SUPPLEMENT

Effects of Full-Fat and Fermented Dairy Products on Cardiometabolic Disease: Food Is More Than the Sum of Its Parts

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ABSTRACT

Current dietary recommendations to limit consumption of saturated fat are largely based on early nutrition studies demonstrating a direct link between dietary saturated fat, elevated blood cholesterol levels, and increased risk of cardiovascular disease. As full-fat dairy products are rich in saturated fat, these dietary guidelines recommend consumption of fat-free or low-fat dairy products in place of full-fat dairy. However, dairy products vary greatly in both their nutrient content and their bioactive ingredients, and research increasingly highlights the importance of focusing on whole foods (i.e., the food matrix) as opposed to single nutrients, such as saturated fat. In fact, the weight of evidence from recent large and well-controlled studies, systematic reviews, and meta-analyses of both observational studies and randomized controlled trials indicates that full-fat dairy products, particularly yogurt and cheese, do not exert the detrimental effects on insulin sensitivity, blood lipid profile, and blood pressure as previously predicted on the basis of their sodium and saturated fat contents; they do not increase cardiometabolic disease risk and may in fact protect against cardiovascular disease and type 2 diabetes. Although more research is warranted to adjust for possible confounding factors and to better understand the mechanisms of action of dairy products on health outcomes, it becomes increasingly clear that the recommendation to restrict dietary saturated fat to reduce risk of cardiometabolic disease is getting outdated. Therefore, the suggestion to restrict or eliminate full-fat dairy from the diet may not be the optimal strategy for reducing cardiometabolic disease risk and should be re-evaluated in light of recent evidence. *Adv Nutr* 2019;10:924S–930S.

Keywords: saturated fat, cardiovascular disease, dairy, yogurt, type 2 diabetes

Introduction

In the United States, dairy products, including cheese, dairy desserts, and milk (low-fat and whole), are among the top contributors of saturated fat in the diet (1). Current US dietary guidelines (2015–2020) (2), supported by the conclusions of the European Food Safety Authority (EFSA) (3), highlight the importance of reducing intake of saturated fat for optimizing cardiometabolic health. Similar conclusions have been reached by the WHO, which recommends that saturated fat contributes <10% of total energy intake (4, 5). The EFSA further recommends keeping saturated fat intake "as low as possible." This advice is based predominantly on observational nutrition studies during the 1960s and 1970s that showed a direct association between saturated fat consumption, raised blood cholesterol concentrations, and increased risk of cardiovascular disease (CVD) (6, 7) but also early clinical trials of replacement of saturated fat by polyunsaturated fat (8). As full-fat dairy products have a relatively high saturated fat content, current dietary guidelines recommend consumption of fat-free or low-fat dairy products in place of full-fat dairy.

However, there are many weaknesses in the evidence and conceptual views linking saturated fat to CVD. First, saturated fat consists of several different fatty acids (chain lengths from 4 to 24 carbon atoms) with completely different physicochemical properties and, subsequently, biological effects in relation to CVD risk (9, 10). Second, the food matrix in which the fatty acids exist in the diet may be more important for the effect on CVD than the absolute content of the food in saturated fatty acids (11); the same may be true even for unsaturated *trans* fatty acids (12). Last but not least, the effect of dietary saturated fat on blood lipid profile (13) and CVD risk (14) depends on the comparator macronutrient, for example, unsaturated fat (and whether it is monounsaturated or polyunsaturated) or carbohydrate (and whether it is refined or not). Inability to account for some or most of these confounding factors may be responsible for the fact that the dietary advice to simply

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decrease total fat intake, particularly saturated fat intake, has been proven to be largely unsuccessful in reducing CVD risk (15). Clearly, this implies we are missing some important links of the chain leading from saturated fat to CVD, and we should thus start looking into the health effects of dietary saturated fat from a different perspective.

