Impact of dairy products on biomarkers of inflammation: a systematic review of randomized controlled nutritional intervention studies in overweight and obese adults

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ABSTRACT

Background: Recent data from cross-sectional studies suggest that consumption of dairy products is inversely associated with low-grade systemic inflammation, but a cause-and-effect relation can be confirmed only with results from randomized controlled trials.

Objective: We reviewed the results of randomized controlled nutritional intervention studies that have assessed the impact of dairy product consumption (ie, milk, yogurt, and/or cheese) on biomarkers of inflammation in adults (aged ≥18 y).

Design: We performed a systematic literature search in PubMed in April 2012, which was limited to randomized controlled trials in humans published in English. Studies that included pregnant or lactating women or that did not include a low-dairy control intervention were excluded.

Results: Eight trials that were conducted in overweight or obese adults were included in the review. The only study that had identified change in the inflammatory profile as its primary outcome measure showed that dairy food consumption improved pro- and antiinflammatory biomarker concentrations compared with the low-dairy control diet. Three of the 7 studies in which inflammation was a secondary or undefined outcome showed improvement in key inflammatory biomarkers, ie, C-reactive protein, IL-6, or TNF-α after dairy product consumption, whereas the other 4 studies showed no effect.

Conclusions: Dairy product consumption does not exert adverse effects on biomarkers of inflammation in overweight or obese adults. Several methodologic factors and limitations among existing studies do not allow differentiation between a beneficial or neutral impact of dairy products on inflammation. Further studies specifically designed to assess inflammation-related outcomes are warranted. Am J Clin Nutr 2013;97:706–17.

INTRODUCTION

Low-grade systemic inflammation is now considered a key etiologic factor in the development and progression of several multifactorial disorders including atherosclerosis (1), metabolic syndrome (MetS) (2, 3), type 2 diabetes (4–6), and cardiovascular diseases (7). Elevated plasma concentrations of C-reactive protein (CRP) and of the proinflammatory cytokines TNF-α and IL-6 have been associated with an increased risk of cardiovascular disease (8–13). From a mechanistic perspective, chemokines such as monocyte chemoattractant protein-1 (MCP-1) have been shown to mediate recruitment of monocytes at sites of vascular inflammation, thereby promoting atherosclerosis (14). On the other hand, proteins such as adiponectin have antiinflammatory and antiatherogenic properties (15, 16).

In addition to age (17), sex (18), obesity (19), smoking habits (20), alcohol consumption (21), and physical activity (22), increasing evidence suggests that diet plays a major role in the modulation of the inflammatory profile (23). The extensive and detailed review from Calder et al (23) has shown that food groups or nutrients that are part of a healthy diet, including fruit and vegetables, whole grains, fish, fiber, omega-3 (n–3) fatty acids, vitamin C, vitamin E, and carotenoids, may protect against low-grade systemic inflammation. In contrast, SFAs and trans fatty acids, as well as dietary patterns characterized by high intakes of red and processed meats, sweets, soft drinks, fried snacks, or refined grains have been shown to promote a proinflammatory state (23). Whereas diet composition has been shown to modify pro- and antiinflammatory processes through many mechanisms in different cell types including adipocytes (24) and peripheral blood mononuclear cells (25), more studies on this topic are clearly warranted (26).

Recent cross-sectional studies suggest that the consumption of dairy products is inversely associated with low-grade systemic inflammation (27–29). Indeed, Panagiotakos et al (28) have shown in the ATTICA study that CRP, IL-6, and TNF-α concentrations in individuals consuming >14 servings of dairy products/wk (ie, >2 servings/d) were, respectively, 29%, 9%, and 20% lower than those in individuals consuming <8 servings/wk (≤1 serving/d). This inverse association was independent of potential confounders such as age, sex, smoking, physical activity, BMI, and other dietary factors.

The cross-sectional nature of these studies precludes definite conclusions on the cause-and-effect relation between dairy food...
consumption and inflammatory outcomes, which can only be investigated through rigorously controlled randomized clinical trials. The purpose of the present systematic review of the literature was to summarize results of randomized controlled nutritional intervention studies in adults that assessed the impact of dairy products consumption on biomarkers of inflammation.

METHODS

The present review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (30).

Study eligibility criteria

The review included randomized controlled trials published in English that assessed the impact of bovine dairy product consumption (ie, milk, cheese, and yogurt) on serum or plasma inflammatory biomarker concentrations in adult men and women compared with low-dairy (control) interventions. No restriction was imposed on publication date or publication status for inclusion in the review.

It was a priori determined that studies with the following characteristics would be excluded from the review: studies that included pregnant or lactating women; studies that included patients suffering from severe inflammation-related disorders (eg, cancer, Crohn disease, arthritis); studies that did not include a low-dairy control intervention; studies in which test interventions consisted of donkey milk, goat milk, or soy beverages only; and studies in which test interventions consisted of high-fat or high-sugar dairy products only (ie, butter, cream, ice cream), because these products are generally not consumed on the basis of their nutritional value.

