Whole dairy matrix or single nutrients in assessment of health effects: current evidence and knowledge gaps[1,2]

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ABSTRACT

Foods consist of a large number of different nutrients that are contained in a complex structure. The nature of the food structure and the nutrients therein (i.e., the food matrix) will determine the nutrient digestion and absorption, thereby altering the overall nutritional properties of the food. Thus, the food matrix may exhibit a different relation with health indicators compared to single nutrients studied in isolation. The evidence for a dairy matrix effect was presented and discussed by an expert panel at a closed workshop, and the following consensus was reached: *1*) Current evidence does not support a positive association between intake of dairy products and risk of cardiovascular disease (i.e., stroke and coronary heart disease) and type 2 diabetes. In contrast, fermented dairy products, such as cheese and yogurt, generally show inverse associations. *2*) Intervention studies have indicated that the metabolic effects of whole dairy may be different than those of single dairy constituents when considering the effects on body weight, cardiometabolic disease risk, and bone health. *3*) Different dairy products seem to be distinctly linked to health effects and disease risk markers. *4*) 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. *5*) In conclusion, the nutritional values of dairy products should not be considered equivalent to their nutrient contents but, rather, be considered on the basis of the biofunctionality of the nutrients within dairy food structures. *6*) Further research on the health effects of whole dairy foods is warranted alongside the more traditional approach of studying the health effects of single nutrients. Future diet assessments and recommendations should carefully consider the evidence of the effects of whole foods alongside the evidence of the effects of individual nutrients. Current knowledge gaps and recommendations for priorities in future research on dairy were identified and presented. *Am J Clin Nutr* 2017;105:1033–45.

Keywords: bioavailability, blood lipids, calcium, dairy nutrients, dairy protein, dairy structure, fermented dairy, MFGM, phosphorous, whole dairy

INTRODUCTION

The nutritional evaluation of the relation between diet and health has traditionally focused on individual food constituents such as proteins, fats, carbohydrates, and micronutrients separately. This reductionist approach (1), which links one nutrient to one health effect, may partly explain some of the discrepancies between a food's predicted health effect on the basis of its nutrient content and its actual health effect when consumed as a whole food. A diet does not consist of single nutrients but of

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whole foods, either alone or alongside many other foods as part of a meal. Foods have complex structures both physically and nutritionally, which affect digestion and absorption and may generate interactions within the food matrix, thereby altering the bioactive properties of nutrients in ways that are not predictable from the nutrition-label information.

Studies have shown that the food matrix can modify the nutritional properties of a food (2, 3). Plant-based foods contain cellular structures that need to be broken down before the encapsulated nutrients and bioactive compounds can be released and absorbed. This breakdown may be achieved by processing (e.g., industrial processing and cooking) and by oral mastication, but despite this, the bioavailability of nutrients may be limited in some foods (3, 4). An example is almonds, for which the food matrix attenuates postprandial lipemia after consumption (3). A slower release rate of nutrients from naturally encapsulated systems was shown to increase satiety after consumption (5). This paradigm may also apply to other foods such as dairy products (6, 7). Dairy products are major sources of high-quality protein and calcium, and their nutritional value has been well recognized (8). However, dairy products are also a major contributor to the saturated fat in the diet and have thus been targeted as one of the main dietary causes of cardiovascular disease (CVD)[20] because saturated fat increases LDL cholesterol (9). The majority of current dietary guidelines have included dairy products as part of a healthy diet but have recommended the consumption of low-fat or fat-free versions to reduce intake of saturated fat (the US population goal is to reduce saturated fat intake to $<10\%$ of total energy intake) (10). However, it has been questioned whether the current dietary recommendations on dairy consumption have taken full account of the effects of whole foods or if they have relied on extrapolations of health effects of single nutrients that are contained in dairy. A difficulty in many epidemiologic studies that have examined dairy intake in relation to health has been the broad categorization of dairy foods. Some studies have referred to dairy as one homogenous food group, whereas other studies have attempted to divide dairy foods into low-fat dairy and high-fat dairy. However, these terms lack a universal standard definition and can lead to dairy products being differentially categorized by different researchers. In addition, these terms do not take into account the different dairy food matrices (i.e., the sum of dairy nutrients within the specific dairy food structure). Because of differences in dairy matrices between various types of dairy products, these foods may have distinct effects on health. Hence, a focus on the dairy matrix rather than on dairy nutrients would allow for the investigation of the health effects of dairy products on the basis of how they are actually consumed by the population.

AIM AND METHODS

The current paper was based on presentations, discussions, and conclusions from a workshop on the dairy matrix. The closed consensus workshop of invited scientists was arranged by the co-chairs AA and IG and was held at Bernstorff Slot, Gentofte, Denmark, 28–29 September 2016. The workshop program and speakers were selected by the co-chairs. A total of 19 experts were initially identified to represent different scientific areas within the dairy matrix. The 19 scientists were invited to the workshop, but 5 scientists declined to participate, and 2 of the 5 scientists suggested replacements for their participation. Hence, 18 scientists consented to participate in the workshop, and 10 of these individuals were invited to present research on the dairy matrix within their scientific areas of expertise. Each presentation was allocated a discussant scientist who was asked to challenge the content of the presentation to achieve a balanced view of the evidence. The overall aim of the workshop was to exploit the synergy between various scientific areas to reach a more-comprehensive understanding of the dairy matrix as well as to identify gaps in the existing knowledge and currently missing evidence. Before the workshop, speakers were asked to write an abstract on the basis of 3–5 key publications within their area of research that have contributed knowledge about the dairy matrix. A total of 42 background publications were chosen from the literature, and the data and viewpoints from these publications, including additional literature, were presented at the workshop. Each presentation was challenged by an extensive discussion that was held in plenum. The workshop was rounded off with group sessions that aimed to identify gaps in the existing knowledge (**Table 1**), and subsequently, the discussion from these sessions were presented and discussed in a plenary session. The outcome of the workshop is presented in this scoping review, which should act as a primer for future research. All workshop participants were from higher-education institutions or research institutes; hence, no industrial representatives or sponsors participated in the workshop or contributed to the scientific paper.

EVIDENCE OF A DAIRY MATRIX EFFECT: SUMMARY OF CONSENSUS AND CONCLUSIONS FROM THE WORKSHOP

The major dairy components that have been shown to affect human health are fat, protein (whey and casein), minerals (calcium, magnesium, and phosphate), sodium, and the components of the milk fat globule membrane (MFGM) (i.e., the biological membrane that surrounds the lipid droplets in milk). Dairy products are heterogeneous in terms of the contents of these components as well as their physical structures (**Table 2**). Although cheese has a high fat content, its composition is more similar to that of yogurt and milk than to that of butter because of protein, mineral, and MFGM contents. High-fat dairy products, with the exception of butter, are specifically rich in the MFGM (11). Yogurt and cheese are both fermented dairy products that contain bacteria with a potential ability to produce bioactive peptides and short-chain fatty acids (SCFAs). However, compared with yogurt and milk, cheese has higher contents of calcium, protein (mostly casein with only small amounts of whey protein), fat, and sodium. Moreover, the structure of cheese is more solid, whereas yogurt has a gel structure, and milk has a liquid structure. For cheese, there are numerous methods of production and ripening, and these methods influence the structure and the extent of protein and fat degradation. In general, for fermented dairy products, the bacterial culture used as well as the types and amounts of ingredients such as stabilizers, texturizers, and flavors are also highly variable. Because of differences in the compositions and structures of different dairy foods, it is plausible that intakes of these foods have different effects on health and even more so when compared with intake of a single nutrient (i.e., a

[20] Abbreviations used: BMD, bone mineral density; CHD, coronary heart disease; CVD, cardiovascular disease; MFGM, milk fat globule membrane; SCFA, short-chain fatty acid; T2D, type 2 diabetes.

