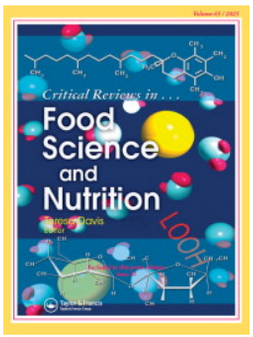

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REVIEW ARTICLE

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Alternative biological functions of lactose: a narrative review

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ABSTRACT

Lactose, commonly known as "milk sugar," offers various health benefits beyond its role as an energy source. As a precursor for essential molecules, lactose impacts calcium absorption, has low cariogenicity, affects satiety, enhances athletic performance, and potentially functions as a prebiotic for gut health. However, not all individuals can digest lactose, with a minority of the population exhibiting gastrointestinal symptoms after its consumption. The ability to digest lactose during adulthood is a genetically conferred trait known as lactase persistence, which is also likely affected by epigenetic alterations and other endogenous factors. In the present review, we highlight the multifaceted health effects of lactose, including its impact on calcium absorption, its low cariogenicity, its role in satiety control, its ability to enhance athletic performance, and its potential benefits as a prebiotic for gut health. Since these benefits are inherently dependent on lactose intake trends and the digestion capacity of populations, we also present the latest available information on the current trends in lactose consumption around the world. Overall, the gathered evidence suggests that moderate lactose consumption is recommended, as it can foster multiple lifelong health benefits.

STATEMENT OF SIGNIFICANCE

- We gather the latest evidence supporting alternate biological functions of lactose beyond its role as an energy supplier, highlighting its influence on calcium absorption, its low cariogenicity and glycemic index, its benefits for sports performance and satiating power as well as its potential prebiotic role for the gut microbiota.
- We compile the most updated data on dairy and lactose consumption across countries, describing the current trends worldwide and discussing the future evolution of lactose intake.

KEYWORDS

Lactose; health; lactose consumption; lactase persistence and non-persistence; calcium; caries; prebiotics

Introduction

Lactose, a disaccharide composed of galactose and glucose, is the main carbohydrate in the milk of terrestrial eutherians although it can be found in minor amounts in other sources, including plants (Brockway et al. 2024; Holsinger 1988; Newburg and Neubauer 1995; Troelsen 2005). It is commonly referred to as "milk sugar". Initially, discovered and isolated in 1663 by Bartolettus, during recent decades its mechanisms of digestion, absorption, and metabolism have been mostly described (Gil, Fontana, and Sánchez de Medina 2017; Koepsell 2020; Martinez-Augustin and Suarez 2024). Despite this, there are still many unresolved questions regarding its functionality. Lactose, like the other components of milk, not only has an energetic function but also plays a key role in multiple processes of critical importance from the neonatal period to adulthood. The monosaccharides that compose it are important in metabolic processes for the formation of macromolecules such as oligosaccharides, glycoproteins, and glycolipids (Zunft and Schulze 1990).

During breastfeeding, lactose is important for the essential energy transfer to newborns. As a disaccharide, lactose is half of the osmolarity of two equivalent monosaccharides and thus is less likely to cause postprandial osmotic stress in infants receiving large amounts of dietary calories from carbohydrates. Moreover, the digestion of lactose into glucose and galactose is almost simultaneous with the absorption of the two monosaccharides across the microvillus membrane thus maintaining low osmolarity in the lumen of the intestine (Newburg 2000). Although, theoretically, the galactose requirements for galactolipid and glycoprotein formation in humans could be met through the epimerization of glucose

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into galactose in tissues, it can be hypothesized that lactose-derived galactose could be an important monosaccharide for infancy during which there is a continuous and active process of myelination (Gil, Fontana, and Sánchez de Medina 2017; Martinez-Augustin and Suarez 2024; Romero-Velarde et al. 2019). Even mammals with low lactose content, such as pinnipeds, contain high amounts of galactose bound to oligosaccharides (Newburg 2000). Lactose intake during infancy could exert a positive influence on calcium absorption as has been shown in animals (Weaver et al. 2011) and in infants (Abrams, Griffin, and Davila 2002). During breastfeeding, lactose, which has a galactose β(1→4) glucose bond, becomes susceptible to hydrolysis by β-galactosidases. It is known that lactose that is not digested reaches the terminal ileum and ultimately the colon, where it is fermented by the intestinal microbiota, supporting colonization by bifidobacteria and other lactic acid bacteria. Therefore, lactose favors *Bifidobacterium* colonization, and antimicrobial peptide induction potentially protects the neonatal intestine against infections (Plaza-Díaz, Fontana, and Gil 2018). Reinforcing its role as a prebiotic, lactose is also the precursor of human milk oligosaccharides (HMOs), which are well-known neonatal intestinal microbiota stimulants (Bode 2015; Brockway et al. 2024; Plaza-Díaz, Fontana, and Gil 2018). The immunomodulatory role of lactose has also been described as being associated with its prebiotic effect. After birth, newborns do not have a fully functional adaptive immune system and depend on their innate immune system. Current evidence suggests that lactose, together with HMOs, may modulate this early defense system, strengthening the immune system and protecting the host against several pathogens (Bode 2015; Damaskos and Kolios 2008; Plaza-Díaz, Fontana, and Gil 2018).

Adults might also benefit from lactose. Indeed, lactose is a carbohydrate with a low glycemic index, indicating a slow increase in glucose concentration in the blood after digestion (Atkinson et al. 2021; Foster-Powell, Holt, and Brand-Miller 2002; Vandenplas 2015) and a relatively low sweetness. Moreover, lactose seems to have a stronger satiating potential than other sugars and carbohydrates (Bowen et al. 2006). The current evidence indicates that lactose is also a very low cariogenic sugar compared to sucrose, which is the most cariogenic sugar (Schaafsma 2008; Shi et al. 2020). Additionally, lactose can act as a prebiotic in adults, promoting a healthier gut microbiota. Finally, contradictory results have been found regarding its beneficial influence on calcium absorption in adults (Brink et al. 1993; Hodges et al. 2019; Obermayer-Pietsch et al. 2004; Zittermann et al. 2000).

Lactose therefore has a range of lifelong health benefits and has several functions in the body apart from its obvious role as an energy source. In Table 1, we present a summary of all these functions, some of which are expanded upon in the different sections of this review. The leverage of all these beneficial properties of lactose by humans is, nonetheless, inherently dependent on its intake from dairy products, especially animal milk. Over the past 50 years, the global landscape of lactose intake has undergone considerable evolution, with marked disparities emerging between regions.

Table 1. The main functions of lactose.

System	Function
Cellular level	Formation of oligosaccharides, glycoproteins, and glycolipids.
Human milk	Contains approximately 70 g/L of lactose (7%) which provides 40% of energy.
Nervous system	Galactose is part of several macromolecules (cerebrosides, gangliosides, and mucoproteins) that are important components of the nerve cell membrane.
Gastrointestinal system	Lactose provides galactose for hepatic glycogen synthesis.
	Microbiota colonization through selective limitation of the progression of bacteria with difficulties in lactose fermentation generates a protective effect against neonatal gastrointestinal infections.
	Generation of a beneficial effect in the host by stimulating growth and bifidobacterial activity.
	The activity of lactase has a higher expression in the mid-jejunum, in which the specific intestinal region for multiple transcription factors can be found.
	Lactose restriction may induce bioavailable calcium, vitamin D, and B12 deficiency since they are found in dairy products; the restriction may cause a decrease in bone mineral density, anemia, and neuropathy.
Metabolism	Source of energy and complex carbohydrates, its enteral administration improves mineral absorption: calcium, magnesium, and copper. Lactose increases calcium (and other minerals) solubility, increasing passive absorption
Immune system	It supports the adaptive immune system, protecting the host against several pathogens.
	Immunomodulatory role due to its participation in the innate immune system through the formation of antimicrobial peptides and/or proteins such as the antimicrobial peptide cathelicidin, which plays a key role in the configuration of intestinal microbiota.

