First Global Summit on the Health Effects of Yogurt

Proceedings of a satellite symposium held at the American Society for Nutrition Scientific Sessions at Experimental Biology 2013 in Boston, MA
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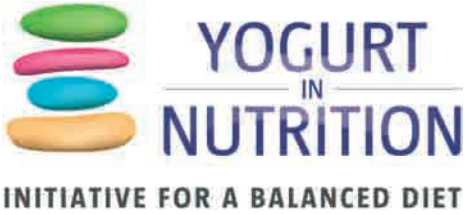

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Supplement—First Global Summit on the Health Effects of Yogurt

Introduction to the Yogurt in Nutrition Initiative and the First Global Summit on the Health Effects of Yogurt[1–3]

Sharon M Donovan and Raanan Shamir

ABSTRACT

Yogurt has been part of the human diet for thousands of years, and during that time a number of health benefits have been associated with its consumption. The goal of the First Global Summit on the Health Effects of Yogurt was to review and evaluate the strength of current scientific knowledge with regard to the health benefits of yogurt and to identify areas where further research is needed. The evidence base for the benefits of yogurt in promoting bone health, maintaining health throughout the life cycle, improving diet quality, and reducing the incidence of chronic diseases, such as obesity, metabolic syndrome, and cardiovascular disease, was presented. When assessing a complex food matrix, rather than specific nutrients, scientists and consumers are faced with new challenges as to how a food item's quality or necessity would be judged as part of an individual's whole diet. To tackle this challenge, speakers described methods for assessing the nutrient density of foods and its application to yogurt, use of yogurt for lactose intolerance, and the cost-effectiveness of yogurt and dairy products in reducing health care expenses. Last, speakers described the role of dairy products in global public health and nutrition, the scientific basis for current dairy recommendations, and future scientific and policy needs related to dairy and yogurt recommendations. *Am J Clin Nutr* 2014;99(suppl):1209S–11S.

On 24 April 2013, the First Global Summit on the Health Effects of Yogurt was held as a satellite symposium to the 2013 Experimental Biology meeting. The symposium was supported by the ASN (Washington, DC), The Nutrition Society (London, United Kingdom), the Dairy Research Institute (Rosemont, IL), and Danone Institute International (Palaiseau, France). The symposium was organized on behalf of the Yogurt in Nutrition Initiative (YINI), which was established in 2012. The overall mission of the YINI is to advance scientific knowledge on the health benefits of yogurt and to broadly disseminate that information. To achieve this mission, YINI has established 3 overall goals: first, to identify and review existing science on the health benefits of yogurt; second, to promote scientific research on the health benefits of yogurt; and last, to broadly disseminate knowledge on the health benefits of yogurt. The First Global Summit on the Health Effects of Yogurt was the initial step in meeting the objectives of the first goal.

Yogurt is prepared from milk fermented by added bacteria, which produce lactic acid that acts on milk protein to give yogurt its texture and its characteristic acidity. Bovine milk is most commonly used to make yogurt, but milk from water buffalo, goats, ewes, mares, camels, and yaks is also used in various parts of the world. In the United States, yogurt is produced by using a culture of *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* bacteria to meet the standard of identity for yogurt. In addition, other lactobacilli and bifidobacteria are also sometimes added during or after culturing yogurt (1, 2).

Yogurt has been consumed for several thousands of years. It is one of the earliest examples of food processing to improve "shelf life." Most historical accounts attribute the creation of yogurt to the Neolithic peoples of central Asia around 6000 BCE, but little remains as direct proof of this (3). It is thought that herdsmen stored milk from their sheep in containers made from the stomachs of animals and the natural enzymes in the stomach lining curdled the milk, essentially making yogurt. Curdling the milk extended the time that it could be consumed safely and likely improved its digestibility by reducing the lactose content (4). Since their discovery, yogurts and other soured-milk products were a component of the diet of some of the earliest civilizations in the Middle East (3). The Roman Pliny the Elder later mentioned production of yogurt by "barbarian tribes" (3).

The first unequivocal description of yogurt is found in a dictionary called *Divanu luga-i turk*, compiled by Kasgarli Mahmut in 1072–1073 in the Middle East. The consumption of yogurt spread rapidly throughout the geographic and cultural region known as the Levant, which encompassed the westernmost protrusion of Asia, comprising most of the Republic of Turkey (5). Recorded history states that in the 13th century, Genghis Khan and his armies lived on yogurt made from horse milk, likely resulting in the exposure of people in the conquered Mongol Empire to this new food (5).

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[2] Presented at the satellite symposium "First Global Summit on the Health Effects of Yogurt," held in Boston, MA, at ASN's Scientific Sessions at Experimental Biology 2013, 24 April 2013. The conference was organized by the ASN, the Nutrition Society, Danone Institute International, and the Dairy Research Institute. The supplement scientific guest editors were Sharon M Donovan, University of Illinois, Urbana, IL, and Raanan Shamir, Schneider Children's Medical Center and Tel Aviv University, Israel.

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Why study the health benefits of yogurt? Yogurt first gained international prominence in the early 1900s when Ilya (Elie) Metchnikov, a Nobel Prize–winning Russian immunologist and bacteriologist, observed that Bulgarians whose diet included the consumption of large quantities of soured milk lived longer than those who did not (6, 7). Although this observation was purely associative, Metchnikov subsequently began research on the causes of human aging while working at the Pasteur Institute in Paris. He found that dietary proteins were degraded by the action of putrefactive intestinal bacteria that he hypothesized caused poisoning of the body and early death. He went on to show that the only food that could restrict the development of putrefactive bacteria in the intestine was Bulgarian yogurt (8).

Over the past century, there has been continued research into the potential health benefits of yogurt. A PubMed (http://www.ncbi.nlm.nih.gov/pubmed) search of the terms "yogurt and health" identified >420 citations, including applications for improving nutritional status (9), maintaining health (10), the prevention and treatment of acute diarrheal disease (11), and the prevention or treatment of chronic diseases such as elevated blood pressure, weight gain, and metabolic diseases (12–15). A recent study that caught the attention of consumers worldwide attributed commercially available yogurt to a "glow of health" in rodents (16). Feeding probiotic bacteria to aged mice induced integumentary changes mimicking peak health and reproductive fitness characteristic of much younger animals (16). Mechanistically, the probiotic yogurt triggered epithelial sebocytogenesis, resulting in thick lustrous fur, which was associated with an IL-10–dependent process (16). The authors postulated that the probiotic-triggered changes in skin and hair arose from microbe-induced effects on tissue inflammation (16).

As presented in this symposium, accumulating preclinical, clinical, and epidemiologic findings provide suggestive evidence for health benefits associated with yogurt consumption, although the strength of the evidence varies depending on the health outcome. Many studies were underpowered, and few randomized controlled clinical trials with yogurt have been conducted.

What research is required to establish the health benefits of yogurt?

- Investigations need to be conducted across the life span from "pediatrics" to "geriatrics," including pregnancy.
- Randomized, placebo-controlled studies are required in healthy and diseased populations.
- Evaluations are required of the individual and combined influences of the nutrients and bacteria contained in yogurt.
- In terms of the bacteria in yogurt, studies must include a complete description of the product being tested. In some cases, the efficacy of yogurt is compared with isolated probiotic bacteria within the same study. For example, Levkovich et al (16) compared isolated *Lactobacillus reuteri* to a commercially available yogurt. Without detailed information on the types and doses of bacteria present in the treatments, it is impossible to compare findings across studies in systematic reviews or meta-analyses.
- Evaluation is required of the impact of delivery matrix on the efficacy of probiotic bacteria (9). As summarized by Sanders (10), the delivery matrix of yogurt may influence probiotic functionality in several ways: by increasing probiotic survival in the product, by increasing probiotic survival and efficacy at the site of action in the host, or by delivering complementary functionality through components of the delivery system or from fermentation-derived bioactive compounds.
- The relative efficacies of live compared with killed bacteria in yogurt need to be compared, as well as the value of adding bacteria to yogurt.
- Mechanistic studies of yogurt and/or the probiotic action on gut health and the microbiome are required (17). For example, McNulty et al (18) conducted a parallel series of studies in animals and monozygotic twins to study the effects of probiotic yogurt containing 5 bacterial species on the gut microbiota. No change in the gut microbiota composition was observed in response to yogurt consumption, but transcriptional and metabolic changes in the host commensal microbiota in response to the probiotic species was noted.

Although much has yet to be learned about the relation between yogurt and its components and health outcomes, the presentations at this symposium indicate that we are effectively advancing our understanding of the efficacy of yogurt. We hope that the presentations provided in this supplement will stimulate scientific discussion and promote targeted research to identify mechanisms and benefits of yogurt on health.

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SMD prepared the initial draft of the manuscript, which was edited by RS. Both authors approved the final manuscript before submission. SMD and RS co-chair the Yogurt in Nutrition Initiative for Health Advisory Board and received financial reimbursement for travel expenses and honoraria for participation in the conference and editing the supplement. SMD has received grant support from the Dairy Research International. RS is President of the Danone Institute International.

REFERENCES

1. Shiby VK, Mishra HN. Fermented milks and milk products as functional foods: a review. Crit Rev Food Sci Nutr 2013;53:482–96.
2. Tunick MH. Dairy innovations in the past 100 years. J Agric Food Chem 2009;57:8093–7.
3. Brothwell D, Brothwell P. Food in antiquity: a survey of the diet of early peoples. Baltimore, MD: Johns Hopkins University Press, 1997.
4. Andrews T. Nectar and ambrosia: an encyclopedia of food in world mythology. Santa Barbara, CA: ABC-CLIO, 2000.
5. Wright CA. A Mediterranean feast. New York, NY: William Morrow, 1999.
6. Podolsky S. Cultural divergence: Elie Metchnikoff's Bacillus bulgaricus therapy and his underlying concept of health. Bull Hist Med 1998;72:1–27.
7. Podolsky SH. The art of medicine: Metchnikoff and the microbiome. Lancet 2012;380:1810–1.
8. Metchnikoff E. The prolongation of life: optimistic studies. New York, NY: GP Putnam's Sons, 1908.
9. Clerfeuille E, Maillot M, Verger EO, Lluch A, Darmon N, Rolf-Pedersen N. Dairy products: how they fit in nutritionally adequate diets. J Acad Nutr Diet 2013;113:950–6.
10. Sanders ME. Use of probiotics and yogurts in the maintenance of health. J Clin Gastroenterol 2008;42:S71–4.
11. Eren M, Dinleyici EC, Vandenplas Y. Clinical efficacy comparison of Saccharomyces boulardii and yogurt fluid in acute non-bloody diarrhea in children: a randomized, controlled, open label study. Am J Trop Med Hyg 2010;82:488–91.
12. Park KM, Cifelli CJ. Dairy and blood pressure: a fresh look at the evidence. Nutr Rev 2013;71:149–57.
13. Ivey KL, Lewis JR, Hodgson JM, Zhu K, Dhaliwal SS, Thompson PL, Prince RL. Association between yogurt, milk, and cheese consumption and common carotid artery intima-media thickness and cardiovascular disease risk factors in elderly women. Am J Clin Nutr 2011;94:234–9.
14. Wang H, Livingston KA, Fox CS, Meigs JB, Jacques PF. Yogurt consumption is associated with better diet quality and metabolic profile in American men and women. Nutr Res 2013;33:18–26.

15. Vergnaud AC, Péneau S, Chat-Yung S, Kesse E, Czernichow S, Galan P, Hercberg S, Bertrais S. Dairy consumption and 6-y changes in body weight and waist circumference in middle-aged French adults. Am J Clin Nutr 2008;88:1248–55.
16. Levkovich T, Poutahidis T, Smillie C, Varian BJ, Ibrahim YM, Lakritz JR, Alm EJ, Erdman SE. Probiotic bacteria induce a 'glow of health'. PLoS ONE 2013;8:e53867.
17. Bisanz JE, Reid G. Unraveling how probiotic yogurt works. Sci Transl Med 2011;3:106ps41.
18. McNulty NP, Yatsunenko T, Hsiao A, Faith JJ, Muegge BD, Goodman AL, Henrissat B, Oozeer R, Cools-Portier S, Gobert G, et al. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. Sci Transl Med 2011;3:106ra106.

Dairy products in global public health[1–4]

Andrew M Prentice

ABSTRACT

Intakes of dairy produce show enormous diversity between regions, cultures, and individuals around the world. At the geographic level, intake maps closely onto the distribution of lactase persistence (LP), a genetic trait that allows milk to be consumed beyond the weaning period without gastrointestinal side effects. The LP trait has been independently selected at least 4 times and is under rapid positive selection, which shows that dairy consumption has positive survival benefits. For people lacking the LP trait, the fermentation of milk into yogurt and related products (a process known for ≥8500 y) aids milk digestion through the breakdown of some lactose and the provision of β-galactosidase, which remains active in the gastrointestinal tract. In global ecologic comparisons, milk and dairy intakes are strongly associated with adult height, and many international advisory bodies recommend the consumption of 400–500 mL milk equivalents/d. There are very few countries where such high intakes are met, and in populations in whom intakes are much lower there is evidence of adaptations that help to maintain bone health with surprisingly low intakes. Despite concerns that the high-saturated-fat content of full-fat dairy products would promote heart disease, recent meta-analyses show that dairy consumption is neutral or beneficial for weight control, coronary disease, diabetes, hypertension, and most cancers. *Am J Clin Nutr* 2014;99(suppl):1212S–6S.

INTRODUCTION

This article is a short overview of the role of dairy product consumption in global public health. Several of the topics touched on are covered in detail in the accompanying articles from this symposium, which also take a closer view specifically of yogurt and related fermented milk products.

The consumption of dairy products varies greatly both between and within populations. The variability within populations is largely driven by personal preferences (including avoidance of lactose intolerance or milk allergies and veganism) and affordability. Variations between populations are driven by culture, religion, availability, affordability, and genetic variability in the ability to tolerate lactose. The daily consumption of substantial quantities of dairy products, usually in wealthy nations, is a marker of high diet quality and is associated, at least in ecologic comparisons, with tall stature.

HISTORICAL ORIGINS OF FERMENTED MILK PRODUCTS

In temperate or hot climates, unfermented milk will "turn" very rapidly and especially when collected in poorly washed vessels contaminated with an accidental starter culture from the previous day's milking. Thus, soured milk would have invented itself as soon as humankind started milking animals. The history of when specific lactose-digesting bacterial cultures were first used and intentionally propagated will never be known with certainty, but residues from ancient fragments of potsherds, apparently designed to act as strainers, have been dated as far back as 8500 y ago (1, 2). As described in an accompanying article in this supplement issue by Savaiano (3), such "domesticated" fermentative organisms serve the very useful dual purposes of partial lactose digestion and provision of β-galactosidase (lactase), which continues to break down lactose after consumption. Both of these attributes would have assisted early humans in tolerating the substantial lactose loads that accompany milk consumption and would otherwise cause seriously debilitating adverse gastrointestinal effects. These were the first steps in allowing humans to take full advantage of their domesticated milk-yielding animals.

EVOLUTIONARY ORIGINS OF LACTASE PERSISTENCE

The second step is a remarkable one that informs us that, over evolutionary time, milk consumption has been highly advantageous for the survival and proliferation of humanity. In all mammalian species, intestinal lactase, highly active when the young are receiving their mother's milk, is downregulated in a coordinated manner speculated to be a natural part of weaning the offspring away from mammary feeding so that the mother can initiate a new reproductive cycle. The result is that older offspring and adults become lactose intolerant; they fail to break down the lactose disaccharide, leaving it as an abundant substrate for the gut microbiota, thus causing gas production, gastric distension and discomfort, flatulence, and diarrhea. Once initiated, the diarrhea can become self-reinforcing but will rapidly resolve with a lactose-exclusion diet (*see* also below).

Human genetic studies have shown that a genetic variation involving a single nucleotide substitution in the promoter region of the lactase gene overrides the natural tendency for the lactase

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gene to be switched off at weaning and confers a trait known as lactase persistence (LP)[5], in which older children and adults maintain their ability to digest the disaccharide (1, 4, 5). The most common and originally discovered variant occurs within a wide haplotype, indicating that the founder mutation occurred very recently (inferred from the fact that there has been little time for further degradation of the surrounding regions). The origin of this Caucasian variant (C/T–13910) has been dated to between 5000 and 20,000 y ago (4); this timescale is consistent with the domestication of milk-yielding animals. Remarkably, evidence from eastern Africa shows that alternate variants yielding the same phenotype of LP have evolved independently on at least 3 additional occasions and probably more (4–6). Research in the Masai shows that the LP variant has coevolved with another gene variant that aids cholesterol metabolism, thus allowing healthy survival with a diet containing high amounts of cholesterol and saturated fat (5).

The very rapid selection of LP and its penetration to near fixation in northwestern Europe indicates a very strong survival advantage, the explanation for which is still a matter of vigorous debate, and which is summarized by Brüssow (1). Even the direction of causality is still not agreed on. Did the domestication of milk-yielding animals spawn the LP mutation or vice versa? This debate has fallen foul of the frequent misconception that evolution acts primarily through viability selection (ie, the survival of offspring through to adulthood and reproduction). In fact, as originally shown in the 1930s (7), fertility selection (ie, the reproductive efficiency of parents especially at times of energy and nutrient restriction) can exert a much more powerful influence on the selection of genes (8), and this needs to be factored into the LP selection debate.

Whatever the explanation turns out to be, it can safely be concluded that the ability and proclivity to consume dairy products have been highly beneficial to human populations on an evolutionary basis. This statement must be balanced, however, by the observation that populations in eastern Asia, where there was no founder for the LP variant, and in whom LP has barely yet penetrated, have also been extremely successful. The success of populations without LP, coupled with the very rapid and powerful selection of the variant in which there was a chance founding mutation, reminds us of the power of evolution to select advantageous traits. Charles Darwin recognized this fact in the final chapter of *The Origin of Species* with the statement that "a grain in the balance shall determine who shall live and who shall die" (9).

ROLE OF LACTOSE IN PERSISTENT DIARRHEA AND OF YOGURT IN ITS TREATMENT

The lactase enzyme is located at the tip of the intestinal villi. Therefore, children in whom the villi have been damaged by organisms such as enteropathogenic *Escherichia coli* (10) have transient lactase deficiency that may exacerbate the diarrhea and lead to its persistence. Children with chronic environmental enteropathy, a condition that affects most young children living in contaminated environments, also have shortened villi and a reduced lactase ability, which may make them more easily susceptible to lactose malabsorption (11). A multicenter study of persistent diarrhea coordinated by WHO showed that 60% of patients with persistent diarrhea responded to a reduced-lactose diet (eg, rice, yogurt, lentils, oil), whereas some of the remaining patients responded well to (temporary) lactose exclusion (12). Yogurt is the treatment of choice in some countries and, along with other reduced lactose formulations, is deemed more effective and appropriate than antibiotics (12).

ROLE OF DAIRY PRODUCTS IN MEETING NUTRIENT NEEDS

There are only 2 foods consumed by humans that have been explicitly designed to meet the entire nutrient needs of a complex organism: milk and eggs. Thus, it is no surprise that diets containing a significant proportion of such foods are nutrient rich and show a generally appropriate balance of the essential nutrients for healthy growth and development, especially concerning amino acid balance. The contribution that customary US intake of dairy products makes to daily nutrient needs is shown in **Figure 1** (13).

In a cost-versus-nutrient-density matrix, milk and milk products appear as high density and low cost in wealthy country settings (14) and hence make excellent contributions to a healthy diet. They appear within all food plate and food pyramid dietary guidelines. However, the equation is different in low-income settings where milk products are expensive (relative to local income levels) and are viewed as prestige foods. Consequently, even herd-owning families will often prioritize sale of their milk over home consumption, thus skewing intake toward the urban elite. The absence of refrigeration also limits overall dairy product consumption but favors fermented products.

GLOBAL VARIATIONS IN MILK INTAKE

Currently, industrialized nations consume ~5 times the milk per capita as do developing nations. The projected increase in developing nations is much faster, such that in 2030 it is projected that there will be a 3-fold gap. Intake in sub-Saharan Africa currently averages ~70 g per capita per day (compared with almost 600 g, which is the industrialized nations' average) (15, 16). In much of Africa, the limitations on consumption are driven by cost, absence of refrigeration, and poor availability. Without these constraints, milk and its fermented products are generally highly-sought-after food items. Intake in East Asia is almost negligible and is much lower than in South Asia. These differences map onto the geographic differences in the prevalence of LP genes (4) and are presumably driven, at least in part, by these genetic differences in milk tolerance.

Because dairy products make such a strong contribution to calcium intake, the adequacy of dietary calcium consumption correlates strongly with the geographic variations in milk consumption. Intakes of calcium are generally reasonable across Europe (17); judged against the WHO/FAO adult recommended nutrient intake (RNI) of 1000 mg/d, mean calcium intakes of 16 European countries were between 687 and 1171 mg/d in males and between 508 and 1047 mg/d in females (17). Other nations fall far shorter with regard to RNIs; for example, in Brazil, 99% of adults (19–60 y) consume inadequate amounts of calcium (18). In China, dairy provides only 4.3% of dietary calcium and calcium intakes range between 20% and 60% of adequate levels, with only 2–3% of people reaching adequate intake targets (18, 19).

[5]Abbreviations used: CVD, cardiovascular disease; LP, lactase persistence; RNI, recommended nutrient intake.

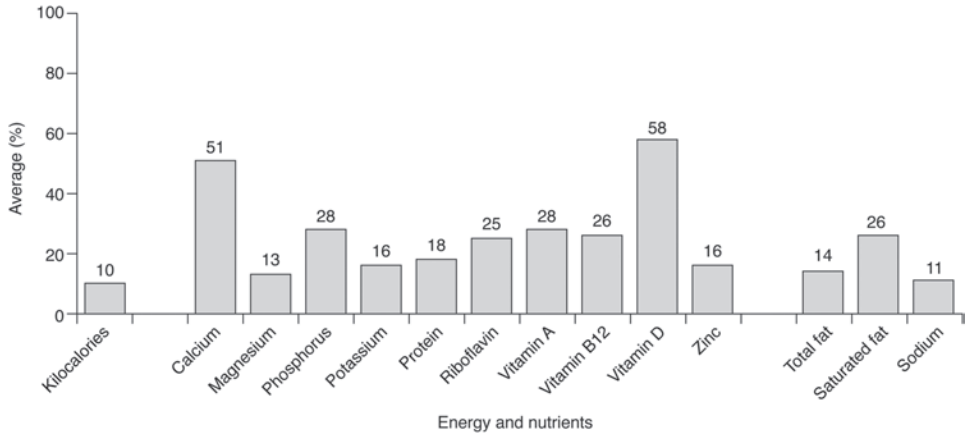

FIGURE 1. Contribution of dairy foods to key nutrient intakes in the United States. Data were obtained from the 2003–2004 and 2005–2006 NHANES 24-h dietary recalls for individuals aged ≥2 y, excluding pregnant and lactating women. Note that, in the United States, milk is routinely fortified with vitamins A and D in the amounts of 2000 and 400 IU/quart, respectively. Reproduced with permission from reference 13.

HEALTH IMPLICATIONS OF DAIRY INTAKE: PROBLEMS IN ASSESSING THE EVIDENCE

Assessing the dietary intake of individuals is problematic and especially when such measurements need to be applied in very large-scale surveys to capture associations with relatively uncommon disease endpoints. Fortunately, however, the range of dairy food intakes tends to be wide, thus facilitating both ecologic and cross-sectional epidemiologic analyses. An additional advantage is that most people's preference for or against dairy products tends to remain relatively constant over time—a fact that strengthens case-control studies of disease.

The other main difficulty in assessing the health implications of dairy intake is that of confounding with other lifestyle factors that may themselves be responsible for any observed association. This is especially true in countries where dairy products are expensive relative to other foods and hence tend to be associated with socioeconomic status.

One potential way around this problem is to use the Mendelian randomization approach (21) based on LP. This method is based on the principle that a trait affecting the exposure variable (in this case LP affecting dairy intake) is randomly allocated through Mendelian inheritance and hence creates a gradient in intake that is nonconfounded and unbiased. This approach has been used in several disease endpoints (eg, reference 20) but loses some potential power because, although LP predicts dairy intake very well on an interpopulation basis, it is less discriminatory on an interindividual basis.

All of the above limitations must be borne in mind when interpreting studies of dairy intake and health. A brief overview of such studies, based on the latest meta-analyses, is provided below. Other articles in this supplement issue provide a more detailed analysis of some of the diseases (23–25).

DAIRY PRODUCTS AND HEALTH OUTCOMES

There is a vast literature covering associations between dairy product intake and a wide range of health outcomes. As with almost all such epidemiology, the literature is mixed, and in addition to the methodologic constraints listed above may additionally be influenced by reporting biases. Nonetheless, the consensus is that the consumption of dairy products has many benefits, and prior concerns that the fat and saturated-fat content of full-fat milk products would contribute to heart disease are not supported by the literature (*see* below). Indeed, the evidence is mixed on the question of whether low-fat dairy products have superior health benefits to their full-fat counterparts.

Growth and bone health

Because calcium is a critical component of bone and most calcium in the body is contained in bone, it would be reasonable to assume that bone health is closely related to calcium intake; Rizzoli (23) summarizes the evidence in support of this elsewhere in this supplement issue. In fact, on a global ecologic basis, there is a perplexing inverse association between dietary calcium intake and bone fracture rates (taken as a proxy measure of bone health and osteoporosis) (26). This likely arises through the influence of other critical determinants of bone health, such as vitamin D status linked to latitude, and high levels of bone-protective physical activity in poorer countries with low milk and dairy intake. It is clear furthermore that there is a considerable physiologic capacity to adapt to low dietary calcium intake and that sudden increases in calcium supply can cause detrimental health responses, presumably by disturbing these protective adaptations (27). The topic of dairy intake and bone health is discussed in more detail elsewhere in this supplement issue (23).

Weight management

In light of the issues of confounding listed above, it is not surprising that observational studies attempting to relate weight control to dairy intake yield mixed and inconsistent results. Randomized controlled trials provide more robust evidence and have been summarized in 2 recent meta-analyses (28, 29).

Abargouei et al (28) analyzed 14 studies to investigate the effects of increasing dairy products in the diet on weight, fat mass, lean mass, and waist circumference. In the absence of cointerventions aimed at energy restriction, increased dairy intake has no discernible effect on any of the above variables, but when combined with energy restriction, dairy intake showed modest additional benefit on weight reduction (−0.61 kg), fat

mass (−0.72 kg), lean mass (+0.58 kg), and waist circumference (−2 cm).

Chen et al (29) included 29 eligible studies and reached broad agreement with Abargouei et al (28) insofar as an increase in dairy products was not helpful for weight maintenance unless accompanied by energy restriction, in which case it offered slight additional benefit, most notably in short-term trials.

Diabetes

There are no published randomized controlled trials of altered dairy intake and diabetes. A meta-analysis of 7 cohort studies by Tong et al (30) showed evidence for a 14% protective effect of dairy intake against type 2 diabetes. Most of this effect was attributable to low-fat dairy and yogurt intake with whole-milk and full-fat products showing no evidence for benefit. It must be stressed that the evidence for benefit was weak, and the evidence for differential effects of low-fat dairy and yogurt was even weaker (because of low study numbers and potential confounding). Importantly, however, there was no suggestion that dairy intake might contribute to the risk of type 2 diabetes.

Although not a meta-analysis, Sluijs et al (31) reported the results of a very large prospective study of dairy intake as a possible risk factor for type 2 diabetes in the European Investigation into Cancer and Nutrition–InterAct Study. On the basis of almost 4 million person-years' follow-up and >12,000 incident cases of type 2 diabetes, this study found that there was no overall association between baseline dairy food consumption and later diabetes, but both cheese intake (RR: 0.88) and total fermented dairy products (cheese, yogurt, and thick fermented milk; RR: 0.88) showed protective trends. Elsewhere in this supplement issue, Astrup (24) describes potential mechanisms by which such effects might occur.

Hypertension

In a meta-analysis of 9 observational and clinical studies, Soedamah-Muthu et al (32) found a slight protective effect of total dairy, low-fat dairy, and milk intake on hypertension. On the basis of fewer studies there was no evidence of protection by high-fat dairy, fermented dairy products, yogurt, or cheese.

Ralston et al (33) analyzed 5 cohort studies with nearly 11,500 cases of elevated blood pressure, with the express intention of separating out the effects of high-fat compared with low-fat dairy. They found a significant inverse association between low-fat dairy intake and elevated blood pressure (RR: 0.84) with no apparent benefit for high-fat dairy. Separating cheese from fluid dairy foods (milk and yogurt) showed a null effect for cheese and a protective effect for fluid dairy foods.

Cardiovascular disease

As discussed by Astrup (24) in this supplement issue, the known association between saturated fat and cardiovascular disease (CVD) would suggest that high-fat dairy products may increase CVD risk. In fact, the evidence does not support this contention (24).

A recent meta-analysis of 17 observational cohort studies (fewer contributing to each different endpoint) reports a modest inverse association between milk intake and overall CVD risk (RR: 0.94 per 200 mL/d) (34). There were no significant associations with coronary artery disease, stroke, or overall mortality, but again the RR tended to be lower than unity rather than higher.

Cancers

The expert panel of the joint World Cancer Research Fund/American Institute for Cancer Research report in 2007 stated that, "Milk probably protects against colorectal cancer. There is limited evidence suggesting that milk protects against bladder cancer. There is limited evidence suggesting that cheese is a cause of colorectal cancer. Diets high in calcium are a probable cause of prostate cancer; there is limited evidence that high consumption of milk and dairy products is a cause of prostate cancer" (35). The World Cancer Research Fund's Continuous Update Project publishes occasional updates based on updated meta-analyses (*see* http://www.dietandcancerreport.org/cancer_resource_center/cup_summaries.php). The 3 reports published since 2007 (on prostate, colorectal, and breast cancer) make no significant additional comments about dairy products, and in general the evidence appears to be neutral.

CONCLUSIONS

In summary, evolutionary evidence shows clearly that the consumption of milk and milk products into later childhood and adulthood has conferred significant advantages in terms of survival and/or reproductive success among our forebears. This ability to consume high lactose loads without unpleasant side effects has been achieved through evolution of the LP trait and through domestication of lactic acid bacteria to create fermented milk products. Large regional differences in the LP genotype correlate, on a global geographic basis, with very large differences in dairy product intake. Populations with a low intake of dairy products have adaptive mechanisms that allow them to grow and maintain good bone health at calcium intakes that are greatly below the RNI in high-income countries. The disturbance of these adaptations has been reported to cause some adverse sequelae, so it should not always be assumed that increasing calcium intake would be beneficial. Thus, a global RNI value may not be appropriate. Despite these caveats, it is clear that the consumption of dairy products, and especially of fermented dairy products, has numerous benefits and is not associated with clear evidence of any detrimental health effects.

RESEARCH NEEDS

As described in accompanying articles in this supplement issue (3, 21–23), the consumption of fermented dairy products has specific physiologic effects, but the details of these effects and their possible modulation remain a significant research target. This is especially true of yogurt. Most large-scale epidemiologic studies have either not seriously endeavored or have found it difficult to disaggregate the effects of yogurt consumption from general dairy consumption. If tractable, this remains an important research topic.

Finally, there may be a future for developing yogurts as a vehicle for next-generation probiotics that are more specifically designed for optimization of the gut microbiota, and hence human health, than existing strains. History may show that the current generation of yogurt-based probiotics can be further refined by interrogating the health correlates of different patterns

of gut microbiota and by using this information as a design template for selecting optimal "transplantable" probiotic configurations.

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REFERENCES

1. Brüssow H. Nutrition, population growth and disease: a short history of lactose. Environ Microbiol 2013;15:2154–61.
2. Salque M, Bogucki PI, Pyzel J, Sobkowiak-Tabaka I, Grygiel R, Szmyt M, Evershed RP. Earliest evidence for cheese making in the sixth millennium BC in northern Europe. Nature 2013;493:522–5.
3. Savaiano DA. Lactose digestion from yogurt: mechanism and relevance. Am J Clin Nutr 2014;99(suppl):1251S–5S.
4. Tishkoff SA, Reed FA, Ranciaro A, Voight BF, Babbitt CC, Silverman JS, Powell K, Mortensen HM, Hirbo JB, Osman M, et al. Convergent adaptation of human lactase persistence in Africa and Europe. Nat Genet 2007;39:31–40.
5. Wagh K, Bhatia A, Alexe G, Reddy A, Ravikumar V, Seiler M, Boemo M, Yao M, Cronk L, Naqvi A, et al. Lactase persistence and lipid pathway selection in the Maasai. PLoS ONE 2012;7:e44751.
6. Schlebusch CM, Sjödin P, Skoglund P, Jakobsson M. Stronger signal of recent selection for lactase persistence in Maasai than in Europeans. Eur J Hum Genet 2013;21:550–3.
7. Fisher R. The genetical theory of natural selection. Oxford, United Kingdom: Clarendon Press, 1930:188–209.
8. Corbett SJ, McMichael AJ, Prentice AM. Type 2 diabetes, cardiovascular disease, and the evolutionary paradox of the polycystic ovary syndrome: a fertility first hypothesis. Am J Hum Biol 2009;21:587–98.
9. Darwin C. On the origin of species by means of natural selection. London, United Kingdom: John Murray, 1859.
10. Kaper JB, Nataro JP, Mobley HL. Pathogenic Escherichia coli. Nat Rev Microbiol 2004;2:123–40.
11. Lunn PG. The impact of infection and nutrition on gut function and growth in childhood. Proc Nutr Soc 2000;59:147–54.
12. International Working Group on Persistent Diarrhoea. Evaluation of an algorithm for the treatment of persistent diarrhoea: a multicentre study. Bull World Health Organ 1996;74:479–89.
13. Rice BH, Quann EE, Miller GD. Meeting and exceeding dairy recommendations: effects of dairy consumption on nutrient intakes and risk of chronic disease. Nutr Rev 2013;71:209–23.
14. Drewnowski A. The contribution of milk and milk products to micronutrient density and affordability of the U.S. diet. J Am Coll Nutr 2011;30(suppl 1):422S–8S.
15. Wang Y, Li S. Worldwide trends in dairy production and consumption and calcium intake: is promoting consumption of dairy products a sustainable solution for inadequate calcium intake? Food Nutr Bull 2008;29:172–85.
16. FAO Trade and Markets Division. Food outlook: global market analysis. Rome, Italy: FAO, June 2011. Available from: Available from: http://www.fao.org/docrep/014/al978e/al978e00.pdf.
17. Elmadfa I, ed. European Nutrition and Health Report 2009. Forum Nutr. Basel, Switzerland: Karger, 2009;62:1–412.
18. Lopes ACSCW, Sichieri R, Migoti SA, Lima-Costa MF. Consumo de nutrientes em adultos e idosos em estudo de base populacional: Projecto Bambui. [Nutrient consumption by adults and seniors in a population-based study: the Bambuí Project.] Cad Saude Publica 2005;21:1201–9 (in Spanish).
19. He Y, Zhai F, Wand Z, Hu Y. [Status of dietary calcium intake of Chinese residents.] Wei Sheng Yan Jui 2007;36:600–2 (in Chinese).
20. Du WW, Wang HJ, Wang ZH, Zhai FY, Zhang B. [Trend of milk consumption among Chinese children and adolescents aged 7 to 17 years old in 9 provinces from 1991 to 2006.] Zhonghua Liu Xing Bing Xue Za Zhi 2010;31:1349–52 (in Chinese).
21. Smith GD, Ebrahim S. "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 2003;32:1–22.
22. Timpson NJ, Brennan P, Gaborieau V, Moore L, Zaridze D, Matveev V, Szeszenia-Dabrowska N, Lissowska J, Mates D, Bencko V, et al. Can lactase persistence genotype be used to reassess the relationship between renal cell carcinoma and milk drinking? Potentials and problems in the application of Mendelian randomization. Cancer Epidemiol Biomarkers Prev 2010;19:1341–8.
23. Rizzoli R. Dairy products, yogurts, and bone health. Am J Clin Nutr 2014;99(suppl):1256S–62S.
24. Astrup A. Yogurt and dairy product consumption to prevent cardiometabolic diseases: epidemiologic and experimental studies. Am J Clin Nutr 2014;99(suppl):1235S–42S.
25. Marette A, Picard-Deland E. Yogurt consumption and impact on health: focus on children and cardiometabolic risk. Am J Clin Nutr 2014;99(suppl):1243S–7S.
26. Prentice A. Diet, nutrition and the prevention of osteoporosis. Public Health Nutr 2004;7:227–43.
27. Olausson H, Goldberg GR, Laskey MA, Schoenmakers I, Jarjou LM, Prentice A. Calcium economy in human pregnancy and lactation. Nutr Res Rev 2012;25:40–67.
28. Abargouei AS, Janghorbani M, Salehi-Marzijarani M, Esmaillzadeh A. Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Int J Obes (Lond) 2012;36:1485–93.
29. Chen M, Pan A, Malik VS, Hu FB. Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012;96:735–47.
30. Tong X, Dong JY, Wu ZW, Li W, Qin LQ. Dairy consumption and risk of type 2 diabetes mellitus: a meta-analysis of cohort studies. Eur J Clin Nutr 2011;65:1027–31.
31. Sluijs I, Forouhi NG, Beulens JW, van der Schouw YT, Agnoli C, Arriola L, Balkau B, Barricarte A, Boeing H, Bueno-de-Mesquita HB, et al; InterAct Consortium. The amount and type of dairy product intake and incident type 2 diabetes: results from the EPIC-InterAct Study. Am J Clin Nutr 2012;96:382–90.
32. Soedamah-Muthu SS, Verberne LD, Ding EL, Engberink MF, Geleijnse JM. Dairy consumption and incidence of hypertension: a dose-response meta-analysis of prospective cohort studies. Hypertension 2012;60:1131–7.
33. Ralston RA, Lee JH, Truby H, Palermo CE, Walker KZ. A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. J Hum Hypertens 2012;26:3–13.
34. Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, Hu FB, Engberink MF, Willett WC, Geleijnse JM. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. Am J Clin Nutr 2011;93:158–71.
35. World Cancer Research Fund; American Institute for Cancer Research. Food, nutrition, physical activity and the prevention of cancer: a global perspective. 2007. Available from: http://www.dietandcancerreport.org/cancer_resource_center/downloads/Second_Expert_Report_full.pdf (cited 14 March 2014).

How sound is the science behind the dietary recommendations for dairy?[1–4]

Connie M Weaver

ABSTRACT

This review examined the evidence behind dietary guidelines for dairy. Most countries recommend consumption of dairy products; and when amounts are specified, recommendations are typically for 2 or 3 servings per day. Specific recommendations for dairy products are based partly on culture and availability but primarily on meeting nutrient requirements. Dairy products are a rich source of many minerals and vitamins as well as high-quality protein. Thus, dairy consumption is a marker for diet quality. A recent report found that yogurt specifically is a good marker of diet quality. The food patterns recommended by the 2010 Dietary Guidelines for Americans Advisory Committee (DGAC) include 3 cups of low-fat milk and milk products. Few people achieve their recommended intakes of several shortfall nutrients without meeting their recommendations for dairy. The evidence for a benefit of dairy consumption is moderate for bone health in children but limited in adults and moderate for cardiovascular disease, blood pressure, and diabetes and limited for metabolic syndrome. Newer data since the recommendations of the 2010 DGAC are presented. However, the strength of the evidence for dairy consumption and health is limited by the lack of appropriately powered randomized controlled trials. *Am J Clin Nutr* 2014;99(suppl):1217S–22S.

WHAT ARE THE DIETARY RECOMMENDATIONS FOR DAIRY?

Dairy foods play a central role in most dietary guidance recommendations. They provide a package of essential nutrients and bioactive constituents for health that are difficult to obtain in diets with no or limited use of dairy products. The contribution of dairy products to providing recommended calcium intakes has largely driven the recommendation for dairy. Since the agricultural revolution when energy sources shifted from plant foods relatively high in calcium in the diets of hunter-gatherers to cereal crops with low calcium content, the major source of dietary calcium has been milk.

In addition to calcium, dairy products provide many other nutrients (**Table 1**) (1). They are a good source of high-quality protein, potassium, magnesium, phosphorus, zinc, selenium, vitamin A, riboflavin, thiamine, vitamin B-12, and vitamin D (when fortified) (2). Not all dairy products are equal sources of nutrients. The calcium content of soft cheeses, in which the curd is formed with acid, is reduced because some calcium is lost in the whey. Nutrients are diluted in the making of ice cream by the addition of fat and sugar. Cheeses are typically salted, which contributes to high sodium intakes. The fat content varies widely depending on the degree of removal of dairy fat. Not indicated in Table 1 is the reduced lactose content in yogurt and cheese, making those products popular in lactose-maldigesting cultures.

Dairy intake recommendations vary from region to region. Some countries, such as the United Kingdom, provide general recommendations to consume milk and other dairy products daily, but most countries have quantitative recommendations that usually range from 2 to 3 servings or cups of milk or yogurt or sometimes the equivalent serving of cheese (**Table 2**). The 2010 *Dietary Guidelines for Americans* specify low-fat dairy products because of concern over the high prevalence of obesity (3).

HOW DAIRY RECOMMENDATIONS ARE SET BY THE *DIETARY GUIDELINES FOR AMERICANS*

Milk has had a major role in one of the food groups since the USDA published the first food guide in 1917. In that first food guide there were only 5 groups; milk was combined with meat. In 1933, 12 food groups were recommended, and milk was expanded to include milk products, which comprised a single major food group. Milk and milk products remained as an independent group in the 1940s with the *Basic Seven* guide, in the *Basic Four* guide from the 1950s to the 1970s, in the Pyramid/MyPyramid guides of the 1980s to 2010, and in the current 2011 MyPlate (4, 5). The food groups of MyPlate include protein, fruit, vegetables, low-fat milk and milk products, and whole grains.

The amount of milk and milk products (and other food groups) is determined by the Dietary Guidelines for Americans Advisory Committee (DGAC)[5] (6) on the basis of *1*) intakes of the food groups needed to achieve the Dietary Reference Intakes (DRIs) for essential nutrients without exceeding energy needs and *2*) the

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[2] Presented at the satellite symposium "First Global Summit on the Health Effects of Yogurt," held in Boston, MA, at ASN's Scientific Sessions at Experimental Biology 2013, 24 April 2013. The conference was organized by the ASN, the Nutrition Society, Danone Institute International, and the Dairy Research Institute. The supplement scientific guest editors were Sharon M Donovan, University of Illinois, Urbana, IL, and Raanan Shamir, Schneider Children's Medical Center and Tel Aviv University, Israel.

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[5] Abbreviations used: BMC, bone mineral content; DGAC, Dietary Guidelines for Americans Advisory Committee; DRI, Dietary Reference Intake; RCT, randomized controlled trial.

