Yogurt and dairy product consumption to prevent cardiometabolic diseases: epidemiologic and experimental studies[1–3]

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ABSTRACT

Dairy products contribute important nutrients to our diet, including energy, calcium, protein, and other micro- and macronutrients. However, dairy products can be high in saturated fats, and dietary guidelines generally recommend reducing the intake of saturated fatty acids (SFAs) to reduce coronary artery disease (CAD). Recent studies question the role of SFAs in cardiovascular disease (CVD) and have found that substitution of SFAs in the diet with omega-6 (n–6) polyunsaturated fatty acids abundant in vegetable oils can, in fact, lead to an increased risk of death from CAD and CVD, unless they are balanced with n–3 polyunsaturated fat. Replacing SFAs with carbohydrates with a high glycemic index is also associated with a higher risk of CAD. Paradoxically, observational studies indicate that the consumption of milk or dairy products is inversely related to incidence of CVD. The consumption of dairy products has been suggested to ameliorate characteristics of the metabolic syndrome, which encompasses a cluster of risk factors including dyslipidemia, insulin resistance, increased blood pressure, and abdominal obesity, which together markedly increase the risk of diabetes and CVD. Dairy products, such as cheese, do not exert the negative effects on blood lipids as predicted solely by the content of saturated fat. Calcium and other bioactive components may modify the effects on LDL cholesterol and triglycerides. Apart from supplying valuable dairy nutrients, yogurt may also exert beneficial probiotic effects. The consumption of yogurt, and other dairy products, in observational studies is associated with a reduced risk of weight gain and obesity as well as of CVD, and these findings are, in part, supported by randomized trials. *Am J Clin Nutr* 2014;99(suppl):1235S–42S.

INTRODUCTION

Despite a dramatic decrease in the incidence of cardiovascular disease (CVD)[4] in the past 60 y, it is still a leading cause of death in Western countries, and the prevalence of CVD is increasing because of the aging population (1). There is robust evidence to suggest that a substantial proportion of the CVD seen today can be prevented by a generally healthier lifestyle in the population as a whole and by targeting lifestyle change to manage cardiovascular risk factors in high-risk individuals (2). Lifestyle advice for reducing the risk of CVD may be summarized by the 5 key elements: eat a healthy, balanced diet with low or no industrially produced *trans* fat (3); be more physically active; keep to a healthy weight; give up smoking; and comply with only moderate alcohol consumption (2). Effective CVD prevention in the US population could potentially reduce the incidence of myocardial infarction (MI) by >60%, reduce the incidence of stroke by ∼30%, and increase life expectancy by an average of 1.3 y (4).

SFAs have played a key role in hypotheses relating diet to the risk of coronary heart disease (CAD): thus, a reduction in SFA intake has been at the heart of most dietary recommendations to reduce the risk of CAD (5, 6). Dairy products can be high in saturated fat, and it is estimated that dairy products (excluding butter) contribute to 24% of the saturated fat intake of the US diet (7); these figures are 25–30% in European countries (8). Paradoxically, it has been suggested that the consumption of dairy products can ameliorate characteristics of the metabolic syndrome, which has an effect on cardiovascular complications (9–11). The metabolic syndrome comprises a cluster of risk factors including dyslipidemia, insulin resistance, increased blood pressure (BP), and abdominal obesity, that together markedly increase the risk of diabetes and CVD. This article provides a review of data arising from observational studies and randomized controlled trials (RCTs) with regard to the impact of dairy product intake on risk factors for cardiometabolic disease and cardiovascular outcomes.

DAIRY PRODUCTS AND BODY WEIGHT

Dairy consumption has been studied extensively for its possible roles in body weight regulation. There is evidence to suggest that the consumption of dairy products reduces body fat but not necessarily body weight (12–14), attributable to a preservation of lean body mass. In addition, limited findings suggest that yogurt may have a more powerful effect on weight and body fat than other dairy foods, but further RCTs are needed to confirm this. Potential mechanisms for these findings are unclear, although

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[4] Abbreviations used: BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; GI, glycemic index; LA, linoleic acid; MI, myocardial infarction; RCT, randomized controlled trial.

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evidence suggests that changes in the gut microbiota may influence weight gain (15).