These disparities are shaped by a complex interplay of factors, including age, sex, socioeconomic status, sociocultural influences, and the availability and accessibility of dairy products. Furthermore, genetic components influencing an individual's ability to digest lactose effectively, namely lactase persistence and lactase non-persistence phenotypes, might also play a role. At the moment, a general idea of the current consumption patterns of the population worldwide remains largely unknown.

The literature on lactose is comprehensive and it is not the intention of the present article to exhaustively review it. There are excellent general and specialized reviews covering the scientific and technological aspects of lactose (Adam, Rubio-Texeira, and Polaina 2004; Anguita-Ruiz, Aguilera, and Gil 2020; Brockway et al. 2024; Chengolova, Ivanova, and Gabrovska 2024; Holsinger 1988; Correa-Rodríguez et al. 2018; Nath et al. 2018; Newburg 2000; Romero-Velarde et al. 2019; Sadovnikova, Garcia, and Hovey 2021; Solomons 1996). In this work, therefore, we focus on emerging alternative biological functions of lactose that might be beneficial for human health such as its potential function in calcium absorption and influence on bone health, its role in the control of satiety and cariogenicity, sports performance, and its potential prebiotic effects. Finally, given the fact that low lactose consumption trends might hinder the leverage of such benefits, we provide an overview of the consumption patterns of lactose and dairy products worldwide, a topic that has not been extensively reviewed before.

Lactose digestion phenotypes: lactase persistence and non-persistence

The capacity to digest lactose by the LPH enzyme in mammals reaches a peak after birth that is not ubiquitous throughout the life course but rather, is a condition subjected to developmental regulation. In most mammals, the LPH activity rapidly decreases after the weaning phase because of decreased enzyme levels (decrease to < 10% of the neonatal values, with reduced activity maintained throughout adult life) (Swallow 2003). This downregulation is a genetically programmed event known as lactase non-persistence (LNP). As a result of LNP, many humans are incapable of digesting lactose in the small intestine when they are adults, and some of them suffer complications when they consume it. Approximately two-thirds of humans worldwide have LNP (Ségurel and Bon 2017). Nonetheless, in the remaining one third, most individuals can maintain the expression of LPH throughout adulhood, and this trait is known as lactase persistence (LP). People who have LP can usually hydrolyze large amounts of lactose during adulthood and can thus consume large quantities of fresh milk without complications. LNP and LP terms simply refer to the ability or not to preserve LPH expression after the weaning phase and must not be confused with the term lactose intolerance, which, on the contrary, refers to the consequences that can result from a LNP status. People with LNP have a much lower capacity of digesting lactose in the small intestine than those with LP; thus they often, but not always, show symptoms after consumption of fresh milk.

The molecular mechanisms controlling LPH activity in humans and driving LP and LNP are complex and have constituted a topic of research during recent decades (Figure 1). *In vivo* studies have demonstrated that the majority of lactose gene (*LCT*) regulatory transcription factors have their binding sites located within or 1 kb upstream of the 5′ flanking sequence of *LCT*, spanning a different gene known as *MCM6* (minichromosome maintenance complex component 6). In particular, the decrease in lactase levels in LNP seems to be directly caused by transcriptional repressors that act at approximately the age of 5 years as a genetically programmed event involving the action of different transcription factors on *MCM6* (Jacob et al. 1996; Lee et al. 2002). Several research papers have indicated that the transcription factor Pdx-1 is the main factor responsible for this reduction in *LCT* expression (Wang et al. 2004). In addition to transcription factors, several epigenetic mechanisms have been suggested to play a role in LNP regulation. In particular, age-dependent DNA methylation in the *LCT* and its upstream regulatory regions has been associated with LNP (Labrie et al. 2016). On the other hand, single nucleotide polymorphisms (SNPs) in the *FUT3* and *FUT2* genes, which correspond to the secretion of the Lewis ABO (H) histo-blood group antigen CA19-9, have been found to cause interpersonal differences in terminal glycosylation of the carbohydrate side chains of the lactase protein (Green et al. 1988). These variants can impact protein stability and suggest that post-transcription factors, not just DNA-binding elements, may also contribute to the natural decline in intestinal lactase levels.

LP, on the other hand, is associated with the occurrence of specific single nucleotide polymorphisms (SNPs) in the *MCM6* regulatory region, such as the −13.910>T variant (Ingram et al. 2009; Olds and Sibley 2003; Swallow 2003). These SNPs create new binding sites for transcription factors like Oct-1 and HNF1-α, enabling continued expression of

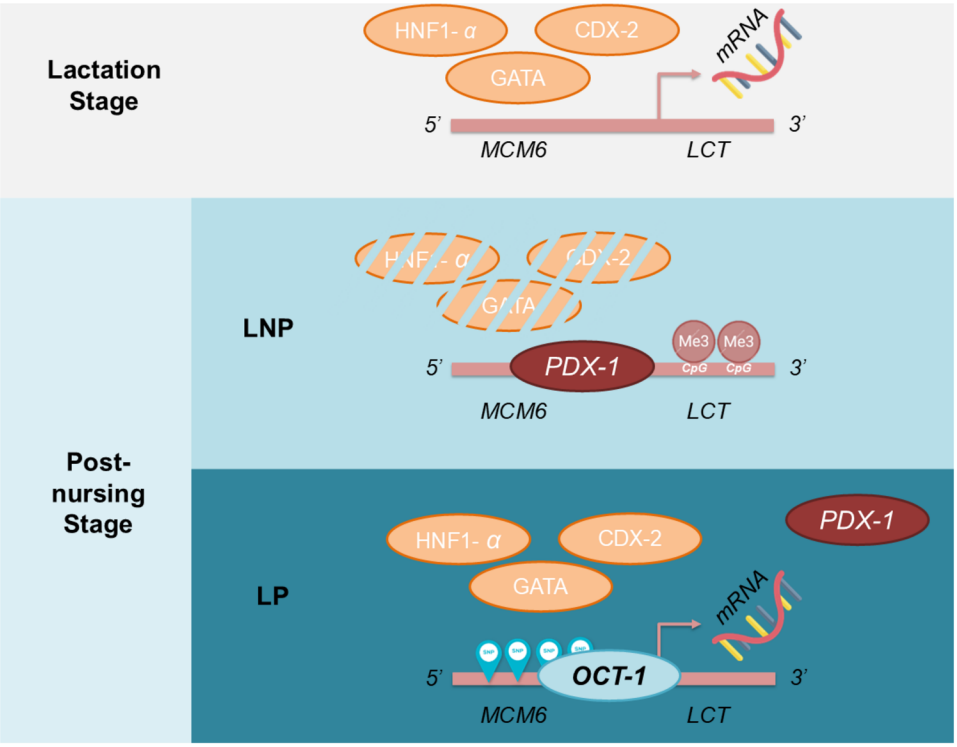

Figure 1. Molecular mechanism of lactase persistence and non-persistence in humans. Oval shapes refer to the transcription factors (TFs) with the reported ability to bind the lactase locus (LCT) promoter. The TFs CDX-2, HNF1-α, GATA, and OCT-1 induce LCT expression.

