Exploring the Links between Diet and Inflammation: Dairy Foods as Case Studies

Julie M Hess,[1] Charles B Stephensen,[2] Mario Kratz,[3] and Bradley W Bolling[4]

[1] National Dairy Council, Rosemont, IL, USA; [2] USDA Western Human Nutrition Research Center and Nutrition Department, University of California, Davis, Davis CA, USA; [3] Fred Hutchinson Cancer Research Center, Public Health Sciences Division, Seattle, WA, USA; and [4] University of Wisconsin-Madison, Department of Food Science, Madison, WI, USA

ABSTRACT

Systemic chronic inflammation may be a contributing factor to many noncommunicable diseases, including diabetes, cardiovascular disease, and obesity. With the rapid rise of these conditions, identifying the causes of and treatment for chronic inflammation is an important research priority, especially with regard to modifiable lifestyle factors such as diet. An emerging body of evidence indicates that consuming certain foods, including dairy foods like milk, cheese, and yogurt, may be linked to a decreased risk for inflammation. To discuss both broader research on diet and inflammation as well as research on links between individual foods and inflammation, the National Dairy Council sponsored a satellite session entitled "Exploring the Links between Diet and Inflammation: Dairy Foods as Case Studies" at the American Society for Nutrition's 2020 LIVE ONLINE Conference. This article, a review based on the topics discussed during that session, explores the links between diet and inflammation, focusing most closely on the relations between intake of dairy fat and dairy foods like milk, cheese, and yogurt, and biomarkers of inflammation from clinical trials. While there is currently insufficient evidence to prove an "anti-inflammatory" effect of dairy foods, the substantial body of clinical research discussed in this review indicates that dairy foods do not increase concentrations of biomarkers of chronic systemic inflammation. *Adv Nutr* 2021;12:1S–13S.

Statement of Significance: Research on the links between modifiable lifestyle factors, such as diet, and the systemic chronic inflammation that is associated with an increased risk of noncommunicable diseases is an important focus for public health. While much work remains to be done, the emerging body of evidence discussed in this review paper indicates that eating dairy foods like milk, cheese, and yogurt does not increase markers of inflammation. This review provides the most current overview of evidence on this topic.

Keywords: dairy, chronic disease, diet, inflammation, immune system

Introduction

Immune system activation and inflammation

Sensor cells of the innate immune system trigger inflammation.

The immune system has evolved in response to exposure to pathogenic microorganisms, including viruses, bacteria, fungi, and eukaryotic parasites (e.g., gut helminths) and is composed of "innate" and "adaptive" components. An immune response is initiated when sensor cells of the innate immune system, which are found in tissues throughout the body, encounter a pathogen. Sensor cells such as macrophages and dendritic cells express receptors that recognize specific components of microbial macromolecules, commonly referred to as microbial-associated molecular patterns (MAMPs). When receptors on sensor cells recognize MAMPs, they can identify to which broad class of pathogens the new pathogen belongs. Some examples of MAMP receptors include Toll-like receptor (TLR) 2, TLR3, and TLR4.

After recognizing a pathogen, both types of primary sensor cells (macrophages and dendritic cells) can trigger inflammation. Macrophage activation leads to local inflammation. Dendritic cells can also trigger inflammation, but they specialize in delivering antigens, short sequences of peptides from viral or bacterial proteins, to draining lymph nodes to initiate adaptive immune responses. This process involves the differentiation of naive B and T lymphocytes into effector and memory B and T cells, which are responsible for acutely fighting the infection and establishing immunologic memory of the pathogen (1).

Damage to host tissue that does not involve microorganisms can also activate innate sensor cells in a process called

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"sterile inflammation." Sterile inflammation is triggered by sensor cells recognizing damage-associated molecular patterns (DAMPs) using some of the same receptors that recognize MAMPs. TLR9, for example, is an MAMP receptor that can recognize viral double-stranded DNA and may also react to mitochondrial and nuclear DNA release from necrotic cells. Sterile inflammation can also be triggered by receptors that detect cellular damage (2). Sterile inflammation may also be driven by chronic exposure of macrophages to metabolic stimuli such as elevated concentrations of glucose, insulin, and SFAs (3, 4). Extracellular SFAs, including palmitic acid (16:0),which is the most abundant fatty acid in milk (5), can directly activate TLR4 signaling by macrophages. As recently reviewed (6), this activation can trigger production of proinflammatory cytokines. SFAs are also converted to membrane phospholipids, diacylglycerols, and ceramides (7) and may also contribute to inflammation in macrophages by increasing cellular stress. The sterile inflammation produced by these and other mechanisms occurs in adipose tissue depots and can be recognized in biopsy samples by the accumulation of macrophages and other inflammatory cells in "crown-like structures" that develop around stressed or dead adipocytes (8).

Local inflammation.

Stimulation of the innate immune system via MAMP (or DAMP) receptors activates macrophages to produce cytokines such as IL-1β, IL-6, and TNF-α. Immune cells also become more responsive to these cytokines by increased expression of cell-surface cytokine receptors. These cytokines initiate inflammation, including the expression of vascular cell adhesion molecule (VCAM)-1 on local endothelial cells, which facilitates adhesion and extravasation of leukocytes at the site of infection. Chemokines like IL-8 and monocyte chemoattractant protein (MCP)-1 are also produced by activated dendritic cells and macrophages (as well as fibroblasts or endothelial cells at the site of immune activation) to attract leukocytes to the site of infection. Leukocytes may include monocytes, activated to become macrophages at infection site, and neutrophils, which play a prominent role in clearing bacterial infections.

