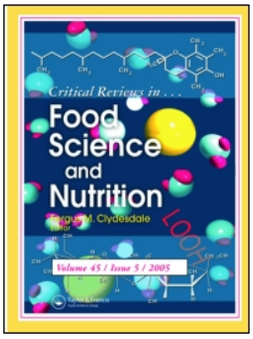

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Dairy products and inflammation: A review of the clinical evidence

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ABSTRACT

Inflammation is a major biological process regulating the interaction between organisms and the environment, including the diet. Because of the increase in chronic inflammatory diseases, and in light of the immune-regulatory properties of breastfeeding, the ability of dairy products to modulate inflammatory processes in humans is an important but unresolved issue. Here, we report a systematic review of 52 clinical trials investigating inflammatory markers in relation to the consumption of dairy products. An inflammatory score (IS) was defined to quantitatively evaluate this interaction. The IS was significantly positive for the entire data set, indicating an anti-inflammatory activity in humans. When the subjects were stratified according to their health status, the IS was strongly indicative of an anti-inflammatory activity in subjects with metabolic disorders and of a pro-inflammatory activity in subjects allergic to bovine milk. Stratifying the data by product categories associated both low-fat and high-fat products, as well as fermented products, with an anti-inflammatory activity. Remarkably, the literature is characterized by a large gap in knowledge on bioavailability of bioactive nutrients. Future research should thus better combine food and nutritional sciences to adequately follow the fate of these nutrients along the gastrointestinal and metabolic axes.

KEYWORDS
Milk; cheese; yoghurt; immune system; chronic diseases; obesity; health

Introduction

Immunity is a major process among the biological phenomena regulating the interaction of higher organisms with the environment, in particular as it provides a mechanism by which external agents are either rejected (e.g., phagocytosis of pathogens) or internalized (e.g., oral tolerance to ingested food) by the organism. One main expression of the immune system is its ability to mount an inflammatory reaction to these stimuli. If sustained, the inflammatory response may, however, turn against the host's own tissues, leading to a range of chronic inflammatory diseases that have now supplanted infectious diseases worldwide (Hunter and Reddy, 2013). The Global Business Intelligence Research estimated the global inflammatory therapeutics market to reach $85.9 billion in 2017 (Global Business Intelligence Research, 2011).

Most chronic inflammatory diseases (e.g., obesity, diabetes) as well as allergic diseases are strongly influenced by nutrition, the metabolism of food being intimately associated with inflammatory processes (Hotamisligil, 2006). In addition, postprandial inflammation is part of the normal stress reaction of the cell in response to the ingestion of food (Hernandez-Aguilera et al., 2013). Nutrients thus appear to be able to modulate the inflammatory status of humans and inflammation has consequently emerged as an important research topic in food and nutrition sciences (Calder et al., 2011; Calder et al., 2013; Klop et al., 2012).

Dairy products represent a particularly interesting food type to study in the context of inflammation. From an evolutionary point of view, ancestors of mammalians may have possessed primitive apocrine-like glands in the skin, approximately 310 million years ago, that incorporated elements of the innate immune system in providing protection to the skin and to eggs that were moistened (Oftedal, 2012). Because of its ability to support the development of the immune system of the infant, to inhibit bacterial growth (e.g., lactoferrin) and to deliver anti-oxidative protection (e.g., vitamins or glutathione), the potential of maternal milk to inhibit inflammation in the offspring has

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consequently raised interest (Lepage and Van de Perre, 2012). Part of these properties may be maintained when boundaries across species and life cycles are crossed, *i.e.* in the context of the consumption of dairy products by human adults (Labonte et al., 2013). In addition, the importance of food in modulating the gut microbiota, a key regulator of immunity, has become more evident during the last decade (Kau et al., 2011). Milk is a natural and culturally accepted vector to deliver supplements to the human organism (Ceapa et al., 2013), in particular prebiotic and probiotics that both modulate the microflora and thus influence immune and inflammatory processes. Besides, milk is amenable to a wide range of technological transformations, including its fermentation by lactic acid bacteria to produce fermented dairy products such as yoghurt or cheese whose metabolites may further modulate the ability of milk to influence immune processes in humans (Augustin and Udabage, 2007). Milk and dairy products are major food products in human nutrition, amounting to 14% of the caloric intake in developed countries (FAO, 2013b). The Food and Agriculture Organization (FAO) forecasted a world milk production of 784 million tons in 2013 (FAO, 2013a), which amounts to an average of circa 100 L milk per year per human being. An evaluation of the ability of dairy products to modulate inflammatory processes in humans is, thus justified.

Studies addressing the impact of dairy products on inflammatory processes present a contradictory landscape. Indeed, dairy products were reported to be beneficial, inactive, as well as detrimental. For illustration, the ATTICA study reported an inverse relationship between the consumption of dairy products and markers of the metabolic syndrome, including the inflammatory markers associated with this syndrome (Panagiotakos et al., 2010). On the other hand, the relatively high concentrations of saturated fat and dietary antigens in cow milk have raised concern and some scientists claimed that dairy products are a major cause in the development of chronic inflammatory disorders and autoimmune diseases (Melnik, 2009). These opposite statements reflect the wide spectrum of information available in the scientific literature on the relationship between the consumption of dairy products and inflammation. Indeed, many articles have been published on this relationship, but systematic reviews are scarce (Labonte et al., 2013) and incomplete. The association between the consumption of dairy products and inflammation in humans, thus merits clarification for the following reasons: (i) milk and dairy products play qualitatively and quantitatively an important role in human nutrition (Haug et al., 2007); (ii) inflammation, in particular low-grade systemic inflammation, has a significant impact on human health and longevity (Candore et al., 2010); (iii) nutrient metabolism and inflammation are mechanistically closely interconnected (Hotamisligil, 2006; Calder et al., 2011; Klop et al., 2012; Calder et al., 2013; Hernandez-Aguilera et al., 2013).

The property of the foods investigated in human nutritional trials are often poorly documented what renders an objective evaluation of the clinical outcome very difficult. This review aimed to narrow the gap between food science and nutritional science. The information usually provided by reviews on medical topics (Moher et al., 2009) was thus complemented with product-related information that is usually requested by regulatory authorities to document the functional properties of the food products and nutrients of interest (EFSA Panel on Dietetic Products Nutrition and Allergies, 2011; FDA Office of Nutrition Labeling and Dietary Supplements, 2009).

The specific goals of this review are to:

- Present a structured overview of published original human studies investigating the impact of the consumption of dairy products on inflammatory processes;
- Develop a method to quantitatively evaluate the results extracted from these studies;
- Use this method, in order to evaluate whether pro- or anti-inflammatory properties of dairy products can be concluded from these studies;
- Identify research gaps that should be filled to allow a better evaluation of the anti- or pro-inflammatory properties of specific dairy products in specific human populations.

Methods

Literature search strategy

A review was conducted using Medline and Scopus search that includes all original research articles written in English, published since January 1990, on the relationship between inflammatory markers and the consumption of dairy products in humans.

A first Medline search was conducted on February 13, 2013. A search of the Scopus database was also conducted on June 18, 2013 and the entries not identified in Medline were included into the evaluation. Medline and Scopus were searched again on December 10, 2013 to identify and include additional articles published until November 30, 2013. The search strategies were as follows:

- *Medline search strategy*. (milk OR cheese OR yog* OR dair*) AND inflam* NOT ("breast milk" NOT "human milk") NOT review*. Filters: Case Reports; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Comparative Study; Controlled Clinical Trial; Multicenter Study; Randomized Controlled Trial; Evaluation Studies; Meta-Analysis; Systematic Reviews; Humans; English;
- *Scopus search strategy*. (((TITLE-ABS-KEY(milk OR cheese OR yog* OR dair*) AND TITLE-ABS-KEY(inflam*) AND NOT TITLE-ABS-KEY("breast milk" not "human milk")) AND DOCTYPE(ar)) AND (humans)) AND (inflammation) AND (LIMIT-TO(LANGUAGE,"English")).

Data collection process

Figure 1 shows the flow diagram with the five phases leading to the quantitative analysis of the 52 clinical studies. Seventy-eight study results were extracted from these clinical studies to measure the impact of dairy products on inflammation in humans.

Phase 1. For phase 1, all studies identified by the search strategy were randomly split into six groups. Each group of studies was distributed to reviewers of one partner institution. Based on title and abstract, only studies that were clearly

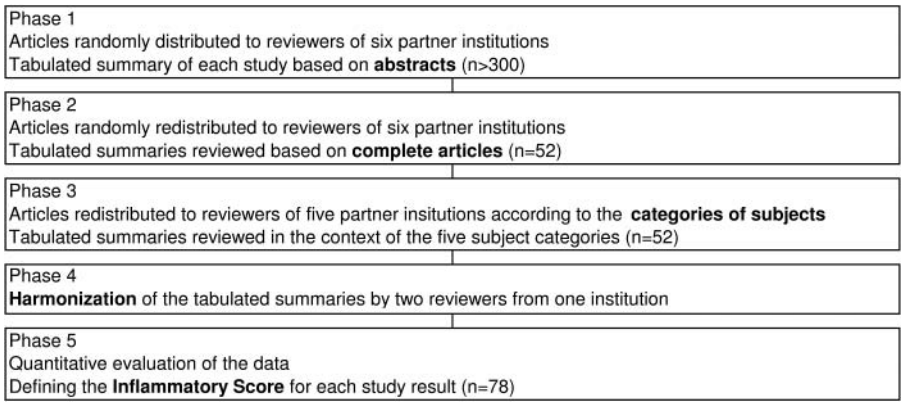

Figure 1. Flow diagram of the five phases conducted to establish an IS for the 78 study results extracted from the 52 human studies in which the impact of dairy products on inflammation was investigated.

associated with inflammatory mediators and with the ingestion of dairy products (i.e., milk, cheese, yoghurt, fermented milk, whey products, and other dairy foods) by humans, were kept for phase 2 of the review process. Studies investigating human milk and/or breastfeeding, were excluded. Studies in which dairy products were used as a vector to deliver ingredients such as probiotics, prebiotics or bioactive nutrients such as vitamins or peptides, were excluded. However, studies were included if non-supplemented dairy products were used as control products and if information was available on the impact of these control products on inflammatory markers compared to the baseline values (e.g., comparison before and after treatment). Studies investigating isolated dairy proteins or lipids, were excluded. The information derived from the abstracts and the titles was summarized in tabulated form (see section "Tabulated summary" below) and used for selecting the studies to be evaluated in phase 2 of the review.

Phase 2. The studies retained, based on their abstracts, were again randomly split into six groups and each group of studies was distributed to reviewers of one partner institution. The tabulated summary was completed, based on the content of the articles. A workshop took place in Lisbon on June 4–6, 2013 during which the reviewers presented an overview of their evaluation of the studies. Based on these presentations the content and form of the tabulated summary were refined.

Phase 3. The study results were grouped into five subject categories (see section "Tabulated summary" below) and each group of studies was accordingly redistributed to the reviewers of one partner institution. The studies were re-evaluated to finalize the content of the tabulated summary. Finally, a non-systematic search of the literature was conducted by the reviewers, for each of the five subject categories, to identify human studies that may not have been identified by the previous searches. The form of the complementary search strategy was left to the discretion of the reviewing authors and no additional studies were identified.

Phase 4. The tabulated summary of all studies was finally revised by two reviewers from one institution, in order to harmonize its content. In particular, the status of each column in the tabulated summary was changed from the description of one clinical study per column to the description of one *study result* per column. This adaptation was motivated by the fact that several studies reported results for more than one dairy product or more than one subject category, each of these study results needing a separate evaluation.

Phase 5. A quantitative estimation of the ability of dairy products to modulate inflammation was conducted, for each study result, based on the content of the tabulated summary and on the establishment of the inflammatory score (IS) (see the next two sections).

Tabulated summary

The tabulated summary was not only defined in broad compliance with the reporting of systematic reviews according to the PRISMA checklist (Moher et al., 2009), but also integrated elements requested by regulatory authorities for the preparation of applications on health claims (EFSA Panel on Dietetic Products Nutrition and Allergies, 2011; FDA Office of Nutrition Labeling and Dietary Supplements, 2009). The tabulated summary contains the following descriptors:

Reference—Presents the bibliographic reference of the clinical trial from which each study result was extracted. Studies for which more than one study result was extracted are indicated and the study results are numbered.

Subject category—The articles are grouped into five categories based on the clinical status of the subjects enrolled in the selected studies:

- HEALTH, for studies investigating healthy subjects;
- MET, for studies on subjects with metabolic and cardiovascular disorders, including obesity and overweight;
- GIT, for studies enrolling subjects with non-allergic gastrointestinal disorders;
- HYPER, for studies with subjects suffering from food hypersensitivity, in particular allergy to dairy products, but not from lactose intolerance;
- OTHERS, for studies describing subjects with all other disorders, in particular lung disease, joint disease, and infection.

Articles discussing both gastrointestinal disorders and food hypersensitivity are included in the category HYPER.

Target indication—Potential health benefit, clinical indication, or safety issue investigated in the study.

Target population—Population targeted by the target indication.

Fat content—The dairy product investigated is categorized as 'high-fat', 'low-fat', or, otherwise, "not available (n.a.)". The classification between high-fat and low-fat dairy products was made based on the information given in the corresponding paper. When the authors did not mention the fat content of the investigated product or when they did not use special terminology such as "fat-reduced, skimmed, semi-skimmed, high-fat, normal-fat," the study product was classified as "n.a.".

Fermentation—The dairy product investigated is categorized as "fermented," "non-fermented," or, otherwise, "n.a.".

Test and control products—Details on the foods used as test or control products (dairy or non-dairy) are reported. Only studies using dairy food products as the test or the control product are considered. For studies with more than one dairy product investigated, each dairy product is reported as a separate study result (one column for each product).

Test and control subjects—For each group enrolled in the study as test or control subjects, the number of subjects in the group, their gender (if available), age (including range) and health or disease status is provided (if appropriate). For studies with more than one group of subject investigated, each group is reported as a separate study result (one column for each group).

Diet—The composition of the dairy products investigated, its quantity, and the duration of the dairy products consumption during the study period is reported.

