Milk, Dairy Products, and Their Functional Effects in Humans: A Narrative Review of Recent Evidence[1]

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ABSTRACT

Milk is a widely consumed beverage that is essential to the diet of several millions of people worldwide because it provides important macro- and micronutrients. Milk is recognized as being useful during childhood and adolescence because of its composition; however, its relatively high saturated fat proportion raises issues of potential detrimental effects, namely on the cardiovascular system. This review evaluates the most recent literature on dairy and human health, framed within epidemiologic, experimental, and biochemical evidence. As an example, the effects of milk (notably skimmed milk) on body weight appear to be well documented, and the conclusions of the vast majority of published studies indicate that dairy consumption does not increase cardiovascular risk or the incidence of some cancers. Even though the available evidence is not conclusive, some studies suggest that milk and its derivatives might actually be beneficial to some population segments. Although future studies will help elucidate the role of milk and dairy products in human health, their use within a balanced diet should be considered in the absence of clear contraindications. *Adv. Nutr. 5: 131–143, 2014.*

Introduction

Milk is an essential component of the diet of ~6 billion people. The world production of milk reaches 730 million tons/y (1,2). Even though mammals produce milk to feed their offspring, in many areas of the world humans continue to consume milk throughout their life. However, it must be emphasized that lactose intolerance is widespread throughout the world and that a large proportion of the world's population would not benefit from the putative benefits of milk.

In addition to milk, several dairy products such as cream, butter, yogurt, kefir, and cheese have been produced and consumed worldwide for millennia. Therefore, the impact of milk and dairy products on human health is quantitatively relevant and has been the subject of several investigations, on both whole products and their isolated components. In particular, the fat portion of milk (largely composed of SFAs) and some of its minor components, notably calcium and oligosaccharides, are being actively researched for their potential health roles.

This review summarizes the most recent studies on milk and human health and critically discusses the putative actions of milk and principal dairy constituents.

Effects on Body Weight

Of all the bioactive milk components, calcium and vitamin D have been chiefly studied for their effects on body weight and adipose tissue. Studies have been performed on these compounds as either isolated molecules (3–9) or as components of milk and dairy products (5,7,8,10–12). Proposed targets include thermogenesis and lipid oxidation (which are enhanced by calcium and vitamin D) (13–15) and increased lipid fecal excretion (16–19).

In the past few years, some studies have been published on other milk components and their potential effects on body weight (20,21). For example, in addition to calcium and vitamin D, dairy proteins are being suggested as reducers of adipose mass (namely, visceral fat) and body weight (11,14,22,23). These effects have been observed in healthy participants as well as in overweight, obese (21,24–27), and diabetic (8,28) patients. In addition to casein, whey protein appears to be particularly effective (29,30), and their actions seem to be mediated by several mechanisms that include increased satiety and decreased appetite (29). In particular, inhibition of gastric secretion by cholecystokinin (31) and some branched amino acids, the abundance of leucine (32), increased secretion of glucagon-like peptide 1 (GLP-1)[4] (33,34) and glucose- dependent

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[4] Abbreviations used: CVD, cardiovascular disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; MCP-1, monocyte chemoattractant protein 1; MetS, metabolic syndrome.

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insulinotropic polypeptide (GIP) (35), the concomitant suppression of ghrelin secretion (36), and the potent satiating effects of α-lactoalbumin (37) synergistically contribute to weight control.

The most recent studies in this area include randomized clinical trials and meta-analyses. A marked reduction in adipose tissue and an increase in lean mass were observed in 90 overweight and obese premenopausal women after 4 mo of a hypocaloric diet that included milk and dairy products. In particular, visceral adipose tissue was significantly affected (26). A study conducted in 903 healthy adolescents (15–16 y) that included at least 2 servings/d [1 serving = 200 mL of milk, 125 g of yogurt, or 28 g of cheese (38)] of dairy reported a significant weight loss and a reduction in body fat (39,40). Male participants also witnessed a protective effect on abdominal obesity. From a mechanistic viewpoint, whey protein administered before a meal exerted insulinotropic effects and reduced postprandial insulinemic fluctuations in healthy participants (41) and in type 2 diabetic patients (42). In the latter, consumption of whey protein before a high-glycemic-load (white bread and potatoes) breakfast or lunch increased insulin response by 30–50% and reduced glycemia by ~20%, compared with controls (42). This effect is quantitatively comparable to that of sulfonilureas (43). In agreement with these studies, Dove et al. (44) reported that the intake of 600 mL of skimmed milk at breakfast (by 34 overweight men and women) had a stronger satiating effect (evaluated 4 h later) than that of an isocaloric intake of fruit juice. A significantly lower consumption of foods offered ad libitum at lunch (i.e., after 4 h) was also recorded (44).