When local inflammation is successful, the infection is controlled, the stimulus for inflammation is removed, and inflammation resolves (1). With chronic inflammation such as is seen in adipose tissue with obesity, stimulation by DAMPs or metabolic stimuli is not resolved with local inflammation (9). For instance, macrophage activation in the wall of coronary arteries can lead to atherosclerosis (10) or chronic inflammation in adipose tissues in obesity (11). Chronic inflammation can also occur following MAMP stimulation due to microbial exposures.

Systemic inflammation and the acute phase response.

If the initial innate response does not stop spread of the pathogen, inflammation continues, and the growing concentration of cytokines in plasma may become high enough to cause systemic effects. For example, hepatocytes respond to IL-1β, IL-6, and TNF-α by increasing production of many positive acute phase proteins, such as C-reactive protein (CRP) and α1-acid glycoprotein (AGP), which have specific roles in pathogen clearance and tissue repair (12). Elevation of CRP concentrations or concentrations of other positive acute phase proteins signifies induction of an acute phase response (APR), which also involves decreased synthesis of negative acute phase proteins (e.g., retinol binding protein and albumin). The APR can be induced rapidly. Plasma CRP concentrations can increase within hours of the initial stimulus from a baseline of $\leq$1 mg/L in healthy individuals to concentrations $>$100 mg/L in the case of bacterial infections such as pneumonia. Once the infection is resolved, concentrations rapidly decrease.

During the APR, the bone marrow may respond by increasing production of innate immune cells such as monocytes, neutrophils, eosinophils, and basophils. The central nervous system responds by inducing fever, lethargy, and anorexia. The muscle may respond by catabolizing protein for glucogenic amino acids to maintain blood glucose. While the APR resolves quickly after an infection, this resolution is not true in the case of chronic inflammatory diseases where the underlying source of inflammation persists. For example, CRP may be chronically elevated in obesity due to persistent underlying inflammation (13).

Adaptive immunity to pathogens.

Adaptive immunity is an important component of protection against infectious diseases. Innate and adaptive immunity provides a coordinated response depending on the type of pathogen involved. Type 1 immunity develops in response to viral and intracellular bacterial infections and involves development of T-helper (Th) type 1 (Th1) cells that produce IFN-γ, cytotoxic T cells that target host cells infected by viruses for death via apoptosis, and innate cells like macrophages that are supported at sites of infection by Th1 cells. Type 2 immunity develops in response to parasitic

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Address correspondence to JMH (e-mail: jmhess@umn.edu).

Abbreviations used: AGP, α1-acid glycoprotein; APR, acute phase response; CRP, C-reactive protein; DAMP, damage-associated molecular pattern; DGA, Dietary Guidelines for Americans; GMP, glycomacropeptide; HLA-DR, human leukocyte antigen-DR isotype; hs-CRP, high-sensitivity C-reactive protein; iAUC, incremental AUC; ICAM, intercellular adhesion molecule; MAMP, microbial-associated molecular pattern; MCP, monocyte chemoattractant protein; RCT, randomized controlled trial; Th, T-helper; TLR, Toll-like receptor; TNFR, TNF receptor; VCAM, vascular cell adhesion molecule.

infections and involves the development of Th2 cells that produce IL-4, IL-5, and IL-13 as well as innate cells such as eosinophils, basophils, and mast cells that help clear intestinal helminth infections. Type 3 immunity develops in response to extracellular bacterial infection and involves the development of Th17 cells that produce cytokines that can elicit neutrophil responses (IL-17) and activate epithelial cells to produce antimicrobial peptides (IL-22). A fourth type of T-helper cell is the T-regulatory (Treg) cell, which can act to dampen the activity of the "proinflammatory" T-helper cells by direct interaction and production of the cytokines IL-10 and transforming growth factor-β.

All of these types of immunity also involve the development of antibody responses generated by B cells. Naive B cells develop into memory B cells and plasma cells. Plasma cells reside in the bone marrow or at submucosal sites and produce antibodies, including the principal serum antibody IgG and the principal antibody produced at mucosal sites, IgA, that is secreted across epithelial surfaces (1).

Adaptive immunity in chronic inflammatory disease.
Adaptive immunity is an important component of autoimmune diseases where failure of regulatory mechanisms allows an adaptive immune response to self-antigens. Autoimmune diseases including type 1 diabetes and multiple sclerosis involve type 1 and 3 immunities as well as activation of the innate immune system (14, 15). Other chronic inflammatory conditions also involve adaptive immunity. In the respiratory tract, type 2 adaptive immunity plays a role in allergic asthma (16), and in the intestinal tract, an adaptive response to commensal bacteria may be a key inducer of irritable bowel syndrome (17). Type 1 adaptive immunity develops in obesity and related conditions, and Th1 cells have been found in inflamed adipose tissue. However, it remains unclear which specific antigens trigger clonal expansion of lymphocytes and accumulation of Th1 cells in adipose tissue (18). While chronic inflammatory diseases often have a prominent innate immune system component, adaptive immune cells may also play a significant role.