Controlled dairy test—Studies that are controlled and in which a dairy product is the test product are labeled as "yes," otherwise as "no".

Randomization—Studies that are randomized are labeled as "randomized," otherwise either "non-randomized" or "n.a.".

Time factor—The studies are categorized as either "longitudinal" or "cross-sectional".

Study results—The study results are generally expressed by presenting the food products investigated, the inflammatory markers measured, and the direction of the effect. Depending on the study design, seven different types of outcome are presented:

- Outcome 1 [Dairy vs Control], when dairy products are the test products and compared against control products;
- Outcome 2 [Dairy (end time vs baseline)], when dairy products at baseline are compared under fasting conditions over several days (dn vs d0), weeks (wn vs w0), or months (mn vs m0);
- Outcome 3 [Dairy (xh vs 0h)], when dairy products at baseline are compared over several hours in challenge postprandial studies (nh vs 0h);
- Outcome 4 [Dairy (test subjects vs control subjects)], for studies in which the effects of dairy products are compared in two populations of subjects;
- Outcome 5 [Dairy : Correlation], for studies in which the consumption of dairy products is quantitatively correlated to inflammatory markers. If available, adjustments for confounders are indicated;
- Outcome 6 [Dietary pattern 1 vs Dietary pattern 2], for studies in which the relative impact on inflammation of different dietary patterns containing dairy products is evaluated;
- Outcome 7 [Dietary patterns : Correlation], for studies in which dietary patterns containing dairy products are correlated with inflammatory markers. If available, adjustments for confounders are indicated.

The type of outcome (1–7) is indicated for each study result.

The strength of the effects was expressed by the direction of the statistically significant change in the inflammatory signal (→: no statistically significant effect; ↑: statistically significant increase; ↓: statistically significant decrease) or of the correlations (corr→: no statistically significant correlation; corr↑: statistically significant positive correlation; corr↓: statistically significant negative correlation). The criteria for statistical significance are indicated as reported in each study but are not documented in this review. To avoid bias, care was taken to document all results obtained with the inflammatory markers, including results in which no statistically significant changes were observed. Inflammatory markers are shown in italics in the table if their increase are associated with an anti-inflammatory effect.

Net change in inflammatory markers—The inflammatory markers shown in Table 1 were considered for inclusion in this review. This list was extracted from recently published work that compiles a comprehensive list of inflammatory markers reported in nutritional studies (Calder et al., 2013). It offered clear harmonizing criteria for inclusion or exclusion of the IS that were evaluated by each reviewer. The net change in inflammatory markers was calculated for each study result by summing up the changes in all inflammatory results measured. A value of −1 was attributed for each change in inflammatory parameters contributing to a pro-inflammatory status (e.g., an increase in a pro-inflammatory parameter or a decrease in an anti-inflammatory parameter). A value of +1 was attributed for each change in inflammatory parameters contributing to an anti-inflammatory status (e.g., a decrease in a pro-inflammatory parameter or an increase in an anti-inflammatory parameter). A value of 0 was attributed for study results in which the inflammatory markers did not change. None of the 78 study results for which the net change in inflammatory markers was measured provided results in which both anti- and pro-inflammatory changes were observed together.

Sustainability of effect over time—This line reports whether sustainability of the inflammatory effect over time was "investigated," "discussed," or "not discussed". A study result investigating and reporting a maintenance of the inflammatory effect after a washout phase of at least one week is labeled "yes".

Dose-response—This line reports whether a dose-response relationship was investigated (yes) or not (no). If yes, a short description is presented.

Bioavailability data—Label as "yes" if information is provided on bioavailability of dairy product components, otherwise label as "no". In cases where bioavailability data was obtained in the study (yes), a short presentation of the information is presented in the table.

Biological plausibility—This line presents whether the mechanism of action by which the dairy constituents exert their anti- or pro-inflammatory effects was discussed or

Table 1. List of inflammatory mediators selected for the evaluation of the articles[1].

Inflammatory mediator	
12-HETE	LTB4
15-HETE	LTB5
15-HPETE	LTC4
2-Arachidonoylglycerol	Lung function in response to indirect challenge *(Allergic asthma)*
5-HETE	LXA4
5-HPETE	Lyso-PA
a-1-Antichymotrypsin	Macrophages (total count, tissue infiltration, CD163+, CD68+, S100+)
a-1-Antitrypsin	MAPK, activated *(Crohn's disease)*
Ab42, increased *(Alzheimer's disease)*	MaR1
Adiponectin, low *(obesity, type 2 diabetes)*	MCP-1 (CCL2)
Anandamide	Microglia, activated *(Alzheimer's disease)*
Antimicrobial antibodies *(Crohn's disease)*	MIP-1a (CCL3)
Antimicrobial peptides	MIP-2a (CXCL2; GROb; GRO-2)
Astrocytes, reactive *(Alzheimer's disease)*	Monocytes (total count, CD66b, CD11c)
Autoantibodies	Neutrophils (total count, tissue infiltration, CD11b)
B lymphocytes (total count)	NF-kB *(Crohn's disease)*
Basophils, mast cells (total count, tissue infiltration)	NO *(cardiovascular diseases)*
Calprotectin *(Crohn's disease)*	Osteopontin *(Allergic asthma)*
Complement C3 (C3)	PAF
Complement C4 (C4)	PD1 (NPD1)
CPN60 *(Crohn's disease)*	PGD2
CRP	PGD3
Cysteinyl-LT *(Allergic asthma)*	PGE1
Eicosanoids *(Rheumatoid arthritis)*	PGE2
Eosinophilic cationic protein *(Allergic asthma)*	PGE3
Eosinophils (total count, tissue infiltration, CD11b)	PGF2a
Eotaxin *(Allergic asthma)*	PGI2
E-selectin (CD62E)	PKR *(Crohn's disease)*
Fibrinogen	Plasminogen activator inhibitor-1 (PAI-1)
GRP78 *(Crohn's disease)*	P-selectin (CD62P)
ICAM-1 (CD54)	RANTES (CCL5)
IFN-g	Rheumatoid factor *(Rheumatoid arthritis)*
IgE, total and allergen specific *(Allergic diseases)*	RvD1
IL-10	RvE1
IL-12 (IL-12A or p35 or IL-12B or p40 heterodimeric)	S100 proteins (S100A12, S100A8/A9) *(Crohn's disease)*
IL-13 *(Allergic asthma)*	Serum amyloid A (SAA)
IL-17A	SMAD7 *(Crohn's disease)*
IL-18	Sphingosine-1-phosphate
IL-1β	sPLA2
IL-1ra	T lymphocytes (total count, tissue infiltration)
IL-23 (IL-23A or p19 or IL-12B or p40 heterodimeric)	Tau, total *(Alzheimer's disease)*
IL-4 *(Allergic asthma)*	TNF-α
IL-5 *(Allergic asthma)*	TNFR (TNFR1 and TNFR2)
IL-6	tPA
IL-8 (CXCL8)	Tryptase *(Allergic asthma)*
Inflammatory gene expression, cytokine expression *(Obesity)*	TXA2
IP-10 (CXCL10)	VCAM-1 (CD106)
Leptin	VEGF *(Psoriasis)*
Leucocytes (WBC) (total count, tissue infiltration)	von Willebrand factor (vWF)

[1]The markers are listed in alphabetical order. Adapted from (Calder et al., 2013).

investigated. The mechanism of action is shortly presented.

Bioactive components—If discussed or investigated, the components of the dairy products considered as responsible for the anti- or pro-inflammatory effect are shortly presented.

Clinical evidence—If available, this line presents the results of clinical endpoints that, if changed, contribute to an upgrading of the overall effect. The list of clinical endpoints includes: non-systemic inflammatory markers (such as, cellular, organ inflammation, joint pain, flare), parameters formally recognized as being associated with the metabolic syndrome including changes in triglycerides, HDL cholesterol, blood pressure, plasma glucose, insulin tolerance, BMI, waist circumference, glucose tolerance, insulin resistance, waist:hip ratio, urinary albumin excretion, albumin:creatinine ratio, markers of oxidative stress known to promote inflammation and other clinical endpoints such as mortality or cardiovascular events.

Financing of research—This line mentions how the study was supported financially and is labeled as either "public", "private", "private and public", or "not presented".

Grading criteria—This line presents the grading criteria used to calculate the IS according to Table 2. The label "None" is attributed a value of 0, indicating a study result in which no net change in inflammatory markers was measured. The label "Anti" is attributed a value of +1, indicating a study result with a positive net change in inflammatory markers. The label "Pro" is attributed a value of −1, indicating a study result with a negative net change in inflammatory markers. For study results with a net change in inflammatory markers different from zero, the labels "Anti" and "Pro" are completed with the numbers 1–11 indicating which one of the quality criteria presented in Table 2 were met. These criteria could be retrieved from the following descriptors in the tabulated summary: (1) "controlled dairy test", (2) "randomization", (3) "time factor", (4) "test

Table 2. Criteria used to establish the IS to quantitatively evaluate the impact of dairy products on inflammatory processes in humans.

Initial grading	
a	Grade 0 for a null net change in inflammatory markers ('None')
b	Grade +1 for a positive net change in inflammatory markers ('Anti')
c	Grade −1 for a negative net change in inflammatory markers ('Pro')
Cumulative upgrade of IS towards positive (+1) or negative (−1) values	
1	Controlled study (product or subject) with dairy test as a test product
2	Randomized study
3	Longitudinal study
4	The dairy product is not solely measured as part of a dietary pattern
5	≥2 inflammatory markers are changed
6	At least one inflammatory marker is measured in vivo (and not ex vivo)
7	The change in inflammatory marker is measured over ≥12h, e.g. not postprandially
8	The effect is still measured after washout period of at least one week
9	A dose-response is demonstrated with the dairy product
10	Bioactive molecules or the biological plausibility have been convincingly investigated
11	A clinical endpoint is changed that can be related to a metabolic dysregulation associated with inflammation

product" or "control product", (5) "study results" and "net change in inflammatory marker", (6–7) "study results", (8) "sustainability of effect over time", (9) "dose-response", (10) "biological plausibility" or "bioactive components", (11) "clinical evidence".

IS—The IS is the sum of the criteria reported above. Study results in which all criteria are fulfilled could thus theoretically reach an IS of −12 for results indicating a pro-inflammatory activity of dairy products and an IS of +12 for results indicating an anti-inflammatory activity of dairy products. Study results with an initial IS of 0 could not be modified by these criteria and the final IS thus remained 0, independently of the quality of the clinical study.

Table S1 provides an example of the calculation of the IS for one study result.

Determination of the IS for groups of study results

A median IS was calculated for the entire data set as well as for the following categories of study results:

- Subjects category (HEALTH, MET, GIT, HYPER);
- Fat content of dairy product (low-fat, high-fat);
- Fermentation status of dairy product (non-fermented, fermented).

Non-parametric statistics were conducted to analyze the data (significance level: $p<0.05$). The two-sided Wilcoxon Signed-Rank test was conducted to identify whether the median IS of the selected categories were statistically different from zero (H0: median IS=0; Ha: median IS≠0). A mean IS>0 indicated an anti-inflammatory effect whereas a pro-inflammatory effect was indicated by a mean IS<0. The Kruskall-Wallis test was conducted to identify difference in the mean IS between different categories of study results.

Results

Tables 3–5 show the tabulated summary of the 78 study results extracted from the 52 human studies retained for this review. Each table contains 25 descriptors covering a wide range of study characteristics including, amongst others, a description of the enrolled subjects, the test and control products, the study designs, and the IS (documented in the last line). Table 3 shows the data for study results with a positive IS, i.e., for results indicative of an anti-inflammatory effect of dairy products. Table 4 shows the data for study results with a negative IS, i.e., for results indicative of a pro-inflammatory effect of dairy products. Finally, Table 5 shows the data for study results with an IS=0, i.e., for results with no modulation of inflammatory processes by dairy products.

Figure 2 shows the overall distribution of the data obtained for each of the inflammatory markers listed in Table 1, that were measured at least once in the set of 78 study results reviewed. Out of the 98 inflammatory markers listed in Table 1, 57 markers were investigated at least once (58%). A total of 309 observations were reported with these inflammatory markers, 131 (42%) being accounted for by three cytokines, i.e., CRP (51 observations), IL-6 (44 observations), and TNF-α (36 observations). For each of these cytokines, the number of observations reporting no effect was the highest (CRP: 34 out of 51; IL-6: 26 out of 44; TNF-α: 23 out of 36) followed by the observations reporting an anti-inflammatory effect (CRP: 16 out of 51; IL-6: 15 out of 44; TNF-α: 11 out of 36). The number of these observations reporting a pro-inflammatory effect was the lowest for all three cytokines (CRP: 1 out of 51; IL-6: 3 out of 44; TNF-α: 2 out of 36). The only parameter systematically pointing to the pro-inflammatory state was 'eosinophil count' (5 out of 5), a parameter that was exclusively measured in studies investigating subjects with milk allergy and thus categorized in the subject category HYPER.

Taking into account the quality of all studies reviewed in the present article, we have developed a quantitative method that calculates an IS based on the range of eleven criteria listed in Table 2. Figure 3 presents the results of this analysis. Panel A first illustrates the number of study results identified with evidence for an anti-inflammatory activity (32 study results), a pro-inflammatory activity (19 results), or no change in inflammatory activity (27 study results). Panel B shows a distribution of the IS calculated for each of these study results, according to the criteria presented in Table 2. Although both panels in Figure 3 illustrate that the study results are well distributed among all three categories (anti-inflammatory, no effect, pro-inflammatory), the data indicating an anti-inflammatory activity appear to prevail over data pointing to a pro-inflammatory activity. This observation was confirmed by the positive mean IS for the set of 78 study results and the rejection of the null hypothesis for the median IS in the two-sided Wilcoxon Signed-Rank test, indicating an anti-inflammatory activity of dairy products (Table 6).

When the results were stratified according to subject categories, differences in the distribution of the study results appeared between these categories (Figure 4). The group of 37 study results investigating healthy subjects, was characterized by study results covering each of the three possible effects (anti-inflammatory, no effect, pro-inflammatory). On the other hand, the group of 24 study results investigating subjects with metabolic disorders, including healthy obese subjects, was characterized by a lack of data pointing to a pro-inflammatory effect. The groups of study results investigating subjects with

Table 3. Tabulated summary of the study results with evidence for an anti-inflammatory effect of dairy products.