Changes in diet and lifestyle factors were evaluated across 3 large prospective studies to determine their impact on long-term weight gain in 22,557 men and 98,320 women included in health studies in the United States (12). Over a 4-y period, it was found that most of the foods that were positively associated with weight gain were starches or refined carbohydrates, whereas conversely, yogurt consumption was associated with a reduction in weight across the study populations (**Figure 1**) (12). The consumption of cheese, vegetables, fruit, nuts, and whole grains also showed a beneficial association with weight reduction or weight maintenance but to a lesser extent than did yogurt consumption. All drinks consumed, with the exception of milk, were positively associated with weight gain, and no significant differences were seen between low-fat and semiskimmed milk compared with whole-fat milk (12).

The effect of dairy consumption on weight and body composition was further investigated in 2 meta-analyses (13, 14). The first meta-analysis of 14 RCTs in 883 adults found that increasing dairy consumption to recommended daily intakes in adults who do not follow any calorie-restricted diet had a small effect on weight loss but also a decrease in fat mass and waist circumference and an increase in lean body mass (13). The consumption of high-dairy, calorie-restricted diets resulted in greater weight loss and a higher reduction in waist circumference and fat mass compared with conventional calorie-restricted diets, with an increase in lean body mass. The second meta-analysis of 29 RCTs in 2101 participants found that overall consumption of dairy products did not result in a significant reduction in weight; however, a subgroup analysis showed that consumption of dairy products in the context of energy restriction did reduce body weight. Furthermore, a modest reduction in body fat was shown in the dairy group across 22 RCTs (14).

Mechanistic explanations for the association between high dairy intake and lower body weight/body fat mass found in observational studies include an effect of increased dairy calcium intake on energy balance (16, 17). One explanation postulated for

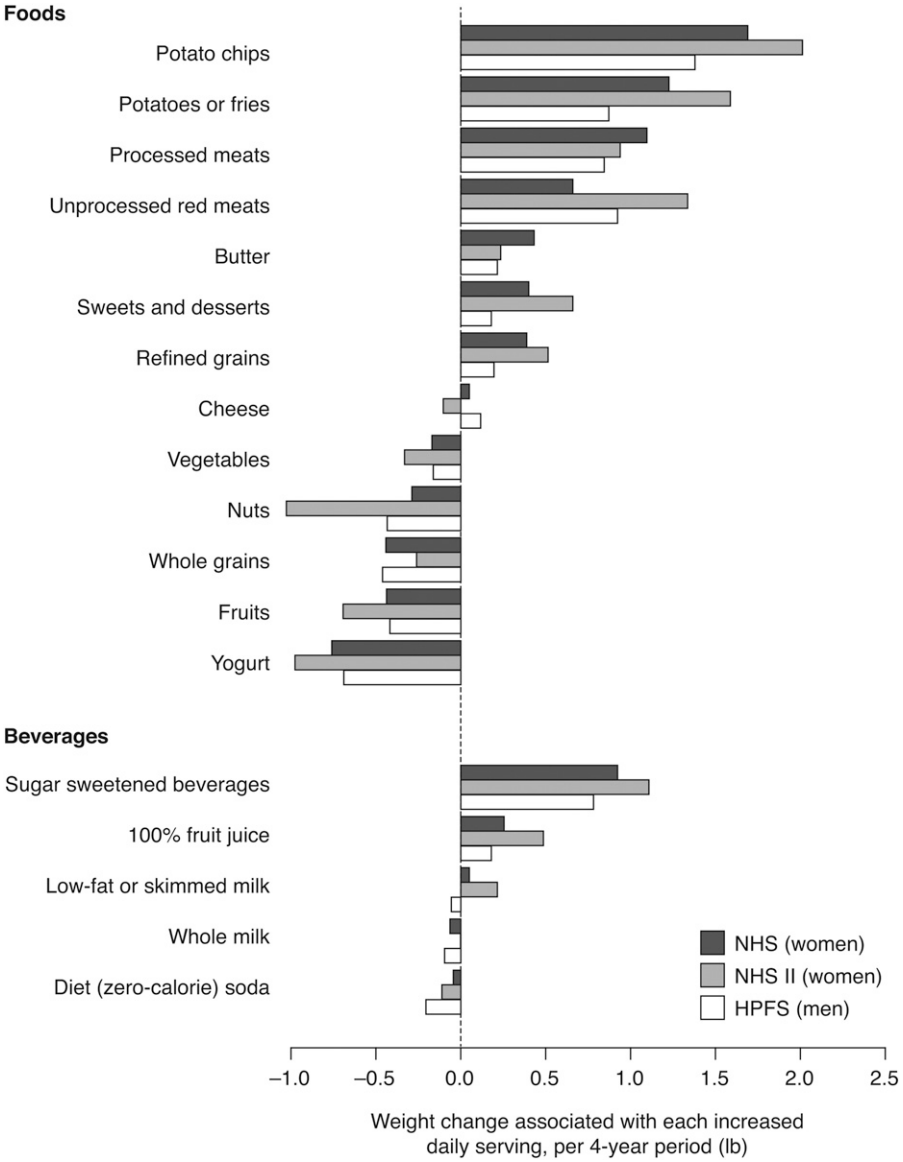

FIGURE 1. Relation between changes in food and beverage consumption and weight changes every 4 y (1 lb = 0.454 kg). Reproduced with permission from reference 12. HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