TABLE 1
Identified gaps in the existing knowledge and future research questions[1]

Epidemiology
How should high-fat and low-fat dairy foods be defined? Does it make sense to pool low-fat and high-fat dairy products when considering the differences in active components and structures between various types of dairy products?
Epidemiologic studies should recognize that milk, yogurt, cheese, butter, and cream are each unique (in other ways apart from their fat contents) and, hence, should be studied accordingly.
Heterogeneity in observational studies needs to be thoroughly addressed in the analysis of future studies (e.g., via stratification). Intake amounts, types, and fortification practices vary between nations, sexes, and age groups, and genetic variation may also exist.
Analysis that is based on observational data from which certain foods are substituted with others is a new but promising approach. More studies that use such an analysis are warranted to determine the optimal diet composition for disease prevention. However, analyses of the substitution of dairy fat with other fats should be supplemented by analyses in which different types of dairy foods are replaced by other relevant foods (e.g., the replacement of cheese for plant oil is not a realistic dietary choice from a food perspective).
To what extent is intake of dairy products a marker of overall healthier or unhealthier diets and lifestyles?
What are the facilitators and barriers to dairy product consumption in different age groups?
Bone health
Protein requirements in children are extrapolated from nitrogen-balance studies in adults. Should bone-outcome measures be used to set protein requirements in children?
Is the amino acid composition of protein important to bone health? Is there an optimal amino acid composition for bone remodeling?
Does fermentation of dairy products have an impact on bone, and if so, what are the mechanisms?
Protein functionality
More data are needed on protein-ileal digestibility of dairy products as well as of other protein sources.
Is there an optimal protein source for the elderly, and does it differ from that of a younger population?
How can the anabolic protein threshold consistently be achieved in the elderly? Is a certain intake of protein in each meal required for optimal muscle-protein synthesis? Should protein recommendations for the elderly be increased because of a higher anabolic threshold?
Proteins are essential for growth, but some amino acids can also act as signals and stimulate the production of other compounds such as IGF-1. It is still unknown whether the endocrine functions of proteins are affected by the dairy matrix.
It is uncertain whether identified bioactive peptides from dairy can be absorbed intact into the blood and whether these peptides have a sufficiently long half-life to exert metabolic effects.
Quantitative data on bioactive peptide release during digestion are lacking.
Do dairy protein or dairy processing types cause different effects on the gut-microbiota composition and activity?
Fat functionality
Does it matter whether the membrane of the MFGM is disrupted, or is the presence of phospholipids the determinant for the metabolic effect of the MFGM? Could a potential difference be explained by the intrinsic proteins and enzymes of the MFGM?
Could the MFGM be involved in the metabolic programming of infants?
What is the metabolic importance of the milk-fat globule structure (homogenized compared with nonhomogenized milk-fat)?
RCTs in humans confirming the suggested specific effect of fermented dairy on insulin sensitivity remain to be conducted.
What is the impact on health of a liquid and solid state of dairy fat (e.g., melted cheese compared with solid cheese)?
What is the precise role of calcium in reduced fat digestion? Fecal calcium–fatty acid soaps need to be chemically confirmed.
What is the role of dairy as bile acid sequestrants? Is phosphate responsible for the increased bile acid excretion, and is there a dose response effect?
Studies with free-living designs have often shown lower effect sizes than have studies with highly controlled designs. It has to be clarified whether the effects of the various mechanisms have a magnitude to impose an effect in the whole diet setting.
What is the role of fat in different dairy matrices on the regulation of nonlipid cardiometabolic risk markers (e.g., inflammation and oxidative stress)?
Can metabolomic and lipidomic approaches be used to explain the unknown metabolic pathways of action of various dairy matrices?
Digestion kinetics
The structure that a food adopts in the stomach is essential to understand its digestion behavior. Research has not been sufficiently conducted on the gastric residence time and postprandial responses to different dairy matrices.
The postprandial kinetics after cheese intake may likely depend on the coagulation method used during cheese processing. It should be investigated whether cheese that is produced solely via acidification (e.g., cream cheese) or rennet (most cheeses) affects the digestion kinetics and appetite differently. Also, it should be investigated whether the postprandial kinetics differ after intake of soft and hard cheese or after intake of cheeses that are produced with different ripening methods.
More research is needed on the effects of dairy processing (e.g., UHT and cooking) on digestion kinetics.

[1] MFGM, milk fat globule membrane; RCT, randomized controlled trial; UHT, ultrahigh temperature.

dietary supplement). This concept was explored at the workshop, and the evidence is summarized in the scoping review that follows, which was structured according to the categories of experimental designs and the area of health or disease.

Evidence from meta-analyses on observational studies on dairy products and disease risk

The majority of observational studies on dairy products and disease risk have either focused on dairy components such as calcium, fat, and protein or on dairy products either as a homogenous food group or according to high or low fat contents. However, disregarding the differences in the composition and food matrix between various types of dairy products may have blurred the analyses and may have led to a misinterpretation of the true associations. The number of observational studies that have focused on dairy products as whole foods is currently increasing, and some of these studies have, in recent years, been pooled in a number of meta-analyses with different endpoints. The results of the meta-analyses on dairy product

TABLE 2
Bioactive components and supramolecular structures in different dairy products[1]

	Calcium, mg/100 g	Phosphorus, mg/100 g	MFGM,[2] mg/100 g	Protein,[3] g/100 g, type	Fermented	Fat structure[4]	Protein network
Cheese[5] (25% fat)	659	510	150	23.2, Casein	Yes	MFG/aggregates/free fat	Solid/viscoelastic
Milk (skimmed, 0.5% fat)	124	97	15	3.5, Whey/casein	No	Tiny native MFG/potential MFGM fragments	Liquid
Milk (whole, 3.5% fat)	116	93	35	3.4, Whey/casein	No	Native MFG or homogenized milk fat droplets/potential MFGM fragments	Liquid
Yogurt (1.5% fat)	136	99	15	4.1, Whey/casein	Yes	Native MFG or homogenized milk fat droplets/potential MFGM fragments	Gel/viscoelastic
Cream (38% fat)	67	57	200	2, —	No	Native MFG or homogenized milk fat droplets/potential MFGM fragments	Liquid
Butter	15	24	—	<1, —	No/yes[6]	Continuous fat phase (water-in-oil emulsion)/MFGM-residue traces	—

[1] All values are approximate amounts. MFG, milk-fat globule; MFGM, milk-fat globule membrane.
[2] General estimation on the basis of Dewettinck et al. (11) and Conway et al. (12).
[3] According to food-composition tables from The Technical University of Denmark (13).
[4] General estimation on the basis of Michalski (14) and Michalski et al. (15) and references therein.
[5] Semihard Danbo type, as a point example among many different cheese types.
[6] Depends on the production method used. With indirect biological acidification, starter culture is added to the butter after churning.

intake and risks of CVD, hypertension, and type 2 diabetes (T2D) were as follows.

