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NARRATIVE REVIEW

Milk and Conjugated Linoleic Acid

A Review of the Effects on Human Health

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Dairy products and milk play an important role in a healthy diet as they contribute to the intake of essential nutrients, high-quality proteins, and fats. Despite the large number of existing studies on the possible association between dairy products and chronic degenerative diseases, studies examining the effects of dairy products and milk on the risk of common causes of mortality such as cardiovascular and neoplastic diseases are scarce and conflicting. Some studies have reported an increased risk of cardiovascular diseases for individuals who consume large amounts of cheese, whereas others have shown no relationship between these products and atherosclerotic biomarkers. **Key words:** *cardiovascular disease*, *dairy*, *milk*, *neoplastic disease*

FOR DECADES, consumption of dairy products has been considered a risk factor for some diseases such as cardiovascular disease (CVD) because of the high content of animal fats. The opinion that dairy products, being rich in saturated fatty acids (SFAs) and cholesterol, could raise low-density lipoprotein cholesterol (LDL-C) levels, and thus increasing the risk of CVD, has been the milestone of human nutrition for years.[1,2] Since the 1980s, the general recommendation for a healthy diet from scientific associations is to reduce the consumption of high-fat dairy products[1] and often guiding the consumers to choose low-fat dairy products.[1] However, in the decade, with specific regard to cheese, observational and experimental studies have not found a significant association between chronic degenerative diseases and some of their predisposing factors.[3-5] Moreover, both epidemiologic and experimental studies suggest that consumption of low-fat milk and low-fat cheeses might be favorably associated with some cardiovascular risk factors.[3-4] The aim of the present review is to weigh the available evidence regarding the effect of milk consumption on human health.

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OBESITY

Obesity is a typical disorder linked both to a poor lifestyle and to the excessive

accumulation of fat in every part of the body, often with a negative impact on the health of the individual. Several in vivo preclinical studies on the consumption of dairy products, using animals as models, showed an inverse relationship between dairy consumption and obesity.[6-8]

Fat fraction

Most of them indicated that the allegedly responsible factor for this effect is the presence of rumenic acid (RA) in milk fat. In a study conducted by Blankson et al,[6] overweight or obese subjects were asked to take from 1.7 to 6.8 g/d of a supplement containing RA and conjugated linoleic acid (CLA) isomer *trans*-10,*cis*-12 in equal proportions for 12 weeks, with a significant reduction in body fat. The results in a similar study were not a reduction in fat mass but a significant increase in lean mass, and the most effective dose of 6.4 g/d was the highest.[7]

Another study by Katzman et al[8] found that CLA was associated with a reduction in weight gain, especially when the intake of CLA was simultaneous with the intake of green tea extract at a dose of 3.4 g/d of CLA, followed by a significant reduction in body fat percentage from 5.1% to 8.1% and an increase in lean body weight from 4.4% to 11%. However, the literature shows other studies where the consumption of certain amounts of CLA has not been associated with any change in body composition. One of the first studies showing the adverse effects of CLA was conducted in 1999 by Atkinson[9] in 71 men and women aged 20 to 50 years with body mass index (BMI) values ranging from normal weight to obesity. These subjects took 2.7 g/d of RA and CLA isomer *trans*-10,*cis*-12, in equal proportions, for 26 weeks and the results were compared with the effects of the daily consumption of safflower oil used as placebo. Even in a study of a group of young women leading a sedentary lifestyle, the introduction of 2.1 g/d of CLA for 45 days did not result in any change in body composition.[10] Similarly, in another study on 85 overweight men, CLA consumption of 4.5 g/d showed no reduction in body weight.[11]

In all of the studies so far, CLA has been taken as a supplement in different formulations, but other studies have also been conducted by studying the effect on the human organism from enriched dairy products or where CLA is normally present. A Spanish study on 60 subjects, males and females between the ages of 35 and 65 years, with symptoms of the metabolic syndrome and with BMI between 25 and 35 kg/m^2, showed a significant reduction (2%-3%) of fat mass in overweight but not in obese ones after taking 500 mL of milk enriched with RA and CLA isomer *trans*-10,*cis*-12 (3 g/d) for 12 weeks.[12]