the observed inverse relation between dairy calcium intake and body weight and body fat is that dietary calcium interferes with fat absorption in the intestine by forming insoluble calcium soaps with fatty acids, and/or binding of bile acids, resulting in a decrease in the digestible energy of the diet (18). A meta-analysis of 3 crossover-design RCTs comparing high dairy calcium with low dairy calcium diets for 1 wk and involving a total of 29 participants showed that increasing the dairy calcium intake by 1241 mg/d resulted in an increase in fecal fat excretion of 5.2 (1.6–8.8) g/d (18). One of these studies showed that SFAs, MUFAs, and PUFAs were all excreted in larger amounts with the high-calcium diet (19).

Dairy foods may also modulate body weight regulation by calcium-independent mechanisms. Dairy proteins suppress short-term food intake, increase satiety, and stimulate food intake regulatory mechanisms known to signal satiation and satiety (20). The effects of different types of protein (whey, casein, and milk), on diet-induced thermogenesis and satiety have been compared in an RCT in 17 slightly overweight men [BMI (in kg/m^2; ± SEM): 29 ± 4] (21). Whey and casein are present in cow milk in proportions of ∼20% and 80%, respectively (22). A crossover-design study comparing 3 isocaloric test meals containing either a whey drink, casein drink, or skimmed milk found that there was no significant effect on subjective appetite sensation but that energy intake at a subsequent lunch was lower after the milk than after either the casein or whey drinks (a difference of 9%; $P < 0.03$). No significant difference in effect on energy expenditure, protein oxidation, or carbohydrate oxidation was observed (21). Milk proteins are also insulinotropic, and peptides derived from them affect the renin-angiotensin system, which may partly explain the association between dairy consumption and reduced prevalence of the metabolic syndrome through mechanisms other than their effect on satiety (20). Thus, milk proteins may be an important factor explaining the association between dairy consumption and healthier body weights (22).

Beyond the effect of dairy product consumption on body weight regulation, cross-sectional studies suggest that the consumption of dairy products is inversely associated with low-grade systemic inflammation. A recent meta-analysis has investigated the impact of dairy product consumption (milk, yogurt, cheese) on biomarkers of inflammation by using data collected in randomized, controlled nutritional intervention studies conducted in overweight and obese adults (23). In the one study that identified change in the inflammatory profile as its primary outcome measure, dairy food consumption was shown to improve both pro- and anti-inflammatory biomarker concentrations compared with the low-dairy control diet. Improvement in key inflammatory biomarkers including C-reactive protein, IL-6, or TNF-α after dairy product consumption was shown in 3 of the 7 other studies in which inflammation was a secondary outcome, although the 4 other studies showed no effect. Further studies may better elucidate the effect of dairy product consumption on inflammation-related outcomes.

DAIRY PRODUCTS AND CARDIOMETABOLIC DISEASES

It is proposed that the consumption of dairy products influences the risk of CVD, including CAD and stroke, or all-cause mortality, although findings from epidemiologic studies have presented conflicting results. A meta-analysis of 17 prospective cohort studies involving 62,779 participants showed a modest inverse association between milk intake and risk of overall CVD, indicating a relative risk reduction in CVD of 6% (**Figure 2**) (24–28). However, milk intake was not associated with a reduction in risk of CAD, stroke, or total mortality. No significant associations were found between total dairy products and total high-fat and low-fat dairy products and CAD, although only limited studies investigated this association (24).

A shortcoming in most of these studies is the lack of biological markers of dairy intakes, and the study of milk fat biomarkers can contribute to knowledge of an association between cardiovascular risk and dairy food consumption. A prospective case-control study in 444 participants in community-based Swedish health programs reported that consumption of cheese was inversely related to a first MI in men and women and that fermented-milk intake was associated with a reduction in MI in men only (29). In agreement with this, biomarkers of milk fat were associated with a lower risk of developing a first MI, especially in women, and a weak negative association was found between milk fat biomarkers and risk factors associated with the metabolic syndrome. A potential causal link between milk fat intake and reduced heart disease risk may be postulated, which contradicts the traditional diet-heart hypothesis that promotes a diet low in saturated fat (including the avoidance of full-fat milk) to optimize cardiovascular health. In addition to cholesterol-elevating longer-chained SFAs, dairy products contain other bioactive compounds that may promote beneficial effects (30). Dairy products also elevate HDL cholesterol, which is associated with a reduced risk of CVD (31).

