Dairy Foods and Dairy Fats: New Perspectives on Pathways Implicated in Cardiometabolic Health

Kristin M Hirahatake,[1] Richard S Bruno,[2] Bradley W Bolling,[3] Christopher Blesso,[4] Lacy M Alexander,[5] and Sean H Adams[6,7]

[1]Department of Epidemiology, College of Health Sciences, University of California, Irvine, CA, USA; [2]Human Nutrition Program, Department of Human Sciences, College of Education and Human Ecology, The Ohio State University, Columbus, OH, USA; [3]Department of Food Science, University of Wisconsin-Madison, Madison, WI, USA; [4]Department of Nutritional Sciences, College of Agriculture, Health and Natural Resources, University of Connecticut, Storrs, CT, USA; [5]Department of Kinesiology, College of Health and Human Development, The Pennsylvania State University, State College, PA, USA; [6]Arkansas Children's Nutrition Center, Little Rock, AR, USA; and [7]Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

ABSTRACT

Low-fat and nonfat dairy products have been promoted as part of a healthy dietary pattern by both US dietary guidelines and professional organizations for several decades. The basis for this recommendation stems in part from the putative negative cardiometabolic effects associated with saturated fat consumption. However, as nutrition research has shifted from a single nutrient to a whole-food/dietary pattern approach, the role of dairy foods and dairy fat in the diet–disease relationship is being reexamined. Most observational and experimental evidence does not support a detrimental relationship between full-fat dairy intake and cardiometabolic health, including risks of cardiovascular disease and type 2 diabetes. Indeed, an expanded understanding of the dairy food matrix and the bioactive properties of dairy fats and other constituents suggests a neutral or potentially beneficial role in cardiometabolic health. To consider how consuming dairy foods, including full-fat dairy, is associated with cardiometabolic health, this review provides an innovative perspective on mechanisms that link dairy consumption to 3 main biological systems at the core of metabolic health, the gastrointestinal, hepatic, and vascular systems. *Adv Nutr* 2020;11:266–279.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. In recent years, there has been a substantial global increase in cardiometabolic diseases such as type 2 diabetes (T2D), hypertension, and obesity (1). In fact, the American Society of Endocrinology, the National Cholesterol Education Program, and the WHO, among others, now recognize cardiometabolic syndrome as a disease entity. Cardiometabolic disease is a combination of metabolic dysfunctions characterized by insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension, and central obesity, and its presence markedly increases CVD morbidity and mortality (2). Diet, among other lifestyle factors such as physical activity and smoking, has an established link with cardiometabolic health (3, 4). Over the past decade, nutrition research related to health outcomes has shifted from a focus on individual nutrients to complete dietary patterns and whole foods. This is reflected by evidence-based dietary recommendations such as the Dietary Guidelines for Americans (DGA). The 2015–2020 DGA specifically identified low-fat and fat-free dairy foods as components of healthy eating patterns (5). Public health recommendations to emphasize low-fat and fat-free dairy are attributed, in part, to the putative negative health effects of saturated fats. Yet, the evidence linking dietary saturated fat with CVD risk and risk indices is far from settled, with many studies demonstrating no association (6–13). Furthermore, the majority of observational and experimental evidence does not support a detrimental relationship between consuming full-fat dairy and cardiometabolic health outcomes, including CVD or T2D [e.g., (12, 14–21)]. In addition, consideration of the health impact of dairy fats and dairy foods must take into account their complex matrix (e.g., milk oligosaccharides, calcium, live and active cultures in yogurt, milk fat globule membranes and polar lipids, and bioactive peptides), which contribute to the gastrointestinal (GI) tract milieu of diet-derived factors that influence the host and microbiome. With these considerations in mind, there is a critical need to revisit current concepts related to dairy fats (and other dairy components) with respect to how they associate with physiological systems relevant to whole-body cardiometabolic health. In contrast to other recent reports that broadly focus on specific dairy foods or dairy-containing diet patterns and CVD disease risk or T2D [e.g.,

(11, 12, 14, 17–19, 22)] the current review aims to consider new perspectives on mechanisms that link dairy-containing diet patterns (or specific dairy components) to 3 main biological systems at the core of metabolic health, the GI, hepatic, and cardiovascular systems. Using this approach, one can build an integrative picture of how dairy foods may impact the splanchnic and vascular systems, which are episodically and chronically exposed to factors associated with individual meals and food patterns.

Current Status of Knowledge

Dairy consumption and gastrointestinal tract function

Dairy foods can broadly affect immune function via specific mechanisms in the gut. The GI tract is closely linked with immune function and maintains homeostasis with the gut microbiota via the mucosal layer, intestinal barrier, and immunocytes (23). These systems affect cardiovascular health via direct effects on GI tract immune cells and/or the flux of microbial antigens and metabolites into the bloodstream, which impact whole-body and vascular site inflammation (24, 25). Dendritic cells in the gastrointestinal tract sample microbial antigens, migrate to the mesenteric lymph nodes and induce the activation of T cells (26). Intestinal activation of Toll-like receptor 4 (TLR4) by endotoxin increases proinflammatory T cell populations and cytokine production (27). In contrast, commensal bacteria may stimulate barrier function and/or produce metabolites (e.g., propionate and butyrate) that dampen intestinal inflammation (28, 29). There are multiple avenues through which the GI tract, and dietary components that modify its structure or function, may have substantial effects on cardiometabolic health. Notably, animal studies have contributed extensively to the current understanding of this area. Although some humans have polymorphisms

conferring lactase persistence, laboratory rodents gradually lose intestinal lactase activity after weaning (30, 31). Lactase activity is typically not described in rodent studies. Since undigested lactose can be fermented in the GI tract by gut microbiota, intestinal lactase activity may be an important variable to consider when interpreting results from animal models.

Metabolic endotoxemia and cardiovascular health.

Immune homeostasis in the intestine is achieved in part through cellular responses to the gut microbiota. Translocation of gut-derived endotoxins, e.g. lipopolysaccharides (LPS), from Gram-negative bacteria generate a proinflammatory response by activating TLR4 (32, 33). Consumption of dietary emulsifiers or high-fat challenge meals can, under some circumstances, activate postprandial inflammation by coabsorption of LPS and lipids (34, 35). Collectively, chronic low-grade LPS exposure is described as "metabolic endotoxemia." This phenomenon has been implicated in obesity and insulin resistance by inducing chronic inflammatory responses (36, 37) that may increase risk of cardiovascular disease (38, 39).

Postprandial inflammation and cardiovascular health.

Recognition of the link between postprandial lipemia, inflammation, and CVD has led to further investigation of how inflammation could develop in the postprandial state. Initially, postprandial lipemia was observed in individuals with coronary artery disease after consuming a high-fat, high calorie (HFHC) challenge meal consisting of heavy whipping cream, chocolate syrup, and sugar (729 kcal/m^2) (40). Subsequently, postprandial lipemia induced by an HFHC meal was associated with inflammation. In healthy individuals, an HFHC challenge meal (white bread, ham, margarine, coffee, and whole milk providing 602 kcal/m^2) increased NF-κB activation in peripheral blood mononuclear cells (PBMCs) after 6–9 h (41).

The postprandial inflammatory response is determined by the metabolic state of the individual (e.g., obese or lean) and by the macronutrients in the test meal (42). It has been shown that both predominately carbohydrate-based and lipid-based meals may induce postprandial inflammation (42). Carbohydrate consumption increases postprandial glucose, which by itself is sufficient to induce oxidative stress and increase circulating IL-6 (43). Impaired glucose tolerance exacerbates inflammation in response to glucose ingestion (43). Lipid consumption alone induces postprandial endotoxemia in rodents (44). Endotoxins are coabsorbed with lipids, and emulsified lipids increase postprandial lipemia and endotoxemia relative to unemulsified fat intake (44, 45). The majority of studies that have utilized high-fat meals to induce postprandial inflammation include carbohydrates (46), so both lipid- and glucose-mediated mechanisms that lead to postprandial inflammation should be considered. A recent analysis of the literature on HFHC meals and postprandial inflammation concluded that the inflammatory response was not associated with the proportion of fat (46). The

postprandial inflammatory response was also inconsistent among studies of HFHC meals. While postprandial IL-6 was increased in 32 of 45 studies, blood IL-1β, TNF-α, and C-reactive protein (CRP) were not consistently induced by a high-fat meal (HFM) [46]. Others have suggested that leukocyte markers of inflammation are more consistent in the postprandial state than concentrations of plasma cytokines [47]. This implies that cell-based markers of inflammation may be more robust indicators of inflammatory status in the postprandial state than circulating cytokines. Since few studies have comprehensively assessed cell-based markers of postprandial inflammation, a complete understanding of the immune response to different dietary components is limited. Recently, the concept that saturated fatty acids robustly activate macrophage inflammation under normal conditions, or even after an HFM, has been challenged [46, 48].

Dairy and postprandial inflammation.

In the context of an HFHC challenge meal, emulsified dairy fats can induce postprandial inflammation, and thus, dairy foods (typically cream, butter, cheese, or milk) have been included in the majority of challenge meals to study postprandial inflammation [46]. In fresh milk, the fat is stabilized by the milk fat globule membrane (MFGM). Subsequent processing by the addition of emulsifying ingredients can alter the physical state of fats in dairy products by redistributing naturally occurring phospholipids and proteins, which may affect the postprandial response. Emulsifying ingredients are also added to dairy foods to achieve desired textures. In a randomized crossover study, obese or normal-weight individuals consumed a mixed meal consisting of 40 g milk fat, 50 g bread, and 160 mL skimmed milk (251 kcal) after an overnight fast [45]. The dairy fat was consumed as an emulsification in the milk (emulsified with milk protein) or spread on the bread (unemulsified). Endotoxemia was not evident in normal-weight individuals ($n = 8$) after either treatment. The emulsified dairy fat substantially increased LPS activity 60 min after the test meal, but the unemulsified dairy fat spread had no effect on postprandial endotoxemia in obese individuals ($n = 8$) [45].