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TABLE 1
Nutrient composition per 100 g of selected dairy foods[1]

	USDA food name and food code						
	Cow milk, producer fluid, 3.7% milk fat (01078)	Milk, nonfat, fluid (skim) (01151)	Yogurt, plain, low fat (01117)	Yogurt, fruit, low fat (01122)	Cheese, cheddar (01009)	Cheese, cottage, nonfat, uncreamed, dry large or small curd (01014)	Ice cream, vanilla (19095)
Energy (kcal)	64	34	63	105	403	72	2.07
Protein (g)	3.3	3.37	5.3	4.9	24.9	10.3	3.5
Total fat (g)	3.7	0.08	1.6	1.4	33.1	0.3	11
SFAs (g)	2.3	0.1	1.0	0.9	21.1	0.2	6.8
MUFAs (g)	1.1	0	0.4	0.4	9.4	0.1	3.0
PUFAs (g)	0.1	0	0	0	0.9	0	0.5
Cholesterol (mg)	14	2	6	6	105	7	44
Carbohydrate (g)	4.7	4.96	7.0	18.6	1.3	6.7	23.6
Calcium (mg)	119	122	183	169	721	86	128
Iron (mg)	0.05	0.03	0.08	0.07	0.68	0.15	0.09
Magnesium (mg)	13	11	17	16	28	11	14
Phosphorus (mg)	93	101	144	133	512	190	105
Potassium (mg)	151	156	234	216	98	137	199
Sodium (mg)	49	42	70	65	621	330	80
Zinc (mg)	0.38	0.42	0.89	0.82	3.11	0.47	0.69
Thiamine (mg)	0.038	0.045	0.044	0.041	0.027	0.023	0.041
Riboflavin (mg)	0.161	0.182	0.214	0.198	0.375	0.226	0.240

[1] Data are from reference 1.

evidence for the relation of intake of food groups and relevant health outcomes. In an iterative process, food intake pattern modeling and interpretation of the evidence on the relation to health developed the food intake patterns for MyPyramid/MyPlate (6, 7). The 12 patterns developed for various energy and nutrient needs of different age and sex groups were created to meet the DRIs for that subpopulation and guidance from evidence-based reviews. For some nutrients, the Recommended Dietary Allowance was used, and for others with insufficient evidence to determine the Recommended Dietary Allowance, the Adequate Intake for a healthy population was used. However, when the review of the literature led to a decision by the DGAC to increase or decrease the amount of a food group to recommend, food modeling was again used to adjust the intake recommendations of other food groups to meet the DRIs for the essential nutrients within each energy pattern.

The intent of food guidance is to be flexible to accommodate the diversity of culture and preferences of the population. For most food groups, there is a large choice of items within the category. However, for the milk and milk products food group, most foods within the category stem from a similar raw ingredient, ie, milk from a domesticated animal supply. The food guides include alternative sources of protein and calcium and guidance for those with milk protein allergy or lactose intolerance. However, few people who avoid dairy products achieve recommended intakes of several shortfall nutrients, such as calcium, potassium, magnesium, riboflavin, and vitamin D.

DAIRY PRODUCTS AND DIET QUALITY

Milk products, along with fruit, vegetables, and whole grains, were identified by the 2005 and 2010 DGAC as foods that need to be increased to meet nutrient needs and for improved health (3, 8). The role of milk products in meeting 3 shortfall nutrients for various age groups is shown in **Table 3** (9).The best and most economical source of the limiting nutrients is dairy (10). Supplements typically do not fill the gap of all these nutrients for those who do not consume recommended intakes of dairy products. By using NHANES 2001–2002 data, Gao et al (11) determined that it is impossible to meet calcium recommendations while meeting other nutrient recommendations with a dairy-free diet within the current US dietary pattern. Fulgoni et al (12) identified calcium-rich foods that could provide as much calcium as a serving of dairy (eg, 1.1 servings of fortified soy beverage, 0.5 servings of fortified orange juice, 1.2 servings of bony fish, or 2.2 servings of leafy greens), but these foods did not provide the equivalent profile of other nutrients and the amounts needed are unrealistic in some cases. By using the 1999–2004 NHANES data, Nicklas et al (13) determined that $<3\%$ of the US population met potassium recommendations and 55% did not meet their Estimated Average Requirement for magnesium. This group recently reported the following major barriers to meeting the Dietary Guidelines recommendations: *1*) inadequate meal preparation skills, *2*) difficulty in changing eating habits, *3*) lack of understanding the specific recommendations, and *4*) taste preference (13).

A number of studies have indicated that milk intake is a marker for dietary quality because of its nutrient contributions (10, 14–16). Recently, the Framingham Heart Study offspring cohort, involving 6526 adults, found that yogurt is also a marker of dietary quality (17). Yogurt consumers compared with nonconsumers had improved diet quality scores (according to the Dietary Guidelines Adherence Index with a maximum score of 20) of 9.4 compared with 8.05. The prevalence of nutrient inadequacy was also much lower in the 64% of women and 41% of men in the cohort who consumed yogurt (**Figure 1**). Yogurt consumption also increased the percentage of individuals exceeding the Adequate Intake for potassium (11.4% compared with 4.7%) and fiber (22.4% compared with 10.0%). Unfortunately, milk or dairy products other

TABLE 2
Selected dietary recommendations for dairy by country

Country and population group	Daily recommendation
Australia	
12–18 y	3 servings of milk, yogurt, cheese, or custard
All others >4 y	2 servings of milk, yogurt, cheese, or custard
Canada	
9–18 y	3–4 servings of milk, yogurt, kefir, or cheese
2–8 y, 19–50 y	2 servings of milk, yogurt, kefir, or cheese
≥51 y	3 servings of milk, yogurt, kefir, or cheese
Chile	
2–5 y	3 cups milk or yogurt or one piece of cheese
10–18 y	3–4 cups milk or yogurt or one piece of cheese
19–59 y	3 cups milk or yogurt or one piece of cheese
≥60 y	2–3 cups milk or yogurt or one piece of cheese
China	
General	300 g dairy milk or dairy products
Breastfeeding women	500 mL dairy milk or dairy products
Finland	
All	500 mL milk or liquid yogurt
France	
General >3 y	3 servings of milk, cheese, or yogurt
India	
1–18 y, pregnant and lactating women	5 portions of milk
Adults	3 portions of milk
Japan	
General	2 servings of milk/milk products
South Africa	
7–13 y	2–3 cups milk, maas, yogurt, sour milk, or cheese
14–25 y	1–2 cups milk, maas, yogurt, sour milk, or cheese
>25 y	1 cup milk, maas, yogurt, sour milk, or cheese
Switzerland	
General	3 portions of milk, yogurt, or cheese
Elderly	3–4 portions of milk, yogurt, or cheese
United Kingdom	
General	Eat some milk and dairy foods every day
Turkey	
Adults	2 servings of milk, yogurt, or cheese
Children, adolescents, pregnant and lactating women	3–4 servings of milk, yogurt, or cheese
United States	
2–3 y	2 cups of low-fat milk, yogurt, or fortified beverage
4–8 y	2.5 cups of low-fat milk, yogurt, or fortified beverage
>9 y	3 cups of low-fat milk, yogurt, or fortified beverage

than yogurt were not evaluated so it is not possible to compare which of the dairy products is the best marker of diet quality.

The nutrient concentration on a weight basis is greater in yogurt and cheese than in milk, but serving sizes are typically less for these products than for milk. Calcium bioavailability was not significantly different among various dairy products prepared from milk endogenously labeled with stable calcium isotopes and tested in women aged 24–42 y (18) (**Figure 2**). Little is known about the bioavailability of most of the other nutrients provided by dairy products.

TABLE 3
Role of milk products in food patterns[1]

	2–8 y		9–18 y		19–50 y		≥51 y	
	Without dairy	With dairy	Without dairy	With dairy	Without dairy	With dairy	Without dairy	With dairy
	% of recommendation		*% of recommendation*		*% of recommendation*		*% of recommendation*	
Calcium	146	54	97	32	134	47	107	38
Potassium	70	43	59	38	68	48	71	49
Magnesium	254	160	114	69	112	79	109	75

[1] Adequate Intakes for calcium and potassium and Estimated Average Requirements for magnesium are shown. Data are from reference 9. With dairy = 2.5–3.5 servings/d; Without dairy = <1 serving/d.

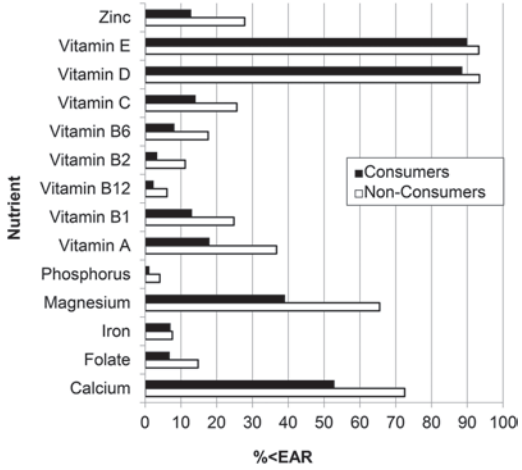

FIGURE 1. Yogurt consumption is associated with better diet quality compared with nonconsumers for all nutrients in generalized estimating equation models ($P < 0.001$). Data are from reference 14. EAR, Estimated Average Requirement.

EVIDENCE FOR A RELATION BETWEEN MILK INTAKE AND HEALTH OUTCOMES

The 2010 DGAC concluded that the evidence for intake of milk and milk products was moderate for a positive relation with bone health in children but limited in adults; moderate for an inverse relation with cardiovascular disease, blood pressure, and type 2 diabetes in adults; limited for an inverse relation with metabolic syndrome; insufficient to assess the relation with serum cholesterol; and strong for no unique relation to weight control (8). The long latency period for chronic disease outcomes make randomized controlled trials (RCTs) with food impractical, except in some cases in vulnerable populations. Consequently, meta-analyses and systematic reviews on the relation between milk and milk product intake and health tend to use RCTs of biomarkers or on prospective or observational studies. This is reasonable for health impacts related to nutrition.

Bone

The consequences of excluding dairy in the diet are most associated with compromised bone health. Effects apparently can begin in utero as evidenced by a study that showed increased consumption of milk and milk products by pregnant women at 28 wk gestation significantly ($P < 0.05$) predicted total body and bone mineral content (BMC) of children at age 6 y (19). Nutrition in the first 2–3 y of life is important for growth. The addition of milk and milk products to the diet is associated with improved linear growth as shown by observational and interventional studies, especially in developing countries (20, 21). The increased growth with milk/milk product intake is attributed to the essential nutrients provided, especially the limiting minerals for bone mineral acquisition, and to stimulation of serum insulin-like growth factor I. Bone accretion is high during the first year of life, but cow milk is not recommended before 1 y of age. Infants rely on breast milk or formula and, on average, they meet their nutrient needs. The pubertal growth spurt is a critical time for building peak bone mass to protect against fracture risk as a child and later in life. Almost half of adult peak bone mass is acquired during adolescence (22). Approximately 95% of adult peak bone mass is acquired by the age of 16.2 y (23), emphasizing that nutrition can only influence peak bone mass appreciably before the end of adolescence. Thereafter, any benefits are to minimizing loss of peak bone mass, a much lower return on investment approach.

A meta-analysis of trials of dairy products and dietary calcium on BMC in children showed significantly higher total body and lumbar spine BMC with higher intakes when the comparison group had low calcium intakes (24). Benefits to growing bone by milk consumption appear to be more than merely providing required nutrients that are important to growing bone. In a growing rat model, when adequate dietary calcium was given as nonfat dry milk, bones were larger and stronger than when calcium was supplied as calcium carbonate (25). Moreover, when rats were switched to the same low-calcium diet during adulthood, rats fed nonfat dry milk during growth retained many of the advantages compared with rats fed calcium carbonate. In a retrospective study in postmenopausal women in NHANES III, low milk intake during childhood was associated with twice the risk of fracture (26). Studies of milk avoiders compared with age-matched cohorts in the same population with the same geographic and cultural environment are the strongest type of observational studies because they are the least confounded by factors such as other dietary constituents, race, sunlight, physical activity, etc. Studies of this type show an advantage to milk drinking in both children and adults. Milk avoiders in New Zealand children had a fracture risk of 34.8% compared with 13.0% for the matched cohort (27). In early pubertal girls in California and Indiana, perceived milk intolerance was inversely related to BMC for several bone sites ($P = 0.009$ for the lumbar spine and trends for total hip, femoral neck, and total body) (28). In contrast, lactose maldigestion, as measured by hydrogen breath analysis, was not related to bone measures.

There are no meta-analyses of RCTs of milk/milk product consumption and fracture outcomes or incidence of osteoporosis; however, there are meta-analyses and systematic reviews of calcium supplementation and fracture and meta-analyses of prospective studies of dairy intake and fracture (29, 30). A meta-analysis of prospective cohort studies concluded that there is no overall association between milk intake and hip fracture risk in women, whereas, in men, evidence was suggestive of a benefit of higher milk intake (31).

There are also matched-cohort studies in milk avoiders and milk consumers. In Finnish women aged 38–57 y, women who were lactose intolerant consumed 570 mg calcium daily

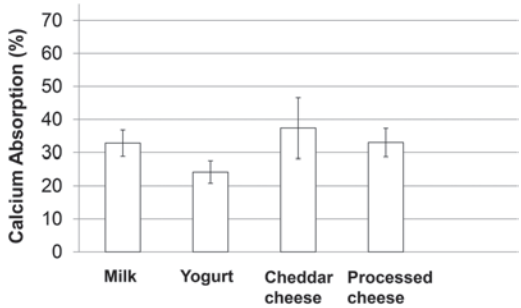

FIGURE 2. Mean (±SEM) calcium bioavailability from dairy products endogenously labeled with a stable calcium isotope in 7 adult women. There were no significant differences by ANOVA. Data are from reference 18.

compared with 850 mg daily in the lactose-tolerant group, and had double the risk of lower body fracture (OR: 2.15; 95% CI: 1.53, 3.04) (32).

Cardiovascular disease and blood pressure

As for bone, there is a lack of adequately powered RCTs on cardiovascular disease and blood pressure; the evidence used by the 2010 DGAC for a benefit of dairy is based on systematic reviews and meta-analyses of prospective and cohort studies (7). A systematic review and meta-analysis (32) showed a reduction in risk of myocardial infarction, ischemic heart disease, hypertension, and stroke in those consuming the highest amount of milk compared with those consuming the lowest amount. This was consistent with another systematic review (29) and a case-control study (34). It is also consistent with large prospective cohort studies published since the 2010 DGAC report (35–38). Also, published after the 2012 DGAC report was a meta-analysis reporting a 13% reduction in risk of all-cause mortality, an 8% reduction in risk of ischemic heart disease, and a 21% reduction in risk of stroke in those with the highest compared with the lowest intake of dairy (39). This contrasts with another meta-analysis of 6 prospective cohort studies that reported no association with milk and risk of coronary heart disease or stroke but a possible inverse relation to overall cardiovascular disease risk (40).

The DASH (Dietary Approaches to Stop Hypertension)-style diet includes low-fat dairy products (41). Because of the reduction in blood pressure associated with this dietary pattern, a diet high in potassium, calcium, and magnesium, which can be accomplished with a diet rich in fruit, vegetables and diary, is promoted in clinical and dietary guidelines.

Little evidence exists for individual dairy foods, although yogurt was associated with better systolic blood pressure, and fluid milk was associated with reduced systolic and diastolic blood pressure (42).

Type 2 diabetes and metabolic syndrome

One meta-analysis of 4 prospective studies constituted the evidence used by the 2010 DGAC to determine the benefit of dairy in reducing risk of diabetes. Those with the highest milk consumption compared with those with the lowest milk consumption had a 15% reduction in risk of type 2 diabetes (18). In a more recent meta-analysis of 7 cohort studies, there was a reduction of 18% in the risk of type 2 diabetes associated with low-fat dairy and a reduction of 17% with yogurt (43). The benefit of dairy on reduced risk of metabolic syndrome was based on 1 systematic review with meta-analysis, 1 prospective cohort study, and 3 cross-sectional cohort studies (8). The systematic review and meta-analysis reported a 26% reduction in risk of metabolic syndrome in those consuming the highest amounts of milk compared with those consuming the lowest amounts (33).

Subsequent to the DGAC report, Nicklas et al (44) reported that perceived lactose intolerance was associated with higher rates of diagnosis of diabetes and hypertension in the national sample of 3452 adults. The authors speculated that reduced dairy intake would reduce diet quality, ie, lower intakes of calcium, magnesium, vitamin D, and other nutrients that may predispose these individuals to higher risk of diseases.

CONCLUSIONS

This review examined the evidence for dietary guidelines for dairy. The evidence is strong for the role of dairy in meeting daily nutrient recommendations. Because milk and other dairy products are concentrated sources of so many essential nutrients, it is difficult to achieve recommended intakes with dietary patterns that contain little or no dairy products. This type of evidence is not from RCTs or prospective studies but from food intake analysis comparing nutrient composition associated with a range of intakes of dairy products to nutrient recommendations. The role of dairy in meeting nutrient recommendations has been shown largely for milk and recently for yogurt. Meeting nutrient recommendations has little to do with fat content or flavorings in the dairy products. The recommendation for low-fat dairy is more of a philosophical argument to reduce energy intake from fat and added sugar than from evidence of health concerns. Milk and cheese contribute 9.2% of intake of energy, 10.9% of fat, and 8.3% of carbohydrate in the diet of Americans, but these products also contribute 46.3% of calcium, 11.6% of potassium, and 7.9% of magnesium in the American diet, which may provide overriding benefits to health (45).

The evidence for a relation between dairy consumption and health is less strong because there are few adequately powered RCTs of sufficient duration to affect health outcomes of long latency periods relevant to milk. Evidence for a benefit is stronger in children for calcium balance and bone mineral density and in adults for blood pressure because these biomarkers of health outcomes can be studied in shorter RCTs. These types of studies are needed to compare the benefit of various dairy products. Because weight change can also be measured over a practical study duration of an RCT, the evidence for concluding that milk has no unique role in weight control was also considered strong by the 2010 DGAC. The evidence for disease outcome measures derives primarily from systematic reviews and meta-analyses of prospective cohort studies. Thus, there is limited to moderate evidence for a benefit of dairy intake on cardiovascular disease, metabolic syndrome, and type 2 diabetes.

The most productive path forward for strengthening our understanding of a health benefit specifically for yogurt or any other dairy product is with RCTs that use biomarkers of health. Yogurt and milk could be compared in balance studies measuring calcium, magnesium, and potassium absorption and retention, as well as blood pressure or other markers of metabolic syndrome.

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REFERENCES

1. USDA. USDA National Nutrient Database for Standard Reference. 2009. Available from: http://ndb.nal.usda.gov/ndb/search/list (cited 17 March 2014).
2. Gaucheron F. Milk and dairy products: a unique micronutrient combination. J Am Coll Nutr 2011;30:400S–9S.
3. US Department of Health and Human Services; USDA. Dietary guidelines for Americans, 2005. 6th ed. Washington, DC: US Government Printing Office, 2005.
4. Davis C, Saltos E. Dietary recommendations and how they have changed over time. In: America's eating habits: changes and

consequences. Agriculture Information Bulletin NO (AIB-750), pp 449. Washington, DC: USDA, Economics Research Service, 1999.
5. Post RC, Maniscalco S, Herrup M, Chang S. What's new on MyPlate? A new message, redesigned web site, and SuperTracker debut. J Acad Nutr Diet 2012;112:18–22.
6. Britten P, Lyon J, Weaver CM, Kris-Etherton P, Nicklas T, Weber J, Davis C. MyPyramid food intake pattern modeling for the Dietary Guidelines Advisory Committee. J Nutr Educ Behav 2006;38:S143.
7. Weaver C, Nicklas T, Britten P. The 2005 Dietary Guidelines Advisory Committee report. Nutr Today 2005;40:102–7.
8. The Dietary Guidelines Advisory Committee. Report of the Dietary Guidelines Advisory Committee on the Dietary guidelines for Americans, 2010. Washington DC: U.S. Department of Agriculture Research Service, 2011.
9. Nicklas TA, O'Neil CE, Fulgoni VL. The role of dairy in meeting the recommendations for shortfall nutrients in the American Diet. J Am Coll Nutr 2009;28:73S–81S.
10. Fulgoni V III, Nichols J, Reed A, Buckley R, Kafer K, Huth P, DiRienzo D, Miller GD. Dietary consumption and related nutrient intake in African-American adults and children in the United States: Continuing Survey of Food Intakes by Individuals 1994–1996, 1998, and the National Health and Nutrition Examination Survey 1999–2000. J Am Diet Assoc 2007;107:256–64.
11. Gao X, Wilde PE, Lichtenstein AH, Tucker KL. Meeting adequate intake for dietary calcium without dairy foods in adolescents aged 9 to 18 years (National Health and Nutrition Examination Survey 2001-2002). J Am Diet Assoc 2006;106:1759–65.
12. Fulgoni VL III, Keast DR, Auestad N, Quann EE. Nutrients from dairy foods are difficult to replace in diets of Americans: food pattern modeling and an analyses of the National Health and Nutrition Examination Survey 2003-2006. Nutr Res 2011;31:759–65.
13. Nicklas TA, Jahns L, Bogle ML, Chester DN, Giovanni M, Klurfeld DM, Laugero K, Liu Y, Lopez S, Tucker KL. Barriers and facilitators for consumer adherence to the Dietary Guidelines for Americans: the HEALTH Study. J Acad Nutr Diet 2013;113:1317–31.
14. Barger-Lux MJ, Heany RP, Pakard PT, Lappe JM, Recker RR. Nutritional correlations of low calcium intake. Clin Appl Nutr 1992;2:39–44.
15. Ranganathan R, Nicklas TA, Yang SJ, Berenson GS. The nutritional impact of dairy product consumption on dietary intakes of adults (1995–1996): the Bogalusa Heart Study. J Am Diet Assoc 2005;105:1391–400.
16. Coudray B. The contribution of dairy products to micronutrient intakes in France. J Am Coll Nutr 2011;30:410S–4S.
17. Wang H, Livingston KA, Fox CS, Meigs JB, Jacques PF. Yogurt consumption is associated with better diet quality and metabolic profile in American men and women. Nutr Res 2013;33:18–26.
18. Nickel KP, Martin BR, Smith DL, Smith JB, Miller GD, Weaver CM. Calcium bioavailability from bovine milk and dairy products in premenopausal women using intrinsic and extrinsic labeling techniques. J Nutr 1996;126:1406–11.
19. Ganpule A, Yajnik CS, Fall CHD, Rao S, Fisher DJ, Kanade A, Cooper C, Naik S, Joshi N, Lubree H, et al. Bone mass in Indian children—relationships to maternal nutritional status and diet during pregnancy: the Pune Maternal Nutrition Study. J Clin Endocrinol Metab 2006;91:2994–3001.
20. Allen LH, Dror DK. Effects of animal source foods, with emphasis on milk, in the diet of children in low-income countries. Nestle Nutr Workshop Ser Pediatr Program 2011;67:113–30.
21. Hoppe C, Mølgaard C, Juul A, Michaelsen MK. High intakes of skimmed milk, but not meat, increase serum IGF-I and IGF BP-3 in eight year old boys. Eur J Clin Nutr 2004;58:1211–6.
22. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, Weaver CM. Peak bone mass. Osteoporos Int 2000;11:985–1009.
23. Teegarden D, Proulx WR, Martin BR, Zhao J, McCabe GP, Lyle RM, Peacock M, Slemenda C, Johnston CC, Weaver CM. Peak bone mass in young women. J Bone Miner Res 1995;10:711–5.
24. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: results of a meta-analysis. Bone 2008;43:312–21.
25. Weaver CM, Janle E, Martin B, Browne S, Guiden H, Lachick P, Lee W-H. Dairy versus calcium carbonate in promoting peak bone mass and bone maintenance during subsequent calcium deficiency. J Bone Miner Res 2009;24:1411–9.
26. Kalkwarf HJ, Khoury JC, Lamphear BP. Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in U.S. women. Am J Clin Nutr 2003;77:257–65.
27. Goulding A, Rockell JE, Black RE, Grant AM, Jones IE, Williams SM. Children who avoid drinking cow's milk are at increased risk for prepubertal bone fractures. J Am Diet Assoc 2004;104:250–3.
28. Matlik L, Savaiano D, McCabe G, VanLoan M, Blue CL, Boushey CJ. Perceived milk intolerance is related to bone mineral content in 10- to 13-year-old female adolescents. Pediatrics 2007;120:e669–77.
29. Alvarez-León EE, Roman-Viñas B, Serra-Majem L. Dairy products and health: a review of the epidemiological evidence. Br J Nutr 2006;96:S94–9.
30. Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, McCloskey E, Mellstrong D, Pols H, Reeve J, et al. A meta-analysis of milk intake and fracture risk: low utility for case finding. Osteoporos Int 2005;16:799–804.
31. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Kanis JA, Orav EJ, Staehelin HB, Kiel DP, Burckhardt P, Henschkowski J, Spiegelman D, et al. Milk intake and risk of hip fracture in men and women: a meta-analysis of prospective cohort studies. J Bone Miner Res 2011;26:833–9.
32. Honkanen R, Kröger H, Alhava E, Turpeinen P, Tuppurainen M, Saarikoski S. Lactose intolerance associated with fractures of weight-bearing bone in Finnish women aged 38-57 years. Bone 1997;21:473–7.
33. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: an overview of evidence from cohort studies of vascular diseases, diabetes and cancer. J Am Coll Nutr 2008;27:723S–34S.
34. Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Stefanadis C. Modelling dairy intake on the development of acute coronary syndromes: the CARDIO2000 study. Eur J Cardiovasc Prev Rehabil 2006; 13:791–7.
35. Larsson SC, Virtamo J, Wolk A. Dairy consumption and risk of stroke in Swedish women and men. Stroke 2012;43:1775–80.
36. Bernstein AM, Pan A, Rexrode KM, Stampfer M, Hu FB, Mozaffarian D, Willett WC. Dietary protein sources and the risk of stroke in men and women. Stroke 2012;43:637–44.
37. Patterson E, Larsson SC, Wolk A, Akesson A. Association between dairy food consumption and risk of myocardial infarction in women differs by type of dairy food. J Nutr 2013;143:74–9.
38. Larsson SC, Orsini N, Wolk A. Dietary calcium intake and risk of stroke: a dose-response meta-analysis. Am J Clin Nutr 2013;97:951–7.
39. Elwood PC, Pickering JE, Givens I, Gallacher JE. The consumption of milk and dairy foods and the incidence of vascular disease and diabetes: an overview of the evidence. Lipids 2010;45:925–39.
40. Soedamah-Muthu SS, Ding El, Al-Delaimy Wk, Hu FB, Engberink MF, Willett WC, Geleijnse JM. Milk and dairy consumption and incidence of cardiovascular disease and all-cause mortality: dose-response meta-analysis of prospective cohort studies. Am J Clin Nutr 2011;93: 158–71.
41. Appel LJ, Moore TJ, Obarzanek E, Vallmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997;336:1117–24.
42. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. Am J Clin Nutr 2008;87:1914–25.
43. Tong X, Dong JY, Wu ZW, Li W, Qin LQ. Dairy consumption of risk of type 2 diabetes mellitus: a meta-analysis of cohort studies. Eur J Clin Nutr 2011;65:1027–31.
44. Nicklas TA, Qu H, Hughes SO, He M, Wagner SE, Foushee HR, Shewchuk RM. Self-perceived lactose intolerance results in lower intakes of calcium and dairy foods and is associated with hypertension and diabetes in adults. Am J Clin Nutr 2011;94:191–8.
45. Huth PJ, Fulgoni VL III, Keast DR, Park K, Auestad N. Major food sources of calories, added sugars, and saturated fat and their contribution to essential nutrient intake in the U.S. diet: data from the national health and nutrition examination survey (2003-2006). Nutr J 2013;12:116.

Nutrient density: principles and evaluation tools[1–3]

Adam Drewnowski and Victor L Fulgoni III

ABSTRACT

Nutrient profiling is the technique of rating or classifying foods on the basis of their nutritional value. Foods that supply relatively more nutrients than calories are defined as nutrient dense. Nutrient profile models calculate the content of key nutrients per 100 g, 100 kcal, or per serving size of food. For maximum effectiveness, nutrient profile models need to be transparent, based on publicly accessible nutrient composition data, and validated against independent measures of a healthy diet. These rigorous scientific standards were applied to the development of the Nutrient-Rich Foods (NRF) family of nutrient profile models. First, the NRF models included nutrients to encourage as well as nutrients to limit. Second, NRF model performance was repeatedly tested against the Healthy Eating Index (HEI), an independent measure of a healthy diet. HEI values were calculated for participants in the 1999–2002 NHANES. Models based on 100 kcal and serving sizes performed better than those based on 100 g. Formulas based on sums and means performed better than those based on ratios. The final NRF9.3 index was based on 9 beneficial nutrients (protein; fiber; vitamins A, C, and E; calcium; iron; potassium; and magnesium) and on 3 nutrients to limit (saturated fat, added sugar, and sodium). Higher NRF9.3 scores were associated with lower energy density and more nutrient-rich diets. The nutrient density of foods, paired with a comprehensive program of consumer education, can become the foundation of dietary recommendations and guidelines. *Am J Clin Nutr* 2014;99(suppl):1223S–8S.

INTRODUCTION

Nutrient profiling is the technique used to rate, rank, or classify foods on the basis of their nutritional value (1). Nutrient profile models provide ratings of overall nutrient density, as determined by a balance between beneficial nutrients and nutrients to limit (2–4). Among the beneficial nutrients to encourage are protein, dietary fiber, and a variety of vitamins and minerals, whereas nutrients to limit include free or added sugars, saturated fat, and sodium (2–4). Given that most foods provide multiple nutrients, developing a formal quantitative system to rate the overall nutritional value of individual foods poses both a scientific and a communications challenge.

The proposed front-of-pack labeling systems, as reviewed by the Institute of Medicine, are intended to help shoppers identify healthier food options readily and at a glance (5). Helping consumers identify and select nutrient-dense foods is expected to lead to higher-quality diets and better health (5–7). Studies based on analyses of NHANES data have pointed to an association between the consumption of nutrient-dense foods, lower energy intakes, higher diet quality overall, and improved health outcomes (3).

Nutrient profiling can also help identify foods that are nutrient rich, affordable, and sustainable. The inclusion of food prices in nutrient density calculations has allowed researchers to create new metrics of affordability and to identify those foods that provide the most nutrients per penny (8, 9). This econometric approach to nutrient profiling (10, 11) was among the first to explore the interrelations between nutrient density, energy density, and energy cost. More recent studies have taken nutrient profiling in a different direction, exploring the relation between the nutrient density of foods and their carbon footprint, as determined by greenhouse gas emissions from life-cycle analysis (12).

Nutrient profiling techniques developed for individual foods can also be applied to meals, menus, and total diets. By showing how the nutrient density concept applies to total diet quality and the economics of food choice behavior, nutrient profiling provides a ready way to put the *Dietary Guidelines for Americans* and MyPlate into practice (6, 7).

PRINCIPLES OF NUTRIENT PROFILING

The intent of composite nutrient density scores is to capture the multiple nutritional attributes of a given food (2, 3, 8). Wholesome, nutrient-rich foods receive high scores, whereas foods that provide calories but few nutrients score lower (2). By including multiple beneficial nutrients to encourage, balanced nutrient profile models shift the emphasis from "bad" nutrients to "good" and "better" foods. Nutrient profiling exemplifies a positive way to convey vital information about nutritional attributes of foods and beverages to the consumer (2, 3, 6, 7).

For nutrient profiling to remain a science, it needs to follow scientific rules (13). Thus far, the procedures for developing, testing, and validating nutrient profile models have not been standardized (14, 15). These include, but are not limited to, the selection of relevant nutrients, the choice of reference daily

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[2] Presented at the satellite symposium "First Global Summit on the Health Effects of Yogurt," held in Boston, MA, at ASN's Scientific Sessions at Experimental Biology 2013, 24 April 2013. The conference was organized by the ASN, the Nutrition Society, Danone Institute International, and the Dairy Research Institute. The supplement scientific guest editors were Sharon M Donovan, University of Illinois, Urbana, IL, and Raanan Shamir, Schneider Children's Medical Center and Tel Aviv University, Israel.

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values, and the basis of calculation: 100 kcal, 100 g, or serving size (14, 15). Nutrient profile models also need to be tested against other food attributes (14) and need to be validated with respect to independent measures of a healthy diet (3, 16).

The basic principles of nutrient profiling have been laid out before (1–3), stressing the need for objectivity, transparency, simplicity, and validation. Briefly, nutrient profile models had to be based on objective nutrition science; they had to be totally transparent and based on open-source data and published algorithms. Nutrient composition databases had to be of high quality and available from public sources. Simple algorithms were preferable to more complex ones, and alternative models were to be tested against other food attributes, notably energy density and energy cost (14, 15). Most important, alternative models were to be validated against independent measures of a healthy diet and, wherever possible, compared with selected health outcomes (16). Here, nutrient composition data for individual foods and beverages had to be supplemented with population-based data on diets and health.

NUTRIENT-RICH FOODS INDEX

The development of the Nutrient-Rich Foods (NRF)[4] Index closely followed the regulatory guidelines in the United States, as formulated by the US Food and Drug Administration (FDA) (1, 2). In particular, the selection of beneficial nutrients followed federal policies and standards (1, 2). Foods are defined as "healthy" by the FDA on the basis of their content of protein, fiber, vitamins A and C, calcium, and iron. Foods are disqualified by the FDA from carrying nutrition and health claims if they contain more than specified amounts of fat, saturated fat, *trans* fat, cholesterol, or sodium. Additional NRF nutrients were suggested by the 2005 *Dietary Guidelines* (17), which identified potassium, magnesium, and vitamin E as shortfall nutrients in the US diet. The goal was to produce a nutrient density score that would be consistent with the Nutrition Facts panel and could be used for front-of-pack labeling.

One way to visualize the nutrient density of foods is to determine the percentage daily value (%DV) of different nutrients per serving, always in relation to calories. Thus, a 6-ounce serving of plain skimmed-milk yogurt supplied <5% DV of daily calories but >30% DV of calcium, >25% DV of phosphorus, >10% DV of potassium and zinc, and >5% DV of magnesium. Similarly, a fruit-flavored low-fat yogurt provided <10% of dietary energy but >25% DV of calcium, >20% DV of phosphorous, close to 15% DV of protein, and >10% DV of potassium. Given the favorable nutrients-to-calories ratio, a yogurt can be defined as a nutrient-rich food.

Nutrient profiling aims to provide an overall nutrient density score on the basis of several nutrients. Reference DVs, based on a 2000-kcal diet, were obtained for protein (50 g); fiber (25 g); vitamins A (5000 IU), C (60 mg), and E (30 IU); calcium (1000 mg); iron (18 mg); potassium (3500 mg); and magnesium (400 mg). Nutrient contents of foods were converted to %DVs per reference amount and then capped at 100% DV so that foods containing very large amounts of a single nutrient would not obtain a disproportionately high index score (1). For nutrients to limit, maximum recommended values were 20 g for saturated fat, 125 g for total sugar, 50 g for added sugar, and 2400 mg for sodium. All scores were initially calculated per 100 kcal, per 100 g, or per serving size of food (14, 15).

The FDA-mandated serving sizes are otherwise known as reference amounts customarily consumed (RACCs). The FDA uses 139 different RACC values that are set lower for energy-dense sugar (4 g), fats and oils (15 g), and cheeses (30 g) than for meats (85 g), vegetables and fruit (120 g), yogurts (220 g), or milk, juices, and other beverages (240 g).

The family of NRF models was developed and tested by using the open-access USDA Food and Nutrient Database for Dietary Studies (FNDDS), which is used to code, process, and analyze the What We Eat in America dietary intake data (18). The FNDDS files include detailed food descriptions, food portions and weights, nutrient descriptions, and links to the USDA Standard Release nutrient composition databases (19). The FNDDS data now include vitamin D but need to be supplemented with the added sugar content of foods. RACC values were developed for 5096 foods in the FNDDS database.

In developing the family of NRF indexes, we first created nutrient-rich subscores based on a variable number *n* of beneficial nutrients (NR*n*). The NR*n* components were expressed as unweighted sums of %DVs (SUM) or as means of %DVs (MEAN) per reference amount. The negative limited nutrient score (LIM) component was based on 3 nutrients only (saturated fat, added sugar, and sodium), which were also expressed as % DVs per reference amount.

NRF indexes were calculated as the arithmetic differences between the positive (NR*n*) and the negative (LIM) components. A ratio-based algorithm was also tested. Food scores obtained by using alternative NR*n*, LIM, and NRF indexes were then compared with the energy density (kcal/100 g), energy cost ($/100 kcal), and nutrient content of the food. Different algorithms and calculation methods developed in past research (14, 15) are shown in **Table 1**.

Index calculations based on 100 kcal and 100 g or serving size gave rise to very different results. Foods that benefited the most from the 100-kcal calculation were low-energy-dense vegetables and salad greens, such as spinach, lettuce, endive, watercress, and cabbage. Foods that benefited more from the 100-g calculation were energy-dense foods, notably nuts and seeds, protein powder, and fortified cereals. RACC-based calculations benefited foods that were consumed in amounts >100 g, including fruit and fruit juices, cooked vegetables and juices, milk and yogurts, and other beverages and mixed foods. By contrast, foods that were consumed in amounts <100 g, such as nuts and seeds, and fortified cereals received lower scores under a RACC-based system.

The LIM subscore performed differently when calculated per 100 g or per RACC. The most pronounced differences were obtained for fats, mixed foods, and beverages. Calculations based on 100 g strongly penalized foods that contained saturated fat and sodium but that were regularly consumed in serving sizes well below 100 g. RACC-based LIM scores penalized beverages that contained added sugar and were consumed in 240-g portion sizes, as opposed to 100 g. A system based on 100 g was more lenient toward sugar-sweetened beverages than a system based on serving size (240 g in the United States).

[4] Abbreviations used: DV, daily value; FDA, US Food and Drug Administration; FNDDS, Food and Nutrient Database for Dietary Studies; HEI, Healthy Eating Index; LIM, limited nutrient score; NRF, Nutrient-Rich Foods (index); NR*n*, subscore based on a variable number *n* of beneficial nutrients; RACC, reference amount customarily consumed.

TABLE 1
Algorithms for NR*n* and LIM subscores and for the composite NRF nutrient profile models[1]

Model	Algorithm	Reference amount	Comment
Subscores NR*n*			
NR*n*_100 g	$\sum_{1-n}$ (Nutrient$_i$/DV$_i$) × 100	100 g	Nutrient$_i$ = content of nutrient *i* in 100 g DV = daily value
NR*n*_100 kcal	(NR*n*_100 g/ED) × 100	100 kcal	ED = energy density (kcal/100 g)
NR*n*_RACC	(NR*n*_100 g/100) × RACC	Serving	RACC = FDA serving size
Subscores LIM			
LIM_100 g	$\sum_{1-3}$ (L$_i$/MRV$_i$) × 100	100 g	L$_i$ = content of limiting nutrient *i* in 100g MRV = maximum recommended value
LIM_100 kcal	(LIM_100 g/ED) × 100	100 kcal	ED = energy density (kcal/100 g)
LIM_RACC	(LIM_100 g/100) × RACC	Serving	RACC = FDA serving size
Composite NRF*n*0.3			
NRF*n*.3_sum	NR*n*_100 kcal – LIM_100 kcal	100 kcal	Difference between sums
NRF*n*.3_mean	NR*n*/*n* – LIM/3	100 kcal	Difference between means
NRF*n*.3_ratio	NR*n*/LIM[2]	None	Ratio

[1] FDA, US Food and Drug Administration; LIM, limited nutrient score; NRF, Nutrient-Rich Foods; NR*n*, subscore based on a variable number *n* of beneficial nutrients; RACC, reference amount customarily consumed.
[2] NR*n*_100 g/LIM_100 g was equivalent to NR*n*_100 kcal/LIM_100 kcal and to NR*n*_RACC/LIM_RACC.

VALIDATION OF NUTRIENT PROFILE MODELS

Choosing the best nutrient profile model from among multiple alternatives is another scientific challenge (2, 19). In some validation studies, food rankings generated by different models were compared with mean ratings for the same foods generated by health professionals or by expert panels (20). Only 3 published, fully transparent models have been validated with respect to objective diet quality measures: the French SAIN/LIM (16), the British FSA-Ofcom model (19), and the NRF9.3 index (3).

In the NRF9.3 validation study (3), each food reported by subjects in the NHANES 1999–2002 was scored by using NR*n*, LIM, and NRF*n*.3 algorithms. The NR*n* and NRF*n*.3 indexes were based on a variable number *n* of beneficial nutrients (where *n* = 6–15). An average nutrient density score for each person was calculated on the basis of either 100 kcal or RACC, and Healthy Eating Index (HEI) 2005 values were independently calculated. Food-based scores per person were then regressed against HEI, with adjustment for sex, age, and ethnicity. The measure of index performance was the percentage of variation in HEI (R^2) explained by each model (3).

As shown in **Figure 1**, the NRF9.3 nutrient profile model based on 100 kcal and on RACC explained the most variation in HEI (44.5% of the variance). The NRF9.3 model was based on protein; fiber; vitamins A, C and E; calcium; iron; potassium; and magnesium. These are the nutrients of concern as identified by US government agencies and expert panels. The 3 nutrients to limit were saturated fat, added sugars, and sodium.

NRF indexes that included beneficial nutrients as well as nutrients to limit performed better than did indexes that were based on nutrients to limit only. The LIM score predicted ~32%

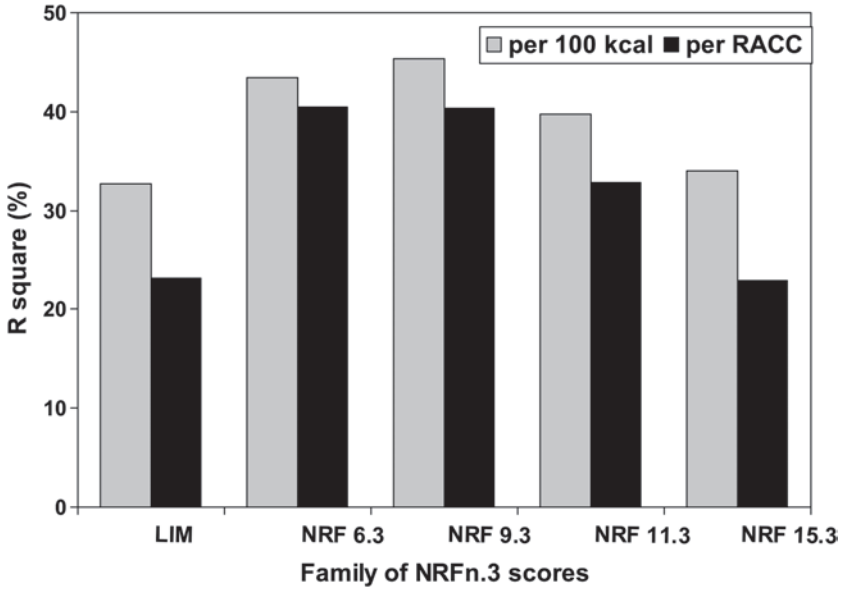

FIGURE 1. Linear regressions of LIM and NRF*n*.3 models on the Healthy Eating Index 2005 calculated for participants aged >4 y in the NHANES 1999–2002 database. Data are from reference 3 (Table 2, page 1551). LIM, limited nutrient score; NRF, Nutrient-Rich Foods; RACC, reference amount customarily consumed.

of the variance in HEI. Maximum variance in HEI was explained with the use of 6 or 9 beneficial nutrients; index performance actually declined with the inclusion of additional vitamins and minerals. The data confirmed previous studies (14, 15) showing that increasing the number of nutrients above 10 in a nutrient profile model provided little or no additional benefit in predicting overall diet quality.