SATURATED FAT AND CVD RISK

Diets high in saturated fat cause an increase in total and LDL cholesterol, and it has long been thought that they increase the risk of CAD and CVD (32). Thus, a reduction in SFA intake has been central to many dietary recommendations to reduce the risk of CAD (5). However, direct evidence for the involvement of saturated fats in CAD is lacking. A meta-analysis of 21 prospective epidemiologic studies with 347,747 participants of whom 11,006 developed CAD or stroke during 5–23 y of follow-up showed that there is no significant evidence that dietary saturated fat is associated with an increased risk of CAD or CVD (33).

Consumers have long been advised to reduce saturated animal fats in the diet to improve health and reduce the risk of CVD. However, observational studies have shown that industrially produced *trans* fatty acids, used in margarines and processed snack/fast foods, represent the most harmful single dietary component in terms of increasing the risk of CVD (2, 34). A daily intake of 5 g *trans* fat, corresponding to 2% of energy intake, is associated with an ∼30% increase in CAD risk (3).

A lower habitual intake of SFAs requires substitution with other macronutrients to maintain energy balance. Substituting PUFAs for saturated fat reduces LDL cholesterol and the total-to-HDL-cholesterol ratio (35). Replacing 1% of energy intake from SFAs with PUFAs has been associated with a 2–3% reduction in the incidence of CAD and a reduction in coronary death (36–38). However, the replacement of saturated fat by carbohydrates, particularly refined carbohydrates, increases concentrations of triglyceride and small LDL particles and reduces HDL cholesterol, effects that can contribute to a higher risk of obesity and insulin resistance (35). A positive association between dietary glycemic

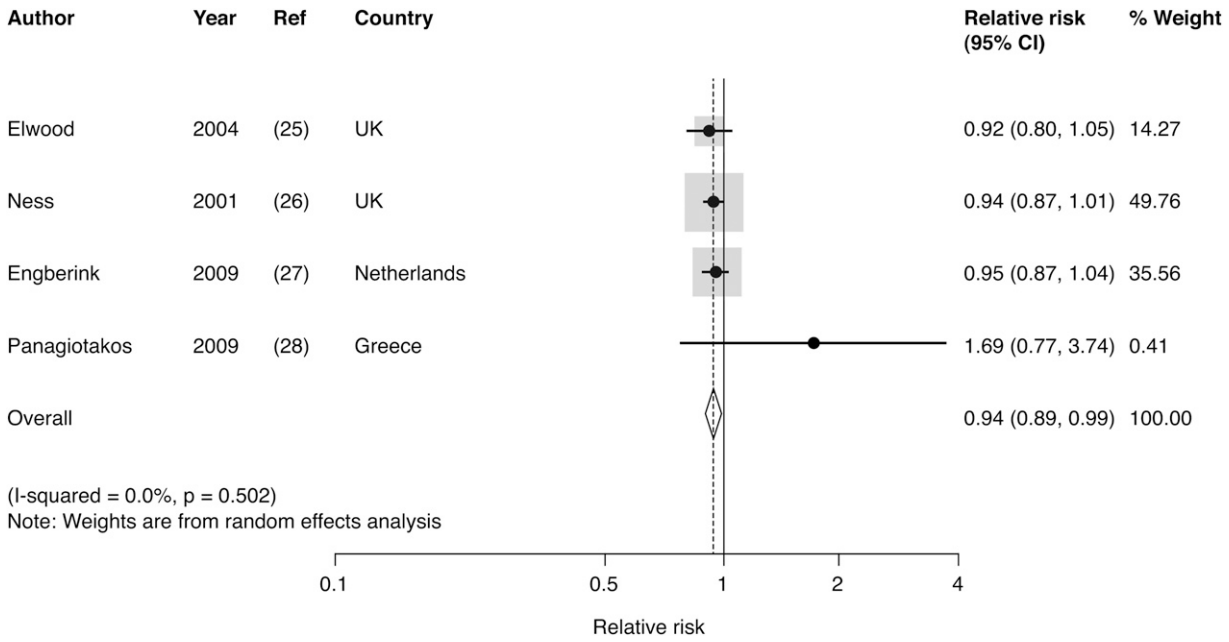

FIGURE 2. Relation between milk consumption (200 mL/d) and cardiovascular disease; dose-response meta-analysis of 4 prospective cohort studies (n = 13,518; number of cases = 2283). Reproduced with permission from reference 24. Ref, reference.

index (GI) and risk of ischemic heart disease has been shown (39–41). Pooled analyses of observational studies suggest that replacing saturated fat with polyunsaturated fat or carbohydrates with low-GI values is associated with a lower risk of CAD, whereas replacing saturated fat with carbohydrates with high-GI values may result in a higher risk of CAD (6).