Saturated Fat and CVD

In contrast to current dietary recommendations, much of the evidence from prospective cohort studies and randomized trials over the past 10 y challenges the advice to reduce saturated fat intake for reducing CVD risk. Rather, it raises the question of whether it is prudent to restrict intake of certain foods, such as full-fat dairy products, solely based on their high saturated fat content. A meta-analysis of prospective cohort studies (3–12 studies for each association) demonstrated that, when comparing high with low intakes of saturated fat, there is no convincing evidence of an association between dietary saturated fat and all-cause mortality, CVD, coronary heart disease (CHD), ischemic stroke, or type 2 diabetes (T2D) (12). However, the evidence and methodologies among the studies analyzed are inconsistent. Importantly, the definition of "low-fat" and "high-fat" dairy products varies considerably among studies (0%–3.5% and 4%–80% of total food calories, respectively), and most studies do not provide information on the total fat content of the experimental diets, making interpretation of the results difficult. These potential confounders need to be controlled for in future trials. An earlier meta-analysis of 21 prospective studies with 347,747 subjects also found no significant evidence that dietary saturated fat is associated with increased risk of CHD, stroke, or CVD (16). Interestingly, an inverse association of saturated fat intake with hemorrhagic stroke, but not ischemic stroke, was reported in 2 of the included studies. No association between saturated fat and stroke was found in 6 other studies. The relation of saturated fat intake with hemorrhagic, but not ischemic stroke, may be caused by differing biological effects of saturated fatty acids in relation to the pathophysiology of different types of stroke. Examination of these 2 disease states as distinct study end points may thus be important for future research.

Biomarkers of fatty acid intake have also been used to examine the association between saturated fat and CVD. A systematic review and meta-analysis that included 17 observational studies of fatty acid biomarkers found no clear evidence of differences in CHD risk between the highest and lowest tertiles of saturated fat intake (17). Clinical trials have also failed to consistently find evidence that dietary saturated fat increases CHD risk or that replacing saturated fat with polyunsaturated fat reduces CHD risk (18, 19), despite observational studies reporting that substitution of 5% of daily calories from dairy fat with polyunsaturated fat (mainly from plants) is associated with a 24% reduction in CVD (20). A recent meta-analysis of randomized controlled trials concluded that replacing saturated fatty acids with mostly n–6 polyunsaturated fatty acids is unlikely to reduce CHD events, CHD mortality, or total mortality and provided evidence that the benefits reported in earlier meta-analyses are due to the inclusion of inadequately controlled trials (21).

Research increasingly highlights the importance of focusing on whole foods (i.e., the food matrix), as opposed to single nutrients, such as saturated fat. A food product is more than the sum of its individual components. Each food has a complex physical and nutritional structure, which can influence the digestion, absorption, and bioactive nature of the nutrients it contains and subsequently their biological effects. This is especially true for full-fat dairy products. It is therefore possible that the combined action of SCFAs, protein, calcium, vitamin D, and probiotics present in the matrix of some dairy foods results in powerful beneficial health effects regardless of the saturated fat content. SCFAs, for example, are known to independently affect lipid, glucose, and cholesterol metabolism in various tissues (22, 23). Likewise, probiotics found in many fermented dairy products (i.e., live microorganisms with biological activity) and their interactions with the gut microbiome can modulate the effect of dairy consumption on cardiometabolic function (24).

Dairy and Cardiometabolic Disease

The findings of a recent large cohort study, which included 136,384 individuals from 21 countries and 5 continents, clearly demonstrated that dairy consumption (predominantly milk and yogurt) is associated with lower risk of mortality and major CVD events (25). Furthermore, a systematic review of meta-analysis of prospective population studies (26) and an earlier prospective cohort study (Whitehall II) (27) have also found an inverse or neutral relationship between intake of dairy products and CVD. In addition, Soedamah-Muthu et al. (28) performed a meta-analysis of 17 prospective cohort studies and found no association between

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Abbreviations used: CHD, coronary heart disease; CVD, cardiovascular disease; EFSA, European Food Safety Authority; DASH, Dietary Approaches to Stop Hypertension; T2D, type 2 diabetes.

intake of dairy and CHD risk, regardless of fat content, but a possible inverse association with overall CVD risk. For every 200-mL increase in milk consumption, there was a 6% reduction in CVD (28). The same research group performed another meta-analysis and found that both total dairy consumption and low-fat dairy consumption were associated with reduced risk of hypertension (29). A small trial in 22 sedentary adult women observed a decrease in systolic blood pressure and improvements in markers of arterial function after 4 wk of milk protein supplementation (30). These results indicate that a beneficial effect of dairy on the risk of developing CVD may be modified by nutritive and nonnutritive components other than fat (see also "Biological Mechanisms").

Qin et al. (31) also performed a meta-analysis of 22 prospective cohort studies that examined the association between consumption of dairy products and CVD risk. Again, results showed an inverse association between dairy consumption (mainly low-fat but also cheese) and overall risk of CVD and stroke but no association between intake of dairy and risk of CHD (31). Guo et al. (32), in their meta-analysis of 29 cohort studies with almost 1 million participants, found no associations between total dairy and milk intakes with the health outcomes of mortality, CHD, or CVD but found inverse associations for total fermented dairy (including sour milk products, cheese, or yogurt) with mortality and CVD risk. Finally, a newly published meta-analysis found that dairy product consumption was inversely associated with CVD (13 studies including 460,798 subjects), but subgroup analyses revealed this association was significant only for women (13% reduction in risk with high intake of dairy) but not for men (33). It is unclear whether this sex difference is mediated by differences in sex hormones or other factors.