A recent meta-analysis (45) that reviewed the effect of 29 randomized clinical trials comprising 2101 cases confirmed the weight-loss effect of milk and dairy products when incorporated into hypocaloric diets. However, no beneficial effect of increasing dairy consumption on body weight and fat loss was seen in long-term studies or in studies without energy restriction, which calls for caution in attributing milk to slimming properties.

Diabetes

A lower incidence of type 2 diabetes and of metabolic dysfunction associated with dairy consumption has been reported by observational studies (46), but the potential mechanisms responsible for these effects have not as yet been elucidated.

A prospective 10-y study in 37,185 women (i.e., the Women's Health Study) reported an inverse correlation between milk and dairy consumption and risk of diagnosed diabetes (28). This association was stronger for skimmed products and led to a 4% risk reduction for 1 additional serving/d. These effects can be hypothetically explained by increased insulinemic response, decreased glycemic fluctuations, and increased secretion of GIP and GLP-1 triggered by milk proteins, as described above, and by FAs such as *trans*-palmitoleic acid (*trans*-16:1n–7; see below) (47).

The Nurses' Health Study II (48) was carried out in 37,083 women, who were followed for 7 y. Every 2 y, women receive a follow-up questionnaire with questions about diseases and health-related topics including pregnancy history, menopausal status, smoking habits, and hormone use. The first FFQ was collected in 1991 and subsequent FFQs are administered every 4 y. This study reported that dairy intake during high school was inversely associated with the risk of developing adult (self-reported) type 2 diabetes. In particular, 2 servings/d were associated with a 38% reduction in risk; the association was stronger when dairy consumption was continued throughout adulthood. A French prospective study (49) conducted in 3435 Parisians followed for 3 y observed that a higher intake of dairy products was associated with a lower incidence of (self-reported) type 2 diabetes, reduced glycemic tolerance, and metabolic syndrome (MetS). An inverse association (14% risk reduction) between milk consumption (especially skimmed or semi-skimmed milk) and type 2 diabetes has also been reported by Tong et al. (50), who published a meta-analysis of 7 cohort studies (328,029 cases). Another recent observational study in 82,076 postmenopausal women enrolled in the Women's Health Initiative Observational Study (which lasted for 8 y) confirmed that consumption of low-fat dairy products was significantly and inversely correlated with a reduced risk of (self-reported) type 2 diabetes, especially in high-BMI and obese women (51).

Mechanistically, a recent study (52) reported a marked amelioration of glycemic variables (i.e., fasting glycemia and hematic concentrations of glycated hemoglobin in type 2 diabetic patients who consumed fermented dairy and yogurt with added vitamin D, with or without calcium) (53). Finally, data from the EPIC (European Prospective Investigation into Cancer and Nutrition) study relative to 16,835 healthy and 12,403 diabetic participants (part of the larger 340,234 participant cohort) of 8 European nations confirmed the inverse association between cheese and fermented dairy consumption and incidence of diabetes. In particular, 55 g/d of cheese and yogurt were associated with a 12% reduction in type 2 diabetes incidence (54).

Finally, a recent study by Mozaffarian et al. (55) in 2617 adults enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) confirmed the lower (−20%) incidence of type 2 diabetes associated with dairy use. This association was independent of sex, ethnicity, and other confounders and strengthens the notion that *trans*-palmitoleic acid might play important roles via its actions on insulin secretion, triglyceridemia, and blood pressure (see below). Indeed, the authors hypothesized that, when these beneficial actions are confirmed, dairy products could be enriched with this FA (55).

Interestingly, lactose, as opposed to glucose and fructose, intake does not appear to be associated with diabetes incidence (56,57). Even though the evidence in favor or against lactose use by diabetic patients is scant, the American Diabetes Association recommends the use of milk and dairy products. This is partly because milk has a relatively low glycemic index due to dairy proteins, in particular casein, which exhibit insulinogenic properties and facilitate glycemic regulation through a mechanism involving elevation of certain plasma amino acids and stimulation of incretins (58). Finally, full-fat milk increases the mean gastric-emptying time compared with half-skimmed milk, and the low pH in fermented milk may delay gastric emptying. Therefore, full-fat or fermented milk might aid in glycemic control (59).

