Dairy products in global public health

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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 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).

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