Reference	(Zemel & Sun, 2008) 1	(Zemel & Sun, 2008) 2	(Sugawara *et al.*, 2012)	(Stancliffe *et al.*, 2011)	(Zemel *et al.*, 2010)	(Holmer-Jensen *et al.*, 2011)
Subject category	MET	MET	OTHER	MET	MET	MET
Target indication	Oxidative stress and inflammation	Oxidative stress and inflammation	Chronic obstructive pulmonary disease	Metabolic syndrome	Overweight and obesity	Low-grade inflammation
Target population	Obese subjects	Obese subjects	Elderly with chronic obstructive pulmonary disease	Metabolic syndrome subjects	Overweight and obese subjects	Obese non-diabetic subjects
Fat content	Low-fat	High-fat	High-fat	N.a.	Low-fat	N.a.
Fermentation	Fermented	N.a.	Non-fermented	N.a.	Non-fermented	Non-fermented
Test product	Yoghurt	High dairy diet (milk, yoghurt, hard cheese)	Nutritional supplement containing whey peptides plus low intensity exercise	Adequate dairy diet	Milk smoothies containing 350 mg calcium	Fat-rich meal supplemented with cod protein, whey isolate, gluten or casein
Control product	Sugar-free, calcium-free gelatin dessert	Low dairy diet	Normal diet plus low intensity exercise	Low dairy diet	Soy smoothies containing 50 mg calcium	
Test subjects	13 F, 5 M / 39±10 y / obese	17 / 42.5±2.6 y / obese	15 M, 2 F / 77.4±5.2 y / COPD	10 M, 10 F / 34.4±9.4 y / overweight and obese with metabolic syndrome	14 M, 6 F/ 31±10.3 y / overweight or mildly obese adults	8 F, 3 M / 52±9.4 y / non-diabetic obese
Control subjects	14 F, 2 M / 42±6 y / obese	17 / 41.3±2.7 y / obese	14 M, 0 F / 77.1±5.8 y / COPD	9 M, 11 F / 39.5±10.2 y / overweight and obese with metabolic syndrome		
Diet	3×6 oz yoghurt, including a caloric deficit of 500 kcal/d / 12 weeks	3 dairy servings / 24 weeks / isocaloric	2×200 kcal of nutritional supplement plus low intensity exercise / 3 months	Adequate dairy (>3.5 servings/d) or low dairy (<0.5 servings/d) / 7, 28, 84 days	3 smoothies/d / 28 days	5'000 KJ fat-rich meal and 45 g protein / single challenge study
Controlled dairy test	Yes	Yes	Yes	Yes	Yes	Yes
Randomization	Randomized	Randomized	Randomized	Randomized	Randomized	Randomized
Time factor	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Longitudinal
Study results	[1]Yoghurt (high Ca) vs control (low Ca): CRP ↓; *adiponectin* ↑	[1]High dairy vs low dairy: CRP ↓; *adiponectin* ↑	[1]Treatment (whey supplement + exercise) vs control (normal diet + exercise): CRP, IL-6, IL-8, TNF-α ↓	[1]Adequate dairy vs low dairy: TNF-α, MCP-1, IL-6, CRP ↓; *adiponectin* ↑	[1]Milk vs soy smoothies: IL-6, TNF-α, MCP-1, CRP ↓; *adiponectin* ↑; IL-15 →	[1]Whey vs cod (4h iAUC postprandial): CCL5/RANTES, MCP-1 ↓, IL-1ra, IFN-g, *adiponectin*, eotaxin, IP-10, MIP-1β, VEGF →
Net change in inflammatory marker	2	2	4	5	5	2
Sustainibility of effect over time	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Dose-response	No	No	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Discussed - Ca signaling, ROS, angiotensin-converting enzyme, fat oxidation, energy utilisation	Discussed - Ca-signaling, ROS, angiotensin-converting enzyme, fat oxidation, energy utilisation	Discussed - cytokine production	Discussed - calcitriol signaling and adiposity-induced inflammatory cytokines	Not discussed	Not discussed
Bioactive components	Investigated - calcium	Investigated - calcium	Discussed - whey peptides	Discussed - calcium, whey protein	Discussed - ACE inhibitors, bioactive peptides, leucine	Not discussed
Clinical evidence	Yes - yoghurt improves fat loss	Yes - calcium-rich foods improve fat loss	Yes - improvement of metabolic and respiratory functions	Yes - reduction of waist circumference and trunk fat	Yes - reduction of oxidative stress markers	Yes - insulinotropic effect of whey proteins
Financing of research	Private	Private	Not presented	Private	Private	Public
Grading criteria	Anti, 1, 2, 3, 4, 5, 6, 7, 10, 11	Anti, 1, 2, 3, 4, 5, 6, 7, 10, 11	Anti, 1, 2, 3, 4, 5, 6, 7, 11	Anti, 1, 2, 3, 4, 5, 6, 7, 11	Anti, 1, 2, 3, 4, 5, 6, 7, 11	Anti, 1, 2, 3, 4, 5, 6, 11
IS	10	10	9	9	9	8

(*Continued on next page*)

Table 3. (Continued)

Reference	(Hunter *et al.*, 2012)	(de Aguilar-Nascimento *et al.*, 2011)	(Panagiotakos *et al.*, 2010) 1	(Panagiotakos *et al.*, 2010) 2	(Panagiotakos *et al.*, 2010) 3	(Panagiotakos *et al.*, 2010) 4
Subject category	HEALTH	MET	HEALTH	HEALTH	HEALTH	HEALTH
Target indication	Oxidative stress	Acute ischemic stroke	Cardiovascular disease	Cardiovascular disease	Cardiovascular disease	Cardiovascular disease
Target population	Smokers	Elderly with acute ischemic stroke fed on enteral formula	Healthy adults	Healthy adults	Healthy adults	Healthy adults
Fat content	Low-fat	N.a.	High-fat	High-fat	Low-fat	High-fat
Fermentation	Non-fermented	Non-fermented	Fermented	Non-fermented	Non-fermented	N.a.
Test product	Non-supplemented milk	Enteral feeding formula containing hydrolized whey protein	High dairy diet (cheese)	High dairy diet (full-fat milk)	High dairy diet (low fat milk)	High dairy diet
Control product	Lemonade	Enteral formula containing hydrolized casein protein	Low dairy diet (cheese)	Low dairy diet (full-fat milk)	Low dairy diet (low fat milk)	Low dairy diet
Test subjects	18 M, 25 F/ 30-63 y / healthy smokers	6 M, 4 F/ 67-88 y / acute ischemic stroke	1514 M, 1528 F / 25-50 y / healthy	1514 M, 1528 F / 25-50 y / healthy	1514 M, 1528 F / 25-50 y / healthy	1514 M, 1528 F / 25-50 y / healthy
Control subjects	—	3 M, 12 F / 66-90 y / acute ischemic stroke	456 M, 292 F / 33-53 y / healthy	456 M, 292 F / 33-53 y / healthy	456 M, 292 F / 33-53 y / healthy	456 M, 292 F / 33-53 y / healthy
Diet	2 weeks lemonade run-in / 400 mL test product 1,2 or 3 / 6 weeks separated by 4 weeks washout	Formula / 20 mL/h / 5 days	Cheese / servings/week: <8; 8-10; 11-14; >14 / frequency of consumption over past year (FFQ)	Full-fat milk / servings/week: <8; 8-10; 11-14; >14 / frequency of consumption over past year (FFQ)	Low-fat milk / servings/week: <8; 8-10; 11-14; >14 / frequency of consumption over past year (FFQ)	Dairy / servings/week: <8; 8-10; 11-14; >14 / frequency of consumption over past year (FFQ)
Controlled dairy test	Yes	Yes	Yes	Yes	Yes	Yes
Randomization	Randomized	Randomized	Randomized	Randomized	Randomized	Randomized
Time factor	Longitudinal	Longitudinal	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Study results	[1]Non-supplemented milk vs lemonade: p-selectin, tPA, MCP-1, IL-8, VCAM →; IL-6, IL-1β, TNF-α ↓	[1]Whey formula vs casein formula: CRP →; IL-6 ↓	[5]Feta cheese: corr↓ with CRP, IL-6; corr→ with TNF-α (not adjusted for confounders)	[5]High-fat milk: corr↓ with IL-6, TNF-α; corr→ with CRP (not adjusted for confounders)	[5]Low-fat milk: corr↓ with CRP, IL-6, TNF-α (not adjusted for confounders)	[5]Full-fat dairy: corr↓ with CRP, IL-6, TNF-α (adjusted for confounders)
Net change in inflammatory marker	3	2	2	2	3	3
Sustainibility of effect over time	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Dose-response	No	No	Yes	Yes	Yes	Yes
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Discussed - anti-inflammatory activities	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Bioactive components	Discussed - whey proteins, lactalbumin, lactoglobulin, lactoferrin	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Clinical evidence	N.a.	No	No - obesity, hypertension and diabetes mellitus did not correlate with the consumption of dairy products	No - obesity, hypertension and diabetes mellitus did not correlate with the consumption of dairy products	No - obesity, hypertension and diabetes mellitus did not correlate with the consumption of dairy products	No - obesity, hypertension and diabetes mellitus did not correlate with the consumption of dairy products
Financing of research	Public	Private	Public	Public	Public	Public
Grading criteria	Anti, 1, 2, 3, 4, 5, 6, 7	Anti, 1, 2, 3, 4, 5, 6, 7	Anti, 1, 2, 4, 5, 6, 7, 9	Anti, 1, 2, 4, 5, 6, 7, 9	Anti, 1, 2, 4, 5, 6, 7, 9	Anti, 1, 2, 4, 5, 6, 7, 9
IS	8	8	8	8	8	8

Reference	(Panagiotakos *et al.*, 2010) 5	(Panagiotakos *et al.*, 2010) 6	(van Meijl & Mensink, 2010)	(Sofi *et al.*, 2010) 1	(Pintus *et al.*, 2013) 1	(Nestel *et al.*, 2012) 1
Subject category	HEALTH	HEALTH	MET	HEALTH	MET	MET
Target indication	Cardiovascular disease	Cardiovascular disease	Metabolic syndrome and cardiovascular disease	Atherosclerosis	Hypercholesterolemia	Systemic inflammation
Target population	Healthy adults	Healthy adults	Overweight and obese subjects	Healthy adults	Mildly hypercholesterolaemic subjects	Overweight or obese subjects
Fat content	Low-fat	Low-fat	Low-fat	High-fat	High-fat	High-fat
Fermentation	N.a.	Fermented	N.a.	Fermented	Fermented	Non-fermented
Test product	High dairy diet	High dairy diet (low-fat yoghurt)	Low-fat dairy (milk and yoghurt)	Pecorino sheep cheese naturally high in CLA	Sheep cheese naturally enriched with CLA	Butter
Control product	Low dairy diet	Low dairy diet (low-fat yoghurt)	Carbohydrate-rich product	Commercial cow cheese low in CLA	Sheep cheese with pill containing 1 g of a palm oil–soybean oil mix	—
Test subjects	1514 M, 1528 F / 25-50 y / healthy	1514 M, 1528 F / 25-50 y / healthy	10 M, 25 F / 50±13 y / BMI: 32±4	4 M, 6 F / 30-65 y / healthy	19 M, 23 F / 30-60 y / mild hypercholesterolaemia	13 / 61.6±7.6 y / overweight or obese
Control subjects	456 M, 292 F / 33-53 y / healthy	456 M, 292 F / 33-53 y / healthy	—	—	—	—
Diet	Low-fat dairy / servings/ week: <8; 8-10; 11-14; >14 / frequency of consumption over past year (FFQ)	Low-fat yoghurt / servings/ week: <8; 8-10; 11-14; >14 / frequency of consumption over past year (FFQ)	Milk (500 mL/d), yoghurt (150 g/d) / 8 weeks	Cheese / 200 g/week / 10 weeks	Naturally enriched sheep cheese or control cheese / 90 g/d / 3 weeks / between 3 weeks washout	50 g butter / postprandial challenge study
Controlled dairy test	Yes	Yes	Yes	Yes	Yes	No
Randomization	Randomized	Randomized	Randomized	Non-randomized	Randomized	N.a.
Time factor	Cross-sectional	Cross-sectional	Longitudinal	Longitudinal	Longitudinal	Longitudinal
Study results	[5]Low-fat dairy: corr↓ with CRP, IL-6, TNF-α (adjusted for confounders)	[5]Low-fat yoghurt: corr↓ with TNF-α; corr→ with CRP, IL-6 (not adjusted for confounders)	[1]Low-fat dairy vs carbohydrate-rich meal: *s-TNFR-2* ↑, TNF-α, s-TNFR-1, MCP-1, ICAM-1, VCAM-1 →	[1]Pecorino vs control cheese: IL-6, IL-8, TNF-α ↓; IL-10, IL-12 →	[1]Enriched sheep cheese vs control cheese: IL-6 (n = 16), CRP (n = 16), leptin (n = 16), *adiponectin* (n = 16) →; anandamide ↓	[3]Butter (3h vs 0h): MCP-1, MIP-1α, ICAM-1, VCAM-1 →; IL-6, IL-1β, TNF-α, CRP ↓
Net change in inflammatory marker	3	1	1	3	1	4
Sustainibility of effect over time	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Dose-response	Yes	Yes	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Not discussed	Not discussed	Not discussed	Discussed - anti-inflammatory and anti-atherogenic pathways	Not discussed	Not discussed
Bioactive components	Not discussed	Not discussed	Not discussed	Discussed - CLA, eventually other nutrients in sheep milk	Not discussed	Not discussed
Clinical evidence	No - obesity, hypertension and diabetes mellitus did not correlate with the consumption of dairy products	No - obesity, hypertension and diabetes mellitus did not correlate with the consumption of dairy products	No	No	No	N.a.
Financing of research	Public	Public	Private	Public	Public	Private
Grading criteria	Anti, 1, 2, 4, 5, 6, 7, 9	Anti, 1, 2, 4, 6, 7, 9	Anti, 1, 2, 3, 4, 6, 7	Anti, 1, 3, 4, 5, 6, 7	Anti, 1, 2, 3, 4, 6, 7	Anti, 2, 3, 4, 5, 6
IS	8	7	7	7	7	6