Search strategy

A systematic literature search was conducted in PubMed (www.ncbi.nlm.nih.gov/pubmed/) with the use of the following terms: (dairy OR milk OR cheese OR yogurt) AND (food OR product OR intake OR consumption) AND (inflammation OR inflammatory markers OR C-reactive protein OR cytokines) NOT (pregnant OR pregnancy OR lactating OR “breast milk”). The following limits were activated during the search: humans; all adult: 19+ years; randomized controlled trial; and English.

The database search was performed on 2 April 2012 by one author (M-EL). The title and abstract of retrieved articles were screened to assess the eligibility of studies. The reference list of each article selected through the electronic search was scanned for the identification of other possibly relevant articles. The entire search and article screening process was re-run on 29 June 2012 independently by a second reviewer (CR) to ensure that all relevant articles had been retrieved and to look for newly published articles. The search was also conducted in Embase (www.embase.com) and the Cochrane Library (www.thecochranelibrary.com) at that time to look for possibly relevant articles that may not have been recorded in PubMed. Results from the different searches were then compared and discordances were resolved by consensus.

Data extraction

For each study included in the review, one author (M-EL) extracted data on study design, context of the interventions (duration, type of dairy products tested, control intervention characteristics), primary outcome (ie, change in inflammatory profile as the primary outcome or not), population characteristics (sex, age, weight status, baseline CRP concentrations), and results on inflammatory biomarker concentrations.

Assessment of the risk of bias within studies

On the basis of the Cochrane Collaboration’s tool for assessing the risk of biased results within studies (31), the following items were evaluated for each study: randomized sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessment, incomplete outcome data, selective reporting, and other possible bias (ie, carry-over effect in crossover studies and baseline imbalance in factors strongly related to outcome measures). The risk of bias within studies was independently assessed by 2 authors (M-EL and CR). The authors thereafter compared their results and discordances were resolved by consensus.

RESULTS

Study selection

As shown in Figure 1, the database search first retrieved 91 research articles. The title and abstract of each article were screened, and 82 articles were discarded because they did not meet the eligibility criteria. The full text of 9 articles was retrieved for detailed evaluation. Five studies met the inclusion criteria and were included in the review. Two additional research articles that met eligibility criteria were identified by checking the reference list of the 5 selected articles. Thus, a total of 7 research articles reporting the results of 8 nutritional intervention trials were identified for inclusion in the review (32–38). The re-run of the search in PubMed as well as in other databases generated the same list of eligible articles, and no new study was identified.

Study characteristics

A summary of the 8 nutritional intervention trials included in the present review is provided in Table 1. Briefly, all 8 trials...
were randomized controlled trials published in English between August 2005 and October 2011, of which 2 had a crossover design (37, 38) and 6 had a parallel design (32–36). All trials included overweight or obese adults aged ≥18 y. Seven of the 8 trials included both men and women (32–35, 37, 38), whereas one study included women only (36). The duration of the interventions ranged from 4 wk (1 mo) in Zemel et al (37) to 48 wk (~1 y) in Thompson et al (33). Because the interventions differed markedly between studies (duration, type of dairy products tested, characteristics of the control intervention), no meta-analysis was performed. The following paragraphs provide a narrative description of each study. The description is categorized according to whether inflammation was the primary outcome of the study. This is based on the argument that sample size calculations for a primary outcome other than inflammation may not have been adequate for the analysis of inflammation as a secondary outcome.

Studies with change in inflammatory profile as the primary outcome

By using a parallel-group design, Stancliffe et al (32) randomly assigned 40 overweight and obese adults with MetS to 1 of 2 isoenergetic weight-maintenance diets that lasted 12 wk each: an adequate-dairy diet (>3.5 servings of dairy/d, of which 3 were provided to participants by the research team and 2 were milk and/or yogurt) was compared with a low-dairy diet (<0.5 serving/d) during which participants were provided with 3 daily servings of prepackaged nondairy foods. These prepackaged nondairy foods were selected by subjects from a list of low-sodium varieties or soy-based substitutes of luncheon meats, packaged fruit cups, granola bars, and peanut butter crackers, as previously described (32). Both diets were constructed and matched to achieve macronutrient and fiber intakes that were comparable to the estimated intake in the United States (values reported by authors: ~35% energy from fat, ~49% energy from carbohydrate, ~16% energy from protein, and 8–12 g fiber/d). However, by design, the 2 diets differed in terms of calcium intake (difference of ~600 mg) and dairy-derived proteins (difference of 28–35 g). By week 12, the adequate-dairy diet significantly reduced TNF-α (~35%; P < 0.01), IL-6 (~21%; P < 0.02), MCP-1 (~24%; P < 0.02), and CRP (~47%; P < 0.02) concentrations, whereas it concurrently increased adiponectin concentrations (~53%; P < 0.005). For the majority of the inflammatory biomarkers, effects were present after only 1 wk of treatment and progressed over time. In general, these effects were also more pronounced in obese subjects than in the overweight subgroup. Although there was no change in body weight, the adequate-dairy diet led to reductions in adiposity indexes (ie, fat mass, trunk fat) as well as in waist circumference (all P < 0.05). The low-dairy diet had no significant impact on inflammatory biomarkers, body weight, or adiposity indexes.