In other analyses, NRF indexes based on 100 kcal (418 kJ) performed similarly to indexes based on RACC. Algorithms based on sums or means of nutrient-based subscores performed better than did algorithms based on dividing one subscore by another (eg, reference 21). Ratio-based scores are inherently problematic and may need to be radically transformed before they will be useful to consumers.

The NRF9.3 index was an unweighted score. Instances of weighted nutrient density scores do exist, and weights have been justified in a variety of ways: biological quality of nutrients, their bioavailability, their ubiquity in the food supply, and relative influence to health. In past studies, weighting has been based on expert opinion. However, new analyses point to novel approaches to weighting nutrients for inclusion in nutrient profiling schemes based on their estimated importance in the population diet (22).

IDENTIFYING NUTRIENT-DENSE FOODS

As shown in **Figure 2**, the median nutrient density of foods, as rated by the NRF system, differed across the major USDA food groups (2, 3). The highest scores were obtained by low-energy-dense vegetables and fruit, followed by legumes and eggs. Fats and oils, grains, and sweets had higher energy density and lower per-calorie nutrient content. Within food groups, whole grains scored higher than refined grains and 100% fruit juices scored higher than soft drinks. Lower-fat dairy products, including fluid milk and yogurts, had higher scores than did products containing more saturated fat.

Individual NRF9.3 scores showed more variance than did median scores for a given food category or food group. Thus, skimmed milk scored 123 on the NRF9.3 score, chocolate skimmed milk scored 56, milk with 2% fat (semiskimmed) scored 43, and whole milk 38. Plain nonfat yogurt scored 94, whereas vanilla-flavored nonfat yogurt scored 38. Lower NRF scores were obtained for ice cream and for some dairy desserts.

BUILDING HEALTHIER DIETS

Studies have shown that nutrient density is an accurate marker of healthy diets, distinguishing between diets that are energy dense and those that are nutrient rich (11). Participants in the 1999–2002 NHANES were then assigned to quintiles on the basis of their dietary NRF9.3 scores. Persons in the top quintile of NRF9.3 scores consumed more beneficial nutrients, including some that were not part of the model (vitamin B-12 and zinc). Their diets were also characterized by more whole grains, low-fat dairy, vegetables, and fruit. However, the more-nutrient-dense diets tended to be more expensive. As shown in **Figure 3**, the top NRF9.3 quintile was associated with significantly higher per-calorie diet costs compared with the lowest NRF9.3 quintile (4).

These findings, associating different nutrient density scores with diet quality measures, have implications for dietary guidance. Quintiles of NRF9.3 scores translated easily into a consumer-friendly 5-point scale (24). Preliminary data suggest that each point on a 5-point scale was approximately equivalent to 10% DV, a criterion favored by the FDA in regulating nutrition and health claims.

Focusing only on nutrients to limit may not necessarily guide consumers toward healthier options, especially if those options are associated with lower enjoyment and higher cost. However, a focus on nutrient density may influence healthier choices, as shown in a pilot intervention trial (25). However, more studies are

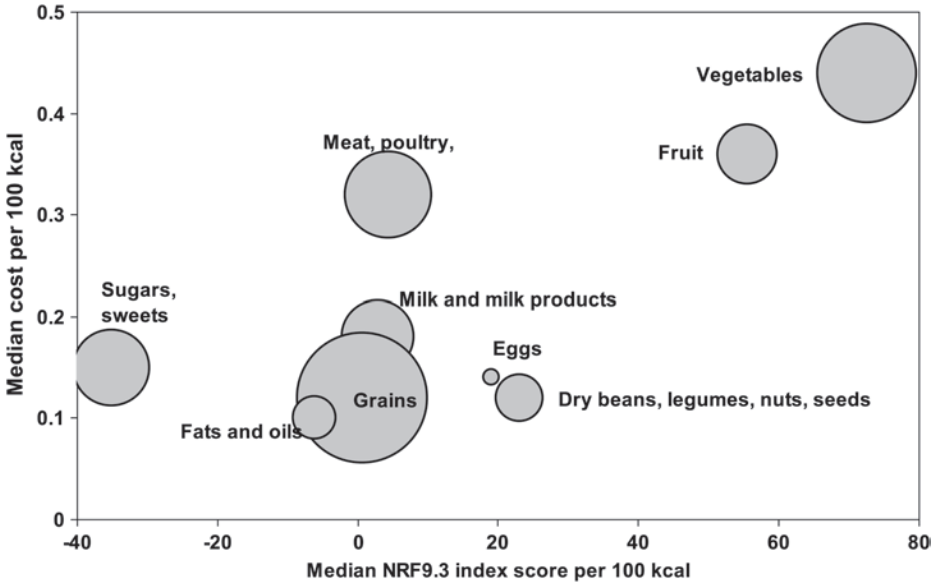

FIGURE 2. Median NRF9.3 index scores for each major USDA food group plotted against median cost per 100 kcal. Higher NRF index scores denote higher nutrient density per 100 kcal (from reference 4, Figure 2). The size of the bubble denotes the number of foods per food group (from reference 4, Table 2). NRF, Nutrient-Rich Foods.

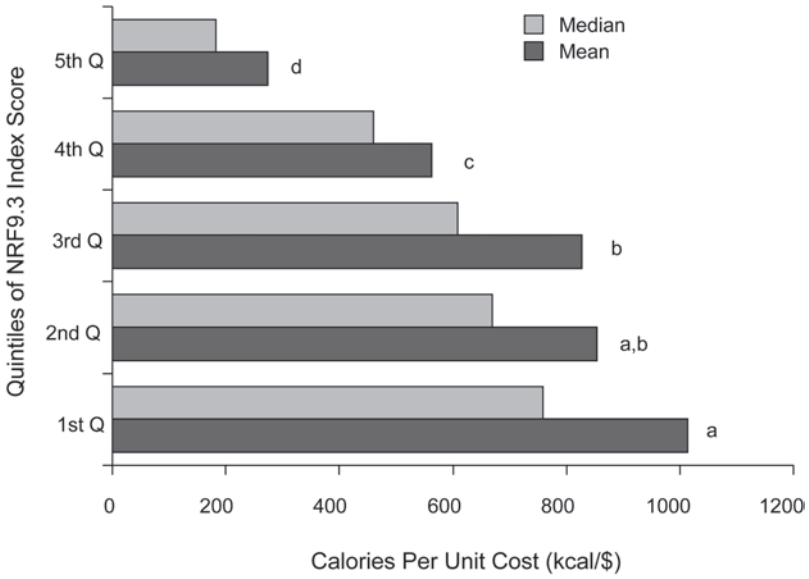

FIGURE 3. Quintiles of NRF9.3 index scores plotted against mean and median calories per unit cost. Higher NRF index score quintiles denote higher nutrient density per 100 kcal. Values with the same lowercase letters are not significantly different (from reference 4). NRF, Nutrient-Rich Foods; Q, quintile.

needed to confirm that nutrient density signposting can lead to positive changes in consumer food purchase behavior (26).

Nutrition experts agree that the US diet tends to be energy dense but nutrient poor (1). Increasing the consumption of lower-energy but nutrient-rich foods would achieve the twin objectives of reducing daily calories and increasing the overall nutrient density of the diet. Identifying foods that are affordable, sustainable, and nutrient rich is the goal of nutrient profiling (2–4). The NRF and other nutrient profiling models were intended to promote the consumption of fewer calories and more beneficial nutrients (2–4).

Paradoxically, much dietary advice emphasizes what nutrients to avoid. The notion of what constitutes a "healthful" food seems to be based on the absence of saturated fat, added sugars, and sodium rather than on the presence of beneficial nutrients that the food contains (1). As witnessed by dramatic increases in the rates of obesity and diabetes over the past 20 y, such negative dietary advice has not been effective. A more positive approach to dietary guidelines may prove to be more successful in the long term (6, 7).

Translating the concept of nutrient density into healthier everyday diets requires the combination of nutrient profiling methods with other strategies for improving food habits and health. Studies need to address food patterns and overall diet quality, especially in relation to sustainability and to monetary cost (23, 24) and greenhouse gas emissions (12). The NRF9.3 is the only index that has been linked to US food prices in an effort to identify affordable nutrient-rich foods that are part of the mainstream US diet.

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The authors' responsibilities were as follows—AD and VLF developed and tested published NRF metrics; VLF presented at the conference; AD took the lead on writing the manuscript; and both authors: approved the final content. VLF received financial reimbursement for travel expenses and an honorarium from the Danone Institute International for his participation in the conference and provides project and consulting services to the Dairy Research Institute. AD has had support for research on nutrient density and climate change from Groupe Danone (France) through the University of Washington. Initial development of the NRF9.3 index was supported by the Nutrient Rich Coalition.

REFERENCES

1. Drewnowski A. Concept of a nutritious food: toward a nutrient density score. Am J Clin Nutr 2005;82:721–32.
2. Drewnowski A, Fulgoni VL 3rd. Nutrient profiling of foods: creating a nutrient-rich food index. Nutr Rev 2008;66:23–39.
3. Fulgoni VL III, Keast DR, Drewnowski A. Development and validation of the Nutrient-Rich Foods Index: a tool to measure nutritional quality of foods. J Nutr 2009;139:1549–54.
4. Drewnowski A. The Nutrient Rich Foods Index helps to identify healthy, affordable foods. Am J Clin Nutr 2010;91(suppl):1095S–101S.
5. Wartella EA, Lichtenstein AH, Yaktine A, Nathan R, eds. Front-of-package nutrition rating systems and symbols: promoting healthier choices. Institute of Medicine, The National Academies Press. Available from: http://www.nap.edu/openbook.php?record_id=13221 (cited 30 July 2013).
6. Drewnowski A, Fulgoni VL 3rd, Young MK, Pitman S. Nutrient-rich foods: applying nutrient navigation systems to improve public health. J Food Sci 2008;73:H222–8.
7. Miller GD, Drewnowski A, Fulgoni V, Heaney RP, King J, Kennedy E. It is time for a positive approach to dietary guidance using nutrient density as a basic principle. J Nutr 2009;139:1198–202.
8. Darmon N, Darmon M, Maillot M, Drewnowski A. A nutrient density standard for vegetables and fruits: nutrients per calorie and nutrients per unit cost. J Am Diet Assoc 2005;105:1881–7.
9. Maillot M, Ferguson EL, Drewnowski A, Darmon N. Nutrient profiling can help identify foods of good nutritional quality for their price: a validation study with linear programming. J Nutr 2008;138:1107–13.
10. Maillot M, Darmon N, Darmon M, Lafay L, Drewnowski A. Nutrient-dense food groups have high energy costs: an econometric approach to nutrient profiling. J Nutr 2007;137:1815–20.
11. Drewnowski A. Defining nutrient density: development and validation of the Nutrient Rich Foods Index. J Am Coll Nutr 2009;28:421S–6S.
12. Vieux F, Soler LG, Touazi D, Darmon N. High nutritional quality is not associated with low greenhouse gas emissions in self-selected diets of French adults. Am J Clin Nutr 2013;97:569–83.
13. Tetens I, Oberdorfer R, Madsen C, de Vries J. Nutritional characterization of foods: Science based approach to nutrient profiling. Eur J Nutr 2007:46(suppl 2):4–14.
14. Drewnowski A, Maillot M, Darmon N. Testing nutrient profile models in relation to energy density and energy cost. Eur J Clin Nutr 2009;63:674–83.
15. Drewnowski A, Maillot M, Darmon N. Should nutrient profiles be based on 100 g, 100 kcal or serving size? Eur J Clin Nutr 2009;63:898–904.
16. Darmon N, Vieux F, Maillot M, Volatier J-L, Martin A. Nutrient profiles discriminate between foods according to their contribution to nutritionally adequate diets: a validation study using linear programming and the SAIN,LIM system. Am J Clin Nutr 2009;89:1227–36.

17. US Department of Health and Human Services; USDA. Dietary guidelines for Americans. Available from: http://www.health.gov/dietaryguidelines/dga2005/document/ (cited 14 March 2014).
18. USDA Food and Nutrient Database for Dietary Studies, 2.0. 2006 [monograph on the Internet]. Beltsville, MD: Agricultural Research Service, Food Surveys Research Group. Available from: http://www.ars.usda.gov/Services/docs.htm?docid=12083 (cited 14 March 2014).
19. Arambepola C, Scarborough P, Rayner M. Validating a nutrient profile model. Public Health Nutr 2008;11:371–8.
20. Scarborough P, Boxer A, Rayner M, Stockley L. Testing nutrient profile models using data from a survey of nutrition professionals. Public Health Nutr 2007;10:337–45.
21. Scheidt DM, Daniel E. Composite index for aggregating nutrient density using food labels: ratio of recommended to restricted food components. J Nutr Educ Behav 2004;36:35–9.
22. Arsenault JE, Fulgoni VL III, Hersey JC, Muth MK. A novel approach to selecting and weighting nutrients for nutrient profiling fo foods and diets. J Acad Nutr Diet 2012;112:1968–75.
23. Drewnowski A, Rehm CD. Vegetable cost metrics show that potatoes and beans provide most nutrients per penny. PLoS ONE 2013:8(5): e63277.
24. Drewnowski A. New metrics of affordable nutrition: which vegetables provide most nutrients for least cost. J Acad Nutr Diet 2013; 113:1182–7.
25. Mobley AR, Kraemer D, Nicholls J. Putting the nutrient –rich food index into practice. J Am Coll Nutr 2009;28:427S–35S.
26. Glanz K, Hersey J, Cates S, Muth M, Creel D, Nicholls J, Fulgoni V 3rd, Zaripheh S. Effect of a Nutrient Rich Foods consumer education program: results from the nutrition advice study. J Acad Nutr Diet 2012;112:56–63.

Yogurt and weight management[1–4]

Paul F Jacques and Huifen Wang

ABSTRACT

A large body of observational studies and randomized controlled trials (RCTs) has examined the role of dairy products in weight loss and maintenance of healthy weight. Yogurt is a dairy product that is generally very similar to milk, but it also has some unique properties that may enhance its possible role in weight maintenance. This review summarizes the human RCT and prospective observational evidence on the relation of yogurt consumption to the management and maintenance of body weight and composition. The RCT evidence is limited to 2 small, short-term, energy-restricted trials. They both showed greater weight losses with yogurt interventions, but the difference between the yogurt intervention and the control diet was only significant in one of these trials. There are 5 prospective observational studies that have examined the association between yogurt and weight gain. The results of these studies are equivocal. Two of these studies reported that individuals with higher yogurt consumption gained less weight over time. One of these same studies also considered changes in waist circumference (WC) and showed that higher yogurt consumption was associated with smaller increases in WC. A third study was inconclusive because of low statistical power. A fourth study observed no association between changes in yogurt intake and weight gain, but the results suggested that those with the largest increases in yogurt intake during the study also had the highest increase in WC. The final study examined weight and WC change separately by sex and baseline weight status and showed benefits for both weight and WC changes for higher yogurt consumption in overweight men, but it also found that higher yogurt consumption in normal-weight women was associated with a greater increase in weight over follow-up. Potential underlying mechanisms for the action of yogurt on weight are briefly discussed. *Am J Clin Nutr* 2014;99(suppl):1229S–34S.

INTRODUCTION

Overweight and obesity lead to increased risk of many deleterious health outcomes, including cardiovascular disease, type 2 diabetes, hypertension, some cancers, and many other chronic conditions and result in a reduced life expectancy (1–4). Because of their comorbidities and associated disability, overweight and obesity are associated with considerable economic costs resulting from reduced working capability and increased health care expenditures (5). Diet plays a key role in long-term maintenance of body weight and body composition (6), but apart from affecting energy balance, we still have a limited understanding of the specific foods, nutrients, and other dietary constituents that might influence weight maintenance.

Dairy products comprise a major food group and are an important nutrient source in the American diet (7, 8). Nutritional qualities of dairy have been widely examined in observational studies and randomized controlled trials (RCTs)[5] that target the change, management, or maintenance of body weight and adiposity (9–12).

Although yogurt and milk have a generally similar nutrient composition (13, 14), yogurt is a relatively unique dairy product. Because of its specific manufacturing procedures and fermentation, many nutrients, including protein, riboflavin, vitamin B-6, vitamin B-12, calcium, potassium, zinc, and magnesium, are more concentrated (ranging from 20% to >100%) in yogurt than in milk (15); and the acidity of yogurt increases the bioavailability of specific nutrients such as calcium (16). In a recent cross-sectional analysis in 6526 American adults, we found that yogurt consumers were more likely than those who did not consume yogurt to have a better overall diet quality and a higher potassium intake and were less likely to have inadequate intakes of riboflavin, vitamin B-12, calcium, magnesium, and zinc (17). Yogurt also has more lactic acid and galactose but less lactose than milk (13, 14). In addition to increased protein concentrations, yogurt has higher concentrations of specific peptides and free amino acids than milk (13, 14). Moreover, probiotics in yogurt have possible health benefits (18, 19). Although there has been growing interest in yogurt's relation to gut and immunologic function and aspects of cardiometabolic health (13–16), this remains understudied in relation to weight maintenance.

The primary purpose of this review is to summarize the existing human evidence on the relation between yogurt and the management and maintenance of body weight and composition. We also briefly explore potential underlying mechanisms. In

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[2] Presented at the satellite symposium "First Global Summit on the Health Effects of Yogurt," held in Boston, MA, at ASN's Scientific Sessions at Experimental Biology 2013, 24 April 2013. The conference was organized by the ASN, the Nutrition Society, Danone Institute International, and the Dairy Research Institute. The supplement scientific guest editors were Sharon M Donovan, University of Illinois, Urbana, IL, and Raanan Shamir, Schneider Children's Medical Center and Tel Aviv University, Israel.

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[5] Abbreviations used: CARDIA, Coronary Artery Risk Development in Young Adults; FFQ, food-frequency questionnaire; NHS, Nurses' Health Study; RCT, randomized controlled trial; SU.VI.MAX, SUpplementation en VItamines et Mineraux AntioXydants; WC, waist circumference.

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assessing the evidence linking yogurt to weight and the potential mechanisms of action, it is important to consider yogurt in the context of overall dairy to determine whether the potential health benefits of yogurt are just a consequence of its being a dairy food or if there are health effects that are unique to yogurt.

YOGURT CONSUMPTION AND WEIGHT AND FAT LOSS: EVIDENCE FROM CLINICAL TRIALS

A recent meta-analysis by Chen et al (11) summarizes the results from 29 RCTs that examined the effects of various dairy interventions on changes in body weight and fat mass. Their findings suggested that, overall, dairy interventions resulted in no significant weight loss but a modest reduction in fat mass. However, when the trials were stratified on the basis of whether or not the treatment diets were energy restricted, there was a modest effect of dairy interventions (compared with control groups) on weight and fat loss when used as part of an energy-restricted diet. Dairy interventions did not promote more loss in weight or fat mass than did control dietary regimens among the trials with ad libitum interventions.

Among these 29 RCTs, yogurt was included as part of the intervention in 15 trials. A combination of yogurt and milk was used as the intervention in 2 trials; 11 allowed participants to choose freely from yogurt, cheese, and milk; but only 2 trials considered yogurt alone as the dairy intervention, a 2005 trial by Zemel et al (20) and a 2011 trial conducted by Thomas et al (21). Both of these were energy-restriction trials. Specifically, Zemel et al (20) randomly assigned 34 obese individuals to a yogurt intervention [a 6-ounce (170-g) serving of fat-free yogurt 3 times/d] or a control diet [including a 6-ounce (170-g) gelatin-based dessert placebo 3 times/d] providing, at most, 1 serving dairy/d as part of a 12-wk, 500-kcal/d deficit diet. The yogurt intervention resulted in a 33% greater reduction in body weight, a 60% greater loss of body fat, and a 31% reduction in the loss of lean body mass than did the control diet. Thomas et al (21) randomly assigned 29 overweight women who were engaged in a resistance-training program to two 6-ounce (170-g) fat-free yogurt supplements (3 times/wk) or two 6-ounce (170-g) isoenergetic sucrose beverages (3 times/wk) as part of a 250-kcal/d energy-deficit diet for a period of 16 wk. Differences in loss of weight, total fat, waist circumference (WC), sagittal diameter, and trunk fat were not significantly different between the yogurt and control groups in this trial.

This summary shows the paucity of intervention data relating yogurt to weight loss and weight maintenance. There are only 2 RCTs (20, 21), one of which shows a significant benefit of yogurt (20), whereas findings from the second were equivocal (21). There are differences between these 2 trials that may be responsible for the discrepant findings, such as differences in participants' weight, control diets, and length of follow-up. However, perhaps the most important difference was the yogurt dose. The yogurt intervention in the trial by Thomas et al (21) provided 1020 g fat-free yogurt per week, whereas the weekly dosage provided in the study by Zemel et al was 3.5-fold higher (20). One important limitation of both of these RCTs in assessing the unique effect of yogurt relative to other dairy products was the lack of a comparable dairy control. Without such a control, we cannot confidently attribute the observed effects on weight and body composition to any special properties of yogurt.

YOGURT CONSUMPTION AND WEIGHT AND WC: EVIDENCE FROM OBSERVATIONAL STUDIES

In addition to the RCTs examining the effect of dairy on weight, there is also an extensive observational literature on dairy and weight management. Louie et al (9) published a systematic review of prospective observational studies of dairy and weight gain in 2011. They identified 19 prospective cohort studies of dairy intake and change in weight or body fat; only 3 considered yogurt as a separate item (22–25). Subsequent to publication of this review, 2 additional studies were published that considered yogurt separately (25, 26). These 5 prospective observational studies are summarized in **Table 1**. Because yogurt (and in some cases dairy) was not the focus of these studies, some of the details with regard to yogurt consumption in these 5 articles were limited.

Pereira et al (22) based their report on a 10-y follow-up of >2700 participants from the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a sample of young adults (mean age: 25 y) from 4 large US metropolitan areas. More than half of the participants were black. A 28-d diet history questionnaire was used at baseline to collect the frequency of consumption for selected foods. The median frequency of yogurt intake in whites was 0.3 times/wk for overweight participants and 0.5 times/wk for normal-weight participants; the median consumption of yogurt was 0 times/wk in black participants irrespective of weight status. Drapeau et al (23) examined food groups and weight change over an average follow-up of 5.9 y in the Quebec Family Study, a small cohort of 248 parents and their offspring (≥18 y) from Quebec, Canada. The mean age of this cohort was 40 y. Yogurt intake was assessed at baseline and at the final study visit by using a 3-d diet record, but the authors did not provide information on the frequency of yogurt consumption in this population. Vergnaud et al (24) examined yogurt intake and change by using data from the SUpplementation en VItamines et Mineraux AntioXydants (SU.VI.MAX) trial, a large antioxidant vitamin and mineral intervention study that recruited participants from throughout France. They based their analysis on 13,017 participants (mean age: 51 y) with an average follow-up of 6 y. Information on dietary intake was collected at baseline via several 24-h dietary recalls. Mean yogurt intakes were 0.52 and 0.67 servings/d (125 g yogurt/serving) in men and women, respectively. Mozaffarian et al (25) used data for >120,000 men and women from the 3 Harvard health professionals' cohorts: the Nurses' Health Study (NHS; 20-y follow-up), NHS-II (12-y follow-up), and the Health Professionals Follow-Up Study (20-y follow-up). Mean ages were 52, 38, and 51 y in the NHS, NHS-II, and Health Professionals Follow-Up Study, respectively. These investigators excluded individuals who were obese or had any chronic disease. Dietary intake was repeatedly assessed during follow-up in these 3 cohorts by Harvard food-frequency questionnaires (FFQs) (27). Although yogurt intake was assessed by the FFQ, the authors did not present information on the usual amounts of yogurt consumed by members of these cohorts in their article. Finally, our recent longitudinal analysis of the Framingham Heart Study offspring cohort (26) included 3440 participants with 11,683

TABLE 1
Summary of prospective observational studies of yogurt consumption and changes in weight and WC[1]

	Pereira et al (22)	Drapeau et al (23)	Vergnaud et al (24)	Mozaffarian et al (25)	Wang et al (26)
Study population	CARDIA	Quebec Family Study	SU.VI.MAX trial	NHS, NHS-II, and HPFS	Framingham Heart Study Offspring Cohort
Age (y)	25 (18–30)[2]	40 (18–65)	51 (35–60)	52 (NHS), 38 (NHS-II), 51 (HPFS)	54 (26–84)
Study size (*n*)	2056 [BMI (in kg/m^2) <25]; 675 (BMI ≥25)	248	13,017	120,877	3440
Follow-up (y)	10	6	6	20 (NHS), 12 (NHS-II), 20 (HPFS)	13
Diet assessment	28-d FFQ (baseline, 7 y)	3-d diet records (baseline, 6 y)	Six or more 24-h dietary recalls	3–5 FFQs	4 FFQs
Yogurt intake	Median (servings/wk): 0.00 (blacks), 0.45 (whites)	Not reported	Mean (servings/d): 0.52 (men), 0.67 (women)	Not reported	Mean (servings/wk): 0.86 at baseline
Results	BMI <25: not reported BMI ≥25—OR (95% CI) for 10-y obesity incidence: 0.47/serving (0.16, 1.43)	6-y Δyogurt not associated with Δweight 6-y Δyogurt positively associated with ΔWC (0.42 cm/serving) (P = 0.02)	Men: normal weight, no association; overweight—6-y Δ weight 1.1 kg less and ΔWC 1.3 cm less for >1.1 servings/d vs <0.2 servings/d (P = 0.01 and P = 0.03) Women: normal weight—6-y Δweight 0.7 kg more for >1.3 servings/d vs <0.4 servings/d (P = 0.04); no association with ΔWC; overweight: no association with Δweight or ΔWC	4-y Δweight 0.82 pounds less for each yogurt serving/d; similar association seen in all 3 cohorts	ΔWeight 0.09 kg/y less for ≥3 servings/wk vs <1 serving/wk (P = 0.03); ΔWC 0.14 cm/y less for ≥3 servings/wk vs <1 serving/wk (P = 0.008)

[1] CARDIA, Coronary Artery Risk Development in Young Adults Study; FFQ, food-frequency questionnaire; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; SU.VI.MAX, SUpplementation en VItamines et Mineraux AntioXydants; WC, waist circumference; Δ, change.
[2] Mean; range in parentheses (all such values).

observations and a median follow-up of 12.9 y. Data on dietary intake and anthropometric measurements were collected at baseline and at 3 follow-up examinations. The Harvard FFQ (27) was used to assess participants' usual dietary intake. At baseline, the mean yogurt intake was 0.86 servings/wk. By the end of follow-up, that intake had increased to 1.35 servings/wk. A standardized serving size of yogurt on the FFQ was 1 cup (227 g).

The findings varied across these 5 studies (Table 1). Results from the CARDIA study (22) reported that the OR for 10-y incident obesity associated with each additional serving yogurt/d was 0.47 (95% CI: 0.16, 1.43) among young adults who were overweight at baseline after adjustment for numerous lifestyle and dietary factors. These results were inconclusive because of the low power to detect an association in the overweight participants. The authors did not present the results for normal-weight participants. The Quebec Family Study (23) found no association between change in yogurt consumption and weight change but observed a positive association with the change in WC after adjustment for age, initial weight or WC, and change in physical activity. These investigators observed that an increase of 1 serving yogurt/d from baseline to the end of follow-up was associated with a 0.42-cm increase in WC over the 6-y follow-up period ($P = 0.02$). The SU.VI.MAX trial examined yogurt intake and changes in weight and WC by participants' sex and weight status (24). Significantly less gain in weight and WC was found in overweight men but not in normal-weight men. Overweight men who consumed >1.1 serving yogurt/d gained, on average, 1.1 kg (55%) less body weight and 1.3 cm (80%) less WC over the 6-y follow-up compared with overweight men who consumed <0.2 servings/d ($P = 0.01$ and $P = 0.03$, respectively). In contrast, there was no association seen between yogurt and weight change in overweight women whereas normal-weight women who consumed >1.3 servings yogurt/d gained, on average, 0.7 kg (53%) more weight than did their counterparts who consumed <0.4 servings yogurt/d over the 6-y follow-up ($P = 0.04$). There was no association between yogurt consumption and WC among women irrespective of baseline weight (24). Mozaffarian et al (25) reported that the 4-y weight gain was, on average, 0.82 pounds (~0.37 kg) less with each additional serving of yogurt/d consumed ($P < 0.001$); this inverse association was similar in all the 3 cohorts that they examined. Finally, in our recent longitudinal analysis of the Framingham Heart Study offspring cohort (26), we observed that participants who consumed ≥3 servings yogurt/wk gained 0.09 kg less body weight/y and 0.14 cm less WC/y than those consuming <1 serving yogurt/wk after adjustment for sex, age, smoking status, physical activity, weight or WC at the start of each examination interval, energy intake, and overall diet quality assessed by the Dietary Guidelines Adherence Index score (28) ($P = 0.03$ and 0.008 for weight and WC, respectively). We observed similar associations with total dairy and both weight change ($P = 0.04$) and WC change ($P = 0.05$). However, it should be noted that the similar observations seen for total dairy and yogurt intake are based on ≥3 servings/d for total dairy but only ≥3 servings/wk for yogurt, suggesting similar potential benefits at a much lower intake of yogurt. Moreover, after yogurt from total dairy intake was excluded, these associations with total dairy intake were weakened and were no longer statistically significant.

There are no clear reasons for the lack of consistent findings between studies. The CARDIA study (22) findings for overweight individuals are underpowered because of the relatively small number of overweight participants and the small proportion of yogurt consumers in this young adult cohort. The Quebec Family Study (23) was the only one of these studies to base intake on 3-d diet records, which may have led to greater misclassification of yogurt intake given the episodic nature of yogurt consumption in North America. Also, the authors of this study took a different analytic approach to examine this relation. Rather than relating absolute intake amounts to changes in weight or WC, they examined the association between the change in yogurt and change in weight and WC over the study's follow-up period. The change in intake may not relate to the typical (ie, average) intake during follow-up. The SU.VI.MAX trial (24) investigators stratified their sample by sex and baseline weight status. Even though the test for interaction between baseline weight, sex, and yogurt consumption was marginally significant ($P = 0.04$), it is possible that the variation in results observed within these stratified analysis was spurious or, as the authors of this study suggested, the differences could be a consequence of different dietary patterns for men and women and for body weight status. More large prospective studies, particularly studies in populations with higher yogurt consumption, are warranted to help clarify the role of yogurt in maintaining a healthy weight.

POTENTIAL UNDERLYING MECHANISMS

Although there is limited human evidence on the role of yogurt in weight change, there is no shortage of hypothesized mechanisms for the effect of yogurt on weight and fat mass. As mentioned previously, yogurt is a concentrated dairy product, providing a greater amount of various water-soluble nutrients (eg, calcium) per serving size than do milk drinks (15). In addition, some nutrients in yogurt are more bioavailable than in other forms of dairy (29). Calcium and other nutrients (eg, whey and casein proteins, bioactive peptides, amino acids, and fatty acids), which are abundant in yogurt (13, 14), have been shown, or have been proposed, to facilitate loss of weight and fat mass (30–32). Higher calcium intake is thought to reduce lipogenesis and stimulate lipolysis and lipid oxidation through its effects on intracellular calcium concentrations, mediated primarily by calcitriol concentrations (30). It has been shown that the increase in circulating calcitriol resulting from low-calcium diets can stimulate calcium influx into adipocytes. Increased intracellular calcium, in turn, promotes adiposity as it stimulates lipogenic gene expression and lipogenesis and inhibits lipolysis, leading to increased lipid in adipocytes. Calcium may also interact with other nutrients and components of dairy foods and with fermentation products because sources of dairy calcium appear to have a greater effect on weight change than does supplemental calcium, perhaps acting synergistically with bioactive peptides and branch chain amino acids (30). The potential roles of calcium and other dairy bioactive compounds in weight maintenance are not unique to yogurt, but, as noted above, the amount and availability of calcium and some of the other potential bioactive constituents of dairy are generally greater in yogurt than in equal amounts of milk.

There is also much recent evidence supporting a role of gut microbiota in weight control (33–35). As a fermented dairy product, yogurt is a good source of probiotic bacteria that may favorably alter the gut microbiota. The dominant gut microbiota of obese mice or humans differs substantially from that of their

lean counterparts and appears to use energy from diets in a more efficient manner, which may promote weight gain (33, 34). Such differences in the energy-harvest capacity of microbiota are transmissible between obese and lean donors (34). It is believed that the bacteria in probiotic yogurt can enhance the growth of beneficial intestinal microbiota and influence gut function and distant tissues through regulation of the immune system (36); such effects may result in weight loss or in prevention of weight gain. A recent mouse study showed that supplementing with a probiotic yogurt inhibited the weight gain resulting from a westernized diet and aging (35). The authors further examined the underlying mechanisms and showed that a bacterium purified from yogurt was able to inhibit fat accumulation via an adaptive immune cell mechanism and that a preexisting diverse gut microbial community was essential for this good bacterium to exert its beneficial effect (35).

Another underlying mechanism may include the potential difference in satiety resulting from the consumption of yogurt compared with other drinks or dairy products. Small short-term RCTs have shown that yogurt is more satiating than other selected foods such as fruit drinks, chocolate bars, and crackers; however, this effect does not translate into lower subsequent energy intakes (37–39).

CONCLUSIONS

Although there is a large body of data that relates dairy intake to weight management, we still know little about the specific role that yogurt might play and whether any beneficial effects of yogurt are unique to its specific properties or merely attributable to the fact that it is a dairy food. As we accumulate additional evidence for or against a benefit of yogurt consumption on weight management, the uncertain weight benefits of yogurt should not deter recommendations for including yogurt as part of a healthy diet, because it is a nutrient-dense, lower-calorie food that can help many Americans meet the dairy recommendations of the 2010 *Dietary Guidelines for Americans* (40).

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REFERENCES

1. World Health Organization. Controlling the global obesity epidemic. Available from: http://www.who.int/nutrition/topics/obesity/en/index.html (cited 30 April 2012).
2. Mathieu P, Lemieux I, Despres JP. Obesity, inflammation, and cardiovascular risk. Clin Pharmacol Ther 2010;87:407–16.
3. Despres JP, Arsenault BJ, Cote M, Cartier A, Lemieux I. Abdominal obesity: the cholesterol of the 21st century? Can J Cardiol 2008;24 (suppl D):7D–12D.
4. Brown WV, Fujioka K, Wilson PW, Woodworth KA. Obesity: why be concerned? Am J Med 2009;122:S4–11.
5. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff (Millwood) 2009;28:w822–31.
6. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, et al; American Heart Association Nutrition Committee. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006;114:82–96.
7. Nicklas TA, O'Neil CE, Fulgoni VL III. The role of dairy in meeting the recommendations for shortfall nutrients in the American diet. J Am Coll Nutr 2009;28(suppl 1):73S–81S.
8. Drewnowski A. The contribution of milk and milk products to micronutrient density and affordability of the U.S. diet. J Am Coll Nutr 2011;30:422S–8S.
9. Louie JC, Flood VM, Hector DJ, Rangan AM, Gill TP. Dairy consumption and overweight and obesity: a systematic review of prospective cohort studies. Obes Rev 2011;12:e582–92.
10. Dougkas A, Reynolds CK, Givens ID, Elwood PC, Minihane AM. Associations between dairy consumption and body weight: a review of the evidence and underlying mechanisms. Nutr Res Rev 2011;24:72–95.
11. Chen M, Pan A, Malik VS, Hu FB. Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012;96:735–47.
12. Abargouei AS, Janghorbani M, Salehi-Marzijarani M, Esmaillzadeh A. Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Int J Obes(Lond) 2012;36:1485–93.
13. Kurmann JA, Rasic JL. Fermented fresh milk products and their cultures. Copenhagen, Denmark: Technical Dairy Publishing House, 1978.
14. Shahani KM, Chandan RC. Nutritional and healthful aspects of cultured and culture-containing dairy foods. J Dairy Sci 1979;62:1685–94.
15. Agricultural Research Service, USDA. National Nutrient Database for Standard Reference, release 26. Available from: http://ndb.nal.usda.gov/ndb/search/list (cited 23 December 2013).
16. Buttriss J. Nutritional properties of fermented milk products. Int J Dairy Technol 1997;50:21–7.
17. Wang H, Livingston KA, Fox CS, Meigs JB, Jacques PF. Yogurt consumption is associated with better diet quality and metabolic profile in American men and women. Nutr Res 2013;33:18–26.
18. Adolfsson O, Meydani SN, Russell RM. Yogurt and gut function. Am J Clin Nutr 2004;80:245–56.
19. Meydani SN, Ha WK. Immunologic effects of yogurt. Am J Clin Nutr 2000;71:861–72.
20. Zemel MB, Richards J, Mathis S, Milstead A, Gebhardt L, Silva E. Dairy augmentation of total and central fat loss in obese subjects. Int J Obes (Lond) 2005;29:391–7.
21. Thomas DT, Wideman L, Lovelady CA. Effects of a dairy supplement and resistance training on lean mass and insulin-like growth factor in women. Int J Sport Nutr Exerc Metab 2011;21:181–8.
22. Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA study. JAMA 2002;287:2081–9.
23. Drapeau V, Despres JP, Bouchard C, Allard L, Fournier G, Leblanc C, Tremblay A. Modifications in food-group consumption are related to long-term body-weight changes. Am J Clin Nutr 2004;80:29–37.
24. Vergnaud AC, Peneau S, Chat-Yung S, Kesse E, Czernichow S, Galan P, Hercberg S, Bertrais S. Dairy consumption and 6-y changes in body weight and waist circumference in middle-aged French adults. Am J Clin Nutr 2008;88:1248–55.
25. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404.
26. Wang H, Troy LM, Rogers GT, Fox CS, McKeown NM, Meigs JB, Jacques PF. Longitudinal association between dairy consumption and changes of body weight and waist circumference: the Framingham Heart Study. Int J Obes (Lond) 2014;38:299–305.
27. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26; discussion 1127–36.
28. Fogli-Cawley JJ, Dwyer JT, Saltzman E, McCullough ML, Troy LM, Jacques PF. The 2005 Dietary Guidelines for Americans Adherence Index: development and application. J Nutr 2006;136:2908–15.
29. Pfeuffer M, Schrezenmeir J. Milk and the metabolic syndrome. Obes Rev 2007;8:109–18.
30. Zemel MB. The role of dairy foods in weight management. J Am Coll Nutr 2005;24:537S–46S.

31. Zemel MB, Thompson W, Milstead A, Morris K, Campbell P. Calcium and dairy acceleration of weight and fat loss during energy restriction in obese adults. Obes Res 2004;12:582–90.
32. Zemel MB, Richards J, Milstead A, Campbell P. Effects of calcium and dairy on body composition and weight loss in African-American adults. Obes Res 2005;13:1218–25.
33. Kallus SJ, Brandt LJ. The intestinal microbiota and obesity. J Clin Gastroenterol 2012;46:16–24.
34. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006;444:1027–31.
35. Poutahidis T, Kleinewietfeld M, Smillie C, Levkovich T, Perrotta A, Bhela S, Varian BJ, Ibrahim YM, Lakritz JR, Kearney SM, et al. Microbial reprogramming inhibits Western diet-associated obesity. PLoS ONE 2013;8:e68596.
36. Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. Nature 2012;489:231–41.
37. Tsuchiya A, Almiron-Roig E, Lluch A, Guyonnet D, Drewnowski A. Higher satiety ratings following yogurt consumption relative to fruit drink or dairy fruit drink. J Am Diet Assoc 2006;106:550–7.
38. Chapelot D, Payen F. Comparison of the effects of a liquid yogurt and chocolate bars on satiety: a multidimensional approach. Br J Nutr 2010;103:760–7.
39. Almiron-Roig E, Grathwohl D, Green H, Erkner A. Impact of some isoenergetic snacks on satiety and next meal intake in healthy adults. J Hum Nutr Diet 2009;22:469–74.
40. USDA. Dietary guidelines for Americans, 2010. Available from: http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/PolicyDoc/PolicyDoc.pdf (cited 30 November 2012).

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

Arne Astrup

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

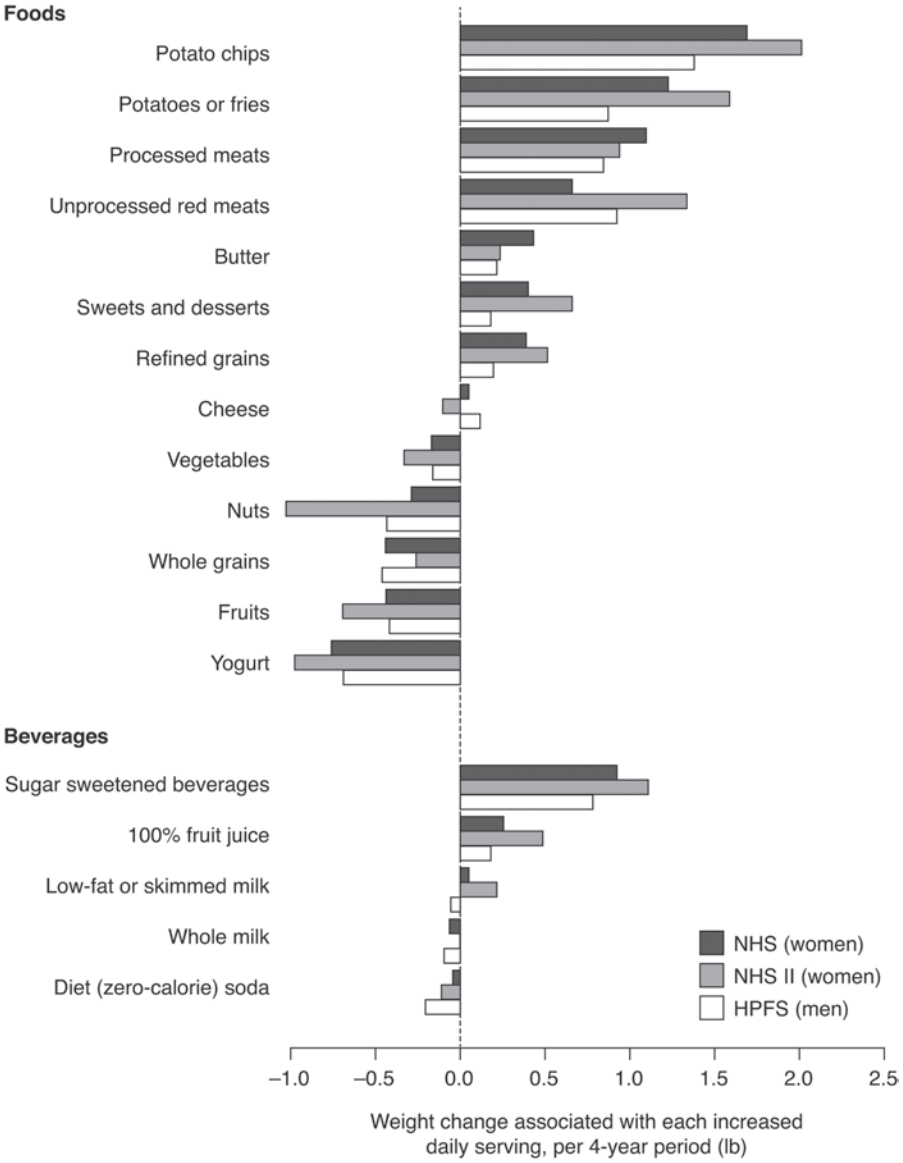

FIGURE 1. Relation between changes in food and beverage consumption and weight changes every 4 y (1 lb = 0.454 kg). Reproduced with permission from reference 12. HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

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; $\pm$ SEM): 29 $\pm$ 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

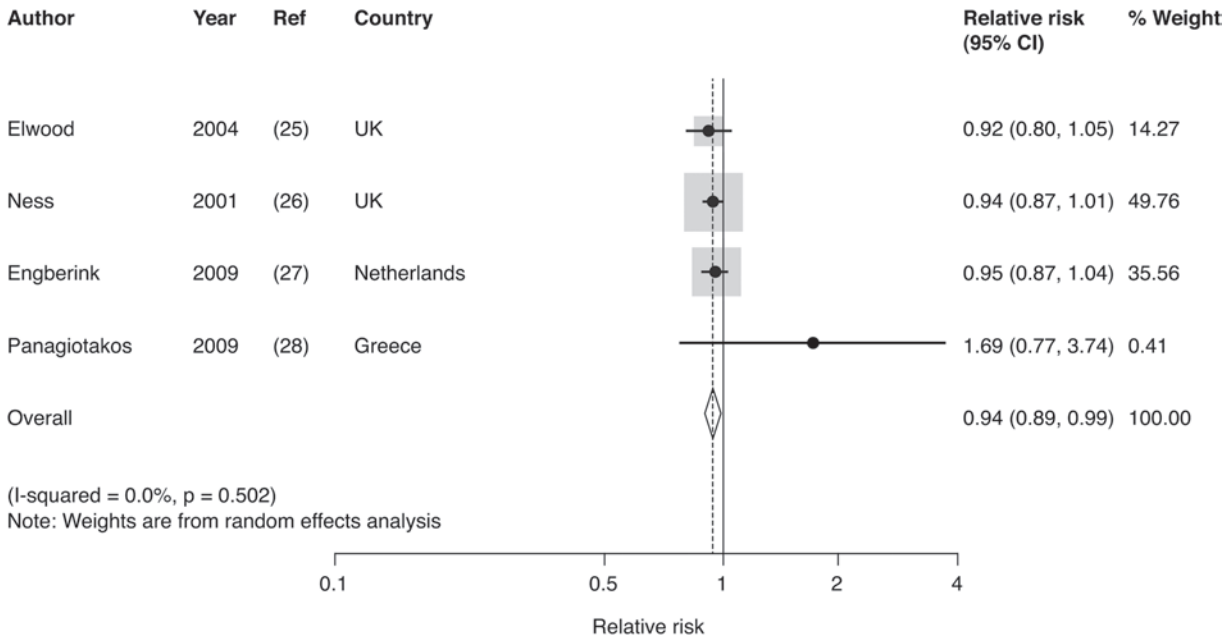

FIGURE 2. Relation between milk consumption (200 mL/d) and cardiovascular disease; dose-response meta-analysis of 4 prospective cohort studies (n = 13,518; number of cases = 2283). Reproduced with permission from reference 24. Ref, reference.