The advice to substitute saturated fats derived from animal sources with vegetable oils rich in PUFAs was based on an assumption that all PUFAs result in a reduction in blood cholesterol. Advice from the American Heart Association supports maintaining an n–6 PUFA intake of ≥5–10% of energy to reduce the risk of CAD relative to lower intake amounts (42). However, there is increasing recognition that the general category of PUFAs comprises multiple species of n–3 and n–6 PUFAs, each with unique biochemical properties and perhaps divergent clinical cardiovascular effects. The clinical cardiovascular benefits of n–3 PUFAs are reported in several RCTs (43, 44); however, such benefits are not necessarily generally applicable to n–6 or other PUFAs. n–6 Linoleic acid (LA) is the most abundant PUFA in edible oils, and a study of the replacement of SFAs with n–6 LA showed an increase in mortality from CVD and CAD over a 3-y follow-up (45–47). In contrast, diets that increased n–3 PUFAs together with n–6 PUFAs showed reduced cardiovascular mortality compared with the high-SFA control diet (46). This would suggest that diets that include oils that are low in n–6 PUFAs (LA) and relatively high in n–3 PUFAs (eg, n–3 α-linolenic acid), which include canola oil (a form of rapeseed oil) and olive oil as part of the Mediterranean diet (48, 49), may provide the best protection for cardiovascular health.

EFFECT OF DAIRY PRODUCTS ON LIPID AND GLUCOSE HOMEOSTASIS

Dairy products contain a high content of SFAs and cholesterol, and it has been a general perception therefore that fatty dairy products are associated with a higher risk of CVD. However, many of the shorter-chain fatty acids found in milk fat and coconut oil have beneficial health effects, with important immune response functions (50). The medium-chain SFAs in coconut oil and butterfat (milk) increase total serum cholesterol but their positive effects on HDL cholesterol are protective in many ways. There is also evidence that the proteins, fats, and calcium in milk are beneficial in lowering BP, inflammation, and the risk of type 2 diabetes (50). Evidence from observational studies indicates that milk or dairy consumption is inversely related to the incidence of CVD; a meta-analysis showed that participants in prospective studies with the highest intake of dairy products had a lower relative risk for all-cause mortality, CVD, stroke, and diabetes (51).

Milk and other dairy products may not affect the lipid profile as adversely as would otherwise be predicted from their fat content and composition. In a study comparing intake of various beverages at an amount of 1 L/d for 6 mo, semiskimmed milk was found to have neutral effects on fat accumulation in visceral adipose tissue, liver, and skeletal muscle and on circulating lipid concentrations as compared with water (52). In contrast, the consumption of 1 L sucrose-sweetened soft drinks every day led to significantly higher changes in liver fat, skeletal muscle fat, and visceral fat and in blood triglycerides (32%; $P < 0.01$) and total cholesterol (11%; $P < 0.01$) compared with the consumption of the 3 other drinks (isocaloric semiskimmed milk, water, or diet cola) (52).

In a crossover study in a small number of men (n = 9) who consumed a high-fat diet enriched with milk minerals (calcium and phosphate) or a control diet, the increase in plasma total- and LDL-cholesterol concentrations were 6% (P = 0.002) and 9% (P = 0.03) lower, respectively, after the milk mineral diet compared with the control period, whereas HDL-cholesterol concentration was not affected. Thus, the addition of milk minerals to a high-fat diet to some extent attenuates the increase in total- and LDL-cholesterol concentrations without affecting HDL-cholesterol concentrations (53).