Studies with change in inflammatory profile as a secondary or undefined outcome

Thompson et al (33), with the use of a parallel design, allocated 90 obese men and women [BMI (in kg/m²) between 30 and 40] to 1 of 3 diets: 1) a high-dairy diet (4 daily servings with at least 2 servings as fluid milk; percentage fat unspecified); 2) a high-dairy diet similar to the first, except for a higher fiber content and a lower glycemic index; and 3) a control diet (2 daily servings of dairy). All diets were designed to provide a 500-kcal/d deficit and lasted 48 wk. Subjects bought and prepared their own food according to a meal plan. Change in body weight was the primary outcome of the study, and change in high-sensitivity CRP (hs-CRP) concentration was a prespecified secondary outcome. Analyses of compliance showed that, on average, 3.13, 3.12, and 1.38 daily servings of dairy products were consumed by the subjects in the high-dairy, high-dairy/high-fiber, and control groups, respectively. All 3 groups consumed equal amounts of energy (P = 0.81). The proportion of energy from fat and carbohydrate was similar in the control and high-dairy diets, but the percentage of energy from fat was lower and the percentage of energy from carbohydrate was higher in the high-dairy/high-fiber diet compared with the other 2 groups (P < 0.05). The percentage of energy from protein was lower in the control group than in the 2 high-dairy groups (P < 0.05). Results showed that all 3 diets led to significant reductions from baseline in hs-CRP concentrations (~17.0%, ~28.6%, and ~22.2% in the high-dairy, high-dairy/high-fiber, and control groups, respectively; all P < 0.0001), but no between-group differences were observed (P = 0.66). The magnitude of weight loss was similar in all 3 groups (P = 0.45).

Zemel and Sun (34), with the use of archived samples from 2 randomized controlled parallel trials (39, 40), retrospectively assessed the impact of high-dairy diets on plasma CRP and adiponectin concentrations in healthy obese subjects (BMI between 30 and 40). The primary outcome of the first study (39) consisted of changes in body fat. Briefly, 39 African American men and women were randomly assigned to consume 1 of 2 isoenergetic diets for 24 wk: a low-dairy diet (~1 serving/d) or a high-dairy diet (3 servings/d with at least 1 serving in the form of fluid milk). In both diets, macronutrient and fiber amounts were set to achieve values corresponding to the average consumption in the United States (values reported by authors: ~35% energy from fat, ~49% energy from carbohydrate, ~16% energy from protein, and ~8–12 g fiber/d). Dairy products in the high-dairy diet were substituted for lean meats in the control diet. Plasma CRP concentrations significantly decreased by 11% (P < 0.03) and adiponectin concentrations significantly increased by 8% (P = 0.003) in subjects who consumed the high-dairy diet (post-compared with prediet values). These changes were observed concurrently to significant reductions in adiposity indexes such as waist circumference, trunk fat, and body fat with the high-dairy diet (all P < 0.01). There were no significant changes in CRP or adiponectin concentrations in subjects who consumed the low-dairy diet. The second study (40) included 38 obese men and women who were randomly assigned to 1 of 2 hyperenergetic diets providing a 500-kcal/d deficit over 12 wk: 1) a yogurt-enriched diet [3 daily 6-ounce (ie 3 × 170 g) servings of a fat-free yogurt] or 2) a control diet (0–1 serving of dairy products/d, including 3 daily servings of a flavored gelatin dessert as a placebo). The placebo was sugar-free and calcium-free. Energy intake and macronutrient content of the 2 diets were similar, with values approximating the average consumption in the United States (values reported by the authors: ~30% energy from fat, ~52% energy from carbohydrate, and ~18% energy from protein). The primary outcomes of this study were changes in body weight and body fat. The yogurt-enriched diet induced significant reductions from baseline in CRP concentrations (~29%; P < 0.01) and significant increases in adiponectin concentrations (~18%; P < 0.05), whereas consumption of the control diet had no impact on CRP or adiponectin concentrations. Observed reductions in body weight, body fat, and other adiposity indexes were significantly greater in subjects...
### Table 1
Summary of randomized controlled trials that assessed the impact of dairy product consumption on circulating inflammatory biomarkers