Protein fraction

To date, numerous studies have focused on the satiating ability of milk proteins and, consequently, on their effect of reducing energy intake. In milk, there are 2 different types of proteins: whey protein and casein. Because of the differences in digestion rate, and amino acids and peptides appearing in plasma, whey proteins may be more satiating than caseins. The Table shows the results of several body weight intervention studies with nonhydrolyzed milk proteins. The first 2 studies showed a positive effect of whey proteins on the reduction of food intake in obese subjects.[13,14] In particular, the first 12-week study on obese subjects with BMI values between 25 and 40 kg/m^2, receiving a preload of whey protein concentrate (65 g) before a meal ad libitum, showed a significant effect on appetite (−41%), on caloric intake (−50%), on anthropometric values with reduced body weight and waist circumference, on body composition with a reduction in fat mass, and an increase in lean body mass at the initial state.[13] The second study conducted by Baer et al,[14] performed for 23 weeks in obese subjects using whey protein, showed comparable results with these studies, with weight reduction (−2.5%), reduction in fat mass (−2.3 kg), reduction in waist circumference (−2.4 cm), and reduction in fasting ghrelin (−13.6%). In

Table. Studies That Have Analyzed the Effect of Milk Proteins on Human Health

Test Sample	Study Design	Biological Outcome	Reference
WPC	Obese ♂ subjects (n = 26)	Appetite: −44%	Tahavorgar et al (2014)[13]
	65 g/d meal preload	Calorie intake: −51%	
	Duration: 12 wk	Anthropometric changes: body weight (−10%), BMI (−19%), and waist circumference (−41%)	
		Body composition: body fat mass (−9%) and lean muscle mass (+9%)	
WPC80	Overweight and obese adult subjects (n = 9)	Weight: −1.8 kg	Baer et al (2011)[14]
	Treatment: WPC80	Fat mass: −2.3 kg	
	Dose: 56 g protein/d meal preload	Waist circumference: −2.4%	
	Duration: 23 wk	Fasting ghrelin: −13.6%	
Skimmed milk, WP, and CN	Overweight adolescents (n = 173)	Lean mass: increased in all groups	Arnberg et al (2012)[15]
	Treatment (A): skimmed milk; (B): WP; (C): CN; and (D): water	Fat mass: increased in all groups, except in (D)	
	Dose: 30 g/d	Leptin: +30 and +15% in (C) and (B), respectively	
	Duration: 12 wk		
Skimmed milk, WP, and CN	Overweight adolescents (n = 203)	BMI, BMI-for-age *z*-scores: increased in groups (A), (B), and (C)	Veldhorst et al (2009)[16]
	Treatment (A): skimmed milk; (B): WP; (C): CN; and (D): water	Weight: increased in groups (A), (B) and (C)	
	Dose: 35 g/d		
	Duration: 12 wk		

(*continues*)

Table. Studies That Have Analyzed the Effect of Milk Proteins on Human Health (*Continued*)

