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The Effects of Dairy Product and Dairy Protein Intake on Inflammation: A Systematic Review of the Literature

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ABSTRACT

Systemic inflammation is associated with obesity and chronic disease risk. Intake of dairy foods is associated with reduced risk of type 2 diabetes and cardiovascular disease; however, the impact of dairy foods on inflammation is not well-established. The objective of this study was to conduct a systematic review to evaluate the effect of dairy product (milk, cheese, and yogurt) and dairy protein consumption on low-grade systemic inflammation in adults without severe inflammatory disorders. A literature search was completed in September 2019 using PubMed and CENTRAL as well as inspection of reference lists from relevant review articles. The search resulted in the identification of 27 randomized controlled trials which were included in this analysis. In the 19 trials which evaluated dairy products, 10 reported no effect of the intervention, while 8 reported a reduction in at least one biomarker of inflammation. All 8 trials that investigated dairy protein intake on markers of inflammation reported no effect of the intervention. The available literature suggests that dairy products and dairy proteins have neutral to beneficial effects on biomarkers of inflammation. Additional clinical studies designed using inflammatory biomarkers as the primary outcome are needed to fully elucidate the effects of dairy intake on inflammation.

Key teaching points

- Systemic inflammation is a key contributor to the progression of metabolic disorders.
- The impact of dairy food consumption on systemic inflammation is unclear.
- This systematic review shows that consumption of dairy products and proteins has neutral to beneficial effects on biomarkers of inflammation.
- Additional studies, including clinical and prospective cohort, designed using inflammatory biomarkers as the primary outcome are warranted.

Introduction

Low-grade, systemic inflammation is considered a key contributor in the pathophysiological progression of metabolic disorders including cardiovascular disease (CVD), type 2 diabetes, and metabolic syndrome (1–3). Indeed, circulating concentrations of C-reactive protein (CRP), cytokines including interleukin (IL)-6, tumor necrosis factor (TNF)-α, their receptors, and monocyte chemoattractant protein (MCP)-1, and cell adhesion molecules including intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule

(VCAM)-1, have been positively associated with CVD risk (4–11). In contrast, some cytokines have anti-inflammatory and anti-atherogenic properties, such as adiponectin and IL-10 (12). Imbalance or overactivation of inflammatory pathways may contribute to the pathogenesis of chronic disease. For example, the abnormal recruitment and migration of inflammatory cells (e.g., monocytes, leukocytes, T-cells, macrophages) in the vascular endothelium can, under certain conditions, contribute to the cascade of events leading to atherosclerosis (12).

A number of physiological and environmental factors are known to influence an individual's inflammatory state and chronic disease risk, with diet being a critical modifiable factor (13). In support of this concept, the Mediterranean Diet has been shown to decrease markers of inflammation (14), while diets high in trans-fat or added sugars reportedly increase inflammation (15,16). Similarly, high intakes of saturated fat have been associated with inflammatory biomarkers in overweight subjects (17,18).

Dairy products are integral components of healthy dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) and the 2015-2020 Dietary Guidelines for Americans (DGA) (19,20). The 2015-2020 DGA recommends that children over 9 years of age and adults consume three cup equivalents of low- or fat-free dairy products each

day. However, most Americans (>2 years of age) do not meet dairy food recommendations, consuming, on average less than two cups dairy food equivalents per day (19,21–25). Dairy products are a major contributor of several nutrients including calcium, vitamin D, riboflavin, vitamin B12, protein, potassium, zinc, choline, magnesium, and selenium (26,27). Moreover, dairy products are the primary food source for three of the four nutrients of public health concern due to underconsumption (calcium, potassium, and vitamin D) as identified by the 2015 Dietary Guidelines Advisory Committee (27–29). The consumption of dairy products has been attributed to the maintenance of bone health and inversely associated with a lower risk of CVD, type 2 diabetes, and metabolic syndrome (30–34).

Despite being associated with reduced chronic disease risk, dairy products are often considered among foods that are associated with inflammation, most likely due to the saturated fat and lactose content of certain dairy products. Several cross-sectional studies suggest an inverse relationship between dairy product consumption and systemic inflammation (35–37). While few studies have primarily examined the link between dairy and inflammation, the current evidence suggests either neutral or anti-inflammatory effects of dairy product consumption (38–40). However, the role of dairy proteins on inflammation is unclear. Thus, given (i) the importance of dairy product consumption in helping achieve nutrient adequacy, (ii) the association of dairy product intake with reduced chronic disease risk, and (iii) the role of inflammation in chronic disease risk, the purpose of this study was to conduct an updated systematic review of literature, in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (41,42), to evaluate the impact of both dairy product and dairy protein consumption on low-grade systemic inflammation.

Materials and methods

This systematic review was conducted in accordance with the PRISMA statement, including relevant PRISMA checklist items (see Supplemental data) (41,42) and for the field of nutrition (41–44). An unpublished review protocol was developed and refined by all investigators prior to implementing the search strategy and reviewing the records returned. The review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42019129639.

Literature search

The comprehensive literature search was originally conducted up to December 21, 2018, and updated September 19, 2019, by one author (KMN) using two independent databases (PubMed and Cochrane Controlled Register of Trials [CENTRAL]) for relevant studies. The search term strategy included the following terms:

- Dairy product/protein terms: yogurt, yoghurt, yoghourt, yogourt, yogurt, cheese, milk, dairy, milk protein, whey, casein;
- Inflammation terms: inflammation, inflammatory marker, c-reactive protein, cytokine, TNF-α, tumor necrosis factor, IL-6, interleukin;
- Excluded terms: pregnant, pregnancy, lactating, breast milk, human milk.