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of individuals enrolled in each study</th>
<th>Sex</th>
<th>Age</th>
<th>Design</th>
<th>Intervention</th>
<th>Duration</th>
<th>Inflammation = primary outcome (yes, no, or unclear)</th>
<th>Baseline CRP concentration [mg/L]</th>
<th>Other inflammatory markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stancil et al., 2011 (32)</td>
<td>40 overweight or obese subjects with MetS</td>
<td>19 M/21 F 37.0 ± 9.9°</td>
<td>Parallel</td>
<td>2 weight-maintenance diets</td>
<td>12 wk</td>
<td>Yes</td>
<td>N/A</td>
<td>CRP:↓, TNF-α, IL-6, ↓ MCP-1</td>
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<td>Other inflammatory markers: ↑ adiponectin</td>
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<tr>
<td>Thompson et al., 2005 (33)</td>
<td>90 obese subjects</td>
<td>13 M/77 F 25-70</td>
<td>Parallel</td>
<td>3 energy-restricted diets</td>
<td>48 wk</td>
<td>No</td>
<td>High-dairy group: 4.7 ± 3.8 mg/L</td>
<td>Within-diet changes (in all 3 diets): ↓</td>
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<td>High-dairy/high-fiber group: 5.6 ± 5.0 mg/L</td>
<td>↔ TNF-α, IL-6, ↔ MCP-1, adiponectin</td>
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<tr>
<th>Study</th>
<th>No. of individuals enrolled in each study</th>
<th>Sex</th>
<th>Age</th>
<th>Design</th>
<th>Intervention</th>
<th>Duration</th>
<th>Inflammation = primary outcome (yes, no, or unclear)</th>
<th>Baseline CRP concentration</th>
<th>CRP</th>
<th>Cytokines</th>
<th>Other inflammatory markers</th>
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<tbody>
<tr>
<td>Zemel and Sun, 2008 (34)³</td>
<td>39 obese but otherwise healthy African American subjects</td>
<td>11 M/23 F³</td>
<td>26–55</td>
<td>Parallel</td>
<td>2 isoe energetic diets</td>
<td>24 wk</td>
<td>No</td>
<td>N/A</td>
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<td>high-dairy (3 servings/d with ≥1 as fluid milk)</td>
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<td>Within-diet changes</td>
<td>High-dairy group:</td>
<td>↓</td>
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<td>↑ adiponectin</td>
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<td>low-dairy (&lt;1 serving/d)</td>
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<td>Low-dairy group:</td>
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<tr>
<td>Hypoenergetic study</td>
<td>38 obese but otherwise healthy subjects</td>
<td>7 M/27 F³</td>
<td>18–50</td>
<td>Parallel</td>
<td>2 energy-restricted diets</td>
<td>12 wk</td>
<td>No</td>
<td>N/A</td>
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<td>yogurt-enriched diet [three 6-ounce (3 × 170 g) servings/d of fat-free yogurt]</td>
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<td>Within-diet changes</td>
<td>Yogurt-enriched group:</td>
<td>↓</td>
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<td>↑ adiponectin</td>
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<td>control diet (0–1 serving of dairy/d, with 3 servings of a flavored gelatin dessert as a placebo)</td>
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<td>Control group:</td>
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<td>Study</td>
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<td>Sex</td>
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<td>Design</td>
<td>Intervention</td>
<td>Duration</td>
<td>Inflammation = primary outcome (yes, no, or unclear)</td>
<td>Baseline CRP concentration</td>
<td>Other inflammatory markers</td>
<td>Observed changes in inflammatory biomarkers</td>
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<td>Wennersberg et al, 2009 (35)</td>
<td>121 overweight subjects with MetS</td>
<td>41 F</td>
<td>30–65</td>
<td>Parallel</td>
<td>2 diets</td>
<td>24 wk (6 mo)</td>
<td>No</td>
<td>Dairy-enriched group: 3.5 ± 3.3 mg/L</td>
<td>Between-diet differences in changes from baseline to 24 wk:</td>
<td>CRP: 3.0 ± 3.0 mg/L</td>
<td>CRP: 3.0 ± 3.0 mg/L</td>
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<td>↔ IL-6, TNF-α, adiponectin</td>
<td>↔</td>
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<td>Rosado et al, 2011 (36)</td>
<td>139 obese Mexican women</td>
<td>139 F</td>
<td>25–45</td>
<td>Parallel</td>
<td>3 energy-restricted diets including</td>
<td>16 wk</td>
<td>No</td>
<td>Low-fat milk group: 5.5 ± 3.0 mg/L</td>
<td>Within- or between-diet differences:</td>
<td>Low-fat milk + micronutrients group: 7.9 ± 3.9 mg/L</td>
<td>Control group: 6.7 ± 3.9 mg/L</td>
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<td>↔ cookroot: 6.7 ± 3.9 mg/L</td>
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<td>Study</td>
<td>No. of individuals enrolled in each study</td>
<td>Sex</td>
<td>Age</td>
<td>Design</td>
<td>Intervention</td>
<td>Duration</td>
<td>Inflammation = primary outcome (yes, no, or unclear)</td>
<td>Baseline CRP concentration$^7$</td>
<td>CRP</td>
<td>Cytokines</td>
<td>Other inflammatory markers</td>
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<tr>
<td>Zemel et al, 2010 (37)</td>
<td>20 overweight or mildly obese but otherwise healthy subjects</td>
<td>14 M/6 F</td>
<td>31.0 ± 10.3$^3$</td>
<td>Crossover</td>
<td>2 isoenergetic diets supplemented with (28 d), with a 4-wk washout between phases</td>
<td>Unclear</td>
<td>Phase 1: 33.6 ± 12.5 µg/mL</td>
<td>Within-diet changes Dairy-based smoothies phase:</td>
<td>Phase 2: 26.2 ± 13.5 µg/mL</td>
<td>↓</td>
<td>↑ TNF-α, IL-6 ↓ MCP-1</td>
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<td>- dairy-based smoothies (3 servings/d, made with nonfat dry milk)</td>
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<td>Dolive-based placebo smoothies phase:</td>
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<td>↑ IL-15 ↑ adiponectin</td>
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<td>- soy-based placebo smoothies (3 servings/d)</td>
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<td>↑ TNF-α, IL-6, ↓ MCP-1</td>
<td>↑ MCP-1</td>
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<tr>
<td>van Meijl and Mensink, 2010 (38)$^6$</td>
<td>40 overweight or obese subjects without CVD</td>
<td>10 M/30 F</td>
<td>18–70</td>
<td>Crossover</td>
<td>2 diets supplemented with 8 wk, with a 2-wk washout between phases</td>
<td>Unclear$^7$</td>
<td>N/A</td>
<td>Between-diet differences (low-fat dairy vs control phase):</td>
<td></td>
<td>↑ IL-6</td>
<td>↑ MCP-1</td>
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<td>- low-fat dairy products (500 mL low-fat milk/d and 150 g low-fat yogurt/d)</td>
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<td>↑ TNF-α (trend)</td>
<td>s-TNFR-1 (trend) and s-TNFR-2 (significant)</td>
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<td>- CHO-rich control products (600 mL fruit juice and 43 g of fruit biscuits)</td>
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<td>↑ IL-6</td>
<td>↔ MCP-1</td>
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$^1$CHO, carbohydrate; CRP, C-reactive protein; CVD, cardiovascular disease; MCP-1, monocyte chemoattractant protein 1; MetS, metabolic syndrome; N/A, unreported baseline CRP concentrations; s-TNFR, soluble TNF-α receptor; ↓, significant reduction; ↔, no change; ↑, significant increase.