Intake of dairy products and risk of CVD

In a meta-analysis of prospective cohort studies by Qin et al. (16), total dairy consumption was inversely associated with overall risks of CVD (RR: 0.88; 95% CI: 0.81, 0.96) and stroke (RR: 0.87; 95% CI: 0.77, 0.99). For the specific dairy products, only cheese intake was inversely associated with risk of stroke (RR: 0.91; 95% CI: 0.84, 0.98) and risk of coronary heart disease (CHD) (RR: 0.84; 95% CI: 0.71, 1.00). However, the meta-analysis was limited by broad categories of dairy and outcome variables, and in addition, no dose-response analyses were conducted. Nevertheless, the findings were supported by a recent meta-analysis in which total dairy intake was associated with lower risk of stroke (RR: 0.91; 95% CI: 0.83, 0.99), and cheese intake was associated with lower risks of CHD (RR: 0.82; 95% CI: 0.72, 0.93) and stroke (RR: 0.87; 95% CI: 0.77, 0.99) (17). Nevertheless, the dose-response analyses did not support an inverse dose-response relation between the dairy variables and CHD or stroke after adjustment for within-study covariance. In the most-recent meta-analysis of dairy intake and stroke, which included 18 cohort studies with 8–26 y of follow-up and a total of 762,414 individuals and 29,943 stroke events, total dairy intake was not associated with stroke risk (18). For specific dairy products, a daily 200-g increment in milk intake was associated with a 7% lower risk of stroke (RR: 0.93; 95% CI: 0.88, 0.98; $P = 0.004$) with considerable heterogeneity ($I^2 = 86$). RRs were 0.82 (95% CI: 0.75, 0.90) in East Asian countries and 0.98 (95% CI: 0.95, 1.01) in Western countries (median intakes: 38 and 266 g/d, respectively) with less, but still considerable, heterogeneity within the continents. On the basis of a limited number of studies, high-fat milk, but not low-fat milk, was directly associated with stroke risk. In contrast, cheese intake was marginally inversely associated with stroke risk (per 40 g/d: RR, 0.97; 95% CI, 0.94, 1.01), which was consistent with previous findings. No association was shown for yogurt, but total intake of fermented dairy products (combining ≥2 of the following products: cheese, yogurt, and sour milk) tended to be associated with a 9% (RR: 0.91; 95% CI: 0.82, 1.01) lower risk of stroke per 200 g/d with no indications of a nonlinear association. A beneficial effect of cheese intake was further supported by another meta-analysis of prospective cohort studies in which cheese intake was inversely associated with total CVD (RR: 0.90; 95% CI: 0.82, 0.99), CHD (RR: 0.86; 95% CI: 0.77, 0.96), and stroke (RR: 0.90; 95% CI: 0.84, 0.97) (19). The inverse association between cheese intake and stroke was of particular interest because of the high sodium content of cheese. Furthermore, a recent meta-analysis suggested that butter consumption was not significantly associated with CVD, CHD, or stroke despite the high content of SFAs (20).

Intake of dairy products and risk of hypertension

The most-recent meta-analysis to assess the relation between dairy intake and hypertension included 9 prospective cohort studies with a total of 57,256 individuals and 15,367 incident hypertension cases (21). Linear inverse associations were shown between intake of total dairy, low-fat dairy, and milk and incident hypertension. Intake of low-fat dairy was associated with 4% lower risk of hypertension (RR: 0.96; 95% CI: 0.93, 0.99) per 200 g/d, whereas high-fat dairy intake was not associated with hypertension (per 200 g/d: RR: 0.99; 95% CI: 0.95, 1.03). A significant inverse linear association was shown between milk intake and incident hypertension with a pooled RR for total milk intake per 200 mL of 0.96 (95% CI: 0.93, 0.99). No associations were shown between total intake of fermented dairy, cheese, or yogurt and risk of hypertension. Thus, specifically low-fat dairy products and milk, in particular, seem to be linked to lower risk of hypertension.

Intake of dairy products and risk of T2D

The most recent meta-analysis on dairy intake and T2D included 22 cohort studies with a total of 579,832 individuals and 43,118 T2D cases (22). Total dairy intake was inversely associated with T2D risk (per 200-g/d increment: RR: 0.97; 95% CI: 0.95, 1.00; $P = 0.04$) with a suggestive but similarly linear inverse association for intake of low-fat dairy (per 200 g/d: RR: 0.96;

95% CI: 0.92, 1.00; $P = 0.072$). The inverse association was strongest for populations >60 y old (per 200 g/d: RR: 0.84; 95% CI: 0.77, 0.93). When analyzed according to the type of dairy products, a nonlinear, strong inverse association was shown between yogurt intake and T2D (at 80 compared with 0 g/d: RR: 0.86; 95% CI, 0.83, 0.90; $P < 0.001$). At higher yogurt intakes, a leveling off in the risk association was evident. In addition, low-fat fermented dairy was not associated with T2D risk, but when high-fat fermented dairy was included, a significant 12% lower risk was shown with intake of 40 g/d, above which there was no further reduction in the RR of T2D. Intakes of cheese, cream, total milk, low-fat milk, high-fat milk, and total high-fat dairy were not shown to be associated with T2D risk. Furthermore, butter has been suggested to be inversely associated with the incidence of T2D (RR: 0.96; 95% CI: 0.93, 0.99; $P = 0.021$) (20). In summary, the dairy products yogurt and butter as well as the group of high-fat fermented dairy products seem to be inversely associated with T2D.

Considerations for future observational studies on dairy and cardiometabolic risk

Because observational studies have only recently started to examine associations for different types of dairy products, the analyses of individual dairy products in the presented meta-analyses were based on a low number of studies. Specifically, data on yogurt and cheese intake from observational studies have been limited, which was likely due to a previous focus on milk intake. However, the latter still warrants further investigation considering recent findings from 2 Swedish cohorts that reported that high total milk intake was associated with higher mortality (23). On the basis of the current literature, it can be recommended that future epidemiologic studies should provide more extensive details about the types of dairy products, including fat contents, as well as details within the specific dairy group (e.g., cheese and yogurt types). In addition, because amounts and types of dairy products that are consumed vary across countries and continents, there was heterogeneity in several of the presented meta-analyses. Future studies should address differences in intakes across continents (e.g., with the use of stratification in the statistical analyses).