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Table 3. (Continued)

Reference	(Wang *et al.*, 2011) 1	(Meyer *et al.*, 2011) 1	(Meyer *et al.*, 2011) 2	(Jones *et al.*, 2013) 1	(Romeo *et al.*, 2011)	(Nestel *et al.*, 2012) 2
Subject category	HEALTH	HEALTH	HEALTH	MET	HEALTH	MET
Target indication	Obesity and cardiovascular disease	Coronary heart disease	Coronary heart disease	Metabolic syndrome (MS)	Cardiovascular disease	Systemic inflammation
Target population	Normal-weight and overweight adolescents	General population	General population	Overweight and obese MS participants	Children	Overweight or obese subjects
Fat content	High-fat	High-fat	High-fat	Low-fat	High-fat	High-fat
Fermentation	Non-fermented	Non-fermented	Non-fermented	N.a.	Non-fermented	Non-fermented
Test product	Dairy fatty acids	Inflammatory risk dietary pattern (IRDP), containing butter	Inflammatory risk dietary pattern (IRDP), containing curd	High dairy, high calcium diet plus caloric restriction	Dairy product enriched with nutrients	Cream
Control product	—	—	—	Low dairy low calcium diet plus caloric restriction	Milk	—
Test subjects	62 M, 51 F / 14.7±1.2 y / overweight	981 M / 45-64 y / healthy	981 M / 45-64 y / healthy	7 M, 13F / 52.1±1.5 y / obese with MS	27 M, 26 F / 8-14 y / healthy	13 / 61.6±7.6 y / overweight or obese
Control subjects	—	—	—	7 M, 11F / 50.1±2.7 y / obese with MS	26 M, 25 F / 8-14 y / healthy	—
Diet	FFQ / measurements of dairy fatty acids	Diet assessment (FFQ)	Diet assessment (FFQ)	3–4 servings low-fat dairy (milk or yoghurt)/d and 350 mg/d Ca supplement or 1 serving of yoghurt/d	600 mL test or control product per day / 5 months	115 ml cream / postprandial challenge study
Controlled dairy test	No	No	No	Yes	No	No
Randomization	N.a.	N.a.	N.a.	Randomized	N.a.	N.a.
Time factor	Cross-sectional	Cross-sectional	Cross-sectional	Longitudinal	Longitudinal	Longitudinal
Study results	[5]Dairy fatty acids: corr↓ with CRP; corr→ with TNF-α (adjusted for confounders)	[7]Pattern including butter: corr ↓ with IL-6, CRP, IL-18 (not adjusted for confounders)	[7]Pattern including curd: corr ↓ with IL-6, CRP; corr → with IL-18 (not adjusted for confounders)	[1]High dairy diet and Ca (0.5h) vs low dairy diet (0.5h): IL-6, TNF-α, IL-1ß →; MCP-1: ↓	[2]Milk (m5 vs m0): E-selectin, VCAM-1, ICAM-1, WBC count (leukocytes, neutrophils, lynphocytes, eosinophils, monocytes) →; *adiponectin* ↓	[2]Cream (3h vs 0h): MCP-1, MIP-1a, ICAM-1, IL-6, IL-1β, TNF-α, CRP ↓; VCAM-1 →
Net change in inflammatory marker	1	3	2	1	1	7
Sustainibility of effect over time	Not discussed	Not dicussed	Not dicussed	No	Not discussed	Not discussed
Dose-response	No	No	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	No	Not discussed	Not discussed
Biological plausibility	Investigated - odd-numbered dairy fatty acids accumulate in epididymal fat rather than being β-oxidized in liver	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Bioactive components	Investigated - dairy fatty acids (15:0, 17:0)	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Clinical evidence	Yes - higher levels of dairy fatty acids associated with lower markers of oxidative stress	Yes - inflammatory dietary pattern significantly associated with all-cause mortality; butter contributed negatively to the effect	Yes - inflammatory dietary pattern significantly associated with all-cause mortality; curd contributed negatively to the effect	No	No - no effect on albumin, ferritin, glucose and insulin	N.a.
Financing of research	Public	Public	Public	Public	Private	Private
Grading criteria	Anti, 4, 6, 7, 10, 11	Anti, 4, 5, 6, 7, 11	Anti, 4, 5, 6, 7, 11	Anti, 1, 2, 3, 4, 6	Anti, 3, 4, 6, 7	Anti, 3, 4, 5, 6
IS	6	6	6	6	5	5

Reference	(Nestel *et al.*, 2012) 3	(Meyer *et al.*, 2011) 3	(Meyer *et al.*, 2011) 4	(Anderson *et al.*, 2012) 1	(Esmaillzadeh *et al.*, 2007) 1	(Nettleton *et al.*, 2006) 1
Subject category	MET	HEALTH	HEALTH	HEALTH	HEALTH	HEALTH
Target indication	Systemic inflammation	Coronary heart disease	Coronary heart disease	Insulin sensitivity and systemic inflammation	Systemic inflammation	Cardiovascular disease
Target population	Overweight or obese subjects	General population	General population	General population	Healthy women	Healthy adults
Fat content	Low-fat	High-fat	High-fat	Low-fat	Low-fat	Low-fat
Fermentation	N.a.	Fermented	Non-fermented	N.a.	N.a.	N.a.
Test product	Low-fat dairy	Inflammatory risk dietary pattern (IRDP), containing cheese	Inflammatory risk dietary pattern (IRDP), containing condensed milk and cream	Food cluster including low-fat dairy products	Dietary patterns including low-fat dairy products	Dietary patterns low-fat milk and yoghurt
Control product	—	—	—	Food cluster high-fat dairy products	—	—
Test subjects	13 / 61.6±7.6 y / overweight or obese	981 M / 45-64 y / healthy	981 M / 45-64 y / healthy	1751 M and F / 70-79 y / healthy	486 F / 40-60 y / healthy	2407 M, 2682 F / 45-84 y / healthy
Control subjects	—	—	—	—	—	—
Diet	400 mL reduced fat milk / postprandial challenge study	Diet assessment (FFQ)	Diet assessment (FFQ)	Diet assessment (FFQ)	Diet assessment (FFQ)	Diet assessment (FFQ)
Controlled dairy test	No	No	No	Yes	No	No
Randomization	N.a.	N.a.	N.a.	N.a.	N.a.	N.a.
Time factor	Longitudinal	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Study results	[2]Low-fat dairy (3h vs 0h): MCP-1, MIP-1α, ICAM-1, VCAM-1 $\rightarrow$; IL-6, IL-1β, TNF-α, CRP $\downarrow$	[7]Pattern including cheese: corr $\downarrow$ with IL-6; corr $\rightarrow$ with CRP, IL-18 (not adjusted for confounders)	[7]Pattern including condensed milk and cream: corr $\downarrow$ with CRP; corr $\rightarrow$ with IL-6, IL-18 (not adjusted for confounders)	[6]Cluster including low-fat dairy vs cluster with high-fat dairy products: IL-6 $\downarrow$; TNF-α, CRP $\rightarrow$	[7]Pattern including low-fat dairy: corr$\downarrow$ with CRP, VCAM-1; corr$\rightarrow$ with TNF-α, SAA, IL-6, E-selectin, ICAM-1 (after adjustment for confounders)	[7]Pattern including low-fat milk and yoghurt: corr$\downarrow$ with CRP, IL-6, ICAM-1; corr$\rightarrow$ with E-selectin (adjusted for confounders)
Net change in inflammatory marker	4	1	1	1	2	3
Sustainibility of effect over time	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Dose-response	No	No	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Not discussed	Not discussed	Not discussed	Discussed - interaction between dietary pattern and PPAR-γ genotype	Not discussed	Not discussed
Bioactive components	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Clinical evidence	N.a.	Yes - inflammatory dietary pattern significantly associated with all-cause mortality; cheese contributed negatively to the effect	Yes - inflammatory dietary pattern significantly associated with all-cause mortality; condensed milk and cream contributed negatively to the effect	Yes - cluster containing low-fat dairy associated with greater insulin sensitivity than cluster with high-fat dairy products	N.a.	No
Financing of research	Private	Public	Public	Public	Public	Public
Grading criteria	Anti, 3, 4, 5, 6	Anti, 4, 6, 7, 11	Anti, 4, 6, 7, 11	Anti, 1, 6, 7, 11	Anti, 5, 6, 7	Anti, 5, 6, 7
IS	5	5	5	5	4	4

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Table 3. (Continued)

Reference	(Dawczynski *et al.*, 2013)	(Hlebowicz *et al.*, 2011) 1
Subject category	MET	HEALTH
Target indication	Hypertriacylglyceridemia and CVD	Cardiovascular disease
Target population	Adults with hypertriacylglyceridemia and risk of CVD	General population
Fat content	High-fat	Low-fat
Fermentation	Fermented	Non-fermented
Test product	Two yoghurts differently enriched with fat (fish oil)	Dietary pattern including low-fat milk
Control product	Yoghurt	Dietary pattern including high-fat dairy products (cheese, whole milk, butter)
Test subjects	1) 17 / 61.6±11.9 y / hypertriacylglyceridemia 2) 16 / 61.8±7.1 y / hypertriacylglyceridemia	2040 M, 2959 F / 45-68 y / healthy
Control subjects	14 / 58.2±7.4 y / hypertriacylglyceridemia	—
Diet	125 g control or test product / 10 weeks	Diet assessment (FFQ) / 13 y of follow-up for CVD events
Controlled dairy test	No	Yes
Randomization	N.a.	N.a.
Time factor	Longitudinal	Cross-sectional
Study results	[2]Yoghurt (w10 vs w0): CRP, IFN-g (T-cells *ex vivo*) →; TNF-α (T-cells *ex vivo*) ↓	[6]Low-fat milk pattern vs high-fat dairy pattern: WBC ↓; CRP →
Net change in inflammatory marker	1	1
Sustainibility of effect over time	Not discussed	N.a.
Dose-response	No	No
Bioavailibility data	Not discussed	Not discussed
Biological plausibility	Not discussed	Not discussed
Bioactive components	Discussed - PUFA	Not discussed
Clinical evidence	No - cardiovascular risk factors not changed after 10 weeks	No
Financing of research	Public	Public
Grading criteria	Anti, 3, 4, 7	Anti, 1, 6, 7
IS	4	4

gastrointestinal disorders (8 study results) and of subjects with allergy to dairy products (6 study results) lacked study results indicative of an anti-inflammatory effect.

These observations were statistically confirmed by comparing the distribution of the IS for the groups of study results investigating healthy subjects and subjects with metabolic disorders (Table 6). Both mean IS were positive and the null hypothesis for the median IS in the two-sided Wilcoxon Signed-Rank test was rejected, pointing to an anti-inflammatory activity of dairy products in these two subject categories. The mean IS of the MET subject category were higher than for the HEALTH subject category, but the Kruskal-Wallis test did not point to a statistically significant difference in the median IS between both subject categories. The mean IS for the GIT subject category was negative, but the Wilcoxon Signed-Rank test on the median IS did not point to a statistically significant effect. However, the mean IS for the HYPER subject category was negative and the null hypothesis for the median IS in the two-sided Wilcoxon Signed-Rank test was rejected, indicating a pro-inflammatory effect of dairy products in subjects allergic to dairy products. Finally, a group of studies in which the subjects could not be attributed to any of the above categories, had a median IS that was statistically not different from zero.

In order to investigate the impact of dairy product processing, in particular fat processing and fermentation on the IS, the study results were stratified according to the fat content and fermentation status of the dairy products investigated.

Thirty-five study results with high-fat dairy products and 20 study results with low-fat products were reported (Figure 5). In contrast to the high-fat products, none of the study results with low-fat products indicated a pro-inflammatory activity. The mean IS of the low-fat product category was, indeed, lower than for the high-fat product category but the Kruskal-Wallis test on the median IS did not demonstrate this difference to reach statistical significance (p=0.083). However, the mean IS of each product category was positive and the null hypothesis for the median IS in the two-sided Wilcoxon Signed-Rank test was rejected, indicating an anti-inflammatory activity for both low-fat and high-fat dairy products (Table 6).

Thirty-three study results could be identified in which non-fermented dairy products were investigated, whereas 16 study results were reported with fermented products (Figure 6). The mean IS of both the non-fermented and fermented product category were positive, but the two-sided Wilcoxon Signed-Rank test on the median IS only indicated a significant anti-inflammatory activity for the fermented product category (Table 6).

In an attempt to identify the bioactive nutrients potentially modulating inflammation, and to complement the human data with preclinical data, we conducted a non-systematic and non-quantitative evaluation of the literature available on the inflammatory properties of dairy products in animal models (unpublished data). Most of these studies reported an anti-inflammatory effect; however, due to the different animal models and protocols used in the selected articles, it was not possible to compare results and to perform an analysis as we did for human studies. It was anyway clear that the importance of identifying the molecule(s) responsible for the effect, and its mechanism of action, is poorly considered in animal studies, too.

Discussion

Pro- and ant-inflammatory properties of dairy products

Overall, the IS of the entire data set composed of 78 study results, extracted from 52 human studies indicates that the consumption of dairy products is associated with anti-inflammatory properties in humans. We qualify this association as weak, although significant, because the IS has a low magnitude that is indicative of a low level of confidence in the effect estimate.

By stratifying the study results according to the health status of the enrolled subjects, we identified a pro-inflammatory activity of dairy products in subjects with milk allergy. This result is mechanistically expected, as hypersensitive reactions can obviously be linked to the pro-inflammatory state (Savilahti and Westerholm-Ormio, 2004). We therefore conclude that the IS is an adequate tool to evaluate the impact of food and dietary patterns on inflammation.

