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Dairy foods and health: an umbrella review of observational studies

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Abstract

Evidence on consumption of dairy foods and human health is mixed. This study aimed to summarize the level of evidence of dairy consumption on various health outcomes. A systematic search for meta-analyses was performed: study design, dose-response relationship, heterogeneity and agreement of results over time, and identification of potential confounding factors were considered to assess the level of evidence. Convincing and probable evidence of decreased risk of colorectal cancer, hypertension, and cardiovascular disease, elevated blood pressure and fatal stroke, respectively, was found for total dairy consumption; possible decreased risk of breast cancer, metabolic syndrome, stroke, and type-2 diabetes, and increased risk of prostate cancer and Parkinson's disease was also found. Similar, yet not entirely consistent evidence for individual dairy products was reported. Among potential confounding factors, geographical localization and fat content of dairy have been detected. In conclusions, dairy may be part of a healthy diet; however, additional studies exploring confounding factors are needed to ascertain the potential detrimental effects suspected.

Introduction

Over the last decades, the role of dairy foods in relation to chronic-degenerative non-communicable diseases, including cardiovascular disease (CVD) (Huth and Park 2012), metabolic disorders (Abedini et al. 2015, Rice Bradley 2018), bone health (Giganti et al. 2014), and various types of cancer (Abid et al. 2014), has been investigated in several epidemiological studies and led to the hypothesis that they might have a positive impact on health (Pereira 2014). However, concerns regarding their potential harms have been often raised, especially in relation to their content in saturated fats, which has been the focus of major attentions because of the detrimental effect on serum lipids, a well-known major cardiovascular risk factor, and hormone dysregulation (i.e., effects on growth factors that may increase the risk of certain cancers) (Lin et al. 2018, Siri-Tarino et al. 2010, Touvier et al. 2015, YuPeng et al. 2015). Despite plenty of studies have been conducted on this matter, a comprehensive systematic evaluation of the evidence on the association between dairy products and human health might be useful to provide an overview with consistent and univocal methodology. Thus, in this study we aimed to investigate the level of evidence for the association between consumption of total dairy products, as well as individual selected dairy food groups, on various health outcomes.

Methods

Study selection

In order to evaluate the level of evidence on consumption of major food sources of vitamin D, an umbrella review of existing prospective cohort studies was performed. A systematic search for research syntheses of different outcomes investigating the association with exposure of fish, dairy products, and egg intake was conducted in Medline and Embase electronic databases up to January 2017. The search was independently performed by two authors (GG and JG) and any discrepancies were solved with discussion. Inclusion criterion was meta-analyses of prospective cohort studies or randomized controlled trials (RCTs) considering dairy product consumption as variable of exposure and any disease condition as outcome. Exclusion criteria were the following: RCTs exploring the relation between the aforementioned exposures and intermediary biomarkers of disease (i.e., blood lipids, blood pressure, etc.) or intermediary clinical conditions (i.e., variation in body weight/BMI, etc.); and systematic review without quantitative evaluation of the association between exposure and outcome.

Data extraction

From each meta-analysis included, the following information was abstracted: name of the first author and year of publication, outcome, number of studies included in the meta-analysis, study design of included studies (i.e., case-control/cross-sectional and prospective), total number of population exposed, number of cases, type of exposure, measure of exposure [including highest versus lowest (reference) category of exposure or dose-response incremental servings per day (linear)], effect sizes [risk ratio (RR), odds ratio (OR), or hazard ratio (HR)].

Data evaluation and evidence synthesis

Whenever more than one meta-analysis was conducted on the same outcome, included the same study design, and the same type of population, concordance for the main outcome of interest, including direction and magnitude (overlapping confidence interval) of the association was evaluated. For further analyses, the most recent/exhaustive study was considered. The pooled analyses of the highest vs. the lowest (reference) category of exposure and dose-response analyses were evaluated. Direction, magnitude, heterogeneity (I^2), and subgroup/stratified analyses for potential confounding factors were considered to have indication of level of evidence. Criteria used for evidence categorization were modified from the Joint WHO/FAO Expert Consultation (Paganoni and Schwarzschild 2017) as shown in Table 1. Briefly, the relation between exposure and outcomes was categorized as following: suggestive/limited/contrasting evidence, when there was availability of solely meta-analysis of case-control studies, limited prospective cohort studies included in meta-analyses (n <3), or evident contrasting results from meta-analyses with the same level of evidence; possible evidence, when there was availability of meta-analyses with lack of information on/significant heterogeneity (I^2 >50%) or identification of potential confounding factors (i.e., different findings in subgroups); probable association, when there was availability of meta-analyses of prospective cohort studies with no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained (and evidence of dose-response relation further investigated); convincing association, when there was concordance between meta-analyses of RCTs and observational studies.