The advantages of observational studies are that they generally represent large populations, examine long-term associations with disease events, and assess real-life exposure before the occurrence of the outcome. However, a disadvantage is that confounding cannot be eliminated in observational studies, and therefore, evidence for causality is generally weak. The associations between dairy intake and disease risk could potentially be influenced by residual confounding. For instance, the overall diet quality may differ between dairy and nondairy consumers, and different types of dairy may cluster within different dietary patterns. Only a few epidemiologic studies have investigated how dairy intake affects diet quality. One study showed that intake of low-fat dairy products clusters within a healthy type dietary pattern, whereas the opposite effect seems to apply for intake of high-fat dairy products (24). Furthermore, another study showed that yogurt consumption was associated with an improved diet quality including a higher consumption of fruit and vegetables, whole grains, and dairy products (25). Nevertheless, the effects of different types of dairy products on diet quality may very likely be population specific.

Observational studies have supported distinct relations between intakes of specific types of dairy foods and risks of CVD, hypertension, and T2D but have not provided evidence of causality; hence, randomized controlled trials have to be considered. In the following sections, studies are presented that compared whole dairy products with dairy constituents or with other dairy products with or without matching dairy constituents.

Intervention studies that compared dairy products to dairy constituents (supplements)

One way of investigating whether there is a specific effect of the dairy matrix on health is to examine intervention studies that have compared a whole dairy food with an isolated nutrient of interest from that food, to explore if there is a difference in the outcome with the whole food than with the isolated nutrient. The results from intervention studies that fit this criterion were as follows.

Effect of whole dairy foods compared with effect of dairy constituents on body weight and body composition

Two studies investigated if a whole dairy food had a different effect on body weight and body composition relative to calcium or milk protein. The first study in overweight and obese premenopausal women compared the effects of cow milk (3 servings/d), soy milk fortified with calcium (3 servings/d), a calcium-carbonate supplement (800 mg/d), and a control diet (no addition) on body weight and waist and hip circumferences (26). All groups consumed an energy-deficit diet (500 kcal/d) for a period of 8 wk. The greatest reductions in body weight, BMI, and body fat were in the cow-milk group. Weight loss in the cow-milk group was significantly greater than that in the control or soy-milk group (weight loss: 5.8%, 4.3%, and 3.8%, respectively) but not relative to the effect of the calcium supplement (4.8% weight loss). These results suggest that there is a dairy matrix effect for the calcium and protein that are contained in milk. Another study compared 12 wk of intake of skimmed milk, casein, or whey protein with water intake (0.5 L/d) on body composition and leptin concentrations in overweight adolescents (27). Compared with water, skimmed milk and milk proteins increased lean mass, fat mass, and leptin concentrations, thereby indicating a dairy protein effect rather than a dairy matrix effect.

Effect of whole dairy foods compared with effect of dairy constituents on markers of CVD risk

The effect of whole dairy compared with that of dairy constituents on cardiovascular outcomes has also been investigated in a number of studies. Previously, it was suggested that calcium supplements were associated with increased risks of CVD events and mortality (28), and hence, it was assumed that calcium-rich foods, such as dairy, would exhibit the same association. However, an acute increase in calcium intake from dairy products (milk and low-fat yogurt) was shown to attenuate postprandial lipemia, whereas supplementary calcium-carbonate intake did not exert a similar effect (29). Another acute study investigated the effect of a calcium supplement (500 mg) compared with that of a meal with a calcium supplement, a dairy product meal, or a calcium-fortified juice on serum calcium and phosphate over a period of 6 h after consumption in a randomized crossover manner (30).

The elevation in serum ionized and total calcium concentrations was delayed when the supplement was consumed with a meal but was most delayed after the dairy product meal, thereby indicating a dairy matrix effect. The authors speculated that the rapid increase in serum calcium with the calcium supplement may partly explain the contrasting cardiovascular effects of calcium supplements and calcium in dairy foods. The different responses to calcium that has been consumed as a supplement or as a dairy product may be due to differences in the chemical forms of calcium [inorganic calcium carbonate or citrate in supplements compared with organic calcium phosphate (hydroxyapatite) in dairy products] or to interactions between calcium and other components in the dairy matrix.

The effect of whole dairy foods on blood pressure may also differ from that of a calcium supplement. One study of an older date investigated the effect of 6-wk intake of milk (1180 mg Ca, 1650 mg K, and 110 mg Mg) compared with that of a mineral-reduced milk (95 mg Ca, 580 mg K, and 10 mg Mg) in an otherwise low-calcium diet (<500 mg/d) on blood pressure (31). The mean systolic blood pressure change with intake of milk (−4.1%) was significantly greater than that with intake of the mineral-reduced milk (−1.3%). This result indicated a small hypotensive effect of milk intake, which was at least partly explained by the mineral content of milk. More recently, a randomized, double-blind, crossover study investigated the blood pressure–lowering effect of Grana Padano cheese (30 g/d) compared with that of a placebo (which consisted of flavored bread mixed with fats and salts in concentrations that were equal to those of the Grana Padano cheese) in a 2-mo crossover study in mildly hypertensive subjects (32). Intake of Grana Padano cheese resulted in a significant decrease in systolic blood pressure and diastolic blood pressure compared with the effect of placebo intake. Therefore, SFAs and salt may have a lower impact on blood pressure when these are present in the cheese matrix, or other components in the cheese matrix (e.g. bioactive peptides) may counteract the effects of SFAs and salt.

Effect of whole dairy foods compared with effect of dairy constituents on bone health

The importance of the dairy matrix on bone health has been studied in 2 trials that compared whole dairy products with dairy nutrients. Fermented dairy products may have a distinct positive effect on the mineral and bone balance because, in addition to the supply of calcium, phosphorus, and protein, fermented dairy products also contain probiotic bacteria. These bacteria may alter the gut microbiota and enhance the capacity to translocate calcium across the intestinal epithelium (33). A 2-y randomized controlled trial examined the effects of calcium supplements, calcium plus vitamin D supplements, or a dairy product (cheese) on bone mass accrual and body composition in 10- to 12-y-old girls with low habitual calcium intake (34). The cheese supplementation resulted in a higher percentage change in the cortical thickness of the tibia than did the placebo, calcium supplementation, or calcium plus vitamin D supplementation. A per-protocol analysis showed that cheese supplementation resulted in a higher whole-body bone mineral density (BMD) in subjects with >50% compliance. Thus, cheese had a superior effect on bone mass accrual compared with that of calcium or calcium plus vitamin D supplementation. Another randomized controlled trial investigated the effect of dairy products or a calcium supplement, both of which provided 1200 mg Ca/d, on markers of bone metabolism and BMD relative to the effects in a control group (35). After 12 mo, compared with the calcium-supplement group and the control group, the dairy group had greater improvements in pelvic and spinal densities and total BMD. Both trials supported a dairy matrix effect on bone health.

