Dairy Fats and Cardiovascular Disease

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Cardiovascular diseases (CVD) remain a major cause of death and morbidity globally and diet plays a crucial role in the disease prevention and pathology. The negative perception of dairy fats stems from the effort to reduce dietary saturated fatty acid (SFA) intake due to their association with increased cholesterol levels upon consumption and the increased risk of CVD development. Recent research and meta-analyses have demonstrated the benefits of full-fat dairy consumption, based on higher bioavailability of high-value nutrients and anti-inflammatory properties.

Keywords: milk ; cheese ; yoghurt ; kefir ; cardiovascular diseases ; inflammation ; saturated fatty acids ; atherosclerosis ; cardiometabolic risk factors

1. Introduction

Despite advances in improved primary prevention and medical treatment, cardiovascular diseases (CVD) are the leading cause of death and morbidity in Europe [1] and worldwide [2]. Every year CVD are responsible for 10,000 deaths in Ireland and 1.8 million in the European Union, due to coronary heart disease (CHD), stroke and related circulatory diseases [1][3]. Increasing evidence supports the pivotal function of nutrition in the development of chronic diseases, especially CVD [4]. Maladaptive diet and lifestyle are the dominant underlying cause of systemic inflammation, which is the core process that drives the development of atherosclerosis [4][5]. Diet and lifestyle are key modifiable risk factors for the prevention of CVD and thus have been the focus of intense research. Globally, striking differences in dietary habits and the rates of chronic disease exist. The identification and subsequent targeting of dietary factors with the greatest potential for reducing CVD, diabetes and obesity are of crucial scientific and public health importance [6].

Milk and dairy products are an important nutrient dense constituent of a healthy diet due to their capacity to provide essential vitamins, minerals, macronutrients and micronutrients important for growth, development and tissue maintenance. This is vital as globally 6 billion people consume milk and dairy products, the majority of them in developing countries [7]. Currently there are milks of varying fat content and milks with varying vitamin and mineral content (often fortified or enriched); there are also concentrated milks, high-protein milks, fermented milks and various other dairy products, including yoghurts and cheeses consumed worldwide. Dairy products are associated with many negative health effects due to previous observations relating to their saturated fatty acid (SFA) content, which may lead to increased low-density lipoprotein cholesterol (LDL) levels, thus an increased risk of cardiovascular disease [8]. There was also a strong correlation evident between dairy fat consumption and coronary heart disease in an early study [9]. However, recent findings have indicated that the link between SFA and CVD may be less clear than previously assumed. Foods are composed of an array of saturated and unsaturated fatty acids, each of which may differentially affect lipoprotein metabolism, as well as contribute significant quantities of other nutrients that may alter CVD risk [4][10]; these include phospholipids, milk proteins, calcium and vitamin D, which have been reviewed in recent literature [4][11]. In addition, recent research trends indicate that dairy products have a neutral [12][13][14] or even a positive effect on cardiovascular health [14][15][16][17][18][19] contrary to previous assumptions [4]. Dairy products have also been associated with positive health benefits against diabetes [20], obesity [21][22][23] and metabolic syndrome [23][24]. The way consumers obtain nutrition and dietary information has substantially changed. There is conflicting advice online with regards to every food type and many consumers are more confused now than ever [25]. Discrepancies in dietary advice due to the increased influence of the food industry, social media and 'fad diets,' which are often endorsed by celebrities and 'diet gurus' [26], among other modern phenomena has damaged consumer confidence in the nutritional value of dairy products.

2. Dietary Guidelines and Dairy Product Consumption

Dairy intake is increasing worldwide, yet theoretically dairy products could both increase and decrease cardiometabolic risk factors. Dairy products have been associated with several cardiometabolic benefits, however the active constituents have not yet been established. Initially, dietary guidelines formulated in the 1980s, demonised dairy products due to their high SFA, cholesterol and calorie content [4]. The rise of the lipid hypothesis led most scientific organisations and dietary guidelines to recommend low-fat (1%) or non-fat dairy consumption, as a result of their characteristically high SFA content [27][28]. Now most countries recommend the consumption of dairy products and when amounts are specified, recommendations are typically for 2 or 3 servings per day [29]. Although often, as occurs in the UK, general recommendations are made with no specific amount mentioned [29]. There remains inconsistent health advice to consumers with many authorities recommending three to four servings a day [27] and labelling dairy as a 'superfood' [30]. On the other hand, some dietary guidelines recommend the complete avoidance of full-fat dairy products [31], others recommend that the consumption of dairy products be limited as much as possible [32]. However, as research advances, some countries such as Australia have revised their dietary guidelines and included dairy products but preferably consumption of low-fat as opposed to full-fat products is advised [33]. Notably, butter and cream do not fall into the category of dairy products in some dietary recommendations due to their significant contribution of fat to the diet [34].