Results

Study selection

Out of 894 articles identified through the search strategy and a first selection based on title and abstract, 101 articles were investigated for further consideration: the exclusion list included 28 articles because including meta-analyses of RCTs (n = 8), had different design (n = 15), different exposure (n = 2), or different outcomes (n = 3). The final selection of articles included 53 studies (Alexander et al. 2016, Aune et al. 2012, Aune et al. 2015, Aune et al. 2013, Bandera et al. 2007, Bischoff-Ferrari et al. 2011, Boyd et al. 1993, Boyd et al. 2003, Caini et al. 2016, Chen et al. 2015, Chen et al. 2017, Chen et al. 2007, Chen et al. 2014, de Goede et al. 2015, de Goede et al. 2016, Dong et al. 2011, Elwood et al. 2004, Gao et al. 2013, Gao et al. 2005, Gijsbers et al. 2016, Guo et al. 2015, Hu et al. 2014, Huncharek et al. 2008, Huncharek et al. 2009, Jiang et al. 2014, Kim and Je 2016, Larsson et al. 2006, Li et al. 2016, Li et al. 2011, Liu et al. 2015, Lu et al. 2016, Mao et al. 2011, Mullie et al. 2016, O'Sullivan et al. 2013, Pimpin et al. 2016, Qin et al. 2015, Qin et al. 2005, Qin et al. 2004, Qin et al. 2007, Ralston et al. 2012, Ralston et al. 2014, Soedamah-Muthu et al. 2011, Soedamah-Muthu et al. 2012, Sun et al. 2014, Tian et al. 2014, Tong et al. 2011, Wang et al. 2016, Wu et al. 2016, Wu and Sun 2016, Xu, Zhang, et al. 2015, Yang et al. 2016, Yu et al. 2016, Zang et al. 2015) on dairy product.

Meta-analyses on dairy product consumption and health outcomes

The characteristics and summary risk estimates for the highest versus the lowest category of total dairy, milk, cheese, butter, and yogurt on unique outcomes of non-overlapping meta-analyses including ≥3 prospective cohort studies are presented in Figure 2, Figure 3, Figure 4, Figure 5, and Figure 6, respectively. The characteristics and summary risk estimates by dose of dairy product consumption evaluated in non-overlapping meta-analyses on total dairy (n = 7) (Alexander et al. 2016, Aune et al. 2012, Aune et al. 2015, de Goede et al. 2016, Gijsbers et al. 2016, Soedamah-Muthu et al. 2012, Zang et al. 2015), milk (n = 9) (Aune et al. 2012, Aune et al. 2015, Bischoff-Ferrari et al. 2011, de Goede et al. 2016, Gijsbers et al. 2016, Jiang et al. 2014, Mullie et al. 2016, O'Sullivan et al. 2013, Xu, Zhang, et al. 2015), cheese (n = 6) (Aune et al. 2012, Aune et al. 2015, Chen et al. 2014, Gijsbers et al. 2016, Jiang et al. 2014, O'Sullivan et al. 2013), butter (n = 1) (Pimpin et al. 2016), and yogurt (n = 2) (Aune et al. 2015, Gijsbers et al. 2016) testing for linear association with unique outcomes are reported in Supplementary Table 1. Meta-analyses on total dairy consumption and stroke mortality, colorectal cancer, metabolic syndrome, elevated blood pressure, stroke, CVD, T2DM, and breast cancer reported a statistically significant association with reduced risk for the highest versus the lowest category of consumption, while those on prostate cancer and Parkinson's disease reported a significant increased risk (Figure 2); meta-analyses on milk consumption showed significant decreased risk of cognitive disorders, metabolic syndrome, colon and colorectal cancer, and elevated blood pressure, while increased risk of prostate and Parkinson's disease (Figure 3); meta-analyses on cheese consumption showed significant decreased risk of T2DM, CHD, CVD, and stroke, while increased risk of prostate cancer (Figure 4); meta-analyses on butter showed no significant results (Figure 5); meta-analyses on yoghurt showed significant decreased risk of T2DM (Figure 6). Among studies reporting a dose-response analysis, increasing consumption of total dairy was linearly associated with significant decreased risk of metabolic syndrome, hypertension, breast and colorectal cancers; milk with decreased risk of colorectal cancer and stroke; cheese with decreased risk of CHD; butter and yoghurt with decreased risk of T2DM (Supplementary Table 1). However, meta-analyses on stroke risk reported evidence of significant heterogeneity of results between studies. Furthermore, some studies showed potential confounding factors that may affect the level of evidence (Supplementary Table 2): total dairy consumption was associated with decreased risk of stroke (Hu et al. 2014), T2DM (Aune et al. 2013), and breast cancer (Zang et al. 2015) only in women and studies conducted in the US, while increased risk of Parkinson's disease was reported only in men (Jiang et al. 2014); total dairy and milk consumption were associated with increased risk of prostate cancer only in studies conducted in the US (Aune et al. 2015); milk was associated with decreased risk of colorectal cancer only in men and studies conducted in Europe and US (Aune et al. 2012); cheese was associated with decreased risk of CVD, CHD and stroke only in women and studies conducted in the US (Chen et al. 2017); cheese was associated with decreased risk of T2DM only in studies conducted in the US (Aune et al. 2013). Moreover, meta-analyses on total dairy consumption and T2DM risk, and milk and colorectal cancer risk showed non-significant associations when the analyses were restricted to studies adjusting for smoking status. Similarly, meta-analyses on total dairy consumption and prostate cancer showed non-significant associations when the analyses were restricted to studies adjusting for alcohol consumption. Among other potential confounding, fat content of dairy foods has been taken into account in several studies: only the analyses restricted to low-fat dairy showed significant decreased risk of breast cancer (RR = 0.85, 95% CI: 0.75, 0.96; I2 = 43%) (Zang et al. 2015), CHD (RR = 0.90, 95% CI: 0.82, 0.98; I2 = 0%) (Alexander et al. 2016), elevated blood pressure (RR = 0.84, 95% CI: 0.74, 0.95; I2 = 38%) (Ralston et al. 2012) and hypertension (RR = 0.96, 95% CI: 0.93, 0.99; I2 = 25%) (Soedamah-Muthu et al. 2012), stroke (RR = 0.90, 95% CI: 0.83, 0.96; I2 = 0%) (Alexander et al. 2016), T2DM (RR = 0.83, 95% CI: 0.76, 0.90; I2 = 0%) (Aune et al. 2013), while no significant associations were reported for whole/full-fat dairy products. In contrast, the association between milk consumption and prostate cancer risk showed increased risk for consumption of low-fat milk (RR = 1.14, 95% CI: 1.05, 1.25; I2 = 51%) and decreased risk for consumption of whole milk (RR = 0.92, 95% CI: 0.85, 0.99; I2 = 0%) (Aune et al. 2015); similarly, an increased risk of ovarian cancer has been also detected for consumption of low-fat milk (RR = 1.35, 95% CI: 1.09, 1.68; I2 = 0%) (Larsson et al. 2006).