Test Sample	Study Design	Biological Outcome	Reference
α-La, CN, whey, or WPC80 in a custard-style breakfast	Healthy adults (n = 24)	−40% appetite at 180 min with α-La	Poppitt et al (2013)[17]
	Appetite assessment over 180 min postbreakfast	−20% food intake at lunch α-La	
	Dose:10/55/35 (normal) or 25/55/20 (high) energy % protein/carbohydrate/fat	No effect with CN, whey, and WPC80	
WPC, GMP, β-Lg, and colostrum WPC	Lean ♂ adults (n = 16)	Greater feeling of subjective fullness with (C)	Akhavan et al (2010)[18]
	Treatment: ad libitum pizza meal vs control (water) Dose: 10-40 g	No reduction in food intake at lunch with (B), (C), and (D) compared with (A)	
WPC	Healthy young ♂ adults (n = 16)	Subjective satiety: higher in all groups	Burton-Freeman et al (2008)[19]
	Treatment: ad libitum pizza meal vs control (water) Dose: 10-40 g	Food intake: reduced in all WP groups with doses >20 g	
WPI, whey without GMP, and GMP isolate	Healthy adults (n = 20)	Premeal subjective satiety: higher in all groups	
	Treatment (A): WPI; (B): whey without GMP; and (C): GMP Dose: 25 g preload 75 min before lunch	(C) group of ♀: +33% CCK concentration 30 min after lunch and lower compensatory food intake on the study day (−1.7 M)	Chungchunlam et al (2014)[20]
GMP isolate, WPI with low and high GMP	Healthy ♀subjects (n = 22) Treatment (A): GMP; (B): WPI low GMP; and (C): GMP Dose: 60 g preload 120 min before lunch	Food intake: > −15% with (B) and (C) compared with (A) Appetite suppression and food intake: no effect of GMP	

Abbreviations: BMI, body mass index; CCK, Cholecystokinin; CN, casein; GMP, glycomacropeptide; WP, whey protein; WPC, whey protein concentrate; WPI, whey protein isolate.

contrast, 2 other studies, conducted on overweight adolescents for 12 weeks, showed a negative effect on the anthropometric parameters. The inconsistency of the literature results shows that the effect of milk proteins on satiety in humans has not yet been fully understood. Several studies published in the literature suggest that the rate of proteins or protein derivatives absorption is fundamental to explaining postprandial phenomena.[21,22]

CARDIOVASCULAR DISEASE

Milk is a complex food and contains substances that have a protective role and substances that have a negative influence on cardiovascular health. The main culprit of increased cardiovascular risk is the presence of SFAs, which account for about 70% of the total fat in milk. It is known that excessive consumption of SFAs is associated with an increased risk of developing disorders in the cardiovascular system. However, the fatty acid profile of SFAs includes 10% of short chain fatty acids, 10% of C18: 0, which are not harmful to CVD. The 3 main SFAs present in milk are palmitic acid (C16: 0; PA), stearic acid (C18: 0; SA), and myristic acid (C14: 0; MA), all performing different functions in lipid plasma and therefore it is difficult to understand their overall effect on cardiovascular health. Palmitic acid has been associated with an increase in LDL-C and total cholesterol (TC) as reported in several studies.[1,23,24] Finally, SA, present at about 12%, seems to reduce the TC/HDL (high-density lipoprotein) ratio, resulting in a protective effect. Instead, by examining the unsaturated component of milk lipids, a possible protective action was observed on the cardiovascular system according to CLA.

Mainly, in the in vitro studies, the isomer of CLA *trans*-10,*cis*-12 has been linked to the negative regulation of peroxisome proliferator-activated receptor (PPAR)-gamma (PPAR-γ), with consequent reduction in macrophage CD36 receptor expression that leads to a reduction in fat deposition in macrophages and to the formation of foaming cells, responsible for the formation of atherosclerotic plaque.[25] However, the decrease in atherosclerotic processes related to the isomer of RA has been associated with a downregulation of proinflammatory genes. Clinical trials in humans have produced inconsistent results and the cause is based on the importance of selecting CLA isomers. Sofi et al[3] administered a diet containing 200 g/wk of sheep's milk for 10 weeks in healthy subjects, naturally rich in CLA (1.56 g/100 g of total lipids), and for another 10 weeks a diet containing 200 g/wk of low-level commercial quality cheese. Eventually, a significant reduction was observed in some inflammatory parameters such as interleukin-6, interleukin-8, and tumor necrosis factor-alpha (TNF-α) were observed only during the intervention period, therefore assuming that consumption of naturally rich RA cheese can cause positive changes in biochemical cardiovascular risk markers.