Human, clinical trials, and best match filters were applied during the PubMed search. No restrictions on publication date were imposed. The identification of studies eligible for review was performed independently by two authors (BDA and KMN) by scanning titles and abstracts using Abstrackr (45), in addition to reviewing reference lists from relevant review articles (38–40,46–48).

Study eligibility criteria

Potentially relevant studies were exported from Abstrackr and full-text articles obtained and independently investigated by two scientists (BDA and KMN). Any disagreements were resolved by discussion, and further disagreements were resolved by a third scientist (CJC). The review included randomized controlled trials (RCT) and observational studies published in English that evaluated the effects of dairy product and/or dairy protein consumption on systemic inflammation biomarker levels. The population of interest included male and female apparently healthy adults, as described by the authors, and non-healthy adults who had a disease diagnosis which included hypercholesterolemia, hypertension, metabolic syndrome, and type 2 diabetes in the identified studies, ≥18 years of age, and without any diagnosis of severe inflammatory-related disorders (e.g., cancer, Crohn's disease, rheumatoid arthritis, lupus, multiple sclerosis; Table 1). Additionally, to be considered inclusionary, studies included dairy products (milk, yogurt, cheese) or proteins as the intervention, not solely measured as part of a dietary pattern, with intervention duration of at least 2 weeks. Studies were excluded with the following

Table 1. PICOS Table for Inclusion of Studies

Parameter	Criteria
Population (P)	Healthy and non-healthy adults (male and female), ≥18 years of age, and without any diagnosis of severe inflammatory-related disorders
Intervention (I)	Dietary intervention or exposure which evaluated dairy products or proteins, not solely measured as part of a dietary pattern, with a minimum of 2-week duration
Comparison (C)	Nondairy or low-dairy control group
Outcome (O)	Inflammatory biomarker(s)
Study design (S)	Randomized controlled trials and observational studies

characteristics: pregnant or lactating women; human milk or non-bovine milk intervention; interventions containing only butter, cream, or ice cream; studies without an appropriate nondairy or low-dairy control group; and/or studies that did not assess an inflammatory biomarker.

Abstraction of data

Data were extracted from eligible studies by two scientists (KMN and BDA). Each scientist extracted data from 50% of the studies and reviewed the remaining 50% of the data extracted by the other. Twenty-eight manuscripts met inclusion criteria for extraction of data.

Data extracted from eligible studies included the following:

i. General information – title, authors, journal, year of publication;
ii. Study design – country of origin, population (healthy or unhealthy); disease/condition (if unhealthy), trial type, blinding, arms, primary outcome, secondary outcome(s);
iii. Participant characteristics – sex, age, body weight, body mass index (BMI), sample size (randomized, evaluable, male, and female);
iv. Intervention – dairy product assignment (control or active), intervention (dairy product or dairy protein), comparator, intervention form, intervention dose, comparator dose, dairy product type, intervention energy content, comparator energy content, intervention protein content, comparator protein content, intervention duration, washout duration;
v. Results – sample type, results summary (difference in means);
vi. Summary – conclusions, strengths, and limitations.

Assessment of methodological quality

To assess the risk of bias in, and quality of, individual studies, the Academy of Nutrition and Dietetics Quality Criteria Checklist was used (49). The assessment tool provided several domains (inclusion/exclusion, bias, generalizability, and data collection and analysis) where potential bias could arise based on specific study designs. The authors made a judgment of the potential bias and its severity for each domain and concluded with an overall judgment rating. This process was conducted independently by two scientists (BDA and KMN), and disagreements were resolved by conferring with a third scientist (CJC). Complete results of the quality analysis can be found in the Supplemental Tables 1a–c.