Other studies using a combination of dairy cream and sugar have yielded inconsistent results on postprandial inflammation. For instance, a 300-kcal intake of cream alone induced postprandial endotoxemia and TLR4 expression in mononuclear cells [49]. In another example, a cream, sugar, and water mix that provided 954 kcal increased postprandial IL-6 in healthy men, but this increase was no different than the increase occurring after a lower-calorie meal [50]. In a double-blind randomized crossover intervention study, postprandial IL-8 was increased by a high-fat shake (53% wt/vol) fresh cream, 3% (wt/vol) sugar and 44% (wt/vol) water with a macronutrient composition of 6 g protein, 95 g total fat (54 g saturated), 22 g carbohydrates, and 954 kcal relative to an average breakfast shake containing 43% (wt/vol) full cream milk, 48% (wt/vol) full cream

yogurt, 4% (wt/vol) lemonade, 4% (wt/vol) fantomalt (a high-energy carbohydrate oral supplement) (Nutricia BV), and 1% (wt/vol) wheat fiber with a macronutrient composition of 17 g protein, 14.5 g total fat (9 g saturated), 49.5 g carbohydrates, 2.3 g fiber, and 400 kcal [50]. In contrast, 1200 kcal provided from milk, cream, sucrose, and protein or 150 kcal from ice cream and whipping cream had no effect on postprandial inflammation [51, 52].

Several studies have evaluated whether dairy products can prevent postprandial inflammation. Schmid et al. compared the effects of an HFHC dairy meal (including cheese and butter), an HFHC nondairy control meal, and an HFHC nondairy meal supplemented with full-fat milk on postprandial inflammatory and metabolic responses in healthy men [53]. Endotoxemia, IL-6, and TNF-α concentrations were not different after the dairy-supplemented meals compared with the nondairy HFHC meal [53]. A subsequent study provided acidified milk or a probiotic yogurt (containing *Lactobacillus rhamnosus* GG) to healthy men ($n = 14$, BMI 18.0 to 25.0 kg/m^2) after 2-wk consumption of dairy products prior to the HFHC meal [54]. Both the milk and yogurt (400 g/d) reduced the postprandial IL-6 and TNF-α integrated AUC, relative to the preintervention baseline HFHC meal [54]. These changes were in parallel with alterations of the gut microbiota during each dietary phase. *Bilophila wadsworthia* decreased with milk consumption, while *Lactobacillus delbrueckii* spp. *bulgaricus* and *Streptococcus salivararius* spp. *thermophilus* increased after yogurt intake [54]. Further analysis of these changes found that yogurt intake altered the expression of 747 genes in the blood transcriptome at 2 h after consumption [55]. In contrast, 55 and 4 genes were changed by the intervention at 4 and 6 h, respectively. Yogurt dampened postprandial genes associated with immune activation, as well as the aryl hydrocarbon receptor (AhR). Targeted analysis of AhR ligands identified a positive correlation between circulating xenometabolite indole-3-acetaldehyde and *AhR* gene expression [55]. Yogurt consumption increased microbe-derived indole derivatives relative to acidified milk, which may explain the differential effects of these 2 products on the AhR [56].

Another study compared the consumption of low-fat, sweetened yogurt to an isocaloric nondairy control snack in obese and nonobese women [57, 58]. Premeal yogurt consumption inhibited the increase of postprandial IL-6 in both obese and nonobese women ($n = 30$ per group) after an HFHC meal [57]. Yogurt consumption also reduced postprandial LPS-binding protein (LBP): sCD14, a marker of endotoxin exposure [57]. Premeal yogurt consumption has also been shown to reduce postprandial hyperglycemia in obese women [58]. Additional daily consumption of 340 g yogurt for 9 wk further decreased postprandial LBP: sCD14 in obese women, although postprandial IL-6 was similar to the acute effect [58].

Collectively, these studies suggest that yogurt and acidified whole milk consumption reduce postprandial inflammation in the context of HFHC challenge meals. In contrast,

consumption of significant amounts of emulsified fat may exacerbate postprandial inflammation in obese individuals. Excessive intake of cream contributes to postprandial inflammation in some cases. Therefore, the dose, metabolic state of the individual and food matrix all impact how dairy affects postprandial inflammation.

Mechanisms by which dairy affects GI tract function.

Studies of dairy in animal models suggest that a number of components could impact GI tract function in a manner that modulates intestinal immune function. For example, after 4 wk, serum LPS activity and fecal Gram-negative bacteria were reduced in mice fed a high-fat diet (45% kcal from fat from soybean oil and anhydrous milk fat) modified to contain 0.25% (wt/wt) milk sphingomyelin, a polar lipid in milk fat (59). Supplementation of 1.5 g/kg/d milk fat globule membrane by daily gavage for 15 d reduced bacterial translocation and increased the expression of claudin tight junction proteins in the ileum of rats with small-bowel resection (60). Low-fat, sweetened yogurt powder also inhibits intestinal barrier dysfunction by increasing tight junctions in human intestinal Caco-2 cells exposed to inflammatory cytokines (61). Probiotics commonly found in fermented dairy products, milk proteins, and peptides have also been shown to directly improve intestinal barrier function through tight junction stabilization in Caco-2 cell culture models (62–66). Results from intervention studies in humans suggest that consumption of 400 g/d fermented milk for 2 wk can alter gut microbiota and microbial xenometabolites that may improve barrier function (54–56, 67). However, a complete understanding of the impact of the dairy matrix on microbiota composition and function is lacking.

Dairy consumption and hepatic function

Relationship of liver function with cardiometabolic health.

The liver is a multifunctional organ, which plays a critical role in health and disease as a hub for whole-body nutrient metabolism, as well as a major site of detoxification enzymes, hormone production, and immune functions. The liver is a major site of lipid biosynthesis, including the production of bile acids, fatty acids, and cholesterol. In many species, it is the major organ responsible for the secretion of endogenous lipids in the form of VLDL and the clearance of circulating lipoproteins, including LDL. Often referred to as the hepatic manifestation of metabolic syndrome, nonalcoholic fatty liver disease (NAFLD) has recently emerged as the most common liver disorder worldwide and is present in the majority of obese individuals (38). NAFLD includes a broad spectrum of conditions occurring in the absence of significant alcohol use, including steatosis, nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma. NASH is expected to become the most common indication for liver transplantation in the future (38). Beyond the liver, NAFLD also worsens health outcomes associated with obesity by increasing the risk for CVD (68). This is thought to be due to liver dysfunction

contributing to systemic inflammation, oxidative stress, and dyslipidemia (69).

Overview of liver lipid metabolism in health and disease.

NAFLD is thought to be driven by hepatic insulin resistance. Ectopic lipid deposition of lipid metabolites (e.g., ceramide, diacylglycerol) and inflammation are thought to contribute to hepatic insulin resistance in NAFLD. Insulin is responsible for 2 primary actions in the liver: *1*) increasing de novo lipogenesis and *2*) reducing gluconeogenesis. Insulin transcriptionally suppresses gene expression of gluconeogenic enzymes and induces the transcription of several genes involved in de novo lipogenesis, by transcriptional and posttranslational actions on the lipogenic transcription factors (70–72). Hepatic insulin resistance is associated with impairments of selective branches of the insulin signaling pathway, with the capacity for insulin to stimulate de novo lipogenesis retained at the same time as the inability to suppress hepatic gluconeogenesis (73). In parallel with increases in hepatic de novo lipogenesis are reductions in β-oxidation. Insulin-induced lipogenesis leads to increased malonyl-CoA production, which in turn inhibits carnitine palmitoyl transferase-1, and as a result, fatty acid oxidation is reduced (74). Consequently, this altered lipid handling further contributes to the progression of liver injury and NAFLD (75).

Hepatic insulin resistance is also related to increased VLDL-triglyceride production, which contributes to atherogenic dyslipidemia (76). LDL receptors are abundant in the liver, and this organ plays a major role in LDL clearance from circulation (77). The cholesterol content of LDL cholesterol is well established as a predictor of cardiovascular events and the primary target of lipid-lowering therapy (78). The liver is also the primary source responsible for the elevated plasma CRP concentration observed in NAFLD (79, 80). Circulating high-sensitivity CRP (hsCRP) is an independent predictor of future myocardial infarctions (81) and cardiovascular events (82). Thus, liver dysfunction has systemic implications for cardiometabolic health, with both lipid and inflammatory contributors to its sequelae.

Clinical studies using dairy products on NAFLD-related measures.

Dairy compared with nondairy diet interventions. The effects of dairy products on liver-derived lipoprotein concentrations have been studied extensively and reviewed previously (83, 84). However, few dietary interventions have examined the effects of dairy products as the primary intervention variable on NAFLD-related measures or in NAFLD patients. NAFLD may be diagnosed in humans through a liver biopsy, considered the gold standard, but is most commonly examined via imaging and other noninvasive diagnostic measures of liver injury, such as serum alanine transaminase (ALT) and aspartate transaminase (AST) (85). Observational studies have inversely linked NAFLD with low-fat dairy intake (86, 87). Thus, dietary patterns which incorporate dairy, such as the DASH (Dietary Approaches

to Stop Hypertension) diet, may be useful in mitigating this disease. An 8-wk parallel intervention study demonstrated benefits of following a calorie-restricted DASH diet ($n = 30$), which incorporated at least 3 servings of low-fat dairy daily, on lowering BMI, serum ALT, HOMA-IR, hsCRP, and serum triglycerides, among other variables, compared to a calorie-restricted control diet ($n = 30$) in patients with NAFLD [88]. However, other differences in the DASH diet compared to the control diet, such as greater fruit and vegetable intake and lower simple sugar intake, likely also contributed to the observed benefits. A 4-wk crossover study in overweight/obese adults ($n = 47$) showed a diet rich in low-fat dairy (4–6 servings/d) increased insulin resistance (HOMA-IR) compared to a diet high in lean red meat with minimal dairy (<1 serving/d) [89]; however, there was no effect on serum inflammation markers [90]. In contrast, in a 6-wk randomized crossover study in adults with metabolic syndrome ($n = 37$), the consumption of 3 servings of low-fat dairy daily (296 mL 1% milk, 170 g nonfat yogurt, 56.7 g 2% cheese) compared to isocaloric carbohydrate-based control foods (42.5 g granola bar and 355 mL juice) significantly lowered plasma ALT, AST, hepatic steatosis index, and mRNA expression of IL-6 and IL-1β in PBMCs. In this study, dairy intake had no effect on HOMA-IR or other plasma inflammatory biomarkers measured [91]. Body weight, waist circumference, and BMI were lower after the low-fat dairy period in women but not men. The authors speculated that the observed decrease in plasma aminotransferases may be due to attenuation of hepatic apoptosis and improvement in hepatocyte function by branched-chain amino acids from casein in milk, and/or an effect of increased circulating vitamin D concentrations following dairy consumption. The specific mechanisms by which at least some dairy foods impact liver fat and liver health indices remain to be elaborated.