Blood Pressure

Whey proteins have long been studied for their potentially positive effects on blood pressure (60,61). For example, Pal and Ellis (62) demonstrated that, in overweight and obese participants, the intake of 54 g/d of whey protein for 12 wk induced a significant reduction in both systolic and diastolic blood pressure, in agreement with Xu et al. (63) who published a meta-analysis of tripeptides and blood pressure. The former are bioactive peptides (64–66) that are formed from proteins via the actions of the microbiota and gastrointestinal enzymes and which are abundant in fermented dairy products (67). Tripeptides are being investigated because of their angiotensin-converting enzyme–inhibiting activities, which might have important clinical consequences. In particular, 2 tripeptides, namely isoleucine-proline-proline (Ile-Pro-Pro) and valine-proline-proline (Val-Pro-Pro) have been incorporated into functional foods because of their safety profile and purported beneficial activities, namely on blood pressure. It is noteworthy that, in addition to their activity on blood pressure, other peptides have been isolated and studied for their putative antithrombotic properties (68). Recently, McGrane et al. (69) reviewed the evidence of the hypotensive effects of milk tripeptides by updating a former 2010 review that *1*) examined 223 articles published between 2004 and 2009 (which outlined the inverse association between milk tripeptide consumption and blood pressure) and *2*) reviewed 163 studies published between July 2009 and December 2010 concerning vitamin D, calcium, phosphorus, and bioactive peptides in low-fat dairy as part of low-fat diets.

A meta-analysis of 7 studies that included ~45,000 participants, of whom 11,500 were hypertensive (70), reported a significantly inverse association between low-fat dairy consumption and hypertension risk. Nine other cohort studies (57,256 participants followed for 2–15 y) confirmed this inverse correlation; furthermore, those who consumed the highest quantity of low-fat dairy products exhibited the lowest risk of hypertension (71).

A prospective study recently published by Louie et al. (72), which analyzed 335 Australian children, their milk consumption at age 18 mo, and their blood pressure at 8 y of age, reported lower blood pressure values in those who consumed at least 2 servings/d.

Cholesterol Concentrations

Milk and dairy products contain cholesterol (~80 mg/100 g) and saturated fat (~15 g/100 g) (73). Therefore, the intake of these products might theoretically have detrimental effects on cholesterol concentrations. However, it is noteworthy that the contribution of dietary cholesterol to cardiovascular risk is being debated and might likely depend on individual predisposition to synthesize versus absorb cholesterol (74,75). Also, the extent and precise nature of the role of saturated fat in cardiovascular disease (CVD) onset and development are being reexamined (76); likely, SFAs cannot be grouped under a single rubric and should instead be considered individually (77).

The first review on the effects of dairy products on cholesterolemia was published in 2000 by St-Onge et al. (78). The authors cited as a first piece of evidence an old study carried out in the African Maasai ethnic group (79). Maasais consume large quantities of milk, which was inversely correlated with blood cholesterol concentrations in that study. Indeed, milk has even been proposed by the authors as an inhibitor of cholesterol synthesis. Further studies (80–82) confirmed the cholesterol-lowering effects of both milk and skimmed milk [which was already suggested by Hepner et al. (83)]. St-Onge et al. hypothesized that this effect was due to the intestinal microbial fermentation of indigestible carbohydrates, which would alter cholesterol synthesis and interfere with its enterohepatic circulation, in turn lowering cholesterolemia.

More recently, a study by Høstmark et al. (84) conducted in 18,770 participants examined the association between cheese consumption in various age groups and circulating concentrations of HDL cholesterol (which was positive) and TGs (which was negative). The authors attributed this effect to the FA composition of cheese and its bacterial content. The results led the authors to propose a revision of the current guidelines on SFA intake, namely that from cheese.

In terms of differential effects of the various dairy products, 1 study compared the effects of isoenergetic (20% of total calories, normalized for lactose and casein) provision of milk (2164 mL), cheese (305 g), and butter (93 g) administered in 3 different sessions during 3 wk (85). Cheese had the weakest effect on increasing LDL cholesterol, but whole milk increased concentrations of LDL cholesterol similar to butter. These results were confirmed by Biong et al. (86): the authors reported (in a controlled dietary study in 9 men and 13 women aged 23–54 y) that consumption of cheese induced a lower increase in cholesterol concentrations than that of an identical amount (42 g) of fat from butter. Different calcium content was proposed as a potential explanation for this differential effect. Nestel et al. (87) administered 40 g/d of either cheese or butter to 14 mildly hypercholesterolemic participants. Total and LDL cholesterol increased significantly after 4 wk in the butter group as compared with the cheese group. Tholstrup et al. (85) also questioned the current guidelines on saturated fat consumption and suggested the inclusion of modest amounts of cheese in the diets of mildly hypercholesterolemic participants. In agreement with this suggestion, Hjerpsted et al. (88) recently replaced 13% of total daily calories with 143 g of cheese or 47 g of butter (with the same lipid content) for 6 wk in a randomized crossover trial in 49 healthy participants. Their data showed that cheese did not increase LDL cholesterol concentrations compared with the run-in period; rather, as compared with butter, it induced a significantly lower increase in total (5.7%) and LDL (6.9%) cholesterol.