The above lines notwithstanding, studies do suggest that saturated fat from sources other than dairy (e.g., meat) may have an adverse effect on CVD. In the Multi-Ethnic Study of Atherosclerosis, substituting 2% of energy from meat-saturated fat with dairy-saturated fat was associated with a 25% reduction in CVD risk (34). The latest meta-analysis of prospective cohort studies on meat intake and CVD found that the highest category of processed meat consumption had a ~21% greater risk of mortality from CVD (35). There was, however, no association between total red meat intake, white meat intake, and mortality from CVD (35). Given that the same types of fat are found in processed meat and nonprocessed meat, these results suggest something else in the food processing may be responsible for the adverse effect on CVD risk, but more research is needed in this area.

Similar to CVD, a systematic review and meta-analysis of 14 cohort studies reported an inverse relationship between modest increases in dairy intake and T2D (36). A second systematic review and dose-response meta-analysis of 17 cohort studies found a significant inverse, dose-dependent association between intake of total dairy products, low-fat dairy products, and cheese, and risk of T2D (37). In a recent meta-analysis of 16 studies and 545,677 subjects, high dairy consumption was associated with a 13% lower risk of T2D among women, but no such protective effect was found among men (33). Moreover, neither the European Prospective Investigation into Cancer and Nutrition (EPIC)–InterAct Study—a nested cohort study in 8 European countries (38)—nor the Rotterdam Study of adults ≥55 y of age (39) found an association (whether positive or negative) between consumption of dairy products (regardless of fat content) and T2D.

Collectively, results from these recent studies, systematic reviews, and meta-analyses do not provide convincing evidence that saturated fat in dairy products increases risk for cardiometabolic disease and instead suggest there may be a potentially beneficial effect. However, more research is warranted to adjust for possible confounding factors and to assess the association between other types of dairy products and health outcomes.

Fermented Dairy and Cardiometabolic Disease

Dairy products vary greatly in both their nutrient content and their bioactive ingredients. The consumption of fermented dairy, such as sour milk products, cheese, and yogurt, has been found to have positive effects on body composition, blood lipid profile, and cardiometabolic disease risk, which may partly relate to microbiota metabolites, such as SCFAs. Despite concerns related to saturated fat content, these beneficial effects are observed regardless of whether the fermented dairy product is low-fat or full-fat. Besides fat, yogurt and cheese contain many other bioactive ingredients. The process of fermentation leads to the structural change of lipids and proteins in cheese and yogurt, which may be responsible for some of their beneficial effects (40). The more ripe the cheese, the greater the beneficial effects for metabolic health, and this may be explained, in part, by the end-products produced by gut bacteria that are powerful enough to affect insulin sensitivity and CVD risk (41).

Several studies, including meta-analyses of observational studies and randomized controlled trials, found no negative effects of cheese consumption on body weight, metabolic function, and CVD risk, despite its saturated fat and sodium contents (42–44). In a highly publicized study on 2 large Swedish cohorts, high milk intake was associated—unexpectedly—with increased mortality and hip fractures. However, an observation that received far less attention is that cheese and yogurt consumption was found to be protective in reducing both mortality and the risk of hip fractures (45). This finding, as well as others, suggests that future research should distinguish between milk and fermented dairy products (42, 43). We carried out a meta-analysis of 29 cohort studies, including the abovementioned Swedish study, and found inverse associations of total fermented dairy (sour milk products, yogurt, and cheese) consumption with all-cause mortality and risk of CVD (32). For example, CVD risk was reduced by ~2% for every 10 g/d of cheese consumption. Also, there was no evidence that low-fat dairy products were better than full-fat dairy products. All inverse associations between CVD and total fermented dairy and cheese were attenuated in sensitivity analyses

when removing 1 large Swedish study, but no positive association between fermented dairy and mortality or CVD was found whatsoever (32). Also, in hypertensive patients, higher consumption of yogurt was associated with a lower risk of CVD, and the beneficial effect was more pronounced among those following a healthier diet (46).