Measuring immune system activation and inflammation in human studies

Nutrition intervention studies are conducted to assess the impact of consuming foods and beverages on a variety of inflammatory diseases, from infectious diseases to autoimmune disease to metabolic diseases associated with obesity to intestinal inflammatory conditions associated with the intestinal microbiota. The markers of inflammation assessed within specific studies depend on the type of inflammation being studied.

The review of immune activation in the following paragraphs can serve as a guide to aspects of innate and adaptive immunity that should be examined in nutrition intervention studies. Recent review articles have detailed immune markers that may be the most useful endpoints to include in nutrition intervention studies (19, 20); therefore, only a brief overview is provided below.

Plasma markers.
Human studies typically use peripheral blood from fasting individuals to assess changes in inflammation and immune activation over time. These studies often measure concentrations of plasma cytokines like TNF-α and IL-6, or of soluble cytokine receptors such as TNF receptor-1 (TNFR-1), that are produced by innate immune activation. Nutrition intervention studies also frequently measure acute phase proteins that indicate a systemic APR such as CRP, serum amyloid A, and AGP. Plasma markers of vascular activation (as a result of local inflammation) may also be assessed. These markers include VCAM-1 and intercellular adhesion molecule (ICAM)-1. Adipokines like leptin or adiponectin, signaling molecules produced by adipocytes that also play a role in regulating inflammation, are often useful to examine, especially in relation to obesity (21). Finally, concentrations of neopterin, a guanidine metabolite and marker of macrophage activation, are often assessed in infectious disease studies that evaluate type 1 immune activation (22). Among the biomarkers of inflammation most consistently associated with chronic disease risk are fasting plasma CRP, IL-6, and adiponectin (23).

Leukocyte concentrations and activation.
Complete blood counts with a differential count of leukocytes (neutrophils, eosinophils, basophils, lymphocytes, and monocytes) and platelets can also be useful indicators of inflammatory disease activity and can be used either by themselves or as ratios (e.g., neutrophil-to-lymphocyte ratio) (24). Blood counts are also readily available in clinical settings.

Neutrophils, monocytes, and eosinophils are the most abundant innate immune cells found in blood, and their level of activation may be assessed using cell-surface expression of proteins involved in normal cellular process that are upregulated via DAMP or MAMP exposure. For example, CD11b is used as a marker of monocyte and neutrophil activation. Along with CD18, it forms the cell adhesion molecule αM-integrin and in studies of cardiovascular disease risk it has been quantified on the surface of blood monocytes (25). CD11b can also be used on T lymphocytes to gauge level of activation. Both cell types—monocytes and T cells—were examined in this manner in the Prevención Con Dieta Mediterŕanea (PREDIMED) study, which examined the effect of a Mediterranean diet on several aspects of health including chronic inflammation and immune activation (26).

Increased expression of major histocompatibility complex (MHC) molecules such as human leukocyte antigen-DR isotype (HLA-DR) also signifies monocyte and T-cell activation. Changes in HLA-DR expression on all monocytes, or on monocyte subsets characterized by CD14 and CD16 expression into classical or alternative phenotypes, may be useful in intervention trials involving nutrition or physical activity interventions (27). Further examples of methods for assessing activation of innate and adaptive immune cells are provided in recent reviews (19, 20).

Current Status of Knowledge

Dietary factors and inflammation

Nutrition, along with weight, alcohol intake, physical activity, and other factors, is considered a modifiable risk factor for chronic diseases associated with systemic inflammation. Dietary factors such as fiber, antioxidants, and omega-3 fatty acids have been associated with decreased concentrations of markers of inflammation, whereas other factors such as saturated fat and sodium have been associated with increased levels of inflammation (28).

Yet, due to the inherent complexity of both inflammation and nutrition science, many details remain unknown about broader links between different dietary factors, including consumption of specific foods, and the elevated markers of immune activation seen in chronic disease states. This article explores the current evidence on the relation between consuming dairy foods and inflammation, focusing on randomized controlled human intervention trials as well as meta-analyses and systematic reviews of clinical trials that evaluate the associations between intake of total dairy, specific dairy foods (milk, cheese, and yogurt), and dairy fats with biomarkers of inflammation. The dairy foods milk, cheese, and yogurt were selected as the focus of this review, because these are the dairy foods recommended for consumption in the 2015–2020 Dietary Guidelines for Americans (DGA) (29). The literature review in this paper is divided into 2 sections: a review of studies that assess links between total dairy and dairy fat intake with biomarkers of inflammation and a review of studies that assess links between specific dairy foods and biomarkers of inflammation.

Literature review: impact of total dairy food intake and dairy fat intake on biomarkers of systemic inflammation

We conducted a literature search for randomized controlled trials (RCTs) and meta-analyses or systematic reviews of RCTs that assessed effects of total dairy intake (milk, cheese, and yogurt) or dairy fat intake (i.e., by comparing the effects of fat-free or low-fat vs. whole-fat dairy products) on biomarkers of chronic systemic inflammation in fasting blood. Biomarkers of systemic inflammation considered include CRP, IL-1β, IL-6, IL-8, TNF-α, MCP-1, adiponectin, and leukocyte numbers. Exposures of interest included cow-milk dairy foods, such as milk, yogurt, and cheese, and excluded studies with products not recommended by the DGA (29) like cream, butter, ice cream, dairy foods supplemented with additional vitamins or minerals, and components of dairy foods like whey and casein. Animal studies as well as studies that focused on biomarkers of inflammation in tissues or biomarkers of postprandial inflammation were excluded from this portion of the review. The following search terms were used: "(dairy[TI] OR milk[TI] OR yogurt[TI] OR joghurt[TI] OR cheese[TI]) AND (inflammation[TI] OR "c-reactive"[TI] OR CRP[TI] OR interleukin[TI]) NOT "dairy cows"[TI]."