The list and main findings of meta-analyses for outcomes with more than one meta-analysis showed substantial consistency between results for most of the outcomes. In contrast, a meta-analysis on yoghurt reported decreased risk of breast cancer; two meta-analyses showed decreased risk and null association of CVD for total dairy and milk consumption (Alexander et al. 2016, Elwood et al. 2004); also a previous study on prostate cancer risk showed null results for total dairy, milk, and cheese consumption (Huncharek et al. 2008); in contrast, a previous study on stroke (ischaemic) showed decreased risk for milk consumption (Elwood et al. 2004). We did not detect any particular flaws or mistakes among meta-analyses and differences are ascribable to updated results.

Summary of evidence

A summary of variables investigated to assess the strength of the evidence relating dairy products consumption with various health outcomes is presented in Supplementary Table 4: the summary evidence is showed in Table 1. There is convincing evidence of association between total dairy consumption and decreased risk of colorectal cancer and hypertension, probable association with decreased risk of CVD, elevated blood pressure, and fatal stroke, and possible association with decreased risk of breast cancer, metabolic syndrome, stroke, and T2DM, while increased risk of prostate cancer and Parkinson's disease. Among specific types of dairy foods, the strongest evidence (probable) for decreased risk of elevated blood pressure and metabolic syndrome and increased risk of Parkinson's disease was associated with milk consumption, while cheese and butter consumption were associated with possible decreased risk of T2DM; other possible associations were found for milk and decreased risk of colorectal cancer and cognitive disorders/increased risk of prostate cancer, yoghurt and decreased risk of T2DM, cheese and decreased risk of CVD, CHD, and stroke.

Discussion

In this umbrella review, the existing evidence on dairy foods consumption and various health outcomes was investigated. Overall, the strongest evidence interested an association with decreased risk of cardiovascular-related diseases for higher consumption of total dairy foods compared to low; moreover, a decreased risk of colorectal cancer was also observed. Among the outcomes that showed potential confounding factors, type of dairy (low-fat vs. whole) may affect T2DM, elevated blood pressure/hypertension, breast, ovarian, and prostate cancer risk. Some concerns aroused concerning specific dairy foods, such as milk and cheese, and increased risk of prostate cancer and Parkinson's disease, respectively.

There is evidence that consumption of dairy foods may affect long-term cardio-metabolic health: results from pooled analyses of cohort studies are in line with those reported in this umbrella review

(Sluijs et al. 2012). A possible explanation could be the potential effect toward blood pressure, but this association was significant in particular for milk, rather than other dairy foods. Some key components such as fats [including mono-unsaturated fatty acids (MUFA)] and proteins (including casein and whey protein) may play a role in cardiovascular prevention. Among proteins, whey protein has been associated with several metabolic benefits, including improved blood pressure control, serum lipid profile, body composition, insulin sensitivity and glucose regulation (Bjornshave and Hermansen 2014). Dairy products are also a rich source of calcium: there is evidence associating dietary calcium intake with several metabolic benefits, including regulation of serum lipids, weight maintenance and body composition, blood pressure regulation, and insulin sensitivity and glucose metabolism (Muldowney and Kiely 2011). Together with calcium, also vitamin D (and its active form 1,25-dihydroxycholecalciferol) has been shown to play a role in shaping body composition through regulation of energy metabolism by controlling the expression of uncoupling proteins, down-regulating leptin, the appetite regulating hormone, and through inhibition of adipogenic transcription factors and lipid accumulation during adipocyte differentiation (Abbas 2016). Furthermore, there is mechanistic evidence that vitamin D might affect blood pressure through regulation of the rennin-angiotensin-aldosterone system and suppression of parathyroid hormone, which are known mechanisms regulating blood pressure (Min 2013). Finally, its effect in regulating parathyroid hormone and intracellular calcium has been also associated with modulation of insulin production and release through effects in pancreatic beta cells and adipocytes (Palomer et al. 2008). An indirect potential effect of vitamin D that may decrease the metabolic risk is its antioxidant action (Pannu et al. 2016) through inflammatory cytokine gene expression and secretion from adipocytes and macrophages (Sun and Zemel 2008), regulation of nuclear factor kappa-light-chain-enhancer of activated B cells inhibition, and increased production of endothelial prostacicline, a prostaglandin with anti-inflammatory activities (Okajima and Harada 2006).