A systematic review recently assessed eight randomized controlled nutritional intervention studies, which have investigated the impact of dairy product consumption on biomarkers of inflammation in overweight and obese adults (Labonte et al., 2013). The authors concluded that the consumption of dairy products did not exert adverse effects on biomarkers of inflammation in these subjects, and that limitations among these studies did not allow for the differentiation between a beneficial or neutral impact of dairy products on inflammation. In our review, stratifying the data according to the health status of the subjects, allowed us to identify 24 study results in the MET subject category. The IS of this data set indicates an anti-inflammatory property of dairy products in subjects with metabolic disorders. Noteworthy, the significantly positive IS was also indicative of an anti-inflammatory effect of dairy products in the HEALTH group. We found, however, a trend towards a higher IS in the MET group, compared to the HEALTH group suggesting a stronger evidence for an anti-inflammatory activity of dairy products in the former subject category. This finding is illustrated by the identification of ten studies reporting a pro-inflammatory activity of dairy products in the HEALTH group, whereas the MET group is the only category in which none of the studies reported a pro-inflammatory activity of dairy products. The specific reactivity of the MET group may be linked mechanistically to the inflammatory nature of obesity. Obesity is associated with a low-grade systemic chronic inflammatory state, characterized by the abnormal production of inflammatory cytokines (Guri and Bassaganya-Riera, 2011; Schwander et al., 2014). As low-grade systemic inflammation links obesity to metabolic pathologies, including insulin resistance, cardiovascular diseases, or type-2 diabetes, targeting obesity-related inflammatory components may be a useful preventive strategy. Low-grade chronic inflammation is modulated by nutrients such as fatty acids, glucose, bioactive plant compounds, vitamins and minerals, which either enhance or alleviate the inflammatory state (Hirai et al., 2010). In this context, as obese subjects are characterized by low-grade systemic inflammation, the MET group may be more prone to the anti-inflammatory action of dairy products than metabolically healthy subjects.

Stratifying the data according to categories of dairy products, revealed an anti-inflammatory activity for both low-fat

Table 4. Tabulated summary of the study results with evidence for a pro-inflammatory effect of dairy products.

Reference	(Iacono *et al.*, 1998)	(Kristjansson *et al.*, 2007)	(Rebholz *et al.*, 2013)	(Henderson *et al.*, 2012)	(Ulsemer *et al.*, 2012)	(Kagalwalla *et al.*, 2011)
Subject category	HYPER	GIT	HEALTH	HYPER	HEALTH	HYPER
Target indication	Chronic constipation	Coeliac disease	Cardiovascular disease risk	Food allergy	General health	Food allergy
Target population	Children with chronic constipation	Subjects with coeliac disease	Healthy adults	Subjects with food allergies	General population	Children with eosinophilic esophagitis
Fat content	High-fat	N.a.	N.a.	N.a.	N.a.	N.a.
Fermentation	Non-fermented	Non-fermented	Non-fermented	N.a.	N.a.	N.a.
Test product	Milk	Milk powder, purified bovine casein and b-lactalbumin	Milk protein supplement	SFED (six food elimination diet): milk, soy, wheat, egg, peanuts/tree nuts, seafood	Spray-dried pasteurised fermented milk products with inactivated B. xylanisolvens	SFED (six food elimination diet): cow's milk, soy, wheat, egg, peanuts/tree nuts, seafood
Control product	Soy milk	—	Carbohydrate placebo	—	Milk powder	—
Test subjects	29 M, 36 F / 34.6±17.1 mo / constipation and perianal lesions with pain on defecation	6 M, 14 F / 25-68 y / coeliac disease	34 F, 68 M / 46 y / healthy	98 / ≤ 21 y / eosinophilic esophagitis	47 M, 43 F / 18-65 y / healthy	25 M, 11 F / 7.6±4.3 y / eosinophilic esophagitis
Control subjects	—	10 M, 5 F / 19-58 y / healthy	—	—	12 M, 16 F / 18-65 y / healthy	—
Diet	470±135 mL/d Milk and 450± 120 mL/d soy milk / 15 days	Single rectal challenge with wheat gluten, dried cow's milk powder in NaCl, α-lactalbumin and casein	Milk protein or placebo / 40 g/d / 2 weeks intervention separated by 3 weeks washout	SFED / 4 months	2 weeks depletion / 1 serving/d / 6 weeks intervention / 2 weeks recovery	SFED / ≥ 6 weeks / reintroduction of foods
Controlled dairy test	Yes	Yes	Yes	No	No	No
Randomization	Randomized	Randomized	Randomized	N.a.	N.a.	N.a.
Time factor	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Longitudinal
Study results	[1]Milk vs soy milk: IgE, infiltration of inflammatory cells in rectal mucosa ↑; CRP →	[4]Milk (coeliac vs healthy): Myeloperoxidase (MPO), NO ↑; Eosinophil cationic protein (ECP) →	[1]Milk protein vs carbohydrate: CRP, IL-6, TNF-α, VCAM-1, ICAM-1, leptin, *adiponectin* →; E-selectin ↑	[6]SFED (m4 vs baseline): eosinophilic esophagitis (eosinophil count) ↓	[2]Milk powder (w3, w6, w8 vs w0): *ex vivo* phagocytotic activity of granulocytes (w3), *ex vivo* NK cell activities (w3, w6), TNF-α (w8) ↑; all other conditions including CRP, WBC and, lymphocyte counts →	[6]SFED (≥w6 vs baseline): eosinophilic esophagitis (eosinophil count) ↓
Net change in inflammatory marker	-2	-2	-1	-1	-3	-1
Sustainibility of effect over time	N.a.	Not discussed	Not discussed	N.a.	No	N.a.
Dose-response	No	No	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Discussed - hypersensitivity and infiltration of eosinophils influence constipation	Discussed - innate immune response to milk protein, and casein	Not discussed	Investigated - re-occurrence eosinophilic esophagitis after milk reintroduction	Not discussed	Investigated - re-occurrence eosinophilic esophagitis after milk reintroduction
Bioactive components	Not discussed	Investigated - bovine casein	Not discussed	Not discussed	Not discussed	Discussed - milk antigens (peptides)
Clinical evidence	Yes - anal lesions tended to disappear after removal of milk and introduction of soy milk	N.a.	No - cardiovascular risk factors do not change significantly	Yes - SFED reduces endoscopic and histopathologic features of eosinophilic esophagitis	No - control milk powder did not modify liver enzyme values	Yes - reduction endoscopic and histopathologic features of eosinophilic esophagitis
Financing of research	Not presented	Private and Public	Public	Private	Private	Private and Public
Grading criteria	Pro, 1, 2, 3, 4, 5, 6, 7, 11	Pro, 1, 2, 3, 4, 5, 6, 7, 10	Pro, 1, 2, 3, 4, 6, 7	Pro, 3, 6, 7, 10, 11	Pro, 3, 4, 5, 6, 7	Pro, 3, 6, 7, 10, 11
IS	-9	-9	-7	-6	-6	-6

Reference	(Spergel *et al.*, 2005)	(Gonsalves *et al.*, 2012)	(Kagalwalla *et al.*, 2012)	(Deopurkar *et al.*, 2010)	(Jyonouchi *et al.*, 2002)	(Meyer *et al.*, 2007)
Subject category	HYPER	HYPER	GIT	HEALTH	GIT	HEALTH
Target indication	Food allergy	Food allergy	Eosinophilic esophageal inflammation	Postprandial oxidative stress and inflammation	Gastrointestinal symptoms	Systemic immunity
Target population	Subjects allergic to milk and patients with eosinophilic esophagitis	Adults with eosinophilic esophagitis	Children with eosinophilic esophageal inflammation	General population	Children with autism spectrum disorder	Healthy subjects
Fat content	N.a.	N.a.	N.a.	High-fat	N.a.	N.a.
Fermentation	N.a.	N.a.	N.a.	Non-fermented	Non-fermented	Fermented
Test product	Elimination diet excluding milk	SFED (six food elimination diet): milk, soy, wheat, egg, peanuts/tree nuts, seafood	Milk	Cream	Milk protein	Probiotic yoghurt
Control product	—	—	—	Water	—	Conventional yoghurt
Test subjects	100 M, 46 F / 6.50±4.50 y / eosinophilic esophagitis	25 M, 25 F / 19-76 y / eosinophilic esophagitis	12 M, 5 F / 5.5±3.2 y / eosinophilic esophagitis	48 / 25-47 y / healthy	59 M,13 F/ 1-17 y / autism spectrum disorder (ASD) 17 M, 7 F / 0.5-13 y / dietary protein intolerance (DPI)	33 F / 22-29 y / healthy
Control subjects	—	—	—	—	12 M, 3 F / 1-16 y / healthy 18 M, 8 F / 0.5-2 y / healthy siblings	—
Diet	Elimination diet milk / 4-8 weeks	SFED / 6 weeks / reintroduction by addition of one food group every 2 weeks	Milk elimination / 6 weeks	33 g cream or 300 mL / postprandial challenge study	*Ex vivo* activation of (PBMCs) by dietary allergens (e.g.milk protein)	100 g/d conventional or probiotic yoghurt / 2 weeks / 2 weeks washout / 200 g/d yoghurt / 2 weeks
Controlled dairy test	No	No	No	Yes	Yes	No
Randomization	N.a.	N.a.	N.a.	Non-randomized	Non-randomized	N.a.
Time factor	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Cross-sectional	Longitudinal
Study results	[2]Milk elimination diet (w4-8 vs baseline): eosinophilic esophagitis ↓	[6]SDEF (w6 vs baseline): eosinophilic esophagitis ↓	[2]Milk elimination (w6 vs w0) : eosinophil count ↓	[3]Cream (1h, 3h and 5 h vs 0h): TNF-α:↑ at 1h and 3h; → at 5h; IL-1β: → at 1h; ↑ at 3h and 5h; IL-6: → at 1h, 3h and 5h; NF-κB: ↑ at 3h	[4]Milk protein (*ex vivo*: ASD and DPI PBMCs vs control PBMCs): TNF-α, IFN-g ↑, IL-5 →	[2]Conventional yoghurt (w2 or w4 vs w0) (*ex vivo* blood culture): TNF-α, IL-1β, ↑; IFN-g, IL-10, IL-6 →
Net change in inflammatory marker	-1	-1	-1	-3	-2	-2
Sustainibility of effect over time	N.a.	N.a.	Not discussed	Not discussed	Discussed	No
Dose-response	No	No	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Investigated - re-occurrence of symptons after milk reintroduction	Investigated - reintroduction of milk leads to re-occurrence eosinophilic esophagitis	Not discussed	Discussed - LPS and TLR-4 signaling, SOCS3 and TLR-4 expression	Discussed - macrophage activation, aberrant innate immune responses against LPS	Discussed - Th1 promoting activity of lactic acid bacteria
Bioactive components	Discussed - milk, egg, soy and beef	Discussed - milk and wheat	Not discussed	Discussed - saturated fats	Investigated - β-lactoglobulin, casein, α-lactalbumin	Not discussed
Clinical evidence	Yes - decrease of symptoms of eosinophilic esophagitis and esophageal inflammation	Yes - reduction of endoscopic and histopathologic features of eosinophilic esophagitis	Yes - histological remission after 6 weeks milk elimination diet	No - increase free fatty acids, triglycerises, VLDL, and endotoxin, no effect on total cholesterol	N.a.	N.a.
Financing of research	Public	Public	Public	Public	Public	Private and public
Grading criteria	Pro, 3, 6, 7, 10, 11	Pro, 3, 6, 7, 10, 11	Pro, 3, 6, 7, 11	Pro, 1, 3, 4, 5, 6	Pro, 1, 4, 5, 7, 10	Pro, 3, 4, 5, 7
IS	-6	-6	-5	-6	-6	-5

(*Continued on next page*)

Table 4. (Continued)

Reference	(Unknown, 1994) 1	(Anderson *et al.*, 2012) 2	(Nettleton *et al.*, 2006) 2	(Vazquez-Agell *et al.*, 2013)	(Hlebowicz *et al.*, 2011) 2	(Esmaillzadeh *et al.*, 2007) 2
Subject category	GIT	HEALTH	HEALTH	HEALTH	HEALTH	HEALTH
Target indication	Ulcerative colitis	Insulin sensitivity and systemic inflammation	Cardiovascular disease	Systemic inflammation	Cardiovascular disease	Systemic inflammation
Target population	General population	General population	Healthy adults	Healthy adults	General population	Healthy women
Fat content	High-fat	High-fat	High-fat	High-fat	High-fat	High-fat
Fermentation	N.a.	N.a.	Fermented	Non-fermented	N.a.	N.a.
Test product	Dietary patterns including 'Western food' (includes butter, cheese)	Food cluster including high-fat dairy products	Dietary patterns including cheese	Cocoa powder with milk or water	Dietary pattern: 'Milk fat' including cheese, whole milk, butter	Dietary patterns including high-fat dairy products
Control product	—	Food cluster including low-fat dairy products	—	Whole milk	Dietary patterns: 'Many foods and drinks' and 'Low-fat and high-fibre' including low-fat milk	—
Test subjects	56 M, 45 F / 10-42 y / ulcerative colitis	1751 / 70-79 y / healthy	2407 M, 2682 F / 45-84 y / healthy	9 F, 9 M / 19-49 y / healthy	2040 M, 2959 F / 45-68 y / healthy	486 F / 40-60 y / healthy
Control subjects	79 M, 64 F / 10-42 y / other diseases	—	—	—	—	—
Diet	Food frequency questionnaire (FFQ)	Diet assessment (FFQ)	Diet assessment (FFQ)	Washout / 40 g cocoa in 250 mL whole milk or 40 g cocoa in 250 mL water or 250 mL whole milk	Diet assesment (FFQ) / 13 y follow-up for CVD events	Diet assessment (FFQ)
Controlled dairy test	Yes	Yes	No	No	Yes	No
Randomization	N.a.	N.a.	N.a.	N.a.	N.a.	N.a.
Time factor	Cross-sectional	Cross-sectional	Cross-sectional	Longitudinal	Cross-sectional	Cross-sectional
Study results	[4]Western food (butter, cheese) (ulcerative colitis patients vs control subjects): ulcerative colitis ↑	[6]Cluster including high-fat dairy products vs cluster including low-fat dairy): IL-6 ↑; TNF-α, CRP →	[7]Pattern including cheese: corr↑ with CRP, IL-6; corr→ with ICAM-1, E-selectin (adjusted for confounders)	[3]Whole milk (6h vs 0h): NF-kB activation in PBMC ↑; ICAM-1, VCAM-1, E-selectin →	[6]'Milk fat' pattern vs 'Many food and drinks' and 'Low-fat and high-fibre' patterns: WBC ↑; CRP →	[7]Pattern including high-fat dairy products: corr↑ with IL-6, SAA; corr→ with CRP, TNF-α, E-selectin, ICAM-1, VCAM-1 (after adjustment for confounders)
Net change in inflammatory marker	-1	-1	-2	-1	-1	-2
Sustainibility of effect over time	N.a.	Not discussed	Not discussed	Not discussed	N.a.	Not discussed
Dose-response	Yes - FFQ with consumption from 'none or hardly' to 'almost daily'	No	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Not discussed	Discussed - no interaction between dietary pattern and PPAR-γ genotype	Not discussed	Discussed - postprandial NF-kB activation after high-fat meal	Not discussed	Not discussed
Bioactive components	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Clinical evidence	No	Yes - cluster containing low-fat dairy associated with greater insulin sensitivity than cluster with high-fat dairy products	N.a.	No	N.a.	N.a.
Financing of research	Public	Public	Public	Public	Public	Public
Grading criteria	Pro, 1, 6, 7, 9	Pro, 1, 6, 7, 11	Pro, 5, 6, 7	Pro, 3, 4, 6	Pro, 1, 6, 7	Pro, 5, 6, 7
IS	-5	-5	-4	-4	-4	-4

