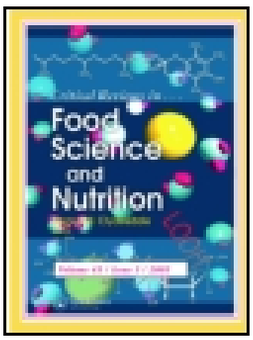

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Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Sina Naghshi, Omid Sadeghi, Bagher Larijani & Ahmad Esmaillzadeh (2021): High vs. low-fat dairy and milk differently affects the risk of all-cause, CVD, and cancer death: A systematic review and dose-response meta-analysis of prospective cohort studies, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1867500

To link to this article: https://doi.org/10.1080/10408398.2020.1867500

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1867500

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REVIEW

High vs. low-fat dairy and milk differently affects the risk of all-cause, CVD, and cancer death: A systematic review and dose-response meta-analysis of prospective cohort studies

Sina Naghshi[a,b], Omid Sadeghi[c], Bagher Larijani[d], and Ahmad Esmaillzadeh[c,e,f]

[a]Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran; [b]Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [c]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [d]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; [e]Obesity and Eating Habits Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; [f]Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Considerable controversy exists regarding the association between milk and dairy consumption and mortality risk. The present systematic review and meta-analysis of prospective studies was undertaken to examine the association of high vs. low-fat dairy and milk consumption with mortality. We searched PubMed/Medline, ISI Web of Science, and Scopus databases through February 2020 for prospective cohort studies that reported the association between milk and dairy consumption and mortality risk. High-fat milk consumption was significantly associated with a greater risk of all-cause (Pooled ES: 1.15; 95% CI: 1.09-1.20, I^2=24.5%, p = 0.22), CVD (Pooled ES: 1.09; 95% CI: 1.02-1.16, I^2=4.5%, p = 0.38) and cancer mortality (Pooled ES: 1.17; 95% CI: 1.08-1.28, I^2=30.1%, p = 0.19). However, total dairy consumption was associated with a lower risk of CVD mortality (Pooled ES: 0.93; 95% CI: 0.88-0.98, I^2=59.7%, p = 0.001). Dose-response analysis revealed a significant non-linear association of total dairy consumption with all-cause and CVD mortality. Moreover, high-fat milk consumption was significantly associated with risk of cancer mortality in linear and non-linear dose-response analysis. In conclusion, we found high-fat milk consumption was associated with a higher risk of all-cause, CVD, and cancer mortality. However, total dairy consumption was associated with a lower risk of CVD mortality.

KEYWORDS

Mortality; death; milk; dairy; cancer; cardiovascular disease

Introduction

Cardiovascular disease (CVD) and cancer remain the two most common causes of death, which accounted for 26.9 million deaths in 2016, worldwide (World Health Organization 2016). Dairy products are widely consumed worldwide. They are the main source of saturated fats, which is thought to have an adverse effect on blood lipids and increase the risk of CVD and mortality. Using this framework, dietary guidelines recommended reduced consumption of high-fat dairy foods for cardiovascular disease prevention (Alexander et al. 2016). However, dairy products contain potentially beneficial compounds such as branched-chain amino acids, medium-chain saturated fats, unsaturated and branched-chain fats, conjugated linoleic acid, milk fat globule phospholipids, calcium, probiotics, multiple anabolic hormones as well (Darling, Laing, and Harkness 1974; Maruyama, Oshima, and Ohyama 2010; Mozaffarian and Wu 2018). Therefore, the effect of dairy intake on health outcomes might be influenced by the combination of these components. Findings from earlier observational studies on the association of total dairy intake with risk of hypertension (Ralston et al. 2012; Soedamah-Muthu et al. 2012), type 2 diabetes (Gao et al. 2013), cardiovascular disease (Qin et al. 2015), colorectal cancer (Aune et al. 2012), and breast cancer (Dong et al. 2011) were mostly null or moderately inverse. However, high intakes of dairy products have been associated with a greater risk of certain cancers (Aune et al. 2015; Larsson, Orsini, and Wolk 2006; Liu et al. 2015). Findings about the contribution of dairy intake to mortality are conflicting. While dairy food intake was associated with increased risk of mortality in some investigations (Goldbohm et al. 2011; Michaëlsson et al. 2014), inverse or null associations were reached in other studies (Bonthuis et al. 2010; Farvid et al. 2017). Finding from a meta-analysis in 2019 indicated a significant inverse association between fermented dairy foods and risk of all-cause mortality and a positive link between milk consumption and risk of CHD mortality (Mazidi et al. 2019). Findings from that meta-analysis might be misleading due to lack of including all eligible

CONTACT Ahmad Esmaillzadeh a-esmaillzadeh@sina.tums.ac.ir Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, P.O. Box 14155-6117, No. 44, Hojatdost Ave, Naderi Ave, Keshavarz Blvd, Tehran, Iran.

Supplemental data for this article is available online at https://doi.org/10.1080/10408398.2020.1867500.

studies (Farvid et al. 2017; Praagman, Dalmeijer, et al. 2015). An overview of systematic reviews and meta-analyses reported that dairy product consumption is not associated with risk of all-cause mortality (Cavero-Redondo et al. 2019). However, CVD and cancer mortality was not considered in that analysis. Additionally, that study did not consider the fat content of milk, while high and low-fat dairy products might differently affect the risk. Moreover, after the release of the previous publication, at least seven large prospective cohort studies were appeared (Dehghan et al. 2018; Ding et al. 2019; Pala et al. 2019; Stasinopoulos, Zhou, and Hyppönen 2020; Um et al. 2017; Um et al. 2019; Virtanen et al. 2019). Therefore, it seems that an updated comprehensive meta-analysis is required to shed light on the association between dairy intake and mortality. Understanding the association between dairy consumption and mortality is important for guiding consumer choices and prioritizing dietary guidelines to reduce the risk. Therefore, we conducted a comprehensive dose-response meta-analysis of prospective cohort studies to examine the association between total, low-fat, and high-fat dairy consumption and risk of all-cause, CVD, and cancer mortality.

Methods

Findings from this systematic review and meta-analysis were reported based on Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline (Moher et al. 2009).

Search strategy

We conducted a systematic search on all articles published up to February 2020 using online databases including PubMed/Medline, ISI Web of Science, and Scopus with no limitation in language or time of publication. Details on the search terms are provided in Supplemental Table 1. In addition, to prevent missing any publication, reference lists of extracted papers and recent reviews were also checked. In the search strategy, unpublished studies were excluded. Furthermore, we removed duplicate citations.

Inclusion and exclusion criteria

Published studies that met the following criteria were included: 1) prospective observational studies conducted on humans; 2) studies that reported hazard ratios (HRs) or relative risks (RRs) or odds ratios (ORs) with corresponding 95% CIs for mortality in relation to dietary intakes of milk, total, low-fat, and high-fat dairy as the exposure of interest. All outcomes were classified based on the World Health Organization's international classification of disease criteria. Since dietary intakes of participants are affected by their disease, we decided to include the studies that were only done on healthy population. If the same dataset had been published in >1 publication, then only the study with more complete findings or more number of cases was included in our meta-analysis.

We excluded letters, comments, reviews, and meta-analyses. We also did not include ecologic studies and those that were conducted on children, adolescences, and cancer patients. Also, if a study reported the effect size for fatal and non-fatal cardiovascular diseases combined, we did not include in our analysis. We also excluded studies that considered individual dairy products as exposure in the meta-analysis of dairy because these items alone are not considered as 'all' or 'total' dairy products.

Data extraction

Data extraction was conducted independently by 2 researchers (SN and OS) and any disagreements were resolved by consultation with the principal investigator (AE). We extracted the following data from each eligible article: name of the first author, publication year, study design, location of study conduct, age range at entry, gender, sample size of the cohort, incidence of death, duration of follow-up, exposure, method of assessment of exposure, health status of participants at entry, comparison categories and relevant effect sizes along with 95% CI, and confounding variables adjusted in statistical analysis. When data were reported for men and women separately, each part was considered as a distinct study. If an included study reported several risk estimates, the fully-adjusted HRs were extracted.