$^2$Baseline CRP concentrations were not significantly different between groups, except for the low-fat milk and “low-fat milk + micronutrients” interventions in Rosado et al (36).

$^3$Mean ± SD.

$^4$Detailed descriptions of the isoenergetic and hypoenergetic studies are found in references 39 and 40, respectively.

$^5$Separate numbers of men and women represent individuals who completed the study, because these data were not reported for individuals who were enrolled.

$^6$Results for CRP are reported in another article by van Meijl and Mensink (42).

$^7$Unclear definition of the primary outcome, but statistical power shown to be sufficient for the assessment of TNF-α, MCP-1, and s-TNFR-1 and -2.
who consumed the yogurt-enriched diet compared with subjects who consumed the control diet (all $P < 0.01$). Thus, the experimental design does not allow identifying yogurt intake per se as the real cause of the favorable changes observed in inflammatory biomarker concentrations after consuming the yogurt-enriched diet.

A parallel-group intervention study was conducted by Wennersberg et al (35) to assess the impact of a 6-mo high-dairy diet on body composition and other factors related to the MetS in 121 overweight men and postmenopausal women characterized with at least 2 traits of the MetS [National Cholesterol Education Program Adult Treatment Panel III criteria (41)]. The primary outcome of the study consisted of changes in waist circumference. Subjects were randomly assigned to a dairy-enriched diet (3–5 daily servings of dairy products of any kind, ie, milk, yogurt, sour milk, cream, cheese, cottage cheese, butter, or ice cream occasionally) or a control diet (habitual diet without changing the intake of dairy products). Diets were not matched for energy and macronutrient intake. Energy intake tended to be higher in the dairy-enriched diet group compared with the control group ($P = 0.07$). Intakes of protein (g), total fat (g), SFAs (g), sugar (g), cholesterol (mg), and calcium (mg) were higher, whereas alcohol intake (%) was lower in the dairy-enriched diet group compared with the control group ($P = 0.03$). Results showed that participants’ baseline intake of dairy products was $\sim 200$ g/d, representing between 0.8 and 1.1 servings of dairy/d. Dairy product consumption (mainly fluid milk and yogurt) increased by an average of 250 g/d in the dairy group, representing 1.0–1.4 servings of dairy/d, whereas there was no change in dairy intake in the control group ($P < 0.0001$ for the difference in dairy intake between the 2 groups). Changes from baseline to 6 mo in hs-CRP, IL-6, TNF-α, and adiponectin concentrations were not significantly different between the milk and control groups (eg, change in hs-CRP: $+2.9\%$ compared with $-3.3\%$, respectively; $P = 0.339$).