Pintus et al[4] conducted a nutritional study using sheep cheese naturally rich in RA, vaccenic acid, and alpha-linolenic acid and a low SFA content in the lipid fraction. A total of 42 subjects diagnosed with hypercholesterolemia were asked to include 90 g/d of this enriched cheese for 3 weeks in their diet. It has been shown that LDL-C decreased significantly (7%), but no changes in the levels of inflammatory markers were detected.[4]

These intervention studies have shown that CLA and enriched α-LNA naturally possess beneficial properties, as they improve the plasma lipid profile and significantly reduce the biosynthesis of endocannabinoids. Recently, Murru et al[26] reported that dietary CLA-enriched cheese influences positively the levels of circulating n-3 highly unsaturated fatty acids (HUFAs), which regulate lipid metabolism, energy balance, and the inflammatory response in humans. In particular, the increase of docosahexaenoic acid in plasma was proportional to the CLA content in the cheese and the authors suggested that the improved n-3 HUFA score resulting from the intake of CLA-enriched cheese may be attributed to the increased activity of PPAR-α. In addition, other components of

milk, such as minerals (calcium, magnesium, and potassium), are known to influence the functioning of the cardiovascular system.[26]

These elements have an antihypertensive effect and therefore can exert an important protective role in CVDs. It has been shown that daily consumption of dairy products is associated with a 20% reduction in the incidence of hypertension and that equilibrium milk minerals are essential for the control of blood pressure.[27] A meta-analysis by Drouin-Chartier et al[28] conducted in prospective cohort studies demonstrated that dairy products were not associated with an increased risk of cardiovascular-related clinical outcomes. Nevertheless, low-fat cheese and yogurt were found to be associated with a reduced risk of stroke, hypertension, and type 2 diabetes.[28]

CANCER

Ruminants have the ability to extract anticarcinogenic components from pasture and feed and transfer them to milk. Milk contains sphingomyelin, butyric acid, and ether lipids that present anticancer potential. Sphingomyelin is a phospholipid present in the fat globule membrane and represents about one-third of total phospholipids. This lipid is involved in several pathways associated with suppression of carcinogenesis through the activities of its metabolites ceramide and sphingosine generated by sphingomyelinase enzyme action. Ceramides and sphingosine regulate the function of several transcription factors involved in the gene expression responsible for inhibition of cell growth, cell-cycle arrest, differentiation, and apoptosis.[29,30] Butyric acid, highly present in ewe milk, is a potent antineoplastic agent and may ameliorate its potency through synergy with other milk fat components. This fatty acid is able to promote histone acetylation in DNA repairing, upregulate the expression of tumor suppressor genes, and downregulate the expression of several proto-oncogene genes.[31] Ether lipids are produced during the digestion of ether lipid contained in feeds, and the organism use them to synthetize membrane phospholipids. They show antiproliferative effects and the ability to induce cell differentiation, prevent metastasis, and regulate the immunoresponse.[32]

The results showing the possible antineoplastic properties of CLA were obtained mainly from in vitro studies, but human studies in the recent years also appear to be important. Different mechanisms of action have been proposed such as modulation of eicosanoid production, interference in cellular signal transduction pathways, inhibition of DNA synthesis, promotion of apoptosis, and modulation of angiogenesis.[33] In one of the most representative studies, a high-fat content in the consumption of dairy products was observed in 60 708 women, aged between 40 and 76 years, with about 14 years of follow-up. It was found that women who consumed 4 or more portions of this type of dairy products, including whole milk, cheese, cream cheese, sour cream, and butter, showed half of the risk of developing colorectal cancer compared with women who consumed less than a portion a day of these products. The direct relationship between the consumption of CLA and the onset of colorectal cancer has identified a reduction of at least 30%. Elwood et al[34] reported that the consumption of milk and dairy products leads to an advantage for survival, attributing it to several factors, including the reduction of pH, the intake of probiotic lactobacilli, the involvement of immunomodulatory peptides, and the contribution of a large amount of calcium.