Reference	(Nettleton *et al.*, 2006) 3
Subject category	HEALTH
Target indication	Cardiovascular disease
Target population	Healthy adults
Fat content	High-fat
Fermentation	N.a.
Test product	Dietary pattern including cheese, whole milk and yoghurt
Control product	
Test subjects	2407 M, 2682 F / 45-84 y / healthy
Control subjects	—
Diet	Diet assessment (FFQ)
Controlled dairy test	No
Randomization	N.a.
Time factor	Cross-sectional
Study results	[7]Pattern including cheese, whole milk, and yoghurt: corr↑ with ICAM-1; corr→ with CRP, IL-6, E-selectin (adjusted for confounders)
Net change in inflammatory marker	-1
Sustainibility of effect over time	Not discussed
Dose-response	No
Bioavailibility data	Not discussed
Biological plausibility	Not discussed
Bioactive components	Not discussed
Clinical evidence	N.a.
Financing of research	Public
Grading criteria	Pro, 6, 7
IS	-3

Table 5. Tabulated summary of the study results with no evidence for an inflammatory modulation of dairy products.

Reference	(Beavers *et al.*, 2009)	(Monagas *et al.*, 2009)	(Dawczynski *et al.*, 2009)	(Raff *et al.*, 2008)	(Lee *et al.*, 2007)	(Unknown, 1994) 2
Subject category	HEALTH	MET	OTHER	HEALTH	MET	GIT
Target indication	Systemic inflammation and oxidative stress	Cardiovascular disease	Rheumatoid arthritis (RA)	Cardiovascular disease and diabetes	Mild hypertension	Ulcerative colitis
Target population	Postmenopausal healthy women	Patients at high risk of cardiovascular disease	Adults with RA	Healthy subjects	Mildly hypertensive subjects	General population
Fat content	Low-fat	Low-fat	High-fat	High-fat	Low-fat	High-fat
Fermentation	Non-fermented	Non-fermented	Fermented	Non-fermented	Non-fermented	Non-fermented
Test product	Soy milk	Skim milk with cocoa powder	n-3 supplemented dairy (yoghurt, cheese, butter)	CLA-enriched butter	Skim milk + whey peptides powder	Milk
Control product	Low-fat milk	Skim milk	Conventional dairy products (yoghurt, cheese and butter)	Butter with low CLA	Skim milk	—
Test subjects	16 F / 53.88±3.65 y / healthy	45 / ≥55 y / cardiovascular disease	37 F, 2 M / 57.9±10.8 y / RA	18 M / 27-35 y / healthy	14 M, 13 F / 55.3±10.4 y / mild hypertension	56 M, 45 F / 10-42 y / ulcerative colitis
Control subjects	15 F / 55.00±3.12 y / healthy	—	—	20 M /19-33 y / healthy	16 M, 10 F / 47.8±11.6 y / mild hypertension	79 M, 64 F / 10-42 y / other diseases
Diet	3 servings/d low-fat milk or soy milk / 28 days	500 mL/d milk or milk + 40 g/d cocoa powder / 4 weeks	200 g yoghurt, 30 g cheese and 20-30 g butter daily / 3 months for test and 3 month control products / washout 8 weeks	CLA enriched butter (4.6 g/d CLA) or control butter (0.3 g/d CLA) / 5 weeks	125 mL/d / 12 weeks	Food frequency questionnaire (FFQ)
Controlled dairy test	No	No	No	No	No	No
Randomization	N.a.	N.a.	N.a.	N.a.	N.a.	N.a.
Time factor	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Cross-sectional
Study results	[2]Low-fat mik (d28 vs d0): TNF-α, IL-1β, IL-6 →	[2]Skim milk (4w vs w0): P-selectin, E-selectin, ICAM-1, VCAM-1, MCP-1, IL-6, CRP, T-lymphocyte adhesion markers, monocyte adhesion markers →	[2]Control dairy (w12 vs w0): CRP, lymphocytes, monocytes, granulocytes →	[2]Control butter (w5 vs w0): CRP, PAI-1 →	[2]Skim milk (w12 vs w0): IL-6, CRP, PAI-1, leucocyte number →	[4]Milk consumption (ulcerative colitis patients vs control subejcts): ulcerative colitis →
Net change in inflammatory marker	0	0	0	0	0	0
Sustainibility of effect over time	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	N.a.
Dose-response	No	No	No	No	No	Yes - FFQ with consumption from 'none or hardly' to 'almost daily'
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Bioactive components	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Clinical evidence	No - no effect on oxidative stress markers	Yes - BMI and weight decreased, blood pressure and heart rate unchanged	No - no changes in joint inflammation	Yes - FVIIc, HOMA-R increased	Yes - blood pressure significantly reduced, metabolic variables unchanged	No
Financing of research	Private and public	Public	Private and public	Public	Public	Public
Grading criteria	None	None	None	None	None	None
IS	0	0	0	0	0	0

Reference	(Nestel *et al.*, 2012) 4	(Nestel *et al.*, 2012) 5	(Sofi *et al.*, 2010) 2	(Wang *et al.*, 2011) 2	(van Bussel *et al.*, 2011)	(Meyer *et al.*, 2011) 5
Subject category	MET	MET	HEALTH	HEALTH	HEALTH	HEALTH
Target indication	Systemic inflammation	Systemic inflammation	Atherosclerosis	Obesity and cardiovascular disease	Endothelial dysfunction and low grade inflammation	Coronary heart disease
Target population	Overweight or obese subjects	Overweight or obese subjects	Healthy adults	Normal-weight and overweight adolescents	Healthy adults	Overall population
Fat content	High-fat	High-fat	High-fat	High-fat	N.a.	N.a.
Fermentation	Fermented	Fermented	Fermented	Non-fermented	N.a.	Non-fermented
Test product	Cheese	Yoghurt	Pecorino sheep cheese naturally rich in CLA	Dietary dairy fatty acids	Dairy products	Inflammatory risk dietary pattern (IRDP) containing milk
Control product	—	—	Commercial cow cheese low in CLA	—	—	—
Test subjects	13 / 61.6±7.6 y / overweight or obese	13 / 61.6±7.6 y / overweight or obese	4 M, 6 F / 30-65 y / healthy	112 M, 80 F / 15.2±1.2 y / normal weight	140 M, 161 F / 42.5±0.6 y / healthy	981 M / 45-64 y / healthy
Control subjects	—	—	—	—	—	—
Diet	110 g cheddar cheese / postprandial challenge study	600 mL yoghurt / postprandial challenge study	Cheese / 200 g per week / 10 weeks	FFQ / measurement of dairy fatty acids	510±334 g dairy/d (dietary history method 6y before biomarker determination) / measurement of serum biomarkers	Diet assessment (FFQ)
Controlled dairy test	No	No	No	No	No	No
Randomization	N.a.	N.a.	N.a.	N.a.	N.a.	N.a.
Time factor	Longitudinal	Longitudinal	Longitudinal	Cross-sectional	Cross-sectional	Cross-sectional
Study results	[3]Cheese (3h vs 0h): MCP-1, MIP-1α, ICAM-1, VCAM-1, IL-6, IL-1β, TNF-α, CRP →	[3]Yoghurt (3h vs 0h): MCP-1, MIP-1α, ICAM-1, VCAM-1, IL-6, IL-1β, TNF-α, CRP →	[2]Control cheese (w10 vs w0): IL- 6, IL-8, TNF-α, IL-10, IL-12 →	[5]Dairy fatty acids: corr→ with CRP, TNF-α (adjusted for confounders)	[5]Dairy: corr→ with von Willebrand factor, E-selectin, VCAM-1, ICAM-1, CRP, SAA, IL-6, IL-8, TNF-α (corrected for confounders)	[7]Pattern including milk: corr → with IL-6, CRP, IL-18 not adjusted for confounders)
Net change in inflammatory marker	0	0	0	0	0	0
Sustainibility of effect over time	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not dicussed
Dose-response	No	No	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Not discussed	Not discussed	Not discussed	Investigated - odd-numbered dairy fatty acids accumulate in epididymal fat rather than being β-oxidized in liver in obese but not normal-weight	Not discussed	Not discussed
Bioactive components	Not discussed	Not discussed	Not discussed	Investigated - dairy fatty acids (15:0, 17:0)	Not discussed	Not discussed
Clinical evidence	N.a.	N.a.	No	Yes - higher levels of dairy fatty acids associated with lower markers of oxidative stress	No	Yes - inflammatory dietary pattern significantly associated with all-cause mortality; milk did not contribute to the effect
Financing of research	Private	Private	Public	Public	Private and public	Public
Grading criteria	None	None	None	None	None	None
IS	0	0	0	0	0	0

(*Continued on next page*)

Table 5. (Continued)

Reference	(Jimenez-Flores *et al.*, 2012)	(Rosti *et al.*, 2011)	(Dalbeth *et al.*, 2012)	(Pal & Ellis, 2011)	(Wennersberg *et al.*, 2009)	(Topuz *et al.*, 2008)
Subject category	HEALTH	GIT	OTHER	MET	MET	GIT
Target indication	Endurance exercise	Food allergy (inflammatory bowel disease)	Gout	Cardiovascular disease risk factors	More than 2 factors metabolic syndrome (MS)	Mucositis induced by chemoterapy
Target population	Young active persons	Infants not being breast-fed	Subjects with recurrent gout flares	Overweight and obese postmenopausal women	Overweight and MS subjects with low dairy intake	Subjects undergoing standard-dose chemotherapy
Fat content	N.a.	N.a.	N.a.	N.a.	N.a.	N.a.
Fermentation	Non-fermented	Non-fermented	Non-fermented	Non-fermented	N.a.	Fermented
Test product	Milk bar	Milk protein formula	Skim milk powder (SMP)	Breakfast including whey protein isolate or sodium caseinate	High dairy consumption	Kefir
Control product	Commercial carbohydrate supplement	Mother milk	Lactose powder	Breakfast including glucose	Low dairy consumption	0.9% NaCl
Test subjects	33 M, 2 F / 20.7±0.4 y / healthy	12 M, 14 F / 87±9 d / formula-fed	37 M, 3 F / 57±16 y / gout	20 F / 57±1 y / overweight and obese	52-56 out of a total of 37 M (51.2±8.1 y) and 76 F (56.7±7.4 y) / obese and 2 MS symptoms	12 M, 5 F / 19-75 y / colorectal cancer
Control subjects	—	14 M, 25 F / 82.6±7.9 d / breast-fed	36 M, 4 F / 56±12 y / gout	—	52-57 out of a total of 37 M and 76 F / obese and 2 MS symptoms	12 M, 8 F / 34-72 y / colorectal cancer
Diet	Carbohydrate (250 kcal) or milk bar (290 kcal) plus intensive excercise / one bar at the end of each day of exercise / 3 days	N.a.	250 mL/d / 3 months	Single ingestion of whey, casein or glucose breakfast	Dairy products / 3 to 5 portions/ d / 6 months	Kefir or NaCl 0.9% / 2 × 250 mL per day / 5 days and 6 chemoterapy cycles
Controlled dairy test	Yes	Yes	Yes	Yes	Yes	Yes
Randomization	Randomized	Non-randomized	Randomized	Randomized	Randomized	Randomized
Time factor	Longitudinal	Cross-sectional	Longitudinal	Longitudinal	Longitudinal	Longitudinal
Study results	[1]Milk bar vs commercial carbohydrate: CRP →	[1]Formula-fed vs breast-fed: fecal calprotectin →	[1]SMP vs lactose: CRP →	[1]Whey breakfast vs control breakfast (6h postprandial, AUC): TNF-α, CRP, IL-6 →	[1]High vs low dairy: CRP, IL-6, TNF-α, C3, C4, VCAM-1, E-selectin, PAI-1, vWF, 8-iso-PGF2a →	[1]Kefir vs control: mucositis grading, TNF-α, IL-1β, IL-6 →
Net change in inflammatory marker	0	0	0	0	0	0
Sustainibility of effect over time	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Discussed
Dose-response	No	No	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Not discussed	Not discussed	Not discussed	Not discussed	Discussed - Whey protein contains ACE-inhibitory peptides	Not discussed
Bioactive components	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Clinical evidence	No - no significant effect on metabolic parameters	N.a.	Yes - frequency of gout flares reduced	No - no effect on blood pressure	Yes - decreased HOMA index, waist circumference and abdominal diameter, metabolic parameters unchanged	N.a.
Financing of research	Public	Public	Private and public	Private and public	Public	Not presented
Grading criteria	None	None	None	None	None	None
IS	0	0	0	0	0	0