Results

Study selection

The initial database search retrieved 451 research articles and additional 272 articles were identified through reviewing
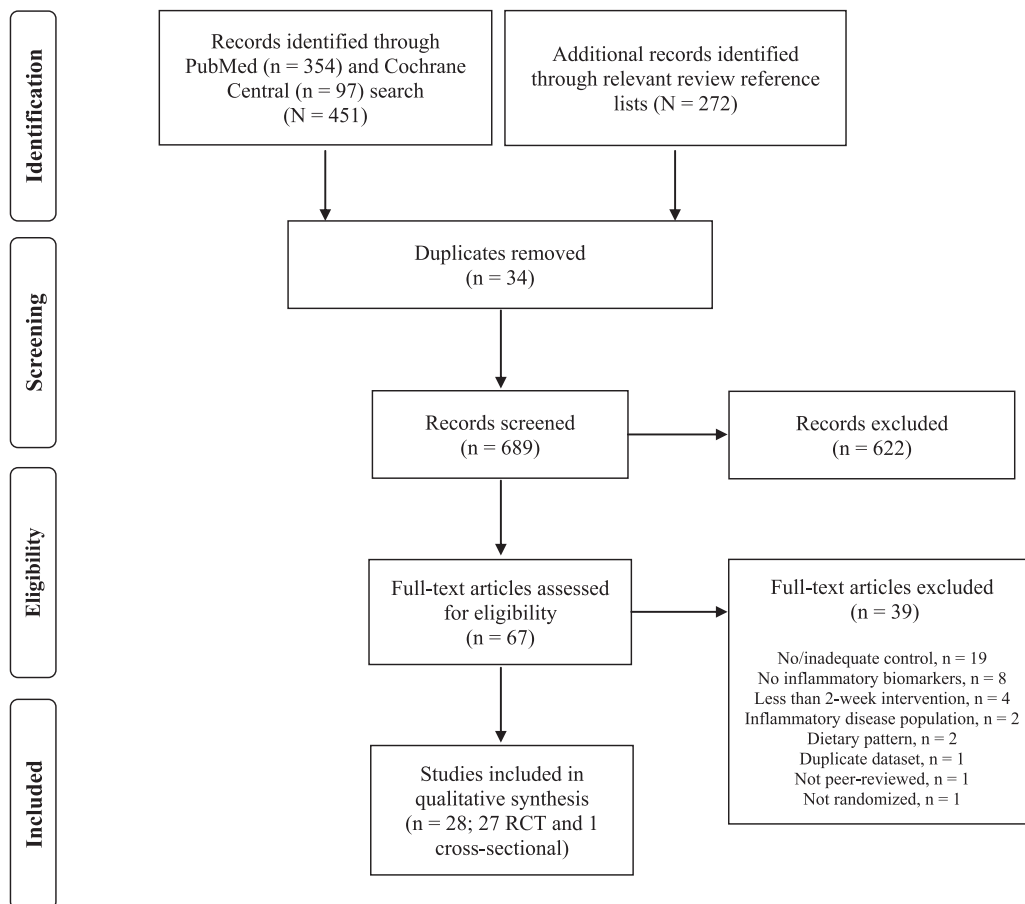

Figure 1. Flow diagram of the literature search and study selection conducted according to the PRISMA guidelines statement (41). Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trials.

reference lists of relevant reviews (Figure 1). After duplicate articles were removed, 691 article titles and abstracts were screened of which 625 were excluded that did not meet eligibility criteria. Full-text articles were retrieved for 67 titles which were reviewed in detail resulting in identification of a total of 28 studies (27 RCT [Tables 2 and 3] and 1 cross-sectional study [36]) for inclusion. Given the limited return of observational evidence, the remainder of the review will focus on summarizing the RCT identified in the search.

Study characteristics and quality

The results from the 27 RCT are separated by those trials which evaluated the effects of dairy products (Table 2, n = 19) and dairy proteins (Table 3, n = 8) on markers of inflammation. Within each table, the studies are grouped by the study population: healthy, overweight/obese but otherwise healthy, or overweight/obese subjects with chronic disease (e.g., metabolic syndrome or type 2 diabetes). In addition, the tables include the sample size, age, trial design, intervention dose and duration, primary outcome, results for inflammatory biomarkers, and the study quality rating. Nearly, 50% of the RCT received a neutral rating (n = 14) and the remaining received a positive rating (n = 13) according to the Academy of Nutrition and Dietetics criteria (49) (Tables 2–3). There was an inherent lack of description of the method of randomization, statistical methods employed, and blinding. In many of these studies, it was not possible to employ a double-blind design due to the form of the interventions; however, the type of blinding or lack thereof was not always made clear.

Dairy product consumption in healthy adults

Two trials evaluated the effect of dairy product consumption in healthy adults on markers of inflammation (Table 2), one of which included both male and female participants (n = 176) (50) and the other only female participants (n = 120) (51). The first trial evaluated the effects of 2–3 servings vs 0 servings of full-fat dairy products each day over a month, while the second evaluated low-fat yogurt vs soy pudding consumption over 9 weeks. Neither study was designed with an inflammatory marker as the primary outcome. Benatar et al. (50) reported no differences in CRP and tumor necrosis factor (TNF)-α receptor II (TNF-RII). In contrast, Pei et al. (51) reported a significant decreased in TNF-α alone (p = 0.0219) and the TNF-α/TNF-RII ratio (p = 0.0013) following low-fat yogurt consumption, relative to the soy pudding control.

Dairy product consumption in overweight and obese but otherwise healthy adults

A total of 13 trials evaluated the effect of dairy product consumption on inflammation in overweight and obese but otherwise healthy adults (Table 2). Ten of these trials included both male and female participants with sample sizes ranging from 18 to 112 participants. The remaining

three trials (52–54) included only female participants and sample sizes of 31, 27, and 69, respectively. Six studies evaluated the effects of milk relative to an isocaloric beverage or no milk (52–57). One study evaluated both milk and yogurt relative to isocaloric quantities of fruit juice and biscuits (58,59). The remaining six studies evaluating the effects of dairy servings relative to a lesser number or no servings of dairy each day. The trials ranged in duration from 28 days to 6 months and in all but two of the trials, the primary outcome was not reported or not an inflammatory biomarker.