Nevertheless, dairy products are nutrient dense, providing a wide range of crucial vitamins (A, B6, B12, D and K), minerals (calcium, iodine, magnesium, potassium, phosphorus and zinc), fats, proteins and other microconstituents [35][36], which are otherwise difficult to obtain in diets with limited use of dairy products [29]. In particular, dairy products can provide up to 60% of the recommended daily allowance (RDA) of calcium [37]. Furthermore, fermented dairy products are an excellent source of vitamin K, a fat-soluble vitamin [36] .

In addition, fermented dairy products, such as yoghurt have a positive effect on intestinal microbiota. Therefore, dairy products generally form an integral role in the dietary guidelines of many countries. However, not all dairy products are created nutritionally equal. For instance, cheeses are often salted, which contributes to high sodium intake. Soft cheeses typically contain less calcium as the curd is formed with acid, some calcium is lost to the whey. The fat content of dairy products can vary greatly, because of the type of milk, degree of fat removal, the animals condition, diet and the milk processing [4][29]. Often ice-cream and similar dessert products are included as dairy products in dietary guidelines. The nutritional quality of these products is diluted by the addition of sugar and fats [29], in particular high amounts of vegetable fats like coconut oil and palm oil, that have questionable positive and negative effects on cardiovascular health due to their high lauric acid and palmitic acid content respectively [38][39][40]. Therefore, ice cream and dairy desserts that contain high levels of vegetable oils should be approached with caution and not considered in dairy research or as part of dairy products in dietary guidelines.

3. Saturated Fat, Cholesterol and Dairy Products

SFA and cholesterol have formed the basis of the 'lipid hypothesis' for CVD development. Consumption of full-fat dairy products was reduced and either substituted by a reduced fat version or intake was restricted based on government dietary guidelines. However, recent perspectives have determined more complex mechanisms for the underlying causes, initiation and development of CVD, that do not necessarily indicate that SFA or cholesterol levels are culpable.

4. Dairy Products and Cardiometabolic Health

Metabolic syndrome, T2DM, hypertension and obesity are all conditions interconnected with CVD due to similarities in their mechanisms, pathology and systemic inflammation. Systemic inflammation persists in elderly people due to immunosenescence and in those who are obese due to their increased mass of adipose tissue and resulting increase in adipokines. This significantly increases an individual's risk for endothelial dysfunction and CVD development [4][41]. Metabolic syndrome is a cluster of metabolic risk factors that are associated with increased risk of CVD and T2DM. Metabolic syndrome is typically classified based on an individual exhibiting abnormalities beyond specific parameters of blood pressure, fasting glucose, waist circumference, fasting triglycerides and HDL cholesterol, all of which can worsen with age [42]. Recent research indicates that dairy products may be associated with several beneficial effects on cardiometabolic outcomes.

5. Anti-Inflammatory Properties of Dairy Products

Low-grade inflammation is the key biological phenomenon underpinning the development and progression of CVD, metabolic syndrome and T2DM. The initiation and resolution of the inflammatory response involves the complex and coordinated expression of inflammatory compounds, which induce a myriad of physiological processes, ranging from local vascular response to systemic responses affecting the whole organism [43]. During atherosclerosis, circulating inflammatory mediators actively contribute to vascular and atheromatous change [43][44]. As thoroughly reviewed by Da Silva and Rudkowska [44], there are multiple studies that have examined the role of dairy components on various cell lines and found that generally these components have an inverse association with inflammation. In particular, long-chain SFA such as palmitic (C16:0) and stearic (C18:0) may exhibit pro-inflammatory effects. Although these fatty acids are both found in abundance in dairy products, as evidenced by the lack of association between dairy products and CVD, it is suggested that the deleterious effects by these SFA in milk is offset by other dairy components [44]. Other SFA such as lauric acid (C12:0) may have a neutral or anti-inflammatory effects, however further research is required in humans [44].