By using a parallel design, Rosado et al (36) investigated the impact of 3 energy-restricted diets (500-kcal/d deficit) on anthropometric and biochemical variables in 139 obese Mexican women. Women consumed one of the following diets for 16 wk: a low-fat milk diet (250-mL servings, 3 times daily), a “low-fat milk with added micronutrients” diet (250-mL servings, 3 times daily), or a control diet (no intake of milk or any other dairy product). Milk was provided to participants in the 2 milk diets and was the only dairy product allowed. Meal plans that included specific quantities of foods regularly consumed in this population were provided to women in the control diet to achieve similar amounts of macronutrient and fiber, which were set to the average consumption in the United States (values reported by the authors: $\sim 35\%$ energy from fat, $\sim 49\%$ energy from carbohydrate, $\sim 16\%$ energy from protein, and 8–12 g fiber/d). Dietary calcium intake differed by $\sim 600$ mg between the 2 diets. Consumption of the dairy-based smoothies led to significant reductions from baseline in concentrations of CRP ($-57\%$; $P < 0.05$), IL-6 ($-13\%$; $P < 0.01$), TNF-α ($-15\%$; $P < 0.002$), and MCP-1 ($-20\%$; $P < 0.0006$) as well as significant increases in adiponectin ($+20\%$; $P < 0.002$), whereas the soy-based control intervention had no effect or even increased inflammatory biomarker concentrations compared with baseline values. Most of the effects were evident after 7 d of dietary change and increased in magnitude at the end of the 28 d. There was no significant change in the antinflammatory cytokine IL-15 with any of the 2 diets. There was also no significant change in body weight, body fat, trunk fat, or lean mass during either dietary treatment. The authors indicated in their article that their objective was to assess the impact of a dairy-rich diet on oxidative and inflammatory stress. However, it was not indicated if the study was designed with the use of inflammation as the primary outcome, and there was also significant discordance between the study design described in the publication and information found in clinicaltrials.gov for this study. Thus, we were not able to determine whether diet-induced change in the inflammatory profile was the primary outcome of this study.

Finally, van Meijl and Mensink (38) compared the impact of the consumption of low-fat dairy products [500 mL low-fat (1.5% wt:wt) milk + 150 g low-fat (1.5% wt:wt) yogurt daily] with carbohydrate-rich control products (600 mL fruit juice with 3 fruit biscuits) on inflammatory biomarkers in 40 overweight or obese subjects in a crossover study. A 2-wk washout period separated the two 8-wk interventions. Subjects maintained their habitual background diet during the entire study. Dietary intakes estimated from a food-frequency questionnaire, presented in another article describing this study (42), showed that total energy intake was similar between diets. However, the percentage of energy from protein and fat (including SFAs and MUFA$s$) as well as intakes of cholesterol and calcium were higher, whereas percentage of energy from carbohydrate and mono- and di-saccharides as well as fiber intake were lower in the low-fat dairy intervention compared with the high-carbohydrate control intervention (all $P < 0.05$). The primary outcome of this study was not clearly identified (38, 42). However, the authors provided evidence of adequate statistical power to detect significant changes of $\geq 10\%$ for TNF-α, MCP-1, and soluble TNF-α receptors (s-TNF$\scriptstyle R$s) 1 and 2 but not IL-6. Plasma IL-6 and MCP-1 concentrations were not different between the interventions (both $P > 0.77$), whereas concentrations of TNF-α tended to be lower after the low-fat dairy intervention than after the high-carbohydrate intervention ($-6.5\%$; $P = 0.07$). A significant 5.5% increase in s-TNF$\scriptstyle R$-2 concentrations was observed after the low-fat dairy diet compared with the high-carbohydrate diet ($P = 0.02$) and was considered by the authors as a beneficial effect of dairy. However, this change is small in magnitude and must be interpreted with caution because its clinical relevance is unknown.
The low-fat dairy diet had no impact on hs-CRP concentrations compared with the high-carbohydrate intervention ($P = 0.147$), as reported in the other article that describes this study (42).

**Risk of bias within studies**

As shown in Table 2, studies by Thompson et al (33) and Rosado et al (36) had the highest transparency in the report of items associated with the risk of biased results, ie, the lowest presence of “unclear risk” statements. These were the only 2 studies to clearly describe both the methods used to randomly assign participants and methods used to conceal the allocation to the interventions before assignment. The majority of studies adequately reported the number of attrition and exclusions related to inflammatory biomarkers analyses, together with reasons (32–36, 38, 39). However, all 8 trials provided insufficient details regarding the blinding of outcome assessors (laboratory staff who analyzed blood samples) to the test compared with control interventions. The blinding of participating and personnel to the test compared with control interventions was also impossible in most of the studies reviewed due to the nature of the interventions. Otherwise, the majority of studies provided insufficient information to evaluate the risk of selective outcome reporting, ie, whether some inflammatory biomarkers were assessed but not reported or simply not assessed. Among crossover studies, a carry-over effect was evidenced for MCP-1 in the study by Zemel et al (37). With regard to baseline imbalance in characteristics that are strongly related to inflammatory outcomes (ie age, sex, obesity indexes, baseline inflammation), half of the studies (33, 36–38) were classified as presenting a low risk of bias. Indeed, in parallel-design studies by Thompson et al (33) and Rosado et al (36), the high-dairy and control groups showed similar baseline characteristics for age, sex, BMI, and hs-CRP concentrations. Baseline imbalance did not apply to the studies by Zemel et al (37) and van Meijl and Mensink (38) due to their crossover design. Moreover, in Zemel et al (37), baseline values for body weight, body fat, trunk fat, and concentrations of CRP, IL-6, IL-15, TNF-α, MCP-1, and adiponectin were similar between the 2 dietary phases. The other 4 studies (32, 34, 35) were classified as presenting an unclear risk of bias regarding baseline imbalance. In the study by Stancliffe et al (32) and in the hypoenergetic study reported by Zemel and Sun (34) and Zemel et al (40), the intervention groups had similar baseline characteristics including age, sex distribution, BMI, blood pressure, and plasma lipid-lipoprotein concentrations. However, baseline CRP concentrations were not formally compared between intervention groups in these 2 studies, and this represents a potential source of bias. In the isoenergetic study reported by Zemel and Sun (34) and Zemel et al (39), baseline CRP concentrations were also not formally considered as a source of confounding. The risk of confounding in this study is, however, higher considering that the number of men and women was unbalanced between the low-dairy (8 men compared with 9 women) and high-dairy (3 men compared with 14 women) diets. In the study by Wennersberg et al (35), the 2 groups were comparable at baseline for most of the characteristics reported, including age, sex distribution, BMI, and hs-CRP concentrations, but adiponectin concentrations, which were an outcome of interest, were higher in the high-dairy group than in the control group at baseline ($P = 0.021$). Detailed justifications associated with the evaluation of the risk of bias within studies are provided in Supplemental Table 1 under “Supplemental data” in the online issue.