The risk of another outcome significantly decreased by consumption of dairy foods was colorectal cancer (especially colon). This finding is in line with previous literature based on a pooled analysis of ten prospective cohorts (Cho et al. 2004). Protection toward cancer may depend on the effect of vitamin D and its influence on calcium metabolism. In fact, 1,25-dihydroxycholecalciferol directly regulates multiple signaling pathways involved in cell proliferation, apoptosis, differentiation, inflammation, invasion, angiogenesis and metastasis (Feldman et al. 2014). Moreover, intracellular calcium has been shown to influence cell growth and apoptosis of cells (Whitfield 2009) and it has been demonstrated to bind bile acids and fatty acids with an overall protective effect toward colon cells (Bernstein et al. 2005). Another proposed mechanism of protection against colorectal cancer associated with dairy consumption is modulation of gut microbiota (Davoodi et al. 2013): in fact, bacterial translocation and consequent increase of inflammation and production of bacterial genotoxins have been hypothesized to be potential risk factors for colorectal cancer initiation and development by inducing DNA damage and producing metabolites that can active carcinogens (Riaz Rajoka et al. 2017). In this context, consumption of dairy foods may have an impact on the balance between microbial production of health-beneficial metabolites, such as butyrate, and potentially tumorigenic metabolites, such as secondary bile acids (Yang and Yu 2018).

Regarding potentially detrimental associations found in this study, there is evidence of increased risk of Parkinson’s disease and prostate cancer related to consumption of milk and cheese, respectively. Regarding Parkinson’s disease, it has been shown that milk proteins (casein and lactalbumin) reduce serum urate levels, which has been hypothesized to be protective against Parkinson’s disease (Crotty et al. 2017, Paganoni and Schwarzschild 2017). Another potential explanation is related to the content in pesticides of dairy foods: specifically, it has been hypothesized that a genetic susceptibility either in metabolism, elimination and transport of pesticides or in the extent of mitochondrial dysfunction, oxidative stress and neuronal loss may play a role in Parkinson’s disease risk (Dardiotis et al. 2013). However, both potential mechanisms are rather weak and merely speculative. Thus, a stronger rationale is needed to explain such association. Regarding prostate cancer risk, earlier hypotheses speculated on the potential role of calcium as risk factor, but such hypothesis is jeopardized by the results of a subgroup analysis provided in one of the meta-analyses reviewed showing that there was no association with intake of non-dairy calcium (Aune et al. 2015). Alternatively, dairy products may play a role toward prostate cancer risk via the insulin-like growth factor (IGF) pathway (including IGF-I, IGF-II, IGFBP-1, IGFBP-2, and IGFBP-3), which has been related to cell proliferation promotion and apoptosis inhibition (Harrison et al. 2017) and, definitely, an increased risk of prostate cancer (Roddam et al. 2008). All hypotheses presented are mere speculation and further research is needed to provide a stronger rationale for the retrieved results.

Results generated from meta-analyses are promising, but some concerns regarding the consistence of such evidence still remains. Specifically, results on total dairy products and metabolic syndrome, stroke, breast cancer and T2DM (all outcomes somehow related to the potential effects of dairy on metabolic pathways) are affected by potential confounding related to sex and geographical location that should be further investigated. The mechanisms contributing to sex-related differences among individuals exposed to dairy consumption have not yet been entirely identified, although it may be hypothesized that sex hormones might be involved. In pre-menopausal women, estrogens levels are generally protecting against cardiovascular and other diseases compared to men of the same age; dairy consumption may somehow interact with hormonal levels and affect the overall risk (Mirmiran et al. 2016).