Platelet-activating factor (PAF) is a potent pro-inflammatory phospholipid mediator implicated in the initiation and progression of atherosclerosis [45]. PAF and PAF-like molecules act through their binding to a unique G-protein coupled seven transmembrane receptors (PAF-receptor), which subsequently triggers multiple intracellular signalling pathways, depending on the target cell and PAF levels in the tissue and blood [43][46]. PAF in general plays a central role in various physiological processes, such as mediation of the normal inflammatory responses, regulation of blood pressure and regulation of coagulation responses [43]. Potential therapeutic approaches to the pro-inflammatory actions of PAF focus on the PAF/PAF-receptor interactions, thus inhibiting the exacerbation of the complex PAF-induced inflammatory response and pathways through competitive and non-competitive displacement of PAF from the PAF-receptor [43]. A number of PAF inhibitors and/or antagonists have been identified in the polar lipid fractions of numerous food types, including dairy products [43]. It seems that bovine, ovine and caprine dairy products possess polar lipids with potent anti-inflammatory activities as demonstrated in a series of in vitro experiments on washed rabbit platelets [4][47]. Research has shown that as milk is fermented to yoghurt and then to cheese, the bioactivity of the PAF inhibitors seems to increase [4]. This indicates that the processes of fermentation and lipolysis play a key role in altering the bioactivity of the polar lipid fractions of milk and this bioactivity increases the further fermentation proceeds [4][43]. These effects have been attributed to microorganisms such as *Lactobacillus delbrueckii* ssp. *bulgaricus* and *Streptococcus thermophilus*. Research also indicates that polar lipids of caprine and ovine milk and dairy products possess greater bioactivity than those of bovine milk and dairy products [47][48][49][50][51].

Many reviews have highlighted that dairy products are associated with positive effects on cardiovascular health, particularly in epidemiological studies. It is clear from **Table 1** that several intervention studies, crossover studies, cross-sectional studies and randomised controlled trials (RCT) indicate that dairy consumption may be cardioprotective due to lower levels of inflammatory markers including TNF-α, IL-6, IL-13, MCP-1 and VCAM-1. **Table 1** indicates that dairy products are associated with a neutral or positive effect on inflammatory markers in both healthy and diseased individuals in various forms of human trials. However, the mechanisms underlying the observed inverse associations between the intake of specific dairy products and inflammation remain elusive. Some mechanisms have been suggested for specific fatty acids such as CLA and various bioactive proteins [4][52]. As highlighted in **Table 1**, many studies that have evaluated the effects of dairy product consumption on inflammatory markers tend to focus on low-fat dairy products, a point that has been previously highlighted by Lordan and Zabetakis [4]. The study of only low-fat dairy product consumption may have several limitations because of the reduced intake of the anti-inflammatory lipids of dairy products. Therefore, the observed neutral effects of dairy product intake on inflammatory markers in **Table 1**, may be due to the assessment of only low-fat dairy products in some studies. The prominent focus on the study of low-fat dairy may be due to the negative perceptions associated with full-fat dairy products in society, thus low-fat dairy products may be consumed more in the populations assessed. In addition, there are also indications that the observed effects of dairy intake on inflammatory markers may be dose dependent [53]. Notably in **Table 1**, fermented dairy products tend to reduce inflammatory markers more than non-fermented products, which mechanistically may explain the observed greater health benefits of fermented dairy consumption versus non-fermented dairy products. Further studies are required to assess the effects of dairy product consumption and dairy lipid constituents on inflammatory markers and cardiovascular health [4].

Table 1. Summary of the findings of observational studies investigating the consumption of dairy products and their derivatives on inflammatory markers related to cardiovascular diseases, obesity and metabolic syndrome in healthy and diseased individuals.

Author, Year	Country	Study Design	Study Focus	Outcome	Conclusion
Thompson, 2005 [54]	USA	Dietary intervention	The effects of high-dairy and high-fibre consumption on weight loss in 90 obese subjects was assessed	CRP was reduced by 0.8 mg/L from baseline ($p < 0.0001$), however there was no significant difference between the dairy diet and the others tested	An insignificant reduction of CRP was observed following dairy consumption in obese participants
Sofi, 2010 [55]	Italy	Dietary intervention	Effect of pecorino cheese naturally enriched with *cis*-9, *trans*-11 CLA on inflammatory markers in 10 healthy participants	Reduction in arachidonic acid-induced platelet aggregation (pre: 87.8 ± 1.76% vs. post: 77.7 ± 3.56%; $p = 0.04$), improvement of erythrocyte filtration rate and a reduction of TNF-α (40.1%), IL-6 (43.2%) and IL-8 (36.5%)	Dietary short-term intake of pecorino cheese rich in *cis*-9, *trans*-11 CLA caused favourable biochemical changes of inflammatory and atherosclerotic markers
Rosado, 2011 [56]	Mexico	Dietary intervention	Effect of adding low-fat milk on anthropometrics, body composition, CRP etc. in energy restricted diets in 139 women	Change in CRP after low-fat milk was 0.2 mg/L (95% CI 1.1–1.6)	Dairy intake had no significant effect on CRP concentrations
Stancliffe, 2011 [53]	USA	Dietary intervention	Effects of an adequate full-fat dairy diet versus low-dairy (both mainly milk and yoghurt) intake on inflammatory markers in 40 overweight individuals with metabolic syndrome over a 12-week period versus a low-fat control	After 7 days, the adequate full-fat dairy diet decreased plasma malondialdehyde and oxidised LDL (35% and 11% respectively, $p < 0.01$), TNF-α decreased by 35% ($p < 0.05$), which further decreased by week 12. By week 12, decreases in IL-6 (21%, $p < 0.02$) and MCP-1 (24%, $p < 0.05$) were observed. Low-dairy intake exerted no effects on oxidative or inflammatory markers	An increase in dairy intake attenuates oxidative and inflammatory stress in metabolic syndrome

