potentially higher risk of hip fracture with milk intake are not entirely clear. D-galactose, a breakdown product of lactose, has been linked to oxidative stress and inflammation, potentially increasing the risk of fracture and mortality[15,16]. Higher levels of D-galactose in milk, compared with lower or non-existent levels in cheese, may partly explain positive associations of milk and inverse association of cheese with hip fracture risk reported in the Swedish Mammography Cohort[15]. Furthermore, milk intake during adolescence modestly increases height, a risk factor for fracture[39], which a study of teenage milk intake yielded higher hip fracture risk in men, and no effect in women in later adulthood[39]. Similarly, a Canadian study also found no association between childhood milk consumption and fracture risk[40].

Fewer studies examined relationships between yoghurt and cheese intake and hip fracture risk, but overall these studies indicated general inverse relationships for yoghurt and hip fracture, and possibly for cheese, though unclear. A seemingly protective association with cheese may be surprising, particularly given that cheese is high in sodium, a micronutrient strongly associated with loss of bone density[41]. The interpretation of this finding is complicated by the fact that the included studies did not adjust for SES except those by Michaelson, Holvik *et al.* and Feart *et al.* In the US and Europe, yoghurt and cheese consumption is positively associated with SES, while SES appears to have a neutral or negative association with milk consumption[42–45]. Indeed, the one Danish prospective study[22] that did adjust for education level did not find any inverse association for milk and hip fracture risk.

Strengths

Our study has notable strengths. It includes a larger number of prospective studies that were available for previous meta-analyses of dairy-fracture risk[1,23,27,46–48], and we also included *de novo* updated estimates from personal communications with Swedish collaborators (Michaelson, personal communication, November 2017). Furthermore, our study included a detailed algorithmically driven dose-response meta-regression incorporating non-linear splines and accounting for differing reference intake levels, which together allowed us to algorithmically identify significant non-linear associations for milk intake that had not been previously identified. Furthermore, our results of null associations for total dairy with hip fracture risk are corroborated by a more recent study[49].

Limitations

This study also has limitations. Data on dairy consumption were collected using food frequency questionnaires, which may have minor variation in the interpretation of one glass of milk. Data on incident hip fractures were obtained through self-reports in some of the studies included. A large proportion of people are discharged to a nursing facilities after suffering from a hip fracture and mortality after hip fracture is high, which may have contributed to lower reports of fracture events and loss to follow-up. Although SES is sometimes associated with cheese and yoghurt intake, however, SES was explored in the Nurses' Health Study and HPFS, which have little SES confounding due to the relatively homogeneous populations of health professionals. That said, there may be other non-linear associations that were not detected due to limited available studies and data points. While the Swedish Mammography Cohort was an influential milk study, it was the most comprehensive study of its kind, and its prominence and large size (and simultaneous publication with the Cohort of Swedish Men in the same *BMJ* paper) indicates that it was unlikely to have be suffered file-drawer publication bias that smaller studies tend to suffer, but which large studies don't. Plus, an analysis without the Swedish Mortality Cohort (SMC) still exhibited non-linearity, albeit smaller slopes. Furthermore, the SMC study's exclusion did not materially change the results for total dairy, yoghurt or cheese, with risk of hip fracture. Moreover, additional follow-up data from the SMC with ~1500 more hip fracture cases only further strengthened the findings. Finally, our study lacked data on dairy intake and hip fracture risk in children; it is possible dairy may have beneficial effects on paediatric populations, but this requires a careful future evaluation of the dairy-bone density literature, given the lack of studies with hip fracture end points in children.

Conclusions

Overall, increasing milk intake is associated with significantly increased risk of hip fracture, while intake and risk have inverse relationships for yoghurt and cheese intake. Because of the divergence in dairy products, total dairy intake is not associated importantly with risk of hip fracture.