Partial conclusion on dairy products compared with dairy constituents (supplements)

To date, studies that have examined the effect of whole dairy foods compared with that of single dairy constituents with focus on body weight, CVD risk, or bone health have provided indications that whole dairy products have a more-beneficial effect on health than do single dairy constituents. This indication supports the concept that dairy products should not be considered equal to a few nutrients but as a function of the total nutrient content within the specific dairy structure. This proposition is worthy of investigation in future trials.

Intervention studies comparing effects of different dairy products on blood lipids while controlling for dietary factors

Different types of dairy products may affect risk markers of disease differently, and this difference could potentially be explained by the additive effects of the active components that are contained in dairy products. A comparison of intake of one type of dairy product with intake of specific dairy components to resemble the composition of another dairy product was investigated in 2 studies.

Tholstrup et al. (36) compared cheese, milk, and butter in whole diets, all of which were balanced for the amount of fat (from cheese, milk, and butter) and for the contents of protein (80% casein and 20% whey protein) and lactose but not of calcium. No significant differences in blood lipids were shown between cheese and milk. However, despite the addition of lactose and milk protein to the butter diet, butter caused significantly higher LDL-cholesterol concentrations and borderline-higher total cholesterol concentrations than cheese did, whereas the effect of milk was intermediate and was not significantly different from that of cheese and butter. Likewise, another study compared cheese intake with intakes of butter and casein and showed a lower total cholesterol concentration and a borderline-lower LDL-cholesterol concentration after the cheese diet than after the butter and casein diet (37). These studies suggested that protein and lactose were not the determinants of the difference between cheese and butter on blood lipids.

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Different types of dairy products as whole foods have also been compared in a number of intervention studies that have illustrated the effects of these foods in the actual forms that they are consumed by the population.

Several studies with free-living or highly controlled full-diet designs have shown that intake of cheese resulted in lower LDL cholesterol than did intake of butter (2, 38, 39). These

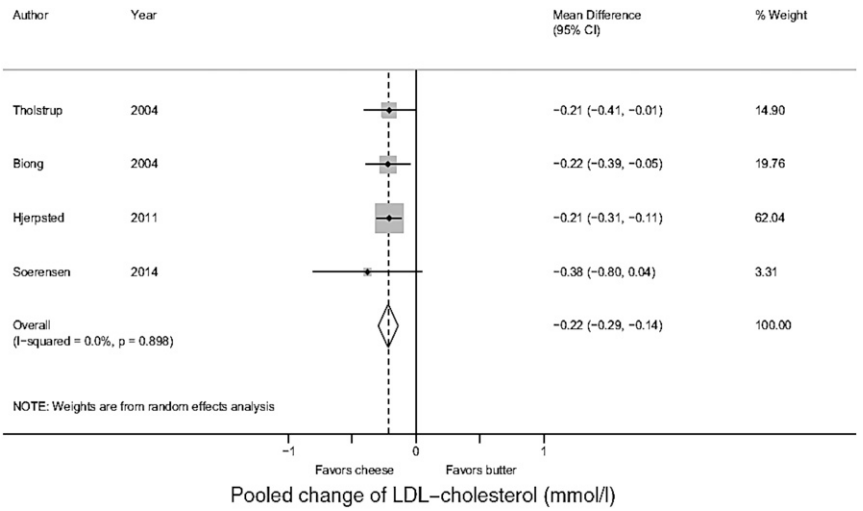

FIGURE 1 Forest plot from a meta-analysis of intervention studies comparing the effects of cheese consumption with those of butter consumption on plasma LDL-cholesterol concentrations. Data shown include author names, year of publication, RRs (95% CIs), and weights to the overall meta-analysis. Study-specific RRs (95% CIs) are represented as shaded squares. Areas of the squares illustrate the weighting within the overall meta-analysis. The diamond represents the pooled RR (95% CI). I^2 indicates the percentage of heterogeneity that was due to between-study variation. Reprinted from reference 40 with permission.

findings were substantiated in a recent meta-analysis of randomized controlled trials (40) (**Figure 1**). The trials suggested that fat that is consumed in isolation (butter) has a different effect than fat that is delivered in the cheese matrix and, thus, provided support of a dairy matrix effect. One of the intervention studies also proposed that cheese did not increase LDL-cholesterol concentrations as compared with a habitual diet with a lower saturated fat content (2). One of the intervention studies, in addition to butter and cheese, also included a milk comparison (38). In the study, cheese and milk were consumed in amounts that provided similar amounts of fat, protein, and calcium. Compared with the butter-control diet, in which protein and fat, but not calcium, were balanced with the amounts in the cheese and milk diets, both cheese and milk attenuated the increase in LDL cholesterol compared with the effect of butter. This result provided support of an effect of dairy calcium on the LDL-cholesterol response, whereas fermentation did not seem to be involved because cheese is fermented but milk is not. It may be important that the fat and calcium are embedded in the same food matrix and that a similar effect cannot be achieved by simply adding calcium to a diet with butter. A study in pigs showed that regular-fat cheese has an HDL-cholesterol–increasing effect compared with that of butter, whereas this effect was not shown with a reduced-fat cheese plus butter that matched the milk-fat content of the regular-fat cheese (41). A tendency toward increased HDL cholesterol from intake of regular-fat cheese but not reduced-fat cheese compared with a carbohydrate control, was also shown in a larger study in humans (42). However, there was no difference in the LDL-cholesterol concentration after intakes of the regular-fat cheese and reduced-fat cheese despite higher saturated fat intake with the consumption of the regular-fat cheese, which suggested that there is an effect of the cheese matrix on the saturated fat in the regular-fat cheese.

The effect of cheese and full-fat yogurt supplementation on blood lipids was also compared in a large, parallel, multicenter study (43). Despite slightly higher energy and calcium intakes from yogurt consumption than from cheese consumption, the 2 dairy products did not affect the blood lipid profile differently.

Furthermore, one study compared the effect of 2 wk of intake of buttermilk (rich in MFGM) or of larger intake of skimmed milk (providing a similar amount of fat as in the buttermilk) with that of intake of butter (low in MFGM) on the blood lipid response (44). Although only a few details were given, the authors reported that a smaller intake of buttermilk was equally efficient as was a larger intake of skimmed milk in lowering total cholesterol, whereas butter intake increased total cholesterol. A more recent study investigated 12 wk of intake of traditionally produced buttermilk (rich in MFGM) compared with that of skimmed milk (low in MFGM) in diets that were supplemented with or without lutein-enriched egg yolk. Egg-yolk consumption significantly increased total-cholesterol and LDL-cholesterol concentrations. Buttermilk consumption did not prevent the total- and LDL-cholesterol–raising effects of egg-yolk consumption compared with the effects of skimmed-milk consumption although there was a tendency toward lower total cholesterol (45). In the 2 studies presented, calcium, which is present in both buttermilk and skimmed milk, may have attenuated the blood lipid response after consumption, whereas this effect would not have applied to butter consumption. Hence, the dairy matrix may determine the impact size of the MFGM content. Nevertheless, the studies suggested a potential role of the MFGM in the regulation of the blood cholesterol balance.