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

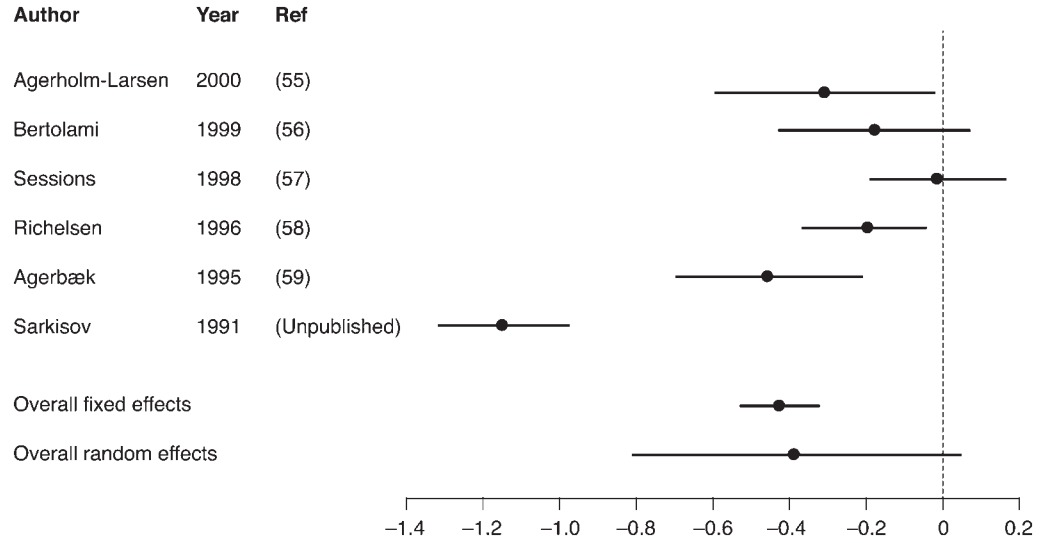

FIGURE 3. Effects of a probiotic milk product on plasma cholesterol; differences in the changes in LDL cholesterol (intervention minus control; mmol/L) with 95% CIs for 6 studies included in a meta-analysis are shown. Estimates of overall fixed and random effects are also shown. Reproduced with permission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

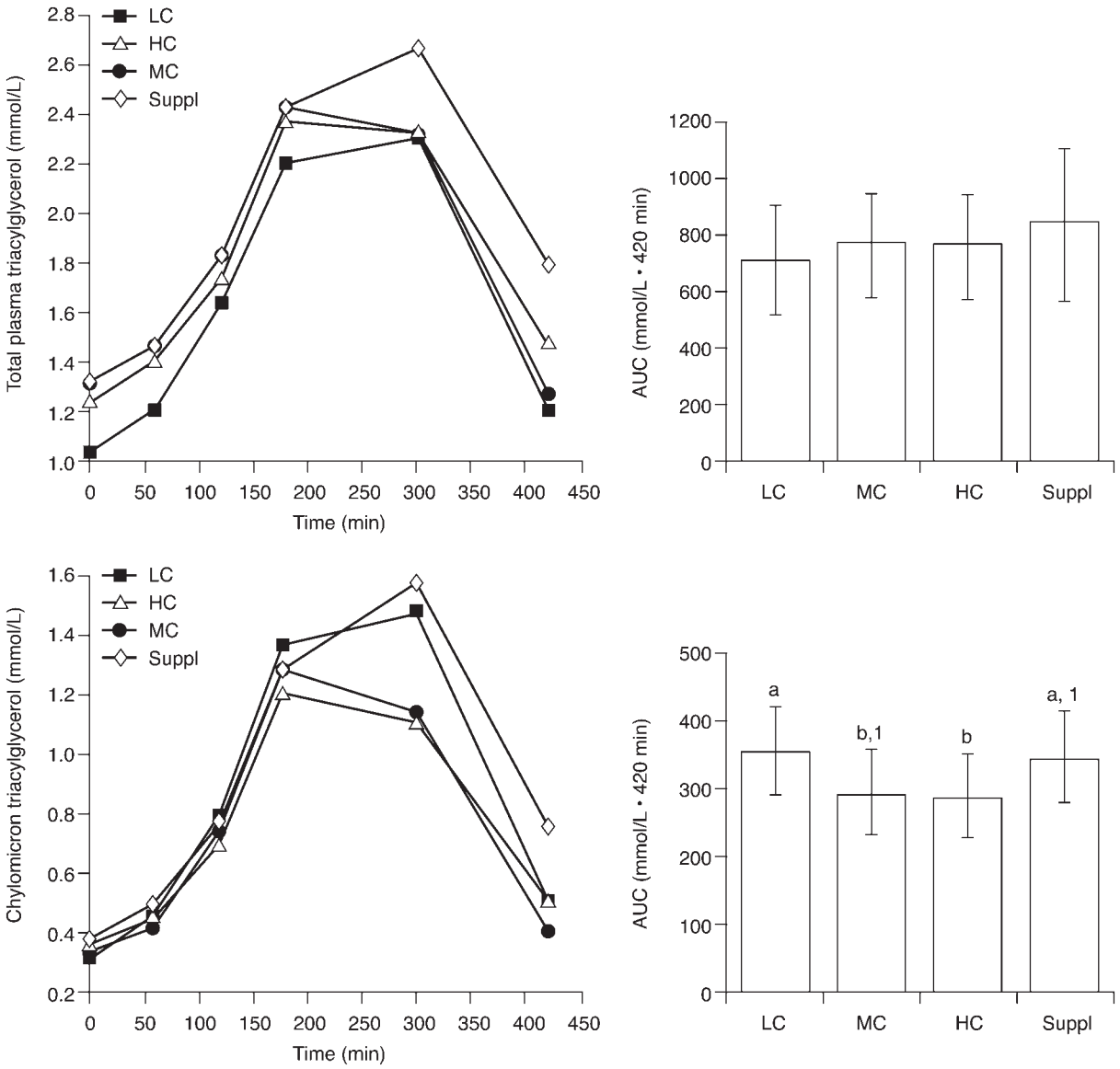

FIGURE 4. Effects of dietary or supplementary calcium intake on postprandial fat metabolism; the postprandial responses in mean plasma total and chylomicron triacylglycerol and AUC in response to 4 test meals are shown. The 4 test meals were as follows: low (LC), medium (MC), and high (HC) amounts of 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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REFERENCES

1. Kattainen A, Salomaa V, Harkanen T, Jula A, Kaaja R, Kesaniemi YA, Kahonen M, Moilanen L, Nieminen MS, Aromaa A, et al. Coronary heart disease: from a disease of middle-aged men in the late 1970s to a disease of elderly women in the 2000s. Eur Heart J 2006;27:296–301.
2. Astrup A. A healthy lifestyle and cardiovascular risk reduction. In: Eckel RH, ed. Metabolic risk for cardiovascular disease. Chichester, UK; Wiley-Blackwell Publishing Ltd, 2010.
3. Stender S, Dyerberg J, Astrup A. High levels of industrially produced trans fat in popular fast foods. N Engl J Med 2006;354:1650–2.
4. Gaziano TA, Galea G, Reddy KS. Scaling up interventions for chronic disease prevention: the evidence. Lancet 2007;370:1939–46.
5. USDA. Dietary guidelines for Americans. 7th ed. Washington, DC: USDA, US Department of Health and Human Services, 2010.
6. Astrup A, Dyerberg J, Elwood P, Hermansen K, Hu FB, Jakobsen MU, Kok FJ, Krauss RM, Lecerf JM, LeGrand P, et al. The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010? Am J Clin Nutr 2011;93:684–8.
7. Huth PJ, DiRienzo DB, Miller GD. Major scientific advances with dairy foods in nutrition and health. J Dairy Sci 2006;89:1207–21.
8. Givens I. Animal nutrition and lipids in animal products and their contribution to human intake and health. Nutrients 2009;1:71–82.
9. Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. JAMA 2002;287:2081–9.
10. Elwood PC, Pickering JE, Fehily AM. Milk and dairy consumption, diabetes and the metabolic syndrome: the Caerphilly prospective study. J Epidemiol Community Health 2007;61:695–8.
11. van Meijl LE, Vrolix R, Mensink RP. Dairy product consumption and the metabolic syndrome. Nutr Res Rev 2008;21:148–57.
12. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404.
13. Abargouei AS, Janghorbani M, Salehi-Marzijarani M, Esmaillzadeh A. Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Int J Obes (Lond) 2012;36:1485–93.
14. Chen M, Pan A, Malik VS, Hu FB. Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012;96:735–47.
15. Kinross JM, von Roon AC, Holmes E, Darzi A, Nicholson JK. The human gut microbiome: implications for future health care. Curr Gastroenterol Rep 2008;10:396–403.
16. McCarron DA, Morris CD, Henry HJ, Stanton JL. Blood pressure and nutrient intake in the United States. Science 1984;224:1392–8.
17. Zemel MB, Shi H, Greer B, Dirienzo D, Zemel PC. Regulation of adiposity by dietary calcium. FASEB J 2000;14:1132–8.
18. Christensen R, Lorenzen JK, Svith CR, Bartels EM, Melanson EL, Saris WH, Tremblay A, Astrup A. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. Obes Rev 2009;10:475–86.
19. Bendsen NT, Hother AL, Jensen SK, Lorenzen JK, Astrup A. Effect of dairy calcium on fecal fat excretion: a randomized crossover trial. Int J Obes (Lond) 2008;32:1816–24.
20. Major GC, Chaput JP, Ledoux M, St-Pierre S, Anderson GH, Zemel MB, Tremblay A. Recent developments in calcium-related obesity research. Obes Rev 2008;9:428–45.
21. Lorenzen J, Frederiksen R, Hoppe C, Hvid R, Astrup A. The effect of milk proteins on appetite regulation and diet-induced thermogenesis. Eur J Clin Nutr 2012;66:622–7.
22. Astrup A, Chaput JP, Gilbert JA, Lorenzen JK. Dairy beverages and energy balance. Physiol Behav 2010;100:67–75.
23. Labonté MÈ, Couture P, Richard C, Desroches S, Lamarche B. Impact of dairy products on biomarkers of inflammation: a systematic review of randomized controlled nutritional intervention studies in overweight and obese adults. Am J Clin Nutr 2013;97:706–17.
24. Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, Hu FB, Engberink MF, Willett WC, Geleijnse JM. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. Am J Clin Nutr 2011;93:158–71.
25. Elwood PC, Pickering JE, Fehily AM, Hughes J, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. Eur J Clin Nutr 2004;58:711–7.
26. Ness AR, Smith GD, Hart C. Milk, coronary heart disease and mortality. J Epidemiol Community Health 2001;55:379–82.
27. Engberink MF, Soedamah-Muthu SS, Boessenkool-Pape J, van Rooij FJ, Hofman A, Witteman JC. Dairy intake in relation to all-cause mortality and risk of cardiovascular disease: the Rotterdam Study. San Francisco, CA: American Heart Association, 2010:140 (poster 71).
28. Panagiotakos D, Pitsavos C, Chrysohoou C, Palliou K, Lentzas I, Skoumas I, tefanadis C. Dietary patterns and 5-year incidence of cardiovascular disease: a multivariate analysis of the ATTICA study. Nutr Metab Cardiovasc Dis 2009;19:253–63.
29. Warensjö E, Jansson JH, Cederholm T, Boman K, Eliasson M, Hallmans G, Johansson I, Sjogren P. Biomarkers of milk fat and the risk of myocardial infarction in men and women: a prospective, matched case-control study. Am J Clin Nutr 2010;92:194–202.
30. Lock AL, Destaillats F, Kraft J, German JB. Introduction to the proceedings of the symposium 'Scientific Update on Dairy Fats and Cardiovascular Diseases'. J Am Coll Nutr 2008;27(suppl):720S–2S.
31. German JB, Gibson RA, Krauss RM, Nestel P, Lamarche B, van Staveren WA, Steijns JM, de Groot LC, Lock AL, Destaillats F. A reappraisal of the impact of dairy foods and milk fat on cardiovascular disease risk. Eur J Nutr 2009;48:191–203.
32. Steinberg D. Thematic review series: the pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy: part II: the early evidence linking hypercholesterolemia to coronary disease in humans. J Lipid Res 2005;46:179–90.
33. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am J Clin Nutr 2010;91:535–46.
34. Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491–9.

35. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fatty acids and risk of coronary heart disease: modulation by replacement nutrients. Curr Atheroscler Rep 2010;12:384–90.
36. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Balter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr 2009;89:1425–32.
37. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2010;7:e1000252.
38. Lloyd-Williams F, O'Flaherty M, Mwatsama M, Birt C, Ireland R, Capewell S. Estimating the cardiovascular mortality burden attributable to the European Common Agricultural Policy on dietary saturated fats. Bull World Health Organ 2008;86:535–41A.
39. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002;287:2414–23.
40. Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC. Glycemic index, glycemic load, and chronic disease risk: a meta-analysis of observational studies. Am J Clin Nutr 2008;87:627–37.
41. Jakobsen MU, Dethlefsen C, Joensen AM, Stegger J, Tjonneland A, Schmidt EB, Overvad K. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. Am J Clin Nutr 2010;91:1764–8.
42. Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, Engler MM, Engler MB, Sacks F. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. Circulation 2009; 119:902–7.
43. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA 2012;308:1024–33.
44. De Caterina R. n-3 Fatty acids in cardiovascular disease. N Engl J Med 2011;364:2439–50.
45. Woodhill JM, Palmer AJ, Leelarthaepin B, McGilchrist C, Blacket RB. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. Adv Exp Med Biol 1978;109:317–30.
46. Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, Ringel A, Davis JM, Hibbeln JR. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ 2013;346:e8707.
47. Ramsden CE, Hibbeln JR, Majchrzak SF, Davis JM. n-6 Fatty acid-specific and mixed polyunsaturate dietary interventions have different effects on CHD risk: a meta-analysis of randomised controlled trials. Br J Nutr 2010;104:1586–600.
48. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–90.
49. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med 2009;169:659–69.
50. Lawrence GD. Dietary fats and health: dietary recommendations in the context of scientific evidence. Adv Nutr 2013;4:294–302.
51. Elwood PC, Pickering JE, Givens DI, Gallacher JE. The consumption of milk and dairy foods and the incidence of vascular disease and diabetes: an overview of the evidence. Lipids 2010;45:925–39.
52. Maersk M, Belza A, Stodkilde-Jorgensen H, Ringgaard S, Chabanova E, Thomsen H, Pedersen SB, Astrup A, Richelsen B. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. Am J Clin Nutr 2012;95:283–9.
53. Lorenzen JK, Jensen SK, Astrup A. Milk minerals modify the effect of fat intake on serum lipid profile: results from an animal and a human short-term study. Br J Nutr (Epub ahead of print 25 Nov 2013).
54. Agerholm-Larsen L, Bell ML, Grunwald GK, Astrup A. The effect of a probiotic milk product on plasma cholesterol: a meta-analysis of short-term intervention studies. Eur J Clin Nutr 2000;54:856–60.
55. Agerholm-Larsen L, Raben A, Haulrik N, Hansen AS, Manders M, Astrup A. Effect of 8 week intake of probiotic milk products on risk factors for cardiovascular diseases. Eur J Clin Nutr 2000;54:288–97.
56. Bertolami MC, Faludi AA, Batlouni M. Evaluation of the effects of a new fermented milk product (Gaio1) on primary hypercholesterolemia. Eur J Clin Nutr 1999;53:97–101.
57. Sessions VA, Lovegrove JA, Dean TS, Williams CM, Sanders TAB, Macdonald IA, Salter AM. The effects of a new fermented milk product on plasma cholesterol and apolipoprotein B concentrations in middle-aged men and women. In: Sadler MJ, Saltmarch M, eds. Functional foods—the consumer, the product and the evidence. London, UK: The Royal Society of Chemistry, 1998:15–9.
58. Richelsen B, Kristensen K, Pedersen SB. Long-term (6 months) effect of a new fermented milk product on the level of plasma lipoproteins—a placebo-controlled and double blind study. Eur J Clin Nutr 1996;50: 811–5.
59. Agerbæk M, Gerdes LU, Richelsen B. Hypocholesterolaemic effect of a new fermented milk product in healthy middle-aged men. Eur J Clin Nutr 1995;49:346–52.
60. Goldbohm RA, Chorus AM, Galindo Garre F, Schouten LJ, van den Brandt PA. Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands. Am J Clin Nutr 2011;93:615–27.
61. Hjerpsted J, Leedo E, Tholstrup T. Cheese intake in large amounts lowers LDL-cholesterol concentrations compared with butter intake of equal fat content. Am J Clin Nutr 2011;94:1479–84.
62. Lorenzen JK, Astrup A. Dairy calcium intake modifies responsiveness of fat metabolism and blood lipids to a high-fat diet. Br J Nutr 2011; 105:1823–31.
63. Lorenzen JK, Nielsen S, Holst JJ, Tetens I, Rehfeld JF, Astrup A. Effect of dairy calcium or supplementary calcium intake on postprandial fat metabolism, appetite, and subsequent energy intake. Am J Clin Nutr 2007;85:678–87.
64. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997;336:1117–24.
65. Ralston RA, Lee JH, Truby H, Palermo CE, Walker KZ. A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. J Hum Hypertens 2012;26:3–13.
66. Cicero AF, Aubin F, Azais-Braesco V, Borghi C. Do the lactotripeptides isoleucine-proline-proline and valine-proline-proline reduce systolic blood pressure in European subjects? A meta-analysis of randomized controlled trials. Am J Hypertens 2013;26:442–9.
67. Turpeinen AM, Järvenpää S, Kautiainen H, Korpela R, Vapaatalo H. Antihypertensive effects of bioactive tripeptides: a random effects meta-analysis. Ann Med 2013;45:51–6.
68. Ricci-Cabello I, Herrera MO, Artacho R. Possible role of milk-derived bioactive peptides in the treatment and prevention of metabolic syndrome. Nutr Rev 2012;70:241–55.
69. Beermann C, Hartung J. Physiological properties of milk ingredients released by fermentation. Food Funct 2013;4:185–99.

Yogurt consumption and impact on health: focus on children and cardiometabolic risk[1–3]

André Marette and Eliane Picard-Deland

ABSTRACT

An accumulating body of epidemiologic data, clinical trials, and mechanistic studies suggests that yogurt consumption as part of a healthy diet may be beneficial to cardiometabolic health. This brief review focuses on children and adolescents, introducing new concepts underlying the effect of yogurt consumption on body weight maintenance and the prevention of cardiovascular diseases. Specific properties of yogurt are discussed, which highlight that yogurt is an easy-to-digest, nutrient-dense, and satiating food that contains high-quality protein and specific amino acids. Moreover, the role of yogurt as a modulator of the gut microbiota in infancy is explored. We also propose the idea that the specific matrix of yogurt has bioavailability and metabolic properties that can be exploited to increase the functionality of this dairy product. *Am J Clin Nutr* 2014;99 (suppl):1243S–7S.

INTRODUCTION

The importance of yogurt as part of a balanced and healthy diet is recognized by regulatory authorities and scientific institutions in most countries. Yogurt is defined by The Codex standard as the product of milk fermentation by *Lactobacillus delbrueckii* subspecies *bulgaricus* and *Streptococcus thermophilus* (1). The unique properties of yogurt provided by its living bacteria and its nutrients have captured the interest of the scientific community. An accumulating body of epidemiologic and clinical evidence suggests that yogurt consumption may act beneficially on weight regulation and metabolic risk factors (2–7). However, the effect of dairy products per se and their components on cardiovascular risk is an area of controversy (8). Childhood obesity is one of the most critical public health challenges in the 21st century (9), and poor eating patterns established in childhood may persist throughout adulthood and are an important determinant of obesity and associated diseases later in life (10). This brief review addresses evidence and new research directions involving yogurt and cardiometabolic health in this specific population.

YOGURT IS ACCESSIBLE AND HAS A HIGH NUTRIENT DENSITY

Recent years have been marked by the appearance on the market of an increasing number of yogurts with different tastes, textures, and nutritional values targeting specific consumers, including children. Palatability and accessibility are key factors to be considered for optimizing the consumption of yogurt in different countries. Moreover, the keen interest in yogurt consumption is, at least in part, attributed to its high nutrient content. According to a nutritional quality tool developed in US, plain yogurt has been shown to have a good Nutrient Rich Food score (Fulgoni et al, 2009). Furthermore, a cross-sectional study in individuals participating in the Framingham Heart Study Offspring and Third Generation cohorts has reported that yogurt consumers have a higher diet quality, as measured by the Dietary Guidelines for Americans Index score, and greater intakes of some nutrients, such as potassium, than do nonconsumers (5).

Yogurt contributes to diet quality in children by providing substantial amounts of macronutrients (protein, a wide range of fatty acids, lactose as the predominant carbohydrate) and essential micronutrients (eg, calcium, potassium, zinc, phosphorus, magnesium, vitamin A, riboflavin, vitamin B-5, vitamin B-12). The proteins in yogurt, derived from milk proteins, are of excellent digestibility and nutritional quality (12), and dairy products contribute significantly to protein intake in children, providing growth and maintenance of muscle mass. Moreover, it is recognized that yogurt and dairy products are a rich source of calcium (100 g of plain whole-milk yogurt = ~10% of the Recommended Dietary Allowance for calcium in children) and of phosphorus per unit of energy compared with the average of other typical foods in an adult diet (13). Calcium and phosphorus contribute to the structural integrity and development of bones (14).

There is a growing body of evidence that the contribution of yogurt consumption exerts beneficial effects beyond its impact on healthy growth and development. Indeed, recent studies have shown that some nutrients in yogurt and dairy products, such as proteins/peptides, specific lipids, vitamin D, calcium, magnesium, and potassium, or the combination of these, could have a beneficial

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effect on cardiometabolic risk factors (15, 16). For example, clinical trials have investigated the effect of yogurt enriched with vitamin D in individuals with type 2 diabetes and observed an improvement in glycemic status (17, 18), lipid profile, and endothelial biomarkers (18). Yogurt made from milk fortified with vitamin D contains a significant amount of this fat-soluble vitamin. There are also mechanistic studies that explain how yogurt's nutrients may contribute to a negative energy balance and the maintenance of a healthy body weight. Weight-loss studies in low calcium consumers have shown that low calcium intake is a risk factor for overweight and obesity, and that this effect may be explained by an increase in fat oxidation, facilitation of appetite control, and fecal loss (19). Studies investigating the effect of calcium and vitamin D intakes on cardiometabolic health are of particular interest because several age groups within populations, including children, do not reach the recommended levels of those nutrients in the United States and other countries (20–22).

In the past few years, an increasing number of cohort studies have emerged to evaluate the association between dairy product intake and body weight and have yielded conflicting results. Louie et al (23) performed a comprehensive literature search of prospective cohort studies to examine the relation between dairy consumption and overweight/obesity risk in adults and in children and adolescents. Of the 10 studies in children and adolescents (aged 2–14 y, follow-up 8 mo to 10 y), 3 found a protective association,6 reported no significant association, and 1 reported an increased risk. There was a higher proportion of studies in adults showing a protective effect (5 of 9 studies). The authors concluded that the evidence for a protective effect of dairy consumption on risk of overweight and obesity is suggestive but not consistent in adults and in children/adolescents.

Until now, few studies have assessed the specific effect of yogurt consumption on weight variables and cardiovascular risk in children and adolescents. Abreu et al (6) performed a cross-sectional study in 903 Azorean adolescents and showed a protective association between ≥2 servings of milk and yogurt and abdominal obesity in boys. Furthermore, the relation between dairy intake and weight variables and cardiovascular disease risk factors was evaluated recently in adolescents from 8 European countries [Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) project]. Waist circumference and the sum of skinfold thicknesses were inversely associated with the consumption of yogurt and milk (and milk- and yogurt-based beverages), and dairy consumption was inversely associated with cardiovascular disease risk score in girls only (7).

Additional research and clinical trials are needed to better understand the relation and the mechanisms between yogurt and weight management and obesity-related diseases in youth. Dairy products, such as yogurt, provide important nutrients to children's diet that could contribute to its potential beneficial effects on weight management and cardiometabolic risk.

YOGURT PROVIDES HIGH-QUALITY PROTEIN AND SPECIFIC AMINO ACIDS

Milk proteins include a casein fraction (~80%) and a soluble protein fraction commonly named whey proteins (~20%). The fermentation and proteolytic activity throughout the shelf-life of yogurt generates bioactive peptides and amino acids (24, 25) with potential health benefits (26). Whey is an inexpensive source of high nutritional quality and, compared with other food proteins, contains the highest concentration of the branched-chain amino acids (BCAAs), especially L-leucine (27). Whey protein could affect both short-term and long-term food intake regulation by providing satiety signals (27). Interestingly, it has been shown that leucine could stimulate protein synthesis and preserve lean body mass during weight-loss regimens (28). Moreover, studies have shown that whey proteins and their bioactive components, such as lactalbumin, angiotensin-converting enzyme inhibitor, and BCAAs, can have muscle-sparing, hypolipidemic, and insulinotrophic effects (28, 29). However, conflicting results have been reported concerning the effects of BCAAs in the regulation of insulin resistance. Indeed, recent studies using metabolomic profiling have suggested that elevation of circulating BCAAs concentrations could predict the development of insulin resistance and type 2 diabetes in adults (30, 31). McCormack et al (32) reported in a cross-sectional cohort that there are increased concentrations of BCAAs already present in young obese children and that increased baseline BCAA concentration is associated with later insulin resistance. In contrast, it has been observed in animal models that increasing dietary leucine intake reduces diet-induced obesity and improves glucose homeostasis (33, 34).One site for BCAA action is the mammalian target of rapamycin (mTOR) and its downstream kinase S6k1, which are kinases in the insulin signaling cascade (35). Larger well-controlled trials are needed, especially in children, to elucidate if the elevation of BCAAs contributes to insulin resistance or represents a biomarker of the physiologic perturbations driving the development of insulin resistance in obesity.

YOGURT AS A MODULATOR OF GUT MICROBIOTA AND METABOLISM

The intestinal microbiota is now recognized to be an important factor in determining the health status of the host. Its composition and activities are stable over time but may be modulated by several factors including age and diet (36). It has been shown in human infants that genetic and environmental factors determine the characteristics of the microbial community (37).

There is increasing evidence that shows that the modulation of the gut microbiota has an impact on energy storage, obesity, and insulin resistance (38–40). Obesity has been associated with phylum-level changes in the microbiota and alteration of representation of bacterial genes and metabolic pathways (41). Moreover, bacterial diversity of the human gut microbiome has been shown to correlate with markers of obesity-related metabolic disorders (42). There is evidence showing that the gut microbiota differed between obese/overweight children and children with a BMI within the normal range (43) or lean children (44). Furthermore, it has been shown that aberrant compositional development of the gut microbiota in children may predict overweight (45).

The consumption of yogurt may ensure some changes to the balance and metabolic activities of the indigenous microbiota as shown by some authors (46, 47). Moreover, yogurt is a vector for probiotics. Animal and human studies have shown that probiotics could have a hypocholesterolemic effect and a potential beneficial impact on body weight (48). However, there are few studies performed in children and adolescents. Interestingly, it was observed in a 10-y follow-up study that perinatal administration of *Lactobacillus rhamnosus GG* inhibited excessive weight gain in

children (49). Moreover, Safavi et al (50) observed beneficial effects of a synbiotic supplement including *Lactobacillus* spp. and *Bifidobacterium* spp. on weight management and cardiometabolic risk factors in children and adolescents aged 6–18 y. The mechanisms by which probiotics can act on weight management remain to be clearly established but could involve interaction with the resident bacteria in the gut, which may affect metabolic pathways implicated in the regulation of fat metabolism (48).

More well-designed large clinical studies are required to evaluate the effect of different probiotic strains on obesity and cardiometabolic risk. There is also a need to identify microbiota-related biomarkers to improve our understanding of the causal relation between the gut microbiota and cardiometabolic diseases. Noninvasive manipulation of gut microbiota composition by specific foods such as yogurt and probiotics in infancy could offer an interesting approach to manage childhood obesity and related disorders.

YOGURT IS EASY TO DIGEST

Yogurt has also been reported to be easy to digest and to bring essential nutrients to children with lactose intolerance and diarrhea. As stated by the NIH, lactose-intolerant children should consume yogurt and dairy products even when having maldigestion or lactose intolerance (51). Most individuals diagnosed with lactose intolerance or lactose maldigestion can tolerate up to 12 g of lactose in a single dose with few or no symptoms and can tolerate even higher amounts if intakes are spread throughout the day (20–24 g) (52). Interestingly, a cause-and-effect relation has been established between the consumption of live yogurt cultures and improved lactose digestion in individuals with lactose maldigestion (53). In developing countries where the rate of malnutrition is high, yogurt could also be particularly useful for the treatment of acute (54) and persistent (55, 56) diarrhea in children.

YOGURT HAS A UNIQUE MATRIX THAT MAY HAVE BIOAVAILABILITY AND METABOLIC PROPERTIES

Yogurt nutrients are part of a larger medium, a microstructure produced by processing. Several factors influence the bioavailability of nutrients in foods, such as the release of the nutrient from the food matrix, interactions with other food components, and the chemical state of the nutrient (57). For example, it has been shown that the kinetics of the release of fatty acids from cheese during digestion are mainly driven by the physical characteristics of the cheese (58). Few studies have investigated the impact of the processing of yogurt and its matrix on nutrient bioaccessibility and bioavailability. Data have shown that components such as lactose and casein phosphopeptides may increase calcium absorption and mineral retention (59). Moreover, acidity found in yogurt as a result of the fermentation can also influence the absorption of minerals. For example, intestinal calcium uptake can be enhanced by the low pH of yogurt, which ionizes calcium (60).

Other examples of matrix interactions in yogurt include the association between bioactive peptides with nonpeptidic milk components, such as oligosaccharides, glycolipids, and fats (61). Whey proteins, phosphopeptides, vitamin B-12–binding protein, β-lactoglobulin, α-lactalbumin, and lactoferrin can also interact with minerals and vitamins to influence their absorption (12, 62). Multiple nutritional properties can explain the beneficial effects of the matrix interaction on health in dairy products, and particularly in fermented products such as yogurt (**Figure 1**). Indeed, yogurt has a unique microstructure and texture, and future research might discriminate between types of dairy products and explore the synergy provided by the food matrix, rather than simply evaluating each component of the food individually.

YOGURT IS A TASTY AND SATIATING SNACK

Unhealthy snacking is frequent in children and teenagers, and many of the available and commonly consumed snacks are nutrient-poor, energy-dense items such as salty snacks and sugar-sweetened beverages (63).Therefore, substituting those products with nutrient-rich foods such as dairy products could have a positive impact on childhood obesity (64). Moreover, as stated in the American Heart Association's scientific statement on sugar and cardiovascular health, even when sugar is added to otherwise nutrient-rich food, such as sugar-sweetened dairy

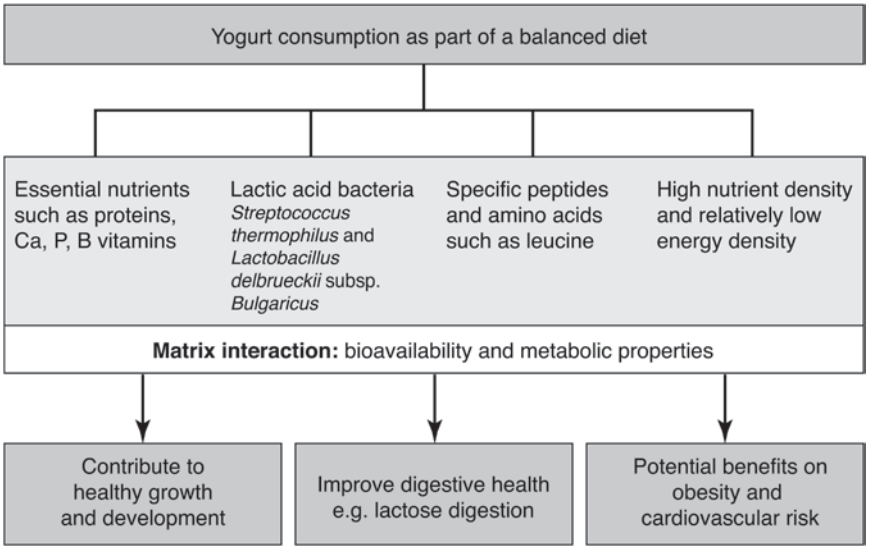

FIGURE 1. Proposed mechanisms by which yogurt consumption as part of a balanced diet exerts beneficial health effects.

products like flavored milk and yogurt, the quality of childhood and adolescent diet is improved. However, if sugars are consumed in excess, deleterious effects may occur (65).

High-protein snacks and meals induce a greater reduction in appetite than do isoenergetic high-fat or high-carbohydrate foods (66, 67). Some of the more frequently consumed high-protein snacks in the United States include dairy products, which usually contain ~10 g of protein/serving (63). The introduction of Greek yogurt into the United States in 2008 may be considered a potentially optimal snack option considering its higher protein content compared with regular yogurt (20–24 g/serving) (68, 69). Interestingly, a study performed in healthy women showed that a 160-kcal afternoon Greek yogurt snack, containing 24 g protein, led to reduced hunger, increased fullness, and delayed subsequent eating compared with snacks containing lower protein amounts (69). This result is in accordance with previous data showing that yogurt has a superior effect on satiety compared with other foods, beverages, and snacks (70, 71). Interestingly, Dougkas et al (72) showed that yogurt has a greater effect on suppressing appetite compared with milk or cheese but did not affect subsequent ad libitum meal energy intake compared with other dairy products.

Furthermore, some studies have shown a potential industrial opportunity to design satiating yogurt. For example, Lluch et al (73) observed that low-fat yogurt enriched with protein and fiber can significantly reduce short-term appetite compared with a nonenriched low-fat yogurt. Cognitive and oral factors, postingestive factors (eg, gastric emptying and intestinal absorption rates), postprandial circulating amino acids, and endocrine factors (eg, ghrelin) may explain the effects of the test dairy products on appetite in this study. Further studies are warranted to explain the effect of yogurt and its micro- and macronutrients on satiety and body weight regulation, considering factors such as eating patterns, portion sizes, and the substitution of other foods or beverages after the consumption of yogurt.

CONCLUSIONS

Yogurt is an accessible, easy-to-digest, and tasty food that provides important nutrients to children and adolescents and thus forms part of a balanced nutrient-rich diet during development and growth. Recent studies have shown that yogurt consumption may have a beneficial role on body weight regulation and cardiovascular health. However, there is limited evidence in children and adolescents. Dairy products are a source of high-quality proteins, and more studies are needed to evaluate the health effect of specific peptides and amino acids such as BCAAs in youth. Furthermore, epidemiologic studies and clinical trials that consider the interactions of yogurt nutrients and bacteria within the food matrix are warranted to evaluate the effect of yogurt on the modulation of the gut microbiota and the prevention of obesity and cardiometabolic diseases.

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REFERENCES

1. WHO/FAO. Codex Alimentarius. Milk and milk products. 2nd ed. Rome, Italy: WHO/FAO, 2011. Available from: http://www.fao.org/docrep/015/i2085e/i2085e00.pdf (cited 13 December 2013).
2. Zemel MB, Richards J, Mathis S, Milstead A, Gebhardt L, Silva E. Dairy augmentation of total and central fat loss in obese subjects. Int J Obes (Lond) 2005;29:391–7.
3. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. Am J Clin Nutr 2008;87:1914–25.
4. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404.
5. Wang H, Livingston KA, Fox CS, Meigs JB, Jacques PF. Yogurt consumption is associated with better diet quality and metabolic profile in American men and women. Nutr Res 2013;33:18–26.
6. Abreu S, Santos R, Moreira C, Vale S, Santos PC, Soares-Miranda L, Marques AI, Mota J, Moreira P. Association between dairy product intake and abdominal obesity in Azorean adolescents. Eur J Clin Nutr 2012;66:830–5.
7. Bel-Serrat S, Mouratidou T, Jiménez-Pavón D, Huybrechts I, Cuenca-García M, Mistura L, Gottrand F, González-Gross M, Dallongeville J, Kafatos A, et al. Is dairy consumption associated with low cardiovascular disease risk in European adolescents? Results from the HELENA study. Pediatr Obes (Epub ahead of print 15 July 2013).
8. Nestel P. Nutrition and metabolism: the changing face of the dairy-cardiovascular risk paradox. Curr Opin Lipidol 2012;23:1–3.
9. WHO. Global strategy on diet, physical activity and health, childhood overweight and obesity, 2012. Available from: http://www.who.int/dietphysicalactivity/childhood/en/ (cited 13 December 2013).
10. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med 1997;337:869–73.
11. Fulgoni VL III, Keast DR, Drewnowski A. Development and validation of the nutrient-rich foods index: a tool to measure nutritional quality of foods. J Nutr 2009;139:1549–54.
12. Bos C, Gaudichon C, Tome D. Nutritional and physiological criteria in the assessment of milk protein quality for humans. J Am Coll Nutr 2000;19(suppl):191S–205S.
13. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, Weaver C. Peak bone mass. Osteoporos Int 2000;11:985–1009.
14. Bonjour JP. Calcium and phosphate: a duet of ions playing for bone health. J Am Coll Nutr 2011;30(suppl 1):438S–48S.
15. Rice BH, Cifelli CJ, Pikosky MA, Miller GD. Dairy components and risk factors for cardiometabolic syndrome: recent evidence and opportunities for future research. Adv Nutr 2011;2:396–407.
16. Chen M, Pan A, Malik VS, Hu FB. Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012;96:735–47.
17. Nikooyeh B, Neyestani TR, Farvid M, Alavi-Majd H, Houshiarrad A, Kalayi A, Shariatzadeh N, Gharavi A, Heravifard S, Tayebinejad N, et al. Daily consumption of vitamin D- or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. Am J Clin Nutr 2011;93:764–71.
18. Shab-Bidar S, Neyestani TR, Djazayery A, Eshraghian MR, Houshiarrad A, Gharavi A, Kalayi A, Shariatzadeh N, Zahedirad M, Khalaji N, et al. Regular consumption of vitamin D-fortified yogurt drink (Doogh) improved endothelial biomarkers in subjects with type 2 diabetes: a randomized double-blind clinical trial. BMC Med 2011;9:125.
19. Tremblay A, Gilbert JA. Human obesity: is insufficient calcium/dairy intake part of the problem? J Am Coll Nutr 2011;30(suppl 1):449S–53S.
20. USDA; US Department of Health and Human Services. Dietary guidelines for Americans 2010. Washington, DC: US Government Printing Office, 2010.
21. Institut de Veille Sanitaire. Étude nationale nutrition santé ENNS, 2006: situation nutritionnelle en France en 2006 selon les indicateurs d'objectif et les repères du Programme national nutrition santé (PNNS). [Nutrition and health survey (ENNS) 2006: the nutritional situation in France according to the National Nutrition and Health Program (PNNS) indicators and guidelines.] Paris, France: Institut de Veille Sanitaire, 2007. Available from: http://www.ladocumentationfrancaise.fr/var/storage/rapports-publics/074000748/0000.pdf (cited 23 December 2013) (in French).
22. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 2008;87(suppl):1080S–6S.