We identified 1 meta-analysis, 2 systematic reviews, and an additional 7 RCTs that were not covered in the systematic reviews or meta-analysis due to their more recent publication dates. We also identified 4 observational studies (30–33), which were excluded due to the comprehensive and fairly conclusive evidence from a variety of RCTs. The limited data from observational studies are in alignment with conclusions from RCTs and suggest no association between total dairy intake and biomarkers of systemic inflammation and no or a modestly inverse association between full-fat dairy intake and biomarkers of systemic inflammation. One of the RCTs identified from this search will be discussed in a subsequent section of this review (34).

Meta-analyses and systematic reviews.

The meta-analysis by Benatar et al. (35) summarized 6 RCTs (36–41) and found no difference in fasting plasma CRP between the high-dairy and low-dairy diets, independent of whether the dairy-rich diets consisted of low-fat or full-fat dairy foods. A limitation of this meta-analysis was that CRP was the only biomarker of inflammation considered. A 2013 systematic review by Labonté et al. (42) included results from 8 RCTs on the impact of a dairy-rich diet compared with a low-dairy diet on biomarkers of inflammation in adults with overweight or obesity. Similar to the results from Bordoni et al. (43), discussed below, this systematic review found that consuming dairy foods did not increase the blood concentration of biomarkers of low-grade systemic inflammation in adults with overweight or obesity.

In a more inclusive systemic review, Bordoni et al. (43) used an "inflammatory score" to evaluate the results of 52 trials focused on dairy effects on biomarkers of inflammation. This scoring system provides a single metric to summarize the impact of dairy foods on 98 biomarkers of inflammation commonly measured in nutrition- and food-related studies, given the complexity of inflammation and the impossibility of characterizing it with a single biomarker. Bordoni et al. (43) found that the "inflammatory score" was lower, overall, in diets containing dairy, with similar results in studies with low-fat and high-fat dairy foods. Interventions with fermented dairy foods lowered biomarkers of inflammation, while interventions with nonfermented dairy foods did not. Furthermore, the authors noted that dairy interventions seemed to exert stronger anti-inflammatory activity in participants with metabolic disorders (including overweight and obesity) and a proinflammatory effect in participants with allergies to bovine milk. Overall, interventions in dairy foods exerted a weakly anti-inflammatory effect in individuals without a sensitivity or allergy to dairy foods, especially those interventions with fermented dairy foods. These studies are summarized in **Table 1**.

Randomized controlled trials.

Results from several additional RCTs published in recent years that were neither covered in the meta-analysis nor the 2 systematic reviews provide some of the strongest evidence on the impact of dairy foods on biomarkers of chronic inflammation. More detail on these studies can be found in **Table 2**.

TABLE 1 Summary of meta-analyses and systematic reviews assessing the impact of dairy food intake on biomarkers of chronic systemic inflammation[1]

Study (reference)	Type of study	Participants	Inflammatory markers assessed	Intervention or exposure variables	Results
Benatar et al. (35)	Meta-analysis	$n = 451$ individuals; 69% female in 6 RCTs that assessed inflammation	CRP	Impact of high vs. low dairy intake or low-fat or high-fat dairy intake on change in CRP	No overall difference in CRP between the high-dairy and low-dairy diets and no effect on CRP with high-fat vs. low-fat dairy intake
Labonté et al. (42)	Systematic review	Overweight or obese adults ≥18 y assessed in 8 RCTs	CRP, IL-6, TNF-α, adiponectin, MCP-1, and TNFR-1	Impact of high vs. low dairy diet on biomarkers of inflammation	Consuming dairy foods did not have an adverse impact on biomarkers of low-grade systemic inflammation
Bordoni et al. (43)	Systematic review	Healthy adults and adults with metabolic and cardiometabolic disorders, gastrointestinal disorders, food hypersensitivity or allergy to dairy products, and other conditions including lung disease, infection, and joint disease assessed in 52 RCTs	Inflammatory score reflecting data from 98 biomarkers of inflammation including adiponectin, B lymphocytes, basophils, CRP, IL-1β, IL-6, IL-8, IL-13, IL-4, IL-5, macrophages, monocytes, neutrophils, TNF-α, and VCAM-1, among many others	Impacts of diets containing low-fat and high-fat dairy foods as well as diets providing fermented and nonfermented dairy foods on inflammatory biomarkers	"Inflammatory scores" were lower, overall, in diets containing dairy, with similar results in studies with low-fat and high-fat dairy foods. Interventions with fermented dairy foods lowered biomarkers of inflammation. Interventions with nonfermented dairy foods did not. Interventions with dairy foods exerted a weakly anti-inflammatory effect in individuals without a sensitivity or allergy to dairy foods.

[1] CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1; RCT, randomized controlled trial; TNFR-1, TNF receptor 1; VCAM-1, vascular cell adhesion molecule-1.