The effects of fermented dairy products on cholesterol have also been investigated. A meta-analysis of controlled, short-term intervention studies conducted over 4–8 wk showed that fermented

yogurt products containing one strain of *Enterococcus faecium* and 2 strains of *Streptococcus thermophilus* produce a 4% decrease in total cholesterol and a 5% decrease in LDL cholesterol (**Figure 3**) (54–59). One 8-wk RCT investigated the effects of various fermented dairy products on risk factors for CVD in overweight and obese individuals (55). Seventy healthy men and women (18–55 y; overweight to obese) were randomly assigned to receive 1 of the following 4 yogurt products (450 mL/d) or 2 placebo pills daily: group 1 received a yogurt fermented with 2 strains of *S. thermophilus* and 2 strains of *Lactobacillus acidophilus* (StLa group); group 2 received a placebo yogurt fermented with δ-acid-lactone; group 3 received a yogurt fermented with 2 strains of *S. thermophilus* and 1 strain of *L. rhamnosus* (StLr group); and group 4 received a yogurt fermented with 1 strain of *E. faecium* and 2 strains of *S. thermophilus* (G group). The dietary composition of the yogurt was otherwise similar. At 8 wk, after adjusting for small changes in body weight, a reduction in LDL cholesterol of 8.4% (0.26 ± 0.10 mmol/L) and an increase in fibrinogen (0.74 ± 0.32 mmol/L) was observed in the G group, which was significant compared with the placebo group and the chemically fermented yogurt group ($P < 0.05$). Systolic BP was also reduced significantly more in the StLa and G groups compared with the StLr group (55).

Cheese is a high-fat fermented dairy product that may be expected to increase serum cholesterol concentrations and thereby increase risk of CVD. However, a prospective cohort study in 120,852 subjects followed for 10 y found no association between cheese intake and risk of ischemic heart disease (60). The effect of cheese and butter intakes, with equal fat contents, on risk markers of CVD was compared in a 6-wk intervention study in 49 men and women who replaced part of their habitual diet with 13% of energy from cheese or butter. After 6 wk, the cheese intervention resulted in lower serum total-, LDL-, and HDL-cholesterol concentrations and higher glucose concentrations than did butter; and cheese did not increase serum cholesterol concentrations compared with a lower saturated fat intake during the run-in period (61).

The reason for the neutral effect of cheese on blood lipids is not known; one postulated explanation is an effect of the high content of calcium in cheese. A 4-way crossover study comparing high-calcium and low-calcium and high-fat and low-fat diets found that dairy calcium reduces the increase in total and LDL cholesterol produced by increased dairy fat without affecting the increase in HDL cholesterol (62). The calcium content of milk, and cheese in particular, lowers postprandial triglycerides (63), which is an important risk factor for CVD and a component of the metabolic syndrome. It has been shown that increased calcium intakes from dairy products (including milk and low-fat yogurt) attenuate postprandial lipidemia (**Figure 4**), most probably because of reduced fat absorption, whereas supplementary calcium carbonate does not exert such an effect (63). This may be a result of differences in the chemical form of calcium or to cofactors in dairy products.

Dairy products may have beneficial effects on other risk factors for CVD, including BP. Diet is the strongest environmental factor influencing BP. The Dietary Approaches to Stop Hypertension trial showed that a dietary pattern abundant in fruit, vegetables, and low-fat dairy products, in the context of a reduced intake of total and saturated fat, can considerably reduce BP in both normotensive and hypertensive individuals, without concomitant weight loss (64). Notably, this diet, which includes dairy products, elicited a more pronounced BP-lowering effect than a diet rich in fruit and vegetables alone. A subsequent systematic review and meta-analysis examined the association between dairy food intake during adulthood and the development of elevated BP by using data from 5 cohort studies involving nearly 45,000 participants and 11,500 cases of elevated BP (65). The analysis showed that the consumption of total dairy foods was associated with a 13% reduction in the risk of elevated BP. This link probably results from consumption of low-fat dairy foods, which were associated with a 16% reduction in risk, whereas high-fat dairy foods showed no association. The investigation of specific categories of dairy foods showed that the consumption of fluid dairy foods (including low-fat and full-fat milk and yogurt) was associated with an 8% reduction in risk, whereas cheese consumption did not produce significant results (65). These findings