23. Louie JC, Flood VM, Hector DJ, Rangan AM, Gill TP. Dairy consumption and overweight and obesity: a systematic review of prospective cohort studies. Obes Rev 2011;12:e582–92.
24. Tamime AY, Robinson RK. Yoghurt: science and technology. Cambridge, UK: Woodhead Publishing, 1999.
25. Adolfsson O, Meydani SN, Russell RM. Yogurt and gut function. Am J Clin Nutr 2004;80:245–56.
26. Nagpal R, Behare P, Rana R, Kumar A, Kumar M, Arora S, Morotta F, Jain S, Yadav H. Bioactive peptides derived from milk proteins and their health beneficial potentials: an update. Food Funct 2011;2:18–27.
27. Luhovyy BL, Akhavan T, Anderson GH. Whey proteins in the regulation of food intake and satiety. J Am Coll Nutr 2007;26:704S–12S.
28. Layman DK, Walker DA. Potential importance of leucine in treatment of obesity and the metabolic syndrome. J Nutr 2006;136:319S–23S.
29. Pal S, Ellis V, Dhaliwal S. Effects of whey protein isolate on body composition, lipids, insulin and glucose in overweight and obese individuals. Br J Nutr 2010;104:716–23.
30. Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab 2009;9:311–26.
31. Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, Lewis GD, Fox CS, Jacques PF, Fernandez C, et al. Metabolite profiles and the risk of developing diabetes. Nat Med 2011;17:448–53.
32. McCormack SE, Shaham O, McCarthy MA, Deik AA, Wang TJ, Gerszten RE, Clish CB, Mootha VK, Grinspoon SK, Fleischman A. Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. Pediatr Obes 2013;8:52–61.
33. Zhang Y, Guo K, LeBlanc RE, Loh D, Schwartz GJ, Yu YH. Increasing dietary leucine intake reduces diet-induced obesity and improves glucose and cholesterol metabolism in mice via multi-mechanisms. Diabetes 2007;56:1647–54.
34. Macotela Y, Emanuelli B, Bång AM, Espinoza DO, Boucher J, Beebe K, Gall W, Kahn CR. Dietary leucine an environmental modifier of insulin resistance acting on multiple levels of metabolism. PLoS ONE 2011;6:e21187.
35. Tremblay F, Lavigne C, Jacques H, Marette A. Role of dietary proteins and amino acids in the pathogenesis of insulin resistance. Annu Rev Nutr 2007;27:293–310.
36. Power SE, O'Toole PW, Stanton C, Ross RP, Fitzgerald GF. Intestinal microbiota, diet and health. Br J Nutr 2013;12:1–16.
37. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol 2007;5:e177.
38. Cani PD, Delzenne NM. Gut microflora as a target for energy and metabolic homeostasis. Curr Opin Clin Nutr Metab Care 2007;10:729–34.
39. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56:1761–72.
40. Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. Nature 2012;489:242–9.
41. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, et al. A core gut microbiome in obese and lean twins. Nature 2009;457:480–4.
42. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, et al. Richness of human gut microbiome correlates with metabolic markers. Nature 2013;500:541–6.
43. Karlsson CL, Onnerfält J, Xu J, Molin G, Ahrné S, Thorngren-Jerneck K. The microbiota of the gut in preschool children with normal and excessive body weight. Obesity (Silver Spring) 2012;20:2257–61.
44. Bervoets L, Hoorenbeeck KV, Kortleven I, Noten CV, Hens N, Vael C, Goossens H, Desager KN, Vankerckhoven V. Differences in gut microbiota composition between obese and lean children: a cross-sectional study. Gut Pathog 2013;5:10.
45. Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. Am J Clin Nutr 2008;87:534–8.
46. Alvaro E, Andrieux C, Rochet V, Rigottier-Gois L, Lepercq P, Sutren M, Galan P, Duval Y, Juste C, Doré J. Composition and metabolism of the intestinal microbiota in consumers and non-consumers of yogurt. Br J Nutr 2007;97:126–33.
47. García-Albiach R, Pozuelo de Felipe MJ, Angulo S, Morosini MI, Bravo D, Baquero F, del Campo R. Molecular analysis of yogurt containing Lactobacillus delbrueckii subsp. bulgaricus and Streptococcus thermophilus in human intestinal microbiota. Am J Clin Nutr 2008;87:91–6.
48. Arora T, Singh S, Sharma RK. Probiotics: interaction with gut microbiome and antiobesity potential. Nutrition 2013;29:591–6.
49. Luoto R, Kalliomäki M, Laitinen K, Isolauri E. The impact of perinatal probiotic intervention on the development of overweight and obesity: follow-up study from birth to 10 years. Int J Obes (Lond) 2010;34:1531–7.
50. Safavi M, Farajian S, Kelishadi R, Mirlohi M, Hashemipour M. The effects of synbiotic supplementation on some cardio-metabolic risk factors in overweight and obese children: a randomized triple-masked controlled trial. Int J Food Sci Nutr 2013;64:687–93.
51. Suchy FJ, Brannon PM, Carpenter TO, Fernandez JR, Gilsanz V, Gould JB, Hall K, Hui SL, Lupton J, Mennella J, et al. NIH consensus development conference statement: lactose intolerance and health. NIH Consens State Sci Statements 2010;27:1–27.
52. Wilt TJ, Shaukat A, Shamliyan T, Taylor BC, MacDonald R, Tacklind J, Rutks I, Schwarzenberg SJ, Kane RL, Levitt M. Lactose intolerance and health. Evid Rep Technol Assess (Full Rep) 2010;192:1–410.
53. European Food Safety Authority. Scientific opinion on the substantiation of health claims related to live yogurt cultures and improved lactose digestion. EFSA J 2010;8:1763.
54. WHO. The treatment of diarrhea: a manual for physicians and other senior health workers, 2005. Geneva, Switzerland: WHO, 2005.
55. de Mattos AP, Ribeiro TC, Mendes PS, Valois SS, Mendes CM, Ribeiro HC Jr. Comparison of yogurt, soybean, casein, and amino acid-based diets in children with persistent diarrhea. Nutr Res 2009;29:462–9.
56. Moore SR. Update on prolonged and persistent diarrhea in children. Curr Opin Gastroenterol 2011;27:19–23.
57. Parada J, Aguilera JM. Food microstructure affects the bioavailability of several nutrients. J Food Sci 2007;72:R21–32.
58. Lamothe S, Corbeil MM, Turgeon SL, Britten M. Influence of cheese matrix on lipid digestion in a simulated gastro-intestinal environment. Food Funct 2012;3:724–31.
59. Guéguen L, Pointillart A. The bioavailability of dietary calcium. J Am Coll Nutr 2000;19(suppl):119S–36S.
60. Bronner F, Pansu D. Nutritional aspects of calcium absorption. J Nutr 1999;129:9–12.
61. Schanbacher FL, Talhouk RS, Murray FA. Biology and origin of bioactive peptides in milk. Livest Prod Sci 1997;50:105–23.
62. Vegarud GE, Langsrud T, Svenning C. Mineral-binding milk proteins and peptides; occurrence, biochemical and technological characteristics. Br J Nutr 2000;84(suppl 1):S91–8.
63. Piernas C, Popkin BM. Snacking increased among US adults between 1977 and 2006. J Nutr 2010;140:325–32.
64. Spence LA, Cifelli CJ, Miller GD. Role of dairy products in healthy weight and body composition in children and adolescents. Curr Nutr Food Sci 2011;7:40–9.
65. Johnson RK, Appel LJ, Brands M, Howard BV, Lefevre M, Lustig RH, Sacks F, Steffen LM, Wylie-Rosett J; American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2009;120:1011–20.
66. Halton TL, Hu FB. The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. J Am Coll Nutr 2004;23:373–85.
67. Soenen S, Westerterp-Plantenga MS. Proteins and satiety: implications for weight management. Curr Opin Clin Nutr Metab Care 2008;11:747–51.
68. USDA, Agricultural Research Service. USDA National Nutrient Database for Standard Reference, Release 26. Nutrient Data Laboratory Home Page. 2013. Available from: http://www.ars.usda.gov/ba/bhnrc/ndl.
69. Douglas SM, Ortinau LC, Hoertel HA, Leidy HJ. Low, moderate, or high protein yogurt snacks on appetite control and subsequent eating in healthy women. Appetite 2013;60:117–22.
70. Tsuchiya A, Almiron-Roig E, Lluch A, Guyonnet D, Drewnowski A. Higher satiety ratings following yogurt consumption relative to fruit drink or dairy fruit drink. J Am Diet Assoc 2006;106:550–7.
71. Chapelot D, Payen F. Comparison of the effects of a liquid yogurt and chocolate bars on satiety: a multidimensional approach. Br J Nutr 2010;103:760–7.
72. Dougkas A, Minihane AM, Givens DI, Reynolds CK, Yagoob P. Differential effects of dairy snacks on appetite, but not overall energy intake. Br J Nutr 2012;108:2274–85.
73. Lluch A, Hanet-Geisen N, Salah S, Salas-Salvado J, L'Heureux-Bouron D, Halford JCG. Short-term appetite-reducing effects of a low-fat dairy product enriched with protein and fibre. Food Qual Prefer 2010;21:402–9.

Yogurt, living cultures, and gut health[1–3]

Lorenzo Morelli

ABSTRACT
Bacteria used to ferment milk to obtain yogurt belong to thermophilic, bile-sensitive species of lactic acid bacteria, which are not ideally suited for survival into the human gut. However, assessing the viability of these bacteria through the digestive tract may be relevant to evaluate their potential to deliver some beneficial effects for the well-being of the consumer. The well-known reduction in the symptoms caused by lactose maldigestion is not the only benefit provided by yogurt starter cultures; some additional effects will be reviewed here, with special attention paid to data that may suggest a strain-dependent effect, features that are not present with lactose hydrolysis. *Am J Clin Nutr* 2014;99(suppl):1248S–50S.

Traditionally, yogurt is considered to be a fermented dairy food carrying viable bacteria with health-promoting effects. *Lactobacillus delbrueckii* subspecies *bulgaricus* and *Streptococcus thermophilus* have generally been used as starters for milk fermentation in yogurt production [for a recent review, *see* Mohammadi et al (1)]. The concentration of these organisms in the human or animal gastrointestinal tract has been poorly examined (2) in comparison with that of other bacteria believed to be beneficial for human well-being (3); it is noteworthy, however, that *L. bulgaricus* and *S. thermophilus* are not included among the members of the autochthonous microbiota of the human intestine. Although the beneficial action of yogurt starter cultures on lactose maldigestion (4) is not related to their survival and multiplication into the human gut, and therefore shared by all members of the bacterial species, some other positive actions seem to be strain specific in a way that is very similar to those of other probiotic bacteria.

One of the most scientifically recognized health effects delivered by yogurt cultures is the reduction in symptoms caused by lactose maldigestion, which requires the presence of viable cells at ingestion but not during intestinal transit (4). This effect is shared by all yogurt starter cultures and results from the presence of the lactose-hydrolyzing enzyme in all strains of the used species of lactic acid bacteria. This species-related trait is recognized at the regulatory level by the FAO, WHO (5, 6), and the European Food Safety Authority (EFSA) (7) and does not require survival and reproduction of the bacterial cells during intestinal transit.

On the other hand, the large majority of clinical studies involving "probiotic" bacteria that show some effects on health have found that benefits are related to the ability of beneficial bacteria to survive and multiply in the gastrointestinal tract and to persist at high amounts in the intestine (2). Moreover, the viability of yogurt starter cultures in the human gut has rarely been assessed in comparison with the full range of studies devoted to assessing survival of probiotic bacteria intentionally added to food.

Studies reporting the fate of *L. bulgaricus* and *S. thermophilus* in sections of the human gut show that survival in the upper part of the gastrointestinal tract is low (ie, only 1% of the bacteria are able to reach the duodenum) (8). The low survival rate of these bacteria in the upper part of the gastrointestinal tract has led to few studies being conducted in fecal samples of individuals consuming yogurt. Results of the assessment of viability in stools of *L. bulgaricus* and *S. thermophilus* ingested by humans in yogurt are summarized in **Table 1**.

García-Albiach et al (9) reported essentially negative results and concluded that they were "consistently unable to detect viable yogurt lactic acid bacteria in fecal samples after repeated yogurt consumption by healthy volunteers." They also noticed a difference between results obtained at the DNA level when fresh or pasteurized yogurt was consumed: "*L. bulgaricus* and/or *S. thermophilus* DNA remains were detected by hybridization assays in only 10% of volunteers who had ingested fresh yogurt." This study could suggest that yogurt cultures are unable to survive intestinal transit and that heat treatment impairs the potential of dead cells to remain intact during the transit. However, 2 additional studies (10, 11), in which the authors used less yogurt per day but with a higher concentration of viable bacteria, reported a different scenario: both trials detected *L. bulgaricus* cells in fecal samples, whereas viable cocci were recovered only in the trial by Mater et al (10). These results may be explained by the following: *1*) the higher amount of ingested cells, *2*) differences in the recovery/detection methods, or *3*) differences in the used strains.

Puzzled by the third hypothesis, I searched the existing literature to verify if there are some indications for strain specificity of certain beneficial actions possibly exerted by different strains of yogurt cultures. Data produced by our laboratory have shown a marked difference in the chromosomal arrangements, as determined by pulsed field gel electrophoresis analysis (12), of

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TABLE 1
Assessment of the survival rate of yogurt cultures in the human gut[1]

Authors, year (ref)	Human subjects	Yogurt intake	Daily dose of *Streptococcus*	Survival of *Streptococcus*	Daily dose of *Lactobacillus*	Survival of *Lactobacillus*	Analytic technique used
	n	*g/d*	*CFU/g feces*		*CFU/g feces*		
García-Albiach et al, 2008 (9)	63 + 16	375	2×10^8		1.3×10^7	$<10^3$	MRS/M17 plate counts + species-specific primers + hybridization (positive 10%) difference between heated and viable cells
Mater et al, 2005 (10)	13	125	8×10^{10}	6.3×10^4 CFU/g feces	8×10^{10}	7.2×10^4 CFU/g	M17-agar plates containing 1000 mg streptomycin/mL and 100 mg rifampicin/mL for selective recovery of *Streptococcus thermophilus* MRS-agar plates containing the same antibiotic concentrations were used for selective recovery of *Lactobacillus delbrueckii*
Elli et al, 2006 (11)	20	250	5×10^9	None	6×10^9	Log of min 3 to max 5.5 subjects	Specific selective media + species-specific primers + strain-specific RAPD

[1] max, maximum; min, minimum; MRS, de Man, Rogosa and Sharpe; RAPD, rapid amplification of polymorphic DNA; ref, reference.

several strains taxonomically identified as *S. thermophilus*. This observation may also indicate a potential difference in the phenotypic behavior. Two major outcomes resulted from this search: one related to the action toward the immune system exerted by an *L. bulgaricus* strain, and second, of the ability of some yogurt cultures to enrich the vitamin content of yogurt, both of which appear to be strain-dependent.

The action on the immune system is not really a new item in the area of yogurt research, but the novelty of the series of studies published by a Japanese group (13) is that they have shown both in vitro and in vivo the immune modulation exerted by a specific strain of *L. bulgaricus*, and also identified the bacterial component responsible for this action. The *L. bulgaricus* strain OLL1073R-1 was shown to produce a capsular polysaccharide, which has a marked effect on the immune system in mice (14, 15). This specific strain was initially studied for its extracellular polysaccharide (16), formed by D-glucose, D-galactose, and phosphorus, but which was also shown to have potential for stimulation of mouse splenocytes and a significant increase in interferon-γ production. When orally administered, the purified polysaccharide augments the natural killer cell activity. Yogurt produced by using *L. bulgaricus* OLL1073R-1 and fed to mice showed a similar amount of immunomodulation as the purified polysaccharide, but this action was not present in yogurt fermented with a different strain of *L. bulgaricus* (15). One clinical trial in humans showed that this strain was able to reduce the incidence of the common cold in elderly people when administered daily in yogurt (**Table 2**) (16).

An additional example of a beneficial action exerted by yogurt cultures, which is not related to lactose digestion, is the improvement of the vitamin B profile in adults (17, 18), with special attention paid to young healthy women (17). A group of nutritionists based in Vienna, Austria, conducted a study in which volunteers consumed 100 g probiotic ($n = 17$) or conventional ($n = 16$) yogurt daily for 2 wk and 200 g/d for another 2 wk. Plasma and urine concentrations of thiamine, riboflavin, and pyridoxine were determined. The main outcome was that plasma concentrations of thiamine increased in both groups ($P < 0.01$).

The same group published in 2001 (18) a similar article in which the thiamine, riboflavin, and vitamin B-6 status of healthy adults who consumed yogurt was not influenced by bacterial flora of the examined yogurt; therefore, it seems highly possible that vitamin production could be strain related, and future genomic studies will be relevant (19) to select the most actively producing vitamin cultures. It is possible to conclude therefore that a new research line is open for scientists: to assess and exploit the strain-specific beneficial properties of traditional yogurt starter cultures.

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LM received financial reimbursement for travel expenses and an honorarium from the Danone Institute International for his participation in the conference. He is a member of the Yogurt in Nutrition Initiative Advisory Board and has received grant funding from Danone Institute International.

TABLE 2
Overview of results obtained in humans by using *Lactobacillus bulgaricus*[1]

Subjects	Duration	Outcomes	Results
$n = 113$ aged 59–84 y; median age = 74.5 y	12 wk	Quality-of-life questionnaires, blood sampling for immune variables, daily dairy consumption	Risk of common cold was 2.6 times as low (OR: 0.39; $P = 0.019$) in the treated group as in the placebo group. The increase in natural killer cell activity was significantly higher in the treated group.

[1] Data are from reference 13.

REFERENCES

1. Mohammadi R, Sohrabvandi S, Mohammad Mortazavian A. The starter culture characteristics of probiotic microorganisms in fermented milks. Eng Life Sci 2012;12:399–409.
2. Bezkorovainy A. Probiotics: determinants of survival and growth in the gut. Am J Clin Nutr 2001;73(suppl):399S–405S.
3. González-Rodríguez I, Ruiz L, Gueimonde M, Margolles A, Sánchez B. Factors involved in the colonization and survival of bifidobacteria in the gastrointestinal tract. FEMS Microbiol Lett 2013;340:1–10.
4. Guarner F, Perdigon G, Corthier G, Salminen S, Koletzko B, Morelli L. Should yoghurt cultures be considered probiotic? Br J Nutr 2005;93: 783–6.
5. FAO/WHO. Report of a joint FAO/WHO Expert Consultation on evaluation of health and nutritional properties of probiotics in food including power milk with lactic acid bacteria. 2001. Available from: ftp.fao.org/es/esn/food/probio_report_en.pdf (cited 25 July 2007).
6. FAO/WHO. Report of a joint FAO/WHO Working Group on drafting guidelines for the evaluation of probiotics in food. 2002. Available from: ftp.fao.org/es/esn/food/wgreport2.pdf (cited 25 July 2007).
7. European Food Safety Authority. Scientific opinion on the substantiation of health claims related to live yoghurt cultures and improved lactose digestion. EFSA Journal 2010;8:1763:1781.
8. Pochart P, Dewit O, Desjeux JF, Bourlioux P. Viable starter culture, β-galactosidase activity, and lactose in duodenum after yogurt ingestion in lactase-deficient humans. Am J Clin Nutr 1989;49:828–31.
9. García-Albiach R, Pozuelo de Felipe MJ, Angulo S, Morosini MI, Bravo D, Baquero F, del Campo R. Molecular analysis of yogurt containing *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* in human intestinal microbiota. Am J Clin Nutr 2008;87:91–6.
10. Mater DD, Bretigny L, Firmesse O, Flores MJ, Mogenet A, Bresson JL, Corthier G. *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *Bulgaricus* survive gastrointestinal transit of healthy volunteers consuming yogurt. FEMS Microbiol Lett 2005;250:185–7.
11. Elli M, Callegari ML, Ferrari S, Bessi E, Cattivelli D, Soldi S, Morelli L, Goupil Feuillerat N, Antoine JM. Survival of yogurt bacteria in the human gut. Appl Environ Microbiol 2006;72:5113–7.
12. Tosi L, Berruti G, Danielsen M, Wind A, Huys G, Morelli L. Susceptibility of *Streptococcus thermophilus* to antibiotics. Antonie van Leeuwenhoek 2007;92:21–8.
13. Makino S, Ikegami S, Kume A, Horiuchi H, Sasaki H, Orii N. Reducing the risk of infection in the elderly by dietary intake of yoghurt fermented with *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1. Br J Nutr 2010;104:998–1006.
14. Kano H, Kita J, Makino S, Ikegami S, Itoh H. Oral administration of *Lactobacillus delbrueckii* subspecies *bulgaricus* OLL1073R-1 suppresses inflammation by decreasing interleukin-6 responses in a murine model of atopic dermatitis. J Dairy Sci 2013;96:3525–34.
15. Nagai T, Makino S, Ikegami S, Itoh H, Yamada H. Effects of oral administration of yogurt fermented with *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and its exopolysaccharides against influenza virus infection in mice. Int Immunopharmacol 2011;11:2246–50.
16. Makino S, Ikegami S, Kano H, Sashihara T, Sugano H, Horiuchi H, Saito T, Oda M. Immunomodulatory effects of polysaccharides produced by *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1. J Dairy Sci 2006;89:2873–81.
17. Fabian E, Majchrzak D, Dieminger B, Meyer E, Elmadfa I. Influence of probiotic and conventional yoghurt on the status of vitamins B1, B2 and B6 in young healthy women. Ann Nutr Metab 2008;52:29–36.
18. Elmadfa I, Heinzle C, Majchrzak D, Foissy H. Influence of a probiotic yoghurt on the status of vitamins B(1), B(2) and B(6) in the healthy adult human. Ann Nutr Metab 2001;45:13–8.
19. Rossi M, Amaretti A, Raimondi S. Folate production by probiotic bacteria. Nutrients 2011;3:118–34.

Lactose digestion from yogurt: mechanism and relevance[1–3]

Dennis A Savaiano

ABSTRACT

Yogurt is traditionally consumed throughout the world among populations who are seemingly unable to digest lactose. This review provides a historical overview of the studies that show lactose digestion and tolerance from yogurt by lactose-intolerant people. The lactose in yogurt is digested more efficiently than other dairy sources of lactose because the bacteria inherent in yogurt assist with its digestion. The bacterial lactase survives the acidic conditions of the stomach, apparently being physically protected within the bacterial cells and facilitated by the buffering capacity of yogurt. The increasing pH as the yogurt enters the small intestine and a slower gastrointestinal transit time allow the bacterial lactase to be active, digesting lactose from yogurt sufficiently to prevent symptoms in lactose-intolerant people. There is little difference in the lactase capability of different commercial yogurts, because they apparently contain *Lactobacillus bulgaricus* and *Streptococcus thermophilus* in sufficient quantities (10^8 bacteria/mL). However, *Lactobacillus acidophilus* appears to require cell membrane disruption to physically release the lactase. Compared with unflavored yogurts, flavored yogurts appear to exhibit somewhat reduced lactase activity but are still well tolerated.
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INTRODUCTION

People with lactose intolerance experience gastrointestinal symptoms when consuming milk or milk products because they lack sufficient small intestinal lactase (β-galactosidase) activity to adequately digest the milk sugar lactose (which comprises galactose and glucose linked by a β-galactoside bond). Undigested lactose consequently enters the colon where it is fermented by the resident microflora, resulting in symptoms including abdominal pain, bloating, diarrhea, and flatulence. Lactase deficiency is common in nonwhite adults, with a prevalence of 50–70% or higher (1–3), because of a genetically programmed loss of lactase after weaning.

Yogurt is produced by incubating concentrated milk with *Lactobacillus bulgaricus* and *Streptococcus thermophilus* (4). The bacteria ferment the milk, reducing the pH and creating the tangy taste associated with yogurt. The lactose content of the finished product is approximately similar to that of unconcentrated milk (4), although there may be small differences (perhaps ~5%) between products and brands according to manufacturing processes. Traditionally, lactose-intolerant populations have consumed yogurt without experiencing symptoms; however, because yogurt contains lactose, this would appear to be counterintuitive. This review provides an overview of the studies that reported on how yogurt is well tolerated by people with lactose intolerance.

EARLY WORK

It was suggested as early as 1974 that fermented dairy foods would be beneficial for lactose intolerance, although, at the time, this was hypothesized to be attributable to a low lactose content (5). However, when natural (live culture) yogurt was fed to rats, they absorbed galactose more efficiently and had greater intestinal lactase activity than rats fed pasteurized yogurt or a simulated yogurt formulation (6). Furthermore, the yogurt bacteria survived for 3 h in the gastrointestinal tract of the rats, and the authors hypothesized that the bacteria contributed to the hydrolysis of lactose (6). These data from experimental animals suggested that there was something more going on than a simple lactose dose effect.

The first human study followed in 1982, although it was not designed to determine the mechanism. In contrast to low-fat milk, a test drink of yogurt or acidophilus milk resulted in no symptoms in lactose-intolerant individuals (1). The reduced lactose quantity in the yogurt/fermented milk was implicated, because the dose of lactose in the test drinks was greater in the low-fat milk (24.6 g) than in the acidophilus milk (18.1 g) or yogurt (11.4 g) (1). The author suggested that lactase-containing microorganisms within the yogurt and fermented milk could continue to be active in the intestinal tract, participating in the hydrolysis of lactose (1). However, with the confounding effect of dose it was not possible to establish the mechanism.

YOGURT LACTASE ACTIVITY

The dose question was settled with a controlled study that showed that the lactose in yogurt is better digested than that in milk, apparently as a result of its lactase activity (4). In this study, the 10 participants were confirmed to be lactose-intolerant on the basis of elevated breath-hydrogen concentrations after a lactose challenge (4). This technique measures the hydrogen produced when undigested lactose is fermented by the colonic microflora from individuals who have low levels of gastrointestinal lactase

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activity. The subjects were given test drinks, each containing similar lactose loads, which comprised lactose in water (20 g lactose), milk (18 g lactose), commercial unflavored yogurt (18 g lactose), or lactulose (a nonabsorbable disaccharide, 10 g in water); and breath-hydrogen concentration was measured for 8 h afterward (4). The ingestion of 18 g of lactose in yogurt resulted in only approximately one-third as much hydrogen excretion as a similar load of lactose in milk or water, indicating a much better digestion of lactose from yogurt (4). The breath-hydrogen curves (**Figure 1**) showed a significantly smaller ($P < 0.01$) total AUC for yogurt (mean ± SE: 108 ± 25 ppm/h) compared with milk (293 ± 33 ppm/h) or lactose solution (255 ± 33 ppm/h), with a smaller portion of yogurt (containing 11 g lactose) producing only 72 ± 22 ppm/h (4). The consumption of yogurt also resulted in fewer symptoms than did a similar quantity of lactose in milk or water, with diarrhea or flatulence reported by 20% of participants after yogurt and 80% of participants after milk (4). The lactase activity of duodenal contents was assessed indirectly in 3 individuals, by measuring lactose disappearance and galactose appearance. It was negligible before the yogurt test, but for at least 1 h afterward there was sufficient lactase activity to digest 50–100% of the lactose in 4 h (4), supporting the findings of the rat study (6). The measured lactase activity of yogurt decreased faster than would be expected from the measured rate of galactose appearance (4). This study suggested that the enhanced absorption of lactose in yogurt resulted from the intraintestinal digestion of lactose by yogurt-derived microbial lactase, with the survival of yogurt-derived lactase in the duodenum. The role of lactase-digesting bacteria in yogurt was further supported by findings that less breath hydrogen was produced by lactose-intolerant individuals after consuming unheated yogurt than when the product had been heated (7, 8).

YOGURT LACTASE ACTIVITY IN THE INTESTINE

The pH varies widely along the length of the gastrointestinal tract, being acidic (pH 1–2.5) in the stomach and increasing to 6.6 in the proximal small intestine and 7.5 in the terminal ileum (9). This pH variability affects the in vivo lactase activity from yogurt. At 4°C and its final postfermented pH of 4, yogurt has minimal lactase activity (4). However, incubation at a pH of 7 and 37°C (and sonication) substantially increases its lactase activity, to 25 U/g, an amount sufficient to hydrolyze 95% of the lactose load in 4 h (4). Other studies have also documented pH effects (10, 11). The lactase activity of yogurt also increases in the presence of bile, as shown in vitro (7), perhaps by increasing the cellular permeability to allow more substrate to enter the bacterial cells (12). Thus, the activity of yogurt lactase is likely to vary at different gastrointestinal sites and should show maximal activity at an approximately neutral pH 7; it is no surprise then that lactase activity of duodenal contents was reported after ingestion of yogurt (4).

However, yogurt has a buffering capacity, requiring nearly 3 times as much acid to change its pH from 4.1 to 2.0 than is required to acidify milk (10). Gastrointestinal pH is influenced by this buffering capacity, as evidenced by the gastric pH remaining >2.7 for 3 h after ingestion of yogurt (10). This may also partly explain how lactase survives passage through the stomach; the integrity of the bacterial cell membrane may also play a role. By using a more direct approach than in previous studies (4), the lactase activity of duodenal contents was assessed after yogurt consumption (11). The fresh, unflavored yogurt contained ~10 g of lactose, and specific strains of *L. bulgaricus* and *S. thermophilus* (the "starter culture"), as well as being tagged with polyethylene glycol (a nonabsorbable internal standard for lactose) and spores of a marker bacterium, *Bacillus stearothermophilus* (an internal standard for bacteria, because it only germinates at 65°C). Lactose malabsorbers were given the yogurt either fresh ($n = 7$) or heated ($n = 3$). In duodenal samples taken after fresh yogurt ingestion, viable starter culture was detected for 60 min in 6 of 7 lactose malabsorbers, with large numbers of *L. bulgaricus* and *S. thermophilus* surviving passage through the stomach (11). The ratio of microbial lactase activity to the marker bacterium remained stable, showing that the enzyme is not degraded for at least 60 min after yogurt ingestion, despite some of the bacteria losing their viability (11). Yogurt ingestion affected duodenal pH, which decreased 15 min after ingestion and remained at <5.1 throughout

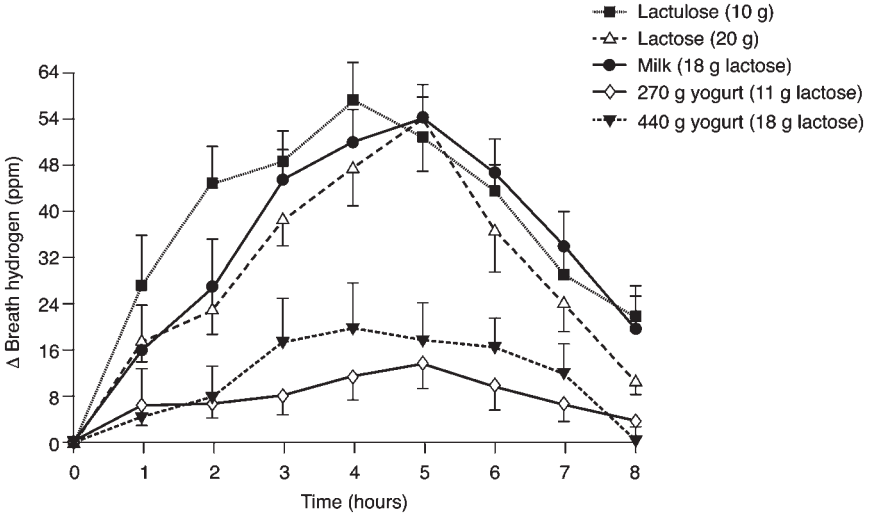

FIGURE 1. Mean (±SE) changes in breath-hydrogen concentrations after ingestion of lactose, milk, yogurt, or lactulose ($n = 10$). The amount of breath hydrogen expelled after ingestion of yogurt was one-third the amount expelled after ingestion of milk despite equivalent lactose loads. Reproduced with permission from reference 4.

(11). Whereas the in vitro lactase activity in yogurt was maximal at a pH of 7, it decreased by 80% when the pH was <5 (11). Hence, lactase activity in the duodenum increased after the ingestion of fresh yogurt, then decreased as duodenal pH lowered (**Figure 2**). Ratios of lactose to polyethylene glycol remained similar to preingested values for 90 min, suggesting that lactase could not hydrolyze the lactose (11). This study showed that after fresh yogurt ingestion, viable starter culture reaches the duodenum and contains lactase activity, confirming previous findings (4). However, it also suggests that the buffering capacity of the yogurt, which protects bacteria from the acidic gastric environment, may have an inhibitory effect on microbial lactase in the duodenum. The authors suggested that lactose digestion by microbial lactase might be occurring in the jejunum or ileum of the small intestine or (less likely) in the colon.

It was subsequently confirmed that >90% of the lactose in yogurt is digested in the small intestine, aided by a slow gastrointestinal transit time (13). This study, which collected ileal contents of lactase malabsorbers, found that the orocecal transit time (determined from breath-hydrogen measurements) of fermentable components after the ingestion of yogurt (mean ± SE: 165 ± 17 min) and heated yogurt (206 ± 19 min) was significantly longer than that with milk (103 ± 19 min; $P < 0.01$ for comparisons of milk with yogurts, no significant difference between fresh and heated yogurt) (13). Significantly less lactose was recovered from the terminal ileum after yogurt (1740 ± 260 mg) than after heated yogurt (2825 ± 461 mg; $P < 0.05$) (**Figure 3**), with approximately one-fifth of yogurt lactase activity reaching the terminal ileum (13). This study showed that the small intestine is the site of most microbial lactase activity. The delay in transit time with yogurt compared with milk may be attributed to the difference in formulation—for example, increased osmolality or the physical thickening that occurs during fermentation (14). Together, these studies (11, 13) confirm that yogurt microbial lactase is detectable in the duodenum but is largely active in the distal small intestine, with only a small amount of lactose entering the colon.

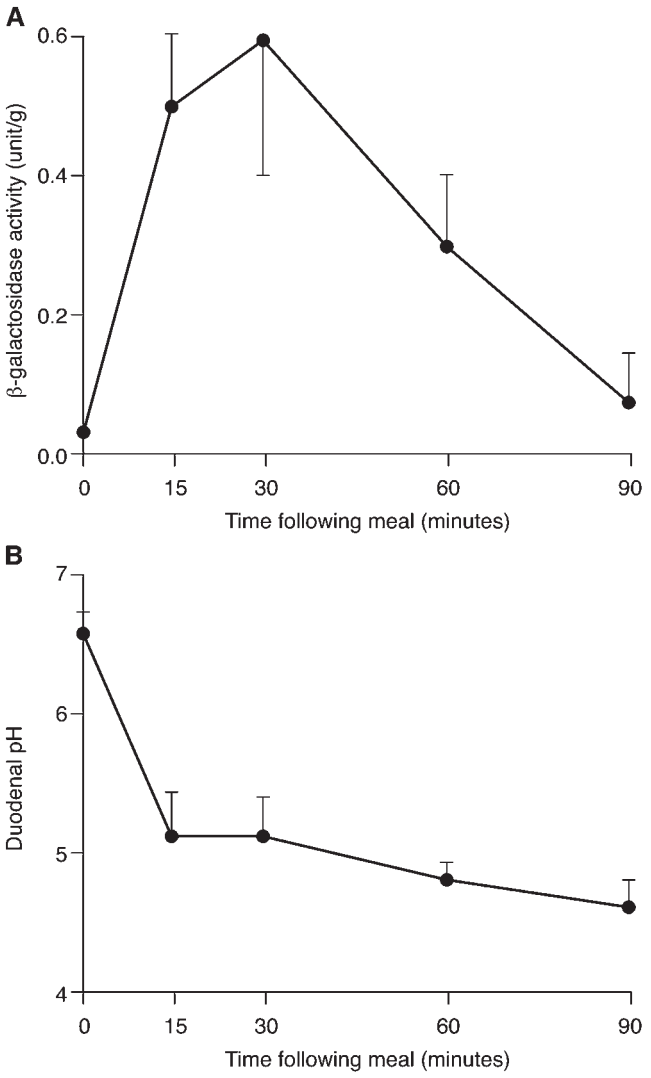

FIGURE 2. After fresh yogurt ingestion, duodenal lactase (β-galactosidase) activity increases (A) before falling again with decreasing duodenal pH (B). Values are means ± SEs; $n = 7$. Reproduced with permission from reference 11.

BACTERIAL LACTASE ACTIVITIES

Having identified that yogurt microbial lactases digest lactose in the small intestine, the logical next question was "Are all bacteria equal?" Most commercial yogurts contain ~10^8 bacteria/mL, and strains may vary by product. Several bacterial strains and doses were compared in lactose-intolerant individuals (15). Yogurt (containing *S. thermophilus* and *L. bulgaricus*) and acidophilus milk (containing *Lactobacillus acidophilus*) were prepared by using commercially processed 2% low-fat milk, with 10^7 or 10^8 bacteria/mL. Lactose maldigestion was monitored by measuring breath-hydrogen excretion at hourly intervals for 8 h after consumption of each test drink containing ~20 g of lactose. The study found that, compared with the milk control (30.78 ppm breath hydrogen), there was little difference between *L. acidophilus* (either of the doses) or yogurt bacteria (10^7/mL), whereas the standard dose of yogurt bacteria (10^8/mL) resulted in significantly less hydrogen (9.81 ppm; $P < 0.05$) (15). This study showed that a 10-fold reduction in the dose of yogurt bacteria rendered their lactase activity ineffective and that the acidophilus milk had no lactase activity. However, sonicating acidophilus milk restores the lactase activity, presumably by releasing the enzyme from the cells (16). In contrast, sonication of yogurt bacteria appears to render them susceptible to gastric acid, reducing their lactase activity (10). It is possible that these differences may be attributable to species- or strain-specific characteristics of the bacteria/enzyme (eg, location of enzyme, cell structure).

Another study evaluated the ability of different strains and species of bacteria to digest lactose in vivo, comparing yogurts (containing mixtures of strains of *Streptococcus salivarius* subsp. *thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus*) and fermented milks (containing individual species of *S. thermophilus*, *L. bulgaricus*, *L. acidophilus*, or *Bifidobacterium bifidus*) that varied in lactase activity (14). All of the yogurts had similar lactose content, and all of the yogurts performed similarly in lactase-deficient individuals (**Figure 4**), regardless of their total or specific lactase activity and any variation in cell counts (2.7–15 × 10^8/g product) (14). The response to fermented milks was more varied (14). The results suggested that, rather than total lactase activity or microbial cell count, another factor (perhaps intracellular substrate transport) was the rate-limiting factor in determining lactose hydrolysis from yogurt.

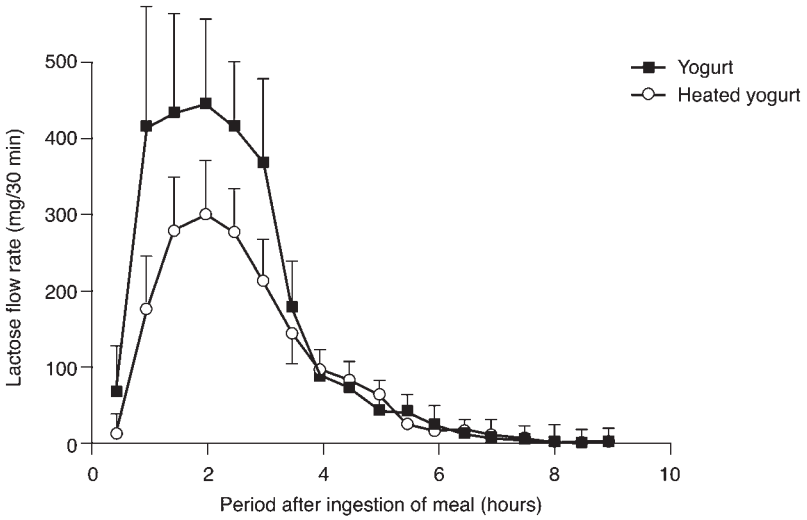

FIGURE 3. Mean (±SE) lactose flow rate through the ileum after ingestion of fresh yogurt or heated yogurt (n = 8 lactose-deficient subjects). Reproduced with permission from reference 13.

EFFECT OF YOGURT CHARACTERISTICS ON LACTOSE HYDROLYSIS

One factor that could influence the lactase activity of yogurt is concurrent food intake. This was investigated by examining the effect of consuming a meal with yogurt (17). Breath-hydrogen expiration, incidence of symptoms, and enzyme and lactose content of gastric aspirates indicated that concurrent food intake does not inhibit, and may slightly improve, lactose digestion from yogurt (17).

Whereas most studies have been conducted using plain (unflavored) yogurt, measuring breath hydrogen after ingestion of flavored yogurt shows that this may be associated with less lactase activity (more malabsorption). In a study measuring breath-hydrogen production in lactase-deficient individuals, unflavored yogurt caused significantly less (37 ppm/h; $P < 0.005$) hydrogen production than milk (185 ppm/h), whereas hydrogen production with flavored yogurt was intermediate (77 ppm/h) (18). The plain and flavored yogurts both contained significant lactase activities (18), so the increased breath hydrogen may be a result of dilution of the yogurt with the flavoring or sugar, an osmotic effect of the sugar in the stomach, or possible end-product inhibition by glucose. However, the subjects had no symptoms after consuming the flavored yogurt (18).

It is possible that there is an influence of shelf life on the lactase activity of yogurt. Whereas most research suggests that all yogurts are effective, there are exceptions. For example, a study that used commercial products off the shelf found considerable differences between them (19). Eight lactose-malabsorbing individuals were challenged with 3 different brands of yogurt (Borden, Dannon, and Royal Maid), each of which contained 20 g lactose (19). Breath-hydrogen measurements were significantly higher for Borden, both in terms of total ppm and peak ppm, although there was no relation with symptoms (19). The authors implicated their small sample size for the observed mild symptoms but suggested that other factors may be involved, including temperature changes during transportation of the products from manufacturer to retailer (19). It is not currently known if yogurts that sit on the shelf for a longer time have diminished lactase activity.

LONG-TERM BENEFITS

Evidence suggests that colonic adaptation to lactose consumption may occur over days to weeks in lactose maldigesters (20, 21), although there may also be a placebo effect (22).

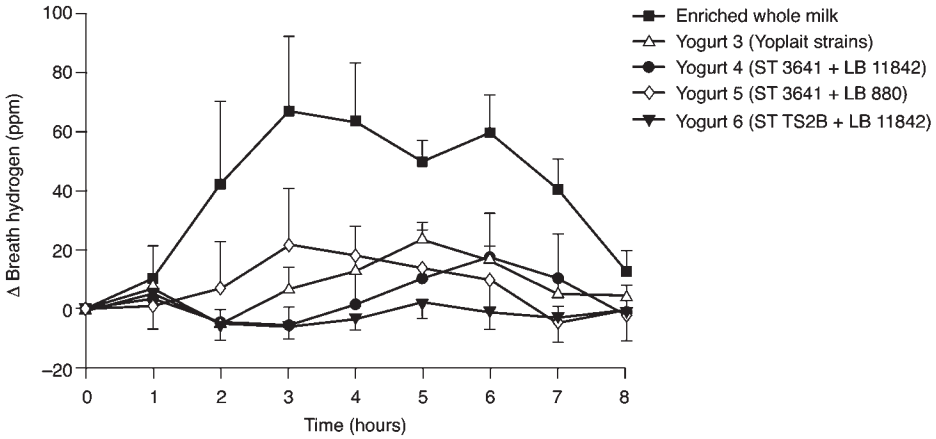

FIGURE 4. Mean (±SE) changes in concentration of breath hydrogen after ingestion of enriched whole milk or yogurts containing various strains of ST and LB or Yoplait strains (n = 7 lactase-deficient subjects). Reproduced with permission from reference 14. LB, *Lactobacillus delbrueckii* subsp. *bulgaricus*; ST, S*treptococcus salivarius* subsp. *thermophilus*.

Adaptation was apparent in a double-blind study that repeatedly provided yogurt (either fresh or heat-treated) to lactose malabsorbers for 15 d and measured breath hydrogen on days 1 and 15 (23). Whereas breath-hydrogen production was minimal and similar on days 1 and 15 for fresh yogurt, the response was improved for heated yogurt after 15 d of consumption (23). This suggests that regular consumption of small doses of lactose might be part of the management strategy for people with lactose intolerance, and that the benefit of yogurt consumption is maintained with regular consumption.

CONCLUSIONS

Autodigestion of lactose by yogurt bacteria improves its absorption, compared with other dairy products, in lactase-deficient people. Yogurt with sufficient numbers of *S. thermophilus* and *L. bulgaricus* (as is the case in most commercial yogurts) is very well tolerated by lactose maldigesters, because it is effectively analogous to taking an enzyme supplement with a dairy food.