Author, Year	Country	Study Design	Study Focus	Outcome	Conclusion
Nestel, 2012 [57]	Australia	Dietary intervention	Assessing the effects of low-fat or fermented dairy product intake on inflammation and atherogenesis on 13 overweight participants, using 5-single meal tests	No significant changes in the levels of inflammatory biomarkers (CRP, IL-6, IL-13, TNF-α, VCAM-1 and others) were observed	Authors could not confirm the reported increments in inflammation after high fat meals
Esmaillzadeh, 2010 [58]	Iran	Cross-sectional	Assessing the effect of dairy products on inflammatory markers in 486 women	Low-fat dairy was inversely associated with CRP ($\beta = -0.04$), IL-6 ($\beta = -0.02$) and VCAM-1 ($\beta = -0.06$); high fat dairy was positively associated with log-transformed values of serum amyloid A ($\beta = 0.08$) and VCAM-1 ($\beta = 0.05$)	Evidence suggests there is an independent relationship between dairy consumption and some markers of inflammation and endothelial dysfunction
Panagiotakis, 2010 [59]	Greece	Cross-sectional	The evaluation of effects of dairy product consumption on levels of inflammatory markers in blood samples from fasting adults with no evidence of previous chronic inflammatory disease	Levels of inflammatory markers such as CRP, IL-6 and TNF-α were 29, 9 and 20% lower, respectively ($p = 0.01$), in people who consumed more than 14 servings of dairy per week compared with those who had fewer than 8 servings per week ($p = 0.05$)	This inverse association between dairy consumption and levels of inflammatory markers in healthy adults indicates that dairy products may be protective against chronic inflammatory diseases

Author, Year	Country	Study Design	Study Focus	Outcome	Conclusion
Wang, 2011 [60]	USA	Cross-sectional	305 adolescents were tested for serum phospholipid fatty acid markers of dairy intake (C15:0 & C17:0), which were linked to biomarkers of inflammation by generalised linear regression analyses adjusted for age, gender, race, tanner score, total energy intake and physical activity	Phospholipid dairy fatty acids, elevated by dairy consumption, were inversely associated with CRP, 8-iso-PGF2α and urinary 15-keto-dihydro-PGF2α in overweight but not in normal weight adolescents (all $p_{interaction}$ < 0.05). However, higher PL dairy fatty acid levels were associated with lower IL-6 among all adolescents. Adjustment for dietary intake of calcium, vitamin D, protein, total flavonoids and ω-3 fatty acids did not alter the findings	Dairy-specific saturated fats C15:0 and 17:0 fatty acids, may contribute to the potential health benefits of dairy products, especially for overweight adolescents
Gadotti, 2017 [61]	Brazil	Cross-sectional	To assess the effect of dairy consumption and plasma inflammatory markers in 259 participants. Subjects were assigned groups depending on inflammatory status and multiple logistic regression tests were conducted to estimate the odds ratio (OR) for the inflammatory cluster across tertiles of dairy consumption	The highest tertile of yoghurt consumption was 0.34 [95% CI: (0.14–0.81)] relative to the reference tertile, demonstrating a linear effect (p_{trend} = 0.015). Cheese consumption exhibited an OR of 2.49 (95% CI: (1.09–5.75)) relative to the reference	Increasing yoghurt consumption might have a protective effect on inflammation, while cheese consumption seems to be associated with a pro-inflammatory status