Table 2. Lactase persistence-associated single nucleotide polymorphisms.

SNP	RS-id	Additional Information
−14010:G > C **	rs145946881	Widely studied and validated
−14009:T > G **	rs869051967	Widely studied and validated
−13915:T > G **	rs41380347	Widely studied and validated
−13910:C > T **	rs4988235	Widely studied and validated
−13907:C > G **	rs41525747	Widely studied and validated
−22.018:G > A	rs182549	In complete LD with the causal −14010:G > C
−14011:C > T *	rs4988233	
−13906:T > A		
−13779:G > C *	rs527991977	
−13744:C > G		
−13730:T > G	rs4954492	
−13603:C > T	rs56348046	
−13495:C > T	rs4954490	
−13914:G > A		Rare variant (q < 5%)
−14062:G > A		Rare variant (q < 5%)
−14028:T > C	rs759157971	Rare variant (q < 5%)
−13753:C > T		Rare variant (q < 5%)
−13693:G > A		Rare variant (q < 5%)
−13806:A > G	ss820496565	Rare variant (q < 5%)
−13964:C > A		Rare variant (q < 5%)
−13771:A > G		Rare variant (q < 5%)
−14010 G > A	rs145946881	Rare variant (q < 5%)
−13926 A > C		Rare variant (q < 5%)

q refers to general population frequency. LD, linkage disequilibrium.

the *LCT* gene and sustained lactase production into adulthood (Troelsen et al. 2003). Currently, there is good functional evidence that the LP trait has a genetic basis and follows a dominant pattern of inheritance, which means that both heterozygous and homozygous genotypes for the minor allele of these SNPs confer the trait. To date, 24 different SNPs have been associated with LP in different populations with varying frequencies across the world (Table 2) (Enattah et al. 2008; Itan et al. 2010; Liebert et al. 2017; Troelsen et al. 2003). These genetic variations follow a dominant inheritance pattern and are distributed among diverse populations, facilitating the ongoing digestion of lactose and allowing individuals to benefit from dairy consumption throughout their lives.

The distribution of LP and LNP phenotypes varies widely among human populations and is primarily influenced by the prevalence of LP genetic variants. This variation has been well-documentedd in several studies, including those conducted by Itan et al. (2010) and Storhaug, Fosse, and Fadnes (2017). Additionally, an umbrella review compiling and updating all frequency data available until 2020 was published by Anguita-Ruiz, Aguilera, and Gil (2020). In this review, the authors constructed online world maps that allow interactive exploration of LP phenotypic and genetic frequencies worldwide (http://bionit.ugr.es/pages/investigacion/software/bioinformatics-methods-software).

Health benefits of lactose

Lactose: not a simple carbohydrate

Lactose is the major carbohydrate source of energy for lactating mammals. Lactose exists evolutionarily in nearly all kinds of milk produced by mammals, although at variable concentrations depending on the species. Milk from primates and some ruminants has the highest lactose concentrations (ranging from approximately 50 to 70 g ~ liter) (Newburg and Neubauer 1995). Compared to other mammals, human milk contains approximately 68–76 g/L of lactose, which provides approximately 40% of the needed energy (Brockway et al. 2024; Troelsen 2005), whereas cow's milk contains only approximately 4.7 g/L of lactose, which provides only 30% of the needed energy (Crittenden and Bennett 2005). Although glucose can be found in several types of foods, lactose is the only significant source of dietary galactose.

Is lactose a potential prebiotic?

Two major requirements need to be fulfilled to consider lactose as a prebiotic carbohydrate: (a) a fraction of lactose should resist small intestinal hydrolysis by lactase, and (b) lactose should represent a "*substrate that is selectively utilized by host microorganisms, conferring a health benefit*" (Gibson et al. 2017).

Prebiotics need to be only partially digested to become available as a substrate for gut microbiota metabolism (Fara et al. 2023; Ferreira-Lazarte et al. 2017). As mentioned earlier, lactose is hydrolyzed by lactase in the small intestine, allowing the absorption of glucose and galactose. However, physiologically, a fraction of lactose escapes intestinal hydrolysis, an event that is dependent primarily on the total lactase enzymatic activity of the subject. Additional factors that reduce lactase activity are related to the presence of intestinal disorders such as infection or inflammation and antibiotic use and are in most cases transitory, resolving upon resolution of these underlying factors. Other factors that should be taken into account when considering lactose digestion are related to the amount of lactose ingested and to the slow hydrolysis and adsorption of lactose into its components (Shkembi and Huppertz 2023), which supports the hypothesis that a fraction of lactose could also escape hydrolysis in healthy people with LP. A quantity of lactose exceeding the lactase enzymatic activity of the intestinal brush border would equal the amount of indigested and unabsorbed lactose that is transported intact through the alimentary canal and may become available for bacterial metabolism mainly in the terminal ileum and colon where the bulk of the gut microbiota reside. In an *in vivo* study carried out in infants with cow's milk protein allergy, the microbiome response to lactose in combination with the diet confirmed that lactose is not completely hydrolyzed in the small intestine (Francavilla et al. 2012). Finally, additional factors involved in lactose digestion include the timing and frequency of lactose intake throughout the day, the ingestion of other foods at the same time, the composition of the intestinal microbiome and the gut – transit time, which should allow the contact of lactose with intestinal lactase and hence its hydrolysis.

Lactose escaping small intestinal hydrolysis can be selectively metabolized by the resident microbiota both in the terminal ileum (Barbara et al. 2016) and in the proximal colon (Forsgård 2019). This activity is dependent upon the presence and metabolism of certain microbial groups (e.g., lactic acid bacteria) that possess β-galactosidase activity. The

ileal microbiota preferentially metabolizes mono- and disaccharides, making lactose a substrate that can contribute to the growth and maintenance of microbiota diversity (total cell counts of approximately 10^9 cfu/g) in the human small intestine (Barbara et al. 2016).

Studies carried out both *in vitro* and *in vivo* in humans have shown that the selective use of lactose in the colon is correlated with the fecal bacterial composition. A recent *in vitro* study (Firrman et al. 2022) of fecal samples harvested from 18 donors and cultured anaerobically with and without lactose indicated that lactose was able to alter the structure of the microbiota by promoting the growth of a few selected taxa expressing the β-galactosidase gene. In addition, lactose contributed to a decrease in *Bacteroidetes* richness, mainly in *Bacteroides,* an event likely related to a reduction in microenvironment pH. In addition, lactose may also contribute to promoting cooperation between lactic acid bacteria (LAB) taxa, lactate utilizers and *Bifidobacterium*. This effect may extend beyond the colon to the small intestine, as the families *Lactobacillaceae, Streptococcaceae, Veillonellaceae*, *Enterococcaceae*, and *Bifidobacteriaceae* are common members of the small intestine gut microbiota as well as the colon.