Risk of bias assessment

We used the risk of bias in non-randomized studies of exposures (ROBINS-E) tool to assess risk of bias of included studies (Bero et al. 2018). The ROBINS-E tool comprises 7 domains through which bias might be introduced. The questions of these domains include: (1) bias due to confounding, (2) bias in selection of participants into study, (3) bias in the classification of exposures, (4) bias due to departure from intended exposures, (5) bias due to missing data, (6) bias in the measurement of outcomes, and (7) bias in the selection of reported results. Studies were categorized as low risk, moderate risk, serious risk, and critical risk of bias under each domain.

Data synthesis and analysis

ORs, RRs, and HRs (and 95% CIs) for comparison of the highest and lowest categories of dairy intake were used to calculate log RR, OR, HR ± SE. The analyses were performed with the use of a random-effects model, in which we calculated both Q-statistic and I^2 as indicators of heterogeneity. I^2 interpreted according to the Cochrane Handbook thresholds (0-40%, might not be important; 30-60%, might represent moderate heterogeneity; 50-90%, might represent substantial heterogeneity; 75-100%, considerable heterogeneity). A random-effects model can account for between-study variations and thus it can provide more conservative results than a fixed-effects model. For studies that reported effect sizes separately for milk, yogurt, cheese, and butter intake or for high/whole fat dairy and low/skim fat dairy or

high/whole fat milk and low/skim fat milk, first we combined the estimates using the fixed-effects model to obtain an overall estimate and then, the pooled effect size was included in the meta-analysis. This was also done for studies that reported the effect sizes separately for low fat, skim fat, and moderate fat milk or dairy. If a study reported the findings separately for mortality from different cancers and cardiovascular diseases, we combined the estimates using a fixed-effects model to obtain an overall estimate for cancer and CVD mortality. In addition, studies that investigated only cancer or CVD mortality in relation to milk and dairy intake were also considered in the meta-analysis of all-cause mortality because they are the part of all-cause mortality. If an estimate was reported for the lowest category of intake compared with the highest category, we computed the highest versus lowest estimates using a method introduced by Orsini et al. Dairy intakes were converted into servings/d using standard conversions from the Food Standards Agency (pint = 585 g; milk, 1 glass = 200 mL; and total dairy =200 g) (Mills and Patel 2006). Assumptions were made to convert all dairy exposure data into serving/d, considering 1 serving dairy products or milk as 200 g or 200 mL, respectively.

In case of finding a significant between-study heterogeneity, we performed subgroup analysis to examine possible sources of heterogeneity. Between-subgroup heterogeneity was examined through fixed-effects model. Publication bias was examined by visual inspection of funnel plots. Formal statistical assessment of funnel plot asymmetry was also done with the use of Egger's regression asymmetry test and Begg's test. In case of significant publication bias, the trim-and-fill method was used to detect the effect of missing studies on the overall effect of meta-analysis. We also conducted a sensitivity analysis in which each prospective cohort study was excluded to examine the influence of that study on the overall estimate.

We used a previously described method by Greenland and Longnecker (1992) and Orsini, Bellocco, and Greenland (2006) for the dose-response analysis. The natural logs of the RRs and CIs across categories of milk and dairy intake were used to compute study-specific slopes (linear trends) and 95% CIs. In this method, the distribution of deaths and the total number of participants and the RRs with the variance estimates for $\geq$3 quantitative categories of exposure were required. We assigned the median or mean amount of milk and dairy intake in each category to the corresponding RR for each study. For studies that reported the intake as ranges, we estimated the midpoint in each category by calculating the mean of the lower and upper bound. When the highest category was open-ended, the length of the open-ended interval was assumed to be the same as that of the adjacent interval. A two-stage random-effects dose-response meta-analysis was applied to examine a possible non-linear association between milk and dairy intake and mortality. This was done through modeling of milk and dairy intake and restricted cubic splines with three knots at fixed percentiles of 10, 50, and 90% of the distribution. Based on the Orsini method, we calculated restricted cubic spline models using generalized least-squares trend estimation method, which takes into account the correlation within each set of reported ORs/RRs/HRs. Then, all the study-specific estimates were combined with the use of the restricted maximum likelihood method in a multivariate random-effects meta-analysis (Jackson, White, and Thompson 2010). A probability value for non-linearity was estimated using null hypothesis testing in which the coefficient of the second spline was considered equal to 0. A linear dose-response association of an additional one serving from milk and dairy with mortality was investigated using the two-stage generalized least-squares trend estimation method. First, study-specific slope lines were estimated and then, these lines were combined to obtain an overall average slope. Study-specific slope lines were combined using a random-effects model. Statistical analyses were conducted using STATA version 14.0. $p < 0.05$ was considered as statistically significant for all tests, including Cochran's Q test.

Results

Literature search

We identified a total of 19,683 articles in our initial search. After exclusion of duplicate papers and those that did not meet the inclusion criteria, we reached 61 full articles of potentially relevant studies (Figure 1). After full-text reviews, we excluded an additional 14 studies for the following reasons: three publications that were conducted on cancer patients, 8 studies that had reported HRs for fatal and non-fatal CVDs combined,(Al-Delaimy et al. 2003; Dalmeijer et al. 2013; Hu et al. 1999; Koskinen et al. 2018; Panagiotakos et al. 2009; Patterson et al. 2013; Sonestedt et al. 2011; von Ruesten et al. 2013) one study that considered yogurt consumption as the exposure rather than total dairy (Schmid et al. 2020) one study that conducted on children and, one study with insufficient data (Bergholdt et al. 2018). Finally, 47 papers were included in this systematic review and meta-analysis (Appleby et al. 1999; Bongard et al. 2016; Bonthuis et al. 2010; Breslow et al. 2000; Chow et al. 1992; Dehghan et al. 2018; Ding et al. 2019; Elwood et al. 2004; Farvid et al. 2017; Fortes et al. 2000; Goldbohm et al. 2011; Hsing et al. 1990; Huang et al. 2014; Kahn et al. 1984; Kinjo et al. 1999; Knoops et al. 2006; Koh et al. 2006; Kojima et al. 2004; Kondo et al. 2013; Louie et al. 2013; Mann et al. 1997; Matsumoto et al. 2007; Mazidi et al. 2019; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Paganini-Hill, Kawas, and Corrada 2007; Pala et al. 2019; Park et al. 2007; Praagman, Dalmeijer, et al. 2015; Praagman, Franco, et al. 2015; Rodriguez et al. 2002; Sauvaget et al. 2003; Sharma et al. 2013; Snowdon, Phillips, and Choi 1984; Soedamah-Muthu et al. 2013; Song et al. 2013; Stasinopoulos, Zhou, and Hyppönen 2020; Talaei et al. 2019; Talaei et al. 2017; Tognon et al. 2017; Tognon et al. 2018; Um et al. 2017; Um et al. 2019; van Aerde et al. 2013; van den Brandt 2019; Virtanen et al. 2019; Wang et al. 2015): 28 publications had reported effect sizes for all-cause mortality (Appleby et al. 1999; Bongard et al. 2016; Bonthuis et al.