Author, Year	Country	Study Design	Study Focus	Outcome	Conclusion
van Meijl, 2010 [62]	Netherlands	Randomised crossover	Effects of low-fat milk and yoghurt intake on inflammatory markers in 35 overweight or obese participants versus carbohydrate controls for 8 weeks	No significant effects on IL-6, MCP-1, ICAM-1 or VCAM-1 versus control. TNF-α index decreased by 53 ($p = 0.015$)	Low-fat dairy consumption may increase concentrations of s-TNFR but it has no effects on other inflammatory markers of chronic inflammation and endothelial function
Zemel, 2010 [63]	USA	Randomised crossover	Effects of a dairy-rich, high calcium diet on oxidative and inflammatory stress in 10 overweight and 10 obese individuals compared with soy supplemented eucaloric diets	After 7 days, dairy intake decreased oxidative stress by lowering 8-isoprostane-$F_{2\alpha}$ (12%, $p < 0.0005$), plasma malondialdehyde (22%, $p < 0.0005$). Adiponectin increased significantly (20%, $p < 0.002$). Inflammatory markers were significantly reduced versus the control diet: IL-6 (13%, $p < 0.01$); TNF-α (15%, $p < 0.002$); MCP-1 (10%, $p < 0.0006$)	An increase in dairy food intake produces significant and substantial suppression of the oxidative and inflammatory stress associated with overweight and obesity
Nestel, 2013 [64]	Australia	Randomised crossover	Consumption of full-fat versus low-fat dairy on biomarkers of inflammation in 12 overweigh individuals	75% of those who consumed low-fat products versus full-fat fermented products tended to have higher levels of inflammatory markers tested (CRP, IL-13, TNF-α, VCAM-1 and others; $p_{trend} < 0.001$)	Short-term diets of low-fat dairy products did not lead to a favourable biomarker profile associated with CVD risk compared with the full-fat dairy products. Full-fat fermented dairy products are more favourable

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Labonté, 2014 [65]	Canada	Randomised crossover	Assessing the impact of dairy intake versus energy equivalent products on inflammatory markers in 112 healthy participants with systemic inflammation	After dairy consumption, no significant changes in CRP (7.3%, $p = 0.47$). However, both the control and dairy diet reduced IL-6 (17.6% and 19.9%, respectively; $p < 0.0001$ for both, $p = 0.77$ for between-diet comparison	Short-term consumption of a combination of low- and high-fat dairy products as part of a healthy diet has no adverse effects on inflammation
Dugan, 2016 [66]	USA	Randomised crossover	Effect of low-fat dairy consumption on hepatic enzymes and inflammation in 37 participants with metabolic syndrome versus a carbohydrate control	Lower levels of TNF-α ($p = 0.028$) and MCP-1 ($p = 0.001$) were observed in women after low-fat dairy intake versus the control group. The hepatic steatosis index was also reduced ($p = 0.001$)	Three servings of dairy per day improved both liver function and systemic inflammation in subjects with metabolic syndrome
Zemel, 2008 [67]	USA	Randomised controlled longitudinal	Evaluation of feeding calcium rich high-dairy eucaloric diet and hypocaloric diet versus low dairy group intake in obese participants over 24 weeks	High-dairy eucaloric diet and a hypocaloric diet resulted in an 11% ($p < 0.03$) and 29% ($p < 0.01$) decrease in CRP, respectively (post-test vs. pre-test), whereas there was no significant change in the low-dairy groups. Adiponectin decreased by 8% in subjects fed the eucaloric high-dairy diet ($p = 0.003$) and 18% for the hypocaloric high-dairy diet ($p = 0.05$)	Dietary calcium suppresses adipose tissue oxidative and inflammatory stress

Author, Year	Country	Study Design	Study Focus	Outcome	Conclusion
de Aguilar-Nascimento, 2011 [68]	Brazil	Randomised controlled longitudinal	Effects of an early enteral formula on the levels of glutathione and inflammatory markers in 25 aged patients with acute ischemic stroke. Group 1 consumed whey, group 2, the control consumed casein	Mortality was similar between groups (33%; $p = 1.00$) and was associated with higher IL-6 levels (group 1: 73.7 ± 24.7; versus group 2: 16.6 ± 2.4 pg/dL; $p = 0.04$) and CRP (82.0 ± 35.6 vs. 48.3 ± 14.5 mg/L; $p = 0.02$). Serum IL-6 was lower ($p = 0.03$) and glutathione was higher ($p = 0.03$) in whey protein-fed patients versus the casein group	Enteral formula containing whey protein may decrease inflammation and increase antioxidant defences in elderly patients with ischemic stroke
Jones, 2013 [69]	Canada	Randomised controlled longitudinal	Assessing a diet rich in calcium and dairy products on weight loss and appetite during energy restriction in 49 overweight and obese individuals for 12 weeks, versus a suitable control. A meal tolerance test was carried out in week 12	MCP-1 was reduced after 30 mins with Dairy/Calcium group compared with the control in the meal tolerance test ($p = 0.04$). No change was observed for IL-6, TNF-α, or IL-1β	Modest reduction in MCP-1