Acknowledgements

The authors appreciate the feedback of Neal Barnard, and the extra efforts of Diane Feskanich in providing data support. The authors are grateful to Karl Michaelsson and Liisa Byberg for providing additional data from the Swedish Mammography Cohort and to Diane Feskanich for providing detailed numbers from the NHS and HPFS cohorts to allow complete dose-response meta-analyses. And acknowledge the support of research assistant Maya Chavez.

All authors contributed to development of the study design and data collection. S. M. and E. L. D. conducted data quality control. E. L. D. conducted analysis. S. M. and E. L. D. wrote the first draft with contributions from V. S. M. and K. B. All authors reviewed and commented on subsequent drafts and provided final approval of the manuscript.

E. L. D., S. M. and K. B. had received consultancy fees from the Physicians Committee for Responsible Medicine. V. S. M. is supported by 2R01HL060712-14, NIH/NHLBI 'Dietary Patterns and Risk of Cardiovascular Disease', has received research support from the Peanut Institute, was a pro bono retained expert for the Center for Science in the Public Interest in litigation related to sugar-sweetened beverages, and was a consultant for the City of San Francisco in litigation related to warning labels on soda.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study were reviewed and approved with exemption by the Harvard Human Subjects Review Board. Because of the literature review and meta-analysis nature of the study, written informed consent was not needed. E. L. D. conducted the research during 2016–2020 while a researcher at the Harvard SPH.