A majority of the trials reported no significant differences in CRP, cytokines, or other inflammatory markers. Bruun et al. (56) reported a significant decrease in uric acid following 6 months of low-fat milk consumption at 1 L/day relative to cola (p = 0.009). Labonte et al. (60) reported decreased CRP relative to baseline in control group, and the decrease from baseline was significantly greater in the control group than the dairy group which included low- and full-fat dairy products (p = 0.04). Van Meijl et al. (58,59) reported no effect of low-fat dairy product consumption on CRP, IL-6, TNF-α, TNF-RI, and MCP-1 but increased TNF-RII (p = 0.020), and decreased TNF-α index (p = 0.015) which may suggest lower biological availability of TNF-α. Finally, three trials by Zemel et al. (57,61–63) showed decreased CRP following consumption of three servings of fat-free and low-fat dairy products vs ≤1 serving dairy/day or three servings of soy for 28 days to 24 weeks (p < 0.05 for all). In addition, decreased TNF-α, MCP-1, and IL-6, and increased adiponectin were reported in one of the trials (p < 0.01 for all) (57).

Dairy product consumption in unhealthy, overweight, and obese adults

Four trials evaluated the effects of dairy product consumption in unhealthy, overweight, and obese participants. In three of these trials (64–67), participants met the criteria for metabolic syndrome (n = 33, 40, and 113, respectively) and were provided 3–5 servings of dairy products per day, relative to the equivalent nondairy products or a lesser quantity of dairy product servings per day. In the fourth trial, participants had been diagnosed with type 2 diabetes (n = 25) and were provided 240 mL/day milk or soy milk (68). All trials included both male and female participants, and two of the trials (66,68) were designed using an inflammatory biomarker as the primary outcome. Three of the four trials reported no significant differences between dairy product (fat-free, low-fat, reduced-fat, and full-fat) intake and control in CRP, cytokines, or other inflammatory markers (64,65,67,68). Stancliffe et al. (66) reported decreased CRP, IL-6, TNF-α, and MCP-1, and increased adiponectin following 84 days of 3 dairy product servings daily, relative to nondairy products (p < 0.02 for all).

Dairy protein consumption in healthy adults

Two trials evaluated the effects of dairy protein consumption in healthy adults, the first of which included both male

Table 2. Randomized Controlled Trials evaluating Inflammatory Biomarkers in response to a *Dairy Product* Intervention

Study (ref)	Subjects[1] (n, age)	Health status	Obesity status[2]	Design	Intervention (protein [g])	Dairy product type[3]	Duration[4]	Primary outcome[5]	Reported change in inflammatory biomarker(s)			Overall quality rating[6]
									CRP	Cytokines	Other inflammatory markers	
Healthy												
Benatar et al. (50)	176 M/F, 47 y	Healthy	Normal	Parallel	2–3 additional servings vs 0 servings dairy/day (NR)	full-fat	1 month	No	↔	NR	NR	Ø
Pei et al. (51)	120 F; ~30 y	Healthy	Normal, Overweight/ Obese	Parallel	339 g/day low-fat yogurt vs 324 g/day soy pudding (9 vs 6–9 g)	low-fat	9 weeks	No	↔	↓ TNF-α, TNF-α/TNF-RII; ↔ IL-6, TNF-RII	NR	+
Healthy – overweight/obese												
Beavers et al. (52)	31 F; ~54 y	Healthy	Overweight	Parallel	24 oz/day reduced-fat milk vs 24.75 oz/day soymilk (24 vs 18 g)	reduced-fat	28 days	Yes	NR	↔ IL-6, TNF-α, IL-1β	NR	Ø
Gjevestad et al. (55, 102)	31 M/F; ~77 y	Healthy	Overweight	Parallel	0.8 L/day milk vs isocaloric CHO drink (40 vs 0 g)	fat-free	12 weeks	No	↔	↔ IL-6, TNF-α	↔ IL-6, IL-1β, IL-18, TNFx mRNA expression	+
Bruun et al. (56, 103)	47 M/F; ~39 y	Healthy	Obese	Parallel	1 L milk/day vs 1 L cola/day (34 vs 0 g)	low-fat[7]	6 months	NR	NR	NR	↓ uric acid	+
Drouin-Chartier et al. (53)	27 F; 57 y	Healthy	Obese	Crossover	~20% vs 0% total energy from milk (100.9 vs 99.8 g)	reduced-fat	6 weeks (6–8 weeks)	No	↔	NR	↔ ICAM, VCAM, adiponectin	+
Labonte et al. (60)	112 M/F; 40 y	Healthy	Overweight	Crossover	3 servings/day dairy vs nondairy products (26 vs 7.7 g)	low-fat and full-fat	4 weeks (4–8 weeks)	Yes	↑	↔ IL-6	↔ adiponectin, mRNA expression[8]	+
Rosado et al. (54)	69 F; ~35 y	Healthy	Obese	Parallel	750 vs 0 mL/day low-fat milk (NR)	low-fat	16 weeks	No	↔	NR	NR	Ø
Thompson et al. (97)	72 M/F; ~42 y	Healthy	Obese	Parallel	4 vs 2 servings dairy/day (NR)	NR	48 weeks	No	↔	NR	NR	+
Turner et al. (101, 104)	47 M/F; 48 y	Healthy	Obese	Crossover	4–6 vs <1 serving(s) dairy/day (118 vs 118 or 103 g)	low-fat	4 weeks (2 weeks)	No	↔	↔ TNF-α, TNF-α/TNF-RII, TNF-RII	NR	+
Van Loan et al. (105)	71 M/F; 33 y	Healthy	Overweight/obese	Parallel	3–4 dairy servings/day vs ≤1 serving dairy/day (74.9 vs 73.9g)	low-fat, reduced-fat, and full-fat	12 weeks	No	↔	↔ IL-6, TNF-α, IL-1β	NR	Ø
Van Meijl et al. (58, 59)	35 M/F; 50 y	Healthy	Obese	Crossover	500 mL low-fat milk + 150 g low-fat yogurt/day vs 600 mL fruit juice + 43 g fruit biscuits/day (24.4 vs 2.8 g)	low-fat	8 weeks (≥2 weeks)	NR	↔	↔ IL-6, TNF-α, TNF-RI, MCP-1; ↑ TNF-RII, ↓ TNF-α index	↔ ICAM, VCAM	Ø
Zemel et al. (61, 63)	34 M/F; ~41 y	Healthy	Obese	Parallel	3 vs 0–1 servings yogurt/day (NR)	fat-free	12 weeks	No	↓	NR	NR	Ø
Zemel et al. (62, 63)	34 M/F; ~42 y	Healthy	Obese	Parallel	3 vs <1 serving dairy/day (NR)	low-fat	24 weeks	No	↓	NR	NR	+
Zemel et al. (57)	18 M/F; 31 y	Healthy	Overweight/obese	Crossover	3 smoothies/day milk vs soy milk (30 g)	fat-free	28 days (28 days)	NR	↓	↓ TNF-α, MCP-1, IL-6; ↔ IL-15	↑ adiponectin	Ø
Unhealthy – overweight/obese												
Dugan et al. (64, 65)	33 M/F; 54 y	Unhealthy – MetS	Obese	Crossover	~3 servings dairy vs nondairy products (31 vs 4 g)	low-fat	6 weeks (4 weeks)	NR	M/F: ↔	M: ↔; TNF-α, MCP-1; F: ↓ TNF-α, MCP-1	M/F: ↔ VCAM, ICAM, adiponectin	+
Miraghajani et al. (68)	25 M/F; 51 y	Unhealthy – T2D	Overweight	Crossover	240 mL/day milk vs soy milk (3.3 vs 2.5 g)	low-fat	4 weeks (2 weeks)	Yes	↔	↔ IL-6, TNF-α,	NR	Ø
Stancliffe et al. (66)	40 M/F; 37 y	Unhealthy – MetS	Obese	Parallel	3 vs <1 servings nondairy/day (28–35 vs <24 g)	NR	84 days	Yes	↓	↓ IL-6, TNF-α, MCP-1	↑ adiponectin	+
Wennersberg et al. (67)	113 M/F; ~54 y	Unhealthy – MetS	Obese	Parallel	3–5 vs ≤2 portions/day dairy (94 vs 78 g)[9]	fat-free, low-fat, reduced-fat, and full-fat	6 months	No	↔	↔ IL-6, TNF-α, MCP-1	↔ VCAM, adiponectin, complement 3 and 4	Ø