Author, Year	Country	Study Design	Study Focus	Outcome	Conclusion
Pei, 2017 [70]	USA	Randomised controlled	Premenopausal women (BMI 18.5–27 and 30–40 kg/m^2) were randomised to consume 339 g of low-fat yoghurt (yoghurt non-obese (YN); yoghurt obese (YO)) or 324 g of soya pudding (control non-obese; control obese (CO)) daily for 9 weeks (n 30/group). Fasting blood samples were analysed for various inflammatory markers	After 9-week yoghurt consumption, YO and YN had decreased TNF-α/sTNFR RII. Yoghurt consumption increased plasma IgM EndoCAb regardless of obesity status. sCD14 was not affected by diet but LBP/sCD14 was lowered in both YN and YO. Yoghurt intervention increased plasma 2-arachidonoylglycerol in YO but not YN. YO peripheral blood mononuclear cells expression of NF-κB inhibitor α and transforming growth factor β1 increased relative to CO at 9 weeks	Consumption of low-fat yoghurt for 9 weeks reduced biomarkers of chronic inflammation and endotoxin exposure in premenopausal women compared with a non-dairy control food
Wannamethee, 2018 [71]	UK	Prospective cohort study	This study investigated serum CLA (measured as a % of total fatty acids) and the risk of incident heart failure in 3806 older men aged between 60 and 79 years using metabolomics. The men were without prevalent HF and were followed up for an average of 13 years, during which there were 295 incident HF cases	CLA was adversely associated with cholesterol levels but was inversely associated with CRP and NT-proBNP. No association between CLA and CHD. High CLA was associated with reduced risk of HF (hazard ratio [95% confidence interval], 0.64 [0.43–0.96]; quartile 4 versus quartile 1). Elevated CLA was associated with reduced HF risk only in those with higher dairy fat intake, a major dietary source of CLA (p = 0.03)	The reduced risk of HF was partially explained by NT-proBNP. High dairy fat intake was not associated with incident coronary heart disease but was associated with reduced risk of HF, largely because of the inverse effect of CLA

BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; CLA = conjugated linoleic acid; CRP = C-reactive protein; EndoCab = endogenous endotoxin-core antibody; HF = heart failure; IL-X = interleukin-β/6/13 etc.; MCP-1 = monocyte chemoattractant protein-1; NF-κB = nuclear factor-κB; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; s-CD14 = soluble cluster of differentiation 14; s-TNFR = soluble tumour necrosis factor receptors; TNF-α = tumour necrosis factor-α; VCAM-1 = vascular cell adhesion molecule-1.

6. Trans Fatty Acids

Trans-fatty acids (TFA) have previously been associated with an increased risk of CVD [72]. TFA affect many CVD risk factors by increasing: LDL; lipoprotein(a); serum triglycerides; LDL particle number; shifting LDL subclasses to more atherogenic small dense LDL; increasing inflammation; and reducing HDL levels [73][74][75]. Thus, many dietary guidelines recommend limiting dietary TFA intake to less than 1% of energy intake [28][76][77] and some countries such as Austria, Hungary, Iceland, Latvia, Norway and Denmark have introduced legal bans that limit the percentage of artificial TFA in oils and fats. In Denmark that limit is just 2% (2 g per 100 g) [78]. Other countries including Lithuania and Sweden are close to adopting similar legislation. Dietary intake of TFA is characterised by both industrial-TFA and ruminant TFA. In the margarine and cooking oil industries, during the process of fat hardening, partial hydrogenation or deodorisation of vegetable oils can lead to the production of artificial industrial TFA. In processed fats, elaidic acids (C18:1t9) are the most prominent TFA, followed by *trans*-vaccenic acid [79][80]. In dairy products and ruminant fat, some *trans*-isomers are produced naturally in small quantities by microorganisms in the rumen of ruminant animals, which occurs due to the partial hydrogenation of *cis*-fatty acids, primarily linoleic acid and α-linolenic acid. The most abundant TFA is *trans*-vaccenic acid (C18:1t11) [79][81]. Other biologically important TFA include conjugated linoleic acids (CLA) such as rumenic acid (C18:2c9t11) and (C18:2t10,c12), which are associated with a number of health benefits [4]. Notably except for CLA, all TFA in industrially produced fat are also found in ruminant fat but the amounts of the individual TFA differ significantly strongly between both types of fat [79].