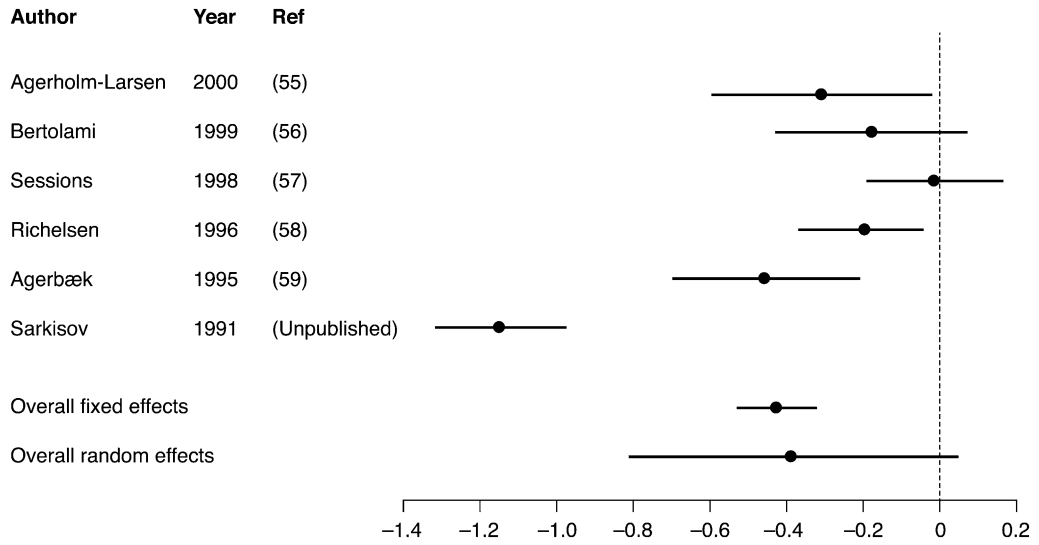

FIGURE 3. Effects of a probiotic milk product on plasma cholesterol; differences in the changes in LDL cholesterol (intervention minus control; mmol/L) with 95% CIs for 6 studies included in a meta-analysis are shown. Estimates of overall fixed and random effects are also shown. Reproduced with permission from reference 54. Ref, reference.