Several potential explanations have been proposed to elucidate the differential effects of cheese and butter on cholesterolemia. One hypothesis is that calcium, the concentrations of which are higher in cheese than in butter, combines with FAs in the intestine and forms insoluble detergents as suggested by the observation of a higher-fat fecal excretion in the cheese compared with the butter groups (88). The higher protein and probiotic content of cheese could also speculatively contribute to its almost neutral effect on plasma cholesterol. As a cautionary note, the study by Tholstrup et al. (85) reported a lack of difference in the cholesterolemic effect of the diets containing whole milk and butter. In other words, as mentioned, whole milk did increase LDL-cholesterol concentrations similar to butter and its use by hypercholesterolemic patients should be considered with caution.

MetS

Oxidative stress and inflammation play major roles in the onset and development of the MetS and its components (89–91). MetS diagnosis requires the presence of central obesity and at least 2 of the following 4 additional factors: high TGs, low HDL cholesterol, high blood pressure, or increased fasting plasma glucose concentration (92).

The Nurses' Health Study first reported an inverse association between a prudent diet that included low-fat dairy products and biomarkers of inflammation (93). Similar observations have been reported by the MESA (94) and prompted a series of investigations that explored mechanisms of actions and potential causation. Zemel et al. (95,96) supplemented 20 obese patients with skimmed milk for 28 d and recorded significantly lower oxidative stress (−22% of plasma malondialdehyde and −12% of 8-iso-PGF$_{2\alpha}$ plasma concentrations) and inflammation [−15% TNF-α, −13% IL-6, −10% monocyte chemoattractant protein 1 (MCP-1), and +20% adiponectin]. The same authors (97) studied 40 obese MetS patients and showed that a 12-wk diet that included 3.5 servings/d of milk and/or yogurt reduced oxidative stress markers (−35% plasma malondialdehyde) after 7 d, as compared with an isocaloric diet that provided 0.5 servings/d of dairy products. After 12 wk, decreased systemic inflammation was also recorded in the dairy group (−35% TNF-α, −21% IL-6, +55% adiponectin), although not in the control arm.

The interesting observation that stems from these intervention studies is that the observed decrease in oxidative stress and inflammation markers was independent of body weight changes and became apparent shortly after the administration of dairy products, suggesting causation.

Epidemiologically, 1 recent Australian study reported an inverse association between MetS and type 2 diabetes incidence and dairy consumption in 1807 and 1824 patients, respectively. In particular, those who had the highest consumption amount of dairy products witnessed a risk reduction in MetS of 59% (72). A similar association was recorded when diabetes incidence was computed.

Finally, a recent meta-analysis (98) of 8 randomized controlled studies in overweight or obese participants concluded that dairy product consumption does not exert adverse effects on biomarkers of inflammation, even though further studies specifically designed to assess inflammation-related outcomes should be implemented (98).

Cardiovascular Health

Several scientific societies and regulatory bodies (e.g., the International Society for the Study of Fatty Acids and Lipids, which is the foremost society; www.issfal.org), the FAO (99), and the European Food Safety Authority (100) recommend optimal profiles of FA intake. Even if no consensus has been reached and such guidelines are being constantly amended according to emerging evidence, some figures are being agreed upon. In particular, most societies concur with regard to adequate intakes (for adults) of >500 mg/d of long-chain omega-3 FAs and a concomitant limitation of <8% of energy from saturated fat.

More recently, a workshop entitled "Saturated fatty acids and cardiovascular disease prevention" (101) gathered several experts in the area of FAs and CVD, who reached the following consensus that also concerns milk and dairy FA profile:

1. Replacing saturated fat (SFAs) with PUFAs lowers cardiovascular risk. This effect is not seen when saturates are replaced with carbohydrates, especially those with a high glycemic index.
2. Even though replacing SFAs with MUFAs lowers LDL cholesterol, this effect does not translate into lower incidence of CVD.
3. LDL cholesterol is the most widely accepted risk factor for CVD; however, the HDL:LDL-cholesterol ratio is more predictive than the sole concentrations of LDL cholesterol.
4. Investigating the effects of dietary interventions on just 1 marker of CVD does not reliably predict clinical outcomes, because they depend on several rather than on just 1 factor.
5. The different SFAs exert varied biologic effects and have differential impact on cholesterolemia. As an example, myristic and palmitic acids are thought to be noxious, and stearic acid and short-to-medium-chain (C4–C10) FAs to be neutral; conjugated linoleic acid is so scarce in the diet that its metabolic effects are negligible.
6. Based on the epidemiologic studies published to date, there is no evidence to indicate that high intakes of dairy products increase CVD risk; conversely, the lipidic part of milk and its byproducts might be beneficial because of its peculiar FA profile, e.g., rumenic and vaccenic acids and the concomitant presence of calcium, whey proteins, and other bioactive molecules (101).