Abbreviations: ↔, no change; ↓, decreased; ↑, increased; Ø, neutral; +, positive; –, negative; CHO, carbohydrate; F, female; g, gram(s); ICAM, intracellular adhesion molecule; IL, interleukin; MCP-1, monocyte chemoattractant protein; M, male; MetS, metabolic syndrome; NR, not reported; ref, reference; y, year(s); TNF-α, tumor necrosis factor alpha; TNFR, tumor necrosis factor receptor; T2D, type 2 diabetes; VCAM, vascular cell adhesion molecule.
[1]The sample size is reported for the total evaluable population and sex indicated unless otherwise noted. Mean age is reported unless otherwise noted and "~" is noted when multiple means were presented, and an average was calculated.
[2]Obesity status was classified using the reported mean/median body mass index (106).
[3]The dairy product interventions were classified as fat-free (non-fat), low-fat (1% milk fat or <3 g fat per serving), reduced-fat (2% milk fat or ≥25% reduced-fat), or full-fat based on the author's description.
[4]Duration of the washout period is noted in parentheses for crossover studies.
[5]"Yes" is noted if the primary outcome for the study design was an inflammatory biomarker, otherwise "no" or "NR" are noted.
[6]Risk of bias and quality were assessed using the Academy of Nutrition and Dietetics, Quality Criteria Checklist (49). A positive rating (+) indicates the reference has clearly addressed inclusion/exclusion, bias, generalizability, and data collection and analysis. A negative rating (–) indicates the preceding issues have not been addressed adequately in the reference. A neutral rating (Ø) suggests the reference is neither exceptionally strong nor weak. Complete results of the quality analysis can be found in the Supplemental Tables 1a–c.
[7]Semi-skimmed milk, 1.5% fat.
[8]mRNA expression of genes included chemokine ligand 2, IL-18, IL-6, IL-1β, nuclear factor κB-1, natriuretic peptide receptor C, peroxisome proliferator-activated receptor α, sterol-regulatory element-binding transcription factor 2, TNF, and TNF receptor-associated factor 3.
[9]Protein for the entire diet consumed by subjects is reported not just the dairy/control intervention.