We conducted a randomized controlled trial to investigate the mechanisms by which cheese does not increase, and may actually decrease, CVD risk (47). Our hypothesis was that since different dairy products have a different nutrient composition, they would also differ in their effects on blood lipid profile, which is a risk factor for CVD. A total of 15 healthy young men consumed a control diet or an isocaloric diet rich in milk or cheese for 14 d in a crossover design. Compared with the milk-rich diet, the cheese-rich diet led to significantly increased microbiota-related metabolites butyrate, hippurate, and malonate (i.e., SCFAs), whereas the expected increase in LDL cholesterol from cheese consumption did not occur (47). The control diet provided ~500 mg calcium/d, while the 2 test diets provided ~1700 mg calcium/d, and studies have suggested that increasing dairy calcium intake by ~1200 mg/d results in an increase in fecal fat excretion by ~5 g/d (48). This may be related to the observed effects of the 2 diets on lipid metabolism. Beneficial changes in total and LDL cholesterol levels were highly correlated with the output of some SCFAs in stool, suggesting that microbial and lipid metabolism could be involved in the dairy-induced effects on cardiometabolic risk factors (see also "Biological Mechanisms").

Regarding risk for T2D, a systematic review and meta-analysis of randomized controlled trials found that increased consumption of dairy products without energy restriction did not result in significant changes in body weight or body composition (49), which is of relevance given that obesity is the major driver of the T2D epidemic (50). In fact, inclusion of dairy products as part of a weight reduction diet has been found to reduce body fat and/or increase fat-free mass (49). In addition, a recent cross-sectional analysis of 114,682 adults found that yogurt and full-fat dairy intakes have an inverse association with overweight and obesity; by contrast, skimmed, semi-skimmed, and nonfermented dairy had positive associations with overweight and obesity (51). There is currently no evidence that low-fat fermented dairy is better than full-fat fermented dairy in decreasing risk of T2D. In fact, the opposite may be true: full-fat dairy appears to be the most protective (32). An inverse association between total dairy and yogurt intake and risk of T2D was reported in a meta-analysis of 22 cohort studies with 579,832 subjects (52). In addition, findings from the Maastricht Study showed that, relative to lower intakes, high intakes of yogurt and fermented dairy products were associated with lower odds of newly diagnosed T2D and impaired glucose metabolism by 25% to 40%, respectively (53). Large cohort studies in the United States and Europe (Health Professionals Follow-Up Study, Nurses' Health Study I and II, and Maastricht Study) as well as a recent meta-analysis of cohort studies have consistently found inverse associations between consumption of fermented dairy products, including yogurt, cheese, and fermented milk, and risk of T2D (36, 37, 53–55). On the basis of 3 prospective cohort studies, a systematic review by Drouin-Chartier et al. (26) found a neutral association between consumption of regular- and high-fat dairy, milk, and fermented dairy and risk of T2D but a protective effect of low-fat dairy and yogurt (and maybe also cheese).

Biological Mechanisms

Relatively little research has evaluated the mechanisms by which dairy products can modify risk for cardiometabolic disease. The wide variety of dairy products (e.g., milk, yogurt, cheese, cream, butter), the large variability in the type and amount of their nutritive and nonnutritive components (e.g., calcium, fatty acids and other lipids, proteins, vitamins, probiotics), and the potential influences of food production characteristics, such as animal breeding and feeding, fermentation, selection and cultivation of bacterial and yeast strains (as fermentation starters), and homogenization, contribute to the complexity of the biologically active content of dairy that can affect downstream molecular and signaling pathways and, ultimately, cardiometabolic function (24).

Body weight, body composition, and fat deposition

Calcium supplementation in animal models of obesity attenuates weight gain and hepatic fat accumulation, likely by correcting signaling through leptin and glucagon-like peptide 1, suppressing lipogeneses in the liver and adipose tissue, reducing 1,25-dihydroxyvitamin D3 concentrations, and altering gut microbiota (24). In human trials, calcium supplementation has not been shown to have a significant effect on body weight or body composition (56), whereas consumption of milk and other dairy products decreases body fat and increases or preserves lean mass, particularly during weight loss (49, 56, 57), indicating a calcium-independent mechanism. The protein in dairy (~80% casein and 20% whey) could be involved, perhaps via its stimulatory effects on satiety, thermogenesis, and proteinosynthesis (58). In longitudinal studies in free-living human subjects, low-fat or full-fat milk or cheese has not been linked to weight gain (i.e., they have a neutral effect), whereas yogurt has been consistently found to attenuate weight gain (24), thereby suggesting that fermentation products such as active probiotics may be important for this effect.