It should be noted that, after an initial report that proposed the "Alpine paradox" (102), considerable research is being undertaken to modulate the FA composition of bovine milk toward a purportedly more healthful profile (103). In particular, milk from grass-fed livestock is being proposed as being more beneficial than that of corn-fed animals (104), although appropriate comparative human studies are lacking.

In 2002, Tavani et al. (105) published research carried out between 1995 and 1999 in 597 myocardial infarction patients, matched with 478 controls. Their data showed that milk and dairy consumption did not increase myocardial infarction risk. A meta-analysis of 21 studies that incorporated 347,747 participants followed for 5–23 y by Siri-Tarino et al. (106) reported no significant association between SFA consumption and increased risk of CVD or cerebrovascular diseases such as stroke. Further to this meta-analysis, the same authors (107) published an extensive review of the effects of various FAs on CVD risk. Their conclusion was that the replacement of SFAs with MUFAs and PUFAs reduces both LDL and HDL cholesterol. Moreover, substituting carbohydrates for SFAs increased CVD risk. Therefore, the most effective strategy to prevent CVD, based on this article, would be to reduce high-glycemic-index carbohydrates in obesity. In a study in 33,625 Dutch participants followed for 13 y, no association between dairy consumption and CVD or stroke incidence was observed; conversely, higher intakes were associated with lower CVD risk, whereas fermented milk products consumption was inversely associated with lower stroke risk (108).

As mentioned, the MetS is multifaceted and greatly increases CVD risk (109). In this respect, a review of observational studies concluded that milk and dairy consumption might contribute to cardiometabolic syndrome prevention; namely, 3–4 servings/d have been associated with cardiometabolic risk prevention (110). Consequently, based on current evidence, the most recent U.S. guidelines suggest to "Increase intake of fat-free or low-fat milk and milk products, such as milk, yogurt, cheese" (111).

In terms of mechanisms, Rice et al. (112) recently summarized the most prevalent hypothesis of how milk products would play preventive roles in cardiometabolism. These products mostly contain TGs with SFAs in the *sn*-2 position; in addition to high proportions of oleic and stearic acids, rumenic and *trans*-palmitoleic acids are also proportionally abundant. Moreover, part of the putative effects might be explained by the presence of several micronutrients such as calcium, vitamin D, whey proteins, and functional peptides (see above).

In terms of effects of milk FAs on CVD, there might be important differences between the individual FAs. A total of 5209 participants who had a daily intake of 10% of total energy from SFAs were followed for 10 y. Those whose proportional intake of SFAs from milk had a lower incidence of CVD compared with those who consumed an equivalent amount of SFAs from bovine meat. In particular, a 5-g/d increase in milk-derived SFAs was associated with a 21% decrease in CVD risk, whereas the same increase in meat-derived SFAs was associated with a 26% increase in CVD risk (113). As a cautionary note, the effects of FAs are difficult to disentangle from those of other milk and meat components; therefore, more studies are needed to attribute potentially cardioprotective properties to milk FAs. A recent review by Huth and Park (114) concluded that the consumption of milk and dairy products cannot, as of today, be positively or negatively associated with cardiometabolic or stroke risk. Likewise, Kratz et al. (115) recently published a meta-analysis of 11 studies that concluded that the intake of high-fat dairy is inversely associated with the prevalence of obesity and (although modestly) with CVD and metabolic disorders. The conclusions of this article were that high-fat milk derivatives do not increase CVD risk and explain the diversified and heterogeneous outcomes of the studies they analyzed by the different animal feed (pasture vs. cereal-based feed), that would influence milk composition, as already observed by Jenkins et al. (116). This potential confounding factor should be added to other ones such as differences in lifestyle, background diets, etc. which results in overall disagreement over the precise role in CVD of milk and its products. One notable example of such disagreement can be found in Bonthuis et al. (117), who carried out a 16-y prospective study on 1529 Australian participants and concluded that the evidence in favor of a CVD-protective role of dairy products (an average of 339 g/d) was scant. Avalos et al. (118) also performed a 16-y prospective study in 751 men and 1008 women from San Diego, CA, and reported a multivariate analysis that showed how women who consumed the highest amounts of low-fat dairy exhibited higher CVD risk. One study, by Goldbohm et al. (119) analyzed 120,852 Dutch men and women (follow-up = 10 y) for their dairy product consumption as related to CVD. A neutral association was reported for men, and a slight increase in CVD mortality was recorded for women. Fermented dairy was associated with modest CVD protection in both sexes. Opposite results came from a recent study performed in Costa Rica in 3630 participants (120), in which dairy consumption was associated with myocardial infarction risk reduction, and from another, larger study in 36,636 Swedish women, followed for 11.6 y, that also reported an inverse association between milk and cheese consumption and myocardial infarction incidence, independent of fat content (121). These data are in agreement with those of Sonestedt et al. (122), who followed 26,445 participants of Malmö (Sweden) for 12 y and reported the following: *1*) dairy consumption is inversely associated with CVD risk, *2*) fermented milk use is significantly inversely associated with CVD risk, and *3*) in women, cheese intake is significantly associated with CVD risk. Yet, a meta-analysis by Soedamah-Muthu et al. (123), who analyzed 17 prospective studies, came to the conclusion that milk consumption (200 mL/d) is modestly associated with lower CVD risk and that there is no correlation between the intake of milk and its derivatives and coronary disease or total mortality, regardless of their lipid content. Two subsequent studies reached the same conclusions. In the first (123), 4526 participants were followed for ~10 y; the results indicated an inverse association between fermented milk products use and total mortality, yet not with diabetes or CVD incidence. The second study (52), in 5953 Danish participants aged 30–60 y who were followed for 5 y, reported a modest beneficial effect of cheese and fermented milk on glycemic control, yet not on type 2 diabetes incidence. Finally, a recent study (124) carried out in 1965 Dutch participants (follow-up = 12.4 y) did not report any association between cardiovascular and all-cause deaths and milk consumption. Moreover, the authors recorded an increased CVD risk associated with the use of high-fat foods. For every SD increase, the use of high-fat dairy products increased cardiovascular mortality by 36%.