Regarding geographical location, there is no specific hypothesis previously formulated and any potential reason is merely speculative. European and US milk undergoes different processing methods: despite nearly all commercial milk is pasteurized (meaning it undergoes extreme heat in order to kill illness-causing bacteria), the US and Canada use the high-temperature short-time pasteurization (HTST), which is cheaper and more efficient but milk has a shorter shelf life (around seven to 10 days) and must be refrigerated; while Europe uses ultra-heat-treated pasteurization (UHT), which heats the milk to an even higher temperature than HTST and lead to a longer shelf life of the milk. Some differences have been accounted between the two methods (i.e., total viable counts are lower in UHT compared to HTST milk (Lorenzen et al. 2011); the denatured proteins in UHT processing may be more accessible to the digestive enzymes than after HTST (Tunick et al. 2016)), but, definitely, there is no data supporting any substantial difference in different effects on health of these two pasteurization techniques; however, we cannot exclude that, if any, they might depend on that. Despite it has been reported that dairy products has generally low content of phthalates, some differences between countries might occur (Serrano et al. 2014). Another difference between US and European milk relies on the type of casein (the main milk protein): digestion of bovine A1 beta-casein (particularly present in Europe), but not the alternative A2 beta-casein, releases beta-casomorphin-7, which activates μ-opioid receptors expressed throughout the gastrointestinal tract resulting in increased gastrointestinal transit time, production of dipeptidyl peptidase-4 and the inflammatory marker myeloperoxidase (Pal et al. 2015). Finally, genetic variants (i.e., mutations in the lactase gene resulting in lactase persistence) have shown to potentially play a role between dairy consumption and cardio-metabolic diseases, certain types of cancer and bone health, as well as lipid metabolism, hormone receptor function, and vitamin D receptor function, but current research has produced mixed results and the potential for differential sensitivity between genotypes to the health effects of dairy food intake has to be further investigated (Comerford and Pasin 2017).

Among other potential confounding/modifying/mediating factors, the fat content of dairy has been called out as potential explanation for the association with some health outcomes; in fact, dairy products, especially butter, has been under investigation due to the high content in saturated fats. However, recent meta-analyses of prospective cohort studies showed a relatively small impact of saturated fats on CVD risk and other outcomes (Chowdhury et al. 2014, de Souza et al. 2015). Equally, overall evidence of dietary fat intake and cancer risk is weak (Xu, Han, et al. 2015). Moreover, there is no consistency in the direction of the association stratified by fat content of dairy, as low-fat dairy consumption was associated with both decreased risk of several cardio-metabolic conditions but also increased risk of prostate and ovarian cancers, while high-fat dairy consumption was associated with decreased risk of prostate cancer. Finally, the retrieved association with decreased risk of CVD is inconsistent with the lack of association with risk of CVD mortality (it would be expected that the associations would agree on the same direction of the risk). These contrasting results need to be further addressed with ad hoc investigations aiming to better define the role of total dietary fats in relation to dairy foods.

Regarding other limitations to be taken into account when interpreting the results presented in this umbrella review, it must be noted that grouping individual foods in major food groups is comfortable and perhaps necessary for certain analyses interesting population studies, but there might be considerable differences in nutrients and compounds content among different type of dairy products. Other potential confounding factors, such as physical activity, smoking, alcohol, or more specifically related to the outcomes investigated (i.e., prostate specific antigen testing) may have also been associated to dairy product consumption. Regarding meta-analyses included, publication bias or small study effects may lead to exaggerated summary estimates. Regarding cohort studies included in the meta-analyses, measurement errors in the dietary assessment is another potential limitation to be taken into account.

In conclusions, consumption of dairy products showed a probable association with CVD and xxx, despite consistence of results is partially debatable.

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Declaration of interests

The authors declare no conflicts of interest.

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Table 1. Level of evidence for the association between dairy (total and individual foods) consumption and health outcomes.

Level of evidence*	Criteria§	Total dairy	Milk	Yogurt	Cheese	Butter
Convincing	Meta-analyses of prospective cohort studies with evidence of dose-response relation, no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassed as possible].	Association with decreased risk of cancer (colorectum), hypertension.	None.	None.	Association with increased risk of cancer (prostate).	None.
Probable	Meta-analyses of prospective cohort studies with no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassed as possible].	None.	None.	None.	None.	None.
Possible	Meta-analysis of prospective cohort studies with no heterogeneity and lack of information on potential confounding factors.	Association with decreased risk of CVD (any), elevated blood pressure, stroke (fatal).	• Association with decreased risk of elevated blood pressure, metabolic syndrome • Association with increased risk of Parkinson's disease.	None.	Association with decreased risk of T2DM.	Association with decreased risk of T2DM.
Limited	Meta-analysis of prospective cohort studies with presence of significant heterogeneity (I^2 >50%) or identification of potential confounding factors (i.e., different findings in subgroups).	• Association with decreased risk of cancer (breast)#, metabolic syndrome#, stroke (total), T2DM#.	• Association with decreased risk of cancer (colorectum)#, cognitive disorders. • Association with increased risk of	Association with decreased risk of T2DM#	Association with decreased risk of CHD (any)#, CVD (any)#, stroke (total)#.	None.