Bastide et al[35] in a review showed that milk consumption can effectively counteract the degenerative effects of the carcinogenic activity of the nitrosil-heme in the intestinal mucosa. In the in vitro studies, the most interesting results have been identified as the reduction in the incidence of breast cancer, gastrointestinal cancer, and bladder cancer on the basis of a modulation of apoptosis and cell cycle. A very important action of the different isomers of CLA against carcinogenesis is based on the control of angiogenesis.

Masso-Welch et al[36] have shown that CLA supplementation of 1-2% significantly reduces angiogenesis by inhibiting the formation of blood vessels functional to carcinogenesis. The main limitations of epidemiologic studies are the difficulty obtaining accurate estimates of the intake of CLA through diet, in the use of specific isomers rather than in the entire pool, and a smaller sample in the different studies with varying eating habits.

OSTEOPOROSIS

One of the most frequent arguments in favor of milk consumption is its calcium content and consequently the role of this mineral on bone health in a highly absorbable form. Low bone mineral density is the main risk factor for osteoporosis. Milk consumption has been associated with high bone mineral density and for this reason it is considered protective against osteoporosis.[37] In fact, one study suggested that milk provides a wide variety of minerals and other components such as peptides, with bioactive properties and CLA isomers, that could play a positive role in bone mineral density, fracture reduction, and prevention of osteoporosis.[31]

CONCLUSION

Numerous studies have been reported to clarify the dose-response of specific molecules contained in milk and the pathogenesis of many human diseases. From the literature, it is beginning to emerge that milk and dairy products, where they are not consumed in high daily quantities, can have a positive effect on the pathogenesis of both cardiovascular and neoplastic diseases and a lowering effect on some risk factors. More research is needed to elucidate the effect of milk and it constituents in the prevention of chronic diseases.

REFERENCES

1. Hu FB, Stampfer MJ, Manson JE, et al. 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):1001-1008. doi:10.1093/ajcn/70.6.1001.
2. de Oliveira Otto MC, Mozaffarian D, Kromhout D, et al. Dietary intake of saturated fatty acids by food source and incident cardiovascular disease: the multiethnic study of atherosclerosis. *Am J Clin Nutr*. 2012;96(2):397-404. doi:10.3945/ajcn.112.037770.
3. Sofi F, Buccioni A, Cesari F, et al. Effects of a dairy product (pecorino cheese) naturally rich in *cis*-9, *trans*-11 conjugated linoleic acid on lipid, inflammatory and haemorheological variables: a dietary intervention study. *Nutr Metab Cardiovasc Dis*. 2010;20(2):117-124. doi:10.1016/j.numecd.2009.03.004.
4. Pintus S, Murru E, Carta G, et al. Sheep cheese naturally enriched in α-linolenic, conjugated linoleic and vaccenic acids improves the lipid profile and reduces anandamide in the plasma of hypercholesterolaemic subjects. *Br J Nutr*. 2013;109:1453-1462. doi:10.1017/S0007114512003224.
5. Albenzio M, Santillo A, Avondo M, et al. Nutritional properties of small ruminant food products and their role on human health. *Small Rum Res*. 2016;135:3-12. doi:10.1016/j.smallrumres.2015.12.016.
6. Blankson H, Stakkestad JA, Fagertun H, Thom E, Wadstein J, Gudmundsen O. Conjugated linoleic acid reduces body fat mass in overweight and obese humans. *J Nutr*. 2000;130(12):2943-2948. doi:10.1093/jn/130.12.2943.
7. Steck SE, Chalecki AM, Miller P, et al. Conjugated linoleic acid supplementation for twelve weeks increases lean body mass in obese humans. *J Nutr*. 2007;137(5):1188-1193. doi:10.1093/jn/137.5.1188.
8. Katzman MA, Jacobs L, Marcus M, Vermani M, Logan AC. Weight gain and psychiatric treatment: is there as role for green tea and conjugated linoleic acid? *Lipids Health Dis*. 2007;6:14. doi:10.1186/1476-511X-6-14.
9. Atkinson R. Conjugated linoleic acid for altering body composition and treating obesity. In: Yurawecz MP, Mossoba MM, Kramer JKG, Pariza MW, Nelson GJ, eds. *Advances in Conjugated Linoleic Acid Research*. Champaign, IL: AOCS; 1999:348-353.
10. Petridou A, Mougios V, Sagredos A. Supplementation with CLA: isomer incorporation into serum lipids and effect on body fat of women. *Lipids*. 2003;38(8):805-811. doi:10.1007/s11745-003-1129-2.
11. Pfeuffer M, Fielitz K, Laue C, Winkler P, Rubin D, Helwig U. CLA does not impair endothelial function and decreases body weight as compared with safflower oil in overweight and obese