A few years ago, the hypothesis was formulated that, in France, despite the presence of cardiovascular risk factors such as a high-fat diet, cardiovascular mortality was lower than that in neighboring countries (125). This apparent incongruence was attributed to the concomitant use of red wine, which is rich in phenolic compounds that act as antioxidants in vitro. Particular attention has been paid to resveratrol, to which several of the alleged healthy effects of wine have been attributed, even though very limited human data are available (126,127). Indeed, the hypothesis that the antioxidant and anti-inflammatory properties of nonalcoholic components might determine health effects different than that of ethanol is intriguing, but is, at present, only suggested by laboratory data and not by conclusive epidemiologic evidence (128,129).

In summary, the available evidence of an effect (whether beneficial or detrimental) of milk and dairy products on CVD is mixed and does not allow drawing firm conclusions. Even though milk and its derivatives are apparently able to positively modulate some risk factors and surrogate markers of cardiovascular health (e.g., insulin response, dyslipidemias, oxidative stress and inflammation markers, blood pressure, etc.), the net effect on CVD is as yet to be ascertained. Potential confounding factors such as fat content and FA profile, background diets, lifestyles, and coingestion of other beneficial or noxious dietary components likely contribute to this unclear picture. Future studies will add evidence to help resolve this issue.

Cognitive Function

Cognitive function can be modulated, to some extent, by food (130), and its decline can be slowed down by adopting appropriate diet and lifestyle (131). Among all dietary components, relatively little attention has been paid to milk and its derivatives. Some studies reported amelioration of cognitive decline linked to augmentation of vascular function brought about by dairy consumption (132–134). However, specific studies have been performed only recently. A recent systematic review (135) identified 8 observational studies that reported a direct association between dairy consumption and better cognitive function. Crichton et al. (136) published a study in ~1000 Australian adults, in whom consumption of low-fat yogurt was positively associated with memory and socialization in men and low-fat cheese was associated positively with socialization and negatively with stress in women. Conversely, regular-fat dairy was associated with increased stress, anxiety, cognitive decline, and worse memory. Of note, this study was performed by using questionnaires and not ad hoc tests. The same group (137) subsequently examined a subgroup of the Maine-Syracuse Longitudinal Study (which consisted of 5 cohorts defined by time of entry into the study, i.e., 1975–2000) and reported, by using neuropsychological tests, that milk use was associated in a dose-dependent fashion with better memory and slower cognitive decline. Quantification of these effects suggests 200 mL of milk/d as the lowest effective amount that, supposedly, would afford neuroprotection. In terms of cognitive development/performance, favorable effects on cognition and school performance were also observed in 469 students who were administered 250 mL/d of milk for 3 mo and who were evaluated by cognitive tests (138). Within the context of neuroprotection and cognitive decline, a recent interesting study by Birnie et al. (139) prospectively analyzed milk consumption during infancy and cognitive function later in life. The study started in 1930 by enrolling 5000 U.K. children and was concluded 65 y later by assessing the ambulation ability of 405 elderly participants. The data showed better (+5%) walking speed and balance (+25%) in those who consumed at least 1 glass of milk/d during their childhood.