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REFERENCES

1. Alm L. Effect of fermentation on lactose, glucose, and galactose content in milk and suitability of fermented milk products for lactose intolerant individuals. J Dairy Sci 1982;65:346–52.
2. Savaiano DA, Levitt MD. Milk intolerance and microbe-containing dairy foods. J Dairy Sci 1987;70:397–406.
3. Wilt TJ, Shaukat A, Shamliyan T, Taylor BC, MacDonald R, Tacklind J, Rutks I, Schwarzenberg SJ, Kane RL, Levitt M. Lactose intolerance and health. Evid Rep Technol Assess (Full Rep) 2010;192:1–410.
4. Kolars JC, Levitt MD, Aouji M, Savaiano DA. Yogurt—an autodigesting source of lactose. N Engl J Med 1984;310:1–3.
5. Gallagher CR, Molleson AL, Caldwell JH. Lactose intolerance and fermented dairy products. J Am Diet Assoc 1974;65:418–9.
6. Goodenough ER, Kleyn DH. Influence of viable yogurt microflora on digestion of lactose by the rat. J Dairy Sci 1976;59:601–6.
7. Gilliland SE, Kim HS. Effect of viable starter culture bacteria in yogurt on lactose utilization in humans. J Dairy Sci 1984;67:1–6.
8. Savaiano DA, AbouElAnouar A, Smith DE, Levitt MD. Lactose malabsorption from yogurt, pasteurized yogurt, sweet acidophilus milk, and cultured milk in lactase-deficient individuals. Am J Clin Nutr 1984;40:1219–23.
9. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 1988;29:1035–41.
10. Martini MC, Bollweg GL, Levitt MD, Savaiano DA. Lactose digestion by yogurt beta-galactosidase: influence of pH and microbial cell integrity. Am J Clin Nutr 1987;45:432–6.
11. Pochart P, Dewit O, Desjeux JF, Bourlioux P. Viable starter culture, beta-galactosidase activity, and lactose in duodenum after yogurt ingestion in lactase-deficient humans. Am J Clin Nutr 1989;49:828–31.
12. Noh DO, Gilliland SE. Influence of bile on beta-galactosidase activity of component species of yogurt starter cultures. J Dairy Sci 1994;77:3532–7.
13. Marteau P, Flourie B, Pochart P, Chastang C, Desjeux JF, Rambaud JC. Effect of the microbial lactase (EC 3.2.1.23) activity in yoghurt on the intestinal absorption of lactose: an in vivo study in lactase-deficient humans. Br J Nutr 1990;64:71–9.
14. Martini MC, Lerebours EC, Lin WJ, Harlander SK, Berrada NM, Antoine JM, Savaiano DA. Strains and species of lactic acid bacteria in fermented milks (yogurts): effect on in vivo lactose digestion. Am J Clin Nutr 1991;54:1041–6.
15. Lin MY, Savaiano D, Harlander S. Influence of nonfermented dairy products containing bacterial starter cultures on lactose maldigestion in humans. J Dairy Sci 1991;74:87–95.
16. McDonough FE, Hitchins AD, Wong NP, Wells P, Bodwell CE. Modification of sweet acidophilus milk to improve utilization by lactose-intolerant persons. Am J Clin Nutr 1987;45:570–4.
17. Martini MC, Kukielka D, Savaiano DA. Lactose digestion from yogurt: influence of a meal and additional lactose. Am J Clin Nutr 1991;53:1253–8.
18. Martini MC, Smith DE, Savaiano DA. Lactose digestion from flavored and frozen yogurts, ice milk, and ice cream by lactase-deficient persons. Am J Clin Nutr 1987;46:636–40.
19. Wytock DH, DiPalma JA. All yogurts are not created equal. Am J Clin Nutr 1988;47:454–7.
20. Johnson AO, Semenya JG, Buchowski MS, Enwonwu CO, Scrimshaw NS. Adaptation of lactose maldigesters to continued milk intakes. Am J Clin Nutr 1993;58:879–81.
21. Hertzler SR, Savaiano DA. Colonic adaptation to daily lactose feeding in lactose maldigesters reduces lactose intolerance. Am J Clin Nutr 1996;64:232–6.
22. Briet F, Pochart P, Marteau P, Flourie B, Arrigoni E, Rambaud JC. Improved clinical tolerance to chronic lactose ingestion in subjects with lactose intolerance: a placebo effect? Gut 1997;41:632–5.
23. Labayen I, Forga L, González A, Lenoir-Wijnkoop I, Nutr R, Martínez JA. Relationship between lactose digestion, gastrointestinal transit time and symptoms in lactose malabsorbers after dairy consumption. Aliment Pharmacol Ther 2001;15:543–9.

Dairy products, yogurts, and bone health[1–3]

René Rizzoli

ABSTRACT

Fracture risk is determined by bone mass, geometry, and microstructure, which result from peak bone mass (the amount attained at the end of pubertal growth) and from the amount of bone lost subsequently. Nutritional intakes are an important environmental factor that influence both bone mass accumulation during childhood and adolescence and bone loss that occurs in later life. Bone growth is influenced by dietary intake, particularly of calcium and protein. Adequate dietary calcium and protein are essential to achieve optimal peak bone mass during skeletal growth and to prevent bone loss in the elderly. Dairy products are rich in nutrients that are essential for good bone health, including calcium, protein, vitamin D, potassium, phosphorus, and other micronutrients and macronutrients. Studies supporting the beneficial effects of milk or dairy products on bone health show a significant inverse association between dairy food intake and bone turnover markers and a positive association with bone mineral content. Fortified dairy products induce more favorable changes in biochemical indexes of bone metabolism than does calcium supplementation alone. The associations between the consumption of dairy products and the risk of hip fracture are less well established, although yogurt intake shows a weakly positive protective trend for hip fracture. By consuming 3 servings of dairy products per day, the recommended daily intakes of nutrients essential for good bone health may be readily achieved. Dairy products could therefore improve bone health and reduce the risk of fractures in later life. *Am J Clin Nutr* 2014;99(suppl):1256S–62S.

INTRODUCTION

Bone growth begins with the development of the skeleton during fetal life and continues until the end of the second decade of life when the maturation process is complete and peak bone mass is achieved. In adult life, bone mineral mass is determined by the amount of bone accumulated at the end of skeletal growth (peak bone mass) and by the amount of bone lost subsequently. At any given age, the key determinants of fracture risk, bone mineral mass, and bone structure result from the difference between the amounts of bone gained and lost (1, 2).

Whereas bone mineral mass gain during childhood and adolescence is influenced by many factors, the major determinants of peak bone mass and strength are genetic (accounting for 60–80% of the variance). The remaining factors may be amenable to positive intervention, including nutrition, particularly the intake of calcium and protein, physical activity, and exposure to a variety of risk factors (1, 2).

The role of calcium intake in influencing bone mineral mass is well recognized (3). An adequate calcium intake increases bone mineral density (BMD)[4] during skeletal growth and prevents bone loss and osteoporotic fractures in the elderly (1). The greatest amount of dietary calcium is obtained from milk and dairy foods, which also provide the human diet with vitamin D (when dairy products are fortified), protein, phosphorus, potassium, and other macro- and micro-nutrients important for bone health (3).

CALCIUM AND PROTEIN AS MAJOR CONSTITUENTS OF DAIRY PRODUCTS

Dairy products may represent the best dietary sources of calcium because of the high content, high absorptive rate, and relatively low cost (4). Moreover, dairy products provide more protein, calcium, magnesium, potassium, zinc, and phosphorus per calorie than any other food (**Table 1**) (3, 6). For example, 250 mg of calcium may be obtained from a 200-mL glass of milk, a 180-g serving of yogurt, or 30 g of hard cheese. The consumption of 3–4 dairy servings/d would allow one to reach the Recommended Daily Intake (RDI) of calcium (7). Whereas a single dairy serving can deliver 250 mg of calcium, to attain an equivalent amount from other dietary sources would require 5–6 servings of vegetables (dark-green leafy vegetables or legumes) or 10–12 servings of whole-grain or refined-grain foods (8). Thus, dairy products are an efficient source of bone nutrients. Dairy products may represent up to 52–65% of the RDI of calcium and 20–28% of the protein requirement (9–13).

EFFECT OF CALCIUM ON BONE GROWTH

The advantages of dairy consumption to bone health are important during growth. The supplementation of pregnant mothers with calcium and other micronutrients is associated with

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[4] Abbreviations used: BMC, bone mineral content; BMD, bone mineral density; FMP, fermented milk product; IGF-I, insulin-like growth factor I; RDA, Recommended Dietary Allowance; RDI, Recommended Daily Intake.

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TABLE 1
Bone nutrient content per 100 g of selected dairy foods[1]

Dairy food (food code)	Calcium	Potassium	Phosphorus	Protein
	mg	*mg*	*mg*	*g*
Milk, full-fat 3.7% (01078)	119	151	93	3.3
Milk, skimmed (01151)	122	156	101	3.4
Yogurt, plain low-fat (01117)	183	234	144	5.3
Yogurt, fruit low-fat (01122)	169	216	133	4.9
Cheddar cheese (01009)	721	98	512	24.9
Cottage cheese, nonfat (01014)	86	137	190	10.3
Ice cream, soft-serve, chocolate (01236)	131	177	116	4.1

[1] Data are from the USDA National Nutrient Database for Standard Reference, release 26 (5).

increased skeletal growth and bone mass/density in the offspring. In one study, children born to women who had a higher frequency of intake of calcium-rich foods during pregnancy (milk, milk products, pulses, nonvegetarian foods, green leafy vegetables, and fruit) had higher total and spine bone mineral content (BMC) and BMD at the age of 6 y (14). In a further study, dietary patterns consistent with advice for healthy eating during pregnancy (high in fruit, vegetables, pasta, yogurt, cheese) were associated with greater bone size and BMD in the offspring at 9 y of age (15).

The beneficial effects of calcium and dairy products on bone mineral mass during growth have been confirmed from meta-analyses of numerous clinical studies on calcium supplementation and increased dietary dairy products in children (16, 17). A positive effect of calcium supplementation was shown on total body BMC and upper limb BMD with daily doses of calcium ranging between 300 and 1200 mg/d in children aged 3–18 y (16). Increased intakes of dietary calcium/dairy products were associated with increases in total-body and lumbar spine BMC in children with low baseline intakes (17). In studies of calcium supplementation for >12 mo, calcium-enriched foods significantly increased bone mass accrual in prepubertal girls and boys (18, 19), and the effect was maintained for 1–3 y after discontinuation of calcium supplementation (19, 20).

Recommended Dietary Allowances (RDAs) of calcium provided by the Institute of Medicine for the North American population range from 700 to 1300 mg/d, depending on age [eg, 1000 mg/d for 4- to 8-y-olds and 1300 mg/d for 9- to 18-y-olds (21)].

Recommendations are not consistent worldwide, and in the European Union the current RDI for calcium is 800 mg/d (22). Nonetheless, calcium intakes do not meet RDIs in many countries. In the United States, mean calcium intake was lowest among teenage girls, at ~900 mg/d (23). Among European girls, the mean calcium intake varied between 600 mg/d in Italy and 1250 mg/d in Finland (24). In France, where the RDI for calcium is 1200 mg/d for adolescents, 63–73% of girls aged 11–17 y consumed less than two-thirds of the RDI (25).

EFFECT OF PROTEIN ON BONE GROWTH

Dietary protein provides the body with the necessary amino acids for building the bone matrix. In addition, dietary protein stimulates the osteotropic hormone insulin-like growth factor I (IGF-I), which is important for bone formation (26). Protein intake in children and adolescents influences bone growth and bone mass accumulation. In well-nourished children and adolescents it appears that variations in protein intake within the "normal" range (~0.8–1.5 g · kg body weight^{-1} · d^{-1}) can affect skeletal growth and thereby modulate the genetic potential for peak bone mass attainment (2, 27). Spontaneous protein intake correlates positively with BMD and BMC as measured in prepubertal boys (11). In a prospective longitudinal study in healthy boys and girls aged 6–18 y, dietary intakes were recorded over 4 y by using yearly administration of 3-d dietary diaries (28). Bone mass and size were measured at the radius diaphysis by peripheral computerized tomography, and a significant positive association was found between long-term protein intake and periosteal circumferences, cortical area, BMC, and a calculated strength strain index. The mean protein intake was relatively high at ~2 kg · kg body weight^{-1} · d^{-1} in prepubertal children and ~1.5 kg · kg body weight^{-1} · d^{-1} in pubertal individuals. Overall protein intake accounted for 3–4% of the variance in bone variables. In this study, no association was found with the intake of calcium or sulfur-containing amino acids (28).

EFFECTS OF DAIRY PRODUCTS ON BONE GROWTH

As well as calcium, phosphorus, and vitamins, 1 L of milk provides ~32–35 g of protein, mostly casein, but also whey proteins, which contain growth-promoting elements (2). In growing children, long-term milk avoidance is associated with smaller stature and lower bone mineral mass. Low milk intake during childhood and/or adolescence increases the risk of fracture before puberty. In children who had avoided drinking cow milk for prolonged periods, fracture risk was 2.7-fold higher than in a matched birth cohort (29, 30).

The earliest controlled studies of milk intervention were conducted in British schoolchildren in the 1920s (31, 32). The consumption of 400–600 mL milk/d had a positive effect on height gain over a 7-mo period. Since then, numerous observational studies (**Table 2**) and randomized controlled trials (**Table 3**) have shown a favorable influence of dairy products on bone health during childhood and adolescence.

In one intervention trial, the effect of milk supplementation on total-body bone mineral acquisition in adolescent girls was evaluated. The intervention group who received 1 pint/d of milk (whole or reduced fat) for 18 mo had significantly greater increases of areal BMD/BMC and significantly higher concentrations of serum IGF-I than the control group (39). In another study in girls aged 10–12 y who had low dietary calcium intake at inclusion, increasing dietary calcium intake by consuming cheese was more beneficial for cortical bone mineral mass accrual than calcium supplementation in tablet form for the same calcium intake (1000 mg/d) (41). The largest randomized controlled intervention trial with dairy products was conducted in

TABLE 2
Beneficial effects of dairy products on bone growth in children and adolescents: data from observational studies[1]

First author, year (reference)	Subjects	Age	Sex	Duration	Type of dairy	Outcome
	n	*y*		*mo*		
Alexy, 2005 (28)	229	6–18	F/M	48	Protein	Positive association between protein intake and diaphyseal bone stability and strength; increased BMC
Black, 2002 (33)	50	3–10	F/M	12	Milk (vs milk avoiders for 4.5 ± 2.5 y)	Milk avoiders had significantly shorter height and lower femoral neck, hip, spine, and radius BMC/BMD
Budek, 2007 (34)	109	17	F/M	Cross-sectional study	Milk	Dietary milk protein (but not dietary meat protein) significantly associated with BMC
Esterle, 2009 (35)	192	12–22	F	Cross-sectional study	Milk	Milk consumption (but not other calcium sources) associated with higher lumbar BMC/BMD
Matković, 1979 (36)	72	30–40	F/M	Cross-sectional study	All dairy	Dairy intake associated with bone mass in young adults
Matković, 2004 (37)	264	15	F	≥36	Milk	Dairy consumption associated with higher trochanter BMD and proximal radius cortical area
Teegarden, 1999 (38)	224	1–19	F	Cross-sectional study	Milk	Milk intake in adolescence correlates with total-body, radius, and spine BMC/BMD

[1] BMC, bone mineral content; BMD, bone mineral density.

10-y-old Chinese girls. Significantly higher gains in height, body weight, BMC, and areal BMD were observed in the groups receiving milk on school days for 2 y (330 mL milk/d fortified with calcium with or without vitamin D supplementation) compared with the control group (42). Consequently, in the *Dietary Guidelines for Americans*, the USDA recommends daily milk intakes of 480 mL/d among children aged 2–8 y and 730 mL milk or equivalent dairy products/d among children aged >9 y (7).

PROTEINS AND BONE AND MUSCLE DURING AGING

Dietary protein clearly has a role in bone health, and protein is a modifiable factor in osteoporosis prevention. Protein undernutrition is frequently seen in the elderly and contributes to the development of osteoporosis. In an elderly population, studies have reported a positive relation between protein intake and lean mass and BMD. Whereas the RDA for protein is 0.8 g/kg body weight for adults (6), mean protein intake to reach a neutral nitrogen balance in elderly hospitalized patients was found to be $\sim 1.06 \pm 0.28\ g \cdot kg^{-1} \cdot d^{-1}$, ie higher than recommendations for healthy elderly people (48). In another study, median dietary protein intake of 1.1 g/kg body weight among elderly individuals was associated with a higher level of maintenance of lean mass over 3 y of follow-up compared with lower dietary protein intakes (49). Studies in younger women have shown that the consumption of high-quality dairy protein after resistance exercise supports muscle anabolism (50, 51). Milk/dairy consumption after resistance exercise has been shown to positively affect body composition in women by promoting losses in fat, gains or maintenance of lean mass, and preservation of bone. In addition, importantly for bone health, resistance exercise plus dairy products improved BMD at clinically important sites and reduced bone resorption (50, 51).

Approximately 2% (1–8%) of the variance in BMD/BMC may be explained by dietary protein intake. A small positive effect of protein supplementation on lumbar spine BMD has been found in randomized placebo-controlled trials (52). There is some evidence for an effect of dietary protein intake on bone fracture risk. In an observational study conducted over 3 y, representing more than 100,000 person-years, hip fracture risk was inversely associated with protein intake (53, 54). A study conducted in elderly patients with recent hip fracture showed that protein supplementation was associated with increased serum concentrations of IGF-I, reduction in proximal femur BMD loss, and shorter stay in rehabilitation hospitals (55).

ROLE OF IGF-I AND AMINO ACIDS PRESENT IN DAIRY PRODUCTS AS REGULATORS

A number of controlled intervention trials have been conducted in adults testing the effects of dairy product consumption (milk, cheese, fortified dairy) on markers of bone activity (**Table 4**). IGF-I is an essential factor for longitudinal bone growth. IGF-I can also exert anabolic effects on bone mass during adulthood. The consumption of a vitamin D and calcium-fortified soft cheese by healthy postmenopausal women increased protein intake, reduced the serum concentration of bone resorption biomarkers [tartrate-resistant acid phosphatase isoform 5b (TRAP 5b) and cross-linked teleopeptide of type 1 collagen (CTX)], and increased serum IGF-I, which is compatible with a nutrition-induced reduction in postmenopausal bone turnover rate (59). Similar findings were found in studies in elderly women (58, 66).

TABLE 3
Effect of dairy products on bone mineral mass accrual: results from randomized clinical trials in adolescents[1]

First author, year (reference)	Subjects	Age	Sex	Duration	Type of dairy	Skeletal site[2]	Difference between intervention and control groups
	n	*y*		*mo*			%
Cadogan, 1997 (39)	82	12	F	18	Milk (568 mL)	Whole-body	2.9
Chan, 1995 (40)	48	11	F	12	Dairy	Spine/whole-body	9.9/6.6
Cheng, 2005 (41)	195	11	F	24	Cheese (= 1000 mg Ca)	Tibia shaft	4.4
Du, 2004 (42)	757	10	F	24	Milk (330 mL)	Whole-body	4.2
Gibbons, 2004 (43)	154	8–10	F/M	18	Fortified dairy drink	Whole-body/hip/spine	NSD
Ho, 2005 (44)	199	14–16	F	12	Fortified soy drink (375 mL)	Spine/hip	NSD
Lau, 2004 (45)	344	10	F/M	18	Milk powder (= 650 mg Ca)	Spine/hip	1.4/1.1
Merrilees, 2000 (46)	91	16	F	24	Milk (= 1160 mg Ca)	Spine/femoral neck/trochanter	1.5/4.8/4.8
Zhu, 2005 (47)	606	10	F	24	Milk (330 mL)	Metacarpal cortical thickness, periosteal diameter	5.7/1.2

[1] BMC, bone mineral content; BMD, bone mineral density; NSD, no significant difference.
[2] BMC and BMD were assessed by X-ray, dual-energy X-ray absorptiometry, or peripheral quantitative computed tomography.

Intakes of aromatic amino acids, which are particularly prevalent in dairy foods, increase IGF-I and stimulate the intestinal absorption of calcium (67). Serum IGF-I concentrations are increased with protein supplementation in elderly frail individuals, which is accelerated by the addition of zinc supplementation (68). Furthermore, in women with a recent hip fracture, protein supplementation achieves peak increases in IGF-I concentration after only 7 d of treatment (69).

DAIRY PRODUCTS AND BONE HEALTH

Observational studies and controlled trials show a significantly positive association between dairy food intake, bone turnover markers, and BMC or BMD (Table 3) (51, 59, 62, 65). The application of an intervention approach combining nutrition, education, and consumption of fortified dairy products for 12 mo induced more favorable changes in biochemical indexes of bone metabolism, such as increased IGF-I, than did calcium supplementation alone among postmenopausal women. The dairy intervention group had greater improvements in pelvis, total-spine, and total-body BMD than did both the calcium supplementation and control groups (64, 70).

BMD or BMC is a surrogate marker for bone strength, whereas the incidence of fracture is the key functional outcome measure. Data on the relation between dairy food intake and fracture risk are limited, and this relation requires further studies. The associations between dairy product consumption, BMD, and hip fracture risk were examined in a 12-y follow-up of the

TABLE 4
Effect of dairy products on bone turnover markers and bone mass: data from controlled intervention trials in adults[1]

First author, year (reference)	Subjects	Age	Sex	Duration	Type of dairy	Outcome
	n	*y*		*mo*		
Adolphi, 2009 (56)	85	58.7 ± 0.3[2]	F	0.5	Fortified fermented milk (175 mL)	Reduction in nocturnal deoxypyridinoline excretion
Bonjour, 2008 (57)	30	59.3 ± 0.3	F	1.5	Milk	Reduction in PTH, CTX, PINP, osteocalcin
Bonjour, 2009 (58)	37	84.8 ± 8.1	F	1	Skimmed soft cheese, 2 servings/d	Reduction in PTH, CTX, TRAP 5b; increase in IGF-I, 25(OH)D
Bonjour, 2012 (59)	71	56.6 ± 3.0	F	1.5	Skimmed soft cheese, 2 servings (100 g)/d	Reduction in PTH, CTX, TRAP 5b; increase in IGF-I
Bonjour, 2013 (60)	89	85.5	F	2	Either vitamin D– and calcium-fortified yogurt (2 × 125 g/d) (vitamin D 10 μg/d and calcium 800 mg/d) or nonfortified control yogurt providing calcium of 280 mg/d	Reduction in PTH, CTX, TRAP 5b
Josse, 2010 (51)	20	22.4 ± 2.4	F	3	Milk (2 × 500 mL/d)	Reduction in PTH, CTX
Kruger, 2006 (61)	82	20–35	F	4	Fortified milk	Reduction in CTX
Kruger, 2010 (62)	1898	>55	F	4	Fortified milk	Reduction in PTH, CTX, PINP, osteocalcin
Kruger, 2012 (63)	63	>55	F	3	Fortified milk	Reduction in CTX
Manios, 2007 (64)	101	60.5 ± 0.7	F	12	Fortified milk and yogurt, 3 servings/d	Reduction in PTH, CTX; increase in BMD
Thorpe, 2008 (65)	130	45.6 ± 8.9	F/M	12	High-protein dairy	Attenuated bone loss

[1] BMD, bone mineral density; CTX, cross-linked teleopeptide of type 1 collagen; IGF-I, insulin-like growth factor I; PINP, procollagen type I N-propeptide; PTH, parathyroid hormone; TRAP 5b, tartrate-resistant acid phosphatase isoform 5b; 25(OH)D, 25-hydroxyvitamin D.
[2] Mean ± SD (all such values).

Framingham Offspring Study. Intake of dairy products was related with hip but not spine BMD, whereas yogurt intake was associated with hip (trochanter) BMD alone. Yogurt intake showed a weakly positive protective trend for hip fracture, whereas no other dairy groups showed a significant association (71).

SPECIFIC ROLES AND POTENTIAL MECHANISMS OF ACTION OF FERMENTED PRODUCTS

The processing of milk, particularly cheese production, was an important development in early agriculture, which can be dated back to the sixth millennium BC in northern Europe (72). Milk processing allows for the preservation of milk in a nonperishable form, which is more easily digested because of the reduced lactose content.

The large intestine possesses an efficacious vitamin D–dependent calcium absorptive capacity, although dietary calcium is generally in a poorly absorbable form when it reaches the large intestine (73). Various dietary sugars are known to stimulate intestinal calcium absorption by a mechanism that is still poorly understood. Of those, lactitol has a positive effect on the absorption of calcium in the large intestine and on the retention of calcium in the body, as shown in animal models, possibly by reducing the pH of the large intestine content, thereby making calcium more readily absorbable (74). In a small study in 12 postmenopausal women, lactulose consumption (5 or 10 g/d) was shown to increase calcium absorption in a dose-response manner (75).

Prebiotic agents, such as galactooligosaccharides, have been shown to increase calcium absorption in postmenopausal women (76). Adolescence is a time of rapid growth, which represents an opportunity to influence peak bone mass. In male adolescents, the consumption of 15 g oligofructose/d was shown to stimulate fractional calcium absorption (77). Among healthy adolescent girls aged 10–13 y who consumed smoothie drinks twice daily with 0, 2–5, or 5 g galactooligosaccharides for 3-wk periods, improvements in fractional calcium absorption were seen with both 5- and 10-g/d doses of galactooligosaccharides compared with the control (0.444, 0.419, and 0.393, respectively), although a dose-response relation was not observed. The increase in absorption was greatest after 24 h, consistent with lower gut absorption (78). Whether a small increase in fractional calcium absorption with galactooligosaccharide supplementation results in a biologically significant increment in bone mineral accrual leading to higher peak bone mass in the long term remains to be shown. Preclinical studies have shown that dietary galactooligosaccharide supplementation improves mineral absorption and bone properties in growing rats through gut fermentation (79). Dietary galactooligosaccharide supplementation increased femur ^{45}Ca uptake, calcium retention, femur and tibia breaking strength, distal femur total and trabecular volumetric BMD, and area and proximal tibia volumetric BMD in the rats ($P < 0.02$) (79). However, there is currently no direct evidence in humans to show that the observed increase in intestinal calcium absorption through gut-enhanced absorptive activity translates to a significant inhibition of bone resorption and either increased bone accumulation during growth or reduced bone loss in adulthood.

Other studies are investigating how probiotic bacterial strains affect the human gut microbiota and host. Fecal bifidobacteria were shown to increase with galactooligosaccharide treatment, which suggests that calcium absorption may be mediated by the gut microbiota, specifically by bifidobacteria (78, 80). Preliminary studies have investigated the effect of fermented milk products (FMPs) on the human gut microbiome in adult monozygotic female twins, although the changes in microbiome expression observed in gnotobiotic mice fed the same FMP bacterial species were not observed in the human study (81). Future studies may elucidate the direct effects of consuming yogurts and foods containing bacterial species with potential health benefits on the gut microbiomes of various human populations, and consequently on various aspects of human health.

COST-EFFECTIVENESS OF DAIRY PRODUCTS

The economic impact of improving dairy product consumption has been estimated in some models (82, 83). By increasing the intake of dairy foods to the recommended 3–4 servings/d, a reduction of at least 20% in osteoporosis-related health care costs could be achieved in the United States, translating to savings of $3.5 billion/y (82). The potential economic impact of increased dairy consumption on osteoporotic fractures has been quantified for selected European countries, such as the Netherlands, France, and Sweden (83). The potential savings on the cost of treating hip fractures exceeded the costs of extra dairy foods in all 3 countries: daily costs of additional dairy products, derived from local market prices, were small and were calculated at €0.44, €0.64, and €0.68 for the Netherlands, France, and Sweden, respectively. The total potential savings on the costs of treating hip fractures were large: ~€129 million for France, €34 million for Sweden, and €6 million for the Netherlands (83).

CONCLUSIONS

At all ages, calcium and protein play a key role in bone health, with particular emphasis on the phase of bone growth during childhood and adolescence and in the preservation of bone strength and prevention of osteoporosis in the elderly. Milk and dairy products are an optimal source of calcium as well as other nutrients (eg, potassium and magnesium) with important effects on bone health. Increasing daily calcium and protein intake with dairy products has the potential to improve and sustain bone health and to protect against fractures during childhood, adolescence, and later in life. A significant positive association between dairy food intake and bone turnover markers, BMC, and BMD has been shown in clinical studies. Data on the relation between dairy food intake and fracture risk are limited, and this relation requires further studies. The specific actions of FMPs are under investigation and have yielded some interesting results to date; the elucidation of the mechanisms involved may lead to a greater understanding of the health benefits of dairy products.

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REFERENCES

1. Rizzoli R, Bianchi ML, Garabedian M, McKay HA, Moreno LA. Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone 2010;46:294–305.
2. Rizzoli R. Nutrition: its role in bone health. Best Pract Res Clin Endocrinol Metab 2008;22:813–29.
3. Caroli A, Poli A, Ricotta D, Banfi G, Cocchi D. Invited review: dairy intake and bone health: a viewpoint from the state of the art. J Dairy Sci 2011;94:5249–62.
4. Sunyecz JA. The use of calcium and vitamin D in the management of osteoporosis. Ther Clin Risk Manag 2008;4:827–36.
5. USDA. USDA National Nutrient Database for Standard Reference. Release 26. 2013. Available from: http://ndb.nal.usda.gov/ndb/nutrients/index
6. Heaney RP. Calcium, dairy products and osteoporosis. J Am Coll Nutr 2000;19(suppl):83S–99S.
7. USDA. Dietary guidelines for Americans. 7th ed. Washington, DC: USDA, US Department of Health and Human Services, 2010.
8. Fulgoni VL III, Huth PJ, DiRienzo DB, Miller GD. Determination of the optimal number of dairy servings to ensure a low prevalence of inadequate calcium intake in Americans. J Am Coll Nutr 2004;23:651–9.
9. Smit E, Nieto FJ, Crespo CJ, Mitchell P. Estimates of animal and plant protein intake in US adults: results from the Third National Health and Nutrition Examination Survey, 1988–1991. J Am Diet Assoc 1999;99:813–20.
10. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. Am J Clin Nutr 2003;77:504–11.
11. Chevalley T, Bonjour JP, Ferrari S, Rizzoli R. High-protein intake enhances the positive impact of physical activity on BMC in prepubertal boys. J Bone Miner Res 2008;23:131–42.
12. Vissers PA, Streppel MT, Feskens EJ, de Groot LC. The contribution of dairy products to micronutrient intake in the Netherlands. J Am Coll Nutr 2011;30(suppl 1):415S–21S.
13. Skinner ML, Simpson JA, Buchholz AC. Dietary and total calcium intakes are associated with lower percentage total body and truncal fat in young, healthy adults. J Am Coll Nutr 2011;30:484–90.
14. Ganpule A, Yajnik CS, Fall CH, Rao S, Fisher DJ, Kanade A, Cooper C, Naik S, Joshi N, Lubree H, et al. Bone mass in Indian children—relationships to maternal nutritional status and diet during pregnancy: the Pune Maternal Nutrition Study. J Clin Endocrinol Metab 2006;91:2994–3001.
15. Cole ZA, Gale CR, Javaid MK, Robinson SM, Law C, Boucher BJ, Crozier SR, Godfrey KM, Dennison EM, Cooper C. Maternal dietary patterns during pregnancy and childhood bone mass: a longitudinal study. J Bone Miner Res 2009;24:663–8.
16. Winzenberg T, Shaw K, Fryer J, Jones G. Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. BMJ 2006;333:775.
17. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: results of a meta-analysis. Bone 2008;43:312–21.
18. Bonjour JP, Carrie AL, Ferrari S, Clavien H, Slosman D, Theintz G, Rizzoli R. Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind, placebo-controlled trial. J Clin Invest 1997;99:1287–94.
19. Chevalley T, Bonjour JP, Ferrari S, Hans D, Rizzoli R. Skeletal site selectivity in the effects of calcium supplementation on areal bone mineral density gain: a randomized, double-blind, placebo-controlled trial in prepubertal boys. J Clin Endocrinol Metab 2005;90:3342–9.
20. Bonjour JP, Chevalley T, Ammann P, Slosman D, Rizzoli R. Gain in bone mineral mass in prepubertal girls 3.5 years after discontinuation of calcium supplementation: a follow-up study. Lancet 2001;358:1208–12.
21. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, et al. The 2011 report on Dietary Reference Intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53–8.
22. Union CotE. Commission Directive 2008/100/EC of 28 October 2008 amending Council Directive 90/496/EEC on nutrition labelling for foodstuffs as regards recommended daily allowances, energy conversion factors and definitions. Official Journal of the European Union 2008;L295:9–12.
23. Bailey RL, Dodd KW, Goldman JA, Gahche JJ, Dwyer JT, Moshfegh AJ, Sempos CT, Picciano MF. Estimation of total usual calcium and vitamin D intakes in the United States. J Nutr 2010;140:817–22.
24. Kardinaal AF, Ando S, Charles P, Charzewska J, Rotily M, Vaananen K, Van Erp-Baart AM, Heikkinen J, Thomsen J, Maggiolini M, et al. Dietary calcium and bone density in adolescent girls and young women in Europe. J Bone Miner Res 1999;14:583–92.
25. Castetbon K, Vernay M, Malon A, Salanave B, Deschamps V, Roudier C, Oleko A, Szego E, Hercberg S. Dietary intake, physical activity and nutritional status in adults: the French nutrition and health survey (ENNS, 2006–2007). Br J Nutr 2009;102:733–43.
26. Heaney RP. Dairy and bone health. J Am Coll Nutr 2009;28(suppl 1):82S–90S.
27. Conigrave AD, Brown EM, Rizzoli R. Dietary protein and bone health: roles of amino acid-sensing receptors in the control of calcium metabolism and bone homeostasis. Annu Rev Nutr 2008;28:131–55.
28. Alexy U, Remer T, Manz F, Neu CM, Schoenau E. Long-term protein intake and dietary potential renal acid load are associated with bone modeling and remodeling at the proximal radius in healthy children. Am J Clin Nutr 2005;82:1107–14.
29. Goulding A, Rockell JE, Black RE, Grant AM, Jones IE, Williams SM. Children who avoid drinking cow's milk are at increased risk for prepubertal bone fractures. J Am Diet Assoc 2004;104:250–3.
30. Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E. Fractures during growth: potential role of a milk-free diet. Osteoporos Int 2007;18:1601–7.
31. Orr JB. Influence of amount of milk consumption on the rate of growth of school children. BMJ 1928;1:140–1.
32. Leighton G, Clark ML. Milk consumption and the growth of school children: second preliminary report on tests to the Scottish Board of Health. BMJ 1929;1:23–5.
33. Black RE, Williams SM, Jones IE, Goulding A. Children who avoid drinking cow milk have low dietary calcium intakes and poor bone health. Am J Clin Nutr 2002;76:675–80.
34. Budek AZ, Hoppe C, Ingstrup H, Michaelsen KF, Bugel S, Molgaard C. Dietary protein intake and bone mineral content in adolescents—The Copenhagen Cohort Study. Osteoporos Int 2007;18:1661–7.
35. Esterle L, Sabatier JP, Guillon-Metz F, Walrant-Debray O, Guaydier-Souquieres G, Jehan F, Garabedian M. Milk, rather than other foods, is associated with vertebral bone mass and circulating IGF-1 in female adolescents. Osteoporos Int 2009;20:567–75.
36. Matković V, Kostial K, Simonovic I, Buzina R, Brodarec A, Nordin BE. Bone status and fracture rates in two regions of Yugoslavia. Am J Clin Nutr 1979;32:540–9.
37. Matković V, Landoll JD, Badenhop-Stevens NE, Ha EY, Crncevic-Orlic Z, Li B, Goel P. Nutrition influences skeletal development from childhood to adulthood: a study of hip, spine, and forearm in adolescent females. J Nutr 2004;134:701S–5S.
38. Teegarden D, Lyle RM, Proulx WR, Johnston CC, Weaver CM. Previous milk consumption is associated with greater bone density in young women. Am J Clin Nutr 1999;69:1014–7.
39. Cadogan J, Eastell R, Jones N, Barker ME. Milk intake and bone mineral acquisition in adolescent girls: randomised, controlled intervention trial. BMJ 1997;315:1255–60.
40. Chan GM, Hoffman K, McMurry M. Effects of dairy products on bone and body composition in pubertal girls. J Pediatr 1995;126:551–6.
41. Cheng S, Lyytikainen A, Kroger H, Lamberg-Allardt C, Alen M, Koistinen A, Wang QJ, Suuriniemi M, Suominen H, Mahonen A, et al. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10–12-y-old girls: a 2-y randomized trial. Am J Clin Nutr 2005;82:1115–26; quiz 1147–8.
42. Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, Fraser DR, Greenfield H. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10–12 years in Beijing. Br J Nutr 2004;92:159–68.
43. Gibbons MJ, Gilchrist NL, Frampton C, Maguire P, Reilly PH, March RL, Wall CR. The effects of a high calcium dairy food on bone health in prepubertal children in New Zealand. Asia Pac J Clin Nutr 2004;13:341–7.
44. Ho SC, Guldan GS, Woo J, Yu R, Tse MM, Sham A, Cheng J. A prospective study of the effects of 1-year calcium-fortified soy milk supplementation on dietary calcium intake and bone health in Chinese adolescent girls aged 14 to 16. Osteoporos Int 2005;16:1907–16.
45. Lau EM, Lynn H, Chan YH, Lau W, Woo J. Benefits of milk powder supplementation on bone accretion in Chinese children. Osteoporos Int 2004;15:654–8.

46. Merrilees MJ, Smart EJ, Gilchrist NL, Frampton C, Turner JG, Hooke E, March RL, Maguire P. Effects of diary food supplements on bone mineral density in teenage girls. Eur J Nutr 2000;39:256–62.
47. Zhu K, Du X, Cowell CT, Greenfield H, Blades B, Dobbins TA, Zhang Q, Fraser DR. Effects of school milk intervention on cortical bone accretion and indicators relevant to bone metabolism in Chinese girls aged 10–12 y in Beijing. Am J Clin Nutr 2005;81:1168–75.
48. Gaillard C, Alix E, Boirie Y, Berrut G, Ritz P. Are elderly hospitalized patients getting enough protein? J Am Geriatr Soc 2008;56:1045–9.
49. Houston DK, Nicklas BJ, Ding J, Harris TB, Tylavsky FA, Newman AB, Lee JS, Sahyoun NR, Visser M, Kritchevsky SB, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. Am J Clin Nutr 2008;87:150–5.
50. Josse AR, Phillips SM. Impact of milk consumption and resistance training on body composition of female athletes. Med Sport Sci 2012; 59:94–103.
51. Josse AR, Tang JE, Tarnopolsky MA, Phillips SM. Body composition and strength changes in women with milk and resistance exercise. Med Sci Sports Exerc 2010;42:1122–30.
52. Darling AL, Millward DJ, Torgerson DJ, Hewitt CE, Lanham-New SA. Dietary protein and bone health: a systematic review and meta-analysis. Am J Clin Nutr 2009;90:1674–92.
53. Munger RG, Cerhan JR, Chiu BC. Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. Am J Clin Nutr 1999;69:147–52.
54. Wengreen HJ, Munger RG, West NA, Cutler DR, Corcoran CD, Zhang J, Sassano NE. Dietary protein intake and risk of osteoporotic hip fracture in elderly residents of Utah. J Bone Miner Res 2004;19:537–45.
55. Schürch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998;128:801–9.
56. Adolphi B, Scholz-Ahrens KE, de Vrese M, Acil Y, Laue C, Schrezenmeir J. Short-term effect of bedtime consumption of fermented milk supplemented with calcium, inulin-type fructans and caseinphosphopeptides on bone metabolism in healthy, postmenopausal women. Eur J Nutr 2009;48:45–53.
57. Bonjour JP, Brandolini-Bunlon M, Boirie Y, Morel-Laporte F, Braesco V, Bertiere MC, Souberbielle JC. Inhibition of bone turnover by milk intake in postmenopausal women. Br J Nutr 2008;100:866–74.
58. Bonjour JP, Benoit V, Pourchaire O, Ferry M, Rousseau B, Souberbielle JC. Inhibition of markers of bone resorption by consumption of vitamin D and calcium-fortified soft plain cheese by institutionalised elderly women. Br J Nutr 2009;102:962–6.
59. Bonjour JP, Benoit V, Rousseau B, Souberbielle JC. Consumption of vitamin D- and calcium-fortified soft white cheese lowers the biochemical marker of bone resorption TRAP 5b in postmenopausal women at moderate risk of osteoporosis fracture. J Nutr 2012;142:698–703.
60. Bonjour JP, Benoit V, Payen F, Kraenzlin M. Consumption of yogurts fortified in vitamin D and calcium reduces serum parathyroid hormone and markers of bone resorption: a double-blind randomized controlled trial in institutionalized elderly women. J Clin Endocrinol Metab 2013; 98:2915–21.
61. Kruger MC, Booth CL, Coad J, Schollum LM, Kuhn-Sherlock B, Shearer MJ. Effect of calcium fortified milk supplementation with or without vitamin K on biochemical markers of bone turnover in premenopausal women. Nutrition 2006;22:1120–8.
62. Kruger MC, Schollum LM, Kuhn-Sherlock B, Hestiantoro A, Wijanto P, Li-Yu J, Agdeppa I, Todd JM, Eastell R. The effect of a fortified milk drink on vitamin D status and bone turnover in post-menopausal women from South East Asia. Bone 2010;46:759–67.
63. Kruger MC, Ha PC, Todd JM, Kuhn-Sherlock B, Schollum LM, Ma J, Qin G, Lau E. High-calcium, vitamin D fortified milk is effective in improving bone turnover markers and vitamin D status in healthy postmenopausal Chinese women. Eur J Clin Nutr 2012;66:856–61.
64. Manios Y, Moschonis G, Trovas G, Lyritis GP. Changes in biochemical indexes of bone metabolism and bone mineral density after a 12-mo dietary intervention program: the Postmenopausal Health Study. Am J Clin Nutr 2007;86:781–9.
65. Thorpe MP, Jacobson EH, Layman DK, He X, Kris-Etherton PM, Evans EM. A diet high in protein, dairy, and calcium attenuates bone loss over twelve months of weight loss and maintenance relative to a conventional high-carbohydrate diet in adults. J Nutr 2008;138:1096–100.
66. Bonjour JP, Benoit V, Pourchaire O, Rousseau B, Souberbielle JC. Nutritional approach for inhibiting bone resorption in institutionalized elderly women with vitamin D insufficiency and high prevalence of fracture. J Nutr Health Aging 2011;15:404–9.
67. Dawson-Hughes B, Harris SS, Rasmussen HM, Dallal GE. Comparative effects of oral aromatic and branched-chain amino acids on urine calcium excretion in humans. Osteoporos Int 2007;18:955–61.
68. Rodondi A, Ammann P, Ghilardi-Beuret S, Rizzoli R. Zinc increases the effects of essential amino acids—whey protein supplements in frail elderly. J Nutr Health Aging 2009;13:491–7.
69. Chevalley T, Hoffmeyer P, Bonjour JP, Rizzoli R. Early serum IGF-I response to oral protein supplements in elderly women with a recent hip fracture. Clin Nutr 2010;29:78–83.
70. Moschonis G, Katsaroli I, Lyritis GP, Manios Y. The effects of a 30-month dietary intervention on bone mineral density: the Postmenopausal Health Study. Br J Nutr 2010;104:100–7.
71. Sahni S, Tucker KL, Kiel DP, Quach L, Casey VA, Hannan MT. Milk and yogurt consumption are linked with higher bone mineral density but not with hip fracture: the Framingham Offspring Study. Arch Osteoporos 2013;8:119.
72. Salque M, Bogucki PI, Pyzel J, Sobkowiak-Tabaka I, Grygiel R, Szmyt M, Evershed RP. Earliest evidence for cheese making in the sixth millennium BC in northern Europe. Nature 2013;493:522–5.
73. Ammann P, Rizzoli R, Fleisch H. Calcium absorption in rat large intestine in vivo: availability of dietary calcium. Am J Physiol 1986;251: G14–8.
74. Ammann P, Rizzoli R, Fleisch H. Influence of the disaccharide lactitol on intestinal absorption and body retention of calcium in rats. J Nutr 1988;118:793–5.
75. Van den Heuvel EG, Muijs T, Van Dokkum W, Schaafsma G. Lactulose stimulates calcium absorption in postmenopausal women. J Bone Miner Res 1999;14:1211–6.
76. van den Heuvel EG, Schoterman MH, Muijs T. Transgalactooligosaccharides stimulate calcium absorption in postmenopausal women. J Nutr 2000;130:2938–42.
77. van den Heuvel EG, Muys T, van Dokkum W, Schaafsma G. Oligofructose stimulates calcium absorption in adolescents. Am J Clin Nutr 1999;69:544–8.
78. Whisner CM, Martin BR, Schoterman MH, Nakatsu CH, McCabe LD, McCabe GP, Wastney ME, van den Heuvel EG, Weaver CM. Galactooligosaccharides increase calcium absorption and gut bifidobacteria in young girls: a double-blind cross-over trial. Br J Nutr 2013;110:1292–303.
79. Weaver CM, Martin BR, Nakatsu CH, Armstrong AP, Clavijo A, McCabe LD, McCabe GP, Duignan S, Schoterman MH, van den Heuvel EG. Galactooligosaccharides improve mineral absorption and bone properties in growing rats through gut fermentation. J Agric Food Chem 2011;59:6501–10.
80. Walton GE, van den Heuvel EG, Kosters MH, Rastall RA, Tuohy KM, Gibson GR. A randomised crossover study investigating the effects of galacto-oligosaccharides on the faecal microbiota in men and women over 50 years of age. Br J Nutr 2012;107:1466–75.
81. McNulty NP, Yatsunenko T, Hsiao A, Faith JJ, Muegge BD, Goodman AL, Henrissat B, Oozeer R, Cools-Portier S, Gobert G, et al. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. Sci Transl Med 2011;3:106ra106.
82. McCarron DA, Heaney RP. Estimated healthcare savings associated with adequate dairy food intake. Am J Hypertens 2004;17:88–97.
83. Lötters FJ, Lenoir-Wijnkoop I, Fardellone P, Rizzoli R, Rocher E, Poley MJ. Dairy foods and osteoporosis: an example of assessing the health-economic impact of food products. Osteoporos Int 2013;24: 139–50.