Yogurt clinical studies. Gut microbiota have been linked with liver function and the development of NAFLD in both rodents [92] and humans [93]. Yogurt has been investigated for its effects on liver function measures as both conventional (live starter cultures) and probiotic-containing yogurt (i.e., yogurt with starter cultures and added probiotics). In a recent 24-wk open-label randomized, controlled, clinical trial, NAFLD patients were instructed to follow a healthy lifestyle and consume either 300 g daily of a synbiotic yogurt containing 1.5 g inulin and *Bifidobacterium animalis* subsp. *lactis* ($n = 34$), 300 g of a conventional yogurt ($n = 34$), or no yogurt as a control ($n = 34$) [94]. After 24 wk, liver steatosis and liver span (a measure of hepatomegaly) assessed by ultrasonography were both shown to be reduced to a significantly greater extent with the synbiotic yogurt group compared to the other 2 groups. The synbiotic yogurt group also had greatly improved serum liver enzymes, with significantly lower levels of ALT, AST, gamma-glutamyl transferase, and alkaline phosphatase. These changes were also observed with reductions in HOMA-IR and serum lipids (cholesterol, triglycerides, and LDL cholesterol) compared to

controls. Relative to controls, grade of steatosis, liver function variables, and lipid profiles improved with conventional yogurt, but to a lesser degree than with synbiotic yogurt. Probiotic yogurt was also shown to be more effective than conventional yogurt in another study in NAFLD patients. In a parallel intervention study, NAFLD patients who consumed 300 g/d of a probiotic-containing yogurt (B. *lactis* Bb12 and *Lactobacillus acidophilus* La5) ($n = 36$) for 8 wk had significant reductions in weight, BMI, ALT, AST, LDL cholesterol, and insulin compared to patients consuming a conventional yogurt ($n = 36$) [95]. A growing body of evidence suggests that probiotic-containing yogurt can reverse or improve liver steatosis indices relative to conventional yogurt and controls, whereas conventional yogurt only modestly improves or has no effect on these indices compared with no yogurt intake.

Cheese, whey, and human liver function. Currently, there are no controlled trials that have specifically examined the effects of cheese intake in NAFLD patients. However, relative to other full-fat dairy products such as butter, cheese intake has not been shown to raise LDL cholesterol concentrations in human intervention studies [96–98], suggesting an effect on the liver's function in lipoprotein secretion or clearance from circulation. A 12-wk randomized parallel intervention study in adults with ≥2 metabolic syndrome risk factors ($n = 139$) demonstrated no significant effects of a diet incorporating 80 g/d of regular-fat cheese ($n = 45$) on body composition, serum lipids, nuclear magnetic resonance–lipoprotein profiles, HOMA-IR, or hsCRP compared to reduced-fat cheese ($n = 48$) or low-cheese control diets ($n = 46$) [99, 100].

High-protein diets containing whey protein have been investigated for their potential benefits in liver function. In particular, the high cysteine content of whey protein may be beneficial in supporting hepatic levels of the antioxidant glutathione, which has been shown to be lower in livers of NAFLD patients [101]. However, data from well-controlled trials are sparse in this area. In a randomized, double-blind, placebo-controlled trial, elderly women ($n = 166$; 70–80 y) consumed 30 g/d of whey protein–supplemented beverage ($n = 82$) or an energy-matched, low-protein, high-carbohydrate control beverage ($n = 84$) for 2 y [102]. After 2 y, there were no significant differences in weight, waist circumference, BMI, insulin, glucose or HOMA-IR between groups. Additionally, there were no significant differences in hepatic steatosis between the treatments, as measured by computed tomography scans, although hepatic steatosis significantly worsened from baseline in the control but not the protein-treated groups. Strong inferences about the effects of cheese and whey intake on liver function and NAFLD are limited by the paucity of studies currently available on this topic, which warrants further investigation.

Animal models using dairy bioactive components on liver function and NAFLD development.

Whole dairy. Whole-dairy foods and dairy bioactive components have been investigated for their effects on liver

function and NAFLD, mostly in rodent models. Adams and colleagues (103) investigated the effects of high-calcium diets with and without nonfat dry milk (NFDM) on metabolic and inflammatory outcomes in diet-induced obese C57BL/6 mice. Male mice were fed an obesogenic soy protein–based high-fat diet (45% kcal as fat, 0.5% wt/wt calcium) for 8 wk, then randomized to consume for an additional 8 wk either the same diet (control; $n = 29$), a high-fat diet with 1.5% (wt/wt) calcium (high-Ca; $n = 30$), or a high-fat diet with high calcium (1.5% wt/wt) from NFDM (NFDM; $n = 30$). Mice fed the NFDM diet had improved glucose tolerance and lower liver triglycerides compared to both the high-calcium and control groups, suggesting the noncalcium dairy matrix components are responsible for benefits seen in these outcomes. Accordingly, feeding studies in rats have shown benefits of cheese on hepatic lipid content in some, but not all, studies (104). Interestingly, diets containing 10% (wt/wt) ripened cheese (15 d and 35 d) reduced hepatic lipids in obese diabetic mice (*db/db*) compared to a diet with 10% (wt/wt) unripened cheese (105), suggesting the duration of ripening affects the cheese matrix and health response.

Polar lipids from dairy and MFGM. In its natural state, milk fat is encased in a tri-layer milk fat globule membrane (MFGM), which is composed of proteins, cholesterol, and polar lipids (106). Polar lipids comprise approximately 1% of the total lipids of milk, and include glycerophospholipids (e.g., phosphatidylcholine) and sphingolipids (e.g., sphingomyelin), which emulsify triglyceride in the aqueous phase of milk (107). The polar lipid content of dairy products can vary considerably due to processing (108). Importantly, these MFGM components may impact the health effects of milk fat triglycerides and cholesterol in dairy products. In particular, sphingomyelin and its sphingolipid metabolites have been examined extensively in rodent models for their properties in inhibiting the intestinal absorption of other lipids (e.g., cholesterol, fatty acids) (). Due to their putative inhibition of the intestinal absorption of other lipids, as well as being a source of choline for liver health, polar lipids from MFGM have been investigated for potential benefits on liver function (109).

Blesso and colleagues have shown that feeding purified dietary sphingomyelin (SM; 0.1–0.25%, wt/wt diet) chronically to high-fat diet–fed C57BL/6 mice attenuates hepatic steatosis (59, 110). However, Yamauchi et al. (111) reported that supplementing 1% (wt/wt) of milk SM for 4 wk did not significantly alter hepatic lipids in genetically obese KK-Ay or low-fat diet–fed C57BL/6 mice. Wat et al. (112) and Kamili et al. (113) reported that chronic supplementation with various milk polar lipid extracts (0.25%–0.35% SM, wt/wt diet) significantly attenuated hepatic steatosis by lowering cholesterol and triglycerides in livers of C57BL/6 mice fed high-fat diets (21% butter fat, 0.15% cholesterol by weight). Effects were also observed in genetically obese KK-Ay mice with polar lipid–supplemented diets (0.5%–1.7% wt/wt) (114). However, some rodent studies have not shown effects on hepatic triglycerides. Supplementing an MFGM isolate

(0.5% polar lipids, 0.1% SM by weight of diet) to AIN-76A diet-fed rats for 12 wk significantly reduced hepatic cholesteryl ester content, with no change in hepatic TG (115). Furthermore, supplementing palm oil–based high-fat diet with 1.2% (wt/wt) milk polar lipids did not impact hepatic lipids in C57BL/6 mice after 8 wk (116). More research should be conducted on the effects of milk polar lipids, particularly those provided as components of whole dairy compared to those which are provided as an isolate. Further research is warranted in the clinical realm, as well, to test how MFGM and other dairy lipids impact human liver phenotypes.

Odd-chain fatty acids from dairy. The odd-chain saturated fatty acids, pentadecanoic acid (15:0) and heptadecanoic acid (17:0), are xenolipids ("nonself" lipid molecules that are derived from microbes) produced by the gut microbiota in ruminant animals and may serve as circulating biomarkers of dairy fat intake in humans (117). Odd-chain fatty acids comprise ∼1.5% of milk fat, with 15:0 being twice as abundant as 17:0 (118). Interestingly, serum concentrations of 15:0 and 17:0 were negatively correlated with NAFLD activity scores and hepatocyte ballooning scores in a cohort of NAFLD patients ($n = 106$) (119). Serum 15:0 was also negatively correlated with the severity of fibrosis and AST, while serum 17:0 was negatively correlated with both AST and ALT. Mice fed methionine-choline–deficient diets supplemented with 15:0 (5% wt/wt) for 4 wk were partially protected from liver injury. Supplementation with 15:0 attenuated elevations in serum AST, normalized liver weights of animals, and reduced the number of ceroid-laden macrophages (119). These results suggest that odd-chain fatty acids found in milk fat may influence liver function; however, more research is needed to confirm these initial findings and to understand if physiologically relevant intakes or systemic levels influence metabolic health or liver function.

Protein and/or bioactive peptides from milk. Administration of whey protein has been shown to improve liver function and reduce NAFLD-related outcomes in mice (120), and in rats in some studies (121), but not others (122). Male Wistar rats fed various whey protein mixtures (whey protein isolate, whey hydrolysate) or individual isolated whey proteins (α-lactalbumin, β-lactoglobulin, or glycomacropeptide) by oral gavage (∼1 g/kg body weight) for 28 wk had lower ALT concentrations and hepatic malondialdehyde, with some whey proteins also improving body weight (whey isolate, α-lactalbumin, and β-lactoglobulin) and hepatic glutathione levels (whey isolate, whey hydrolysate, and β-lactoglobulin) (121). In another study, female C57BL/6 J mice were fed high-fat diets for 11 wk, with or without 100 g whey protein isolate per liter drinking water (120). Compared to high-fat diet controls, mice fed the whey protein isolate had fewer hepatic lipid droplets evaluated by histological analysis, as well as lower concentrations of nonpolar lipids (mainly triglycerides) in

livers. However, a recent study in low-fat diet–fed male Wistar rats reported that while orally administering a whey protein concentration (WPC-80) at 0.5 g/kg body weight for 21 d increased hepatic glutathione concentrations and induced liver injury compared to saline ingestion, including significantly increasing ALT, AST, hepatic malondialdehyde, IL-1β and TGF-β1 concentrations (122). Further studies are needed to clarify these contrasting effects of whey protein in some rodent studies. In addition to whey protein, hydrolyzed casein derived from dairy products may also be a source of bioactive compounds/peptides for protection of liver function. The inclusion of an extensively hydrolyzed form of casein, instead of nonhydrolyzed casein, to a high-fat, high-sucrose diet (45% kcal as mainly lard) was shown to lower body weight, serum lipids, and macrovesicular steatosis in LDLr$^{-/-}$.Leiden mice after 21 wk (123).