Chemoprevention

Milk contains compounds that might theoretically exert chemopreventive actions. In 1994, Kampman et al. (140) published an observational study in which 331 men and 350 women were followed for 4 and 8 y, respectively. No association between milk and fermented milk consumption and colorectal cancer was reported (141). Subsequent studies provided mixed results: although some researchers found positive associations between dairy use and prostate (142–145) and ovary (146) cancers, others found the opposite when colorectal (147), lung (148,149), or breast (150) cancers were investigated. What is possibly the largest prospective cohort study in this field was published in 2009 by Park et al. (151), who analyzed, via the use of a questionnaire, diets and cancer incidence in 293,907 men and 198,903 women, with a follow-up of 7 y. Their data showed that calcium and dairy intake was inversely associated with gastrointestinal (especially colorectal) cancer incidence. The multivariate analysis showed a calcium-associated reduction in gastrointestinal cancer risk of 16% for men and 23% for women. Other cancers were also inversely associated with milk and cheese intake, namely those of the head and neck, esophagus, stomach, colon, and bladder. This putatively protective effect of dairy intake has been ascribed to the milk content of potentially chemopreventive compounds such as calcium, vitamin D, conjugated linoleic acid, etc. (152). In particular, calcium has been suggested to inhibit cell proliferation, stimulate differentiation and apoptosis in the gastrointestinal tract and in the mammalian gland, and bind to FAs and biliary salts in the intestine, therefore lessening their potentially noxious effects on the mucosa. However, calcium would also interact with vitamin D and with insulin-like growth factor 1, in turn increasing the risk of prostate cancer (142,153). Indeed, Park et al. (151) did report increased prostate cancer risk linked to higher dairy and calcium consumption. In 2 European studies (154,155), the inverse association between milk use and colorectal cancer was confirmed. In the first study (154), 45,241 participants were followed for 12 y and their intake of yogurt was monitored (mean: 85 g/d for men and 98 g/d for women) and plotted against colorectal cancer incidence, showing an inverse association that was stronger in men. A systematic review by Aune et al. (155) took into account 19 cohort studies and reported a significantly inverse association between milk (200 mL/d) and total dairy (400 g/d), yet not cheese (50 g/d), consumption and colorectal cancer incidence.

With regard to breast cancer, after the first report by Knekt et al. (156) of a significantly inverse association between milk use and breast cancer incidence in 4697 Finnish women, Shin et al. (157) published a cohort study in which they did not find any association between dairy, calcium, or vitamin D consumption and breast cancer incidence in postmenopausal women. Conversely, in premenopausal women, a significant reduction in breast cancer risk associated with low-fat dairy products was reported. Of note, a subsequent meta-analysis (158) of >20 studies (that included a total of 351,041 women with a follow-up of 15 y) did not find any association between these 2 variables. In agreement with these data, a successive review (150) did not find convincing evidence that milk consumption is associated with lower breast cancer incidence. Conversely, Dong et al. (159) conducted a meta-analysis in 1,063,471 participants in 18 prospective cohort studies and reported an inverse association between dairy, although not milk, use and breast cancer, notably in premenopausal women and when low-fat products were separately analyzed (160,161). In summary, there is no evidence that milk and dairy use increases or reduces the incidence of breast cancer.

A similar picture is shown with milk and bladder cancer. One meta-analysis by Mao et al. (162) (who analyzed 19 cohort case-control studies totaling 7867 bladder cancer patients) reported that high milk consumption was associated with a 16% reduction in bladder cancer risk; this inverse association was stronger in Asian participants than in North American participants and was not seen in Europeans. Finally, the statistical significance depended on the type of dairy product that was analyzed. Another meta-analysis (163) examined 14 studies on milk (4879 cases of bladder cancer) and 6 studies on dairy products (3087 cases) conducted in a total of 324,241 participants. No correlations between variables were found.

With regard to other cancers, no clear evidence emerges from most of the studies that have been published thus far, including lung (149), ovary (146), esophagus and stomach (164–166), and oropharyngeal (167,168) cancers. Positive associations between dairy use and prostate cancers have been published, and several mechanisms of action have been proposed to explain this hypothetical effect (142–144,169,170). The lay public is familiar with the "China Study" (which was actually a book rather than a peer-reviewed article), which concluded that animal protein, namely casein given to laboratory animals, provoked tumors such as prostate cancer. On the basis of current evidence, the effects of casein—particularly isolated casein, separated from other components of dairy that often work synergistically—cannot be generalized to all forms of milk protein, much less all forms of animal protein. In fact, experiments in rodents suggest some antitumor activity of dairy protein fraction and, more specifically, of the whey protein component of milk because of its glutathione-increasing effects (171). In short, even though a cancer-promoting effect of casein and other milk proteins cannot be ruled out, the evidence in favor or against such effect is still too limited to draw firm conclusions.