In an intervention study of 31 lactose malabsorbers and 31 lactose absorbers (Li et al. 2018), the supplementation of 250 mL/d of whole milk for four weeks in the diet selectively altered the gut microbiota composition, significantly increasing the relative abundance of *Bifidobacterium* in those with LNP. The results of the study also indicated that the alterations differed across different enterotypes, without significant effects on the overall microbiota richness or diversity.

Recent metagenomic studies using fecal samples from adults highlighted that the abundance of *Bifidobacterium* was dependent on the interaction between genotype and intake of dairy products, providing evidence of the positive correlation between lactose and the presence of *Bifidobacterium* (Bonder et al. 2016; Kurilshikov et al. 2021).

A recent review showed that prolonged lactose intake could reduce the intensity and the frequency of gastrointestinal (GI) symptoms in lactose malabsorbers (JanssenDuijghuijsen et al. 2024). This could be linked to the phenomenon called "colonic adaptation" for which lactose feeding allows the growth of lactose-digesting bacteria and the induction of the bacterial β-galactosidase resulting in the production of metabolites such as lactate, short-chain fatty acids (SCFAs) and the gases H_2, CO_2, and CH_4 (Forsgård 2019). Among these bacteria, lactose could support a specific increase in bifidobacteria and fermenting lactose without gas production could contribute to reduce GI symptoms (Francavilla et al. 2012; JanssenDuijghuijsen et al. 2024). Therefore, colonic adaptation could explain the tolerance of lactose in lactase-deficient individuals, although the debate on this topic is still open. The above mentioned *in vitro* study (Firrman et al. 2022) showed that lactose was converted mainly into lactate and acetate in a so-called mixed fermentation. An increase in butyrate was not observed, probably due to the lower pH that was created. Interestingly, in fecal samples without the addition of lactose, the levels of branched-chain SCFAs (BCSCFAs), which are derived from amino acid fermentation, were significantly increased. This allowed the authors to speculate that lactose, which provides an additional carbon source, especially in those with LNP, could contribute to maintaining the balance between carbohydrate and protein metabolism in favor of carbohydrates (Firrman et al. 2022), suggesting that this may result in a beneficial effect (Barbara et al. 2016).

The metabolites resulting from lactose fermentation can have effects on gastrointestinal (GI) functions: SCFAs are known to have beneficial effects on GI physiology (e.g., intestinal transit, the epithelial barrier, enteric nervous system signaling and immune system stimulation). In addition, SCFAs can be utilized by other microbes, thus regulating microbial quorum sensing (Tan et al. 2014). In addition to local effects in the colon, SCFAs have recently been suggested to modulate the complex interactions between the gut and the brain, so-called gut-brain interactions.

Accordingly, through the interactions with G protein-coupled receptors and/or histone deacetylases, SCFAs can influence psychological functioning; via direct humoral effects, indirect hormonal and immune pathways and neural routes, SCFAs can exert their effects on the brain (Dalile et al. 2019).

Taken together, these data support the concept that lactose could be considered a potential prebiotic with beneficial effects on the host. On the other hand, in LNP individuals, excessive lactose malabsorption can lead to GI symptoms, including abdominal discomfort due to excessive intestinal osmotic effects and fermentation of lactose by resident microbiota in the lower GI tract (Forsgård 2019). In this respect, it should be noted that GI symptoms are mainly secondary to individual sensitivity, making subjects sensitive to different doses, even a very small amount (Catanzaro, Sciuto, and Marotta 2021). Symptoms occur both when lactose exceeds the capacity of the colonic microbiota for fermentation and when the SCFA load exceeds the colon capacity for reabsorption, considering that lactose fermentation to SCFAs causes an eightfold increase in osmotic load (Misselwitz et al. 2019). Indeed, in sensitive individuals, lactose is part of the family of fermentable oligo-, di-, monosaccharides and polyols, the so-called FODMAPs, which may induce symptoms due to a reduced individual capability to metabolize these carbohydrates in the small intestine, particularly in the presence of changes in the intestinal microbiota (i.e., intestinal dysbiosis). Individuals with irritable bowel syndrome (IBS) may benefit from a low FODMAP diet (Sanz Morales et al. 2022), although such restrictive diets over time can lead to a potential deficiency of nutrients, particularly calcium and iron, and decrease microbiota diversity with a reduction in beneficial bacterial groups such as lactobacilli, bifidobacteria and *Fecalibacterium prausnitzii*. For this reason, the importance of the gradual reintroduction of tolerated FODMAPS to arrive at a personalized low-FODMAP diet, thus preventing nutritional deficiencies, should be emphasized (Sanz Morales et al. 2022). In this regard, the role of lactose could be useful since it supports the growth of bifidobacteria that ferment lactose without gas production. In brief, the discussion about lactose as a prebiotic remains open even if the evidence that lactose may be selectively utilized by host microorganisms to confer health benefits is growing.

Glycemic index and satiety

A significant body of research has demonstrated the satiating effects of dairy foods. To date, the magnitude of the appetite-suppressing effect is dependent on the overall quantity of dairy foods consumed (Onvani et al. 2017). While the satiating effects of milk have largely been attributed to its protein content (Gilbert et al. 2011), some studies have also identified lactose as a potential contributor (Corney et al. 2023; Dougkas et al. 2012). One mechanism by which lactose may exert a positive impact on satiety is due to its low glycemic index (GI). Compared to most other sugars (except fructose), lactose has a particularly low GI of 46, as outlined in Table 3 (Foster-Powell, Holt, and Brand-Miller 2002). Additionally, the monosaccharide galactose is more slowly absorbed than glucose. This has been demonstrated in research in recreationally active females who consumed a galactose-containing beverage (45 g galactose), which resulted in lower postprandial glycemia and insulinemia than a glucose-containing beverage (45 g glucose) (Duckworth, Backhouse, and Stevenson 2013). In comparison to glucose ingestion, galactose ingestion has also been shown to significantly suppress hunger and reduce energy intake over a subsequent 24-h period (Duckworth et al. 2016).

A second mechanism by which lactose may assist in regulating satiety is through the regulation of "the hunger hormone" ghrelin, an orexigenic hormone known to act as a key regulator of food intake and appetite (Pradhan, Samson, and Sun 2013). Bowen et al. showed that when a group of healthy men were fed 56 g (1025 kJ) of preloaded lactose or glucose, 3 h later energy intake was 11% lower ($p < .05$) in the lactose-consuming group than in the glucose-consuming group (Bowen et al. 2006). Furthermore, overall appetite ratings were significantly greater ($p < .05$) after the glucose preload than after the lactose preload (Bowen et al. 2006). The authors suggested that the variable satiety responses observed after consumption of glucose and lactose may be related to ghrelin, since both ghrelin levels and appetite ratings remained suppressed longer after the lactose preload than after the glucose preload (Bowen et al. 2006). Taken together, these data showed that, due to its low GI and its potential satiating role through ghrelin, lactose is more beneficial to health than other sugars.

Improving bone health through increased calcium absorption

Along with calcium in milk, lactose has been studied both *in vitro* and *in vivo* as a potential stimulator of calcium absorption, therefore reducing bone fragility or fracture risk.

Table 3. Glycemic index (GI) values of common sugars[a].