References

1. Bian S, Hu J, Zhang K, *et al.* (2018) Dairy product consumption and risk of hip fracture: a systematic review and meta-analysis. *BMC Public Health* **18**, 165. doi:10.1186/s12889-018-5041-5. Epub 2018/01/24. PubMed PMID: 29357845; PubMed Central PMCID: PMCPMC5778815.
2. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, *et al.* (2011) Milk intake and risk of hip fracture in men and women: a meta-analysis of prospective cohort studies. *J Bone Miner Res* **26**, 833–839. doi:10.1002/jbmr.279.
3. Bolland MJ, Leung W, Tai V, *et al.* (2015) Calcium intake and risk of fracture: systematic review. *BMJ (Clin Res ed)* **351**, h4580. doi:10.1136/bmj.h4580. Epub 2015/10/01. PubMed PMID: 26420387; PubMed Central PMCID: PMCPMC4784799.
4. Kanis JA, Johansson H, Oden A, *et al.* (2005) A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int* **16**, 799–804. Epub 2004 Oct 21. PubMed PMID: 15502959.
5. Malmir H, Larijani B & Esmaillzadeh A (2020) Consumption of milk and dairy products and risk of osteoporosis and hip fracture: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr* **60**, 1722–1737. doi:10.1080/10408398.2019.1590800. Epub 2019 Mar 26.
6. Hidayat K, Du X, Shi BM, *et al.* (2020) Systematic review and meta-analysis of the association between dairy consumption and the risk of hip fracture: critical interpretation of the currently available evidence. *Osteoporos Int* **31**, 1411–1425. doi:10.1007/s00198-020-05383-3. Epub 2020 May 7. PMID: 32383066.
7. O'Neil CE, Keast DR, Fulgoni VL, *et al.* (2012) Food sources of energy and nutrients among adults in the US: NHANES 2003–2006. *Nutrients* **4**, 2097–2120. doi:10.3390/nu4122097.
8. Chan JM, Stampfer MJ, Ma J, *et al.* (2001) Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. *Am J Clin Nutr* **74**, 549–554.
9. Giovannucci E (1998) Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. *Cancer Causes Control* **9**, 567–582. [PubMed: 10189042].
10. Giovannucci E, Rimm EB, Wolk A, *et al.* (1998) Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res* **58**, 442–447.
11. Larsson SC, Orsini N & Wolk A (2006) Milk, milk products and lactose intake and ovarian cancer risk: a meta-analysis of epidemiological studies. *Int J Cancer* **118**, 431–441.
12. Moher D, Liberati A, Tetzlaff J, *et al.* (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* **62**, 1006–1012.
13. Greenland S & Longnecker MP (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* **135**, 1301–1309.
14. Bauer SR, Hankinson SE, Bertone-Johnson ER, *et al.* (2013) Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. *Medicine (Baltimore)* **92**, 123–131.
15. Higgins JPT & Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**, 1539–1558.
16. Michaelsson K, Wolk A, Eva Lemming W, *et al.* (2018) Intake of milk or fermented milk combined with fruit and vegetable consumption in relation to hip fracture rates: a cohort study of Swedish women. *J Bone Miner Res* **33**, 449–457.
17. Michaëlsson K, Wolk A, Langenskiöld S, *et al.* (2014) Milk intake and risk of mortality and fractures in women and men: cohort studies. *Br Med J* **349**, g6015.
18. Benetou V, Orfanos P, Zylis D, *et al.* (2011) Diet and hip fractures among elderly Europeans in the EPIC cohort. *EJCN* **65**, 132–139.
19. Feart C, Lorrain S, Ginder Coupez V, *et al.* (2013) Adherence to a Mediterranean diet and risk of fractures in French older persons. *Osteoporos Int* **24**, 3031–3041. doi:10.1007/s00198-013-2421-7. Epub 2013 Jun 20. PubMed PMID: 23783645.
20. Sahni S, Tucker KL, Kiel DP, *et al.* (2013) Milk and yogurt consumption are linked with higher bone mineral density but not hip fracture: the Framingham Offspring Study. *Arch Osteoporos* **8**, 119.
21. Lousuebsakul-Matthews V, Thorpe DL, Knutsen R, *et al.* (2014) Legumes and meat analogues consumption are associated with hip fracture risk independently of meat intake among Caucasian men and women: the Adventist Health Study-2. *Public Health Nutr* **17**, 2333–2343.
22. Bergholdt HKM, Larsen MK, Varbo A, *et al.* (2018) Lactase persistence, milk intake, hip fracture and bone mineral density: a study of 97 811 Danish individuals and a meta-analysis. *J Intern Med* **284**, 254–269.
23. Sahni S, Mangano KM, Tucker KL, *et al.* (2014) Protective association of milk intake on the risk of hip fracture: results from the Framingham original cohort. *J Bone Miner Res* **29**, 1756–1762.
24. Feskanich D, Meyer HE, Fung TT, *et al.* (2018) Milk and other dairy foods and risk of hip fracture in men and women. *Osteoporosis Int* **29**, 385–396. doi:10.1007/s00198-017-4285-8. Epub 2017/10/28. PubMed PMID: 29075804.
25. Huang Z, Himes JH & McGovern PG (1996) Nutrition and subsequent hip fracture risk among a national cohort of white women. *Am J Epidemiol* **144**, 124–134. PubMed PMID: 8678043.
26. Cumming RG, Cummings SR, Nevitt MC, *et al.* (1997) Calcium intake and fracture risk: results from the study of osteoporotic fractures. *Am J Epidemiol* **145**, 926–934.
27. Feskanich D, Willett WC, Stampfer MJ, *et al.* (1996) Protein consumption and bone fractures in women. *Am J Epidemiol* **143**, 472–479.
28. Meyer HE, Pedersen JI, Loken EB, *et al.* (1997) Dietary factors and the incidence of hip fracture in middle-aged Norwegians – a prospective study. *Am J Epidemiol* **145**, 117–123.