Reference	(Arvola *et al.*, 2006)	(Wojcik *et al.*, 2001)	(Nestel *et al.*, 2012) 6	(Nestel *et al.*, 2012) 7	(Asemi *et al.*, 2013)	(Strisciuglio *et al.*, 2013)
Subject category	HYPER	HEALTH	MET	MET	MET	GIT
Target indication	Rectal bleeding in infants with and without milk allergy	Post-exercice recovery	Systemic inflammation	Systemic inflammation	Pregnancy with gestational diabetes mellitus (GDM)	Ulcerative colitis
Target population	Infants with rectal bleeding	General population	Overweight or obese subjects	Overweight or obese subjects	Pregnant women with GDM	Children with ulcerative colitis
Fat content	N.a.	Low-fat	High-fat	High-fat	Low-fat	N.a.
Fermentation	N.a.	Non-fermented	N.a.	N.a.	N.a.	N.a.
Test product	Milk elimination diet	Milk-based carbohydrate-protein beverage	High-fat dairy meals including cheddar cheese, butter, cream, or yoghurt	High-fat fermented dairy (cheese, yoghurt)	DASH diet (including low-fat dairy)	Milk protein elimination diet
Control product	Normal diet	Aspartame-flavored placebo	Low- fat milk	High-fat unfermented dairy (butter, cream, ice cream)	DASH but less fruits and vegetables and more fat	Free Diet
Test subjects	19 / 4-24 weeks / rectal bleeding	8 M / 23.5±0.7 y / healthy untrained	13 / 61.6±7.6 y / overweight or obese	12 / 59±8.2 y / overweight or obese	32 F / 18-40 y / pregnant with GDM	14 M, 15 F / 4.6-17y / newly diagnosed ulcerative colitis
Control subjects	21 / 4-24 weeks / rectal bleeding	9 M (placebo) / 23.5±0.7 y / healthy untrained	—	—	—	—
Diet	Milk elimination or normal diet / 1 month	Beverage immediately and 2h after exercise	110 g cheddar or 115 mL cream or 50 g butter or 600 mL yoghurt or 400 mL reduced fat milk / postprandial challenge study	2 weeks run-in / dairy (fermented or not fermented) / 4 weeks / 2 weeks washout / dairy (fermented or not fermented) / 4 weeks	DASH / 4 weeks	Milk elimination or free diet / 1 year
Controlled dairy test	Yes	Yes	Yes	Yes	Yes	Yes
Randomization	Randomized	Randomized	Randomized	Randomized	Randomized	Randomized
Time factor	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Longitudinal
Study results	[6]Milk elimination diet vs normal diet: tissue inflammation (identified by rectal bleeding and bloody stools) →	[1]Milk-based beverage vs placebo: TNF-α, IL-1β, IL-6 →	[1]Postprandial response between each of the high- fat and the low-fat dairy groups: MCP-1, MIP-1α, ICAM-1, VCAM-1, IL-6, IL-1β, TNF-α, CRP →	[1]Fermented vs unfermented dairy (4w): MCP-1, MIP-1α, ICAM-1, VCAM-1, IL-6, IL-1β, TNF-α, CRP →	[7]DASH diet containing dairy: corr→ with CPR	[6]Milk protein elimination diet vs free diet: Histological Matt score, CRP, calprotectin →
Net change in inflammatory marker	0	0	0	0	0	0
Sustainibility of effect over time	N.a.	Discussed	Not discussed	Not discussed	Not discussed	Not discussed
Dose-response	No	No	No	No	No	No
Bioavailibility data	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Biological plausibility	Discussed - inflammation processes in developing GIT	Discussed - modulation of protein synthesis and catabolism	Not discussed	Not discussed	Not discussed	Discussed - gut inflammation or inadequate caloric intake
Bioactive components	Discussed - milk protein	Discussed - protein and carbohydrates	Not discussed	Not discussed	Discussed - arginine (not related to dairy), magnesium and calcium	Discussed - milk protein antigens
Clinical evidence	No	No - no improvement of muscle glycogen replacement or muscle function	N.a.	N.a.	Yes - DASH reduced fasting plasma glucose, serum insulin, and HOMA-IR score; increased antioxidant capacity and glutathione levels	No - milk protein elimination vs free diet: remission rate (PUCAI) →
Financing of research	Public	Public	Private	Private	Public	Not presented
Grading criteria	None	None	None	None	None	None
IS	0	0	0	0	0	0

(*Continued on next page*)

Table 5. (Continued)

Reference	(Iwasa *et al.*, 2013)	(Jones *et al.*, 2013) 2	(Pintus *et al.*, 2013) 2
Subject category	HEALTH	MET	MET
Target indication	Glucose metabolism and muscle damage after exercise	Metabolic syndrome (MS)	Hypercholesterolemia
Target population	Athletes	Overweight and obese MS subjects	Mildly hypercholesterolaemic subjects
Fat content	Low-fat	Low-fat	High-fat
Fermentation	Fermented	N.a.	Fermented
Test product	Milk fermented with *Lactobacillus helveticus*	High dairy high calcium diet plus caloric restriction	Sheep cheese naturally enriched with CLA
Control product	Unfermented milk	Low dairy low calcium diet plus caloric restriction	Sheep cheese with pill containing 1 g of a palm oil–soybean oil mix
Test subjects	18 M / 21.6±0.8 y / healthy	7 M, 13F / 52.1±1.5 y / obese MS	19 M, 23 F / 30-60 y / mild hypercholesterolaemia
Control subjects		7 M, 11F / 50.1±2.7 y / obese MS	
Diet	200 mL of each beverage / 3x before and after exercise	3–4 servings dairy (low-fat milk or yoghurt)/d and 350 mg/d Ca supplement or 1 serving yoghurt/d / 12 weeks	Naturally enriched sheep cheese or control cheese / 90 g/d / 3 weeks / between 3 weeks washout
Controlled dairy test	Yes	Yes	Yes
Randomization	Randomized	Randomized	Randomized
Time factor	Longitudinal	Longitudinal	Longitudinal
Study results	[1]Fermented vs non-fermented milk: TNF-α, CRP →	[1]High vs low dairy (w12): IL6, TNF-α, MCP-1, IL-1ß →	[2]Sheep cheese (w3 vs w0): IL-6 (n = 16), CRP (n = 16), leptin (n = 16), *adiponectin* (n = 16), anandamide →
Net change in inflammatory marker	0	0	0
Sustainibility of effect over time	N.a.	No	Not discussed
Dose-response	No	No	No
Bioavailibility data	Not discussed	No	Not discussed
Biological plausibility	Discussed - activated antioxidants contribute to supression of muscle damage and glucose impairment	Not discussed	Not discussed
Bioactive components	Discussed - peptides	Not discussed	Not discussed
Clinical evidence	Yes - Muscle soreness and reduction of antioxidant capacity suppressed by fermented milk, blood glucose unchanged	No - no higher weight loss	No - sheep cheese decreased total cholesterol and LDL-cholesterol
Financing of research	Public	Public	Public
Grading criteria	None	None	None
IS	0	0	0

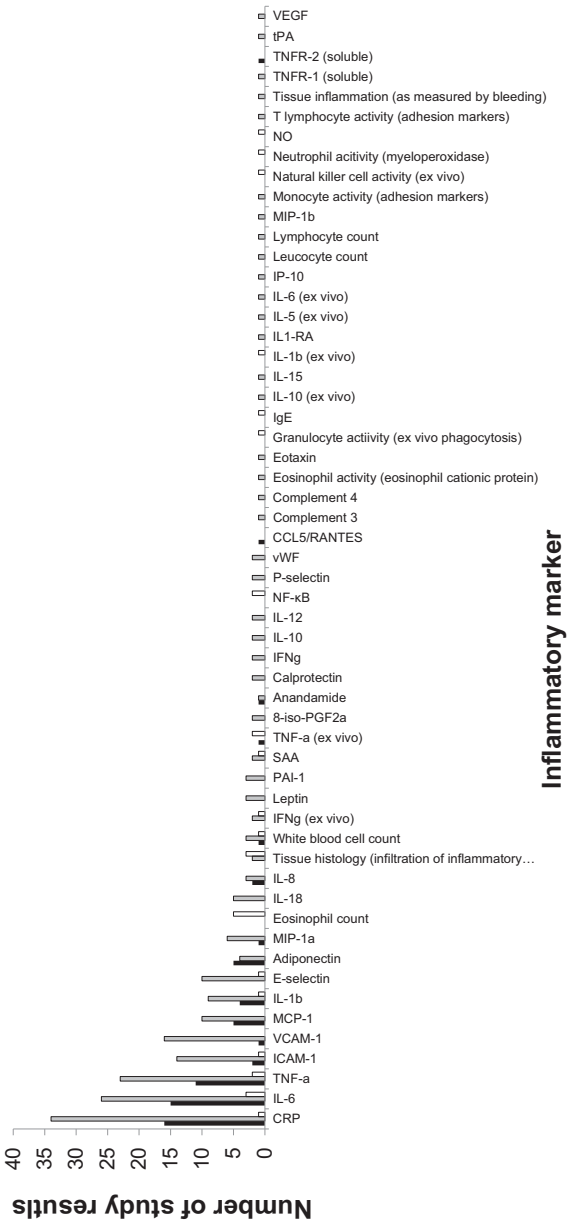

Figure 2. Distribution of the inflammatory markers measured in the 52 human studies. The *x*-axis presents the inflammatory markers. The *y*-axis presents the number of study results reporting a specific analytical result with the corresponding inflammatory marker. The color code indicates the direction of change of the inflammatory marker: significant anti-inflammatory change (black bars), no significant change (grey bar), significant pro-inflammatory change (white bars). The inflammatory markers are ranked in descending order with regard to their frequency of reporting in all 52 studies reviewed.

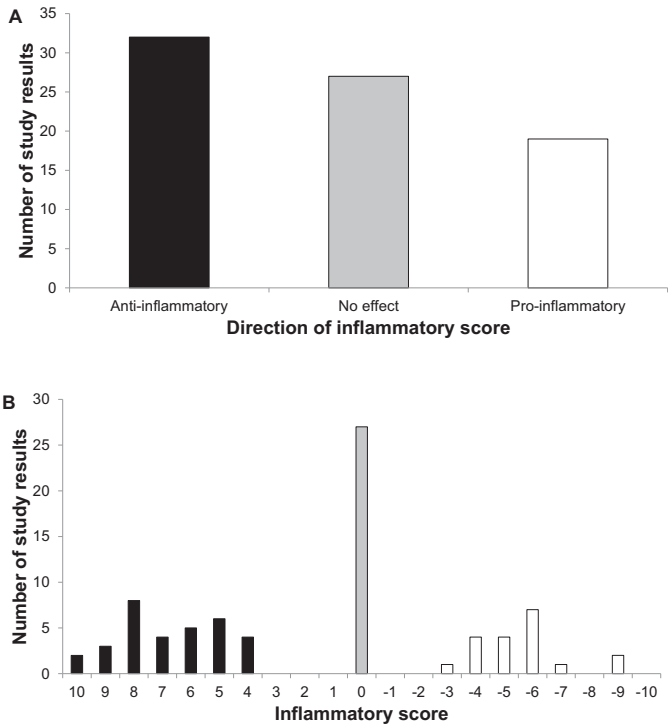

Figure 3. Distribution of the study results labeled as "anti-inflammatory", "no effect", and "pro-inflammatory" for the entire data set composed of 78 study results. (A) Number of study results labeled as "anti-inflammatory", "no effect", "pro-inflammatory" based on the initial grading defined in Table 2. (B) Distribution of the Inflammatory Score. The color code indicates the direction of change of the inflammatory marker, i.e., significant anti-inflammatory change (black bars), no significant change (grey bars), and significant pro-inflammatory change (white bars).

and high-fat dairy products. The IS indicated an anti-inflammatory activity of high-fat dairy products despite the fact that nine studies were identified in which these products were associated with a pro-inflammatory activity. The pro-inflammatory activity identified with high-fat dairy products in these studies was mainly attributed to the presence of saturated fat. Fat consumption, in particular saturated fat (Steinberg, 2005) and *trans*-fatty acids (Micha and Mozaffarian, 2009), has been associated with inflammatory processes in humans. However, recent opinions in nutrition research advocate that the adverse health effects formerly associated with saturated fats, were most likely due to other factors (Lawrence, 2013). The positive IS, calculated for the high-fat products, is thus in line with this reevaluation of the impact of fat consumption on human health. Additionally, as both low-fat and high-fat products were associated with a positive IS, the molecules with a potential anti-inflammatory activity in milk may cover a broad range of nutrients, including polyunsaturated fatty acids (German and Dillard, 2006), proteins (Chatterton et al., 2013), and glycans (Newburg, 2013).

The IS of the product category "fermented dairy products" indicates a beneficial anti-inflammatory contribution, possibly resulting from the bacteria present in dairy products or their metabolic activity. The anti-inflammatory activity of strains of lactic acid bacteria and bifidobacteria has indeed been reported (Lomax & Calder, 2009;Tsai et al., 2012). The recent awareness of the role of the gut microbiota in the modulation of the immune system (Hakansson and Molin, 2011), further raises interest in the integration of bacteria with anti-inflammatory properties into dairy products (Dunne et al., 2001). Moreover, products deriving from the fermentation of milk with bacteria, in particular bioactive peptides (Ceapa et al., 2013) and glycans (Newburg, 2013), which both interact with gut microbes or immune cells, may contribute to an anti-inflammatory activity of dairy products.

Research gaps

Our review also aimed at identifying research gaps preventing a comprehensive understanding of inflammatory processes in food and nutrition sciences. In particular, we have identified the following gaps:

No consensus is available yet which clearly defines clinically relevant inflammatory markers. For illustration in Europe, the EFSA was required, following a consultation of stakeholders, to give guidance on potential markers of inflammation. In its response, the EFSA stated that "for function claims referring to reduction of inflammation, a change in markers of inflammation such as various interleukins does not indicate a beneficial physiological effect per se, but should be accompanied by a beneficial physiological or clinical outcome" (EFSA Panel on Dietetic Products, 2011). This position is an important challenge to the food and nutrition research community, given the difficulties associated with the identification of validated clinical markers of disease reduction by dietary interventions. In that context, the importance of validating sets of molecules present in the circulation as biomarkers of low-grade inflammation has been emphasized (Calder et al., 2013). At the same time, the predictive value tentatively attributed by the authors of this review to these sets of inflammatory markers, illustrates the gap with the position of regulatory authorities. The present review further highlights this gap: human studies complementing the inflammatory markers

Table 6. Inflammatory Score for the impact of dairy products on humans.