Sugar	GI Value
Glucose (reference)	100
Lactose[b]	46–65
Fructose	19
Sucrose	68
Maltose	105

[a]Adapted from (Foster-Powell, Holt, and Brand-Miller 2002).
[b]The range is given by Björck, Liljeberg, and Ostman (2000).

The hydrolysis of lactose to the monosaccharides glucose and galactose, and the concomitant production of organic acids, reduces the pH in the GI tract, thereby enhancing the transport and absorption of calcium ions as calcium gluconate in the intestinal tract (Ilesanmi-Oyelere and Kruger 2020). In 1970 it was first described that controlled intake of a 60 g lactose supplement per day in healthy lactose-tolerant volunteers resulted in higher calcium and phosphorus balances than in lactose-intolerant subjects (Condon et al. 1970). Furthermore, lactose malabsorption and/or intolerance have been linked to a greater risk of bone loss and fractures, which could be attributed to decreased dairy intake (Obermayer-Pietsch et al. 2004). According to the available evidence, neither dietary lactose nor lactase deficiency has a significant impact on calcium absorption in healthy adult humans (Hodges et al. 2019; Smith et al. 1985; Tremaine et al. 1986). Although the presence of lactose can stimulate calcium absorption in animals (Weaver et al. 2011) and infants (Abrams, Griffin, and Davila 2002), this effect has not been confirmed in adult humans (Brink et al. 1993; Zittermann et al. 2000). Similarly, using a calcium isotope, no relationship was found between lactose intake (regardless the milk source) and calcium absorption in postmenopausal women, regardless of lactose malabsorption status (Horowitz et al. 1987). Obermayer-Pietsch et al. (2004) found that calcium intake in LNP postmenopausal women was 55% lower than in their LP counterparts, likely due to the aversion to milk commonly developed by LNP individuals. Subsequently, Obermayer-Pietsch et al. (2007) also demonstrated that LNP not only reduces calcium intake but also impairs calcium absorption in the presence of high lactose concentrations. These findings suggest that lactose's role in calcium absorption is multifaceted, influenced by factors such as the food source or dosage of lactose, genetics and epigenetic mechanisms regulating lactase activity, and even the aging process. While there is no evidence supporting a lactose-enhancing effect on calcium absorption in lactose-tolerant adults, it is clear that lactose can affect calcium absorption in lactase-deficient individuals. Conversely, in infants, lactose markedly enhances calcium absorption, emphasizing the critical roles of age and lactase activity in mediating lactose's effects.

Lactose – the least cariogenic sugar

As reflected in the WHO guidelines, not all sugars affect the development of dental caries equally (WHO 2022). According to the available evidence, sucrose is the most cariogenic of all sugars, while lactose and galactose are far less cariogenic (Schaafsma 2008; Shi et al. 2020). The cariogenic effect of sucrose is attributed to the fact that it can be readily fermented, induces a low pH environment in the oral cavity and causes oral plaque bacteria to be more cariogenic (Shi et al. 2020). Consequently, high and frequent consumption of sugar-sweetened beverages, which are commonly formulated with added sugars such as sucrose, is associated with an increased risk of dental caries and erosion (Valenzuela et al. 2021) and the reduced intake of these beverages is the focus of public health strategies and campaigns around the world.

The cariogenicity of lactose has been researched since the 1940s in animal models; however, inconsistencies in study designs have made these initial studies difficult to interpret (Aimutis 2012). Later studies in a well-defined rat model demonstrated that the ingestion of lactose solutions *ad libitum* led to fewer dental caries than did drinking sucrose or fructose solutions (Aimutis 2012; Bowen et al. 2006).

In 1976, the cariogenicity of lactose was tested in humans using an intraoral cariogenicity test. Lactose, sorbitol, mannitol and melibiose were demonstrated to be significantly less cariogenic than sucrose (Koulourides et al. 1976).

The majority of studies assessing the cariogenicity of sugars have focused solely on a single bacterial species (in most cases, *S. mutans*) (Shi et al. 2020). More recently, other bacteria, including *Prevotella* spp., *Lactobacillus* spp., *Dialister* spp., *Filifactor* spp., *Streptococcus*, *Porphyromonas*, *Actinomyces* and *Scardovia wiggsiae* have also been shown to be associated with caries development (Shi et al. 2020). The responses of these bacteria to sucrose and lactose intake have been explored in a recent study in 3- to 5-year-old children with and without caries (Shi et al. 2020). Plaques were sampled from the oral cavity and the response to lactose and sucrose was measured. Distinct patterns of microbial response to lactose and sucrose were identified, suggesting that lactose has a relatively smaller impact on the microbial community than does sucrose. This recent work supports earlier animal studies and intraoral tests, consistently demonstrating lactose's lower cariogenicity, particularly in comparison to sucrose (Shi et al. 2020).

One mechanism that may be responsible for the lower cariogenicity of lactose is its lower acidogenic potential (Woodward and Rugg-Gunn 2020). While the fermentation of sucrose leads to high acid production and the resulting lower pH creates an environment conducive to caries development, lactose consumption results in slower and lower acid production and a higher pH in the oral cavity (Schaafsma 2008). Johansson reported that sucrose reduced the pH below 5.0, a level below the critical pH level of 5.5, which creates a cariogenic environment, while lactose reduced it to approximately 6.0 (Johansson 2002).

This property of lactose has also been demonstrated in an *in vitro* model by Dashper and colleagues, who measured acid production by *S. mutans* in response to soy and dairy milk beverages at a constant pH of 5.5 or 6.5, as well as the change in pH in response to their consumption (Dashper et al. 2012). They showed that the rate of acid production by *S. mutans* in milk beverages was five to six times lower at pH 6.5 than that in soy beverages and three to five times lower at pH 5.5, demonstrating the lower potential acidogenicity of dairy milk than of soy milk. Furthermore, the pH decrease in the presence of *S. mutans* over 10 min was negligible in the milk beverages, but a significant decrease in pH occurred in the soy beverages (Dashper et al. 2012). While lactose has consistently been shown to be the least cariogenic sugar, other aspects of milk and dairy products may also contribute to its cariostatic nature, protecting against caries development (Woodward and Rugg-Gunn 2020). A summary of the key components in milk and dairy products linked to dental health can be found in Table 4.

Table 4. The impact of milk/dairy components on dental health[a].

Milk/Dairy Components	Dental Health Effect
Lactose	Limited cariogenicity
Calcium	Protective
Phosphorus	Protective
Casein	Protective
Lactoferrin, lysozyme and lactoperoxidase	Protective

[a]Adapted from: (Shkembi and Huppertz 2023).