How dairy matrix components interfere with the assumed effect of saturated fat on lipid metabolism

Calcium, phosphorus, MFGM, and starter cultures (in the fermented dairy types) are all dairy constituents that have been suggested to contribute to the modification of the blood lipid response to SFA intake. The blood lipid response is presumably attenuated by decreasing intestinal fat absorption and bile-acid recycling, the modulation of the gut microbiota, or the alteration of gene expression.

Lowering of fat digestibility by dairy constituents

A reduced intestinal absorption of fat from dairy products that are rich in calcium, phosphorus, and the MFGM (such as cheese) has been shown by the increased fat excretion in feces (38, 46–48) and a reduced plasma chylomicron triglyceride concentration in the postprandial state (29). However, differences within the dairy matrix may influence the level of fat and energy absorbed by the gut. A study showed higher fecal energy excretion in pigs that were fed a diet with regular-fat cheese than a diet with butter, whereas a diet with reduced-fat cheese and butter caused a nonsignificant intermediate response (41). Furthermore, a study in humans that examined equally high intakes of reduced-fat cheese and regular-fat cheese showed no difference in body weights between groups after 3 mo of intake despite higher energy intake with the consumption of regular-fat cheese (42). The results of these studies suggest that there is an enhanced fecal fat excretion with intake of regular-fat cheese, thereby providing support of a dairy matrix effect.

Lowering of fat digestibility by calcium and phosphate. Two mechanisms for calcium have been suggested that underlie a reduced intestinal fat absorption after dairy intake. The first mechanism is the precipitation of calcium and free fatty acids as largely insoluble calcium–fatty acid soaps. The second mechanism is the precipitation of calcium and phosphate in insoluble amorphous calcium phosphate, which adsorbs bile acids and possibly also fatty acids to the surface and, hence, increases fecal bile acid and fat excretion (49–52). In vitro and in vivo, saponification was suggested to have increased with an increasing fatty acid saturation and chain length (49, 53). However, a study showed significantly higher fecal excretions of all fatty acid groups (SFAs, MUFAs, and PUFAs) in humans who consumed a high-calcium diet (with low-fat dairy) than a low-calcium diet (54). Also, when fecal excretions of fatty acids were expressed as percentages of intake, the difference between diets was greater for MUFAs than for SFAs. The fecal excretion of fatty acids probably depends on the location of the fatty acids on the glycerol backbone because fatty acids in the *sn*-1 and *sn*-3 positions are released by lipase (55) and are, therefore, more susceptible to binding by calcium than are fatty acids in the *sn*-2 position. The increase in fecal fat excretion by dairy calcium has been shown in several (38, 47, 54, 56–58) but not all (2, 59) studies. A study by Weaver et al. (59) showed that the change in fecal calcium excretion (by dairy products or a supplement) predicted the change in fecal fat excretion as the fraction of intake. However, this mechanism was not found to affect the energy balance. Energy balance was previously proposed to be influenced by the excretion of calcium–fatty acid soaps mostly in infants (15).

The methods that were used for the extraction of fat have varied between studies and may have resulted in a more or less absolute fat extraction from the feces samples. Also, it is important that fecal fat excretion is expressed as an absolute amount (grams per day) instead of as a concentration in feces because the volume of feces varies within and between subjects. In addition, studies that have chemically characterized the chemical form of fecal calcium have been few and of older dates. Hence, there is a need for new in vivo studies with a chemical characterization of calcium–fatty acid soaps and amorphous calcium-phosphate compounds that preferably focus on the ratios at which fat, calcium, and phosphate appear in whole dairy foods.

Lowering of cholesterol absorption by the MFGM. A study in mice proposed a mechanism whereby the MFGM reduces intestinal cholesterol absorption after dairy intake on the basis of the inhibition of cholesterol micellar solubility (60). It was shown in vitro that, in the presence of buttermilk, the micellar solubility of cholesterol was reduced probably because of the presence of sphingomyelin in buttermilk MFGM fragments (61). Because sphingomyelin is not completely hydrolyzed in the human small intestine, such sphingomyelin-cholesterol complexes suggest a potential ability of the MFGM to limit cholesterol absorption (62); however, such an effect was not confirmed in a study in humans that measured surrogate markers of intestinal fat absorption (63).

Link between fat digestibility and blood lipid response

There has been evidence of a connection between increased fecal fat excretion and an attenuated blood lipid response after intake of dairy products that are rich in calcium, phosphate, and the MFGM. An intervention study in humans showed a strong correlation between fecal fat excretion and changes in total cholesterol and LDL cholesterol after intakes of diets with cheese or milk or butter (**Figure 2**) (38). Also, a crossover study in humans that examined 4 full diets with combinations of low calcium or high calcium and low fat or high fat showed that the response in LDL cholesterol and HDL cholesterol depended on the saturated fat content of the diet, and only the LDL-cholesterol response was attenuated by simultaneous high dietary calcium intake (64). Because the Phosphorus contents of the diets in the study were also high in the high-calcium diets and low in the low-calcium diets, Phosphorus may have contributed to the attenuation of LDL cholesterol. Calcium phosphate was previously shown to increase fecal bile-acid excretion and reduce LDL cholesterol (65). These effects were presumably due to decreased enterohepatic bile-acid circulation and the consequently increased hepatic de novo bile acids synthesis from its precursor cholesterol, which may have led to an upregulation of hepatic LDL-receptor expression and an increased clearance of LDL cholesterol from the circulation. Hence, amorphous calcium phosphate may influence blood lipids through fecal bile-acid excretion.

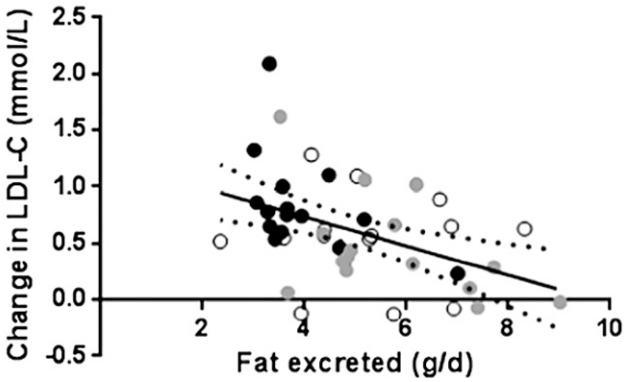

FIGURE 2 Correlations (95% CIs) between changes in LDL cholesterol and fecal fat excretion during the butter-control (black), milk (open), and cheese (gray) periods (R^2 = 0.163, P = 0.002) (n = 15). LDL-c, LDL cholesterol. Reprinted from reference 38 with permission.