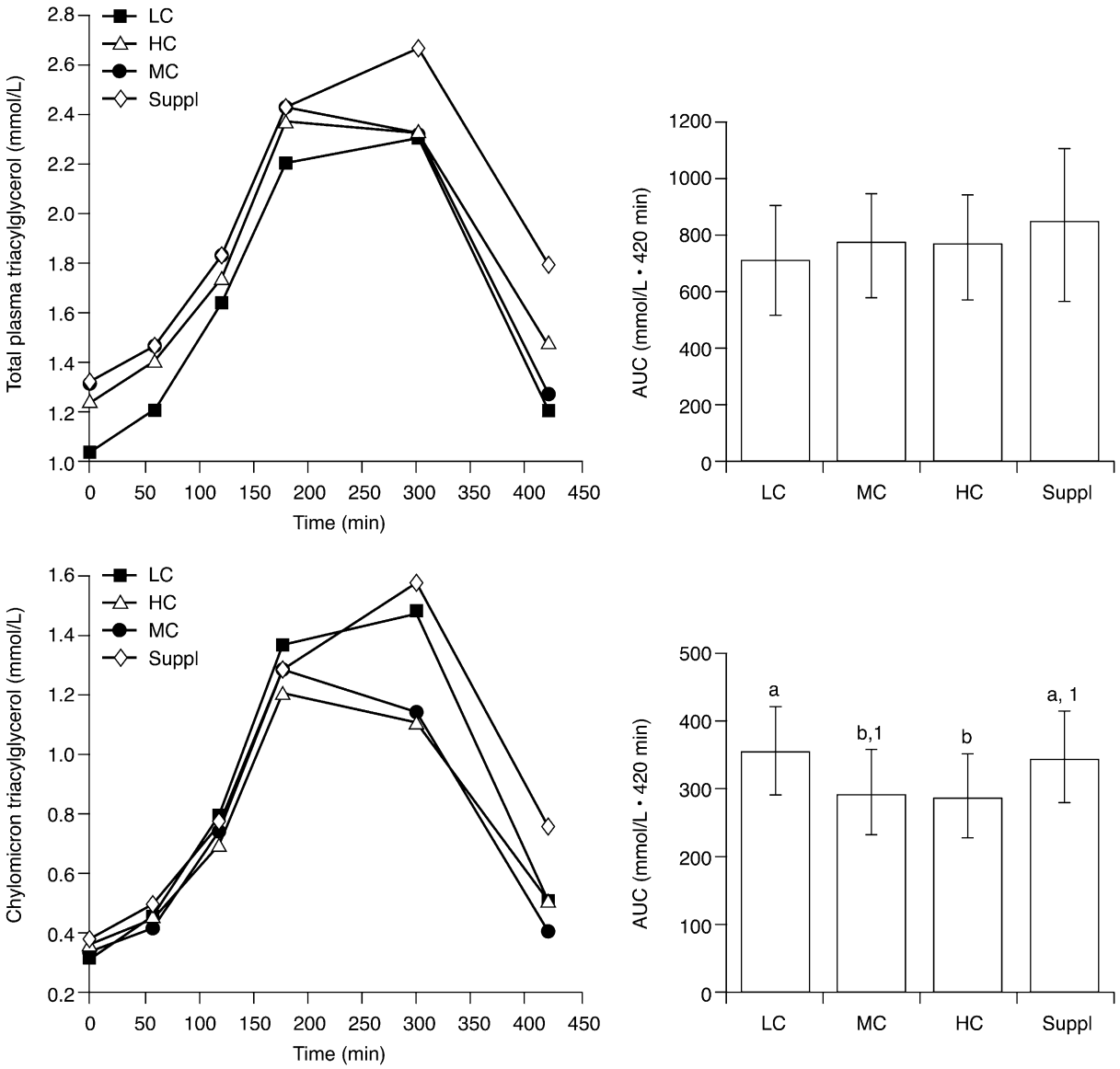

FIGURE 4. Effects of dietary or supplementary calcium intake on postprandial fat metabolism; the postprandial responses in mean plasma total and chylomicron triacylglycerol and AUC in response to 4 test meals are shown. The 4 test meals were as follows: low (LC), medium (MC), and high (HC) amounts of calcium from dairy products or high amounts from supplementary calcium carbonate (Suppl) (n = 17). The mean AUCs were adjusted for the baseline concentration; bars represent 95% confidence limits. Values without a common lowercase letter are significantly different, $P < 0.05$. [1]n = 16 because of missing values. Reproduced with permission from reference 63.

highlight the potential role of dairy products in prevention and/or treatment of hypertension and support the current recommendations for the consumption of 2–3 servings low-fat dairy products/d (5).

Further studies have investigated the potential antihypertensive effects of bioactive lactotripeptides found in fermented milk and yogurt products. Several RCTs and meta-analyses showed that some tripeptides derived from milk proteins, such as iso-leucine-proline-proline and valine-proline-proline, decrease BP to a moderate extent through putative mechanisms that may involve the inhibition of angiotensin-converting enzyme, the production of vasodilators, or an effect on sympathetic nervous activity (66, 67). The effect is greater in Asian subjects than in European subjects. Although a small effect on BP was shown, predominantly systolic BP, the results suggested that rather small daily dosing of lactotripeptides in fermented dairy products may offer an option for the nonpharmacologic treatment of prehypertension or mild hypertension as part of lifestyle advice.

Milk-derived bioactive peptides exert several other important health-promoting activities, aside from their antihypertensive effect, including involvement in the regulation of insulinemia, modulation of the lipid profile, and stimulation of the satiety response, all of which may affect the prevention and treatment of metabolic syndrome and its complications (68). Other activities of bioactive peptides under investigation include antimicrobial, antioxidative, immunomodulatory, and opioid- and mineral-binding effects, which may be targeted to new therapeutic solutions concerning carcinogenic intoxications, treatment of diarrhea, reduction of intestine pathogens, and supporting natural immune defense; and these are reviewed elsewhere (69).

CONCLUSIONS

The consumption of dairy products has been shown to have a beneficial effect on risk factors that contribute to the metabolic syndrome, including dyslipidemia, insulin resistance, BP, and abdominal obesity, which together markedly increase the risk of diabetes and CVD. Dairy products provide valuable nutrients, including protein and calcium, and the consumption of dairy products in observational studies, and to some extent in RCTs, is associated with reduced risk of body fat gain and obesity as well as CVD. Fermented milk products, particularly yogurt, may also exert beneficial probiotic effects. Recent studies have questioned the role of saturated fat, and both observational studies and meta-analysis show that high-GI carbohydrates and n–6 PUFAs may increase cardiovascular risk if they replace saturated fat. However, the effect of particular foods on CAD cannot be predicted solely by their content of total SFAs because individual SFAs have different effects on CAD risk, and major food sources of SFAs contain other nutrients influencing CAD risk. Cheese is an example. Dairy products such as cheese do not exert the negative effects on blood lipids as predicted solely by the content of saturated fat. Calcium and other bioactive components may modify the effects on LDL cholesterol and triglycerides. Thus, the effect of diet on a single biomarker is insufficient evidence to assess CAD risk; a combination of multiple biomarkers and epidemiologic evidence using clinical endpoints is needed to substantiate the effects of diet on CAD risk. Further research is needed to clarify the role of SFAs compared with carbohydrates in CAD risk and to compare specific foods to appropriate alternatives.

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