The first trial worth discussing in some detail is a randomized controlled crossover trial specifically designed to assess the impact of dairy on biomarkers of inflammation by Labonté et al. (44). Healthy men and women with low-grade systemic inflammation consumed either a dairy-rich diet or a control diet for 4 wk. The dairy diet did not differentially affect IL-6 or adiponectin concentrations compared with the control diet limited in dairy. The concentration of CRP decreased in both intervention groups, to an extent that was slightly, but statistically significantly greater in the control group. Despite this significant differential change, because the CRP concentration was still reduced from baseline in the dairy group, the effect size was small. No differential impact was seen for IL-6 and adiponectin, and the authors concluded that these data "suggest that short-term consumption of a combination of low- and high-fat dairy products as part of a healthy diet has no adverse effects on inflammation."

In a smaller study (45), dairy consumers with metabolic syndrome participated in a crossover study where they consumed a diet rich in low-fat dairy or a carbohydrate-rich control diet. There were no differences in impact on biomarkers of inflammation between the diets in men; however, women had lower TNF-α ($P = 0.028$) and MCP-1 ($P = 0.001$) concentrations after consuming the dairy diet, which may have been due to slight differential weight loss that occurred during the dairy intervention in women.

A randomized parallel-intervention study from Raziani et al. (46) assessed differences in CRP concentrations among participants assigned to 12 wk of a whole-fat cheese intervention, low-fat cheese intervention, or a nondairy carbohydrate-rich control. Fasting plasma CRP, an exploratory endpoint and the only biomarker of inflammation included, did not change by intervention group. While this study was limited by only offering interventions with cheese

TABLE 2 Summary of RCTs comparing impacts of low-fat and whole-fat dairy on biomarkers of chronic systemic inflammation[1]

Study and reference	Type of study	Participants	Inflammatory markers assessed	Intervention	Results
Labonté et al. (44)	Randomized crossover trial	$n = 112$ healthy men and women 18 to 70 y with low-grade systemic inflammation indicated by hs-CRP >1 mg/L and <10.0 mg/L	hs-CRP, IL-6, adiponectin	Participants randomized to consume a dairy-rich diet (375 mL of low-fat milk, 175 g of low-fat yogurt, 30 g of whole-fat cheddar cheese) or a control diet (fruit juice, vegetable juice, cashew nuts, cookie) for 4 wk before switching to the other diet, following a washout period of 4–8 wk	Dairy diet did not differentially affect IL-6 or adiponectin concentrations compared to the control diet limited in dairy. Concentration of hs-CRP decreased in both intervention groups, to an extent that was slightly, but significantly, greater than the control group. Authors concluded that "short-term consumption of a combination of low- and high-fat dairy products as part of a healthy diet has no adverse effects on inflammation."
Dugan et al. (45)	Randomized crossover trial	$n = 37$; 13 male and 24 female low-dairy consumers with metabolic syndrome	CRP, TNF-α, and MCP-1, and others	Participants randomized to consume diet rich in low-fat dairy (300 mL 1% milk, 180 g of nonfat yogurt, and 120 g of 2% cheese per day) or a carbohydrate-rich control diet (45 g granola bar and 360 mL of juice per day) for 6 wk with a 4-wk wash-out in between phases	There were no differences in impact on biomarkers of inflammation between the diets in men; however, women had lower TNF-α ($P = 0.028$) and MCP-1 ($P = 0.001$) concentrations after consuming the dairy diet, which may have been due to slight weight loss that occurred during the dairy intervention in women.
Raziani et al. (46)	Randomized parallel-intervention study	$n = 139$ adults with $\geq$2 metabolic syndrome risk factors completed the study; 92 females and 47 males	Fasting plasma CRP	Participants were randomized to 12 wk of a whole-fat cheese intervention (80 g/10 MJ Danbo (Riberhus; Arla)and cheddar cheeses), low-fat cheese intervention (80 g/10 MJ low-fat Danbo and cheddar cheese), or a nondairy carbohydrate-rich control (white wheat bread and jam)	No significant differential changes in weight or BMI. Fasting plasma CRP, an exploratory endpoint and the only biomarker of inflammation included, did not change by intervention group.

(*Continued*)

TABLE 2 (*Continued*)

Study and reference	Type of study	Participants	Inflammatory markers assessed	Intervention	Results
Bendtsen et al. (47)	Parallel-design RCT	$n = 52$ participants (age: 44 ± 1 y) with obesity; 11 males and 69 females	Fasting plasma hs-CRP	Participants randomized to follow hypocaloric diets for 24 wk: low-dairy diet group consumed <600 mg of calcium per day, while those in the high-dairy group 1500 mg of calcium per day (with 1200 mg consumed from dairy foods)	No differential changes in body weight or fat mass and no statistically significant differences in the change in fasting plasma hs-CRP (an exploratory endpoint) between the groups.
Eelderink et al. (48)	Randomized crossover study	$n = 45$ participants (age: 58.9 ± 4.3 y) who were overweight and postmenopausal (for 25 females in the study)	Fasting plasma hs-CRP	Participants completed 2 phases of 6 wk each, separated by a 4-wk washout of a *1*) high-dairy diet including 5–6 servings per day of dairy foods, with 1 serving defined as 200 g of low-fat yogurt, 30 g of low-fat cheese, or 250 mL of low-fat milk, and *2*) low-dairy diet with <1 serving of dairy foods per day	Fasting plasma hs-CRP was 1.00 mg/L at the end of the low-dairy diet compared to 1.20 mg/L after the high dairy diet ($P = 0.065$). Results indicated a slightly, but significantly, higher body weight (by 0.4 kg) after the high-dairy diet, with a trend for higher fat mass (by 0.5 kg).
Schmidt et al. (51)	RCT	$n = 67$ adults (age 46 to 68) with metabolic syndrome	Fasting plasma CRP, IL-6, and adiponectin	Participants completed 12-wk intervention diets containing either 3.3 servings per day of nonfat milk, nonfat yogurt, and low-fat cheese (low-fat dairy group), 3.3 servings per day of full-fat milk, yogurt, and cheese (full-fat dairy group), or a control diet limited in dairy	Among 59 participants that were included in analyses of biomarkers of low-grade systemic inflammation, no differential effect of the 3 intervention diets was seen for hs-CRP, IL-6, and total adiponectin in fasting plasma.