		• Association with increased risk of cancer (prostate) #, Parkinson's disease#.	cancer (prostate)#.			
Insufficient	Meta-analysis of case-control studies, limited prospective cohort studies included in meta-analyses (n <3), or evident contrasting results from meta-analyses with the same level of evidence.	• Association with decreased odds of cancer (bladder) • Association with increased odds of cancer (diffuse large B-cell lymphoma, ovarian)	Association with increased odds of cancer (diffuse large B-cell lymphoma).	None.	None.	None.
No evidence	Non-significant results from meta-analyses of either prospective or case-control studies.	No association with risk of cancer (chronic lymphocytic leukaemia/small lymphocytic lymphoma, endometrial, esophagus, lung, NHL, stomach), CHD, mortality (CVD, cancer), stroke (hemorrhagic, ischaemic).	No association with risk of cancer (bladder, breast, colon, chronic lymphocytic leukaemia/small lymphocytic lymphoma, esophagus, lung#, myeloma, ovarian, stomach), CHD (any)#, CVD, hip fracture, mortality (all-cause, CVD), stroke (hemorrhagic, ischaemic, fatal, total), kidney stones, T2DM.	No association with risk of cancer (breast, diffuse large B-cell lymphoma, ovarian, prostate), CHD (any), CVD (any), Parkinson's disease, stroke (total).	No association with risk of cancer (bladder, breast, colorectum, chronic lymphocytic leukaemia/small lymphocytic lymphoma, diffuse large B-cell lymphoma, myeloma, ovarian, stomach), mortality (all-cause, CVD), elevated blood pressure, Parkinson's disease.	No association with risk of cancer (bladder), CHD (any), CVD (any), mortality (all-cause), stroke (total).

*all the associations should be biologically plausible; potential confounding factors should be taken into account.
§ modified from the Joint WHO/FAO Expert Consultation
# presence of potential confounding factors

POSTPRINT VERSION
Godos J, Tieri M, Ghelfi F, et al. Dairy foods and health: an umbrella review of observational studies. *Int J Food Sci Nutr*. 2020;71(2):138-151. doi:10.1080/09637486.2019.1625035

Figure legend

Figure 1. Flow chart for study selection.

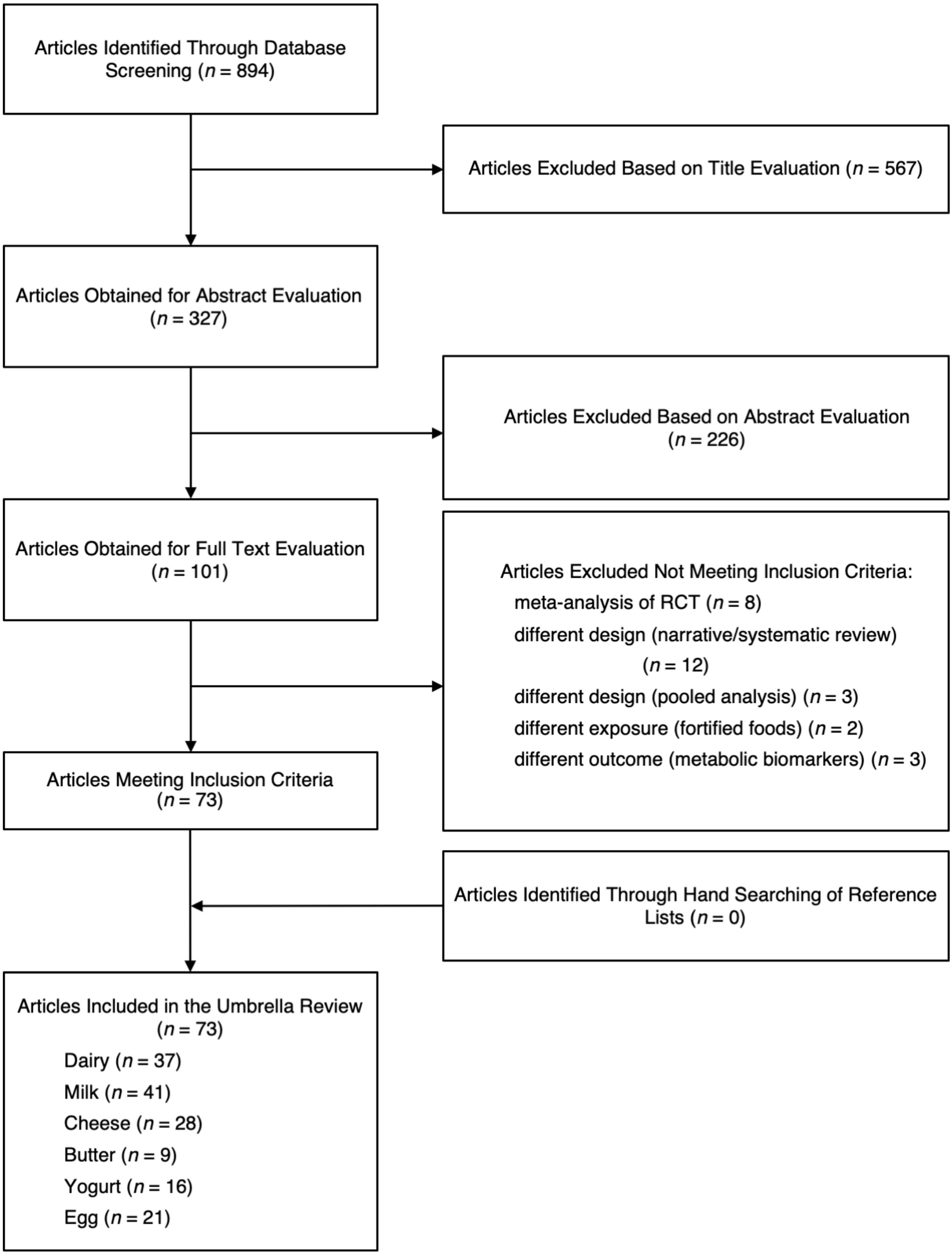

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Figure 2. Summary results from meta-analyses of prospective cohort studies on total dairy consumption on various health outcomes included in umbrella review.