Probiotics found in dairy products. Kefir, a fermented milk product and potential source of probiotics, has been reported in rodents to have beneficial effects on liver outcomes in NAFLD induced by high-fat diet (124), high-fructose corn syrup–enriched diet (125), and genetic deficiency of leptin (*ob/ob* mice) (126). The isolation and administration of a potential probiotic from fermented milk was reported to have beneficial effects on NAFLD in rats (127). *Lactobacillus paracasei* Jlus66 (4×10^{10} cfu) administered to 60% kcal high-fat diet–fed rats for 20 wk decreased body and liver weights, serum ALT, and NAFLD lesion score compared to control animals fed a high-fat diet.

Calcium. Due to the putative effects of calcium on forming insoluble fatty acid soaps in the GI tract and increasing fecal fat excretion (128), dietary calcium may be an important dairy component which affects liver fat accretion. Accordingly, male C57BL/6 mice that were fed a calcium-adequate high-fat diet (0.5% calcium, 20% corn oil wt/wt) for 18 mo had significantly lower NAFLD-related liver injury (hepatic inflammation, fibrosis, and overall NAFLD activity scores) and greater gut microbial diversity than mice fed a calcium-deficient high-fat diet (0.04% calcium wt/wt) (129). Furthermore, in male Wistar rats that were overfed as pups, feeding a diet that was 2-fold enriched in calcium (10 g/kg of diet) for 2 mo significantly improved histological steatosis scores and liver oxidative stress markers (130).

Dairy consumption and cardiovascular function

Diets containing higher levels of dairy foods have been reported to be associated with neutral or lower risks for CVD-related morbidity and mortality (14, 131, 132). A mediating benefit of higher dairy food intakes on CVD risk is attributed to its blood pressure–lowering effects, which have been reviewed (133) and are the focus of several systematic reviews and meta-analyses (134–137). However, reduced blood pressure is unlikely to fully explain the mechanisms by which dairy foods may lower CVD risk. Evidence from controlled trials that will be discussed herein support that dairy foods improve vascular function independent of any blood pressure–lowering effect.

The challenge to evaluating dairy foods with regard to CVD risk relates to the decades-long development of this disorder. However, vascular dysfunction has an early etiologic origin and mediates the progression of CVD. Brachial artery flow-mediated dilation (FMD) is a well-established method to evaluate vascular function and has prognostic value to predict cardiovascular events (138–140). This technique in combination with measures of cardiometabolic biomarkers has been applied in controlled clinical studies to help establish the mechanistic benefit of dairy foods.

Postprandial effects.
In the acute setting, the controlled administration of dairy foods or their bioactive components have been examined for their impact on vascular health in the postprandial period. In a double-blind, randomized controlled trial with cross-over design, persons with metabolic syndrome ingested 1% low-fat milk (474 ml) or an isocaloric volume of rice milk that was matched for micronutrients but had a higher proportion of its energy from carbohydrate (40 g compared with 24 g) in lieu of less protein (1 g compared with 16 g) (141). During the 3-h postprandial period, FMD responses were unaffected by low-fat milk, whereas FMD decreased following rice milk ingestion; blood pressure was unaffected regardless of treatment. The vasoprotective activity of low-fat milk was attributed to its lack of impact on postprandial hyperglycemia-induced oxidative stress that otherwise limits nitric oxide bioavailability. Indeed, rice milk significantly increased circulating glucose in association with increasing lipid peroxidation. Rice milk also increased postprandial levels of asymmetric dimethylarginine (ADMA) relative to arginine (ADMA/ARG). In contrast, low-fat milk did not increase postprandial lipid peroxidation and actually increased circulating ARG. This suggests that its limited impact on hyperglycemia protects against oxidative stress, which is otherwise known to increase arginase-mediated catabolism of ARG (142). These biochemical findings are consistent with evidence that FMD responses are at least, in part, mediated in a nitric oxide-dependent manner (143).

Controlled feeding trials.
Based on postprandial hyperglycemia mediating vascular dysfunction, a randomized cross-over trial in persons with prediabetes examined the vasoprotective activities of nonfat dairy milk or its casein and whey proteins when co-ingested with glucose (144). While glucose alone (75 g) decreased FMD responses, glucose-induced decreases in FMD during the 3-h postprandial period were prevented when nonfat milk (474 ml containing 16 g total protein) or isonitrogenous amounts of either casein or whey protein were co-ingested with glucose. Consistent with the co-ingestion of whey or casein with carbohydrate similarly attenuating acute hyperglycemia in individuals with prediabetes (145), each dairy-based treatment similarly lowered areas under

the curve ($AUC_{0-3\,h}$) for plasma glucose while increasing cholecystokinin (144). This suggests that hyperglycemia was attenuated by delaying glucose absorption. Further, the lipid peroxidation biomarkers malondialdehyde and F_2-isoprostanes (that were otherwise increased by glucose) were attenuated by all dairy-based treatments in association, with lower methylglyoxal and endothelin-1. $AUC_{0-3\,h}$ of nitric oxide metabolites were similarly higher among all dairy-based treatments, which occurred coincident with greater ARG availability and lower ADMA/ARG, and with symmetric dimethylarginine relative to ARG (SDMA/ARG) but without affecting tetrahydrobiopterin redox status.

In a similarly designed controlled trial in individuals with prediabetes, postprandial vascular function and metabolic health was examined in response to dairy milk fat per se (146). Participants ingested glucose alone or glucose with either nonfat dairy milk (0.4 g fat) or full-fat dairy milk (16.2 g fat) prior to assessing FMD and cardiometabolic biomarkers during the 3-h postprandial period. Despite prospective observational reports linking dairy fat with CVD risk (147, 148), findings of this controlled study (146) showed that dairy milk, regardless of its fat content, similarly protected against glucose-induced impairments in vascular function. In agreement with others (141, 144), the vasoprotective mechanism was likely attributable to limiting glucose-induced oxidative stress: the latter decreases ARG and increases both ADMA/ARG and SDMA/ARG. Together, these findings support that dairy milk, mediated through its proteins and without any detriment of its lipid fraction, helps to promote vascular function by improving nitric oxide bioavailability.

Potential mechanisms of action: gut–vessel interactions.
Evidence from a large-scale prospective observational study indicated that 2-h blood glucose following a glucose tolerance test, but not fasting glucose, predicted CVD-related mortality in persons with impaired glucose tolerance or those with overt diabetes (149). This further highlights that postmeal glucose excursions may be important to regulate vascular function. Although insulinotropic effects of milk proteins ($\geq$20 g/serving) have been observed (150), the doses are generally higher than typical consumption patterns of dairy foods. Thus, rather than due to enhanced glucose clearance, the glucose-lowering effects of dairy foods are at least partly mediated at the level of the gut. This is consistent with dairy milk or milk proteins increasing circulating cholecystokinin (146) in agreement with separate clinical studies suggesting slower gastric emptying (145, 151). Further, C-peptide concentrations increased among individuals with prediabetes following the acute ingestion of whey protein isolate (50 g) compared with maltodextrin (145). Both whey protein isolate and sodium caseinate also increased glucose-dependent insulinotropic polypeptide to a greater extent than maltodextrin, but neither dairy-derived protein affected glucagon-like peptide-1 (GLP-1) levels. However, the effects of whey protein on GLP-1 may be dose dependent, consistent with a higher dose (70 g) but not a lower dose

(30 g) increasing peak GLP-1 during a 3-h postprandial period (151). Overall, the evidence from controlled studies supports the cardioprotective benefits of dairy milk along the gut–vessel axis. Whether the attenuation of oxidative stress by dairy foods contributes to changes in vascular function remains unknown. Limited evidence indicates that, at least acutely, nitro-γ-tocopherol is unaffected by low-fat dairy milk ingestion (141). That this nitrative stress biomarker increases by proinflammatory responses (152) suggests that dairy foods protect against acute vascular dysfunction independent of inflammation, but further study is needed.

Potential mechanisms of action: microcirculation.
The microcirculation controls 80% of systemic vascular resistance, and dysfunction of the microcirculation is highly predictive of long-term CVD risk (153, 154). One of the earliest detectable functional manifestations of CVD is remodeling of the resistance vasculature and an attendant loss of endothelium-dependent vasodilation due to a reduction in nitric oxide. Thus, the mechanistic impact of dairy on microcirculatory control is a relatively unexplored area of investigation.

Independent of blood pressure reduction, dairy-derived bioactive proteins protect vascular endothelial function through multiple putative mechanisms, including acting as free-radical scavengers (155, 156), reducing NADPH oxidase (157), inhibiting lipid peroxidation (158), and improving antioxidant enzyme capacity through increased expression and activity (159, 160). The majority of the studies that have mechanistically demonstrated these effects have been performed in isolated cell and animal models (161, 162). Collectively, the results of these studies suggest that dairy proteins can preserve endothelial function by limiting reactive oxygen species (ROS).

An additional proposed mechanism underlying the protective effects of dairy on microcirculatory control involves angiotensin-converting enzyme (ACE) inhibition (163–165). In particular, casein-derived lactotripeptides including Val-Pro-Pro and Ile-Pro-Pro exhibit modest ACE-inhibitory properties. In a study involving stage I hypertensive men ($n = 24$), in a double-blind placebo controlled design, 1 wk of supplementation with casein hydrolysate improved vascular responsiveness during reactive hyperemia (166). Subsequent microarray analysis of the aorta in a spontaneously hypertensive rat model indicated the target changes in gene expression related to vascular function were increases in endothelial NO synthase and connexin 40, and alterations in pro/anti-inflammatory transcription factors, including NF-κB and peroxisome proliferator–activated receptor γ, respectively (167).

To date, few studies have interrogated the putative mechanisms underlying the impact of whole dairy foods on microcirculatory control in humans. In observational studies, low-fat milk, yogurt, and cheese consumption was associated with improved retinal microvascular quality in subjects with elevated CVD risk (168). However, in prospective studies,

acute low-fat milk consumption resulted in reduced NO-dependent vasodilation in the skin compared to both a water control and a eucaloric rice beverage comparison. The human cutaneous circulation has emerged as a representative vascular bed for assessing mechanisms mediating vascular dysfunction and is a validated in vivo model for assessing endothelial function in the microcirculation (169–171). Despite observing a reduction in NO-dependent vasodilation, the total magnitude of the vasodilator response remained unchanged (172). These data suggest that other non-NO–dependent pathways, including vasoprotective hyperpolarizing factors, may be modulated by dairy in the acute (single meal) setting.