Yogurt: role in healthy and active aging[1–4]

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ABSTRACT

Yogurt consumption has been associated with health benefits in different populations. Limited information, however, is available on nutritional and health attributes of yogurt in older adults. Yogurt is abundant in calcium, zinc, B vitamins, and probiotics; it is a good source of protein; and it may be supplemented with vitamin D and additional probiotics associated with positive health outcomes. Aging is accompanied by a wide array of nutritional deficiencies and health complications associated with under- and overnutrition, including musculoskeletal impairment, immunosenescence, cardiometabolic diseases, and cognitive impairment. Furthermore, yogurt is accessible and convenient to consume by the older population, which makes yogurt consumption a feasible approach to enhance older adults' nutritional status. A limited number of studies have specifically addressed the impact of yogurt on the nutritional and health status of older adults, and most are observational. However, those reported thus far and reviewed here are encouraging and suggest that yogurt could play a role in improving the nutritional status and health of older adults. In addition, these reports support further investigation into the role of yogurt in healthy and active aging. *Am J Clin Nutr* 2014;99(suppl):1263S–70S.

INTRODUCTION

Yogurt is a nutrient-dense probiotic food, with unique properties that enhance the bioavailability of some of these nutrients and potentially enhancing health. These properties make it worth exploring whether yogurt may be particularly well suited to ameliorate some of the most common nutritional deficits, and their related health risks, in the elderly. So far, few studies have evaluated the effect of yogurt on health outcomes in the elderly. In this review, we summarize the existing evidence and identify gaps in our knowledge that need to be addressed by well-designed studies. Studies of yogurt supplementation in the elderly are compiled in **Table 1**.

NUTRITIONAL VALUE OF YOGURT

Yogurt and diet quality in the elderly

An evaluation of dietary intake showed that yogurt consumption is associated with greater adherence to healthy dietary guidelines, as assessed by the *Dietary Guidelines for Americans* 2005 (1). Those consuming an average of 2.3 servings yogurt/wk were more likely than nonconsumers to eat more healthy foods, including fruit, vegetables, nuts, fish, and whole grains, and had a smaller proportion of their energy intake from processed meat, refined grains, and beer (2). Results further showed that yogurt consumers have significantly reduced prevalence of nutrient deficiencies for riboflavin, vitamin B-12, calcium, magnesium, and zinc (2).

Many factors contribute to malnutrition in the elderly, including chronic and infectious disease, decrease in physical activity and metabolic rate, physical disability, difficulty chewing and ingesting food, polypharmacy, limited income, and decrease in mobility. In addition to the rich nutritional composition of yogurt and its potential effects on health, there are benefits that make it feasible for the elderly to increase yogurt intake. Yogurt has a relatively long shelf-life, and there are no obstacles in consumption for individuals with chewing difficulty. Lactose intolerance, which is prevalent in the older population, is not an issue with yogurt, in contrast to other dairy products. Therefore, increasing yogurt consumption by older adults could represent a convenient and economical strategy to enhance their intake of key macronutrients and micronutrients for this age group.

Consumption and type

Yogurt can be commercially produced with substantial variety in composition, flavors, and additives. These include whole-milk, low-fat, or nonfat forms; plain or flavored; inclusion of fruit; addition of natural or artificial sweeteners; and occasional supplementation with vitamin D. Flavored fermented dairy products cannot exceed 50% (by mass) of nondairy additives such as fruit or sweeteners (3). Yogurt consumption accounts for as much as 32% of dairy intake in Europe, with a range of consumption in different European countries, yet accounts for only 5% in the United States (2). As reported in the National Nutrient Database for Standard Reference (NDBsr26)[5], among the 1000 most

[1] From the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA.

[2] Presented at the satellite symposium "First Global Summit on the Health Effects of Yogurt," held in Boston, MA, at ASN's Scientific Sessions at Experimental Biology 2013, 24 April 2013. The conference was organized by the ASN, the Nutrition Society, Danone Institute International, and the Dairy Research Institute. The supplement scientific guest editors were Sharon M Donovan, University of Illinois, Urbana, IL, and Raanan Shamir, Schneider Children's Medical Center and Tel Aviv University, Israel.

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[5] Abbreviations used: BMD, bone mineral density; CVD, cardiovascular disease; LAB, lactic acid bacteria; NDBsr26, National Nutrient Database for Standard Reference version 26; NK, natural killer.

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TABLE 1
Studies of yogurt consumption in the elderly[1]

Area and first author (ref)	Study design	Population	Key findings
Bone and muscle health			
Bonjour (4)	Randomized, double-blind controlled trial, 2-mo supplementation with vitamin D and calcium-fortified yogurt or nonfortified yogurt control	Institutionalized elderly women (n = 89; mean ± SD age: 85.5 ± 6.6 y)	PTH and bone resorption markers decreased after supplementation
Ferrazzano (5)	Cross-sectional in vitro study exploring the effect of CCPs (contained in yogurt) on dental enamel mineralization	Human molars (n = 80; unspecified age)	Yogurt CCPs protected molars against demineralization and promoted remineralization
Heaney (6)	Crossover study; subjects consumed a jelled fruit-flavored snack or fruit-flavored yogurt for 7–11 d	Postmenopausal women (n = 29; mean ± SD age: 61 ± 4 y)	Decreased bone resorption, as seen by a significant decrease in urinary N-telopeptide
Sahni (7)	Longitudinal study (12-y follow-up)	Framingham Offspring Study (n = 3212; mean ± SD age: 55 ± 1.6 y)	Yogurt intake was positively associated with trochanter bone mineral density and was mildly protective against hip fractures; authors stated that this protection needs to be verified further
Cardiometabolic disease			
Goldbohm (8)	Prospective cohort study (Netherlands Cohort Study)	Men and women (n = 120,852; age range: 50–69 y)	Fermented milk intake was inversely associated with all-cause mortality in men and women
Margolis (9)	Prospective cohort study (Women's Health Initiative Observational Study)	Postmenopausal women, nondiabetic at enrollment (n = 82,076; age range: 50–79 y)	Yogurt intake was associated with a significantly lower risk of type 2 diabetes
Sonestedt (10)	Prospective cohort study (Swedish Malmö Diet and Cancer cohort, 12-y follow-up)	Men and women, no cardiovascular disease on enrollment (n = 26,445; age range: 44–74)	Fermented dairy product consumption was inversely related to cardiovascular disease
Immunology			
Makino (11)	Meta-analysis of 2 independent randomized studies in which subjects consumed yogurt or milk for 8 or 12 wk	Healthy elderly subjects (study 1: n = 57; median age: 74.5 y; study 2: n = 85; median age: 67.7 y)	In the yogurt group there was a significantly lower risk of catching the common cold, and a significant increase in natural killer cell activity
Schiffrin (12)	Observational study with one treatment group consuming yogurt with *Lactobacillus johnsonii* for 1 mo	Elderly men and women with or without hypochlorhydria (positive breath test for hydrogen, n = 23; negative breath test, n = 13; mean ± SD age: 76.9 ± 7.3 y)	Endotoxemia and leukocyte phagocytosis decreased in both groups after yogurt consumption; monocyte and neutrophil activity (ex vivo production of cytokines or reactive oxygen species, respectively) increased in the positive breath test group after consumption
Cognition			
Crichton (13)	Cross-sectional study	Men and women (n = 1183; age range: 39–65 y)	Low-fat yogurt intake was associated with memory recall (self-reported) and social functioning in men

[1] CCP, casein phosphopeptide; PTH, parathyroid hormone; ref, reference.

commonly consumed foods in the United States are low-fat yogurt, plain or with fruit, or plain whole-milk yogurt. They range in protein content from 3.5 to 5.3 g and in caloric energy from 61 to 105 kcal/100-g serving (14). There is also an increasing popularity of strained yogurt, more commonly known as Greek yogurt or *labneh*, where straining the fermented milk after coagulation removes the liquid whey as well as some of the lactose, creating a richer consistency (15), and which is required to contain at least 5.6% protein compared with the minimum of 2.7% for unstrained yogurt (3). Forms of Greek yogurts referenced in the NDBsr26 within a similar range of caloric energy as unstrained yogurt contain these higher protein amounts (ie, 10.2 and 7.5 g for plain or with fruit, respectively, per 100-g serving) (14). Historically, yogurt was strained to decrease its water content and to help delay spoilage, and this condensed form of yogurt is a traditional component of Mediterranean, Middle Eastern, and South Asian cuisines (15).

The nutritional characteristics of yogurt are comparable to the milk from which it was produced, although usually in higher concentration, and certain nutrients are affect by factors such as bacterial strains, heat exposure during the fermentation process, and extra ingredients added (16).

Probiotics

As defined by the 2003 Codex Standard for Fermented Milks, yogurt must contain viable, live, and abundant cultures of the lactic acid bacteria (LAB) *Lactobacillus bulgaricus* and *Streptococcus thermophiles* species at a minimum concentration of 10^7 CFU/g at the time of manufacture (3, 17, 18). It may also be supplemented with additional bacteria that contribute desirable factors (19), and these labeled microorganisms should be present at $\geq 10^6$ CFU/g (3). To qualify for the seal of "live and active culture yogurt" by the National Yogurt Association, amounts of *L. bulgaricus* and *S. thermophiles* at the point of manufacture must be $\geq 10^8$/g (16). Yogurt is considered a probiotic food by virtue of the live microorganisms it contains, which clinical studies have shown to confer various health benefits with consumption (17, 19). It is important, therefore, to consider not only the type of bacterial strains but also the concentrations of live yogurt bacteria at ingestion, and how much remains viable in the ileum and duodenum.

Minerals

Yogurt is a rich source of dietary minerals, and the NDBsr26 reports that a 100-g serving of plain low-fat yogurt includes amounts of calcium at 183 mg, magnesium at 17 mg, potassium at 234 mg, phosphorous at 144 mg, and zinc at 0.9 mg (14). The concentrations of these minerals are higher in yogurt compared with milk by nearly 50% (2). Furthermore, fermentation with LAB to create yogurt results in an acidic environment that can enhance the bioavailability of these minerals. The lower pH maintains calcium and magnesium in their ionic forms, potentially allowing for their greater absorption in the intestine and increasing amounts of soluble zinc bound to ligands that can facilitate transportation across the intestinal wall, which results in enhanced absorption of zinc (16, 20). However, the effect of higher luminal pH on enhancing the status of calcium and magnesium from yogurt needs to be determined in vivo.

Vitamins

Yogurt is also a good source of B vitamins: a 100-g serving of plain low-fat yogurt contains riboflavin, niacin, vitamin B-6, and vitamin B-12 at amounts of 0.21, 0.11, 0.05, and 0.56 mg, respectively (14). However, fermentation, pasteurization, and other production processes can negatively affect the vitamin content. For Greek-style yogurt, the process of straining can lead to the loss of certain micronutrients, particularly the water-soluble vitamins (15). The choice of bacterial strain can further influence vitamin integrity, because some LAB consume B vitamins for growth, whereas others can synthesize them. Commercial processes therefore combine different bacterial strains to mitigate issues of vitamin depletion, with some combinations aimed at restoring or amplifying the amounts of these vitamins in the final yogurt product (16).

Protein

Yogurt is an excellent source of essential amino acids of high biological quality and generally contains a higher protein content than milk. Furthermore, the proteolytic activity of bacterial cultures in yogurt enables some predigestion of milk proteins, resulting in greater amounts of free amino acids that allow for better protein digestibility (16).

HEALTH RISKS AND NUTRITIONAL DEFICIENCIES IN THE ELDERLY THAT COULD BE ADDRESSED WITH YOGURT CONSUMPTION

Musculoskeletal

Bone health and aging

With aging there is a decrease in bone density and an increased requirement for vitamin D and calcium. The physiologic changes leading to poor bone health include decreased calcium absorption, along with increased bone loss and bone remodeling throughout the life span (21). Vitamin D deficiency is common in the elderly because of the age-related decrease in cutaneous vitamin D_3 production, poor nutrition, and lifestyle factors such as prolonged periods spent indoors (22). This, together with an equally large prevalence of calcium deficiency and low protein consumption in the elderly, are significant factors for poor bone health, leading to a higher risk of osteoporosis, muscle weakening, falls, and fractures. Several studies have shown that vitamin D and calcium supplementation have positive effects on bone health, including reduction in falls and fractures and enhanced muscle performance (21, 23, 24). This seems to be the case, especially when focusing on populations that are vitamin D deficient (25). Previous evidence has shown that higher consumption of dairy products, which are rich in calcium, may protect adults against bone loss (26). However, it has not yet been fully established whether calcium supplementation may lead to this effect in the absence of vitamin D supplementation.

Muscle health and aging

The decline in muscle mass that accompanies aging, termed *sarcopenia*, is exacerbated by poor nutrition (27). It has been suggested that, although long-term trials are still needed, a slight short-term increase in protein intake in older individuals may

lead to enhanced bone and muscle health without affecting renal function (28).

Potential benefits of yogurt on musculoskeletal health

Yogurt may be an important source of protein and calcium in the elderly that could potentially lead to enhancement in bone and muscle health. An assessment of dairy product consumption and its relation with bone mineral density (BMD) of the hip (at the femoral neck and trochanter) and spine, as well as with incidence of hip fracture, was conducted by Sahni et al (18) among participants in the Framingham Offspring Study. For BMD analysis (n = 2506), it was found that participants in the high-yogurt-consumption group of >4 servings/wk had greater BMD in all bone sites compared with nonconsumers, although the increase was only significant at the trochanter (0.809 ± 0.009 compared with 0.787 ± 0.003 g/cm^2; P = 0.05), and not significant for femoral neck or spine BMD [0.933 ± 0.009 compared with 0.914 ± 0.003 g/cm^2 (P = 0.32) and 1.242 ± 0.016 compared with 1.225 ± 0.005 g/cm^2 (P = 0.27), respectively]. A decrease of 1 SD in femoral neck BMD has previously been shown to be associated with an ~40% increase in risk of osteoporotic hip fracture (19); however, the difference in hip fracture risk seen in this study in yogurt consumers compared with nonconsumers was not significant (P-trend = 0.10) (7).

Yogurt extract has also been found to protect against demineralization and even enhance remineralization of tooth enamel in vitro (5). In a randomized, double-blind, controlled intervention in which elderly nursing home residents consumed either yogurt fortified with calcium (800 mg/d) and vitamin D_3 (10 μg/d) or a nonfortified yogurt control (280 mg calcium/d) for ~2 mo, it was found that the group consuming the fortified yogurt experienced a significant reduction in parathyroid hormone and bone resorption markers compared with the control group (4). Similarly, a crossover study in which postmenopausal women consumed either fruit-flavored yogurt or a fruit-flavored jelled snack for 7–11 d showed that there was a significant reduction in N-telopeptide (NTx), a urinary marker of bone resorption, after yogurt consumption compared with after consumption of the jelled snack (6). Lower amounts of bone resorption indicate a more positive bone balance and reflect the potential for better bone health (30). More long-term studies are needed to evaluate the effect of yogurt consumption on bone and muscle health of both community-dwelling and institutionalized elderly individuals. In addition, the optimal nutritional composition of yogurt for enhancement of bone health must be established.

Obesity

The nutritional composition of yogurt, as well as an established correlation between yogurt consumption and increased diet quality (2), may be used to address not only nutritional deficiencies but also weight maintenance in the elderly. The loss of lean muscle tissue and concomitant reduction in muscle function and mobility that are associated with aging lead to a greater proportion of body fat mass, which can result in a tendency toward becoming overweight or obese. Epidemiologic studies indicate that dairy products, and in particular yogurt, may have the potential to reduce the risk of obesity. Lifestyle and dietary factors were assessed for their association with long-term weight gain in ~120,000 male and female participants from the Nurses' Health Studies and the Health Professionals Follow-Up Study over a period of 12–20 y (31). The authors found that average weight gain across all cohorts was 1.52 kg per 4-y period (95% CI: −1.86, 5.62 kg). However, a significant inverse association was observed between long-term weight gain and higher consumption of certain foods, where an increase in the number of servings per day was associated with less weight gain for yogurt (−0.37 kg), nuts (−0.26 kg), fruit (−0.22 kg), whole grains (−0.17 kg), and vegetables (−0.10 kg) per 4-y period ($P < 0.01$; adjusted for age, baseline BMI at each 4-y period, sleep duration, changes in physical activity, alcohol use, television watching, smoking, and dietary factors). The authors postulated that increased consumption of these foods displaced intake of other foods that may be higher in calories and fat and have lower fiber content but stated that the effect of yogurt could be related to altered gut bacteria as well as other weight-related behavior that was not captured in the study (31). In an analysis conducted on the cross-sectional relation between dairy consumption and metabolic outcomes in data from the NHANES, yogurt was associated with fewer metabolic disorders. Specifically, in men and women, yogurt consumption was inversely related to BMI, waist circumference, systolic blood pressure, and fasting glucose. In women, yogurt consumption was also related to higher HDL cholesterol (32). In a study to assess the cross-sectional association of yogurt with diet quality and metabolic profile in ~6500 participants in the Framingham Offspring Study, Wang et al (2) found that yogurt consumers, on average, exhibited significantly improved metabolic variables, including lower BMI and blood pressure, reduced concentrations of triglycerides, fasting glucose, and insulin and greater HDL cholesterol compared with nonconsumers, after adjustment for demographic and lifestyle factors that included diet quality.

Evidence from randomized controlled trials in overweight and obese individuals further indicates that dietary calcium, particularly when sourced from dairy, can promote weight and fat loss (33). In a 12-wk isocaloric, energy-restricted dietary intervention that included 400–500 mg calcium supplementation/d, participants in the experimental and control groups (n = 34; aged 18–50 y) were prescribed diets established on the basis of energy needs that included adjustment for activity level records and matched for macronutrient proportions, and which were subsequently monitored weekly by diet records and measures of compliance. The experimental group consumed 3 daily 6-ounce servings of yogurt and showed significantly greater weight reduction than did controls exposed to caloric restriction and 0–1 daily servings of an alternative dairy product (6.63 ± 0.6 compared with 4.99 ± 0.5 kg, respectively; $P < 0.01$), although the control group consumed fewer calories than did the yogurt group, at an average 1303 ± 190 kcal/d compared with 1437 ± 190 kcal/d, respectively. The yogurt group also experienced a significantly higher proportion of abdominal fat loss (yogurt compared with control: −4.43 ± 0.47 compared with −2.75 ± 0.73 kg; $P < 0.005$) and less loss of lean body mass (yogurt compared with control: −1351 ± 156 compared with −1968 ± 212 g; $P < 0.05$). There was a significant increase in circulating glycerol (representing amplified lipolysis) and a reduction in waist circumference among the yogurt group. The participants were not blinded to treatment, and data on tobacco use and physical activity were collected but not reported, although the authors stated that baseline levels were maintained throughout

the study (33). To our knowledge, no studies have focused on the effect of yogurt on obesity in the elderly.

Inflammatory and cardiometabolic diseases

A review published by Labonté et al (34) on effects of dairy products on inflammatory biomarkers in randomized controlled trials of a nutritional intervention in overweight or obese adults showed conflicting results, with 4 of the 8 studies showing improvement in inflammatory biomarkers with dairy consumption. However, most of the reviewed studies failed to address yogurt consumption individually. The only one to do so found that yogurt-enriched diets resulted in reduced C-reactive protein and increased adiponectin concentrations compared with controls (33, 34).

Although there are a substantial number of studies that have sought to characterize the relation between dairy products and various long-term health outcomes, few have examined yogurt individually. Nevertheless, those that provided direct analysis of yogurt have generally shown that yogurt is associated with a reduced risk of chronic diseases. Margolis et al (9) found that higher yogurt consumption is linked to a lower risk of diabetes in postmenopausal women. In this prospective cohort study in 82,076 postmenopausal women, aged 50–79 y, from the Women's Health Initiative it was found that there was a significant inverse relation between low-fat dairy food consumption and the risk of developing type 2 diabetes, with an RR of ~0.7 (P-trend $<$ 0.0001, after adjustment for age, race, and total energy intake, and with the trend remaining significant after adjustment for additional variables) in the highest quintiles of consumption compared with the lowest quintile. A similar yet weaker trend was observed for total dairy product consumption that included high-fat dairy products, but the association was lost when high-fat dairy foods were examined separately. Although median yogurt consumption was generally low in this population, at 0.5 servings/wk, and 38% of participants reported seldom or never eating yogurt, an increased frequency of yogurt intake was associated with a significantly reduced risk of developing type 2 diabetes. Women with the most frequent yogurt consumption (≥2 servings/wk) had the lowest risk of developing type 2 diabetes (RR: 0.52; $P < 0.0001$, after adjustment for age, race, and total energy intake, and with the trend remaining significant after adjustment for additional variables) compared with those who consumed yogurt less than once per month. Some effect modification by BMI was also observed, because consuming more low-fat dairy foods offered additional protection against diabetes risk among women with a higher BMI compared with leaner women and helped mitigate some of the additional risk of diabetes seen in study participants who were obese. This study suggests that dairy consumption, particularly of low-fat dairy foods and specifically yogurt, may be protective against diabetes in an older population of women, particularly among those who are overweight or obese. Results from the Swedish prospective cohort study in Malmö showed a significant inverse relation between fermented dairy products (yogurt and cultured sour cream) and cardiovascular disease (CVD) in adults aged 44–74 y (10). Higher consumption of fermented milk was associated with lower homeostatic model assessment (HOMA) index (P-trend = 0.005), and cheese consumption was associated with higher HDL cholesterol (P-trend = 0.002), whereas consumption of other types of dairy products was positively associated with cardiovascular risk factors. There was a significantly lower risk of CVD for individuals in the highest quintiles of consumption of dairy foods compared with those with low consumption [12% decreased risk of CVD (95% CI: 0%, 22%) for the highest quintile; P-trend = 0.04], in particular for those with a high consumption of fermented milk products [15% decreased risk of CVD (95% CI: 5%, 24%); P-trend = 0.003]. This reduction in CVD risk remained significant after several covariates, including age, race, energy intake, and physical activity, were adjusted for.

In the Italian cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC), dietary intake of yogurt was related to decreased colorectal cancer risk in men and women (35). In a study to evaluate the relation between dairy product consumption and risk of cardiovascular and all-cause related deaths in the Netherlands Cohort Study, fermented milk products were found to have a modest but significant inverse relation with all-cause mortality among men ($RR_{continuous}$: 0.91; 95% CI: 0.86, 0.97 per 100 mL/d) and women ($RR_{continuous}$: 0.92; 95% CI: 0.85, 1.00 per 100 mL/d) within the 10-y follow-up period. Posteriori analysis of yogurt consumption showed that 61% of male study participants consumed yogurt, at an average 66 mL yogurt/d, and 75% of female study participants consumed yogurt, at an average 71 mL yogurt/d. A slight inverse association with mortality was observed among men (P-trend =0.039; $RR_{continuous}$: 0.96; 95% CI: 0.92, 1.00 per 100 mL/d), although no association was found among women ($RR_{continuous}$: 1.00; 95% CI: 0.95, 1.05 per 100 mL/d) (8). Although the mechanism of inverse relation between yogurt and all-cause mortality is not known, several publications recently have shown the gut microbiota to play a role in determining the risk of several chronic and metabolic diseases (6). Thus, yogurt's live bacterial content might provide one possible explanation for the reported association between yogurt and lower risk of all-cause mortality reported here.

Immunosenescence

Dysregulation of inflammatory and immune responses occurs with aging, resulting in chronic low-grade inflammation and immunosenescence that puts the elderly at greater risk of infection and development of metabolic and chronic diseases such as type 2 diabetes, CVD, and certain cancers (11, 37). The immune system undergoes several changes throughout the life span that increase the risk of impairment against external and internal dangers in the host. Several reviews have described these changes in depth. Briefly, there is impairment in T cell–mediated immunity, alterations in cytokine production, impaired innate immunity, limited antibody production, a decrease in the percentage of naive cells, and an increase in the percentage of memory cells with impaired response (38–40). Initiating and maintaining an appropriate immune response to pathogenic challenge are also influenced by nutritional status. Protein-energy malnutrition and/or insufficient concentrations of essential micronutrients can impair immune function (41, 42). Lesourd and Mazari (43) observed that among apparently healthy elderly even slight reductions in serum albumin below the normal range of 35–40 g/L indicated diminished nutritional state and were associated with increased age-related alterations in T cell subsets

and function and decreased lymphocyte proliferation. Among undernourished elderly individuals, protein-energy malnutrition and deficiencies in zinc, vitamin B-6, and folate are linked to impaired immune response, at least some of which were ameliorated with supplementation of these nutrients (43).

Several diseases are more likely to occur in the elderly because of immunosenescence. Pneumonia is especially prevalent among nursing home and frail elderly populations, and it is associated with low zinc status (44, 45). Vulnerability to tuberculosis, HIV/AIDS, herpes zoster, urinary tract infections, and gastrointestinal infections also increase with aging. Infectious diseases are both associated with and may be exacerbated by nutritional deficiencies that can impair cell-mediated and humoral immunologic function (41). The intestinal flora is also affected by aging, partly as a result from changes in diet, reduced intestinal motility, excessive and, in some cases, chronic use of antibiotics, changes in gastrointestinal architecture, and impairment of gut immunity. Furthermore, the numbers and diversity of protective bacteria species decline with age (46). In recent years, a group in Ireland has been characterizing the gut microbiota of elderly Irish individuals through the creation of the ELDERMET project. A high prevalence of *Clostridium perfingens* (commonly found in fecal samples in elderly and hospitalized patients, especially in individuals in long-term residential care) was inversely correlated with *Bifidobacterium* species (47). These results show that hospitalized elderly subjects may have unhealthy intestinal microflora and suggest a potential benefit for foods supplemented with probiotics.

Yogurt consumption may enhance immune response, thereby reducing infectious disease risk. The components of yogurt that may be involved in enhancing immunity include zinc, vitamin B-6, protein, and bacteria. Evidence supporting this comes from either human and animal studies showing that deficiencies of these vitamins lead to immune impairment or supplementation studies showing immune enhancement. For example, zinc supplementation of zinc-deficient nursing home elderly individuals led to enhancement in lymphocyte proliferation (48). In addition, zinc deficiency, which is highly prevalent in frail elderly individuals, was associated with risk of pneumonia (45, 49). The potential of yogurt in simultaneously providing these nutrients and enhancing immune response warrants further investigation. Probiotic consumption has been associated with enhancement of innate immunity (50), reduction in duration and severity of respiratory infection (51), and enhancement of gut-associated immunity (52).

There are few studies, however, on the effect of yogurt on immunity in humans, and even fewer studies in elderly populations. Double-blind randomized controlled trials of adequate size are needed to determine the effect of yogurt on relevant markers of the immune response and related clinical outcomes, such as incidence of infection and the underlying mechanisms. A study conducted by Schiffrin et al (12) in healthy elderly individuals determined the effect of yogurt with probiotics on gut health, measured as intestinal permeability to macromolecules, innate immunity, and changes in plasma endotoxin concentrations. They compared a group of healthy elderly individuals with hypochlorhydria, measured as low or negative hydrogen in breath, with a group with positive hydrogen breath test measurements. In both groups, there was a decrease in plasma endotoxin concentrations and leukocyte phagocytosis and an increase in monocyte and neutrophil activity measured through ex vivo assays.

Makino et al (11) showed that daily consumption of yogurt with live culture may lead to resistance to respiratory infection, specifically colds, in the elderly. They conducted 2 independent studies in healthy elderly individuals in which a group consuming yogurt daily was compared with a group consuming milk daily for 8 or 12 wk. They showed a significantly lower risk of developing colds in the elderly individuals who consumed yogurt. Although they saw a significant increase in lymphocyte blastoid transformation in both milk and yogurt groups after the consumption period, the increase in the yogurt group was significantly greater than in the milk group. They also conducted cytotoxicity assays by measuring natural killer (NK) cell activity, which they classified into low, normal, or high in relation to the activity range in the study population. Subjects in the yogurt group with low NK cell activity at baseline experienced a significant increase in cytotoxicity after intake. Conversely, the NK cytotoxicity in subjects with above-normal NK cell activity at baseline returned to the normal range after intake. None of these changes were significant in the milk group. The existing evidence on the potential benefits of yogurt on immunity in elderly populations is limited but encouraging, and further investigation is warranted, especially through randomized controlled human trials to confirm and expand on these observations.

Cognition and mental health

Although there is limited assessment of the influence yogurt may have on cognition and long-term mental health, this is an important area to explore because of the rich content of B vitamins in yogurt and evidence of its anti-inflammatory effects that may be protective against cognitive impairment, as well as the recent evidence indicating a connection between the gut microbiota and cognition. In a longitudinal study conducted by Vercambre et al (53) of the relation between dietary habits of ~4800 French women, born between 1925 and 1930, and age-related mental decline assessed in 2006, the odds of reduced capacity for instrumental activities of daily living showed a significant inverse relation with concentrations of riboflavin and vitamins B-6 and B-12. They did not find an association with dairy products, and the specific influence of yogurt is difficult to gauge, because it was grouped with milk in their analysis. However, in a cross-sectional analysis in 1183 men and women in Australia, aged 39–65 y, self-reported measures of memory recall and social functioning were significantly associated with the consumption of low-fat yogurt among men (13). Similarly, a randomized controlled study conducted recently by Tillisch et al (54) compared brain response by using fMRI in women (aged 18–55 y) who consumed a fermented milk product supplemented with several probiotic species compared with women who consumed a nonfermented milk product or undergoing no intervention. They reported that consumption of the fermented milk product led to functional changes in a wide array of regions of the brain that control emotion and sensation. It will be interesting to know whether similar results can be reproduced in older adults (>65 y).

SUMMARY AND CONCLUSIONS

Thus far, the most robust evidence that suggests a potential benefit of yogurt consumption on elderly health outcomes is from

observational studies or indirectly from studies that have evaluated the effect of isolated nutrients or probiotics known to be abundant in yogurt on different health outcomes. Few clinical studies have determined the effect of yogurt as a whole food on biological markers of health or diseases in the elderly. The existing studies are encouraging, however, and suggest that yogurt could play an important role in improving the nutritional and health status of the elderly when provided as part of a healthy diet. Furthermore, these studies support the need for additional investigation on the role of yogurt in healthy and active aging individuals. In particular, clinical trials and studies conducted over longer periods are needed to evaluate the sustained effects of yogurt on nutritional status and health of older adults.

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REFERENCES

1. USDHHS, USDA. Dietary Guidelines for Americans, 6th ed. Washington, DC: US. Government Printing Office, 2005.
2. Wang H, Livingston KA, Fox CS, Meigs JB, Jacques PF. Yogurt consumption is associated with better diet quality and metabolic profile in American men and women. Nutr Res 2013;33:18–26.
3. Codex Alimentarius Commission. Codex standard for fermented milks. Rome, Italy: FAO, 2003.
4. Bonjour J-P, Benoit V, Payen F, Kraenzlin M. Consumption of yogurts fortified in vitamin D and calcium reduces serum parathyroid hormone and markers of bone resorption: a double-blind randomized controlled trial in institutionalized elderly women. J Clin Endocrinol Metab 2013; 98:2915–21.
5. Ferrazzano GF, Cantile T, Quarto M, Ingenito A, Chianese L, Addeo F. Protective effect of yogurt extract on dental enamel demineralization in vitro. Aust Dent J 2008;53:314–9.
6. Heaney RP, Rafferty K, Dowell MS. Effect of yogurt on a urinary marker of bone resorption in postmenopausal women. J Am Diet Assoc 2002;102:1672–4.
7. Sahni S, Tucker KL, Kiel DP, Quach L, Casey VA, Hannan MT. Milk and yogurt consumption are linked with higher bone mineral density but not with hip fracture: the Framingham Offspring Study. Arch Osteoporos. 2013;8:119.
8. Goldbohm RA, Chorus AM, Garre FG, Schouten LJ, van den Brandt PA. Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands. Am J Clin Nutr 2011;93: 615–27.
9. Margolis KL, Wei F, de Boer IH, Howard BV, Liu S, Manson JE, Mossavar-Rahmani Y, Phillips LS, Shikany JM, Tinker LF, et al. A diet high in low-fat dairy products lowers diabetes risk in postmenopausal women. J Nutr 2011;141:1969–74.
10. Sonestedt E, Wirfält E, Wallström P, Gullberg B, Orho-Melander M, Hedblad B. Dairy products and its association with incidence of cardiovascular disease: the Malmö Diet and Cancer Cohort. Eur J Epidemiol 2011;26:609–18.
11. Makino S, Ikegami S, Kume A, Horiuchi H, Sasaki H, Orii N. Reducing the risk of infection in the elderly by dietary intake of yoghurt fermented with Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1. Br J Nutr 2010;104:998–1006.
12. Schiffrin EJ, Parlesak A, Bode C, Christian Bode J, van't Hof MA, Grathwohl D, Guigoz Y. Probiotic yogurt in the elderly with intestinal bacterial overgrowth: endotoxaemia and innate immune functions. Br J Nutr 2009;101:961–6.
13. Crichton GE, Murphy KJ, Bryan J. Dairy intake and cognitive health in middle-aged South Australians. Asia Pac J Clin Nutr 2010;19:161–71.
14. USDA, Agricultural Research Service. USDA national nutrient database for standard reference, release 26. Nutrient Data Laboratory homepage. 2013. Available from: http://www.ars.usda.gov/ba/bhnrc/ndl (cited 24 January 2014).
15. Nergiz C, Kemal Seçkin A. The losses of nutrients during the production of strained (Torba) yoghurt. Food Chem 1998;61:13–6.
16. Adolfsson O, Meydani SN, Russell RM. Yogurt and gut function. Am J Clin Nutr 2004;80:245–56.
17. Guarner F, Perdigon G, Corthier G, Salminen S, Koletzko B, Morelli L. Should yoghurt cultures be considered probiotic? Br J Nutr 2005;93: 783–6.
18. Corthier G. The health benefits of probiotics [editorial]. 2004. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.198.1141&rep=rep1&type=pdf (cited 1 July 2013).
19. Borchers AT, Keen CL, Gershwin ME. The influence of yogurt/Lactobacillus on the innate and acquired immune response. Clin Rev Allergy Immunol 2002;22:207–30.
20. De la Fuente MA, Montes F, Guerrero G, Juárez M. Total and soluble contents of calcium, magnesium, phosphorus and zinc in yoghurts. Food Chem 2003;80:573–8.
21. Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. Am J Clin Nutr 2008;88(suppl):537S–40S.
22. Mithal A, Bonjour J-P, Burckhardt P, Dawson-Hughes B, Eisman JA, El-Hajj Fuleihan G, Josse RG, Lips P, Morales-Torres J. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 2009; 20:1807–20.
23. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, Flicker L, Wark J, Jackson RD, Cauley JA, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 2012;367:40–9.
24. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab 2007;92:1415–23.
25. Dawson-Hughes B. Serum 25-hydroxyvitamin D and muscle atrophy in the elderly. Proc Nutr Soc 2012;71:46–9.
26. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. Am J Clin Nutr 2004;80:1066–74.
27. Mithal A, Boonen S, Burckhardt P, Degens H, Hajj Fuleihan G, Josse R, Lips P, Morales Torres J, Rizzoli R, Yoshimura N, et al. Impact of nutrition on muscle mass, strength, and performance in older adults. Osteoporos Int 2013;24:1555–66.
28. Gaffney-Stomberg E, Insogna KL, Rodriguez NR, Kerstetter JE. Increasing dietary protein requirements in elderly people for optimal muscle and bone health. J Am Geriatr Soc 2009;57:1073–9.
29. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, Eisman JA, Fujiwara S, Kroger H, Mellstrom D, et al. Predictive value of BMD for hip and other fractures. J Bone Miner Res 2005;20:1185–94.
30. Heaney RP, McCarron DA, Dawson-Hughes B, Oparil S, Berga SL, Stern JS, Barr SI, Rosen CJ. Dietary changes favorably affect bone remodeling in older adults. J Am Diet Assoc 1999;99:1228–33.
31. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404.
32. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. Am J Clin Nutr 2008;87:1914–25.
33. Zemel MB, Richards J, Mathis S, Milstead A, Gebhardt L, Silva E. Dairy augmentation of total and central fat loss in obese subjects. Int J Obes (Lond) 2005;29:391–7.
34. Labonté MÈ, Couture P, Richard C, Desroches S, Lamarche B. Impact of dairy products on biomarkers of inflammation: a systematic review of randomized controlled nutritional intervention studies in overweight and obese adults. Am J Clin Nutr 2013;97:706–17.
35. Pala V, Sieri S, Berrino F, Vineis P, Sacerdote C, Palli D, Masala G, Panico S, Mattiello A, Tumino R, et al. Yogurt consumption and risk of colorectal cancer in the Italian European Prospective Investigation into Cancer and Nutrition cohort. Int J Cancer 2011;129:2712–9.
36. Kinross JM, Darzi AW, Nicholson JK. Gut microbiome-host interactions in health and disease. Genome Med. 2011;3:14.

37. Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, Cesari M, Nourhashemi F. Proinflammatory cytokines, aging, and age-related diseases. J Am Med Direct Assoc 2013;14:877–82. Available from: http://www.sciencedirect.com/science/article/pii/S1525861013002806 (cited 14 July 2013).
38. Miller RA. The aging immune system: primer and prospectus. Science 1996;273:70–4.
39. Nikolich-Zugich J. T cell aging: naive but not young. J Exp Med 2005; 201:837–40.
40. Nikolich-Zugich J. Ageing and life-long maintenance of T-cell subsets in the face of latent persistent infections. Nat Rev Immunol 2008;8: 512–22.
41. Pae M, Meydani SN, Wu D. The role of nutrition in enhancing immunity in aging. Aging Dis 2012;3:91–129.
42. Ahmed T, Haboubi N. Assessment and management of nutrition in older people and its importance to health. Clin Interv Aging 2010;5: 207–16.
43. Lesourd B, Mazari L. Nutrition and immunity in the elderly. Proc Nutr Soc 1999;58:685–95.
44. Meydani SN, Leka LS, Fine BC, Dallal GE, Keusch GT, Singh MF, Hamer DH. Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. JAMA 2004; 292:828–36.
45. Meydani SN, Barnett JB, Dallal GE, Fine BC, Jacques PF, Leka LS, Hamer DH. Serum zinc and pneumonia in nursing home elderly. Am J Clin Nutr 2007;86:1167–73.
46. O'Toole PW, Claesson MJ. Gut microbiota: changes throughout the lifespan from infancy to elderly. Int Dairy J 2010;20:281–91.
47. Lakshminarayanan B, Harris HMB, Coakley M, O'Sullivan O, Stanton C, Pruteanu M, Shanahan F, O'Toole PW, Ross RP, ELDERMET Consortium. Prevalence and characterization of Clostridium perfringens from the faecal microbiota of elderly Irish subjects. J Med Microbiol 2013;62:457–66.
48. Dao MC, Barnett JB, Hamer D, Kandel R, Brandeis G, Fine B, Dallal GE, Jacques P, Schreiber R, Meydani SN. Increase in serum zinc levels after supplementation of zinc deficient nursing home elderly. FASEB J 2010; April 24:723.4. Available from: http://www.fasebj.org/cgi/content/meeting_abstract/24/1_MeetingAbstracts/723.4.
49. Barnett JB, Hamer DH, Meydani SN. Low zinc status: a new risk factor for pneumonia in the elderly? Nutr Rev 2010;68:30–7.
50. Gill H, Prasad J. Probiotics, immunomodulation, and health benefits. Adv Exp Med Biol 2008;606:423–54.
51. de Vrese M, Winkler P, Rautenberg P, Harder T, Noah C, Laue C, Ott S, Hampe J, Schreiber S, Heller K, et al. Probiotic bacteria reduced duration and severity but not the incidence of common cold episodes in a double blind, randomized, controlled trial. Vaccine 2006;24:6670–4.
52. Calder PC. Feeding the immune system. Proc Nutr Soc 2013;72: 299–309.
53. Vercambre M-N, Boutron-Ruault M-C, Ritchie K, Clavel-Chapelon F, Berr C. Long-term association of food and nutrient intakes with cognitive and functional decline: a 13-year follow-up study of elderly French women. Br J Nutr 2009;102:419–27.
54. Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain-Raspaud S, Trotin B, Naliboff B, et al. Consumption of fermented milk product with probiotic modulates brain activity. Gastroenterology 2013;144:1394–401.e4.