Regulation of blood lipid response by MFGM and milk phospholipids

It is still unclear whether the MFGM (intact around the native milk-fat globules or as free released fragments) affects the fecal fat excretion in humans. Some studies have suggested that the MFGM could in fact reduce or prevent the increase in fasting total cholesterol, LDL cholesterol, and triglycerides, usually suspected to be caused by SFA intake (63, 66, 67). In one study, a buttermilk-powder formulation (rich in MFGM fragments) significantly reduced fasting total cholesterol and triglycerides compared with the effect of a placebo powder formulation, whereas the reduction in LDL cholesterol was only borderline significant and strongest in subjects with high baseline LDL-cholesterol concentrations (63). The changes in concentrations of LDL cholesterol and triglycerides were not correlated, which suggested that there are different metabolic pathways of regulation. In addition, the buttermilk formula was shown to increase the plasma lathosterol concentration, which is a surrogate marker of endogenous cholesterol synthesis. In another randomized isoenergetic study, 8 wk of intake of whipping cream (rich in the intact MFGM) did not raise plasma cholesterol in overweight adults compared with the effect of intake of butter oil (emulsified fat depleted of MFGM), which markedly raised the LDL cholesterol (66). Moreover, whipping cream intake differentially regulated 19 genes, and most of the changes in gene expression were correlated with changes in blood lipids. The effects of intake of formulated drinks enriched with milk phospholipids as MFGM concentrates from buttermilk compared with other phospholipid sources on blood lipids have also been investigated in 2 studies. A parallel study tested a drink that was formulated from a buttermilk concentrate, thereby enriched in sphingolipids (25% of MFGM polar lipids in cow milk) compared with a drink that was formulated with skimmed milk and enriched with egg-phospholipid and butter oil (67). No significant difference in blood lipids was shown between groups. Another study included 2 trials that investigated intake of milk-phospholipids (2 g) compared with intake of milk fat and soya phospholipids on lipid metabolism and other risk factors for CVD (68). In the first trial, subjects consumed milk that was enriched with either 2 g milk phospholipids from a buttermilk concentrate or 2 g milk fat for 8 wk. In the second trial, subjects consumed milk that was enriched with either 3 g milk phospholipids from the same buttermilk concentrate or 2.8 g soya phospholipids for 7 wk. The milk phospholipids did not affect plasma lipids, the insulin sensitivity, or inflammatory markers in the 2 trials. In summary, on the basis of these few studies, the effects of formulated drinks that are enriched with the MFGM via a buttermilk concentrate appeared to be less pronounced than the effects of the intact MFGM that are provided by buttermilk, cream, or cheese, which supports a stronger effect of whole dairy (i.e., the dairy matrix compared with its isolated or reformulated constituents). The mechanisms that are induced by the MFGM are unclear and deserve further investigation but might be associated with a decrease in intestinal cholesterol absorption or the regulation of the expression of genes.

Regulation of blood lipid response by dairy matrix fermentation

Intake of fermented dairy products has been shown to have a beneficial effect on blood lipid concentrations. This effect may be due to fermented dairy products favoring a gut microbiota with a specific production of SCFA (69). SCFAs are rapidly absorbed by the colon and metabolized in the liver, and an altered production ratio of SCFAs may influence the blood lipid balance because the serum acetate:propionate ratio has been associated with serum total- and LDL-cholesterol concentrations (70–72). A metabolomics investigation of a study that compared milk, cheese, and butter intakes showed that both cheese and milk intake increased concentrations of fecal SCFAs (73). Specifically, cheese intake increased fecal butyrate, propionate, and malonate concentrations and decreased fecal acetate and glycerol concentrations. Furthermore, there were significant correlations between fecal propionate and butyrate concentrations and LDL-cholesterol concentrations. This outcome indicated that dairy consumption, and especially cheese intake, increases fecal SCFA concentrations or alters the production ratio of these SCFAs, and this effect is likely a result of the modification of the gut microbiota. Low- and high-fat fermented dairy may not have similar impacts on the gut microbiota. A previous study in pigs pointed toward distinct effects of reduced-fat cheese and regular-fat cheese on gut microbiota in diets with equal milk fat (41). Regular-fat cheese caused a lower Firmicutes-to-Bacteroidetes ratio, and compared with a butter control, the changes in the relative abundance of more bacterial genera were shown after intake of regular-fat cheese (e.g., a higher abundance of *Lactobacillus* and *Oscillibacter*).

Studies comparing similar dairy products with different structures or textures on digestion and absorption kinetics, appetite sensations, and muscle-protein synthesis

In addition to the nutrient matrix, the physical structures and textures of dairy products could influence the health effects of different types of dairy foods. Only a few studies have compared different structures or textures of dairy products in relation to absorption kinetics and appetite. One study investigated the effects of a semisolid yogurt (378 g), drinkable yogurt (378 g), dairy beverage (400 mL), and fruit drink (400 mL), which were matched for palatability and energy contents, on subjective appetite sensations (74). Compared with the dairy beverage and fruit drink, the semisolid and liquid yogurts resulted in reduced hunger and increased feelings of fullness. However, subsequent food intake did not differ after intakes of the beverages. Another study, which compared 2 isoenergetic meals with a liquid structure or a semisolid structure, showed a longer gastric emptying time and a prolonged satiety response after the semi-solid meal (grated cheese and low-fat yogurt) (6). These studies suggested that there is a prolonged satiety response after intake of a semisolid dairy matrix and yogurt than a liquid dairy matrix.

Acid and rennet gels of dairy products with identical nutrient compositions have been shown to exhibit major differences in the protein-digestion kinetics and amino-acid bioavailability in pigs (75). A rennet gel that was produced with heat-treated milk showed a prolonged residence time in the stomach compared with that of an acid gel or a stirred acid gel. Also, the rennet gel caused a slower release of milk proteins in the duodenum. A delayed gastric emptying was also seen after intake of yogurt than after intake of milk (76), and yogurt was shown to lower and prolong the jejunal release of protein (77). Furthermore, different dairy matrix structures were shown to affect the

number of identified peptides released with rennet gels inducing 2 and 3 times fewer peptides than induced by milk and acid gels, respectively (78). This result is consistent with the delayed protein-digestion kinetics and amino-acid absorption that has been observed with rennet gels.

The dairy proteins casein and whey are present in different ratios and amounts in dairy foods (Table 2), and these proteins were shown to cause a distinct postprandial release of peptides. Medium-size peptides (750–1050 kDa) were released during 6 h after casein ingestion, whereas larger peptides (1050–1800 kDa) were released during the first 3 h after whey-protein ingestion (79). In the jejunum, twice as many peptides were detected and sequenced after casein ingestion than after whey-protein ingestion, and accordingly, β casein was shown to be the most important precursor of peptides. An acute study in humans in which the protein ratio in the yogurt matrix was manipulated toward a higher whey protein content decreased subsequent ad libitum energy intake compared with the effect of yogurt with lower whey and a higher casein content (80). Also, a study in a murine model revealed a lower body-weight gain for mice that were fed whey protein compared with casein (81). Metabolomics studies in both animals and humans have suggested that this outcome is a result of whey protein affecting endogenous metabolism through the Krebs cycle (81, 82). Therefore, the balance between casein and whey proteins in dairy products may be important for their overall effects on body weight through mechanisms that involved appetite regulation and endogenous energy metabolism. A high protein-digestion rate is necessary in the elderly to induce protein metabolism and prevent age-related sarcopenia because of an age-related higher threshold for the inducement of an anabolic stimulus by plasma amino acids (83). The anabolic threshold is lower in younger adults, and therefore, protein kinetics may be less important in this population group with the exception of elite athletes who have higher substrate requirements. Even small differences in the protein-digestion rate may be sufficient to affect postprandial protein metabolism (84). For dairy products, pasteurization (72°C for 20 s) does not seem to affect the protein-digestion rate, whereas an ultrahigh-temperature treatment (140°C for 5 s) increased the digestion rate (85). The latter effect can probably be explained by heat-induced interactions with whey protein (mainly β lactoglobulin) with the subsequent partial dissociation of the casein micelles.