The matrix and fat composition of dairy may protect the microvasculature from the detrimental effects of sodium. Independent of the effects on blood pressure, sodium reduces NO in the microcirculation through increasing superoxide production through NADPH oxidase (173, 174). However, recent data demonstrate that detrimental effects of sodium are mitigated when ingested in a dairy complex (natural cheese) (173). NO-dependent vasodilation in the cutaneous microcirculation was impaired 90 min after sodium ingestion at 560 mg and 1120 mg from a pretzel snack and 560 mg from nondairy cheese (soya), which was ameliorated with the localized treatment of the nonspecific antioxidant ascorbate. Similar to the animal and cell culture studies, the conclusions from this study suggest that the mechanisms mediating this vasoprotective effect are through decreasing oxidant stress (175). However, the exact component of the dairy cheese matrix mediating this effect or the influence of the dairy fat composition on these responses are unknown. Longer-term controlled and free-living studies incorporating low- and full-fat dairy cheese as a source of bioactive peptides and sodium in a sustainable dietary pattern are needed, to determine the precise mechanisms underlying these vascular effects.

Conclusions

Considerations of how specific foods or food components may impact whole-body health and function will benefit from an integrative perspective: one that takes dietary patterns, food matrices, and multitissue physiology into account. In this review, we have considered how full-fat dairy and other forms of dairy foods impact systems directly relevant to cardiometabolic health, including the gastrointestinal tract, liver, and vasculature. This unique perspective, bolstered by epidemiological and observational literature, generally supports the concept that dairy foods (including full-fat dairy) included as part of healthy dietary patterns do not negatively impact factors such as chronic or postprandial inflammation, CVD risk markers, vascular function, or liver fat homeostasis. In fact, on balance, epidemiological, randomized controlled trials and mechanism-based evidence points to a neutral-to-protective association of dairy with respect to cardiometabolic health. This unique perspective, complemented by epidemiological and observational literature, generally supports the concept

that dairy foods (including select forms of full-fat dairy such as milk, yogurt, and cheese) included as part of healthy dietary patterns does not contribute to deterioration of metabolic health, e.g. by negatively impacting factors such as chronic or postprandial inflammation, CVD risk markers, vascular function or liver fat homeostasis. In fact, on balance, epidemiological and mechanism-based evidence points to a neutral to protective association of dairy with respect to cardiometabolic health.

References

1. Ndisang JF, Rastogi S. Cardiometabolic diseases and related complications: current status and future perspective. Biomed Res Int 2013;2013:467682.
2. Saljoughian M. Cardiometabolic syndrome: a global health issue. US Pharm 2016;41(2):HS19–21.
3. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017;23(Suppl 2):1–87.
4. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(25 Pt B):2960–84.
5. Committee DGA. Scientific report of the 2015 Dietary Guidelines Advisory Committee. USDA and US Department of Health and Human Services: Washington (DC), 2015; pp. 1689–99.
6. Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, Iqbal R, Kumar R, Wentzel-Viljoen E, Rosengren A, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet 2017;390(10107):2050–62.
7. Mente A, Dehghan M, Rangarajan S, McQueen M, Dagenais G, Wielgosz A, Lear S, Li W, Chen H, Yi S, et al. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. Lancet Diabetes Endocrinol 2017;5(10):774–87.
8. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am J Clin Nutr 2010;91(3):535–46.
9. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fat, carbohydrate, and cardiovascular disease. Am J Clin Nutr 2010;91(3):502–9.
10. Skeaff CM, Miller J. Dietary fat and coronary heart disease: summary of evidence from prospective cohort and randomised controlled trials. Ann Nutr Metab 2009;55(1–3):173–201.
11. Morio B, Fardet A, Legrand P, Lecerf JM. Involvement of dietary saturated fats, from all sources or of dairy origin only, in insulin resistance and type 2 diabetes. Nutr Rev 2016;74(1):33–47.
12. Drouin-Chartier JP, Cote JA, Labonte ME, Brassard D, Tessier-Grenier M, Desroches S, Couture P, Lamarche B. Comprehensive review of the impact of dairy foods and dairy fat on cardiometabolic risk. Adv Nutr 2016;7(6):1041–51.
13. Telle-Hansen VH, Christensen JJ, Ulven SM, Holven KB. Does dietary fat affect inflammatory markers in overweight and obese individuals?—A review of randomized controlled trials from 2010 to 2016. Genes Nutr 2017;12:26.

14. Soedamah-Muthu SS, de Goede J. Dairy consumption and cardiometabolic diseases: systematic review and updated meta-analyses of prospective cohort studies. Curr Nutr Rep 2018;7(4):171–82.

15. Drouin-Chartier JP, Brassard D, Tessier-Grenier M, Cote JA, Labonte ME, Desroches S, Couture P, Lamarche B. Systematic review of the association between dairy product consumption and risk of cardiovascular-related clinical outcomes. Adv Nutr 2016;7(6):1026–40.

16. Lovegrove JA, Givens DI. Dairy food products: good or bad for cardiometabolic disease? Nutr Res Rev 2016;29(2):249–67.

17. Diez-Fernandez A, Alvarez-Bueno C, Martinez-Vizcaino V, Sotos-Prieto M, Recio-Rodriguez JI, Cavero-Redondo I. Total dairy, cheese and milk intake and arterial stiffness: a systematic review and meta-analysis of cross-sectional studies. Nutrients 2019;11(4) 741.

18. Gholami F, Khoramdad M, Esmailnasab N, Moradi G, Nouri B, Safiri S, Alimohamadi Y. The effect of dairy consumption on the prevention of cardiovascular diseases: a meta-analysis of prospective studies. J Cardiovasc Thorac Res 2017;9(1):1–11.

19. Lordan R, Tsoupras A, Mitra B, Zabetakis I. Dairy fats and cardiovascular disease: do we really need to be concerned? Foods 2018;7(3):29.

20. Salas-Salvado J, Guasch-Ferre M, Diaz-Lopez A, Babio N. Yogurt and diabetes: overview of recent observational studies. J Nutr 2017;147(7):1452S–61S.

21. Hirahatake KM, Slavin JL, Maki KC, Adams SH. Associations between dairy foods, diabetes, and metabolic health: potential mechanisms and future directions. Metabolism 2014;63(5):618–27.

22. Yu E, Hu FB. Dairy products, dairy fatty acids, and the prevention of cardiometabolic disease: a review of recent evidence. Curr Atheroscler Rep 2018;20(5):24.

23. Ahluwalia B, Magnusson MK, Ohman L. Mucosal immune system of the gastrointestinal tract: maintaining balance between the good and the bad. Scand J Gastroenterol 2017;52(11):1185–93.

24. Richards JL, Yap YA, McLeod KH, Mackay CR, Marino E. Dietary metabolites and the gut microbiota: an alternative approach to control inflammatory and autoimmune diseases. Clin Transl Immunology 2016;5(5):e82.

25. Yap YA, Marino E. An insight into the intestinal web of mucosal immunity, microbiota, and diet in inflammation. Front Immunol 2018;9:2617.

26. McNamee EN, Masterson JC, Veny M, Collins CB, Jedlicka P, Byrne FR, Ng GY, Rivera-Nieves J. Chemokine receptor CCR7 regulates the intestinal TH1/TH17/Treg balance during Crohn's-like murine ileitis. J Leukoc Biol 2015;97(6):1011–22.

27. Massot B, Michel M-L, Diem S, Ohnmacht C, Latour S, Dy M, Eberl G, Leite-de-Moraes MC. TLR-induced cytokines promote effective proinflammatory natural Th17 cell responses. J Immunol 2014;192(12):5635–42.

28. Belzer C, Chia LW, Aalvink S, Chamlagain B, Piironen V, Knol J, de Vos WM. Microbial metabolic networks at the mucus layer lead to diet-independent butyrate and vitamin B12 production by intestinal symbionts. MBio 2017;8(5).

29. Luhrs H, Gerke T, Muller JG, Melcher R, Schauber J, Boxberge F, Scheppach W, Menzel T. Butyrate inhibits NF-κB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol 2002;37(4):458–66.

30. Montgomery RK, Buller HA, Rings EH, Grand RJ. Lactose intolerance and the genetic regulation of intestinal lactase-phlorizin hydrolase. FASEB J 1991;5(13):2824–32.

31. van de Heijning BJ, Kegler D, Schipper L, Voogd E, Oosting A, van der Beek EM. Acute and chronic effects of dietary lactose in adult rats are not explained by residual intestinal lactase activity. Nutrients 2015;7(7):5542–55.

32. Abreu MT, Arnold ET, Thomas LS, Gonsky R, Zhou Y, Hu B, Arditi M. TLR4 and MD-2 expression is regulated by immune-mediated signals in human intestinal epithelial cells. J Biol Chem 2002;277(23): 20431–7.

33. Brun P, Castagliuolo I, Di Leo V, Buda A, Pinzani M, Palu G, Martines D. Increased intestinal permeability in obese mice: new evidence in the pathogenesis of nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 2007;292(2):G518–25.

34. Laugerette F, Alligier M, Bastard JP, Drai J, Chanseaume E, Lambert-Porcheron S, Laville M, Morio B, Vidal H, Michalski MC. Overfeeding increases postprandial endotoxemia in men: inflammatory outcome may depend on LPS transporters LBP and sCD14. Mol Nutr Food Res 2014;58(7):1513–8.

35. Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature 2015;519(7541):92–6.

36. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56(7):1761–72.

37. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet–induced obesity and diabetes in mice. Diabetes 2008;57(6):1470–81.

38. Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol 2017;23(47):8263–76.

39. Cainzos-Achirica M, Miedema MD, McEvoy JW, Cushman M, Dardari Z, Greenland P, Nasir K, Budoff MJ, Al-Mallah MH, Yeboah J, et al. The prognostic value of high sensitivity C-reactive protein in a multi-ethnic population after >10 years of follow-up: The Multi-Ethnic Study of Atherosclerosis (MESA). Int J Cardiol 2018;264:158–64.

40. Patsch JR, Miesenbock G, Hopferwieser T, Muhlberger V, Knapp E, Dunn JK, Gotto AM, Jr, Patsch W. Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. Arterioscler Thromb 1992;12(11):1336–45.

41. Blanco-Colio LM, Valderrama M, Alvarez-Sala LA, Bustos C, Ortego M, Hernandez-Presa MA, Cancelas P, Gomez-Gerique J, Millan J, Egido J. Red wine intake prevents nuclear factor-kappaB activation in peripheral blood mononuclear cells of healthy volunteers during postprandial lipemia. Circulation 2000;102(9):1020–6.

42. Manning PJ, Sutherland WH, McGrath MM, de Jong SA, Walker RJ, Williams MJ. Postprandial cytokine concentrations and meal composition in obese and lean women. Obesity (Silver Spring) 2008;16(9):2046–52.

43. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans. Circulation 2002;106(16):2067–72.

44. Laugerette F, Vors C, Géloën A, Chauvin M-A, Soulage C, Lambert-Porcheron S, Peretti N, Alligier M, Burcelin R, Laville M, et al. Emulsified lipids increase endotoxemia: possible role in early postprandial low-grade inflammation. J Nutr Biochem 2011;22(1):53–9.

45. Vors C, Drai J, Pineau G, Laville M, Vidal H, Laugerette F, Michalski MC. Emulsifying dietary fat modulates postprandial endotoxemia associated with chylomicronemia in obese men: a pilot randomized crossover study. Lipids Health Dis 2017;16(1):97.

46. Emerson SR, Kurti SP, Harms CA, Haub MD, Melgarejo T, Logan C, Rosenkranz SK. Magnitude and timing of the postprandial inflammatory response to a high-fat meal in healthy adults: a systematic review. Adv Nutr 2017;8(2):213–25.

47. Herieka M, Erridge C. High-fat meal induced postprandial inflammation. Mol Nutr Food Res 2014;58(1):136–46.

48. Ono-Moore KD, Blackburn ML, Adams SH. Is palmitate truly proinflammatory? Experimental confounders and context-specificity. Am J Physiol Endocrinol Metab 2018;315(5):E780–94.

49. Deopurkar R, Ghanim H, Friedman J, Abuaysheh S, Sia CL, Mohanty P, Viswanathan P, Chaudhuri A, Dandona P. Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the

expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. Diabetes Care 2010;33(5):991–7.

50. Esser D, Oosterink E, op 't Roodt J, Henry RM, Stehouwer CD, Muller M, Afman LA. Vascular and inflammatory high fat meal responses in young healthy men; a discriminative role of IL-8 observed in a randomized trial. PLoS One 2013;8(2):e53474.

51. Mariotti F, Valette M, Lopez C, Fouillet H, Famelart MH, Mathe V, Airinei G, Benamouzig R, Gaudichon C, Tome D, et al. Casein compared with whey proteins affects the organization of dietary fat during digestion and attenuates the postprandial triglyceride response to a mixed high-fat meal in healthy, overweight men. J Nutr 2015;145(12):2657–64.

52. Johnson AM, Kurti SP, Smith JR, Rosenkranz SK, Harms CA. Effects of an acute bout of moderate-intensity exercise on postprandial lipemia and airway inflammation. Appl Physiol Nutr Metab 2016;41(3):284–91.

53. Schmid A, Petry N, Walther B, Butikofer U, Luginbuhl W, Gille D, Chollet M, McTernan PG, Gijs MA, Vionnet N, et al. Inflammatory and metabolic responses to high-fat meals with and without dairy products in men. Br J Nutr 2015;113(12):1853–61.

54. Burton KJ, Rosikiewicz M, Pimentel G, Butikofer U, von Ah U, Voirol MJ, Croxatto A, Aeby S, Drai J, McTernan PG, et al. Probiotic yogurt and acidified milk similarly reduce postprandial inflammation and both alter the gut microbiota of healthy, young men. Br J Nutr 2017;117(9):1312–22.

55. Burton KJ, Pimentel G, Zangger N, Vionnet N, Drai J, McTernan PG, Pralong FP, Delorenzi M, Vergeres G. Modulation of the peripheral blood transcriptome by the ingestion of probiotic yoghurt and acidified milk in healthy, young men. PLoS One 2018;13(2):e0192947.

56. Pimentel G, Burton KJ, von Ah U, Butikofer U, Pralong FP, Vionnet N, Portmann R, Vergeres G. Metabolic footprinting of fermented milk consumption in serum of healthy men. J Nutr 2018;148(6): 851–60.

57. Pei R, DiMarco DM, Putt KK, Martin DA, Chitchumroonchokchai C, Bruno RS, Bolling BW. Premeal low-fat yogurt consumption reduces postprandial inflammation and markers of endotoxin exposure in healthy premenopausal women in a randomized controlled trial. J Nutr 2018;148(6):910–6.

58. Pei R, DiMarco DM, Putt KK, Martin DA, Gu Q, Chitchumroonchokchai C, White HM, Scarlett CO, Bruno RS, Bolling BW. Low-fat yogurt consumption reduces biomarkers of chronic inflammation and inhibits markers of endotoxin exposure in healthy premenopausal women: a randomised controlled trial. Br J Nutr 2017;118(12):1043–51.

59. Norris GH, Jiang C, Ryan J, Porter CM, Blesso CN. Milk sphingomyelin improves lipid metabolism and alters gut microbiota in high fat diet-fed mice. J Nutr Biochem 2016;30:93–101.

60. Li Y, Wu J, Niu Y, Chen H, Tang Q, Zhong Y, Lambers TT, Cai W. Milk fat globule membrane inhibits NLRP3 inflammasome activation and enhances intestinal barrier function in a rat model of short bowel. JPEN J Parenter Enteral Nutr 2018;43(5):677–85.

61. Putt KK, Pei R, White HM, Bolling BW. Yogurt inhibits intestinal barrier dysfunction in Caco-2 cells by increasing tight junctions. Food Funct 2017;8(1):406–14.

62. Hashimoto K, Nakayama T, Shimizu M. Effects of B-lactoglobulin on the tight-junctional stability of Caco-2-SF monolayer. Biosci. Biotechnol. Biochem 1998;62(9):1819–21.

63. Hashimoto K, Takeda K, Nakayama T, Shimizu M. Stabilization of the tight junction of the intestinal Caco-2 monolayer by milk whey proteins. Biosci. Biotechnol. Biochem 1995;59(10):1951–2.

64. Yasumatsu H, Tanabe S. The casein peptide Asn-Pro-Trp-Asp-Gln enforces the intestinal tight junction partly by increasing occludin expression in Caco-2 cells. Br J Nutr 2010;104(7):951–6.

65. Anderson RC, Cookson AL, McNabb WC, Park Z, McCann MJ, Kelly WJ, Roy NC. Lactobacillus plantarum MB452 enhances the function of the intestinal barrier by increasing the expression levels of genes involved in tight junction formation. BMC Microbiol 2010;10:316.

66. Hering NA, Luettig J, Krug SM, Wiegand S, Gross G, van Tol EA, Schulzke JD, Rosenthal R. Lactoferrin protects against intestinal inflammation and bacteria-induced barrier dysfunction in vitro. Ann N Y Acad Sci 2017;1405(1):177–88.

67. Veiga P, Pons N, Agrawal A, Oozeer R, Guyonnet D, Brazeilles R, Faurie JM, van Hylckama Vlieg JE, Houghton LA, Whorwell PJ, et al. Changes of the human gut microbiome induced by a fermented milk product. Sci Rep 2014;4:6328.

68. Lonardo A, Sookoian S, Pirola CJ, Targher G. Non-alcoholic fatty liver disease and risk of cardiovascular disease. Metabolism 2016;65(8):1136–50.

69. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010;363(14):1341–50.

70. Yellaturu CR, Deng X, Cagen LM, Wilcox HG, Mansbach CM2nd, Siddiqi SA, Park EA, Raghow R, Elam MB. Insulin enhances post-translational processing of nascent SREBP-1c by promoting its phosphorylation and association with COPII vesicles. J Biol Chem 2009;284(12):7518–32.

71. Tobin KA, Ulven SM, Schuster GU, Steineger HH, Andresen SM, Gustafsson JA, Nebb HI. Liver X receptors as insulin-mediating factors in fatty acid and cholesterol biosynthesis. J Biol Chem 2002;277(12):10691–7.

72. Hegarty BD, Bobard A, Hainault I, Ferre P, Bossard P, Foufelle F. Distinct roles of insulin and liver X receptor in the induction and cleavage of sterol regulatory element-binding protein-1c. Proc Natl Acad Sci U S A 2005;102(3):791–6.

73. Li S, Brown MS, Goldstein JL. Bifurcation of insulin signaling pathway in rat liver: mTORC1 required for stimulation of lipogenesis, but not inhibition of gluconeogenesis. Proc Natl Acad Sci U S A 2010;107(8):3441–6.

74. McGarry JD, Leatherman GF, Foster DW. Carnitine palmitoyltransferase I. The site of inhibition of hepatic fatty acid oxidation by malonyl-CoA. J Biol Chem 1978;253(12): 4128–36.

75. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. J Clin Invest 2004;114(2):147–52.

76. Adiels M, Olofsson SO, Taskinen MR, Boren J. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. Arterioscler Thromb Vasc Biol 2008;28(7):1225–36.

77. Dietschy JM. Theoretical considerations of what regulates low-density-lipoprotein and high-density-lipoprotein cholesterol. Am J Clin Nutr 1997;65(5 Suppl):1581S–9S.

78. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Jr, Stone NJNational Heart, Lung, and Blood Institute;, et al.; National Heart, Lung, and Blood Institute Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110(2):227–39.

79. Yoneda M, Mawatari H, Fujita K, Iida H, Yonemitsu K, Kato S, Takahashi H, Kirikoshi H, Inamori M, Nozaki Y, et al. High-sensitivity C-reactive protein is an independent clinical feature of nonalcoholic steatohepatitis (NASH) and also of the severity of fibrosis in NASH. J Gastroenterol 2007;42(7):573–82.

80. Kotronen A, Yki-Jarvinen H. Fatty liver: a novel component of the metabolic syndrome. Arterioscler Thromb Vasc Biol 2008;28(1):27–38.

81. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 1998;97(20):2007–11.

82. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342(12):836–43.

83. Huth PJ, Park KM. Influence of dairy product and milk fat consumption on cardiovascular disease risk: a review of the evidence. Adv Nutr 2012;3(3):266–85.

84. Astrup A. Yogurt and dairy product consumption to prevent cardiometabolic diseases: epidemiologic and experimental studies. Am J Clin Nutr 2014;99(5 Suppl):1235S–42S.

85. Kwok R, Tse YK, Wong GL, Ha Y, Lee AU, Ngu MC, Chan HL, Wong VW. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease–the role of transient elastography and plasma cytokeratin-18 fragments. Aliment Pharmacol Ther 2014;39(3):254–69.

86. Ferolla SM, Ferrari TC, Lima ML, Reis TO, Tavares WC, Jr, Couto OF, Vidigal PV, Fausto MA, Couto CA. Dietary patterns in Brazilian patients with nonalcoholic fatty liver disease: a cross-sectional study. Clinics (Sao Paulo) 2013;68(1):11–7.