Dietary intake industrial TFA increased after a surge in the production of industrial fats between the 1960s and 1980s, in response to public health recommendations to ironically replace animal products and tropical oils, both high in SFA [82]. However, as research advances generalising fatty acids by the degree of unsaturation or the configuration of double bonds alone is unlikely to predict biological responses. Thus, emerging evidence suggests that TFA from ruminant sources only may not be as detrimental to health as previously thought [72][83], in fact some may even have cardioprotective effects [75]. Ruminant *trans*-fatty acids constitute a typically 2–5% of the fat in dairy products [84]. Generally, ruminant TFA accounts for 2–9% of fatty acid intake [85]. In addition, the TRANSFAIR Study estimates that as much as half of all *trans*-fats consumed are ruminant TFA in specialty diets, such as the Mediterranean diet [86], which is associated with positive cardiovascular health benefits [87]. A study was conducted feeding either industrial TFA or ruminant TFA to LDL receptor deficient mice (LDLr−/−); mice fed a diet of cholesterol supplemented with industrial TFA (elaidic acid) stimulated atherosclerosis and plaque formation, whereas plaque formation was reduced in mice that were fed the same cholesterol rich diet but consumed butter rich in vaccenic TFA (18:1t11) instead of industrial TFA [85]. This may indicate a protective effect for ruminant vaccenic TFA against atherosclerosis. A case control study in Costa Rica found that an adequate concentration of c9,t11-CLA in adipose tissue was associated with a lower risk of myocardial infarction (MI; highest versus lowest quintile; OR = 0.51; 95% CI = 0.36–0.71; $p < 0.0001$) and that dairy intake was not associated with risk of MI, despite a strong risk associated with saturated fat intake [88]. A meta-analysis of cohort studies found no association between ruminant TFA intake and CVD risk (RR, 0.92 (95% CI, 0.76–1.11); $p = 0.36$), however suggested further research for confirmation. Further studies indicate that c9, t11-CLA exhibit potent anti-inflammatory effects against IL-6 and TNF-α expression, as well as adiponectin secretion in 3T3-L1 adipocytes [89][90]. A recent study has also shown that high dairy fat intake was not associated with incident coronary heart disease but was associated with reduced risk of HF, largely because of the inverse effect of the presence of serum CLA (measured as a % of total fatty acids), which is elaborated further in **Table 1** [71]. Furthermore, as reviewed by Lordan and Zabetakis [4], CLA enriched dairy products has a neutral or positive effect on circulating inflammatory markers and lipid profiles of healthy and diseased participants.

There is also evidence to suggest that circulating *trans*-palmitoleic acid (C16:1t9), which occurs in both dairy fat and partially hydrogenated oils, is associated with lower atherogenic dyslipidaemia, insulin resistance and the incident of diabetes, which may explain previously observed metabolic benefits of dairy consumption [91]. However, controversy remains, thus more research is required to differentiate between artificial and ruminant TFA on CVD risk factors [92]. It is clear that TFA of industrial origin are associated with an increased risk of CVD. Putative evidence suggests that TFA of ruminant origin may be associated with beneficial effects against CVD, however further research with a focus on dairy products is required to confirm these observations.

7. Fermented Dairy Products and Cardiovascular Health

Fermented milk beverage consumption is on the rise due to consumers' perception of its healthy effects, widely disseminated by increasing numbers of studies describing the importance of the different nutrients and bioactive compounds [93]. Fermented dairy products include various yoghurts, cheeses and fermented milk products such as *kefir*. Fermented dairy products are synonymous with the delivery of probiotics, which are a microorganisms that are alive when they arrive to the gut and have the potential for therapeutic and preventative health benefits upon consumption by improving host intestinal microbiota [94]. Fermented dairy products tend to possess more health benefits than fluid milk upon consumption [47]. Increased consumption of fermented dairy foods is associated with reduced LDL cholesterol [10], reduced hypertension risk [95] and CVD risk [17], there is also a suggestion that there may be a dose response [96].

Although these patterns are observed in several studies (**Table 1**), dairy food intake is associated with many confounders that are generally associated with better health outcomes such higher educational levels and socioeconomic status [31][97]. Furthermore, children who consume >60 g of yoghurt a day have a higher overall diet quality, nutrient intake, lower pulse pressure (4–10 years old) and lower HbA1c concentrations (11–18 years old) indicating favourable cardiometabolic health [98].

A recent study comparing fermented and non-fermented dairy products with all-cause mortality in a Swedish cohort found that there was a 32% increased hazard (HR: 1.32; 95% CI: 1.18–1.48) in high consumers of non-fermented milk (≥2.5 times/day), when compared to consumers of milk (≤1 time/week), Whereas butter was 11% (HR: 1.11; 95% CI: 1.07–1.21). All non-fermented milk-fat types were independently associated with increased HRs but were lower in consumers of medium and low-fat milk, when compared with full-fat milk. Fermented milk intake (HR: 0.90; 95% CI: 0.86–0.94) and cheese intake (HR: 0.93; 95% CI: 0.91–0.96) were negatively associated with mortality [99]. Meta-analyses have shown that fermented dairy products can have an inverse association with T2DM [100][101] and cheese consumption was not associated with an increased risk of all-cause mortality [12][102]. In a crossover-controlled study, yoghurt consumption has also been shown to increase HDL levels in 29 hypocholesterolaemic women The HDL concentration increased significantly by 0.3 mmol/L (p = 0.002). The ratio of LDL/HDL cholesterol desirably decreased from 3.24 to 2.48 (p = 0.001) [103]. A recent meta-analysis supports the observed associations that fermented dairy product consumption had a positive or neutral effect on CVD risk [104]. In particular, fermented dairy intake was associated with a reduced risk of stroke and T2DM. Other studies have found that fermented dairy products have mostly positive or neutral effects on fasting plasma glucose levels [105], however one study has shown that fermented milk lowers fasting plasma glucose levels in patients with T2DM [106].