[1] CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; MCP-1, monocyte chemoattractant protein-1; RCT, randomized controlled trial.

and assessing only 1 biomarker of inflammation, its results are in line with those of Dugan et al. (45) and Labonté et al. (44). The dairy-rich diets, even one containing whole-fat cheese, did not trigger an increase in a key biomarker of inflammation. Bendtsen et al. (47) assessed the impact of hypocaloric diets with high or low amounts of dairy foods in a 24-wk parallel-design RCT. The researchers observed no differential changes in body weight or fat mass and no statistically significant differences in the change in fasting plasma high-sensitivity CRP (hs-CRP) between the groups.

In another recent study by Eelderink et al. (48), middle-aged, overweight men and postmenopausal women were assigned in a randomized crossover study to high- and low-dairy diets. The results indicated a slightly, but significantly, higher body weight (by 0.4 kg) after the high-dairy diet, with a trend for higher fat mass (by 0.5 kg). Fasting plasma hs-CRP, measured as an exploratory endpoint, was 1.00 mg/L at the end of the low-dairy diet compared with1.20 mg/L after the high-dairy diet ($P = 0.065$). This statistical trend may indicate a slight increase in low-grade systemic inflammation with a higher dairy diet. Sensitivity analyses that adjusted for differential changes in body weight or fat mass were not conducted. However, Eelderink et al. conducted secondary post hoc analyses to assess differences among metabolically different subgroups based on BMI and other factors and did not identify differences in BMI as the basis for the trend increase in hs-CRP among those consuming the high-dairy diet. While some previous studies have indicated that eating dairy foods may contribute to higher body weight (49) and higher BMI (50), in the results of this study it remains unclear

whether the small increase in plasma CRP is due to the dairy per se or to the associated increase in body weight with the high-dairy diet.

Last, Schmidt et al. (51) randomly assigned 67 men and women with the metabolic syndrome to follow 1 of 3 intervention diets: 3.3 servings per day of low-fat and fat-free dairy, 3.3 servings of whole-fat dairy, or limited dairy. No differential effect of the 3 intervention diets was seen for hs-CRP, IL-6, or total adiponectin in fasting plasma. This study again indicated that diets rich in dairy, whether low-fat or full-fat, do not differentially affect measures of systemic inflammation compared with a diet low in dairy products.

The available evidence consistently demonstrates that diets rich in dairy foods do not differentially affect the concentration of biomarkers of systemic inflammation such as hs-CRP, IL-6, TNF-α, or adiponectin in fasting blood. With very few exceptions, this null effect is seen across numerous well-designed studies with a variety of intervention durations, participant characteristics, types and amounts of dairy foods studied, a wide variety of control foods, and a variety of biomarkers of inflammation included as endpoints. While questions remain whether a diet rich in dairy may have mild anti-inflammatory effects under some circumstances or in some populations, the available literature does provide strong evidence that dairy foods are not generally proinflammatory, with the notable exception of individuals with allergies to dairy.

Impact of Eating Yogurt or Cheese on Biomarkers of Systemic Inflammation

Systematic reviews.

This second portion of the review focuses on studies that assessed links between specific dairy foods like yogurt or cheese and biomarkers of inflammation. Systematic reviews of RCTs have evaluated the evidence linking intake of individual dairy foods with markers of inflammation and report similar results to those discussed in the sections on total dairy food intake and dairy fat intake above. The most recent systematic review (28) identified 19 RCTs on dairy food consumption that also assessed biomarkers of inflammation (CRP, IL-6, TNF-α, MCP-1, ICAM-1, and VCAM-1). Eighteen of the trials reviewed reported either no impact of dairy food intake on inflammation or an anti-inflammatory effect of dairy food intake (28). Six of these studies evaluated the impact of milk, specifically, compared with an isocaloric beverage or no milk in healthy overweight or obese adults. While inflammatory biomarkers were not the primary outcomes in 4 of the studies, "a majority of the trials reported no significant differences in CRP, cytokines, or other inflammatory markers" (28). A 2019 systematic review reported similar results, with a majority of the 16 studies it reviewed finding a neutral or anti-inflammatory impact of milk or other dairy food intake among both healthy individuals and those with metabolic abnormalities like obesity or other chronic diseases (52). This 2019 systematic review included studies with a wide range of inflammatory markers as primary outcomes, including but not limited to CRP, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, TNF-α, and MCP-1, and the expression of proinflammatory genes in peripheral blood mononuclear cells as well as 5 studies on specific dairy products, including milk, yogurt, and kefir (52).

Randomized controlled trials.

Several RCTs have assessed the ability of yogurt and cheese, specifically, to impact postprandial or chronic inflammation (34, 53–55). These studies are summarized in **Table 3**.