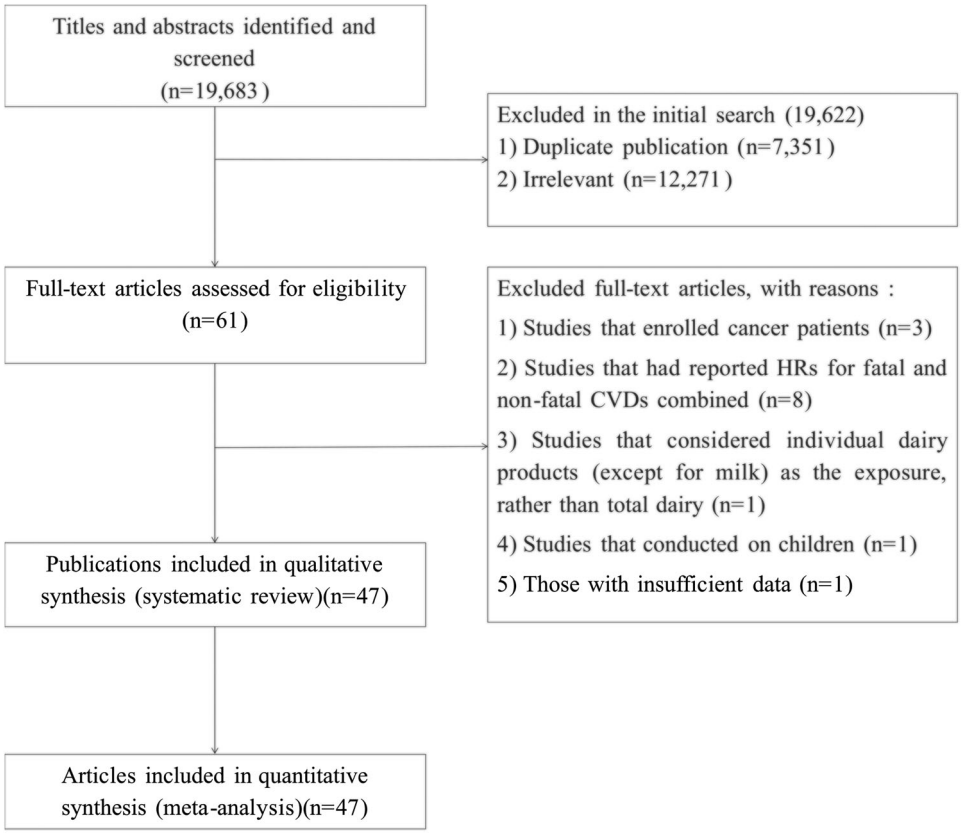

Figure 1. Flow diagram of study selection.

2010; Dehghan et al. 2018; Ding et al. 2019; Elwood et al. 2004; Farvid et al. 2017; Goldbohm et al. 2011; Huang et al. 2014; Kahn et al. 1984; Knoops et al. 2006; Mazidi et al. 2019; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Paganini-Hill, Kawas, and Corrada 2007; Pala et al. 2019; Praagman, Dalmeijer, et al. 2015; Soedamah-Muthu et al. 2013; Stasinopoulos, Zhou, and Hyppönen 2020; Talaei et al. 2019; Tognon et al. 2017; Tognon et al. 2018; Um et al. 2017; Um et al. 2019; van Aerde et al. 2013; van den Brandt 2019; Virtanen et al. 2019; Wang et al. 2015), 23 articles for CVD mortality (Bonthuis et al. 2010; Dehghan et al. 2018; Ding et al. 2019; Farvid et al. 2017; Goldbohm et al. 2011; Huang et al. 2014; Kinjo et al. 1999; Kondo et al. 2013; Louie et al. 2013; Mann et al. 1997; Mazidi et al. 2019; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Pala et al. 2019; Praagman, Dalmeijer, et al. 2015; Praagman, Franco, et al. 2015; Sauvaget et al. 2003; Stasinopoulos, Zhou, and Hyppönen 2020; Talaei et al. 2019; Talaei et al. 2017; Um et al. 2017; Um et al. 2019; Wang et al. 2015), and 24 papers for cancer mortality (Breslow et al. 2000; Chow et al. 1992; Ding et al. 2019; Farvid et al. 2017; Hsing et al. 1990; Huang et al. 2014; Koh et al. 2006; Kojima et al. 2004; Matsumoto et al. 2007; Mazidi et al. 2019; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Pala et al. 2019; Park et al. 2007; Praagman, Dalmeijer, et al. 2015; Rodriguez et al. 2002; Sharma et al. 2013; Snowdon, Phillips, and Choi 1984; Song et al. 2013; Stasinopoulos, Zhou, and Hyppönen 2020; Um et al. 2017; Um et al. 2019; van den Brandt 2019; Wang et al. 2015).

Characteristics of included studies

Characteristics of included prospective cohort studies are provided in Supplemental Tables 2–4. Participants in these studies ranged from 162 to 497,828 people, with an age range between 25 and 101 years. In total, 2,967,447 participants were included in 47 papers we considered. During the follow-up periods ranging from 4.2 to 32 years, total number of deaths that occurred from all causes was 221,649; from CVD was 51,588 and from cancer was 61,761. Eleven publications had included only men (Bongard et al. 2016; Chow et al. 1992; Elwood et al. 2004; Hsing et al. 1990; Koh et al. 2006; Ness, Smith, and Hart 2001; Park et al. 2007; Rodriguez et al. 2002; Snowdon, Phillips, and Choi 1984; Song et al. 2013; Virtanen et al. 2019) and one study included only women (Um et al. 2019). Out of the remaining studies, six studies had reported HRs for men and women, separately (Goldbohm et al. 2011; Kojima et al. 2004; Kondo et al. 2013; Michaëlsson et al. 2014; Sharma et al. 2013; Wang et al. 2015). In total, 15 publications were conducted in the United States (Breslow et al. 2000; Chow et al. 1992; Ding et al. 2019; Hsing et al. 1990; Kahn et al. 1984; Koh et al. 2006; Mazidi et al. 2019; Paganini-Hill, Kawas, and Corrada 2007; Park et al. 2007; Rodriguez et al. 2002; Sharma et al. 2013; Snowdon, Phillips, and Choi 1984; Song et al. 2013; Um et al. 2017; Um et al. 2019), and 31 in non-US countries (Appleby et al. 1999; Bongard et al. 2016; Bonthuis et al. 2010; Elwood et al. 2004; Farvid et al. 2017; Fortes et al. 2000; Goldbohm et al. 2011; Huang et al. 2014; Kinjo et al. 1999; Knoops et al. 2006; Kojima et al. 2004; Kondo et al. 2013; Louie et al. 2013;

Table 1. Summary risk estimates for the association between total, low-fat, and high-fat dairy intake and risk of mortality in adults aged ≥18 years.

		Publication, n	Pooled ES (95% CI)[1]	P-value	I2 (%)[2]	P-heterogeneity[3]
The highest vs. lowest comparison of total dairy intake						
All-cause mortality						
	Total dairy	33	0.99 (0.95-1.03)	0.57	67.3	<0.001
	Low-fat dairy	8	0.95 (0.89-1.01)	0.09	56	0.02
	High-fat dairy	7	0.99 (0.95-1.03)	0.60	0	0.45
CVD mortality						
	Total dairy	16	0.93 (0.88-0.98)	0.01	59.7	0.001
	Low-fat dairy	6	0.94 (0.83-1.06)	0.30	50.2	0.06
	High-fat dairy	5	0.92 (0.78-1.10)	0.36	59.5	0.04
Cancer mortality						
	Total dairy	19	1.03 (0.98-1.07)	0.23	37.8	0.03
	Low-fat dairy	–	–	–	–	–
	High-fat dairy	–	–	–	–	–
Linear dose-response association (per 1serving increase)						
All-cause mortality						
	Total dairy	20	0.99 (0.97-1.01)	0.28	78.4	<0.001
	Low-fat dairy	9	0.99 (0.97-1.02)	0.83	57.8	0.01
	High-fat dairy	8	0.98 (0.92-1.03)	0.39	53.5	0.03
CVD mortality						
	Total dairy	13	0.98 (0.96-1.00)	0.10	67.7	<0.001
	Low-fat dairy	7	0.97 (0.91-1.03)	0.25	54	0.04
	High-fat dairy	6	0.96 (0.85-1.09)	0.53	71.1	0.004
Cancer mortality						
	Total dairy	9	1.00 (0.98-1.02)	0.90	70.4	0.001
	Low-fat dairy	–	–	–	–	–
	High-fat dairy	–	–	–	–	–

Abbreviation: ES: effect size, CI: confidence interval
[1]Obtained from the random-effects model.
[2]Inconsistency- percentage of variation across studies due to heterogeneity.
[3]Obtained from the Q-test.