		N	Q1[1]	Median	Q3[1]	Mean	p[2]	p[3]
All data								
	ALL study results	78	0	0	6	1.4	0.009	
Subject category								
	HEALTH	37	−3.2	0	6	1.7	0.017	0.083
	MET	24	0	4.5	7.5	3.9	0.001	
	GIT	8	−5.5	−2.5	0	−3.1	0.066	
	HYPER	6	−6	−6	−6	−5.5	0.034	
	OTHER	3	0	0	6.75	3.0	0.317	
Product category								
	High-fat	35	−2.25	0	6	1.7	0.017	0.084
	Low-fat	20	0	4.5	7.5	4.2	0.001	
	Non-fermented	33	0	0	6	1.8	0.108	0.845
	Fermented	16	0	0	7	2.4	0.037	

[1]Abbreviations: Q1, first quartile; Q3: third quartile.
[2]Wilcoxon Signed-Rank test (two-sided).
[3]Kruskal-Wallis test.

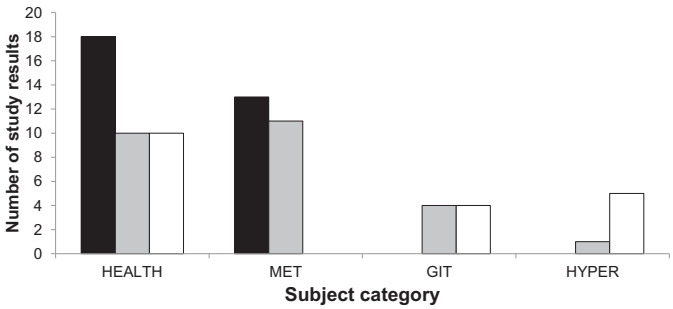

Figure 4. Distribution of the study results labeled as "anti-inflammatory", "no effect", and "pro-inflammatory" among the subject categories. Subject categories: HEALTH, healthy subjects; MET, subject with metabolic disorders including obesity; GIT, subjects with gastrointestinal disorders; HYPER, subjects with hypersensitivity, including allergy, to milk products. The color code indicates the direction of change of the inflammatory marker, i.e., significant anti-inflammatory change (black bars), no significant change (grey bars), and significant pro-inflammatory change (white bars).

with convincingly addressing clinical outcomes, as described by the descriptor "Clinical evidence" in Tables 3–5, are unsurprisingly scarce.

Validation issues are raised by new analytical technologies that now allow researchers to quantitate large sets of inflammatory markers in a single measurement (Liu et al., 2005; Breen et al., 2011; Thompson et al., 2012). Although these analytical issues were not discussed in the set of human trials reviewed, particular care should be taken in the future to better characterize the performance of these tests.

Regulatory authorities clearly highlight the importance of characterizing the food products investigated in human trials in their guidance for the authorization of health claims (EFSA Panel on Dietetic Products Nutrition and Allergies, 2011; FDA Office of Nutrition Labeling and Dietary Supplements, 2009). However, the studies reported in this review give little emphasis on the characterization of the dairy products investigated, as

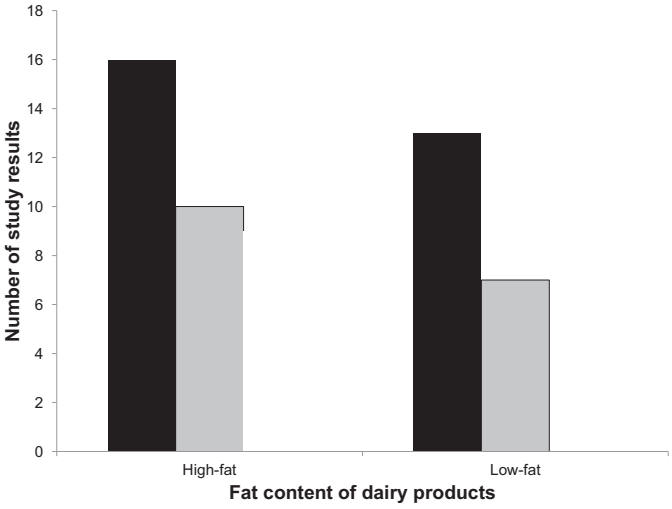

Figure 5. Distribution of the study results labeled as "anti-inflammatory", "no effect", and "pro-inflammatory" among the dairy product categories "high-fat" and "low-fat". The color code indicates the direction of change of the inflammatory marker, i.e., significant anti-inflammatory change (black bars), no significant change (grey bars), and significant pro-inflammatory change (white bars).

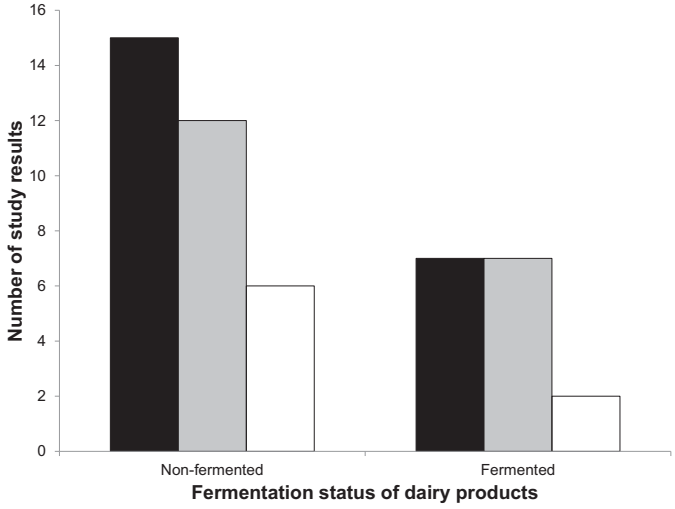

Figure 6. Distribution of the study results labeled as "anti-inflammatory", "no effect", and "pro-inflammatory" among the dairy product categories "fermented" and "non-fermented". The color code indicates the direction of change of the inflammatory marker, i.e., significant anti-inflammatory change (black bars), no significant change (grey bars), and significant pro-inflammatory change (white bars).

illustrated by a range of uncharacterized descriptors in Tables 3–5 (e.g., identification of bioactive nutrients, bioavailability data, dose-response effects, sustainability of the effect of the food product over time). In particular, integrating the variable 'dose' into study designs could allow researchers to draw a causal relationship between the food investigated and the physiological response measured in humans (Schwander et al., 2014). Also, although dozens of nutrients with immunomodulatory activity have been proposed in the literature (Ballard and Morrow, 2013), the bioactive nutrients potentially modulating inflammation in the reviewed studies, remain largely unknown even considering animal studies. The major reason for this gap is clearly inherent to the complex molecular composition of food. In light of the importance of the food matrix on the properties of bioactive nutrients, we endorse that food and nutrition research should shift its focus from the characterization of the nutritional and immunomodulatory properties of isolated nutrients to the characterization of foods, meals, and even dietary patterns.

The scientific basis for claims on bioactive food and nutrients established by national regulatory authorities is not harmonized, thereby hindering internationally harmonized market access (Aggett et al., 2012). To date, a very high number of requested health claims (more than 80%) have been rejected by the EFSA's NDA Panel, who underlined the need to identify the molecule(s) responsible of the claimed effect, and their mechanisms of action. The mechanisms of action of bioactives are usually studied in vitro, whereas in vivo studies are very often focused on demonstrating an effect on specific endpoints, without considering the underlying mechanisms. Evidence of the anti-inflammatory effectiveness of dairy components could be retrieved from in vitro studies, but they were not considered in this review for a specific reason, i.e., bioactive components are just one part of food, embedded in a very complex matrix. Cell supplementation in in vitro studies, as well as intervention studies administering bioactives as pure compounds assume that there are no confounding effects related to the food matrix. The food matrix, as well as food processing (Bordoni et al., 2011) can, indeed modify the digestibility and bioavailability of bioactive compounds, thus introducing a fundamental bias when translating in vitro data to humans. The ideal in vitro study should thus digest food in a static or dynamic model of digestion, have the digested nutrients transported through an intestinal cellular layer mimicking the gastrointestinal barrier, ideally with a model integrating the gut microbiota, and finally measure the ability of the absorbed nutrients to modulate inflammation. Such integrated in vitro models have not yet been successfully developed, although first steps in that direction have already been taken (Vergeres et al., 2012). Meanwhile, the COST action FA1005 '*Improving health properties of food by sharing our knowledge on the digestive process*' (INFOGEST) has published an harmonized protocol of in vitro digestion (Minekus et al., 2014). To perform in vitro digestion prior to in vitro studies will help to bypass the enormous, and unscientific, gap in our knowledge related to the assumption, without any demonstration, that the in vivo effects of foods are related to the mechanisms of action observed in vitro supplementing cells with pure molecules. In vitro studies supplementing cells with digested food can mimic in a closer way the in vivo effects and underlying mechanism of actions of food bioactives, thus evidencing the cause-effect relationship as requested by the body authorities.

Strengths and limitations of the IS

The literature focusing on the impact of dairy products on inflammatory processes in humans revealed a very heterogeneous methodological landscape. The IS was therefore defined in order to take these limitations into account as follows:

Inflammation is a complex phenomenon that cannot be described by a single biomarker (Calder et al., 2013). Indeed, more than fifty inflammatory markers were reported in the pool of the 52 human studies reviewed. The data consisted of cellular markers of inflammation and measures of tissue infiltration, but the majority of studies concentrated on a few soluble circulatory cytokines. Furthermore, the number of markers measured in each study varied from one to more than ten. These points all raised the issue of the weighting of each study result in this heterogeneous environment. For the sake of simplicity, and to avoid over-interpreting the data, we decided to (i) rate each of the inflammatory markers listed in Table 1 at the same level and (ii) to increase the IS by one unit in cases in which changes in the concentration of more than one inflammatory markers were pointing in the same direction (see point 5 in Table 2). Note, however, that the IS was not upgraded by additional grades for studies in which more than two inflammatory markers were concordantly changed as this would have given too much weight to this criterion compared to the ten other criteria presented in Table 2.

As milk is amenable to a wide range of technological transformations and important in human diets, a large spectrum of dairy products was investigated in the 52 reviewed studies. As each of these products may differently modulate inflammation, we addressed this issue by defining a limited range of product categories in which the data could be stratified and analyzed (low-fat vs. high fat; fermented vs. non-fermented).

The health status of the subjects enrolled in the 52 studies was quite diverse, reflecting the generic importance of inflammatory processes in modulating human health and disease. The clinical indications targeted by these studies were consequently heterogeneous and we therefore classified the study results according to a limited, but clinically meaningful, set of subject categories (HEALTH, MET, GIT, HYPER).

Given the relative paucity of high-quality studies on the topic of dairy and inflammation, we chose an inclusive strategy which means that we considered all available publications on dairy and systemic inflammation, including randomized controlled trials, cross-over design trials and longitudinal cohort studies. This approach enabled us to analyze data from studies per se not considered in systemic reviews and we could thus provide a wide overview of studies dealing with dairy and inflammation. The downside of this strategy is that some studies of low quality, small sample size and short duration, were included in this review.

The last issue that became evident during the reviewing process, is the usage of dairy products as controls in human studies actually aiming at investigating the ability of other food products to modulate inflammatory processes. This phenomenon was particularly the case for clinical studies using the milk matrix to supplement the test meals with bioactive

components. Given the potential bioactivity of dairy products, we decided to also evaluate their properties even when used as control products, although this might pose the risk of misleading information when comparing data against baseline within randomized groups (Bland and Altman, 2011).

Conclusions

We have established the IS as a new tool to conduct a quantitative evaluation of human studies investigating the impact of dairy products on inflammation. Taken together, our review suggests that dairy products, in particular fermented products, have anti-inflammatory properties in humans not suffering from allergy to milk, in particular in subjects with metabolic disorders. As the clinical relevance of inflammatory markers is currently debated among researchers and regulatory authorities, the translation of these findings into dietary guidelines remains to be clarified.

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SUPPLEMENTAL TABLE 1 Example of the tabulation of a study result

Reference	(Zemel & Sun, 2008) 1
Subject category	MET
Target indication	Oxidative stress and inflammation
Target population	Obese subjects
Fat content	Low-fat
Fermentation	Fermented
Test product	Yoghurt
Control product	Sugar-free, calcium-free gelatin dessert
Test subjects	13 F, 5 M / 39±10 y / obese
Control subjects	14 F, 2 M / 42±6 y / obese
Diet	3x6 oz yoghurt, including a caloric deficit of 500 kcal/d / 12 weeks
Controlled dairy test	Yes
Randomization	Randomized
Time factor	Longitudinal
Study results	[1]Yoghurt (high Ca) vs control (low Ca): CRP ↓; *adiponectin* ↑
Net change in IM	2
Sustainibility of effect over time	Not discussed
Dose-response	No
Bioavailibility data	Not discussed
Biological plausibility	Discussed - Ca signaling, ROS, angiotensin-converting enzyme, fat oxidation, energy utilisation
Bioactive components	Investigated - calcium
Clinical evidence	Yes - yoghurt improves fat loss
Financing of research	Private
Grading criteria	Anti, 1, 2, 3, 4, 5, 6, 7, 10, 11
IS	10

Initial grading	Anti (+1)
Incremental grading	
(1) Controlled study with dairy as test product:	Yes (+1)
(2) Randomized study:	Yes (+1)
(3) Longitudinal study:	Yes (+1)
(4) The dairy product is not solely measured as part of a dietary pattern:	Yes (+1)
(5) More than two IM changed:	Yes (+1)
(6) At least one IM was measured *in vivo* (and not *ex vivo*):	Yes (+1)
(7) The change in IM was measured over more than 12h, e.g. not postprandially:	Yes (+1)
(8) The effect is still measured after a washout period of at least one week:	No
(9) A dose-response is demonstrated with the dairy product:	No
(10) Bioactive molecules or the biological plausibility have been convincingly investigated:	Yes (+1)
(11) A clinical endpoint is changed that can be related to a metabolic dysregulation associated with inflammation:	Yes (+1)
Inflammatory Score	10