The future of yogurt: scientific and regulatory needs[1–4]

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ABSTRACT

Lactation biology, microbial selection, and human diversity are central themes that could guide investment in scientific research, industrial innovation, and regulatory policy oversight to propel yogurt into the central role for health-promoting food products. The ability of yogurt to provide the nourishing properties of milk together with the live microorganisms from fermentation provides a unique combination of food assets. Academic research must now define the various targets on which these biological assets act to improve health and develop the metrics that can quantitatively document their benefits. The food industry must reconcile that yogurt and its microorganisms cannot be expected to provide measurable benefits for all consumers, at all doses, and at all times. A supportive regulatory oversight must demand safety and yet encourage innovations that support a value proposition for yogurt in health. Health valuation in the marketplace will be driven by parallel innovations, including accurate assessment technologies, validated microbial ingredients, and health-aware consumers. *Am J Clin Nutr* 2014;99(suppl):1271S–8S.

INTRODUCTION

Yogurt is perhaps the most complex and biologically active of all foods in the marketplace. Its assets, costs, and values are all linked to its biological nature. The science to understand its potential benefits and the regulatory policies to ensure its safety must recognize the complex biology underlying what is, on first glance, simple yogurt. Yogurt is the combination of 3 factors: milk, the product of hundreds of millions of years of lactation evolution; industrial bacteria, the result of centuries of human selection of microbial cultures; and finally, consumers, including the reality of human variation and the need to address the breadth of our diversity. Understanding all 3 is necessary to fully appreciating the potential value of yogurt in the future.

MILK AND LACTATION

Lactation is at the core of mammalian success. The emergence of Mammalia ~200 million y ago brought a remarkable aspect of reproductive strategy of mothers: to feed infants with the secretions of an epithelial gland tissue network (1). Through the ensuing millennia, selective pressure drew remarkable constituents into this increasingly complex nourishment system. Milk is ostensibly encoded by the lactation genetic elements (2). This subset of the mammalian genome has been under selective pressure by maternal and infant survival and their long-term reproductive success. Therefore, selective pressure through mammalian evolution was relentless on the balance of the beneficial attributes of milk and their cost (3, 4). Everything in milk costs the mother, putting her survival at a selective disadvantage. Hence, if a constituent in milk does not result in value for the infant, it is at strong negative pressure because of its cost to the mother. However, if any element of milk provides a nutritional, protective, or developmental advantage to the infant, it is difficult to imagine a more positive selective pressure on a genetic trait. At its core, yogurt is a milk-delivery system for noninfants.

MICROBIAL CULTURE

Microorganisms are an integral part of our food supply, both directly and indirectly. Although much academic research, industrial technologies, and regulatory surveillance have been designed to eliminate microorganisms from food, this view is now changing. Microorganisms are increasingly viewed as valuable assets in the bioprocessing of commodities, with their own contributions of metabolites, structures, and bioactive components (5). Yogurt is a model of such assets. The future of food processing will include more "biological" innovations as microorganisms become controllable. In truth, microorganisms have participated throughout history as important modifiers of the safety, nutritional value, and flavor of a select group of high-value foods. Microorganisms provide hydrolytic enzymes to degrade plant components (phytate). Microorganisms release metabolites (ethanol and lactic acid). Finally, microorganisms release biopolymers that act on other organisms as signals. These biopolymers range from endotoxins that act on the host to quorum-sensing factors that act on the microorganisms in the lumen. In traditional yogurt, the mixed-culture system of *Lactobacillus* and *Streptococcus* (6) delivers a remarkable combination of enzymes and metabolites that enhance

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safety, nourishment, taste, and flavor. The future of food fermentation in its broadest biotechnology perspectives can learn valuable lessons from this traditional artisan system.

The most innovative and scientifically challenging new dimension of nutrition and diet research is the intimate relation between humans and microorganisms. All sciences related to food are similarly realizing the importance of microorganisms as constituents in and on our foods, as biotechnology partners in and on our processing technologies, and as ecological partners in and on—us. New tools and models are revealing an astonishing importance to the diversity of microbes inhabiting specific ecological sites throughout humans (7–11). This research also shows just how much we "pay attention" to them. The microbiota, the diverse populations of microorganisms in and on humans, affects the following:

- the development of the response and regulation of immunity from barrier composition to integrity and acquired immunity from protection to allergy;
- metabolic regulation, from fuel scavenging to whole-body tissue prioritization;
- physiologic processes such as acute blood flow regulation; and
- neurologic processes from infant development to adult regulation.

The disciplines of nutrition and food science are wrestling with the following questions: what components of the bacteria are we sensing to influence our health and how are foods influencing the "health" of the microbial ecosystems within us? Yogurt is the food that today most relates to that relation.

HUMAN DIVERSITY

Food and nutrition are still struggling with a fundamental truth: humans are not the same. Although sex, age, and lifestyle differences have always been recognized as demanding dietary diversity, more subtle differences are now emerging for which solutions must be found. These differences include essential nutrients, but they do not stop there. Lactation and milk provide innovative solutions to mammalian diversity. The first nutritional priority of milk is the provision of all essential nutrients at the minimum level for infant growth and development. Because these same nutrients are as essential to the mother as to the infant, providing essential nutrients in milk comes at a potentially devastating cost to the mother. Hence, milk delivers essential nutrients in bioavailable forms (12, 13). The value of yogurt differs between adults. For example, the elderly are at risk of nutrient deficiencies resulting from low caloric intakes and poor nutrient absorption. Certain genetic polymorphisms are associated with poor uptake of nutrients, including folate (*MTHFR*; 14). Food components can slow nutrient absorption (eg, iron; 15–17). Digestion differs between humans, notably the digestion of lactose. The vast majority of the human population is lactose intolerant after infancy. Genetic polymorphisms in the lactase gene regulatory regions emerged with dairying as an agricultural practice (18). The presence of this endogenous genetic lactose "tolerance" in adults presumably provided selective advantages to those who had this attribute (19). Yogurt provides this enzymatic activity with external microorganisms.

YOGURT: PAST, PRESENT, AND FUTURE

Past success

In its history, yogurt has been a unique product combining valuable elements of lactation, microbial culture, and human diversity. Yogurt delivered the nutritional elements of milk, essential nutrients in highly absorbable forms, bioactive proteins, and lipids. The safety and stability of yogurt as a dairy product were enhanced by the culture by lactic acid bacteria, lowering the pH and producing significant quantities of lactic acid. Finally, because yogurt reduces the lactose amount and provides active bacteria with the lactase enzyme, this rendered it a dairy product for humans who were lactose intolerant.

Present reality

The current role of yogurt in the diet is one of the more successful and yet contentious issues in the entire food marketplace. Yogurt enjoys considerable market share in the overall diet of many parts of the world and yet consumers have little understanding of its value to their health. Even the core assets of yogurt are not universally accepted in the regulatory arena or understood by consumers. The value propositions of yogurt have been altered significantly in the context of the regulatory judgments of recent actions of the European Food Safety Authority and the US Food and Drug Administration. These 2 agencies have been working to establish consensus language to guide scientific research to substantiate health claims for foods (20, 21). The path is complex, and yet certain themes are instructive. Most examples of successful development of scientific evidence that has reached regulatory approval have relied on simple nutrient status (calcium and bone) or have use well-established biomarkers of accepted metabolic relations to long-term disease (cholesterol and heart disease). Yogurt, with its role of delivering live bacteria, does not fall within either of these simple categories. It is therefore not surprising that there is not yet any scientific consensus on the benefits of yogurt and the presence/abundance of live bacteria beyond its traditional role of providing essential nutrients in a dairy product to those with lactose intolerance (22). Thus, despite considerable evidence that yogurt as a food product is beneficial to health, its scientific evidence portfolio, regulatory position, and consumer perception remain underappreciated. This current situation does, however, provide the opportunity for a bright future, if investments are applied.

Future promise of yogurt

Yogurt has the potential to be the vital player in the spectrum of food products that provide a wide range of health benefits to individuals through specific influence on their intestinal microbiota. To reach this potential, however, important strides in both scientific understanding and regulatory oversight must be made. The scientific understanding of the intestinal microbiota is still being assembled. For yogurt, how much of the intestinal microbiota and its influence on whole-body health are alterable by diet. For regulatory oversight, the scientific, industrial, and regulatory communities must agree on quantifiable measures of those microbiota-dependent health properties. Within such a context, companies can then show with these metrics that these

health properties have been significantly improved by their dietary interventions.

Industry must invest in the development of yogurt's potential. Industrial processes and products will need to become more transparent and their expectations for claimable health benefits more clearly defined. Industry will also need to participate in the development, validation, and implementation of technologies that accurately measure yogurt products and their quality, safety, and efficacy. It would be most efficient if the science and its regulatory applications were pursued in parallel.

THE INTESTINE AND ITS COMPLEX MICROBIOTA

The mucosal surfaces of humans are teeming with microorganisms. The intestinal mucosa and the intestinal contents of each human host a large reservoir of microorganisms that are now described as relatively constant as an ecosystem despite the continuous passage of diverse bacteria from the diet (8). Whereas "resilience" of the ecosystem is a relative term, the numbers (~100 trillion) and the complexity of each individual's microbiota are dauntingly complex. Variation among humans exists in every aspect measured: age, geography, etc (23). Despite the complexity and diversity, the gut microbiota population and the human host are apparently working in a mutualistic way to maintain the microbiota as a coherent system (24), if not numerically, at least functionally (25). These efforts at maintaining functions, presumably the result of billions of years of mutualistic coevolution, underlie and at least instruct a broad range of human immunologic (26), metabolic (27), physiologic (25), even neurologic processes (28). When these systems falter, both acute and chronic disease results. The science of how to and why guide our microbiota will drive a next generation of foods.

RESEARCH TARGETS AND KNOWLEDGE MANAGEMENT NEEDED FOR YOGURT

The basic information needed from scientific research and its translation from agriculture to yogurt to personal health is shown in **Figure 1**. The scientific tools to build the data are largely in place. It is now possible to direct these tools to yogurt. The translation of the knowledge will require new ingredients, products, and processes, and technologies to measure and document them. Research scientists, regulatory agencies, and industrial partners will need to work together to ensure that their respective goals and methods are aligned. Such coordination will be facilitated by developing bioinformatics tools to merge the disparate data sets—for example, of microbial genomes, milk components, and human microbiota functions—into a more comprehensive and annotated knowledge of the relations between the input variables of yogurt (bacteria and milk) and their consequences in different humans.

The success of this research and development agenda will depend on close collaboration and appropriate commitment in

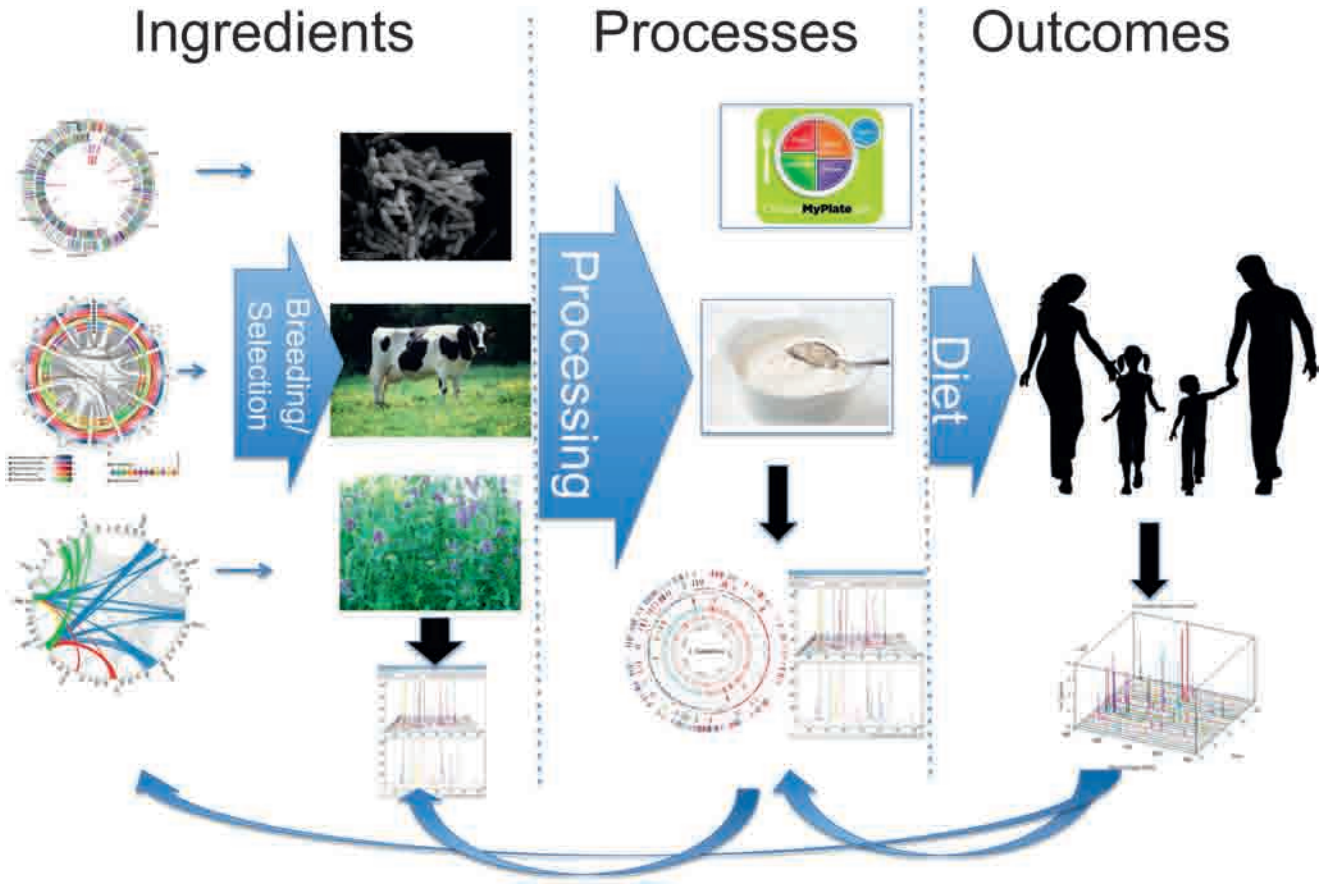

FIGURE 1. The knowledge flows needed to understand the benefits of yogurt and to deliver them to appropriate consumers.

TABLE 1
Summary of research and translation targets for yogurt

	Academic	Industrial	Regulatory
Ingredients			
Milk	Analytic method development Compositional analysis and annotation	Method deployment Compositional analysis of ingredients	Method validation and international standardization of methodologies for composition and quality
Bacteria	Genomic sequencing and annotation Microbial ecology Strain annotation	Strain-specific documentation	Establish standard nomenclatures for quantity, bioviability, and strain specificity of bacteria
Processes			
Unit operations and fermentation	Quantitative understanding of effects of temperature, pressure, homogenization, and shear on milk and bacteria	Support for and partnering with academic institutions for pilot scale production	Validation of new technologies for quality and safety Coherent, transparent regulations for standard of identity and labeling
Health outcomes	Discovery of targets of health as function and performance	Diversify products for different consumers and diverse endpoints. Construct publicly accessible databases of product compositions	Visible criteria for regulatory approval Validation of intermediate endpoints of health Support for standards of health measures Regulatory policy oversight for health assessment

time and resources by all 3 vested sectors: academic research, regulatory agencies, and industrial partners. The challenge is that these 3 sectors have very different goals for research (**Table 1**). Academic scholars need projects that provide long-term competitive funding. For industry, the key is to identify investable values emerging from research. For regulatory policy, transparency in protecting public safety is the priority. Academic research will generate peer-reviewed publications, yet the knowledge must also lead to products, markers, and devices. Regulatory bodies need to participate actively in building consensus, standardization, and validation of quality and safety metrics and diagnostic markers of efficacy. Industry has the opportunity to move beyond simple food product development and participate in the commercialization of technologies to document health efficacy. The interactions and knowledge flows between partners are shown in **Figure 2**. Importantly, both research and practice are working on similar overall goals; they are not necessarily using identical materials and tools and thus they need to communicate, translate from one domain to another, and ensure that outcomes are measurable.

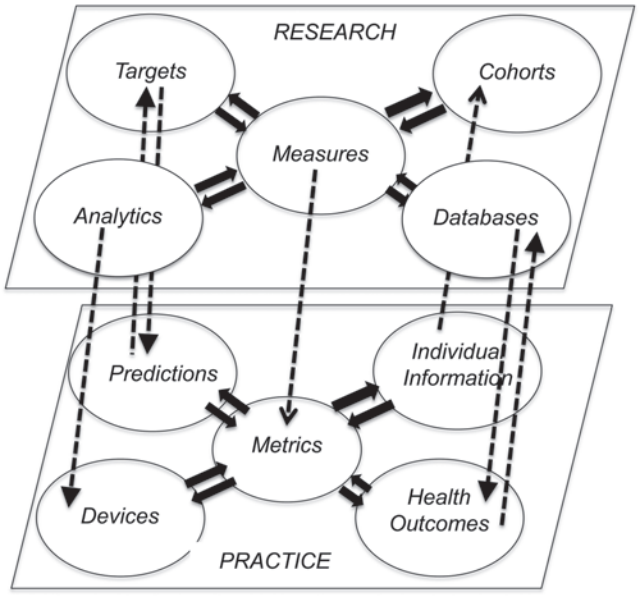

FIGURE 2. The distinct databases of research and practice for health improvements by yogurt as a food product.

INGREDIENTS

The core ingredients of yogurt sound deceptively simple: milk and bacteria. The diversity of both is a challenge and an opportunity.

Milk

Milk is not necessarily a uniform commodity ingredient for yogurt. The basic composition of milk differs according to multiple variables, including the animal's breed (29, 30) and diet (31), milking style (32), and the animal's rumen (33). Although processing has emphasized uniformity, milk research now has the tools available to build a more detailed understanding of the components of milk and to alter their concentrations. For example, milk proteins are not only sources of amino acids for nutrition. Research shows the sequence and structural complexity of milk proteins (34). Milk proteins are, in part, strings of encrypted peptides, the activity of which is released on selective proteolytic digestion. The first generation of research suggests that these peptides have unique biological activities, many of which could be released before yogurt consumption (35). Similar complex structures and functions are being

recognized for the lipids, oligosaccharides, and various small molecules in milk (36).

The future of yogurt will depend not only on building a more detailed knowledge of milk's structures and functions but also on understanding the diverse structures that can be released during production. Such a future will be accelerated by an accessible, annotated database of milk components. Regulatory scrutiny of the marketplace will also require that industries deploy the analytic toolsets capable of documenting the presence of bioactive components in the raw material ingredients and final products.

Bacteria

Bacteria used to produce traditional yogurt are increasingly well described, their growth properties defined, and entire genomes sequenced (6, 37). Annotating the yogurt bacterial genomes for flavor, structure, and stability traits is an important goal for yogurt product quality. With the growing recognition that yogurt provides a viable delivery system for probiotics, a broader range of the *Lactobacillus* bacteria are being explored for their ability to enhance the health properties and value of yogurt (38). The first comprehensive genome-sequencing project for the lactobacilli established a strategy for the entire field (39). Since this visionary start, research has been competitive and comprehensive approaches have not emerged to build a unified and consensus knowledge set of the yogurt bacteria. Nonetheless, scientific progress has been impressive, with increasingly detailed genomic knowledge of the diversity of microorganisms available to milk and cultured dairy products and of their functional differences (40). New technologies such as pangenomic sequencing and detailing gene by gene, functional trait by functional trait, and metabolite by metabolite differences in strain functionalities represent a model for building the future knowledge base of yogurt.

The informatics tools for managing comprehensive sets of bacteria in mixed cultures, their interactions with milk as a matrix, the components produced from milk and microbial metabolites in the ingredient streams for yogurt, and the precise health metrics after their consumption are not yet in place and will need to be developed. On the positive side, this means that experimental designs and methods, marker validation, and informatics tools can be placed simultaneously into a coherent systems approach for yogurt innovations and validations (41).

PROCESSES

Yogurt processing is integral to the final product quality, safety, and health efficacy. Recent successes in expanding the diversity of yogurt processing and composition, notably "Greek style" yogurt, have shown that there is considerable flexibility to innovate within the category. These same successes, however, highlight the lack of industry standards for product labeling, lack of policy consensus of yogurt standards of identity, and lack of scientific support for the purported benefits. For example, so-called Greek-style yogurt swept into the 2010 yogurt marketplace with a simple proposition of being higher in solids and protein. Although this modification in composition is traditionally accomplished by a filtration step during the final stages of processing, many products labeled "Greek style" achieve a higher solids and protein composition by explicitly adding milk protein ingredients at the beginning or end of the process. Producers, regulators, and consumers are now debating: are these methods the same?

As yogurt diversifies, regulatory policy will be faced with important decisions as to what constitutes "yogurt," how far the compositions can diverge before products can no longer be considered within the category, and how to label these various alternatives. Industries are faced with the conflicting pressures of formulating and positioning products within the rapidly changing, competitive marketplace and maintaining labeling standards and consumer transparency.

Food processing is about to be transformed by genomics sequencing tools. Genomics sequencing–based microbial detection systems are now available for relatively routine surveillance of entire processing facilities. Techniques can map entire microbial communities from cows and plants to entire crops and food-processing and health facilities (42–45). Detailed knowledge of the microbial communities, including bacteria, yeast, molds, and even bacteriophages, within entire yogurt-processing environments, will enhance safety, quality, and going forward, the health propositions possible.

HEALTH OUTCOMES AND YOGURT

Yogurt is already perceived by consumers as having health benefits. Going forward, yogurt is a food category poised to translate scientific research. In many respects, yogurt is ideally situated to lead science and technology into a future of greater health through diet. The question is, can research be mobilized to realize this future?

Progress in discovering the relations between yogurt and health would be significantly enhanced with 3 simple changes in strategy:

1) Focus on prevention and protection rather than therapeutic cure.

2) Unify lactation research across all mammals, including human and bovine.

3) Develop markers based on mechanisms of action to translate science into regulatory dossiers of efficacy and demonstrated proof of benefits.

Prevention

Health is approached largely from a disease-centric perspective. Diseases are defined by specific functional departures from "normal" health. The goal of curative health science is to understand the mechanisms underlying those diseases and to discover interventions—chemical, biological, or procedural—to reverse them. Preventing diseases before they occur is not necessarily the same. Prevention implies that interventions (again, chemical, biological, or procedural) act preemptively on healthy individuals to lower the risk of disease (ie, to improve health). Prevention in practice would strengthen processes that block agents that cause diseases, to rebalance endogenous processes that are chronically dysregulated sufficiently to lead to disease and to enhance the activity or sensitivity of surveillance processes that detect damaged molecules, cells, or tissues that would become diseased. The

challenge for science is to bring these broad principles into mechanistically defined and demonstrable action. Scientists are using very imaginative approaches to identity the targets of disease diagnostics and therapeutics; those same toolsets can now be applied to discover the targets, metrics, and products of prevention.

Lactation

Lactation has been driven by relentless Darwinian selective pressure for protection and prevention. Yogurt would profit by bringing a scientifically detailed, molecular understanding of how milk from all mammals, especially humans, achieves its benefits. Once established, those mechanisms can be translated into innovative yogurt products and benefits. The following 4 broad categories of benefits to infants would be of immediate value across the age spectrum, if science could unravel the mechanisms by which milk achieves these effects: immunity, metabolism, physiology, and microbiota.

Immunity is a massively complex system consisting of multiple innate structures and functions together with an even greater diversity of acquired processes. Appropriate functioning of immunity is necessary to the protection of life and the prevention of disease. Yet, imbalances in immunity can cause disease. Failure to regulate immunity appropriately thus contributes both to increased risk of infectious disease when immune responses are insufficient and yet contributes to increased risk of diseases of inflammation and autoimmunity when immunity is inappropriate and excessive. Diets that prevent disease must therefore improve both aspects of immunity. The failure of the immune system to respond sufficiently to pathogenic invasion is seen in young infants, as a result of delayed development, and in the elderly who are at risk of immune senescence and suppression (46). Human milk has been documented to enhance the development of acquired immunity in infants and these same mechanisms could translate to adults, if they were understood (47).

Scientific consensus has not yet developed a full nomenclature to describe inflammation. Nonetheless, however it is defined, inflammation is associated with, if not considered central to, virtually all noncommunicative, degenerative diseases (heart disease, diabetes, cancer, arthritis, asthma, stroke, etc) (48). If inflammation could be reduced, the benefits to long-term health would be remarkable. However, there is a problem. Inflammation is also at key points essential to the successful immune response to pathogens. Therefore, interventions to reduce inflammation carry the risk of increased infectious disease. The balance of immunity is at the core of this diverse protection system, and at present no strategy has emerged that can maintain appropriate immune response and simultaneously prevent chronic inflammation. Yet, human milk is very well described as providing multiple, diverse mechanisms that are anti-inflammatory, while at the same time enhancing overall immune protection of the infant (49). The mysteries of inflammation—from the diverse mechanisms that cause it to the ingredients to manage it—are hidden within lactation biology.

Metabolism in higher organisms is in many ways as complex and pervasive as immunity. The appropriate distribution of fuels and substrates to support all of the disparate systemic processes is the function of metabolic regulation. The inappropriate distribution of fuel is now recognized to be driving obesity, cachexia, heart disease, diabetes, and many cancers (50). Once again, aggressive pharmacologic approaches to alter metabolic regulation are fraught with risk. Milk has not only been shown to be associated with appropriate metabolic regulation in infants, but dairy intake has also been associated with risk protection in adults (51). Thus, the mechanism by which milk supports metabolism is evidently translatable across all ages and mammalian species. The secrets to metabolic control are in lactation biology.

Physiologic processes, when unbalanced, are increasingly recognized as drivers of chronic disease. Simple blood flow is an example of the complexity of the problem. When physiologic processes are working appropriately, blood flow is acutely directed to tissues in demand, fueling performance and removing byproducts. When not working appropriately, impaired blood flow, measured as hypertension, is a major driver of cardiovascular disease (52). Milk clearly targets blood flow regulation. One of the classes of bioactive factors (antihypertensive peptides) and their targets of action (angiotensin-converting enzyme) have already been brought to practice as functional food ingredients (53). The path to understanding physiologic regulation is through lactation biology.

The microbiota of humans is a key contributor to the regulation of metabolic, physiologic, immunologic, and even neurologic processes. The most compelling evidence for the importance of the microbiota to human health and the ability to manipulate it through diet comes from milk. The mammary gland and lactation providing milk for infant nourishment have been central to mammalian evolutionary success (54). Milk nourishes the infant and yet costs the mother. One class of molecules has been particularly perplexing in this context. Glycans (complex sugar polymers and their conjugates) are indigestible by infants (55). Ongoing research has established that these components are selectively feeding not the infant but specific bacteria within the infant's intestine (56–58). The diverse saccharide structures and linkages in the glycans of milk are matched to stereospecific catalytic activities of a group of bacterial enzymes within the genomes of bacteria unique to infants (58–60). The microbiota of breastfed infants is remarkably distinct during the first year of life (61, 62). Milk itself is a source of living microorganisms, implicating milk as a delivery system for maternally derived bacteria destined for the infant (63, 64). Once again, the roadmap to colonizing and guiding a complex microbial ecosystem in the intestine of humans is contained within the lactation genome of mammals. Research just needs to "decode" it.

METRICS/DIAGNOSTICS OF YOGURT AND HEALTH

A key to improving health in the population and to capturing value in food products and services is to develop the technologies to accurately measure individual health. Success in diagnosing disease by identifying analytes in blood associated with particular diseases has driven the drug marketplace. Unfortunately, this basic strategy will need to be modified for measuring health and preventing disease, because there is no disease to diagnose. Health itself must be assessed. Assessing health means measuring the functioning of the various systems, structures, and processes that constitute the normal healthy state. In a food marketplace in which consumers are measured for personal health, the value of yogurt can be shown by its ability to enhance those functions.

Disease is typically detected by static measures: diagnostics. The processes of health are revealed by challenging those processes explicitly (65–67). The challenge approach to health assessment includes the measurement of the dynamic fluxes of metabolites through specific biochemical pathways in response to a defined nutritional input. A standard glucose challenge, for example, has been a hallmark of metabolic assessment for decades, and this principle has been shown to be expandable to multiple nutrients (65). This "challenge" principle shows aspects of metabolism that are unavailable in the fasted state. Analogous to running a race to assess the performance of athletes, analyzing the metabolic, immunologic, physiologic, and even neurologic responses to a standard stimulus can assess the quality of the performance of those systems.

Scientists can and should drive a new view of health, measurable by absolute, quantitative criteria. The metrics of what to measure, when, how accurately, and in response to what challenge are appropriate research goals for academic science. However, scientists developing health metrics must now go beyond simply chronicling disease processes. Finally, these scientific measures must move out of the laboratories and into common practice. This ultimate goal of building a health assessment marketplace will require devices that are sufficiently accurate to be of predictive value but sufficiently noninvasive, cost-effective, and convenient to be practical. Engineers will need to be at least as diligent and engaged in building the tools of health measurement as they are in the tools of automotive performance. Deploying personal health measures will build a more knowledgeable consumer population. A more knowledgeable consumer population will drive a more competitive and more valuable marketplace. To reach this more measured consumer population, regulators will need to guide, validate, and monitor the accuracy of health measurement as an industry. In a measured health marketplace, yogurt's value will rise.

Health assessment needs a policy advocate. There needs to be a regulatory body that champions the development of health assessment indicators out of academic research. Although disease diagnostics provide a framework, there are some important differences. The costs of approving disease diagnostics are high, for good reason. The consequences of an error, either type 1 (false positive) or type 2 (false negative), based on a diagnostic outcome decision for disease can be catastrophic. Hence, the time and effort needed to minimize error rates for disease diagnostics are justified. However, for measures of health, the situation is different. Health will be measured more routinely, and the decisions taken are less impactful. Hence, a distinct regulatory oversight system for the development, validation, and monitoring of the marketplace of health assessment should be more flexible and reactive.

CONCLUSIONS

The long history of the health values of yogurt are chronicled throughout this series of accompanying articles in the supplement issue. The future of yogurt is in the hands of scientists, technologists, and policy makers. There is a clear opportunity to build the knowledge, tools, and products needed to position a portfolio of new foods based on the concepts of traditional yogurt. Academic research, industrial partners, and policy regulators working together will achieve this future. Research will need to establish the mechanisms by which yogurt acts on specific aspects of health and the metrics to document them. Industries will accelerate progress by providing materials for development and clinical trials. Regulators will provide a more competitive commercial marketplace for health by supporting the development, validation, and deployment of technologies to measure human health and to show the value of health-supporting food products.

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REFERENCES

1. Lefèvre CM, Sharp JA, Nicholas KR. Evolution of lactation: ancient origin and extreme adaptations of the lactation system. Annu Rev Genomics Hum Genet 2010;11:219–38.
2. Lemay DG, Neville MC, Rudolph MC, Pollard KS, German JB. Gene regulatory networks in lactation: identification of global principles using bioinformatics. BMC Syst Biol 2007;1:1–24.
3. Hinde K, German JB. Food in an evolutionary context: insights from mother's milk. J Sci Food Agric 2012;92:2219–23.
4. Hinde K, Milligan LA. Primate milk: proximate mechanisms and ultimate perspectives. Evol Anthropol 2011;20:9–23.
5. Gobbetti M, Cagno RD, De Angelis M. Functional microorganisms for functional food quality. Crit Rev Food Sci Nutr 2010;50:716–27.
6. Sieuwerts S, Molenaar D, van Hijum SA, Beerthuyzen M, Stevens MJ, Janssen PW, Ingham CJ, de Bok FA, de Vos WM, van Hylckama Vlieg JE. Mixed-culture transcriptome analysis reveals the molecular basis of mixed-culture growth in Streptococcus thermophilus and Lactobacillus bulgaricus. Appl Environ Microbiol 2010;76:7775–84.
7. Ley RE, Lozupone CA, Hamady M, Knight R, Gordon JI. Worlds within worlds: evolution of the vertebrate gut microbiota. Nat Rev Microbiol 2008;6:776–88.
8. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature 2012;489:220–30.
9. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, Pettersson S. Host-gut microbiota metabolic interactions. Science 2012;336:1262–7.
10. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol 2007;5:e177.
11. Sommer F, Backhed F. The gut microbiota—masters of host development and physiology. Nat Rev Microbiol 2013;11:227–38.
12. Meisel H, FitzGerald RJ. Biofunctional peptides from milk proteins: mineral binding and cytomodulatory effects. Curr Pharm Des 2003;9:1289–95.
13. German JB, Dillard CJ, Ward RE. Bioactive components in milk. Curr Opin Clin Nutr Metab Care 2002;5:653–8.
14. Yang QH, Botto LD, Gallagher M, Friedman JM, Sanders CL, Koontz D, Nikolova S, Erickson JD, Steinberg K. Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine concentrations in the United States: findings from the Third National Health and Nutrition Examination Survey DNA bank. Am J Clin Nutr 2008;88:232–46.
15. Singh M, Sanderson P, Hurrell RF, Fairweather-Tait SJ, Geissler C, Prentice A, Beard JL. Iron bioavailability: UK Food Standards Agency workshop report. Br J Nutr 2006;96:985–90.
16. Sanz-Penella JM, Laparra JM, Sanz Y, Haros M. Assessment of iron bioavailability in whole wheat bread by addition of phytase-producing bifidobacteria. J Agric Food Chem 2012;60:3190–5.
17. Mario Sanz-Penella J, Laparra JM, Sanz Y, Haros M. Bread supplemented with amaranth (Amaranthus cruentus): effect of phytates on in vitro iron absorption. Plant Foods Hum Nutr 2012;67:50–6.
18. Itan Y, Jones BL, Ingram CJ, Swallow DM, Thomas MG. A worldwide correlation of lactase persistence phenotype and genotypes. BMC Evol Biol 2010;10:1–11.
19. Ingram CJ, Mulcare CA, Itan Y, Thomas MG, Swallow DM. Lactose digestion and the evolutionary genetics of lactase persistence. Hum Genet 2009;124:579–91.
20. Ellwood KC, Trumbo PR, Kavanaugh CJ. How the US Food and Drug Administration evaluates the scientific evidence for health claims. Nutr Rev 2010;68:114–21.

21. Vero V, Gasbarrini A. The EFSA health claims 'learning experience'. Int J Food Sci Nutr 2012;63(suppl 1):14–6.
22. Katan MB. Why the European Food Safety Authority was right to reject health claims for probiotics. Benef Microbes 2012;3:85–9.
23. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, et al. Human gut microbiome viewed across age and geography. Nature 2012;486:222–7.
24. Hooper LV, Macpherson AJ. Immune adaptations that maintain homeostasis with the intestinal microbiota. Nat Rev Immunol 2010;10: 159–69.
25. Lozupone C, Faust K, Raes J, Faith JJ, Frank DN, Zaneveld J, Gordon JI, Knight R. Identifying genomic and metabolic features that can underlie early successional and opportunistic lifestyles of human gut symbionts. Genome Res 2012;22:1974–84.
26. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 2013;341:569–73.
27. Raybould HE. Gut microbiota, epithelial function and derangements in obesity. J Physiol 2012;590:441–6.
28. Forsythe P, Kunze WA, Bienenstock J. On communication between gut microbes and the brain. Curr Opin Gastroenterol 2012;28:557–62.
29. Perna A, Intaglietta I, Simonetti A, Gambacorta E. Effect of genetic type and casein haplotype on antioxidant activity of yogurts during storage. J Dairy Sci 2013;96:3435–41.
30. Skibiel AL, Downing LM, Orr TJ, Hood WR. The evolution of the nutrient composition of mammalian milks. J Anim Ecol 2013;82(6):1254–64.
31. Romanzin A, Corazzin M, Piasentier E, Bovolenta S. Effect of rearing system (mountain pasture vs. indoor) of Simmental cows on milk composition and Montasio cheese characteristics. J Dairy Res 2013;80 (4):390–9.
32. Martin B, Pomiès D, Pradel P, Verdier-Metz I, Rémond B. Yield and sensory properties of cheese made with milk from Holstein or Montbeliarde cows milked twice or once daily. J Dairy Sci 2009;92:4730–7.
33. Kurokawa Y, Shibata H, Tateno S, Kanda S, Takaura K, Ishida S, Itabashi H. Rumen fermentation, milk production and conjugated linoleic acid in the milk of cows fed high fiber diets added with dried distillers grains with solubles. Anim Sci J 2013;84:106–12.
34. Dallas DC, Guerrero A, Khaldi N, Castillo PA, Martin WF, Smilowitz JT, Bevins CL, Barile D, German JB, Lebrilla CB. Extensive in vivo human milk peptidomics reveals specific proteolysis yielding protective antimicrobial peptides. J Proteome Res 2013;12:2295–304.
35. Madureira AR, Tavares T, Gomes AM, Pintado ME, Malcata FX. Invited review: physiological properties of bioactive peptides obtained from whey proteins. J Dairy Sci 2010;93:437–55.
36. Ward RE, German JB. Understanding milk's bioactive components: a goal for the genomics toolbox. J Nutr 2004;134:962S–7S.
37. Thevenard B, Rasoava N, Fourcassié P, Monnet V, Boyaval P, Rul F. Characterization of Streptococcus thermophilus two-component systems: in silico analysis, functional analysis and expression of response regulator genes in pure or mixed culture with its yogurt partner, Lactobacillus delbrueckii subsp. bulgaricus. Int J Food Microbiol 2011; 151:171–81.
38. Vázquez C, Botella-Carretero JI, García-Albiach R, Pozuelo MJ, Rodríguez-Baños M, Baquero F, Baltadjieva MA, del Campo R. Screening in a Lactobacillus Delbrueckii subsp. Bulgaricus collection to select a strain able to survive to the human intestinal tract. Nutr Hosp 2013;28:1227–35.
39. Makarova K, Slesarev A, Wolf Y, Sorokin A, Mirkin B, Koonin E, Pavlov A, Pavlova N, Karamychev V, Polouchine N, et al. Comparative genomics of the lactic acid bacteria. Proc Natl Acad Sci USA 2006; 103:15611–6.
40. Smokvina T, Wels M, Polka J, Chervaux C, Brisse S, Boekhorst J, van Hylckama Vlieg JE, Siezen RJ. Lactobacillus paracasei comparative genomics: towards species pan-genome definition and exploitation of diversity. PLoS ONE 2013;8:e68731.
41. Lemay DG, Zivkovic AM, German JB. Building the bridges to bioinformatics in nutrition research. Am J Clin Nutr 2007;86:1261–9.
42. Bokulich NA, Ohta M, Richardson PM, Mills DA. Monitoring seasonal changes in winery-resident microbiota. PLoS ONE 2013;8:e66437.
43. Bokulich NA, Mills DA. Facility-specific "house" microbiome drives microbial landscapes of artisan cheesemaking plants. Appl Environ Microbiol 2013;79:5214–23.
44. Bokulich NA, Mills DA, Underwood MA. Surface microbes in the neonatal intensive care unit: changes with routine cleaning and over time. J Clin Microbiol 2013;51:2617–24.
45. Setati ME, Jacobson D, Andong UC, Bauer F. The vineyard yeast microbiome, a mixed model microbial map. PLoS ONE 2012;7: e52609.
46. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. Nat Immunol 2013;14:428–36.
47. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin North Am 2013;60:49–74.
48. Tabas I, Glass CK. Anti-inflammatory therapy in chronic disease: challenges and opportunities. Science 2013;339:166–72.
49. Goldman AS. Evolution of immune functions of the mammary gland and protection of the infant. Breastfeed Med 2012;7:132–42.
50. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 2012;59:635–43.
51. Rice BH, Quann EE, Miller GD. Meeting and exceeding dairy recommendations: effects of dairy consumption on nutrient intakes and risk of chronic disease. Nutr Rev 2013;71:209–23.
52. Floras JS. Blood pressure variability: a novel and important risk factor. Can J Cardiol 2013;29:557–63.
53. Phelan M, Kerins D. The potential role of milk-derived peptides in cardiovascular disease. Food Funct 2011;2:153–67.
54. Lemay DG, Lynn DJ, Martin WF, Neville MC, Casey TM, Rincon G, Kriventseva EV, Barris WC, Hinrichs AS, Molenaar AJ. The bovine lactation genome: insights into the evolution of mammalian milk. Genome Biol 2009;10:1–18.
55. Zivkovic AM, German JB, Lebrilla CB, Mills DA. Human milk glycobiome and its impact on the infant gastrointestinal microbiota. Proc Natl Acad Sci USA 2011;108(suppl 1):4653–8.
56. Ward RE, Niñonuevo M, Mills DA, Lebrilla CB, German JB. In vitro fermentability of human milk oligosaccharides by several strains of bifidobacteria. Mol Nutr Food Res 2007;51:1398–405.
57. Sela DA, Garrido D, Lerno L, Wu S, Tan K, Eom HJ, Joachimiak A, Lebrilla CB, Mills DA. Bifidobacterium longum subsp. infantis ATCC 15697 alpha-fucosidases are active on fucosylated human milk oligosaccharides. Appl Environ Microbiol 2012;78:795–803.
58. Sela DA, Chapman J, Adeuya A, Kim JH, Chen F, Whitehead TR, Lapidus A, Rokhsar DS, Lebrilla CB, German JB, et al. The genome sequence of Bifidobacterium longum subsp. infantis reveals adaptations for milk utilization within the infant microbiome. Proc Natl Acad Sci USA 2008;105:18964–9.
59. Marcobal A, Barboza M, Sonnenburg ED, Pudlo N, Martens EC, Desai P, Lebrilla CB, Weimer BC, Mills DA, German JB, et al. Bacteroides in the infant gut consume milk oligosaccharides via mucus-utilization pathways. Cell Host Microbe 2011;10:507–14.
60. Garrido D, Nwosu C, Ruiz-Moyano S, Aldredge D, German JB, Lebrilla CB, Mills DA. Endo-β-N-acetylglucosaminidases from infant gut-associated bifidobacteria release complex N-glycans from human milk glycoproteins. Mol Cell Proteomics 2012;11:775–85.
61. Underwood MA. Human milk for the premature infant. Pediatr Clin North Am 2013;60:189–207.
62. Donovan SM, Wang M, Li M, Friedberg I, Schwartz SL, Chapkin RS. Host-microbe interactions in the neonatal intestine: role of human milk oligosaccharides. Adv Nutr 2012;3(suppl):450S–5S.
63. Ward TL, Hosid S, Ioshikhes I, Altosaar I. Human milk metagenome: a functional capacity analysis. BMC Microbiol 2013;13:1–12.
64. Quigley L, O'Sullivan O, Stanton C, Beresford TP, Ross RP, Fitzgerald GF, Cotter PD. The complex microbiota of raw milk. FEMS Microbiol Rev 2013;37:664–98.
65. Krug S, Kastenmüller G, Stückler F, Rist MJ, Skurk T, Sailer M, Raffler J, Römisch-Margl W, Adamski J, Prehn C, et al. The dynamic range of the human metabolome revealed by challenges. FASEB J 2012;26:2607–19.
66. Pellis L, van Erk MJ, van Ommen B, Bakker GC, Hendriks HF, Cnubben NH, Kleemann R, van Someren EP, Bobeldijk I, Rubingh CM, et al. Plasma metabolomics and proteomics profiling after a postprandial challenge reveal subtle diet effects on human metabolic status. Metabolomics 2012;8:347–59.
67. Zivkovic AM, Wiest MM, Nguyen U, Nording ML, Watkins SM, German JB. Assessing individual metabolic responsiveness to a lipid challenge using a targeted metabolomic approach. Metabolomics 2009; 5:209–18.