Homogenization strongly modifies the structure of milk-fat globules, and therefore, the metabolic impact of the consumption of homogenized dairy products has been questioned (86). To our knowledge, the effect of homogenization on lipid-absorption kinetics has not yet been investigated in humans but was investigated in vitro with the use of nutrient-matched formulae, one of which was based on raw milk and one of which was based on homogenized milk (87). An increased postprandial release of free fatty acids during in vitro gastric digestion was observed with the homogenized formula. This was explained as being due to the homogenized formula having a smaller lipid-particle size with an increased relative surface area, which made the lipids more accessible for lipases. Finally, differences in the fat-droplet interface composition was also suggested to affect the digestion kinetics of differently processed milks (88).

In summary, the microstructures and macrostructures of the dairy matrix may influence the metabolic response after consumption. Therefore, different dairy matrix structures should be taken into consideration, in addition to the content of bioactive components, when evaluating the nutritional properties of whole dairy foods. Because different dairy structures may provide a better fit for the dietary needs of individual population groups, this assessment should be further investigated and included when re-evaluating current dietary guidelines. For instance, elite athletes and the elderly may be given the advantage of a high and efficient nutrient-release rate, whereas obese or diabetic persons may benefit from a lower nutrient-release rate.

How the matrix of fermented dairy may affect insulin sensitivity

It has been suggested that different protein sources (i.e., dairy, meat, fish, egg, and plants) are differently associated with risk of T2D (89). Of dairy products, yogurt and cheese, in particular, are associated with lower risk of T2D (18, 90). This association suggests that, in addition to the protein and mineral contents, other bioactive factors in fermented dairy products may influence T2D risk. Ripened dairy products contain branched-chain amino acids and milk-derived peptides. Aside from the antihypertensive effect of milk-derived peptides, these may also be involved in the regulation of insulinemia and the stimulation of the satiety response (91). Bioactive peptides or amino acids that are produced during cheese ripening were recently shown to improve insulin sensitivity and reduce circulating free fatty acids in pigs (56). In humans, postprandial increments in branched chain amino acids from whey (i.e. leucine, valine, and isoleucine) were shown to be correlated with the postprandial insulin response, and insulin responses were shown to be correlated with glucose-dependent insulinotropic polypeptide concentrations (92). Furthermore, a crossover study showed that 6 mo of intake of 4 daily servings of low-fat milk and yogurt, compared with a 6-mo low-dairy control period, reduced fasting plasma insulin by 9% and reduced insulin resistance by 11% in overweight and obese adults (93).

Finally, the stimulation of a beneficial gut microbiota, after intake of probiotics, has been suggested to modulate gut function through the regulation of the immune system (94). This stimulation has also been discussed to facilitate weight loss or weight maintenance associated with insulin sensitivity. Because of a low number of studies in humans in this field, more research on fermented dairy products and glucose homeostasis is needed.

In conclusion, evidence to date indicates that the dairy matrix has specific beneficial effects on health because the metabolic effects of whole dairy on body weight, cardiometabolic disease risk, and bone health differ from those of single dairy constituents. Also, different dairy product types seem to be distinctly linked to various health effects and disease risk markers. In addition, different processing methods and dairy structures can enhance interactions in the dairy matrix, thereby modifying the metabolic effects of dairy consumption. Therefore, the nutritional value of dairy products should be considered as the biofunctionality of the sum of nutrients within dairy matrix structures. Hence, there is a need for further research on the health effects of whole dairy foods alongside the more-traditional approach of studying the health effects of single nutrients. Such research would help to support dietary guidelines that consider the effect of whole foods on health rather than only focusing on a few individual nutrients within a food.

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JML is a member of the Observatoire French Dairy Interbranch Sector (CNIEL) des habitudes alimentaires, acts as an expert for Lactalis, Yoplait, and Danone, and has received funding for conferences for the European Milk Forum. AM has received funding from Arla Foods, United Kingdom, Unilever PLC, Dairy Australia, Teagasc – The Agriculture and Food Development Authority, Ireland, and the United Kingdom Biotechnology and Biological Sciences Research Council and is on the editorial board of Food Research International. MCM has received speaking honoraria from the Dairy Council for Northern Ireland and the European Milk Forum. 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AA has served as a member of advisory boards (of the Dutch Beer Knowledge Institute, Netherlands; IKEA, Sweden; Lucozade Ribena Suntory Ltd., United Kingdom; McCain Foods Ltd., United States; McDonald's, United States; and Weight Watchers, United States), a consultant (for the Nestlé Research Center, Switzerland, and Nongfu Spring Water, China), an expert witness (for Lantbrukarnas Riksförbund Mjölk, Stockholm 2015), a speaker (at LRF Mjölk, Gothenberg, 2016; the Global Dairy Platform, Berlin, 2015; the Dairy Council United Kingdom, Glasgow and Cardiff, 2015; the European Milk Forum, dairy councils of the Republic of Ireland and Northern Ireland, Dublin and Belfast, 2014; and the European Milk Forum, Paris, 2014), and as an editorial board member (associate editor of *The American Journal of Clinical Nutrition* and board member of the Annals of Nutrition and Metabolism & Annual Review of Nutrition). AA has been a recipient of expenses or modest honoraria (<$2000) for lectures that were given at meetings that were supported by corporate sponsors. AA has cooperated with the Universities of Copenhagen and Wageningen on a Global Dairy Platform–funded meta-analysis on dairy products and cardiometabolic disease, and has received recent or current dairy and health research funding from the United Kingdom Biotechnology and Biological Sciences Research Council, United Kingdom Medical Research Council, Dairy Council, Agriculture and Horticulture Development Board, The Barham Foundation Trust, and various companies. IG has served in the following capacities: member of the British Nutrition Foundation scientific advisory committee; member of the advisory committee of the UK Food Standards Agency; member of the scientific advisory panel of the University College Dublin Institute of Food and Health; consultant to the scientific panel of the Estonian Biocompetance Centre of Healthy Dairy Products; member of the panel on dairy, health, and lipids of the International Chair on Cardiometabolic Risk; member of the International Expert Movement to Improve Dietary Fat Quality; member of the research assessment panel of IBERS, University of Aberystwyth; member of the discussion panel on obesity of the European Healthy Lifestyle Alliance; member of the International Expert Movement to Improve Dietary Fat Quality; and consultant to the Dairy Council on Fats in Dairy Products and Cardiometabolic Disease. The remaining authors reported no conflicts of interest related to the study.

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