male subjects. *J Am Coll Nutr*. 2011;30(1):19-28. doi:10.1080/07315724.2011.10719940.

12. Laso N, Brugué E, Vidal J, et al. Effects of milk supplementation with conjugated linoleic acid (isomers *cis*-9, *trans*-11 and *trans*-10, *cis*-12) on body composition and metabolic syndrome components. *Br J Nutr*. 2007;98(4):860-867. doi:10.1017/S0007114507750882.
13. Tahavorgar A, Vafa M, Shidfar F, Gohari M, Heydari I. Whey protein preloads are more beneficial than soy protein preloads in regulating appetite, calorie intake, anthropometry, and body composition of overweight and obese men. *Nutr Res*. 2014;34(10):856-861. doi:10.1016/j.nutres.2014.08.015.
14. Baer DJ, Stote KS, Paul DR, et al. Whey protein but not soy protein supplementation alters body weight and composition in free-living overweight and obese adults. *J Nutr*. 2011;141(8):1489-1494.
15. Arnberg K, Mϕlgaard C, Michaelsen KF, Jensen SM, Trolle E, Larnkjær A. Skim milk, whey, and casein increase body weight and whey and casein increase the plasma C-peptide concentration in overweight adolescents. *J Nutr*. 2012;142(12):2083-2090.
16. Veldhorst M, van Vught A, Westerterp-Plantenga M. The effects of casein-, whey- and soy protein on satiety, energy expenditure, and body composition. In: Cho SS, ed. *Weight Control and Slimming Ingredients in Food Technology*. Hoboken, NJ: Wiley-Blackwell; 2009:121-133.
17. Poppitt SD, Strik CM, McArdle BH, McGill AT, Hall RS. Evidence of enhanced serum amino acid profile but not appetite suppression by dietary glycomacropeptide (GMP): a comparison of dairy whey proteins. *J Am Coll Nutr*. 2013;32(3):177-186.
18. Akhavan T, Luhovyy BL, Brown PH, Cho CE, Anderson GH. Effect of premeal consumption of whey protein and its hydrolysate on food intake and postmeal glycemia and insulin responses in young adults. *Am J Clin Nutr*. 2010;91(4):966-975.
19. Burton-Freeman BM, Keim NL. Glycemic index, cholecystokinin, satiety and disinhibition: is there an unappreciated paradox for overweight women? *Int J Obes (Lond)*. 2008;32(11):1647-1654.
20. Chungchunlam SM, Henare SJ, Ganesh S, Moughan PJ. Effect of whey protein and glycomacropeptide on measures of satiety in normal-weight adult women. *Appetite*. 2014;78:172-178.
21. Boirie Y, Danging M, Gachon P, Vasson MP, Maubois JL, Beaufrère B. Slow and fast dietary proteins differently modulate postprandial protein accretion. *Proc Natl Acad Sci U S A*. 1997;94(26):14930-14935. doi:10.1073/pnas.94.26.14930.
22. Pennings B, Boirie Y, Senden JMG, et al. Whey protein stimulates postprandial muscle protein accretion more effectively than do casein and casein hydrolysate in older men. *Am J Clin Nutr*. 2011;93(5):997-1005. doi:10.3945/ajcn.110.008102.
23. Keys A, Anderson JTA, Grande F. Serum cholesterol response to changes in diet. IV. Particular saturated fatty acids in the diet. *Metabolism*. 1965;14:776-787. doi:10.1016/0026-0495(65)90004-1.