Mann et al. 1997; Matsumoto et al. 2007; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Pala et al. 2019; Praagman, Dalmeijer, et al. 2015; Praagman, Franco, et al. 2015; Sauvaget et al. 2003; Soedamah-Muthu et al. 2013; Stasinopoulos, Zhou, and Hyppönen 2020; Talaei et al. 2019; Talaei et al. 2017; Tognon et al. 2017; Tognon et al. 2018; van Aerde et al. 2013; van den Brandt 2019; Virtanen et al. 2019; Wang et al. 2015), and one study conducted in 21 countries (Dehghan et al. 2018). To examine milk and dairy intake, 36 articles had used food frequency questionnaire, four studies had used weighed diet records or food recalls (Bongard et al. 2016; Kondo et al. 2013; Mazidi et al. 2019; Virtanen et al. 2019), two studies had used diet history (Knoops et al. 2006; Tognon et al. 2018), and four studies had used "Questionnaire" (Kahn et al. 1984; Kinjo et al. 1999; Ness, Smith, and Hart 2001; Paganini-Hill, Kawas, and Corrada 2007). Stasinopoulos et al (Stasinopoulos, Zhou, and Hyppönen 2020) reported in their study that milk intake was estimated using the computer-based touchscreen questionnaires. All studies except for one adjusted the associations for age. Most papers controlled for some conventional risk factors, including body mass index (n = 36), smoking (n = 45), and alcohol consumption (n = 32). Some others had also adjusted for physical activity (n = 26), energy intake (n = 27), and other dietary variables or nutrients (n = 25). Based on the ROBINS-E tool, 25 publications had a low-risk of bias in all components (Supplemental Table 5).

Findings from the meta-analysis on all-cause mortality

Total dairy consumption and risk of all-cause mortality, which was examined in thirty-three papers (Bongard et al. 2016; Bonthuis et al. 2010; Breslow et al. 2000; Chow et al. 1992; Dehghan et al. 2018; Ding et al. 2019; Farvid et al. 2017; Fortes et al. 2000; Goldbohm et al. 2011; Hsing et al. 1990; Huang et al. 2014; Knoops et al. 2006; Koh et al. 2006; Kojima et al. 2004; Kondo et al. 2013; Louie et al. 2013; Matsumoto et al. 2007; Mazidi et al. 2019; Pala et al. 2019; Park et al. 2007; Praagman, Dalmeijer, et al. 2015; Praagman, Franco, et al. 2015; Rodriguez et al. 2002; Sauvaget et al. 2003; Sharma et al. 2013; Snowdon, Phillips, and Choi 1984; Soedamah-Muthu et al. 2013; Song et al. 2013; Talaei et al. 2017; Tognon et al. 2018; Um et al. 2017; Um et al. 2019; Virtanen et al. 2019), included a total of 2,166,556 participants with 130,325 deaths. No significant association was seen (Pooled ES: 0.99; 95% CI: 0.95-1.03, $p = 0.57$) (Table 1). However, significant between-study heterogeneity was seen ($I^2 = 67.3\%$; $p < 0.001$).

Seven cohort studies examined the association of high-fat dairy consumption and risk of all-cause mortality,(Bonthuis et al. 2010; Dehghan et al. 2018; Farvid et al. 2017; Louie et al. 2013; Praagman, Franco, et al. 2015; Soedamah-Muthu et al. 2013; Um et al. 2019) with a total of 227,194 participants and 30,086 deaths. The summary ES for all-cause mortality comparing the highest and lowest dairy intakes in these studies was 0.99, indicating no significant association (95% CI: 0.95-1.03, $p = 0.60$) (Table 1). No significant heterogeneity among the studies was observed ($I^2 = 0\%$; $p = 0.45$). Low-fat dairy consumption, which was considered in eight studies (Bonthuis et al. 2010; Dehghan et al. 2018; Farvid et al. 2017; Goldbohm et al. 2011; Louie et al. 2013; Praagman, Franco, et al. 2015; Soedamah-Muthu et al. 2013; Um et al. 2019) with a total of 247,976 participants and 46,222 deaths, was not associated with risk of all-cause

Table 2. Summary risk estimates for the association between total, low-fat, and high-fat milk intake and risk of mortality in adults aged ≥18 years.

		publication, n	Pooled ES (95% CI)[1]	P-value	I2 (%)[2]	P-heterogeneity[3]
The highest vs. lowest comparison of milk intake						
All-cause mortality						
	Milk	27	1.01 (0.96-1.06)	0.66	95.1	<0.001
	Low-fat milk	8	1.02 (0.95-1.10)	0.54	80.1	<0.001
	High-fat milk	9	1.15 (1.09-1.20)	<0.001	24.5	0.22
CVD mortality						
	Milk	15	1.01 (0.93-1.10)	0.82	93.2	<0.001
	Low-fat milk	4	1.00 (0.92-1.09)	0.97	47.3	0.12
	High-fat milk	5	1.09 (1.02-1.16)	0.008	4.5	0.38
Cancer mortality						
	Milk	13	1.01 (0.97-1.05)	0.69	65	<0.001
	Low-fat milk	7	1.00 (0.96-1.05)	0.86	0	0.55
	High-fat milk	7	1.17 (1.08-1.28)	<0.001	30.1	0.19
Linear dose-response association (per 1serving increase)						
All-cause mortality						
	Milk	16	1.03 (0.99-1.06)	0.14	92.8	<0.001
	Low-fat milk	6	0.99 (0.97-1.02)	0.69	82	<0.001
	High-fat milk	6	1.10 (1.00-1.21)	0.05	89.4	<0.001
CVD mortality						
	Milk	9	1.02 (0.98-1.06)	0.40	89.1	<0.001
	Low-fat milk	4	1.01 (0.97-1.04)	0.70	69.4	0.02
	High-fat milk	4	1.06 (0.95-1.18)	0.29	65.3	0.03
Cancer mortality						
	Milk	8	1.03 (0.99-1.06)	0.24	71.3	0.001
	Low-fat milk	6	1.00 (0.98-1.02)	0.99	0	0.71
	High-fat milk	6	1.13 (1.01-1.28)	0.03	77.7	<0.001

Abbreviation: ES: effect size, CI: confidence interval.
[1]Obtained from the random-effects model.
[2]Inconsistency- percentage of variation across studies due to heterogeneity.
[3]Obtained from the Q-test.

mortality. (Pooled ES comparing the highest and lowest intakes: 0.95; 95% CI: 0.89-1.01, $p = 0.09$) (Table 1). There was an evidence of significant heterogeneity between studies ($I^2 = 56\%$; $p = 0.02$).

With regard to milk intake and risk of all-cause mortality, a total of 1,846,284 subjects participated in twenty-seven articles (Appleby et al. 1999; Bongard et al. 2016; Bonthuis et al. 2010; Breslow et al. 2000; Dehghan et al. 2018; Ding et al. 2019; Elwood et al. 2004; Farvid et al. 2017; Kahn et al. 1984; Mann et al. 1997; Matsumoto et al. 2007; Mazidi et al. 2019; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Paganini-Hill, Kawas, and Corrada 2007; Pala et al. 2019; Park et al. 2007; Praagman, Franco, et al. 2015; Sauvaget et al. 2003; Snowdon, Phillips, and Choi 1984; Soedamah-Muthu et al. 2013; Stasinopoulos, Zhou, and Hyppönen 2020; Tognon et al. 2017; Um et al. 2017; Um et al. 2019; Virtanen et al. 2019; Wang et al. 2015), in which 184,178 deaths occurred. The summary ES for all-cause mortality comparing the highest and lowest milk consumption indicated no significant association (ES: 1.01; 95% CI: 0.96-1.06, $p = 0.66$), with significant heterogeneity among the studies ($I^2 = 95.1\%$; $p < 0.001$) (Table 2). However, high-fat milk consumption was associated with a greater risk of all-cause mortality (Pooled ES: 1.15; 95% CI: 1.09-1.20, $p < 0.001$), with low heterogeneity among studies ($I^2 = 24.5\%$; $p = 0.22$) (Table 2). Low-fat milk consumption, which was examined in eight studies (Breslow et al. 2000; Ding et al. 2019; Pala et al. 2019; Park et al. 2007; Song et al. 2013; Tognon et al. 2017; Um et al. 2017; Um et al. 2019) with a total of 758,411 participants and 83,321 deaths was not significantly associated with all-cause mortality (Pooled ES: 1.02; 95% CI: 0.95-1.10, $p = 0.54$) (Table 2). However, significant between-study heterogeneity was seen ($I^2 = 80.1\%$; $p < 0.001$).