Lactose and sports performance

The important role of carbohydrates in sports performance before, during and after exercise is well established (Odell, Podlogar, and Wallis 2020). However, the amount (low *vs* high-carbohydrate diet), timing and types of carbohydrates are still under debate (Aragon et al. 2017). The ingestion of adequate carbohydrates before endurance exercise is recommended as a strategy for increasing carbohydrate storage; however, a lack of evidence prohibits specific guidance on whether the types of carbohydrates ingested at this time impact the effectiveness of preexercise fueling differently (Podlogar and Wallis 2022). It has been suggested that lactose has a similar oxidation rate to glucose and could therefore be used as a preexercise fuel (Stellaard et al. 2000). In addition to carbohydrate intake before exercise, the consumption of readily oxidized carbohydrates during exercise is recommended to optimize performance in bouts of exercise lasting more than 45 min (Burke et al. 2011; Thomas, Erdman, and Burke 2016). While glucose, glucose polymers and glucose-fructose mixtures are specifically recommended (Burke et al. 2011; Thomas, Erdman, and Burke 2016), recent evidence has demonstrated that lactose ingested at moderate amounts (48 g per hour) can be as readily oxidized as sucrose while sparing endogenous carbohydrates and increasing fat oxidation (Odell, Podlogar, and Wallis 2020). Finally, lactose may also be a vehicle for delivering glucose and galactose in postexercise recovery for the restoration of glycogen stores (Odell, Podlogar, and Wallis 2020). Moreover, dietary galactose has been shown to increase postexercise liver glycogen resynthesis (Odell and Wallis 2021). Although lactose intake is still seldom included in current sports nutrition guidelines, it is becoming increasingly apparent that this carbohydrate could have a beneficial impact on the diets of athletes and recreationally active individuals.

Dairy consumption and estimation of lactose consumption around the world

The leverage of all these beneficial properties of lactose by humans is, nonetheless, inherently dependent on its intake from dairy products, especially animal milk, and its later proper digestion. Over the past 50 years, the global landscape of lactose intake has undergone considerable evolution, with marked disparities emerging between regions. For the next decade, dairy consumption is expected to increase by 1.2% per annum at the global level, and as a result, lactose consumption will also increase (OECD-FAO 2023). This anticipated increase is mostly attributable to population growth and per capita income growth in developing countries; however,

many other intersecting factors impact consumption trends (OECD-FAO 2023; Rogers 2024). The distribution of LP/LNP phenotypes worldwide, age, sex, socioeconomic status, sociocultural factors, availability/accessibility, and country of residence, all significantly impact daily intake (Auclair, Han, and Burgos 2019; Dror and Allen 2014; OECD-FAO 2023; Oliveira and Canella 2022; Singh et al. 2015; Wang and Li 2008). For instance, individuals in wealthier countries were found to consume significantly greater volumes of milk, ranging from 0.72 servings/day in high-income countries to 0.30 servings/day in low-income countries (Singh et al. 2015). Figure 2 shows the average per capita trends in milk consumption from 1961 to 2020 at the continental level, which can be used as an indicator of lactose intake at the global level. Figure 3 depicts a recent snapshot (2020) of the highest and lowest average per capita milk consumption within each continent and, where available, the average LP phenotype for these countries.

North America

In North America, dairy consumption is relatively high in comparison to other regions, specifically Asia and South America, and represents one of the largest percentages of total cheese consumption in the world (OECD-FAO 2023). Of note, it's important to consider that cheese intake cannot be directly compared to milk consumption (e.g., hard cheeses contain minimal amounts of lactose). Despite the relatively high dairy consumption of north America in comparison to other regions, recent trends show decreases in total dairy consumption since the mid-to-late-1900s, specifically in milk intake (Auclair, Han, and Burgos 2019; Dror and Allen 2014; Bach 2008; Islam, Shafiee, and Vatanparast 2021; OECD-FAO 2023; Sikorski et al. 2023; Stewart and Kuchler 2022; Wang and Li 2008). For instance, the percentage of Canadians consuming milk decreased from 70.2% to 56.1% from 2004 to 2015 (Islam, Shafiee, and Vatanparast 2021). This steady decrease in milk intake was offset by an increase in the intake of other dairy products such as cheese and yogurt; however, by 2019 a decreasing trend in total dairy consumption was evident (Stewart and Kuchler 2022). In Mexico and Central America, per capita milk and milk product intake have increased since the 1960s with relative changes of approximately +50% occurring at 94 kg/year/capita and 86 kg/year/capita milk consumption in 2020, respectively (Our World in Data 2020). Moreover, in the United States and Mexico, LP is estimated to be present in approximately 48% and 52% of individuals, respectively (Figure 3); however, a high degree of variance has been reported in Americans based on ethnicity; high prevalence in white Americans of European or Scandinavian descent (83%–93%) but is much lower among Mexicans from rural areas (approximately 30%) and African Americans (12%–40%) (Anguita-Ruiz, Aguilera, and Gil 2020). Interestingly, lactose intolerance is estimated to affect only approximately 13% of the American population, whereas in Canada it impacts approximately 16% of the population; however, lactose intolerance varies widely among individuals and may be greater or less common depending on ethnicity, age, and dietary habits (Canadian Digestive Health Foundation 2023; Keith et al. 2011). As a result, many Americans and Canadians opt to limit dairy consumption or choose lactose-free products, thus impacting national lactose consumption trends (Canadian Digestive Health Foundation 2023; Keith et al. 2011). In the United States, the average person is estimated to consume approximately 17 grams of lactose/day, which roughly equates to the amount of lactose found in between 1.25 and 1.5 cups of milk (Canadian Digestive Health Foundation 2023).

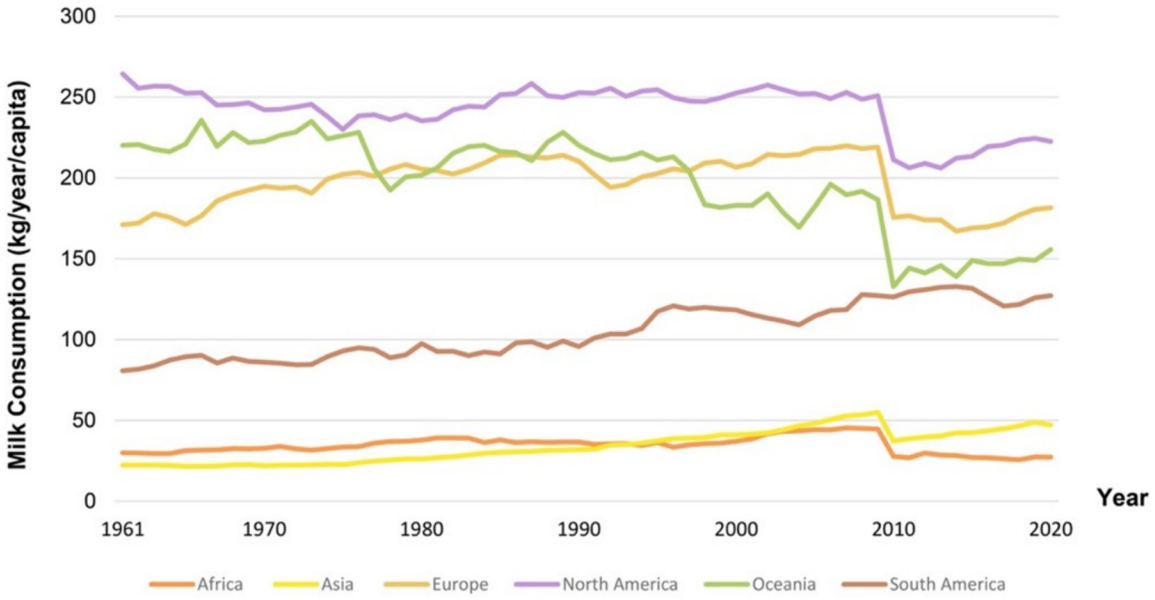

Figure 2. Global per capita milk consumption at the continent level. Milk consumption data include milk and milk products (dairy products made from milk) but exclude butter. The data are based on per capita food supply at the consumer level; however, the data do not account for food waste at the consumer level. Figure developed by the Vatanparast Nutritional Epidemiology Laboratory, based on food supply data obtained from the Food and Agriculture Organization of the United Nations (Our World in Data, 2023).