Table 3. Randomized Controlled Trials evaluating Inflammatory Biomarkers in response to a *Dairy Protein* Intervention

Study (ref)	Subjects[1] (n, age)	Health status	Obesity status[2]	Design	Intervention	Duration[3]	Primary outcome[4]	Reported change in inflammatory biomarker(s)			Overall quality rating[5]
								CRP	Cytokines	Other inflammatory markers	
Healthy											
Ballard et al. (69)	20 M/F; 25 y	Healthy	Normal	Crossover	5 g/day whey vs placebo[6]	2 weeks (1–2 weeks)	No	↔	↔ IL-6, IL-8, TNF-α	↔ ICAM, VCAM, MCP-1	Ø
Steinberg et al. (70)	28 F; 55 y	Healthy	Normal/over-weight	Crossover	25 g/day milk vs soy protein	6 weeks (4 weeks)	NR	NR	NR	↔ ICAM, VCAM, nitric oxide products	+
Healthy – overweight/obese											
Anderson et al. (71)	35 F; ~45 y	Healthy	Obese	Parallel	67.2 g/day casein vs 62.1 g/d soy protein	16 weeks	No	↔	NR	↔ homocysteine	+
Greany et al. (72)	34 F; 58 y	Healthy	Overweight	Crossover	26 g/day milk vs soy protein	6 weeks (2 weeks)	NR	↔	NR	↔ ICAM, VCAM, homocysteine	Ø
Rebholz et al. (73)	72 M/F; 46 y	Healthy	Overweight/ obese	Crossover	40 g/day milk protein vs soy protein or CHO powder	8 weeks (3 weeks)	NR	↔	↔ IL-6, TNF-α	↔ ICAM, VCAM, adiponectin	+
Unhealthy – overweight/obese											
Frota et al. (74)	38 M/F; 57 y	Unhealthy – HCL	Overweight	Crossover	28.2 g/day casein vs 25.2 g/day cowpea protein	6 weeks (4 weeks)	No	↔	NR	↔ ICAM, VCAM	Ø
Jenkins et al. (75)	23 M/F; 57 y	Unhealthy – HCL	Overweight	Crossover	30 g/day casein vs barley protein	4 weeks (2 weeks)	No	↔	NR	NR	Ø
Lee et al. (76)	22–25 M/F; ~52 y	Unhealthy – HTN	Overweight	Parallel	3 vs 0 g/day whey protein	12 weeks	No	↔	↔ IL-6	NR	Ø

Abbreviations: ↔, no change; ↓, decreased; ↑, increased; Ø, neutral; +, positive; −, negative; CHO, carbohydrate; F, female; g, gram(s); HCL, hypercholesterolemia; HTN, hypertension; ICAM, intracellular adhesion molecule; IL, interleukin; M, male; MCP-1, monocyte chemoattractant protein; NR, not reported; ref, reference; y, year(s); TNF-α, tumor necrosis factor alpha; VCAM, vascular cell adhesion molecule.

[1]The sample size is reported for the total evaluable population and sex indicated unless otherwise noted. Mean age is reported unless otherwise noted and "~" is noted when multiple means were presented, and an average was calculated.

[2]Obesity status was classified using the reported mean/median body mass index (106).

[3]Duration of the washout period is noted in parentheses for crossover studies.

[4]"Yes" is noted if the primary outcome for the study design was an inflammatory biomarker, otherwise "no" or "NR" are noted.

[5]Risk of bias and quality were assessed using the Academy of Nutrition and Dietetics, Quality Criteria Checklist (49). A positive rating (+) indicates the reference has clearly addressed inclusion/exclusion, bias, generalizability, and data collection and analysis. A negative rating (−) indicates the preceding issues have not been addressed adequately in the reference. A neutral rating (Ø) suggests the reference is neither exceptionally strong nor weak. Complete results of the quality analysis can be found in the Supplemental Tables 1a–c.

[6]The placebo was a non-nutritive sweetener.

and female participants (n = 20) (69), while the second included only female participants (n = 28). Neither was designed using an inflammatory biomarker as the primary outcome. Ballard et al. (69) evaluated the effects of 5 g/day whey protein for 2 weeks, relative to a non-nutritive sweetener, and reported no changes in CRP, cytokines (IL-6, IL-8, TNF-α), or other inflammatory biomarkers (ICAM, VCAM, MCP-1). Steinberg et al. (70) evaluated the effects of 25 g/day milk protein for 6 weeks, relative to soy, and reported no significant differences in any of the inflammatory biomarkers (ICAM, VCAM, nor nitric oxide products) assessed as well.

Dairy protein consumption in overweight and obese but otherwise healthy adults

A total of three trials evaluated the effects of daily dairy protein intake in overweight or obese but otherwise healthy adults, two of which included only female subjects (n = 35 and 34, respectively) (71,72), and the third trial included both male and female participants (n = 72) (73). None of the trials were designed using an inflammatory biomarker as the primary outcome. The trials provided 26–67 g/day casein or milk protein for 6–16 weeks or soy protein and no significant differences were reported in any of the inflammatory biomarkers assessed (CRP, IL-6, ICAM, VCAM, homocysteine, and adiponectin).

Dairy protein consumption in unhealthy, overweight, and obese adults

Three trials evaluated the effects of dairy protein intake (casein or whey) in overweight and obese participants with hypercholesterolemia (74,75) or hypertension (76), relative to a nondairy protein (74,75) or no protein (76) control (n = 22–38). None of these trials were designed using an inflammatory biomarker as the primary outcome variable. After 4–12 weeks of supplementation, no significant differences were reported in any of the inflammatory biomarkers assessed (CRP, IL-6, ICAM, nor VCAM).