Findings from the meta-analysis on CVD mortality

Sixteen cohort studies investigated the association between total dairy intake and risk of CVD mortality (Bonthuis et al. 2010; Dehghan et al. 2018; Ding et al. 2019; Farvid et al. 2017; Goldbohm et al. 2011; Huang et al. 2014; Kondo et al. 2013; Louie et al. 2013; Mazidi et al. 2019; Pala et al. 2019; Praagman, Dalmeijer, et al. 2015; Praagman, Franco, et al. 2015; Sauvaget et al. 2003; Talaei et al. 2017; Um et al. 2017; Um et al. 2019). These studies included a total of 675,916 participants, among them 29,359 mortality cases were found. The summary effect size for CVD mortality, comparing the highest and lowest intakes of total dairy was 0.93 (95% CI: 0.88-0.98, $p = 0.01$), indicating a significant inverse association (Table 1). There was significant heterogeneity between studies ($I^2 = 59.7\%$; $p = 0.001$). However, this association was not significant for high-fat dairy consumption and CVD mortality based on five studies (Bonthuis et al. 2010; Farvid et al. 2017; Louie et al. 2013; Praagman, Franco, et al. 2015; Um et al. 2019). These studies included a total of 86,288 participants with 6,029 deaths, the pooled ES was 0.92 (95% CI: 0.78-1.10, $p = 0.36$), with significant heterogeneity among the studies ($I^2 = 59.5\%$; $p = 0.04$) (Table 1). Such a non-significant association was also seen about low-fat dairy consumption (Pooled ES: 0.94; 95% CI: 0.83-1.06, $p = 0.30$), with moderate heterogeneity among the studies ($I^2 = 50.2\%$; $p = 0.06$) (Table 1).

Fifteen cohort studies were included in the analysis of milk intake and CVD mortality (Bonthuis et al. 2010; Ding

et al. 2019; Farvid et al. 2017; Kinjo et al. 1999; Mann et al. 1997; Mazidi et al. 2019; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Pala et al. 2019; Praagman, Franco, et al. 2015; Sauvaget et al. 2003; Stasinopoulos, Zhou, and Hyppönen 2020; Um et al. 2017; Um et al. 2019; Wang et al. 2015). These studies involved a total of 1,360,032 participants, among them 42,859 mortality cases were found. The pooled effect size for CVD mortality was 1.01 (95% CI: 0.93-1.10, $p = 0.82$), indicating no clear significant association, with high between-study heterogeneity (I^2 =93.2%; $p < 0.001$) (Table 2). However, with regard to high-fat milk consumption, based on five studies (Ding et al. 2019; Pala et al. 2019; Talaei et al. 2019; Um et al. 2017; Um et al. 2019) with a total of 324,844 participants and 17,327deaths, we found a significant positive association with risk of CVD mortality (Pooled ES: 1.09; 95% CI: 1.02-1.16, $p = 0.008$), with no significant heterogeneity among the studies (I^2 = 4.5%; $p = 0.38$) (Table 2). No significant association was observed between low-fat milk intake and risk of CVD mortality, such that based on four cohort studies (Ding et al. 2019; Pala et al. 2019; Um et al. 2017; Um et al. 2019) on 319,412 participants with 17,163 mortality cases, the summary effect size was 1.00 (95% CI: 0.92-1.09, $p = 0.97$) (Table 2). There was an evidence of moderate heterogeneity between studies (I^2 = 47.3%; $p = 0.12$).

Findings from the meta-analysis on cancer mortality

Total dairy intake and risk of cancer mortality were investigated in nineteen papers (Breslow et al. 2000; Chow et al. 1992; Ding et al. 2019; Farvid et al. 2017; Hsing et al. 1990; Huang et al. 2014; Koh et al. 2006; Kojima et al. 2004; Matsumoto et al. 2007; Mazidi et al. 2019; Pala et al. 2019; Park et al. 2007; Praagman, Dalmeijer, et al. 2015; Rodriguez et al. 2002; Sharma et al. 2013; Snowdon, Phillips, and Choi 1984; Song et al. 2013; Um et al. 2017; Um et al. 2019) with a total of 1,690,746 participants and 35,118 mortality cases. The summary effect size for cancer mortality, comparing the highest and lowest total dairy intakes, was 1.03 (95% CI: 0.98-1.07, $p = 0.23$) (Table 1). However, significant heterogeneity among the studies was observed (I^2 = 37.8%; $p = 0.03$).

Total milk consumption and risk of cancer mortality which was examined in thirteen publications, (Breslow et al. 2000; Ding et al. 2019; Farvid et al. 2017; Matsumoto et al. 2007; Mazidi et al. 2019; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Pala et al. 2019; Park et al. 2007; Snowdon, Phillips, and Choi 1984; Um et al. 2017; Um et al. 2019; Wang et al. 2015) included a total of 1,310,551 participants with 47,342 deaths. No significant association was seen (Pooled ES: 1.01; 95% CI: 0.97-1.05, $p = 0.69$), with significant heterogeneity among the studies (I^2 =65%; $p < 0.001$) (Table 2). However, high-fat milk consumption was significantly associated with increased risk of cancer mortality; such that based on seven cohort studies (Breslow et al. 2000; Ding et al. 2019; Pala et al. 2019; Park et al. 2007; Song et al. 2013; Um et al. 2017; Um et al. 2019) on 655,155 participants, with 22,744 mortality cases, the pooled ES was 1.17 (95% CI: 1.08-1.28, $p < 0.001$), with no significant between-studies heterogeneity (I^2 = 30.1%; $p = 0.19$) (Table 2). Low-fat milk intake was not associated with risk of cancer mortality (Pooled ES: 1.00; 95% CI: 0.96-1.05, $p = 0.86$) (Table 2). No significant heterogeneity among the studies was observed (I^2 = 0%; $p = 0.55$).

Linear and non-linear dose-response analysis

Based on sixteen, (Bonthuis et al. 2010; Breslow et al. 2000; Dehghan et al. 2018; Ding et al. 2019; Farvid et al. 2017; Goldbohm et al. 2011; Koh et al. 2006; Kondo et al. 2013; Louie et al. 2013; Mazidi et al. 2019; Praagman, Dalmeijer, et al. 2015; Praagman, Franco, et al. 2015; Song et al. 2013; Talaei et al. 2017; Um et al. 2017; Um et al. 2019) out of thirty-three, studies on the association between total dairy consumption and all-cause mortality in the dose-response analysis, we found a significant association (P-nonlinearity = 0.002) (Figure 2). No significant association between total dairy consumption and all-cause mortality was found in the linear dose-response analysis (Pooled ES for an additional one serving per day: 0.99; 95% CI: 0.97-1.01, $p = 0.28$) (Table 1). Furthermore, non-linear dose-response analysis showed no significant association between high-fat (P-nonlinearity =0.39) and low-fat dairy consumption and risk of all-cause mortality based on seven (Bonthuis et al. 2010; Dehghan et al. 2018; Farvid et al. 2017; Louie et al. 2013; Praagman, Franco, et al. 2015; Soedamah-Muthu et al. 2013; Um et al. 2019) and eight (Bonthuis et al. 2010; Dehghan et al. 2018; Farvid et al. 2017; Goldbohm et al. 2011; Louie et al. 2013; Praagman, Franco, et al. 2015; Soedamah-Muthu et al. 2013; Um et al. 2019) studies respectively (P-nonlinearity = 0.51) (Figure 2). This was also the case for linear dose-response analysis for high-fat (Pooled ES: 0.98; 95% CI: 0.92-1.03, $p = 0.39$) and low-fat dairy consumption and all-cause mortality (Pooled ES: 0.99; 95% CI: 0.97-1.02, $p = 0.62$) (Table 1).