Outcome	No. of studies	No. of subjects	No. of cases	RR (95% CI)	I^2	Ref.
Stroke mortality	8	197,032	14,723	0.80 (0.76, 0.84)	0%	Hu et al. 2014
Colorectal cancer	12	1,170,942	11,579	0.81 (0.74, 0.90)	42%	Aune et al. 2011
Metabolic syndrome	8	31,944	6,870	0.85 (0.73, 0.98)	44%	Kim et al. 2016
CVD mortality	3	73,145	1,910	0.87 (0.62, 1.20)	47%	O'Sullivan et al. 2013
Elevated BP	5	15,883	2,874	0.87 (0.81, 0.94)	0%	Ralston et al. 2012
Stroke	18	764,635	28,138	0.88 (0.82, 0.94)	62%	Hu et al. 2014
CVD	7	91,057	7,641	0.88 (0.81, 0.96)	30%	Qin et al. 2015
T2DM	12	426,055	26,976	0.89 (0.82, 0.96)	42%	Aune et al. 2013
Breast cancer	16	NA	NA	0.90 (0,83, 0.98)	32%	Zang et al. 2015
Stroke ischemic	6	427,803	12,439	0.92 (0.82, 1.03)	63%	Hu et al. 2014
CHD	10	253,260	8,792	0.94 (0.82, 1.07)	59%	Qin et al. 2015
Lung cancer	6	58,997	8,857	0.96 (0.89, 1.03)	68%	Yu et al. 2015
Stroke hemorrhagic	4	451,847	6,625	0.96 (0.73, 1.25)	83%	Hu et al. 2014
Cancer mortality	6	317,920	14,385	0.99 (0.95, 1.03)	0%	Lu b et al. 2016
Gastric cancer	10	727,284	3,221	1.00 (0.89, 1.14)	30%	Sun et al. 2014
NHL	3	527,966	2,031	1.02 (0.88, 1.17)	0%	Wang et al. 2016
Prostate cancer	15	848,395	38,107	1.09 (1.02, 1.17)	43%	Aune et al. 2014
Parkinson's disease	5	304,193	1,083	1.40 (1.20, 1.63)	8%	Jiang et al. 2014

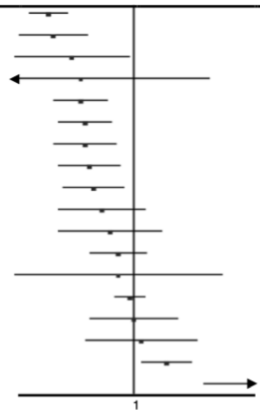

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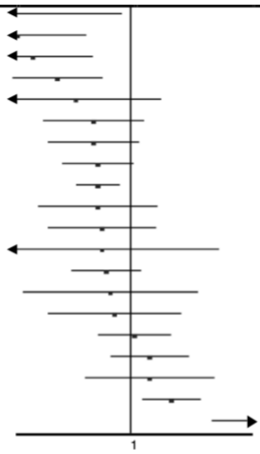
Figure 3. Summary results from meta-analyses of prospective cohort studies on milk consumption on various health outcomes included in umbrella review.



Outcome	No. of studies	No. of subjects	No. of cases	RR (95% CI)	I^2	Ref.
Cognitive disorders	7	11,782	2,025	0.72 (0.53, 0.98)	NA	Wu et al. 2016
Metabolic syndrome	3	10,223	NA	0.75 (0.63, 0.89)	0%	Chen et al. 2015
Colon cancer	8	429,337	2,190	0.78 (0.67, 0.92)	NA	Huncharek et al. 2009
Colorectal cancer	10	655,483	5,011	0.83 (0.74, 0.93)	0%	Aune et al. 2011
T2DM	7	167,982	15,149	0.87 (0.70, 1.07)	71%	Aune et al. 2013
Stroke	10	525,609	22,382	0.91 (0.80, 1.04)	NA	Hu et al. 2014
Bladder cancer	5	192,360	1,038	0.91 (0.81, 1.02)	No	Li et al. 2011
Breast cancer	16	775,778	19,747	0.92 (0.84, 1.02)	53%	Wu et al. 2016
Elevated BP	4	38,889	10,795	0.92 (0.87, 0.98)	0%	Ralston et al. 2012
Stroke mortality	5	395,135	13,651	0.92 (0.79, 1.06)	NA	Hu et al. 2014
Stroke ischemic	4	NA	NA	0.93 (0.81, 1.06)	76%	Alexander et al. 2016
Stroke hemorrhagic	3	NA	NA	0.93 (0.69, 1.25)	87%	Alexander et al. 2016
CVD	4	128,719	9,883	0.94 (0.86, 1.03)	38%	Alexander et al. 2016
Lung cancer	6	58,997	8,857	0.95 (0.76, 1.15)	70%	Yu et al. 2015
CVD mortality	7	338,421	17,806	0.96 (0.81, 1.13)	82%	O'Sullivan et al. 2013
All-cause mortality	6	43,797	17,272	1.01 (0.92, 1.11)	38%	O'Sullivan et al. 2013
CHD	6	NA	NA	1.05 (0.95, 1.16)	5%	Alexander et al. 2016
Gastric cancer	7	169,113	2,129	1.05 (0.89, 1.23)	7%	Sun et al. 2014
Prostate cancer	15	566,149	11,392	1.11 (1.03, 1.21)	20%	Aune et al. 2014
Parkinson's disease	5	304,193	1,083	1.45 (1.23, 1.73)	16%	Jiang et al. 2014

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Figure 4. Summary results from meta-analyses of prospective cohort studies on cheese consumption on various health outcomes included in umbrella review.