Discussion

Systemic inflammation contributes to the risk and progression of chronic disease, which is in turn influenced by a number of factors including diet (13). This systematic review evaluated the effects of dairy product or dairy protein interventions on markers of inflammation. Overall, the results of this review show that the consumption of dairy products has no adverse effects and potentially beneficial effects and dairy proteins have no adverse effects on systemic inflammation. Additionally, the results indicate that the beneficial effects were most commonly reported in trials that evaluated overweight/obese populations with an average age ~42 years. Specifically, of the 8 studies (51,56–58,61,62,64,66) that reported beneficial findings, 7 were in overweight/obese populations with mean ages of ~39, 50, 41, 42, 31, 54, and 37 years, respectively. The differences in results between

trials reporting beneficial and neutral effects could potentially be a result of less variability in or higher baseline systemic inflammation in the participants evaluated (77).

To our knowledge, three systematic reviews (38–40) have previously been completed evaluating the effects of dairy product consumption on inflammation, none of which evaluated the effect of dairy proteins. Labonte et al. (38) completed their systematic search in 2012 and included eight trials in overweight and obese adults, all of which were included in this study. The authors similarly concluded that dairy product intake did not result in adverse effects on markers of inflammation. Bordoni et al. (39) completed their extensively inclusive systematic search in 2013 and included 52 clinical studies. Studies accumulated additional points based on study characteristics (e.g. intervention type and duration, design, number of inflammatory markers changed). Based on this approach, the authors concluded that dairy products are anti-inflammatory, specifically in interventions with fermented dairy products or in trials which evaluated subjects with metabolic disorders. It is difficult to directly compare this review to this study as the authors created a scoring system ("inflammatory score") based on the net change in inflammatory markers (null, positive, or negative). Finally, the most recent review by Ulven et al. (40) was completed in 2018 and included 16 trials, 4 of which overlap with this study (51,55,60,64). The authors concluded that most studies did suggest dairy product consumption led to anti-inflammatory effects in healthy and metabolically abnormal subjects. Thus, there is consistency among the systematic reviews completed to date showing a lack of association between dairy product consumption and systemic inflammation, and in some circumstances dairy consumption may be associated with reduced inflammation.

A unique contribution of this work is the review of the relationship between dairy protein consumption and inflammation. Some studies have suggested that animal protein intake is associated with increased CVD and mortality (78–80). For example, Tharrey et al. (79) examined data from the Adventist Health Study-2 cohort and reported that "Meat" protein was associated with an increased hazard ratio for cardiovascular mortality. We identified eight trials which evaluated the effects of dairy proteins on markers of inflammation. Seven of the eight trials evaluated CRP, and all reported no effect of the intervention. Similarly, in the three trials that evaluated inflammatory-related cytokines and six trials that evaluated other inflammatory markers, there was no effect of the dairy protein intervention. Accordingly, the evidence reviewed suggests that dairy protein consumption is not linked with inflammation.

According to the 2015-2020 DGA, American Heart Association, and American College of Cardiology, dairy foods such as low-fat milk, cheese, and yogurt are integral components in healthy eating patterns and specifically for reduction of low-density lipoprotein cholesterol and blood pressure (19,81,82). However, dairy products are often considered among foods that are associated with increased inflammation, mostly due to the saturated fat content (83).

A systematic review by Telle-Hansen et al. (84) of 37 RCT suggests minor or no effects of dietary fat intake on inflammatory markers in overweight/obese subjects. Emerging evidence indicates that dairy product consumption is linked to lower risk for CVD and metabolic syndrome, and the lack of detrimental effects from intake of saturated fat can be attributed to the heterogeneity of saturated fatty acids unique to the dairy food matrix (85). Specifically, a systematic review by Drouin-Chartier et al. (34) concluded that neither total dairy product nor cheese consumption was associated with higher risk for coronary artery disease or CVD, and total dairy product and cheese intake were associated with lower stroke risk. Similarly, in a crossover RCT, healthy participants (>21 years of age), who consumed a modified, high-dairy fat, DASH dietary pattern for three weeks, showed similar blood pressure lowering effects, but in addition reduced very-low-density lipoprotein cholesterol and triglycerides, as compared to the standard DASH dietary pattern (86). Specific to inflammation, Byrd et al. (87) recently published novel dietary and lifestyle inflammation scores. Both high-fat and low-fat dairy had negative weights and, as such, were associated with lower dietary inflammation scores in this analysis. A complete mechanistic understanding of the role of dairy foods and vascular function and ultimately cardiovascular risk in humans is lacking. Studies *in vitro* and *in vivo* suggest dairy foods reportedly improve vascular function regardless of blood pressure-lowering effect by reducing oxidative status (88). In addition, inclusion of dairy cheese in an 8-day high-sodium diet prevents vascular dysfunction in older adults by decreasing oxidative stress suggesting the dairy matrix and fat protect the vasculature from the effects of sodium (89).