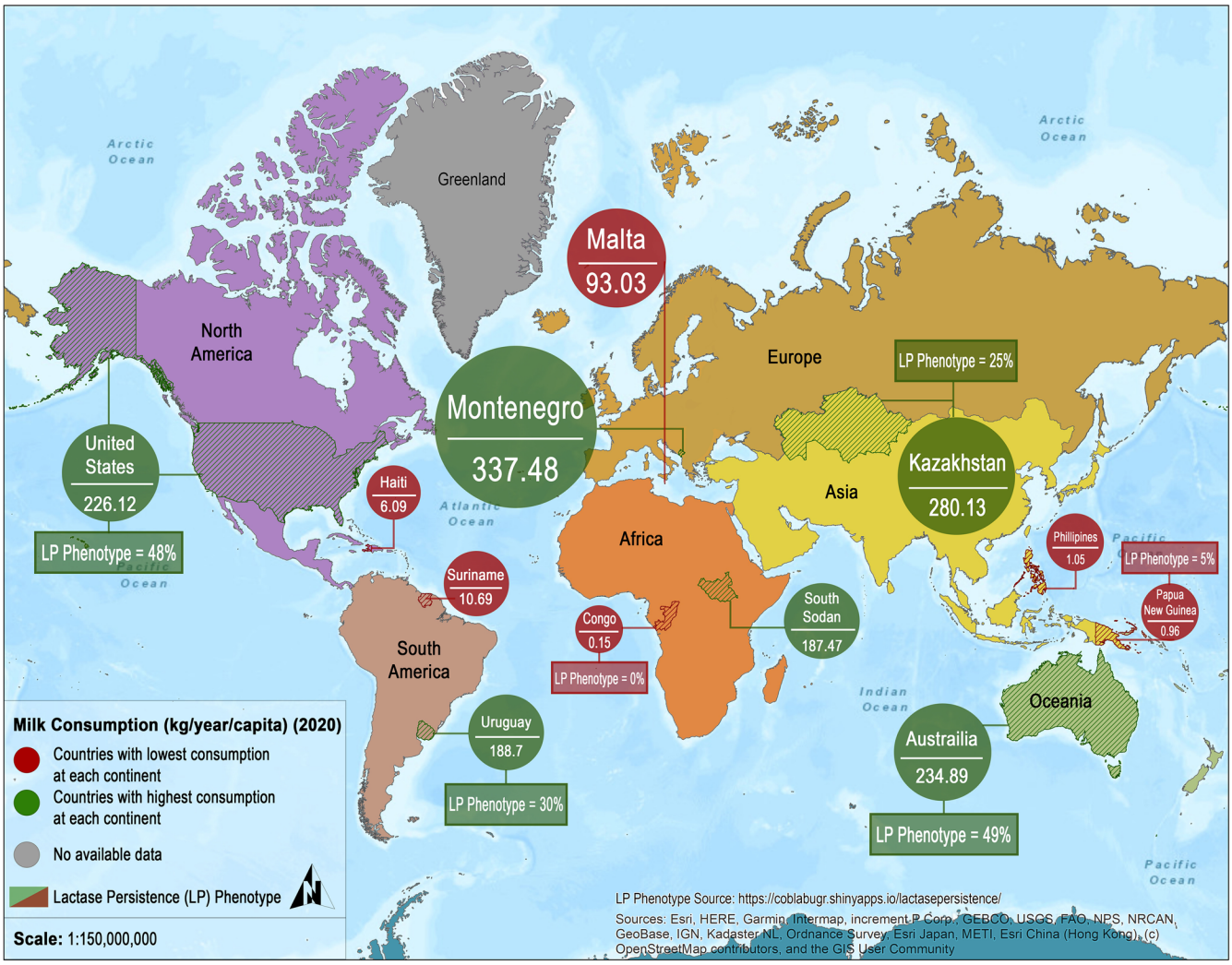

Figure 3. Geographical information system mapping of the highest and lowest average per capita milk consumption at the continent level. Milk consumption data include milk and milk products (dairy products made from milk) but exclude butter. The data are based on per capita food supply at the consumer level; however, the data do not account for food waste at the consumer level. Figure developed by the Vatanparast Nutritional Epidemiology Laboratory, based on food supply data obtained from the Food and Agriculture Organization of the United Nations (Our World in Data, 2023).

Europe

In Europe, daily dairy consumption is also generally high, contributing to one of the highest global prevalences of total cheese consumption (OECD-FAO 2023). However, the overall per capita demand for dairy products has begun to decrease and dairy products with a higher fat content have transitioned over the last several years (OECD-FAO 2023). Evidently, within the European Union, many countries have different sociocultural landscapes and influences on local dairy industries, resulting in a wide range of dairy consumption trends. For instance, from 1950 to 2019, dairy intake significantly decreased in Northern Europe (by 42 g/d/decade), significantly increased in Western Europe (by 27 g/d/decade), and was unchanged in the United Kingdom (Sikorski et al. 2023). A 2002 cohort study based on 10 European countries revealed Italy (with a LP prevalence of 30%) to have the lowest total dairy consumption (150–160 g/d) and Sweden and Spain to have the highest total dairy consumption (approx. 480 g/d) (Hjartåker et al. 2002). Among all dairy products, milk was consistently consumed in the highest proportion across all countries, ranging from 74% to 83% of total dairy intake in Spain to only 34%–39% in France (Hjartåker et al. 2002). The high consumption of dairy products in European countries could be attributed to the fact that approximately 95% of modern Europeans, most notably in Northern Europe, possess the LP allele, but it could be also influenced by other socioeconomic and sociocultural factors, including economic stability and milk industry availability/accessibility (Anguita-Ruiz, Aguilera, and Gil 2020; Evershed et al. 2022; Wilkin 2022).

Asia

Due to the large populations of many Asian countries, the Asian continent is the region with the highest consumption of dairy products globally; however, when accounting for population density, the per capita consumption level is among the lowest (Our World in Data 2020; Ava 2014). Most Asian countries have low LP rates (e.g., 0% in South Korea, Vietnam, Cambodia, and 15% in China), which impacts dairy consumption patterns and drives demand for

lower lactose and lactose-free products. For example, the Philippines, Laos, North Korea, and Cambodia rank among the 15 lowest countries for per year per capita milk and milk product consumption. Despite this, Kazakhstan and Uzbekistan rank among the world's top ten countries (Figure 3) (Our World in Data 2020). Historically, from 1950 to 2019, dairy intake increased in East Asia and Southeast Asia by 18.8 and 13.3 g/d/decade, respectively; conversely, in the Middle East, dairy intake decreased by 18.8 g/d/decade (Sikorski et al. 2023). Dairy consumption rates are projected to increase in Asia and the Middle East due to continued population and economic growth, among other factors (Ava 2014; Rogers 2024). However, due to the very low levels of LP in those from Asian countries (e.g., 0% in South Korea, Vietnam, Cambodia, and 15% in China), the market for lower lactose and lactose-free products is also expected to expand (Anguita-Ruiz, Aguilera, and Gil 2020; Ava 2014).