Combining data from twelve papers (Bonthuis et al. 2010; Dehghan et al. 2018; Ding et al. 2019; Farvid et al. 2017; Kondo et al. 2013; Louie et al. 2013; Mazidi et al. 2019; Praagman, Dalmeijer, et al. 2015; Praagman, Franco, et al. 2015; Talaei et al. 2017; Um et al. 2017; Um et al. 2019) in the dose-response association of total dairy consumption and CVD mortality, a significant non-linear association was reached (P-nonlinearity < 0.001) (Figure 2). Moreover, each additional serving of dairy intake per day was marginally associated with a lower CVD mortality (Pooled ES:0.98; 95% CI: 0.96-1.00, $p = 0.10$) (Table 1). No significant non-linear association was found between high-fat (P-nonlinearity = 0.30) and low-fat (P-nonlinearity =0.23) dairy consumption and risk of CVD mortality based on five (Bonthuis et al. 2010; Farvid et al. 2017; Louie et al. 2013; Praagman, Franco, et al. 2015; Um et al. 2019) and six (Bonthuis et al. 2010; Farvid et al. 2017; Louie et al. 2013; Praagman, Franco, et al. 2015; Um et al. 2019; van den Brandt 2019) studies, respectively (Figure 2). Such a non-significant association was also observed in the linear dose-response analysis of high-fat (Pooled ES: 0.96; 95% CI: 0.85-

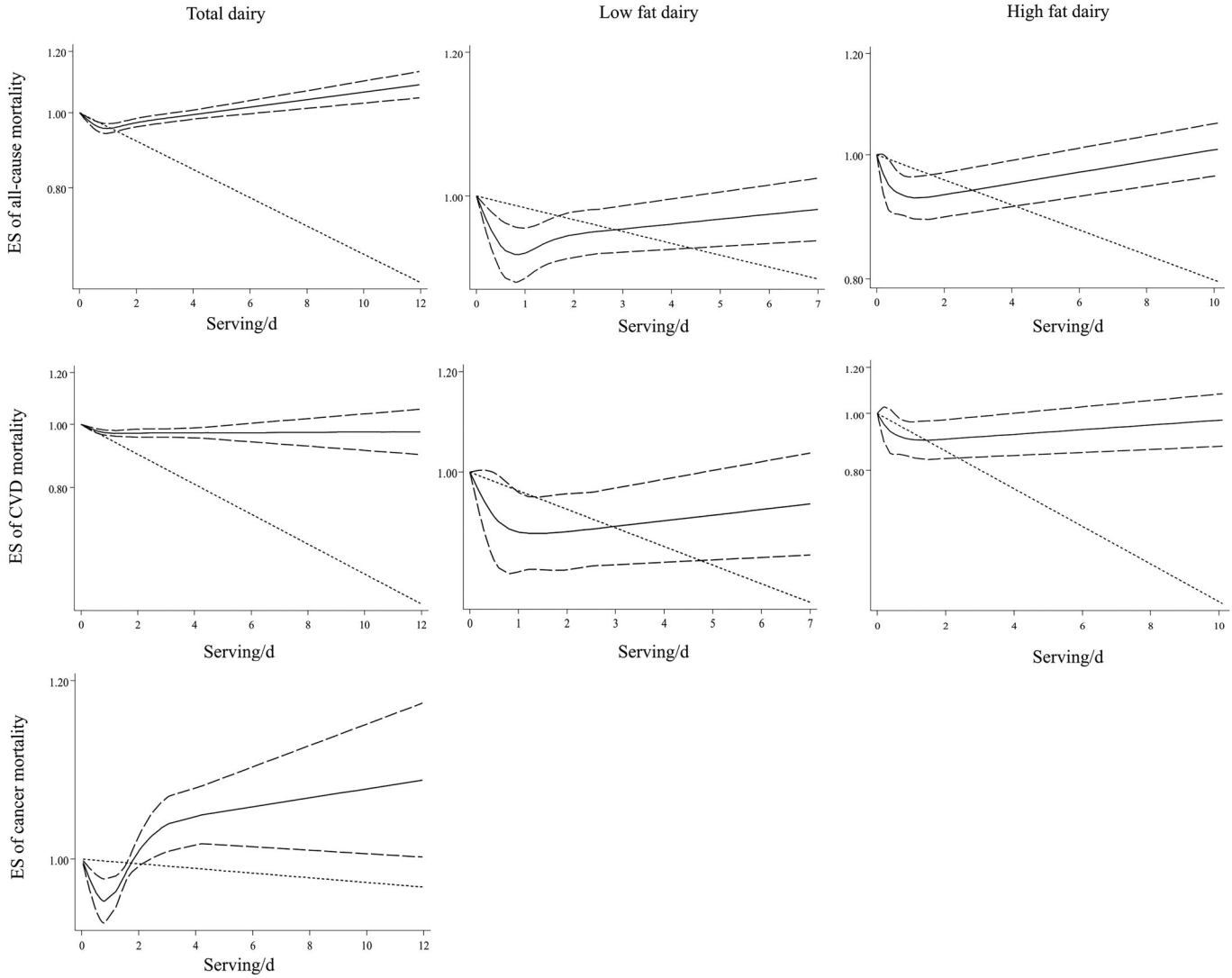

Figure 2. Non-linear dose-response association of total, high-fat, and low-fat dairy consumption (based on serving/day) with risk of mortality from all-cause, CVD, and cancer in adults aged ≥18 years. Dietary intake of dairy was modeled with restricted cubic splines in a multivariate random-effects dose-response model. Dotted line indicates the linear model. Solid line indicates the spline model. Dashed line presents the 95% CI. CVD: cardiovascular disease, ES: effect size, CI: confidence interval.

1.09, $p = 0.53$) and low-fat dairy and CVD mortality (Pooled ES: 0.97; 95% CI:0.91-1.03, $p = 0.25$) (Table 1).

In terms of cancer mortality, total dairy consumption was not associated with risk of cancer mortality in the non-linear (P-nonlinearity =0.89) (Figure 2) and linear dose-response analysis (Pooled ES:1.00; 95% CI:0.98-1.02, $p = 0.90$) (Table 1).

Out of twenty-seven articles on the association between milk intake and risk of all-cause mortality, twelve studies (Bonthuis et al. 2010; Dehghan et al. 2018; Elwood et al. 2004; Farvid et al. 2017; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Paganini-Hill, Kawas, and Corrada 2007; Pala et al. 2019; Praagman, Franco, et al. 2015; Snowdon, Phillips, and Choi 1984; Soedamah-Muthu et al. 2013; Um et al. 2019) were included in the non-linear dose-response analysis, in which we found no significant association ($p = 0.34$) (Figure 3). This was also the case for low-fat ($p = 0.88$) and high-fat milk ($p = 0.18$) based on five studies (Breslow et al. 2000; Pala et al. 2019; Song et al. 2013; Um et al. 2017; Um et al. 2019) (Figure 3). The linear dose-response analysis revealed that an additional one serving per day milk intake (Pooled ES: 1.03; 95% CI: 0.99-1.06, $p = 0.14$) and low-fat consumption (Pooled ES: 0.99; 95% CI: 0.97-1.02, $p = 0.69$) was not associated with all-cause mortality (Table 2). However, an additional one serving per day high-fat milk intake was marginally associated with a 10% higher risk of death from all causes (Pooled ES: 1.10; 95% CI: 1.00-1.21, $p = 0.05$) (Table 2).

