be generated in a programmable manner, from regular tilings of triangles, cubes and hexagons to mosaic-like tessellations involving combinations of shapes (Fig. 1b). The fact that such complex patterns could be formed on the basis of a simple logic suggests that there might have been a low threshold for the evolution of single cells into multicellular systems.

Kim *et al*. developed a mathematical model to simulate the interface formed between four strains that were initially spatially localized, allowing the authors to examine how seeding conditions affected the geometry of this interface. For example, they looked at how changing the binding affinity of the nanobody–antigen pair affected the width of the interface, and how different bacterial growth rates changed the interface's curvature.

The boundaries separated different cell types that had distinct biophysical properties, and that behaved in different ways. Kim *et al*. showed that these differences affected the wettability of the areas delineated by the boundaries. Likewise, the formation of interfaces could be controlled by introducing adhesion-inhibiting molecules into the medium. This mechanism allowed the colonies to be engineered into letters forming legible words, for instance.

The study is an elegant demonstration that a small number of adhesins suffices to organize cell collectives within well-defined boundaries at the macroscopic scale. The team's four-bit logic could be used to engineer synthetic tissues from single cells, or to develop zones with distinct biophysical properties in cell-based biomaterials. The approach could even form the basis of biosensing devices that can respond to external signals by producing visible interfaces, similar to digital displays, that can be read by the human eye.

Although Kim and colleagues' study stops short of realizing these practical applications, the potential of their adhesion toolkit is clear. The biophysical principles uncovered by the authors could be used to engineer microbial consortia with defined metabolic capabilities, as well as smart living materials[4,5] and organoids[6]. Some of these applications will require similar adhesion tools for other microorganisms, such as yeast, and for mammalian cells. But existing methods for expressing nanobodies and antigens on the surfaces of these cells are a good starting point for such developments.

Kim *et al*. have established a set of general principles for engineering programmable biosensors, biomaterials and artificial tissues with predictable patterns, based on a simple adhesion toolkit. And although further work will be needed to demonstrate the utility of the approach, the study shows that synthetic biology can help to answer complex biological questions, such as how tissue boundaries form during development.

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1. Kim, H. *et al. Nature* **608**, 324–329 (2022).
2. Piñero-Lambea, C. *et al. ACS Synth. Biol.* **4**, 463–473 (2015).
3. Glass, D. S. & Riedel-Kruse, I. H. A. *Cell* **174**, 649–658 (2018).
4. Chen, B. *et al. Nature Chem. Biol.* **18**, 289–294 (2022).
5. Gilbert, C. *et al. Nature Mater.* **20**, 691–700 (2021).
6. Gaharwar, A. K., Singh, I. & Khademhosseini, A. *Nature Rev. Mater.* **5**, 686–705 (2020).

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Food

# The mystery of early milk consumption in Europe

**Shevan Wilkin**

What underpins how humans evolved the capacity to consume milk during adulthood? A look at the connection between health and the genetic changes needed to break down milk offers a surprising new perspective. **See p.336**

For decades, it was assumed that the beginnings of human consumption of animal milk occurred in tandem with the spread of the genetic changes needed for people to digest milk into adulthood. However, studies of ancient milk-drinking populations — using methods such as the analysis of ancient DNA, lipids and proteins — indicate that the relationship between these developments is more complex than that. Examination[1] of ancient dairy fat and protein residues shows that consumption of animal milk began in Anatolia (a region corresponding to the bulk of what is Turkey today) in the seventh millennium BC. By 5000 BC, this behaviour had spread across Europe[2] and the Eurasian steppe[3,4], and into northern Africa[5]. Although milk use was widespread in each of these regions by at least 5000 BC, the genetic underpinnings that enable adults to digest milk were extremely rare. Such genetic changes enable expression of the milk-digesting enzyme lactase to be retained beyond childhood, a state termed lactase persistence (LP). On page 336, Evershed *et al*.[6] offer a fresh perspective on the origins of lactase persistence.

**"The ability to consume large amounts of dairy might have boosted the odds of both reproduction and survival."**

Today, about one-third of the world's population can be categorized as being lactase persistent, yet early milk consumers in Eurasia (between approximately 9,000 and 2,000 years ago) lacked a version (allele) of the gene needed for LP, and this adaptation did not start to become common in Europe until roughly 3,000 years ago[7,8]. Numerous possibilities to explain the spread of LP alleles are often discussed, but little quantitative work has been done so far to explore the evolutionary reasons that might reveal the pattern of prevalence of these alleles.