An RCT evaluated the impact of yogurt intake on biomarkers of chronic inflammation and endotoxin exposure in healthy women (34, 53). In this study, women with obesity [body mass indices, or BMI (in kg/m^2), between 30 and 40] and women without obesity (BMI: 18.5–27) consumed either a commercial low-fat yogurt or a nondairy soy pudding control with a similar macronutrient content (34, 53). Fasted participants consumed 226 g of yogurt or the control food for breakfast, immediately prior to consuming a high-fat, high calorie challenge meal to induce postprandial inflammation. Eating yogurt before the challenge meal reduced postprandial IL-6 net incremental AUC (iAUC) in participants with or without obesity compared with participants consuming the control food ($P = 0.033$). Likewise, postprandial LPS binding protein (LBP):plasma soluble CD14 (sCD14) net iAUC was lower in yogurt consumers compared with those who consumed the control food ($P = 0.031$). Participants with obesity who consumed yogurt had higher postprandial sCD14 net iAUC than those consuming the control food, but this was not apparent in nonobese participants ($P = 0.032$ for obesity $\times$ treatment interaction). These data suggest that premeal yogurt consumption may modestly reduce acute postprandial inflammation induced by a high-fat, high-calorie challenge meal in women.

To examine the effect of the repeated consumption of yogurt on fasting markers of inflammation, participants consumed 339 g of yogurt or the control food daily for an additional 9 wk and repeated analysis of fasting and postprandial markers of inflammation (34, 53). The change in fasting plasma TNF-α/sTNFRII was less than the change in control foods ($P = 0.0013$, treatment). However, changes in fasting concentrations of IL-6 and hs-CRP were no different than in the control groups. Changes in the LBP to sCD14 ratio were significantly less in yogurt consumers than in the control groups ($P = 0.0477$, treatment). Concentrations of sCD14 itself, the primary outcome of the study, remained no different between groups. Pei et al. (34, 53) concluded that regular consumption of low-fat yogurt over a 9-wk period modestly reduced fasting biomarkers of chronic inflammation and low-grade endotoxemia in women relative to those consuming the nondairy control food.

Yogurt consumption also inhibited postprandial and short-term inflammation in a study conducted in 14 healthy men (54). Participants consumed either yogurt supplemented with *Lactobacillus rhamnosus* GG or acidified milk as part of a randomized, double-blind crossover trial. The

TABLE 3 Summary of RCTs comparing the impacts of eating yogurt or cheese on biomarkers of inflammation[1]

Study and reference	Type of study	Participants	Inflammatory markers assessed	Intervention	Results
Pei et al. (76)	RCT	$n = 120$ premenopausal females (60 with obesity and 60 without obesity)	IL-6, TNF-α, soluble TNF II (sTNF-RII), hs-CRP, LBP:sCD14	Participants consumed 339 g of yogurt or 324 g of soy pudding daily for 9 wk.	Eating low-fat yogurt over a 9-wk period modestly reduced fasting biomarkers of chronic inflammation and low-grade endotoxemia in women relative to those consuming the nondairy control food.
Pei et al. (34)	RCT	$n = 120$ premenopausal females (60 with obesity and 60 without obesity)	IL-6, TNF-α, LBP:sCD14	Participants consumed either 226 g of a commercial low-fat yogurt or a nondairy soy pudding control snack ($n = 30$ participants/group) with similar macronutrient content immediately prior to consuming a high-fat, high-calorie challenge meal.	Premeal yogurt consumption modestly reduced acute postprandial inflammation induced by the high-fat, high-calorie challenge meal.
Burton et al. (54)	Randomized, double-blind crossover trial	$n = 14$ healthy males of normal weight	TNF-α, IL-6	Participants consumed either yogurt supplemented with *Lactobacillus rhamnosus* GG or acidified milk. Each trial phase included a 4-wk run-in period, during which participants consumed 400 mL per day of whole milk, followed by a 2-wk intervention phase during which participants consumed 400 g/d of yogurt or acidified milk and underwent 2 postprandial tests. The first day of each intervention, the postprandial response of participants to 800 g of their assigned intervention foods was assessed. At the end of the intervention period, participants consumed 400 g of the intervention food prior to a high-fat challenge meal.	Both probiotic yogurt and acidified milk reduced postprandial inflammatory markers linked to high-fat meals
Schmid et al. (58)	Randomized crossover trial	$n = 19$ healthy males (age: 41.8 ± 9.0 y) with BMI of 27.8 ± 8.2 kg/m^2	CRP, IL-6, TNF-α	Participants randomized to consume: a high-fat dairy meal, high-fat nondairy meal eaten with milk, and a high-fat nondairy control meal.	Dairy fat, largely from cheese, did not impact measures of postprandial inflammation relative to other nondairy mixed meals.

(*Continued*)

TABLE 3 (*Continued*)

Study and reference	Type of study	Participants	Inflammatory markers assessed	Intervention	Results
Brassard et al. (55)	RCT	$n = 92$ males and females with abdominal obesity defined as waist circumference ≥94 cm for men or ≥80 cm for women	hs-CRP	Participants consumed 1 of 5 diets for 4 wk each with 4-wk washouts in between: a diet rich in saturated fat from cheese, a diet rich in saturated fat from butter, a diet rich in MUFAs, a diet rich in PUFAs, or a low-fat, high-carbohydrate diet.	Concentrations of hs-CRP were not different between interventions. The intake of cheese relative to other fat sources, and even compared to a low-fat diet, did not impact hs-CRP.