**DISCUSSION**

The present article reviewed the evidence from randomized controlled trials regarding the impact of dairy product consumption on circulating inflammatory biomarkers in adults. We first observed that this topic had been addressed in very few studies thus far, with only 8 trials meeting the eligibility criteria for review. All of these 8 studies were undertaken in overweight or obese men and women. Half of the studies pointed toward a potentially beneficial effect of dairy product consumption on low-grade systemic inflammation, whereas the other half suggested no effect. Several methodologic factors and limitations in the analysis of these data need to be considered.

Whether inflammation was considered the primary outcome in studies reviewed is a crucial methodologic factor that needs to be discussed. Only one trial had clearly identified change in the inflammatory profile as its primary outcome measure and provided sample size calculation on the basis of the variability in CRP. Results indicated significant antiinflammatory effects of consuming $>3.5$ servings of dairy products/d compared with consuming $<0.5$ serving/d (32). It is stressed that the inflammation-lowering effects of dairy products may have been triggered, at least to some extent, by favorable changes in adiposity indexes, as they are well-known correlates of inflammatory biomarker concentrations (43, 44). The authors argued that the rapid onset of the effects of the high-dairy diet on inflammatory biomarkers, ie, within 7 d of intervention, suggested an adiposity-independent effect as well. However, long-term analyses considering the potential impact of reduced adiposity on inflammatory biomarker concentrations were not performed. On the other hand, between-diet differences in specific dietary components such as calcium and dairy proteins may be responsible, at least partly, for the inflammation-lowering effects of the high-dairy diet. Previous studies in mouse models have suggested that dietary calcium reduces inflammatory cytokine expression in adipocytes through the suppression of calcitriol (34, 45). Milk-derived proteins such as lactoferrin may also exert antiinflammatory effects (46) through the regulation of the recruitment and activation of cytokine-releasing immune cells (47). Finally, bioactive peptides from dairy have been shown to inhibit angiotensin-I-converting enzyme (48), thereby limiting the production of angiotensin II, which is known to induce the secretion of inflammatory cytokines in the vascular wall (49) and adipose tissue (50).

There is a strong possibility that the 7 studies in which change in inflammatory biomarkers was a secondary or undefined outcome were not sufficiently powered to detect significant differences between high-dairy and control (low-dairy) interventions. This is particularly the case for 3 (33, 35, 36) out of the 5 (33–36) studies that were definitely not designed a priori to assess inflammation-related outcomes, having provided sample size calculations for changes in body weight or waist circumference and having shown no impact of dairy consumption on key circulating inflammatory biomarkers (Table 1). Results from the other 2 studies (39, 40), both reported in reference 34 as a posteriori analyses, showed significant reductions from baseline in hs-CRP concentrations as well as significant increases in adiponectin concentrations after the consumption of high-dairy diets. Despite the weight-maintenance
### TABLE 2
Evaluation of the risk of bias in randomized controlled trials that assessed the impact of dairy product consumption on circulating inflammatory biomarkers

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment¹</th>
<th>Blinding of participants</th>
<th>Blinding of personnel</th>
<th>Blinding of outcome assessment²</th>
<th>Incomplete outcome data²</th>
<th>Selective reporting</th>
<th>Other possible bias²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stancliffe et al, 2011 (32)</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Thompson et al, 2005 (33)</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Zemel and Sun, 2008 (34)²</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Isoenergetic study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wennersberg et al, 2009 (35)</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Rosado et al, 2011 (36)</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Zemel et al, 2010 (37)</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk of baseline imbalance, but high risk of carry-over effect</td>
</tr>
<tr>
<td>van Meijl and Mensink, 2010 (38)</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk of baseline imbalance or carry-over effect</td>
</tr>
</tbody>
</table>