To address this gap, Evershed and colleagues began to unravel the complexities behind the spread of a particular allele associated with LP in modern European populations. The authors demonstrate, through their analysis of present-day UK health data, that the ability to digest milk thanks to LP alleles does not seem to offer any benefit in terms of evolutionary fitness (as assessed through characteristics such as lifespan or having children). These data, combined with extensive archaeological data supporting the consumption of milk fats (lipids) from ceramic vessels (Fig. 1), have enabled Evershed and colleagues to present two exciting hypotheses for how and why LP spread across Europe over the past two millennia.

Infants and small children produce lactase naturally; the enzyme breaks down the molecule lactose into two digestible sugars, enabling infants to consume breast milk. However, until about 3,000 years ago, this ability was typically mainly 'switched off' after weaning. People lacking lactase in adulthood are described as lactase non-persistent (LNP). After consuming milk, LNP individuals can experience mild to severe symptoms that might include bloating, cramps and diarrhoea. Although up to 95% of modern Europeans[9], in certain regions, are lactase persistent, this has not always been the case.

One challenge when trying to investigate dietary health as it relates to populations

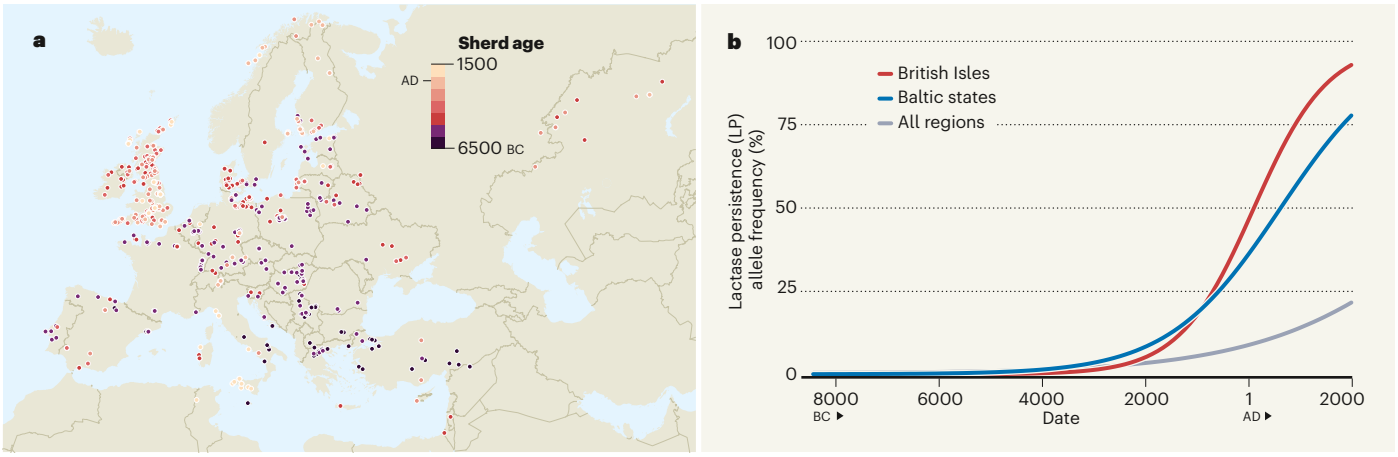


**Figure 1 | The rise of milk consumption.** Evershed *et al.*[6] investigated factors contributing to the rise in use of animal milk by adult humans. **a**, Analysis of pottery fragments (sherds) associated with traces of milk residues and found at archaeological sites offers a timeline for the emergence of dairy consumption in Europe and Eurasia. **b**, A rise in genetic changes (alleles) that help adults to digest milk, a phenomenon termed lactase persistence (LP), occurred long after the onset of dairy consumption. The rise in prevalence of these alleles varied in different regions analysed by the authors. By assessing modern health data for individuals with or without alleles needed for LP, Evershed and colleagues propose some new ways to explain the spread of LP. (Image based on Fig. 1a and Fig. 3 of ref. 6.)

captured in the archaeological record is the inability to know who might have experienced negative health consequences after drinking milk in the past. However, scientists have the option to look at modern data for comparison. Although modern studies rarely provide perfect comparisons for ancient populations, these data present an adequate starting point for understanding past behaviours that might not be otherwise examinable.