Seven (Bonthuis et al. 2010; Farvid et al. 2017; Michaëlsson et al. 2014; Ness, Smith, and Hart 2001; Pala et al. 2019; Praagman, Franco, et al. 2015; Um et al. 2019), out of fifteen, articles on the association between milk intake and CVD mortality were included in the dose-response analysis. We found no significant non-linear association (P-nonlinearity = 0.69) (Figure 3). The same findings were also observed between consumption of low-fat (P-nonlinearity = 0.90) and high-fat milk (P-nonlinearity = 0.46) and CVD mortality based on three studies (Pala et al. 2019; Um et al. 2017; Um et al. 2019) (Figure 3). Linear dose-response analysis revealed that an increased consumption of one serving per day milk (Pooled ES: 1.02; 95% CI: 0.98-1.06, $p = 0.40$),

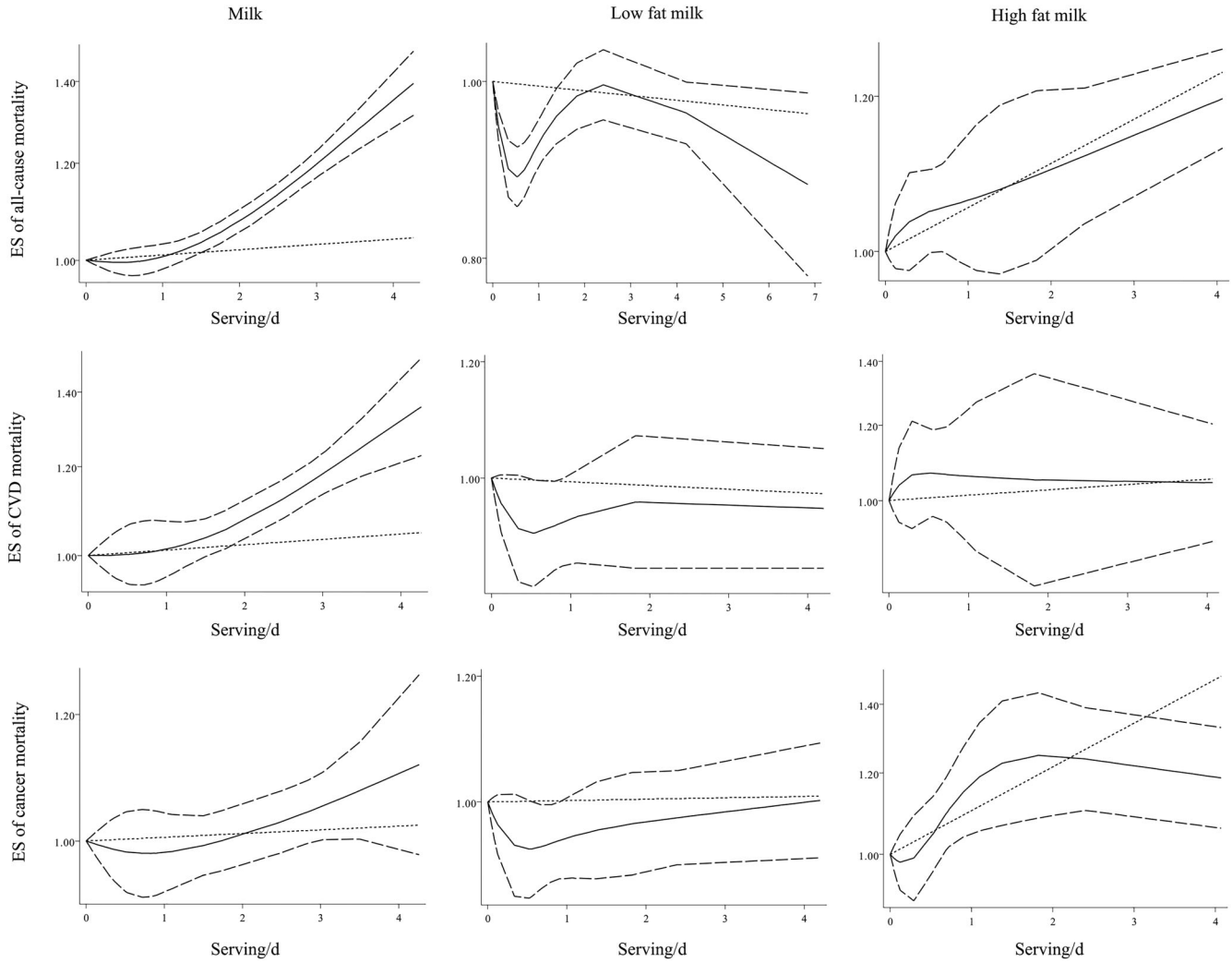

Figure 3. Non-linear dose-response association of total, high-fat, and low-fat milk consumption (based on serving/day) with risk of mortality from all-cause, CVD, and cancer in adults aged ≥18 years. Dietary intake of milk was modeled with restricted cubic splines in a multivariate random-effects dose-response model. Dotted line indicates the linear model. Solid line indicates the spline model. Dashed line presents the 95% CI. CVD: cardiovascular disease, ES: effect size, CI: confidence interval.

high fat-milk (Pooled ES: 1.06; 95% CI: 0.95-1.18, $p = 0.29$) and, low-fat milk (Pooled ES: 1.01; 95% CI: 0.97-1.04, $p = 0.70$) was not associated with CVD mortality (Table 2).

Non-linear dose-response analysis of total milk ($p = 0.47$) and low-fat milk consumption with cancer mortality revealed no significant association ($p = 0.91$) (Figure 3). The same finding was also obtained in the linear dose-response analysis for an additional one serving of milk (Pooled ES: 1.03; 95% CI: 0.99-1.06, $p = 0.24$) and low-fat milk consumption (Pooled ES: 1.00; 95% CI: 0.98-1.02 $p = 0.99$) (Table 2). However, non-linear dose-response analysis of high-fat milk intake and cancer mortality indicated a significant association ($p = 0.03$) (Figure 3). Moreover, a significant linear dose-response association of high-fat milk consumption with cancer mortality was also significant (Pooled ES: 1.13; 95% CI: 1.01-1.28 $p = 0.04$) (Table 2).

Subgroup, sensitivity analyses, and publication bias

To test the robustness of the results and investigate the between-study heterogeneity, we conducted subgroup analyses. Supplemental Table 6 presents findings for the different subgroups. Total dairy consumption was significantly associated with a greater risk of mortality in females, in studies that used FFQ for assessment of total dairy intake, those with a follow-up duration of >15 years and, those that not controlled for total energy intake. In terms of CVD mortality and total dairy consumption, we found a significant inverse association in studies done on both genders, those that were performed in US and non-US countries, those with a follow-up duration of <15, in studies that applied FFQ, food recall and food record for dietary assessment, those that controlled for BMI and total energy intake, as well as studies that did not control for total energy intake. In terms of low-fat dairy and all-cause mortality an inverse association was obtained in both genders and females, in studies that used FFQ for dietary assessment, those with a follow-up duration of >15, as well as among studies that considered BMI and total energy intake as covariates. In addition, low-fat dairy intake was associated with a lower risk of CVD mortality in studies conducted on both genders. In terms of milk intake, a higher risk was obtained in both genders, in studies that applied FFQ for high-fat milk

assessment, those with a follow-up duration of >15 years, as well as in studies that controlled the analyses for BMI and total energy intake in their analysis. Milk intake was associated with a lower risk of CVD mortality in studies that were conducted in non-US countries and those did not control for energy and BMI, but a greater risk was seen in females. In terms of milk intake and cancer mortality, a higher risk was obtained in females, in studies that applied FFQ, those that controlled the analyses for energy intake and, those with a follow-up duration of >15 years. However, an inverse association was seen in studies that not considered total energy intake as a covariate. In terms of high-fat milk intake and all-cause mortality, a higher risk was obtained in studies that performed on both genders, among studies that were conducted in US countries, in studies that considered BMI and total energy intake as covariates, those with a duration follow-up of >15, as well as studies that used FFQ for dietary assessment. This was also the case between high-fat milk intake with CVD and cancer mortality. However, this association was significant for cancer mortality in studies with a follow-up duration of <15 years. Low-fat milk was associated with increased risk of all-cause mortality in both genders, in studies with a follow-up duration of <15 years and, those that were conducted in non-US countries.

With regard to the significant positive association between high-fat milk consumption and mortality from CVD, findings from the sensitivity analyses indicated that the whole findings were dependent on some studies; such that excluding some studies, for instance, the ones by Ding et al, Um et al, Pala et al resulted in a non-significant association between high-fat milk consumption and risk of CVD mortality.

There were no missing studies imputed in regions of the contour enhanced funnel plots. No publication bias was found based on Begg's rank correlation test and Egger's linear regression test. The application of the trim and fill method did not change the average effect size, further suggesting that results were not affected by publication.