87. Shi L, Liu ZW, Li Y, Gong C, Zhang H, Song LJ, Huang CY, Li M. The prevalence of nonalcoholic fatty liver disease and its association with lifestyle/dietary habits among university faculty and staff in Chengdu. Biomed Environ Sci 2012;25(4):383–91.

88. Razavi Zade M, Telkabadi MH, Bahmani F, Salehi B, Farshbaf S, Asemi Z. The effects of DASH diet on weight loss and metabolic status in adults with non-alcoholic fatty liver disease: a randomized clinical trial. Liver Int 2016;36(4):563–71.

89. Turner KM, Keogh JB, Clifton PM. Red meat, dairy, and insulin sensitivity: a randomized crossover intervention study. Am J Clin Nutr 2015;101(6):1173–9.

90. Turner KM, Keogh JB, Meikle PJ, Clifton PM. Changes in lipids and inflammatory markers after consuming diets high in red meat or dairy for four weeks. Nutrients 2017;9(8):886.

91. Dugan CE, Aguilar D, Park YK, Lee JY, Fernandez ML. Dairy consumption lowers systemic inflammation and liver enzymes in typically low-dairy consumers with clinical characteristics of metabolic syndrome. J Am Coll Nutr 2016;35(3):255–61.

92. Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL, Eisenbarth SC, Jurczak MJ, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature 2012;482(7384):179–85.

93. Zhu L, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, Gill SR. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology 2013;57(2):601–9.

94. Bakhshimoghaddam F, Shateri K, Sina M, Hashemian M, Alizadeh M. Daily consumption of synbiotic yogurt decreases liver steatosis in patients with nonalcoholic fatty liver disease: a randomized controlled clinical trial. J Nutr 2018;148(8):1276–84.

95. Nabavi S, Rafraf M, Somi MH, Homayouni-Rad A, Asghari-Jafarabadi M. Effects of probiotic yogurt consumption on metabolic factors in individuals with nonalcoholic fatty liver disease. J Dairy Sci 2014;97(12):7386–93.

96. Biong AS, Muller H, Seljeflot I, Veierod MB, Pedersen JI. A comparison of the effects of cheese and butter on serum lipids, haemostatic variables and homocysteine. Br J Nutr 2004;92(5):791–7.

97. Hjerpsted J, Leedo E, Tholstrup T. Cheese intake in large amounts lowers LDL-cholesterol concentrations compared with butter intake of equal fat content. Am J Clin Nutr 2011;94(6):1479–84.

98. Nestel PJ, Chronopulos A, Cehun M. Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. Eur J Clin Nutr 2005;59(9):1059–63.

99. Raziani F, Tholstrup T, Kristensen MD, Svanegaard ML, Ritz C, Astrup A, Raben A. High intake of regular-fat cheese compared with reduced-fat cheese does not affect LDL cholesterol or risk markers of the metabolic syndrome: a randomized controlled trial. Am J Clin Nutr 2016;104(4):973–81.

100. Raziani F, Ebrahimi P, Engelsen SB, Astrup A, Raben A, Tholstrup T. Consumption of regular-fat vs. reduced-fat cheese reveals gender-specific changes in LDL particle size—a randomized controlled trial. Nutr Metab (Lond) 2018;15:61.

101. Altomare E, Vendemiale G, Albano O. Hepatic glutathione content in patients with alcoholic and non alcoholic liver diseases. Life Sci 1988;43(12):991–8.

102. Ooi EM, Adams LA, Zhu K, Lewis JR, Kerr DA, Meng X, Solah V, Devine A, Binns CW, Prince RL. Consumption of a whey protein-enriched diet may prevent hepatic steatosis associated with weight gain in elderly women. Nutr Metab Cardiovasc Dis 2015;25(4):388–95.

103. Thomas AP, Dunn TN, Drayton JB, Oort PJ, Adams SH. A dairy-based high calcium diet improves glucose homeostasis and reduces steatosis in the context of preexisting obesity. Obesity (Silver Spring) 2013;21(3):E229–35.

104. Higurashi S, Nara T, Kato K, Kadooka Y. Cheese consumption prevents fat accumulation in the liver and improves serum lipid parameters in rate fed a high-fat diet. Dairy Sci Technol 2016;96(4):539–49.

105. Geurts L, Everard A, le Ruyet P, Delzenne NM, Cani PD. Ripened dairy products differentially affect hepatic lipid content and adipose tissue oxidative stress markers in obese and type 2 diabetic mice. J Agric Food Chem 2012;60(8):2063–8.

106. Lopez C, Briard-Bion V, Ménard O, Beaucher E, Rousseau F, Fauquant J, Leconte N, Robert B. Fat globules selected from whole milk according to their size: different compositions and structure of the biomembrane, revealing sphingomyelin-rich domains. Food Chem 2011;125(2):355–68.

107. Rombaut R, Dewettinck K. Properties, analysis and purification of milk polar lipids. Int Dairy J 2006;16(11):1362–73.

108. Rombaut R, Camp JV, Dewettinck K. Phospho- and sphingolipid distribution during processing of milk, butter and whey. Int J Food Sci Technol 2006;41(4):435–43.

109. Norris GH, Blesso CN. Dietary sphingolipids: potential for management of dyslipidemia and nonalcoholic fatty liver disease. Nutr Rev 2017;75(4):274–85.

110. Norris GH, Porter CM, Jiang C, Millar CL, Blesso CN. Dietary sphingomyelin attenuates hepatic steatosis and adipose tissue inflammation in high-fat-diet-induced obese mice. J Nutr Biochem 2017;40:36–43.

111. Yamauchi I, Uemura M, Hosokawa M, Iwashima-Suzuki A, Shiota M, Miyashita K. The dietary effect of milk sphingomyelin on the lipid metabolism of obese/diabetic KK-A(y) mice and wild-type C57BL/6 J mice. Food Funct 2016;7(9):3854–67.

112. Wat E, Tandy S, Kapera E, Kamili A, Chung RW, Brown A, Rowney M, Cohn JS. Dietary phospholipid-rich dairy milk extract reduces hepatomegaly, hepatic steatosis and hyperlipidemia in mice fed a high-fat diet. Atherosclerosis 2009;205(1):144–50.

113. Kamili A, Wat E, Chung RW, Tandy S, Weir JM, Meikle PJ, Cohn JS. Hepatic accumulation of intestinal cholesterol is decreased and fecal cholesterol excretion is increased in mice fed a high-fat diet supplemented with milk phospholipids. Nutr Metab (Lond) 2010;7(1):90.

114. Watanabe S, Takahashi T, Tanaka L, Haruta Y, Shiota M, Hosokawa M, Miyashita K. The effect of milk polar lipids separated from butter serum on the lipid levels in the liver and the plasma of obese-model mouse (KK-Ay). J Funct Foods 2011;3(4):313–20.

115. Zhou AL, Hintze KJ, Jimenez-Flores R, Ward RE. Dietary fat composition influences tissue lipid profile and gene expression in Fischer-344 rats. Lipids 2012;47(12):1119–30.

116. Lecomte M, Couedelo L, Meugnier E, Plaisancie P, Letisse M, Benoit B, Gabert L, Penhoat A, Durand A, Pineau G, et al. Dietary emulsifiers from milk and soybean differently impact adiposity and inflammation in association with modulation of colonic goblet cells in high-fat fed mice. Mol Nutr Food Res 2016;60(3):609–20.

117. Jenkins B, West JA, Koulman A. A review of odd-chain fatty acid metabolism and the role of pentadecanoic acid (c15:0) and heptadecanoic acid (c17:0) in health and disease. Molecules 2015;20(2):2425–44.

118. Dohme-Meier F, Bee G. Feeding Unprotected CLA methyl esters compared to sunflower seeds increased milk CLA level by inhibited milk fat synthesis in cows. Asian-Australas J Anim Sci 2012;25(1):75–85.

119. Yoo W, Gjuka D, Stevenson HL, Song X, Shen H, Yoo SY, Wang J, Fallon M, Ioannou GN, Harrison SA, et al. Fatty acids in non-alcoholic steatohepatitis: focus on pentadecanoic acid. PLoS One 2017;12(12):e0189965.

120. Shertzer HG, Woods SE, Krishan M, Genter MB, Pearson KJ. Dietary whey protein lowers the risk for metabolic disease in mice fed a high-fat diet. J Nutr 2011;141(4):582–7.

121. Hamad EM, Taha SH, Abou Dawood AG, Sitohy MZ, Abdel-Hamid M. Protective effect of whey proteins against nonalcoholic fatty liver in rats. Lipids Health Dis 2011;10:57.

122. Zebrowska-Gamdzyk M, Maciejczyk M, Zalewska A, Guzinska-Ustymowicz K, Tokajuk A, Car H. Whey protein concentrate WPC-80 intensifies glycoconjugate catabolism and induces oxidative stress in the liver of rats. Nutrients 2018;10(9):1178.

123. Schoemaker MH, Kleemann R, Morrison MC, Verheij J, Salic K, van Tol EAF, Kooistra T, Wielinga PY. A casein hydrolysate based formulation attenuates obesity and associated non-alcoholic fatty liver disease and atherosclerosis in LDLr-/-.Leiden mice. PLoS One 2017;12(7):e0180648.

124. Kim DH, Kim H, Jeong D, Kang IB, Chon JW, Kim HS, Song KY, Seo KH. Kefir alleviates obesity and hepatic steatosis in high-fat diet-fed mice by modulation of gut microbiota and mycobiota: targeted and untargeted community analysis with correlation of biomarkers. J Nutr Biochem 2017;44:35–43.

125. Chen HL, Tsai TC, Tsai YC, Liao JW, Yen CC, Chen CM. Kefir peptides prevent high-fructose corn syrup-induced non-alcoholic fatty liver disease in a murine model by modulation of inflammation and the JAK2 signaling pathway. Nutr Diabetes 2016;6(12):e237.

126. Chen HL, Tung YT, Tsai CL, Lai CW, Lai ZL, Tsai HC, Lin YL, Wang CH, Chen CM. Kefir improves fatty liver syndrome by inhibiting the lipogenesis pathway in leptin-deficient *ob/ob* knockout mice. Int J Obes (Lond) 2014;38(9):1172–9.

127. Ye H, Li Q, Zhang Z, Sun M, Zhao C, Zhang T. Effect of a novel potential probiotic *Lactobacillus paracasei* Jlus66 isolated from fermented milk on nonalcoholic fatty liver in rats. Food Funct 2017;8(12):4539–46.

128. Christensen R, Lorenzen JK, Svith CR, Bartels EM, Melanson EL, Saris WH, Tremblay A, Astrup A. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. Obes Rev 2009;10(4):475–86.