Outcome	No. of studies	No. of subjects	No. of cases	RR (95% CI)	I^2	Ref.
T2DM	7	178,429	14,810	0.82 (0.77, 0.87)	0%	Gao et al. 2013
CHD	8	NA	7,631	0.86 (0.77, 0.96)	14%	Chen et al. 2016
CVD	7	NA	8,076	0.90 (0.82, 0.99)	0%	Chen et al. 2016
Stroke	7	NA	10,449	0.90 (0.84, 0.97)	0%	Chen et al. 2016
Breast cancer	14	NA	NA	0.98 (0.89, 1.07)	43%	Zang et al. 2015
CVD mortality	4	33,716	4,777	1.00 (0.81, 1.24)	15%	O'Sullivan et al. 2013
Elevated BP	4	38,889	10,739	1.00 (0.89, 1.12)	11%	Ralston et al. 2012
All-cause mortality	4	23,076	17,753	1.03 (0.97, 1.09)	0%	O'Sullivan et al. 2013
Ovarian cancer	3	170,327	728	1.04 (0.60, 1.81)	70%	Larsson et al. 2006
Prostate cancer	11	887,759	22,950	1.07 (1.01, 1.13)	0%	Aune et al. 2014
Colorectal cancer	7	283,225	1,874	1.11 (0.90, 1.36)	16%	Ralston et al. 2013
Parkinson's disease	4	296,689	955	1.26 (0.99, 1.60)	29%	Jiang et al. 2014

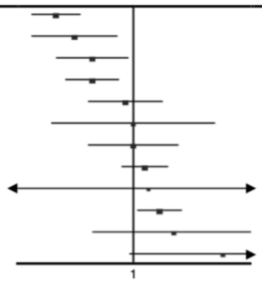
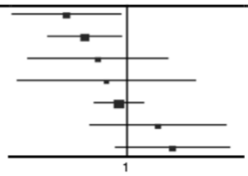


Figure 5. Summary results from meta-analyses of prospective cohort studies on butter consumption on various health outcomes included in umbrella review.

Outcome	No. of studies	No. of subjects	No. of cases	RR (95% CI)	I^2	Ref.
Stroke	3	147,408	4,123	0.94 (0.84, 1.06)	13%	Qin et al. 2015
All-cause mortality	3	31,466	16,703	0.96 (0.85, 1.08)	78%	O'Sullivan et al. 2013
CHD	5	182,692	7,055	1.02 (0.88, 1.20)	31%	Qin et al. 2015

Figure 6. Summary results from meta-analyses of prospective cohort studies on yogurt consumption on various health outcomes included in umbrella review.

Outcome	No. of studies	No. of subjects	No. of cases	RR (95% CI)	I^2	Ref.
T2DM	7	254,892	19,082	0.86 (0.75, 0.98)	59%	Aune et al. 2013
Breast cancer	5	225,057	6,793	0.90 (0.82, 1.00)	0%	Wu et al. 2016
CVD	3	NA	NA	0.93 (0.78, 1.12)	43%	Alexander et al. 2016
Parkinson's disease	3	292,165	870	0.95 (0.76, 1.20)	15%	Jiang et al. 2014
Stroke	3	101,517	7,370	0.98 (0.92, 1.06)	0%	Qin et al. 2015
CHD	4	NA	NA	1.08 (0.91, 1.28)	42%	Alexander et al. 2016
Prostate cancer	5	564,833	17,709	1.12 (0.97, 1.29)	67%	Aune et al. 2014



Godos J, Tieri M, Ghelfi F, et al. Dairy foods and health: an umbrella review of observational studies. *Int J Food Sci Nutr*. 2020;71(2):138-151. doi:10.1080/09637486.2019.1625035

Supplementary material

Supplementary Table 1. Summary results from meta-analyses investigating continuous linear exposure to dairy (total and individual foods) consumption and health outcomes. NA, not available.

Supplementary Table 2. Significance and direction of results from selected meta-analyses on dairy (total and individual foods) consumption and health outcomes. "S" denotes significant results; NS denotes non-significant results; symbols "+" and "-" denote direction of the association. NA, not available.

Supplementary Table 3. Results of meta-analyses (highest vs. lowest category of exposure) on dairy (total and individual foods) consumption and health outcomes with limited number of prospective cohort studies (<3) or case-control studies (either alone or mixed with prospective cohort studies).

Supplementary Table 4. Variables investigated to address the strength of evidence from selected meta-analyses on dairy (total and individual foods) consumption and health outcomes.