Blood pressure and lipid profile

Calcium supplements (59) and casein-derived peptides (60) may decrease systolic and diastolic blood pressure. Beneficial effects on the arterial wall properties and blood pressure have been observed in trials of nonfat and low-fat milk consumption (61, 62) but not when full-fat milk is consumed (63, 64), suggesting that differences in dairy fat type and content may be relevant for the blood pressure–reducing effect to manifest. Nevertheless, a randomized controlled crossover trial in 36 participants, who completed three 3-wk dietary periods in random order with a 2-wk washout

in between, evaluated the effects of a standard Dietary Approaches to Stop Hypertension (DASH) diet, which included consumption of low-fat dairy and a higher-fat, lower-carbohydrate modified DASH diet, which included consumption of full-fat dairy, compared with a control diet (65). Results indicated that consumption of full-fat dairy in the modified higher-fat DASH diet was not associated with an increase in blood pressure over the standard low-fat DASH diet. There was also a beneficial effect of full-fat dairy on triglyceride levels and LDL cholesterol particle size, both of which are linked to CVD risk (65). The low-fat DASH diet improved LDL cholesterol but worsened other CVD risk factors, such as triglyceride and HDL cholesterol levels (65). These findings indicate that full-fat dairy foods could be incorporated in the DASH dietary pattern without impairing its beneficial effects on blood pressure and may in fact be superior to low-fat dairy in terms of the effects on blood lipid profile. This is interesting because, according to current dietary recommendations, saturated fat intake from full-fat dairy would be expected to raise LDL cholesterol concentration. However, randomized trials demonstrate a large heterogeneity in this response depending on the type of dairy product consumed. Compared with butter, cheese (66) and whipping cream (67) lower total and LDL cholesterol concentrations, despite otherwise identical dairy total and saturated fat contents. The same is true when comparing intake of saturated fat from milk and cheese with the same type and amount of saturated fat from nondairy sources (44). Furthermore, it has now become clear that the effect of replacing saturated fat in the diet on blood lipids and lipoproteins depends not only on the chain length of the saturated fatty acid being replaced but also on the replacement nutrient (13). These findings underscore the complexity of the factors potentially contributing to the observed health effects of dairy products. The systematic and comprehensive assessment of these factors in future studies will thus be important for better understanding of the mechanisms of action of dairy on human health.

Insulin sensitivity and glucose homeostasis

Dairy products are good sources of protein, particularly proteins rich in the branched-chain amino acids (comprising ~21% of total dairy proteins) leucine, isoleucine, and valine, which have been associated with insulin resistance and T2D in epidemiological studies, supposedly by activating important signaling pathways such as the mammalian target of rapamycin (68, 69). However, more often than not (70), observational studies and clinical trials identify dairy products as a key component of a dietary pattern that is inversely associated with features of insulin resistance, such as lower postprandial glucose (i.e., improved glucose tolerance), increased postprandial insulin (i.e., improved β-cell function), and greater insulin-stimulated glucose uptake (i.e., improved muscle insulin action) (71, 72). This is in line with the protective effect of dairy consumption, particularly yogurt, on the risk of developing T2D (52) but also with the weight of evidence from epidemiological studies and small clinical trials of dairy protein consumption and improved glucose homeostasis in patients with T2D (73).

The importance of incretins (74) and inflammatory mediators (24) in the health effects of dairy remains elusive. Likewise, many other hypotheses have been put forth regarding the potential mechanisms of action of dairy on the basis of preliminary findings from studies in culture systems and animal models, but none has been rigorously tested in appropriate experimental settings in humans (24). Evidently, research into the potential mechanisms responsible for the effects of dairy products on cardiometabolic function and subsequent disease risk is still in its infancy, and this is an important area for future research.

Conclusions

The findings from the aforementioned studies are in line with the consensus reached at an expert workshop in Gentofte, Denmark, in 2016, which included the following statement: "Current evidence does not support a positive association between intake of dairy products and risk of CVD (i.e. stroke and CHD) and T2D." The workshop also concluded that "different dairy structures and common processing methods may enhance interactions between nutrients in the dairy matrix, which may modify the metabolic effects of dairy consumption" (23).

What becomes increasingly clear is that the recommendation to restrict dietary saturated fat to reduce risk for cardiometabolic disease is getting outdated. The weight of evidence from recent meta-analyses of both observational studies and randomized controlled trials indicates that full-fat dairy products, particularly yogurt and cheese, do not exert the detrimental effects on blood lipid profile and blood pressure as previously predicted on the basis of their sodium and saturated fat contents; they do not increase cardiometabolic disease risk and may in fact protect against CVD and T2D. Therefore, the suggestion to restrict or eliminate full-fat dairy from the diet may not be the optimal strategy for reducing cardiometabolic disease risk and should be re-evaluated in light of recent evidence.

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