129. Aslam M, Aggarwal S, Sharma KK, Galav V, Madhu SV. Postprandial hypertriglyceridemia predicts development of insulin resistance glucose intolerance and type 2 diabetes. PLoS One 2016;11(1):e0145730.

130. Conceicao EP, Moura EG, Soares PN, Ai XX, Figueiredo MS, Oliveira E, Lisboa PC. High calcium diet improves the liver oxidative stress and microsteatosis in adult obese rats that were overfed during lactation. Food Chem Toxicol 2016;92:245–55.

131. Dehghan M, Mente A, Rangarajan S, Sheridan P, Mohan V, Iqbal R, Gupta R, Lear S, Wentzel-Viljoen E, Avezum A, et al. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. Lancet 2018;392(10161):2288–97.

132. Guo J, Astrup A, Lovegrove JA, Gijsbers L, Givens DI, Soedamah-Muthu SS. Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. Eur J Epidemiol 2017;32(4):269–87.

133. Ballard KD, Bruno RS. Protective role of dairy and its constituents on vascular function independent of blood pressure-lowering activities. Nutr Rev 2015;73(1):36–50.

134. Kris-Etherton PM, Grieger JA, Hilpert KF, West SG. Milk products, dietary patterns and blood pressure management. J Am Coll Nutr 2009;28(Suppl 1):103S–19S.

135. Ralston RA, Lee JH, Truby H, Palermo CE, Walker KZ. A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. J Hum Hypertens 2012;26(1):3–13.

136. Soedamah-Muthu SS, Verberne LD, Ding EL, Engberink MF, Geleijnse JM. Dairy consumption and incidence of hypertension: a dose-response meta-analysis of prospective cohort studies. Hypertension 2012;60(5):1131–7.

137. Varenna M, Manara M, Galli L, Binelli L, Zucchi F, Sinigaglia L. The association between osteoporosis and hypertension: the role of a low dairy intake. Calcif Tissue Int 2013;93(1):86–92.

138. Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis. J Am Heart Assoc 2015;4(11).

139. Ras RT, Streppel MT, Draijer R, Zock PL. Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis. Int J Cardiol 2013;168(1):344–51.

140. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. Int J Cardiovasc Imaging 2010;26(6):631–40.

141. Ballard KD, Mah E, Guo Y, Pei R, Volek JS, Bruno RS. Low-fat milk ingestion prevents postprandial hyperglycemia-mediated impairments in vascular endothelial function in obese individuals with metabolic syndrome. J Nutr 2013;143(10):1602–10.

142. Mah E, Bruno RS. Postprandial hyperglycemia on vascular endothelial function: mechanisms and consequences. Nutr Res 2012;32(10):727–40.

143. Green DJ, Dawson EA, Groenewoud HM, Jones H, Thijssen DH. Is flow-mediated dilation nitric oxide mediated? A meta-analysis. Hypertension 2014;63(2):376–82.

144. McDonald JD, Mah E, Chitchumroonchokchai C, Dey P, Labyk AN, Villamena FA, Volek JS, Bruno RS. Dairy milk proteins attenuate hyperglycemia-induced impairments in vascular endothelial function in adults with prediabetes by limiting increases in glycemia and oxidative stress that reduce nitric oxide bioavailability. J Nutr Biochem 2019;63:165–76.

145. Hoefle AS, Bangert AM, Stamford A, Gedrich K, Rist MJ, Lee YM, Skurk T, Daniel H. Metabolic responses of healthy or prediabetic adults to bovine whey protein and sodium caseinate do not differ. J Nutr 2015;145(3):467–75.

146. McDonald JD, Mah E, Dey P, Olmstead BD, Sasaki GY, Villamena FA, Bruno RS. Dairy milk, regardless of fat content, protects against postprandial hyperglycemia-mediated impairments in vascular endothelial function in adults with prediabetes by limiting oxidative stress responses that reduce nitric oxide bioavailability. J Nutr Biochem 2019;63:129–39.

147. Hu FB, Stampfer MJ, Manson JE, Ascherio A, Colditz GA, Speizer FE, Hennekens CH, Willett WC. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. Am J Clin Nutr 1999;70(6):1001–8.

148. Chen M, Li YP, Sun Q, Pan A, Manson JE, Rexrode KM, Willett WC, Rimm EB, Hu FB. Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. Am J Clin Nutr 2016;104(5):1209–17.

149. DECODE Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161(3):397–405.

150. Graf S, Egert S, Heer M. Effects of whey protein supplements on metabolism: evidence from human intervention studies. Curr Opin Clin Nutr Metab Care 2011;14(6):569–80.

151. Hutchison AT, Piscitelli D, Horowitz M, Jones KL, Clifton PM, Standfield S, Hausken T, Feinle-Bisset C, Luscombe-Marsh ND. Acute load-dependent effects of oral whey protein on gastric emptying, gut hormone release, glycemia, appetite, and energy intake in healthy men. Am J Clin Nutr 2015;102(6):1574–84.

152. Christen S, Jiang Q, Shigenaga MK, Ames BN. Analysis of plasma tocopherols alpha, gamma, and 5-nitro-gamma in rats with inflammation by HPLC coulometric detection. J Lipid Res 2002;43(11):1978–85.

153. de Waard GA, Nijjer SS, van Lavieren MA, van der Hoeven NW, Petraco R, van de Hoef TP, Echavarria-Pinto M, Sen S, van de Ven PM, Knaapen P, et al. Invasive minimal microvascular resistance is a new index to assess microcirculatory function independent of obstructive coronary artery disease. J Am Heart Assoc 2016;5(12).

154. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, Johnson BD, Sopko G, Bairey Merz CN. Coronary microvascular

reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010;55(25):2825–32.

155. Nongonierma AB, FitzGerald RJ. Dipeptidyl peptidase IV inhibitory and antioxidative properties of milk protein-derived dipeptides and hydrolysates. Peptides 2013;39:157–63.

156. Hernández-Ledesma B, Miralles B, Amigo L, Ramos M, Recio I. Identification of antioxidant and ACE-inhibitory peptides in fermented milk. J Sci Food Agric 2005;85(6):1041–8.

157. Zemel MB, Sun X. Dietary calcium and dairy products modulate oxidative and inflammatory stress in mice and humans. J Nutr 2008;138(6):1047–52.

158. Diaz M, Decker EA. Antioxidant mechanisms of caseinophosphopeptides and casein hydrolysates and their application in ground beef. J Agric Food Chem 2004;52(26):8208–13.

159. O'Keeffe MB, FitzGerald RJ. Antioxidant effects of enzymatic hydrolysates of whey protein concentrate on cultured human endothelial cells. Int Dairy J 2014;36(2):128–35.

160. Phelan M, Aherne-Bruce SA, O'Sullivan D, FitzGerald RJ, O'Brien NM. Potential bioactive effects of casein hydrolysates on human cultured cells. Int Dairy J 2009;19(5):279–85.

161. Sipola M, Finckenberg P, Korpela R, Vapaatalo H, Nurminen ML. Effect of long-term intake of milk products on blood pressure in hypertensive rats. J Dairy Res 2002;69(1):103–11.

162. Sipola M, Finckenberg P, Vapaatalo H, Pihlanto-Leppala A, Korhonen H, Korpela R, Nurminen ML. Alpha-lactorphin and beta-lactorphin improve arterial function in spontaneously hypertensive rats. Life Sci 2002;71(11):1245–53.

163. Xu JY, Qin LQ, Wang PY, Li W, Chang C. Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials. Nutrition 2008;24(10):933–40.

164. Murakami M, Tonouchi H, Takahashi R, Kitazawa H, Kawai Y, Negishi H, Saito T. Structural analysis of a new anti-hypertensive peptide (beta-lactosin B) isolated from a commercial whey product. J Dairy Sci 2004;87(7):1967–74.

165. van der Zander K, Jakel M, Bianco V, Koning MM. Fermented lactotripeptides-containing milk lowers daytime blood pressure in high normal-to-mild hypertensive subjects. J Hum Hypertens 2008;22(11):804–6.

166. Hirota T, Ohki K, Kawagishi R, Kajimoto Y, Mizuno S, Nakamura Y, Kitakaze M. Casein hydrolysate containing the antihypertensive tripeptides Val-Pro-Pro and Ile-Pro-Pro improves vascular endothelial function independent of blood pressure-lowering effects: contribution of the inhibitory action of angiotensin-converting enzyme. Hypertens Res 2007;30(6):489–96.

167. Yamaguchi N, Kawaguchi K, Yamamoto N. Study of the mechanism of antihypertensive peptides VPP and IPP in spontaneously hypertensive rats by DNA microarray analysis. Eur J Pharmacol 2009;620(1–3):71–7.

168. Karatzi K, Aissopou EK, Tsirimiagou C, Fatmeli E, Sfikakis PP, Protogerou AD. Association of consumption of dairy products and meat with retinal vessel calibers in subjects at increased cardiovascular risk. Nutr Metab Cardiovasc Dis 2016;26(8):752–7.

169. Roustit M, Cracowski JL. Assessment of endothelial and neurovascular function in human skin microcirculation. Trends Pharmacol Sci 2013;34(7):373–84.

170. Bruning RS, Santhanam L, Stanhewicz AE, Smith CJ, Berkowitz DE, Kenney WL, Holowatz LA. Endothelial nitric oxide synthase mediates cutaneous vasodilation during local heating and is attenuated in middle-aged human skin. J Appl Physiol 2012;112(12):2019–26.

171. Holowatz LA, Thompson-Torgerson CS, Kenney WL. The cutaneous circulation as a model of generalized microvascular function. J Appl Physiol, 2007.

172. Alba BK, Stanhewicz AE, Kenney WL, Alexander LM. Acute dairy milk ingestion does not improve nitric oxide-dependent vasodilation in the cutaneous microcirculation. Br J Nutr 2016;116(2):204–10.

173. DuPont JJ, Greaney JL, Wenner MM, Lennon-Edwards SL, Sanders PW, Farquhar WB, Edwards DG. High dietary sodium intake impairs endothelium-dependent dilation in healthy salt-resistant humans. J Hypertens 2013;31(3):530–6.

174. Greaney JL, Dupont JJ, Lennon-Edwards SL, Sanders PW, Edwards DG, Farquhar WB. Dietary sodium loading impairs microvascular function independent of blood pressure in humans: role of oxidative stress. J Physiol 2012.

175. Stanhewicz AE, Alba BK, Kenney WL, Alexander LM. Dairy cheese consumption ameliorates single-meal sodium-induced cutaneous microvascular dysfunction by reducing ascorbate-sensitive oxidants in healthy older adults. Br J Nutr 2016;116(4):658–65.