¹ Before assignment of participants to the interventions.
² Blinding of the staff who performed laboratory analyses.
³ Incomplete report of the number of attrition and exclusions related to inflammatory biomarker analyses, together with explanations.
⁴ Baseline imbalance in factors strongly related to outcome measures or carry-over effect in crossover studies.
⁵ Detailed descriptions of the isoenergetic and hypoenergetic studies are found in references 39 and 40, respectively.
⁶ "Unclear risk" applies to the comparison between the 2 milk interventions and the control intervention. Thus, participants and personnel were blinded to the low-fat milk vs the “low-fat milk + micronutrients” intervention.
⁷ "Unclear risk" applies to the comparison between the 2 milk interventions and the control intervention. Thus, outcome assessors were blinded to the low-fat milk vs the “low-fat milk + micronutrients” intervention.
context of the isoenergetic study (39), significant reductions were observed in waist circumference, trunk fat, and body fat after consumption of the high-dairy diet. In the energy-restricted study (40), reductions in body weight, body fat, and other adiposity indexes were significantly greater in magnitude in subjects who consumed the yogurt-enriched diet compared with subjects who consumed the control diet. Therefore, it is likely that the favorable changes from baseline observed in the inflammatory profile after consumption of high-dairy diets in these 2 studies may have been confounded by concurrent favorable changes in adiposity indexes.

Other major factors limiting the generalizability of results on the basis of the available randomized controlled trials are the heterogeneity of dairy products used and lack of detail regarding the type and fat content of these products. In 5 of the 8 studies (32, 33, 35, 38, 39), test interventions consisted of a combination of different dairy products. In 4 of those studies (32, 33, 35, 39), the average fat content of dairy products that participants had added to their diet was not reported. We are therefore unable to distinguish the effects of specific dairy products (milk compared with yogurt compared with cheese or low-fat compared with high-fat dairy products) on inflammation. We are also unable on the basis of the available information to evaluate the impact of other potentially important sources of variability on the inflammatory response to various dairy products, such as differences in sugar content (eg, plain compared with aromatized products), protein content (eg, regular compared with Greek-style yogurt), and fortification with probiotics (eg, inulin), probiotics, omega-3 fatty acids, or phytosterols.

The difference in the amount of dairy products consumed by subjects between the test (high-dairy) and control (low-dairy) interventions is another factor that may contribute to heterogeneity between studies. In trials by Thompson et al (33) and Wennersberg et al (35), dairy product intake differed by <2 servings between the high-dairy and control groups, thereby limiting the capacity to observe changes in inflammatory biomarkers with dairy intake. In contrast, 4 (32, 34, 37) of the 6 (32, 33, 35, 36–38) studies in which dairy product intake differed by ≥3 daily servings between the high-dairy and control diets showed improved inflammatory biomarker concentrations. Differences in the nutritional content of the dairy and control diets were also important in many studies, and this represents another factor contributing to heterogeneity between studies.

In addition, differences in the nature of inflammatory biomarkers analyzed in each study need to be pointed out as a factor that limits the generalizability of results. CRP, IL-6, and TNF-α were analyzed concurrently in half of the studies together with at least one of the following markers: adiponectin, MCP-1, IL-15, or s-TNF-1 and -2 (32, 35, 37, 38). On the other hand, 2 studies reported data on CRP concentrations only (33, 36), and 2 others assessed adiponectin in addition to CRP (34). Interpretation is obviously more limited in studies that assessed only 1 or 2 inflammatory biomarkers than in studies in which a more comprehensive assessment of the inflammatory profile was performed. The sensitivity of the assays used to assess changes in inflammatory biomarkers in response to dairy and their CVs are other potential sources of heterogeneity between studies. Most studies have used ELISA or high-sensitivity immunoassays to assess changes in biomarkers of inflammation with dairy intake. However, half of the studies (33, 34, 36) did not report their CVs for their assays. Considering that precision metrics and CVs for the measurement of inflammatory biomarkers are not available in all included studies, it is not possible to establish the extent to which heterogeneity between studies is due to differences in methodologies used to assess inflammatory outcomes.

The evaluation of the risk of bias highlighted that the majority of studies did not clearly report how several items known to affect the validity of results were addressed, including detail on the randomization process, allocation concealment, blinding of outcome assessment, and selective outcome reporting. Although it is likely that investigators have dealt adequately with these methodologic issues, we cannot exclude the possibility of biased results among studies included in the present review. Future studies obviously need to fill gaps in the report of items associated with the risk of biased results.

In conclusion, results from available randomized controlled trials conducted to date suggest that dairy product consumption has no adverse effect on low-grade systemic inflammation among overweight and obese adults. On the other hand, several methodologic factors and limitations do not allow us to conclude if the impact of dairy products on inflammation is beneficial or simply neutral. Additional well-controlled and adequately powered nutritional intervention studies specifically designed to assess the effects of dairy products on inflammatory biomarker concentrations are therefore warranted. A better characterization of the type and amount of dairy products tested in each study will be needed to draw clear conclusions. To gain mechanistic knowledge about the effects of dairy products on inflammation, outcome measures in future studies should also include inflammation-related genes expression.

REFERENCES

IMPACT OF DAIRY PRODUCTS ON INFLAMMATION