[1] CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; LBP, LPS binding protein; RCT, randomized controlled trial.

probiotic yogurt and acidified milk both decreased concentrations of biomarkers of inflammation (iAUC TNF-α, IL-6, and chemokine ligand 5) when compared with baseline tests conducted while participants were consuming plain whole milk ($P < 0.001$). Changes in inflammation biomarker concentrations were related to differences in the fecal microbiota, postprandial insulin concentrations, downregulation of inflammatory transcriptome in cells recovered from blood, and modulation of the plasma metabolome (54, 56, 57). The authors therefore concluded that both probiotic yogurt and acidified milk could reduce postprandial inflammation linked to high-fat meals and impact the gut microbiota of healthy men, indicating potential for a treatment of chronic low-grade inflammation.

Schmid et al.'s (58) randomized crossover trial of 19 healthy males assessed the differences between a high-fat dairy meal, high-fat nondairy meal eaten with milk, and a high-fat nondairy control meal on markers of postprandial inflammation. Changes in postprandial IL-6 and TNF-α 6 h after consuming the meals were not different between groups. The authors concluded that dairy fat, largely from cheese, did not appear to impact postprandial inflammation relative to other nondairy mixed meals.

Finally, a randomized crossover trial assessing the impact of consuming SFAs from dairy foods (cheese and butter) on cardiometabolic risk factors also evaluated hs-CRP (55). Men and women with abdominal obesity consumed diets rich in either saturated fat (from dairy foods), MUFAs, PUFAs, or a low-fat and high-carbohydrate diet. Concentrations of hs-CRP were not different between interventions. The intake of cheese relative to other fat sources, and even compared with a low-fat diet, did not impact the inflammatory marker hs-CRP.

Interventions providing yogurt seem to acutely elicit a neutral or beneficial impact on biomarkers of inflammation, while interventions with other dairy foods like cheese seem to be neutral. However, more research is needed to understand the details of these relations.

Fermented milk bioactives

To provide additional context, a brief overview of the bioactive components in fermented dairy foods that may be responsible for its impact on inflammation is provided below. Interactions between the proteins, lipids, carbohydrates, vitamins, and minerals that make up the milk matrix, or structure, are altered by milk processing and fermentation (59–61). The microbes used to produce fermented dairy foods like yogurt and cheese may interact with the gut microbiota or produce metabolites that impact immune function upon consumption. Protein metabolism can be altered by the fermented dairy matrix and interactions with bioactive proteins, as reviewed elsewhere (62).

Bioactive proteins and lipids in milk can exert anti-inflammatory effects, which may contribute to a negative association between dairy food consumption and biomarkers of inflammation. Milk contains both casein and whey proteins. Whey proteins include α-lactalbumin and β-lactoglobulin as well as less abundant proteins such as lactoferrin (63). Dietary whey protein, α-lactalbumin, and lactoferrin reduce inflammation in rodent models of chronic disease (64, 65). In isolation, these proteins may exert anti-inflammatory activity by inhibiting colonic inflammation, improving intestinal barrier function, or modulating cytokines (64, 65). The milk-fat globule membrane also contains bioactive components such as phospholipids and sphingolipids that may also exert anti-inflammatory effects (66). Although polar lipids are a fraction of total milk lipids, preclinical studies indicate that they may protect against inflammation (67).

Fermenting milk into products like cheese and yogurt alters the dairy matrix and may contribute to the differences in health impacts observed with these products in comparison to fluid milk (68). During cheesemaking, proteolysis of κ-casein by chymosin liberates glycomacropeptide (GMP), a bioactive glycoprotein that has been isolated from cheese whey and may have immunomodulatory properties (69). In a preclinical study, GMP modulated cecal SCFA production and dampened IFN-γ production in splenic CD8+ T cells stimulated with phorbol 12-myristate 13-acetate, and ionomycin (70). Sawin et al. (70) concluded that this prebiotic activity of GMP, in stimulating SCFA production and reducing the prevalence of sulfate-reducing bacteria like *Desulfovibrio*, may, in part, explain how GMP exerts its anti-inflammatory effects.

The cultures in cheese and yogurt may also interact with the intestinal barrier, gut microbiota, and immunocytes (71–73). Metabolites produced by these cultures also interact with the immune system. As one example, exopolysaccharides synthesized by *Streptococcus thermophilis* and other bacterial strains commonly used to make fermented dairy foods may dampen inflammation (74, 75). The profile of putative bioactive components that may contribute to the impact of dairy foods on inflammation can vary significantly among different dairy foods. However, evidence for the anti-inflammatory activity of components of cultured dairy is mainly derived from cell-based assays and experiments in rodents. Due to differences in metabolism, the complexity of dietary patterns, and immune function between these models and humans, clinical intervention studies must also be assessed to better understand and characterize the impact of consuming individual dairy foods on immune function in humans.

Conclusions

While there is insufficient evidence to recommend specific dairy foods as "anti-inflammatory," the substantial body of clinical research discussed in this review indicates that dairy foods do not increase concentrations of biomarkers of chronic systemic inflammation. Future research to identify more clearly whether certain dairy foods, particularly yogurt, may even exert anti-inflammatory effects, and—if so—through which mechanisms, would enhance our understanding of the relation between dairy foods and chronic inflammation further.

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