Milk Components with Putative Functional Properties

Recently, several oligosaccharides have been categorized in milk and have been suggested as potentially bioactive ingredients. Even though bovine milk contains only trace amounts of these beneficial components (172), some researchers are working toward producing human milk oligosaccharides in transgenic animals (173). Due to the lack of suitable commercial standards for bovine oligosaccharides, we can only identify >70 fully annotated oligosaccharides in human milk and ~40 in bovine milk, of which 24 contain sialic acid (172). Oligosaccharides are composed of a lactose core bound to lactose-amine units via β1–3 or β1–6 links and carrying fucose or sialic acid in their terminal position (172,174,175). It is noteworthy that these molecules are abundant in human milk and have been proposed as important for child development. Neutral oligosaccharides—namely the monomer *N*-acetylglucosamine and fucose—are essential to the development of the microbiota of breast-fed neonates because of their immunomodulating actions (176). Conversely, acidic oligosaccharides (where the monomer is sialic acid) help to prevent the adhesion of pathogens to the intestinal mucosa (177). Bovine milk also contains these oligosaccharides, which are abundant in colostrum (178,179). Oligosaccharides are prebiotics and help to create a healthy microbiota (180–182). Even though a thorough discussion on the role of the microbiota in human health goes beyond the aim of this article, this is an important and dynamic field of research that is attracting considerable attention and is being addressed from several viewpoints (183–185). Even though many fruits and vegetables contain oligosaccharides and some of them have been synthesized, those from milk are remarkable in that they exhibit a branched rather than a linear structure. Moreover, they contain fucose and sialic acid, which are almost absent in other oligosaccharides. This structural difference might confirm that milk oligosaccharide activities are different than oligosaccharides of synthetic or vegetal origin. It must be underscored that the concentration of oligosaccharides in bovine milk decreases in a time-dependent fashion: ad hoc investigations are being carried out to formulate these compounds as nutraceuticals or as probiotic components of functional foods (172).

Finally, it is noteworthy that some kinds of cheeses, namely those infected with *Penicillium* such as Roquefort, Stilton, or Gorgonzola, exhibit high concentrations of andrastins A–D, which are potent inhibitors of farnesyltransferase, a key enzyme in cholesterol synthesis (186). Other peptides formed during ripening-induced proteolysis might further contribute healthful, albeit as yet unexplored, properties that would partially explain the relatively low incidence of CVD in high-cheese-consumption countries.

Milk is also often fortified, e.g., with vitamin D or omega-3 FAs (187), because it provides an excellent vehicle for fat-soluble molecules (see below) and can be marketed to target population groups after appropriate regulatory evaluation (188). In summary, either fortified or "natural" milk and dairy products contain several compounds—even though they are often present in low concentrations—that might in the future be exploited for pharma-nutrition applications (189).

Conclusions

Milk and its derivatives are proposed as being useful foods throughout all life periods, in particular during childhood and adolescence, when their contents of calcium, protein, phosphorus, and other micronutrients might promote skeletal, muscular, and neurologic development. However, their relatively high saturated fat proportion [milk fat contains ~70% SFAs; myristic and palmitic acids combined account for ~50% (190), whereas the remainder are mostly short- and medium-chain FAs and oleic acid (191,192)] has flagged them as potentially detrimental food items, especially in terms of cardiovascular health. The recent literature reviewed in this article helps shed some light on the role of milk in a balanced diet. The vast majority of epidemiologic and intervention studies performed during the past few years suggest that dairy products do not adversely affect surrogate markers of CVD and cardiovascular prognosis. Indeed, some studies suggest that SFAs, namely, shorter-chain SFAs, from milk and its derivatives are benign with regard to inflammation (193) and might actually be beneficial to some population segments (193). The available evidence suggests that calcium does not play a major role in coronary calcification (194) [at least from an epidemiologic viewpoint: randomized clinical trials are inconclusive (195)] and its intake is inversely associated with blood pressure, whereas its potential contribution to prostate cancer development is still controversial (196). Therefore, the hypothesized association between calcium intake and cardiovascular risk is not currently supported by scientific evidence, and, in fact, the reverse might be true. In addition, some milk components such as *trans* fatty acids [which might have different physiologic actions than the industrial ones (197,198)], butyric acid [which might be helpful for the intestinal mucosa's trophism (199)], conjugated linoleic acid [even though the jury is still out as far as its putative health effects are concerned, there are efforts to increase its concentrations in bovine milk (103)], phospholipids (200), tripeptides, calcium, phosphorus, lactoferrin (201), and oligosaccharides might exert useful, although as yet unproven, physiologic actions. Furthermore, milk has been shown to be an efficient vehicle for lipid-soluble nutrient absorption (187) because milk fat appears to be highly dispersed in very small micelles (202).

In conclusion, whereas future studies will help to elucidate the role of milk and dairy products in human health, their use within a balanced diet should be considered in the absence of clear contraindications.

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