South America

Dairy consumption in South America varies considerably by country, with the per capita supply of milk and milk products in 2020 as low as 11 kg/year/capita in Suriname to as high as 189 kg/year/capita in Uruguay with an estimated 72% of the population (2009) consuming dairy (Ares and Gámbaro 2008; Our World in Data 2020). Argentina and Brazil follow closely behind Uruguay, as they are the top dairy consumers in South America, with approximately 162 and 151 kg/year/capita supplies of milk and milk products, respectively (Our World in Data 2020). However, the Brazilian Household Budget Survey (2002–2018) revealed decreasing trends in the per capita purchase of milk and yogurt that correlated with household income, with wealthier households purchasing more dairy products (Oliveira and Canella 2022). Furthermore, the 2008–2009 Brazilian National Dietary Survey, revealed that only 12.4% and 13.5% of the population consumed milk and cheese, respectively, emphasizing the impact of other factors, such as income, on the purchase and consumption patterns of dairy (Souza et al. 2013). Relatively low frequencies of the LP allele are also common among South American populations (i.e., 6% in Peru, 20% in Colombia, 30% in Uruguay, and 37% in Brazil), specifically indigenous populations (i.e., 10% among the Mestizo peoples inhabiting Chile) (Anguita-Ruiz, Aguilera, and Gil 2020).

Africa

Comprehensive data on dairy consumption patterns within the African continent are lacking. However, data on the per capita supply of milk and milk products at the consumer level show a generally low intake of milk and milk products since 1961 with a gradual continental spike in 2009, followed by an eventual decline in 2020 (Figure 2) (Our World in Data 2020). The majority of African countries have a low consumption of milk globally; for example, the Democratic Republic of Congo, Congo, Nigeria, Cote d'Ivoire, Togo, Ghana, and Liberia are among the ten countries with the lowest per year per capita milk consumption (Our World in Data 2020). LP in the African continent varies drastically, for example, compared with those in nonpastoralist groups, the LP alleles of the nomadic and pastoralist communities in Africa, specifically the Maasai, Fula, and Beja populations, are more prevalent (70–88%) compared to non-pastoralist groups (Anguita-Ruiz, Aguilera, and Gil 2020; Bleasdale et al. 2021). Recent research has linked LP among African pastoralist communities in Kenya and Sudan to a history of dairying, and it has been postulated that early consumption of dairy has a role in driving selection for LP either due to the nutritional benefits of dairy consumption in arid environments or to withstand famine, similar to the mechanisms in European populations, although causal relationships have not been confirmed (Bleasdale et al. 2021). Total dairy consumption is expected to increase in Africa over the next couple of decades (OECD-FAO 2023).

Oceania

Oceania ranks third in terms of the highest per capita milk consumption among all continents (2020), although this is largely due to Australia's high milk intake, as the remaining countries in Oceania have relatively low milk consumption (Figures 2 and 3) (Our World in Data 2020). In Australia, the per capita consumption of milk has remained relatively consistent from 1985 to 2010, however, the consumption of cheese and yogurt has increased (Doidge and Segal 2012). Moreover, in 1995, 55% of Australian males and 71% of females consumed less than two servings of dairy per day, which at the time meant that the majority of the population did not meet the national recommendation for two servings of dairy/day (Doidge and Segal 2012). Like in other low dairy-consuming regions in Africa, several populations in Oceania have a low frequency of LP; however, Australia and New Zealand have higher frequencies at 40%–50% and 50%–60%, respectively (Anguita-Ruiz, Aguilera, and Gil 2020). The LP phenotype is considerably low at 5% in Papua New Guinea, a country with low milk consumption, whereas the LP phenotype in Australia, a country with higher milk consumption, is relatively high at 49% (Figure 3).

Milk consumption patterns worldwide are complex and heterogeneous, influenced by various factors such as sociocultural norms, economic development, and genetic predispositions, which vary across geographical regions. While milk consumption is projected to increase globally over the next decade, as depicted in Figure 2, it is important to note the sharp decline in average per capita milk consumption around 2010 at the global level. Although some reports, such as those from the Economic Research Service (ERS) of the U.S. Department of Agriculture, have acknowledged this trend, the specific drivers behind this rapid decline remain unclear and require further investigation. One possible explanation is the rise of plant-based milk alternatives, such as almond, soy, cashew, and rice-based products, which have gained significant popularity. Between 2013 and 2017, sales of plant-based milk alternatives in the U.S. increased by 36%, while cow's milk

purchases declined by 12%. Despite this shift, cow's milk remained a staple in 92% of households in 2017, suggesting that plant-based options are replacing cow's milk at an estimated one-to-one rate. However, since the increase in plant-based milk sales accounts for only one-fifth of the decline in cow's milk purchases, it is unlikely to be the primary cause of the overall trend. Also, our recent study using Canadian data from 2004 to 2015 revealed a significant decrease in plain milk consumption, dropping from 70.2% to 56.1%, while plant-based milk consumption increased modestly from 1.8% to 3.0% (Islam, Shafiee, and Vatanparast 2021). This highlights the need to explore multiple contributing factors to fully understand the global decline in milk consumption.

Conclusions and future research trends

Lactose has been criticized due to the GI symptoms associated with its consumption in patients suffering from lactose intolerance. However, the development of GI symptoms due to lactose intolerance occurs in a small proportion of the adult population, with a high percentage of individuals able to properly digest moderate amounts of lactose and benefit from its multiple effects on health. Apart from its main role as energy source, lactose has multiple additional beneficial effects on human health. Several of these effects have been extensively studied and documented in a multitude of *in vitro* and *in vivo* studies. In the present review, we address its role as a potential prebiotic and immunomodulatory molecule, its influence on calcium absorption and satiety, and its low cariogenic potential. Dairy consumption in general, and lactose intake in particular, is a critical factor limiting these potential health benefits of lactose for human populations. These trends are influenced by a variety of factors, including the distribution of the LP traits, age, sex, socioeconomic status, cultural practices, and geographical factors such as availability and accessibility. In this regard, a promising area of research involves evaluating epigenetic and environmental factors that influence lactase expression beyond genetic predisposition, which might ultimately affect consumption trends as well. In this review, we also explore the current trends in daily dairy consumption across different continents, a topic that has not been extensively reviewed before. Our review highlights that over the next decade, global dairy consumption is expected to increase by approximately 1.2% per year, which will consequently lead to a rise in lactose intake. However, certain regions, such as Asia, still have relatively low dairy consumption, which may limit the potential health benefits of lactose for these populations. This highlights a critical opportunity for stakeholders to implement targeted interventions and strategies to enhance dairy consumption in these areas.

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Abbreviations

Cdx-2 caudal type homeobox 2
GALK galactokinase
GALT galactose 1-phosphate uridylyl-transferase
GALE UDP-galactose 4-epimerase
GATA Family of zinc finger transcription factors, important regulators of cell lineage differentiation during vertebrate development
HNF1-α hepatocyte nuclear factor 1α
LCT lactose gene
MCM6 minichromosome maintenance complex component 6 gene
meQTLs methylation quantitative trait loci
LNP lactase nonpersistence
LP lactase persistence
LPH lactase-phlorizin hydrolase
SNPs single nucleotide polymorphisms
UGPP UDP-glucose pyrophosphorylase; also termed UTP-glucose-1-phosphate uridylyltransferase

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