Discussion

In this systematic review and meta-analysis, high-fat milk consumption was significantly associated with a higher risk of all-cause, CVD, and cancer mortality. However, total dairy consumption was associated with a lower risk of CVD mortality. Although dairy products contain potentially beneficial compounds, the health benefits of high dairy consumption have not been established yet. In addition, some concerns exist about the risks of possible adverse health outcomes that might arise from high dairy and in particular high milk consumption. Despite this, the current dietary guidelines recommended consumption of two to three servings of dairy products in a day. Our updated literature search identified several systematic reviews and meta-analyses on this topic, but none synthesized low- and high-fat milk intake on all-cause and CVD mortality. To the best of our knowledge, this is the most comprehensive and up-to-date study that systematically and quantitatively summarized earlier investigations on the association of milk and dairy consumption with mortality.

In the current study, no associations were found between total dairy consumption and risk of all-cause and cancer mortality. However, an inverse association was seen with CVD mortality. In line with ours, dairy consumption was not associated with risk of all-cause mortality in an Overview of Systematic Reviews and Meta-Analyses (Cavero-Redondo et al. 2019). In addition, based on a meta-analysis on 11 cohort studies, total dairy intake was not associated with risk of cancer mortality (Lu et al. 2016). In contrast to our findings, no significant association was observed between fermented milk consumption and CVD mortality in a meta-analysis (Larsson et al. 2015). Another meta-analysis in 2019, reported no significant association between total dairy intake and risk of mortality from CHD and cancer. However, higher fermented dairy consumption has been associated with a reduced risk of mortality from all causes (Mazidi et al. 2019). In further meta-analysis fermented dairy consumption was also associated with a lower risk of cardiovascular disease (Guo et al. 2017). These inconsistent associations between total dairy consumption and risk of mortality from all-cause and CVD in some meta-analyses might be attributed to missing some published papers in those analyses. Moreover, some meta-analyses had focused on fermented dairy products, rather than total dairy.

We found high-and low-fat dairy consumption was not significantly associated with risk of all-cause and CVD mortality. In a previous meta-analysis, consumption of low- and high-fat dairy was not associated with CHD mortality (Mazidi et al. 2019). Another meta-analysis revealed a neutral dose-response association between low- and high-fat dairy consumption and risk all-cause mortality (Guo et al. 2017). The non-significant association between low- and high-fat dairy consumption and risk of all-cause mortality in the current analysis might be explained by the small number of included studies.

In our study, no associations were seen between milk consumption and mortality from all causes, CVD, and cancer. Such a non-significant association has also been reported in other meta-analyses (Larsson et al. 2015). In contrast, milk consumption was associated with a higher risk of CHD mortality in another meta-analysis (Mazidi et al. 2019). It should be noted that only three studies were included in that meta-analysis. We found that low-fat milk consumption was not associated with all-cause, CVD, and cancer mortality, while high-fat milk consumption was associated with a greater risk of all-cause, CVD, and cancer mortality. Our results were in agreement with another meta-analysis in which whole milk intake was associated with a higher risk of mortality from prostate cancer (Lu et al. 2016). This might be attributed to its content of calcium(Michaëlsson et al. 2013), hormones(Ganmaa et al. 2012), lactose and galactose(Reuter et al. 2010) and, saturated fat (Hegsted 1998), which are associated with a greater risk of certain cancers and cardiovascular diseases.

Overall, our findings highlight the beneficial effects of low-fat dairy consumption and possible adverse effects of

high-fat milk on human health. It must be kept in the mind the dairy is a diverse food group that includes fermented and non-fermented products with many different nutrients, and their effects on health outcomes cannot be fully attributed to one nutrient or a single biomarker. Exact mechanisms by which milk and dairy consumption might alter risk of mortality among generally healthy adults are unknown. Saturated fatty acids in high-fat dairy products might increase low-density lipoprotein concentration in the blood, which is an established risk factor for promoting atherosclerosis. Consumption of milk is also associated with high plasma levels of insulin-like growth factor1,(Harrison et al. 2017; Qin, He, and Xu 2009) which is a predictor for elevated risk of some cancers and mortality (Genkinger et al. 2006; Shi et al. 2004). The intake of D-galactose from non-fermented milk is substantially higher than that from other food sources, such as cheese and fermented dairy products (Gross and Acosta 1991). D-galactose given to laboratory animals (mice, rats, and drosophila flies) is an established experimental model for premature aging, including shortened life span produced by oxidative stress and chronic inflammation, but whether this mechanism can be generalized to humans needs further scientific support (Cui et al. 2004; Cui et al. 2006; Song et al. 1999). On the other hand, the relatively high potassium and calcium content of dairy products has led to the suggestion that greater dairy intake may reduce blood pressure (Willett and Ludwig 2020). Also, regular fat dairy has favorable effects on satiety and glucose metabolism and therefore might help to improve cardiovascular and diabetes outcomes (Astrup et al. 2016; Ley et al. 2006). The fermentation of milk products can generate bioactive peptides with different health effects. These peptides are absorbed directly and can inhibit angiotensin-converting enzyme and reduce blood pressure (Jäkälä and Vapaatalo 2010). Casein and whey are two predominant proteins in milk, which possess anti-mutagenic and antioxidative properties (Parodi 2007). The bioactive peptides in dairy products might also have lipid-lowering properties (Marcone, Belton, and Fitzgerald 2017).

Our study has several strengths. First, the large number of participants and deaths included, allowed us to quantitatively assess the association of dairy intake and risk of mortality, thus provides high statistical power, which contributes to stable risk estimates. Second, the dose-response analysis was performed to evaluate the linear and non-linear relations, which can provide the most compelling evidence for quantitative evaluation of associations that tests the shape of these possible associations. Third, because all included studies were prospective in nature, which can minimize the recall and selection bias. In addition, no evidence of publication bias was found. Finally, we evaluated the associations separately for high- and low-fat products as well as for cause-specific mortality. Our findings also need to be interpreted in the context of several limitations. Due to the observational nature of included studies, causality cannot be inferred. Unmeasured and insufficiently measured variables would result in inevitable residual confounding in the included studies. Small number of included studies that considered high- or low-fat milk or dairy, as the exposure, is another limitation. Most included studies had estimated dairy intake based on a single measurement at study baseline, and changes in diet throughout the follow-up were not considered. There was an overlap in the categories of dairy and milk consumption across studies, however, we handled this problem by performing dose-response analysis. In addition, different methods of dietary assessment including FFQ, dietary recall, and record were used in the included cohorts. Moreover, some studies in this review did not report sufficient information to be included in the dose-response meta-analysis. As we considered studies on apparently healthy adult individuals, our findings cannot be generalized to those with specific diseases such as cancer patients. Human populations consume a food or food group in the form of a dietary pattern. Therefore, finding relationship between intake of a food and health outcomes is difficult. For instance, the association between dairy consumption and mortality may be affected by other dietary and lifestyle factors including physical activity, smoking, dietary intakes of fruits, vegetables, and fiber. The confounding effect of some of these factors, not all, were controlled in some studies included in the current meta-analysis. Therefore, our findings on the association between dairy consumption and mortality should be considered with caution. Further studies are needed to assess the association with considering all confounding variables.

Conclusions

We found a significant inverse association between total dairy consumption and risk of CVD mortality. However, high-fat milk consumption was associated with a greater risk of all-cause, CVD, and cancer mortality. These findings might provide complementary data for policymakers in the field of nutrition. Based on these findings, replacement of high-fat dairy products by low-fat choices might have a large effect on longevity. Moreover, dairy product consumption should not be discouraged and perhaps even be encouraged as a rich source of nutrients and bioactive components in low- and middle-income countries, where dairy consumption is low.

Authors' contribution

OS and SN contributed to literature search, data extraction, and, data analysis. AE contributed to study conception, manuscript drafting, and data analysis. BL contributed to study conception, manuscript drafting, data analysis and approving the final manuscript. All authors acknowledge the full responsibility for the analyses and interpretation of the report. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Disclosure statement

Authors declared no personal or financial conflicts of interest.

Funding

The meta-analysis was funded by the Research Council of School of Nutritional Sciences and Dietetics of Tehran University of Medical Sciences, Tehran, Iran.

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