In the United Kingdom today, milk and milk products provide an optional dietary supplement, although their consumption is affected by cultural factors such as veganism, dieting for weight loss or abstentions for religious reasons. Evershed and colleagues report that the British population studied, regardless of whether they were lactase persistent or LNP, typically consumed fresh milk regularly. This suggests that the ability to drink milk without negative side effects was probably not a strong factor driving the ancient spread of LP alleles.

The authors propose instead two alternative evolutionary avenues to explain the rise in prevalence of alleles for LP, related to shortages of food or the consequences of increased exposure to disease-causing agents (in relation to animals, crops or from living in close proximity to others without proper sanitation). In either situation, or in a combination of both scenarios, an individual's ability to diversify their diet away from crops and meat, which might be affected by shortages, and to take advantage of the hydration and calories afforded by dairy products, could be extremely beneficial. Furthermore, the inability to consume milk, or the likelihood that an individual might experience symptoms of lactose intolerance after milk consumption, would probably have exacerbated the negative health consequences of those who were starving or afflicted by disease. The authors postulate that, for these reasons, those with the ability to ingest large amounts of fresh milk would have fared much better than those who lacked this ability, driving a rise in the prevalence of LP alleles.

The food-shortage hypothesis is especially compelling because, although many modern LNP individuals can drink a glass of milk with meals without symptoms[10], they would probably experience symptoms if increased milk consumption were necessary. In times of nutritional stress in early milk-producing populations, the ability to consume large amounts of dairy might have boosted the odds of both reproduction and survival. Similarly, the authors suggest that an increase in diseases arising from contact with animals (zoonoses) could have resulted in stressful health consequences and further necessitated the consumption of milk products, thereby presenting an advantage for those with an LP allele. By the European Iron Age (approximately 2,000 years ago), both processes might have been acting in concert, as growing populations became increasingly reliant on agricultural and livestock products, which, in turn, would have increased exposure to zoonotic diseases.

Evershed and colleagues demonstrate that, in either scenario, or both, the response of ancient European populations to periods of nutritional stress was a probable driver for LP. This raises interesting possibilities for tracing the spread of LP, or lack thereof, in other regions. Parts of southwest Asia share the same LP adaptation as that found in Europe, but three different LP alleles have evolved in Africa[8]. In the Middle East, an entirely different allele has developed, whereas the rest of Asia is mainly LNP. Future studies in populations for which milk is a crucial resource rather than a supplemental part of the diet might help us to understand alternative evolutionary pathways to LP.

Future investigation of African, Middle Eastern and the Eurasian steppe regions will further add to our understanding of LP evolutionary trajectories. Many of these African, Middle Eastern and steppe populations depended heavily on the calories and hydration provided by milk for thousands of years. Expanded studies into these regions that combine biomolecular data with methods similar to those used by Evershed and colleagues might reveal how cultural and environmental factors (such as fermentation, adapted gut microorganisms or microbes in the milk itself) might have either increased the spread of LP or negated the need for an LP adaptation, enabling widespread dairy use in ancient and contemporary non-European populations.

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1. Evershed, R. P. *et al. Nature* **455**, 528–531 (2008).
2. Salque, M. *et al. Nature* **493**, 522–525 (2013).
3. Wilkin, S. *et al. Nature Ecol. Evol.* **4**, 346–355 (2020).
4. Wilkin, S. *et al. Nature* **598**, 629–633 (2021).
5. Dunne, J. *et al. Nature* **486**, 390–394 (2012).
6. Evershed, R. P. *et al. Nature* **608**, 336–345 (2022).
7. Burger, J. *et al. Curr. Biol.* **30**, 4307–4315 (2020).
8. Ségurel, L. & Bon, C. *Annu. Rev. Genom. Hum. Genet.* **18**, 297–319 (2017).
9. Itan, Y., Powell, A., Beaumont, M. A., Burger, J. & Thomas, M. G. *PLoS Comput. Biol.* **5**, e1000491 (2009).
10. Bayless, T. M., Brown, E. & Paige, D. M. *Curr. Gastroenterol. Rep.* **19**, 23 (2017).

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