As current dietary guidelines generally place an emphasis on the reduction of SFA intake, it would be expected that cheese consumption would be associated with an increased risk of CVD. Cheese provides a high intake of SFA and cholesterol and is also a major source of calcium and protein [107]. Epidemiological evidence indicates that cheese consumption may be less atherogenic than previously assumed. Observational studies have failed to identify a significant association between high cheese or dairy fat intake and coronary heart disease [108][109][110]. Cheese consumption has been associated with a significantly reduced risk of stroke and CHD [111]. Similar effects have been observed in yoghurts, which are a diverse complex nutrient-rich matrix that have been associated with lower incident risk of CVD [112], diabetes [20] and metabolic syndrome, particularly when consumed with fruit [113][114]. Mechanistically these effects may be due to the presence of bioactive lipids and peptides with anti-inflammatory properties [4], and/or the observed effects of high calcium intake from cheese, which may lower SFA intake, reducing the risk of high cholesterol levels.

In summary, fermented dairy products have positive effects on cardiovascular health (**Figure 1**) and may be even more beneficial than non-fermented dairy products. However, none of the putative bioactive compounds in dairy foods such as proteins, lipids, phospholipids, vitamin D, vitamin K, or probiotic bacteria has consistently explained the benefits of dairy intake on cardiovascular health. The process of fermentation leads to the structural change of lipids and proteins in cheese and yoghurt, which may be responsible for some of the observed effects [4][115]. Several bioactive peptides and phospholipids present in fermented dairy products have protective effects, including the anti-inflammatory effects of phospholipids and the antioxidant properties of plasmalogens. The structure of lipids and phospholipids in the milk fat globule membrane (MFGM) may also play a role in modulating plasma cholesterol levels, further supporting the evidence surrounding the food-matrix effect [115][116]. How these different constituents and properties influence cardiovascular risk factors is poorly understood. Mechanistic studies are key to identifying the missing links that explain the positive cardiovascular health benefits of consuming fermented dairy products.

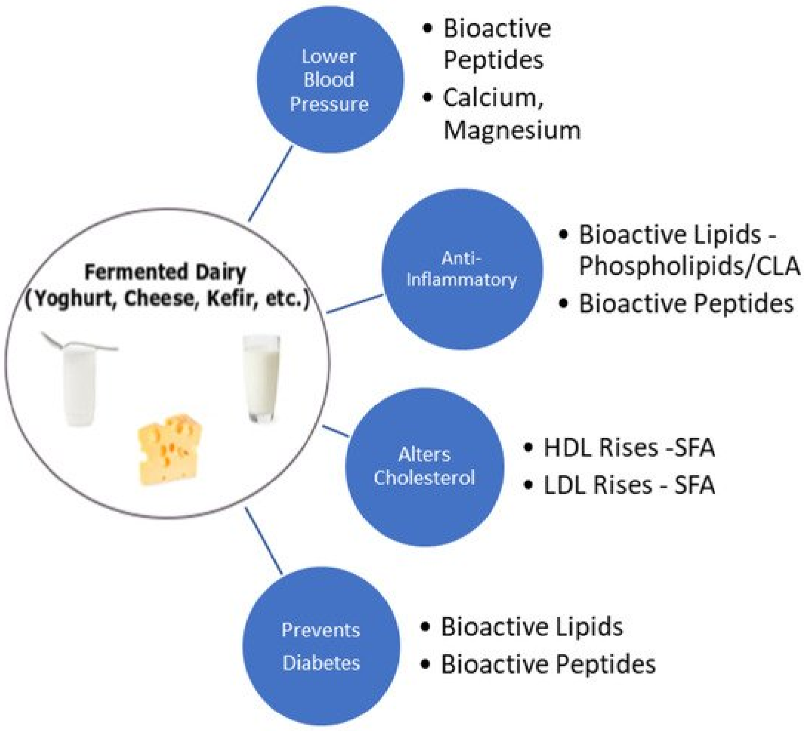

Figure 1. Effects of dairy product consumption on cardiometabolic risk factors and cardiovascular health. CLA: conjugated linoleic acid; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; SFA: saturated fatty acid.

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