Components of dairy product matrix such as vitamin D, calcium, protein, live and active cultures in fermented dairy, and bioactive peptides appear to suppress the inflammatory response (63,88,90) and may ultimately have vascular effects. Dairy foods may regulate immune function within the GI tract by interacting with the mucosal layer, improving intestinal barrier function, and stimulating immunocytes which can in turn affect cardiovascular health, for example, through flux of metabolites into the bloodstream (88). Further, *in vitro* and *in vivo* studies suggest dairy components may beneficially modulate immune function in the GI tract via reducing lipopolysaccharide activity, Gram-negative bacteria, and bacterial translocation, increasing tight junction proteins, and improving barrier function (88). In support of this, supplementation of fermented milk for 2 weeks at 400 g/day resulted in altered gut microbiota and microbial metabolites that improve barrier function in healthy men (91–93). Taken together, these findings suggest the dairy food matrix may modulate the effects of dairy fat on chronic disease risk (94). This notion is supported in this study where various dairy products types (fat-free, low-fat, reduced-fat, and full-fat) were utilized in the 19 trials that evaluated the effects of dairy product consumption on markers of inflammation and showed neutral to beneficial effects. This agrees with results from other studies suggesting the Mediterranean and DASH

dietary patterns, which incorporate dairy products, are associated with reduced inflammation (95,96).

This study identified important knowledge gaps that need to be addressed in future studies. First, the majority of studies included in this systematic review were not designed using an inflammatory marker as the primary outcome and, in turn, baseline systemic inflammation of trial participants was not commonly considered in the trial design. Only four of the 27 trials reported design and completion of sample size calculations using variability associated with an inflammatory biomarker (52,60,66,68). Of these four trials, two reported no significant differences in any of the inflammatory biomarkers assessed (CRP, IL-6, TNF-α, IL-1β) (52,68) and two trials reported significant changes in inflammatory biomarkers including CRP (60) and CRP, IL-6, TNF-α, MCP-1, and adiponectin, relative to controls (66). Further, 16 of the 27 RCT were specifically designed using non-inflammatory-related outcomes as the primary outcome variable; thus, a majority of the trials included in the review may be insufficiently powered to detect differences in inflammatory biomarkers.

A second gap identified among the trials is the lack of consistency in which biomarkers of inflammation were measured. A majority of papers evaluated CRP or one or more other circulating inflammatory-related cytokines. However, some studies included cellular markers of inflammation and/or markers of tissue infiltration. This lack of consistency makes comparison across studies difficult and limits the generalizability of the results. Further, future studies should use appropriate controls to allow for a more robust understanding of the impacts of dairy foods on inflammation. For example, in several of the studies the difference between the dairy product or dairy protein interventions and the control may not have been large enough to induce change (67,69,76,97). Additionally, the control intervention employed in each study varied and included controls that did not match the macronutrient composition of dairy. Due to the complex nature of inflammation, completion of additional well-controlled clinical trials using inflammatory biomarkers as the primary outcome and systematic reviews with a consistent methodology is warranted (98–100).

Additional methodological gaps include controlling for sex and intervention length. To the best of our knowledge, 21 trials evaluated both male and female populations and although 9 of these note controlling for sex in the statistical model (36,56,60,66–69,75,101), many of these trials do not report controlling for sex or report results by sex with the exception of the trial by Dugan et al. (64,65). As there is insufficient evidence to suggest males and females would respond similarly, analysis by sex in future studies would be ideal as well as longer-term interventions to allow generalizability. Of the eight studies (51,56–58,61,62,64,66) that reported beneficial findings, intervention lengths ranged from 28 days to 24 weeks. Thus, it is possible that treatment durations of <28 days (69) were insufficient at inducing an effect. Finally, there seems to be a lack of observational studies on the relationship between dairy products or dairy proteins and inflammation, as only one observational study was

identified in our search. The cross-sectional study by Panagiotakos et al. (36) evaluated over 3000 overweight participants who consumed <8, 8–11, 11–14, or >14 dairy product servings/week and concluded dairy product consumption was inversely associated with inflammatory biomarker levels including CRP, IL-6, and TNF-α. Although other observational studies were identified in our search, they were subsequently excluded due to the lack of an appropriate control or relevant outcomes, thus more adequately designed observational studies using inflammatory markers as the primary outcome, could help to eliminate this knowledge gap.

Strengths of this systematic review include using the appropriate methodology for conducting nutrition-related systematic reviews and ensuring that only relevant studies were included (41–44). In addition, the inclusion of studies examining the effects of dairy proteins on biomarkers of inflammation was, to our knowledge, a novel aspect to this review. Finally, we did not impose any restrictions on publication date in our search strategy to allow for a more thorough search. Limitations of this review include restricting our search strategy to two databases and inclusion of trials published in English only, which could have resulted in overlooked eligible studies. We attempted to limit overlooked trials by reviewing reference lists from relevant review articles (38–40,46–48). In addition, we did not conduct a quantitative analysis; however, the systematic review by Bordoni et al. (39) and the recent validation study by Byrd et al. (87), which both utilized inflammatory scores, came to similar conclusions. Lastly, we did not include studies that examined the role of dairy on inflammatory biomarkers in subjects with inflammatory disorders, limiting the generalizability of the findings.

The preponderance of the evidence shows that consumption of dairy products or dairy proteins does not adversely affect biomarkers of inflammation in healthy and overweight or obese individuals and potentially provides beneficial effects. The results of this study provide additional support for the role of dairy product consumption in reducing chronic disease risk. Further, research is warranted specifically on adequately and consistently designed trials and subsequent systematic review.

Author's contributions

KMN, BDA, and CJC designed the study and wrote the manuscript. KMN developed the search strategy and conducted the search. KMN and BDA reviewed abstracts and full-text articles and completed the data extraction and risk of bias assessment. All authors read and approved the final manuscript.

Disclosure statements

KMN and BDA have no relevant interests to declare. CJC is currently employed by the National Dairy Council.

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