29. Fujiwara S, Kasagi F, Yamada M, *et al.* (1997) Risk factors for hip fracture in a Japanese cohort. *J Bone Miner Res* **12**, 998–1004.
30. Holvik K, Meyer HE, Laake I, *et al.* (2018) Milk drinking and risk of hip fracture. The Norwegian Epidemiologic Osteoporosis Studies (NOREPOS). *Br J Nutr*, 1–21. doi:10.1017/S0007114518003823. PubMed PMID: 30588895.
31. Feskanich D, Singh V, Willet WC, *et al.* (2002) Vitamin A intake and hip fractures among postmenopausal women. *JAMA* **287**, 47–54.
32. Hales CM, Fryar CD, Carroll MD, *et al.* (2018) Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. *JAMA* **319**, 1723–1725. doi:10.1001/jama.2018.3060. PubMed PMID: 29570750; PubMed Central PMCID: PMC5876828.
33. Bonjour JP & Lecerf JM (2011) Dairy micronutrients: new insights and health benefits. *J Am Coll Nutr* **30**, 399S.
34. Lamberg-Allardt C, Brustad M, Meyer HE, *et al.* (2013) Vitamin D - a systematic literature review for the 5th edition of the Nordic Nutrition Recommendations. *Food Nutr Res* **3**, 57.
35. Christakos S (2012 Mar) Mechanism of action of 1,25-dihydroxyvitamin D3 on intestinal calcium absorption. *Rev Endocr Metab Disord* **13**, 39–44. doi:10.1007/s11154-011-9197-x. PubMed PMID: 21861106.
36. O'Mahony L, Stepien M, Gibney MJ, *et al.* (2011) The potential role of vitamin D enhanced foods in improving vitamin D status. *Nutrients* **3**, 1023–1041.
37. Spiro A & Buttriss JL (2014) Vitamin D: an overview of vitamin D status and intake in Europe. *Nutr Bull* **39**, 322–350.
38. Burgaz A, Akesson A, Oster A, *et al.* (2007) Associations of diet, supplement use, and ultraviolet B radiation exposure with vitamin D status in Swedish women during winter. *Am J Clin Nutr* **86**, 1399–1404.
39. Feskanich D, Bischoff-Ferrari HA, Frazier AL, *et al.* (2014) Milk consumption during teenage years and risk of hip fractures in older adults. *JAMA Pediatr* **168**, 54–60. doi:10.1001/jamapediatrics.2013.3821.
40. Allison RM, Birken CS, Lebovic G, *et al.* (2020) TARGet kids! Collaboration. consumption of cow's milk in early childhood and fracture risk: a prospective cohort study. *Am J Epidemiol* **189**, 146–155. doi:10.1093/aje/kwz216. PMID: 31712819; PMCID: PMC7156142.
41. World Health Organization (2013) *Nutrition, Physical Activity and Obesity.* Sweden. http://www.euro.who.int/__data/assets/pdf_file/0003/243327/Sweden-WHO-Country-Profile.pdf
42. Devine A, Criddle RA, Dick IM, *et al.* (1995) A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr* **62**, 740–745. [PubMed: 7572702].
43. James WP, Nelson M, Ralph A, *et al.* (1997) Socioeconomic determinants of health. The contribution of nutrition to inequalities in health. *Br Med J* **314**, 1545–1549.
44. Prattal RS, Groth MV, Oltersdorf US, *et al.* (2003) Use of butter and cheese in 10 European countries. *Eur J Publ Health* **13**, 124–132.
45. Sanchez-Villegas A, Martınez JA, Prattala R, *et al.* (2003) A systematic review of socioeconomic differences in food habits in Europe: consumption of cheese and milk. *Eur J Clin Nutr* **57**, 917–929.
46. Deshmukh-Taskar P, Nicklas TA & Yang SJ (2007) Berenson GS does food group consumption vary by differences in socio-economic, demographic, and lifestyle factors in young adults? The Bogalusa Heart Study. *J Am Diet Assoc* **107**, 223–234.
47. Feskanich D, Willet WC, Stampfer MJ, *et al.* (1997) Milk, dietary calcium, and bone fractures in women: a 12 year-year prospective study. *Am J Public Health* **87**, 992–997.
48. Feskanich D, Willett WC & Colditz GA (2003) Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. *Am J Clin Nutr* **77**, 504–511. PubMed PMID: 12540414.
49. Webster J, Greenwood DC & Cade JE (2022) Foods, nutrients and hip fracture risk: A prospective study of middle-aged women. *Clin Nutr* **41**, 2825–2832. doi:10.1016/j.clnu.2022.11.008. PMID: 36402009.