24. Keys A. *Seven Countries: A Multivariate Analysis of Death and Coronary Health Disease*. Cambridge, MA: Harvard University Press, 1980.
25. Stachowska E, Baskiewicz M, Marchlewicz M, et al. Conjugated linoleic acids regulate triacylglycerol and cholesterol concentrations in macrophages/foam cells by the modulation of CD36 expression. *Acta Biochim Pol*. 2010;57(3):379-384.
26. Murru E, Carta G, Correddu L, et al. Dietary conjugated linoleic acid-enriched cheeses influence the levels of circulating n-3 highly unsaturated fatty acids in humans. *Int J Mol Sci*. 2018;19(6):1730. doi:10.3390/ijms19061730.
27. Engberink MF, Hendriksen MA, Schouten EG, et al. Inverse association between dairy intake and hypertension: the Rotterdam Study. *Am J Clin Nutr*. 2009;89(6):1877-1883. doi:10.3945/ajcn.2008.27064.
28. Drouin-Chartier JP, Brassard D, Terssier-Grenier M, et al. Systematic review of the association between dairy product consumption and risk of cardiovascular related clinical outcomes. *Adv Nutr*. 2016;7(6):1026-1040. doi:10.3945/an.115.011403.
29. Ballou LR, Laulederkind SJF, Rosloniec EF, Raghow R. Ceramide signalling and the immune response. *Biochim Biophys Acta*. 1996;1301(3):273-287. doi:10.1016/0005-2760(96)00004-5.
30. Merrill AH, Schmelz EM, Dillehay DL, et al. Sphingolipids—the enigmatic lipid class: biochemistry, physiology, and pathophysiology. *Toxicol Appl Pharmacol*. 1997;142(1):208-225. doi:10.1006/taap.1996.8029.
31. Parodi PW. Cows' milk fat components as potential anticarcinogenic agents. *J Nutr*. 1997;127(6):1055-1060. doi:10.1093/jn/127.6.1055.
32. Diomede L, Colotta F, Piovani B, Re F, Modest EJ, Salmona M. Induction of apoptosis in human leukemic cells by the ether lipid 1-octadecyl-2-methyl-rac-glycerol-3- phosphocholine. A possible basis for its selective action. *Int J Cancer*. 1993;53(1):124-130. doi:10.1002/ijc.2910530123.
33. Dilzer A, Park Y. Implication of conjugated linoleic acid (CLA) in human health. *Crit Rev Food Sci Nutr*. 2012;52:488-513. doi:10.1080/10408398.2010.501409.
34. Elwood PC, Givens DI, Beswick AD, et al. The survival advantage of milk and dairy consumption: an overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr*. 2008;27(6):723S-734S. doi:10.1080/07315724.2008.10719750.
35. Bastide NM, Pierre FH, Corpet DE. Heme iron from meat and risk of colorectal cancer: a meta-analysis and a review of the mechanisms involved.

Cancer Prev Res. 2011;4(2):177-184. doi:10.1158/1940-6207.CAPR-10-0113.

36. Masso-Welch PA, Zangani D, Ip C, et al. Isomers of conjugated linoleic acid differ in their effects on angiogenesis and survival of mouse mammary adipose vasculature. *J Nutr*. 2004;134(2):299-307. doi:10.1093/jn/134.2.299.
37. Cashman KD. Milk minerals (including trace elements) and bone health. *Int Dairy J*. 2006;16:1389-1398. doi:10.1016/j.idairyj.2006.06.017.